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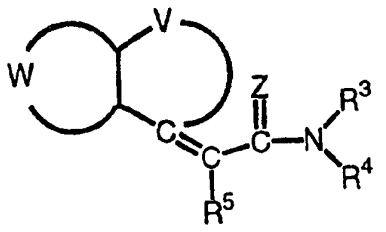
(54) Title: BICYCLIC AMIDE DERIVATIVES AND THEIR USE AS MUSCLE RELAXANTS



(I)

(57) Abstract

The present invention relates to amide and thioamide compounds of formula (I), synthesis thereof, intermediates, salts, solvates and physiologically functional derivatives thereof, pharmaceutical compositions containing them and to the use of certain amide and thioamide compounds and compositions thereof in medicine and therapy, particularly as muscle relaxants.

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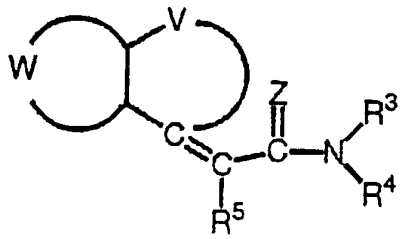
Bicyclic amide derivatives and their use as muscle relaxants

The present invention relates to amide and thioamide compounds, synthesis thereof, intermediates, salts, solvates and physiologically functional derivatives thereof, pharmaceutical compositions containing them and the use of such compounds and compositions in medicine and therapy, particularly as muscle relaxants.

The major limiting side effects of many clinically effective muscle relaxants and anticonvulsants are the induction of sedation and incoordination in the recipient, which severely limits the usefulness of these compounds. Similar side effects have been found with drugs used in the treatment of anxiety, such as, benzodiazepines. Although these effects may be transient, patients on such therapy are often unable to drive or participate in certain occupations.

It has been found that amides and thioamides of formula (I) have potent muscle relaxant activity but with significantly reduced liability to the sedation and incoordination side-effects observed with known muscle relaxants.

According to one aspect of the present invention there are provided compounds of general formula (I):



(I)

wherein V is

(a) $(CR^1R^2)_mB$,

(b) $B(CR^1R^2)_m$ or

(c) $(CR^1R^2)_mB(CR^1R^2)_m$

wherein B is CR^1R^2, O, NR^6, C=O or $S(O)_m$ and

wherein R^1 and R^2 are the same or different and are

(a) H;

(b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl or C_{1-6}alkylenearyl all optionally substituted with one or more halogen, C_{1-6} alkyl(optionally substituted with one or more halogen, OR^6 or NR^6R^{6a}), $OC(O)R^6$, OR^6, NR^6R^{6a} or $S(O)_mR^6$; or

R^1R^2 together with the carbon atom to which they are attached form a C_{3-4} ring, or a C_{2-5} heterocyclic ring (comprising one or more heteroatoms of O, NR^6, and $S(O)_m$), the carbon atoms of said rings optionally substituted with one or more halogen, C_{1-6} alkyl(optionally substituted with one or more halogen, OR^6 or NR^6R^{6a}), $OC(O)R^6$, OR^6, NR^6R^{6a} or $S(O)_mR^6$;

(c) OR^6;

(d) $OC(O)R^6$;

(e) $NC(O)R^6$; or

(f) halogen(e.g., fluorine);

wherein R^6 and R^{6a} are the same or different and are H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylene (C_{3-6} cycloalkyl), aryl or C_{1-6} alkylenearyl all optionally substituted with one or more halogen, C_{1-6} alkyl(optionally substituted with one or more halogen, OH, C_{1-6}alkoxy, NH_2 or substituted amino(as defined hereinafter)); or any combination thereof;

W is an aryl or a heteroaryl ring substituted with one or more

(a) halogen;

(b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkylene(C_{3-6}cycloalkyl), aryl, C_{1-6}alkylenearyl, C_{1-6} alkoxy, aryloxy, or C_{1-6} alkyleneoxyaryl all optionally substituted with one or more halogen, OR^6, or NR^6R^{6a};

(c) OR^6;

(d) NR^6R^{6a}, $NR^6NR^6R^{6a}$, $CONR^6R^{6a}$ or $S(O)_mNR^6R^{6a}$ wherein both of the R^6 and R^{6a} are the same or different and are as described hereinbefore or R^6R^{6a} together with the nitrogen atom to which they are attached denote a

C_{2-7} ring optionally substituted with one or more halogen, C_{1-6} alkyl(optionally substituted with one or more halogen, OR^6 or NR^6R^{6a}), OR^6 or NR^6R^{6a};

(e) $C(Y)R^6$ wherein Y is O, NOR^6, NR^6 or S;

(f) CO_2R^6;

(g) OR^6O(cyclic) wherein R^6 is other than H;

(h) $OC(O)R^6$;

(i) $OP(O)(OR^6)_2$;

(j) $OP(O)(R^6)_2$ wherein R^6 is other than H;

(k) $OS(O)(OR^6)$;

(l) $OS(O)_2(OR^6)$;

(m) $S(O)_mR^6$ wherein R^6 is other than H;

(n) $NHS(O)_mR^6$ wherein R^6 is other than H;

(o) $N=NR^6$;

(p) NO;

(q) NO_2;

(r) SCN; or

(s) CN or a combination thereof;

when one m is present, m is 0,1 or 2;
when more than one m is present, m can be the same or different and is 0,1 or 2;

R^3 and R^4 are the same or different and are

(a) H; or

(b) C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkylene(C_{3-6}cycloalkyl), aryl or C_{1-6}alkylenearyl all optionally substituted with one or more halogen, C_{1-6} alkyl(optionally substituted with one or more halogen, OR^6 or NR^6R^{6a}), OR^6 or NR^6R^{6a}; or

R^3 and R^4 together with the nitrogen atom to which they are attached denote a C_{2-7} ring or a C_{1-4} heterocyclic ring (comprising one or more heteroatoms selected from the group consisting of O, NR^6, and $S(O)_m$) the carbon atoms of said rings optionally substituted with one or more halogen, C_{1-6} alkyl (optionally substituted with one or more halogen, OR^6 or NR^6R^{6a}), OR^6 or NR^6R^{6a} or any combination thereof;

R^5 is

(a) H;
(b) halogen;
(c) CN;
(d) $C(O)OR^6$;
(e) $C(O)NR^3R^4$;
(f) C_{1-6} alkyl, aryl or C_{1-6} alkylenearyl all optionally substituted with one or more halogen, $OC(O)R^6$, OR^6, NR^6R^{6a} or SR^6;
(g) OR^6; or
(h) SR^6 or any combination thereof; and

Z is O or S;
or salts, solvates or physiologically functional derivatives thereof.

Preferred compounds of formula (I) include those wherein V is
(a) $(CR^1R^2)_mB$,
(b) $B(CR^1R^2)_m$ or
(c) $(CR^1R^2)_mB(CR^1R^2)_m$
wherein B is CR^1R^2, O, NR^6, or $S(O)_m$ and
wherein R^1 and R^2 are the same or different and are selected from
(a) H;
(b) C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl all optionally substituted by one or more NR^6R^{6a};
(c) hydroxy;
(d) $OC(O)R^6$; or
e) halogen(e.g., fluorine) or any combination thereof;

W is aryl or heteroaryl substituted with one or more
(a) halogen (e.g., flluorine or chlorine); or
(b) C_{1-6} alkyl optionally substituted with one or more halogen (e.g., fluorine), OR^6 or CN or a combination thereof;

when one m is present, m is 1 or 2;

when more than one m is present, m can be the same or different and is 1 or 2;

R^3 and R^4 are the same or different and are

(a) H; or

(b) C_{1-6} alkyl, C_{3-6} cycloalkyl(e.g., cyclopropyl, cyclobutyl), C_{1-6} alkylene(C_{3-6} cycloalkyl) or any combination thereof; or together with the nitrogen to which they are attached denote a C_{2-7} ring;

R^5 is H or halogen;

R^6 and R^{6a} are as defined hereinbefore; and

Z is O;

or salts, solvates or physiologically functional derivatives thereof.

More preferred compounds of formula (I) include those wherein V is

(a) $(CR^1R^2)_mB$ or

(b) $B(CR^1R^2)_m$

wherein B is CR^1R^2 or O and

wherein R^1 and R^2 are the same or different and are selected from

(a) H;

(b) CH_3, CH_2 CH_3;

(c) C_{1-6} alkyl substituted by NR^6R^{6a};

(d) hydroxy;

(e) $OC(O)R^6$; or

(f) fluorine, or any combination thereof;

W is phenyl or naphthyl substituted with one or more

(a) halogen(e.g., fluorine or chlorine),

(b) CH_3;or

(c) CF_3, or any combination thereof;

when one m is present, m is 1 or 2;

when more than one m is present, m can be the same or different and is 1 or 2;

R^3 and R^4 are
(a) H;
(b) CH_3;or
(c) cyclopropyl, or any combination thereof;

R^5 is H or halogen(preferably fluorine);

R^6 and R^{6a} are as defined hereinbefore; and

Z is O;

or salts, solvates or physiologically functional derivatives thereof.

Particularly preferred compounds of formula (I) include those wherein V is $B(CR^1R^2)_m$ wherein B is CR^1R^2 or O and
wherein R^1 and R^2 are the same or different and are H, CH_3 or OH or any combination thereof;

W is a phenyl ring substituted with one or more with halogen (preferably fluoro or chloro or any combination thereof);

when one m is present, m is 1 or 2;
when more than one m is present, m can be the same or different and is 1 or 2;

R^3 and R^4 are H, CH_3 or cyclopropyl or any combination thereof;

R^5 is H; and

Z is O;
or salts, solvates or physiologically functional derivatives thereof.

Most preferred compounds of formula (I) include those wherein V is
$B(CH_2)_m$
wherein B is CR^1R^2 and

wherein R^1 and R^2 are the[illegible], CH_3, CH_3 or OH or any combination thereof;

W is a phenyl ring substitut[illegible]en (prefer[illegible]oro or chloro) or any combination thereof;

when one m is present, m is
when more than one m is pre[illegible]e or differe[illegible] or 2;

R^3 and R^4 are the same or d[illegible]H_3 or cyclo[illegible]ny combination thereof;

R^5 is H; and

Z is O;
or salts, solvates or physiologic[illegible]erivatives ther[illegible]

Representative compounds of fo[illegible]

	EXAMPLE	MP °C
(E)-2-(4-Chloro-1-indanylidene)acetamide	1;k	196-198
(E)-2-(6-Fluoro-1-indanylidene)acetamide	l;k	180-183
(E)-N-Cyclopropyl-2-(1-indanylidene)acetamide		115-116
(E)-2-(4-Fluoro-1-indanylidene)acetamide	15;i	198-200
(E)-2-(5-Fluoro-1-indanylidene)acetamide	21;e	191-193
(E)-2-(3-Phenyl-1-indanylidene)acetamide		219-222
(E)-N-Cyclopropyl-2-(3-phenyl-1-indanylidene)acetamide		138-139
(E)-N-Methyl-2-(3-phenyl-1-indanylidene)acetamide		170-172
(E)-2-(1-Indanylidene)acetamide		150-151
(E)-2-(5-Methoxy-1-indanylidene)acetamide		213-216
(E)-N-Cyclopropyl-2-(4-fluoro-1-indanylidene)acetamide	16	121-122
(E)-2-(6-Fluoro-3-methyl-1-indanylidene)acetamide	44;i	149-151
(E)-2-(6-Fluoro-3-methyl-1-indanylidene)-N-methylacetamide	45	168-169
(E)-N-Cyclopropyl-2-(6-fluoro-3-methyl-1-indanylidene)acetamide	46	132-134
(E)-2-(6-Fluoro-3,3-dimethyl-1-indanylidene)acetamide	41;i	167-168
(E)-2-(6-Fluoro-3,3-dimethyl-1-indanylidene)-N-methylacetamide	42	157-158
(E)-N-Cyclopropyl-2-(6-fluoro-3,3-dimethyl-1-indanylidene)acetamide	43	149-150
(E)-2-(6-Fluoro-3-ethyl-1-indanylidene)-N-methylacetamide	like 64;i	141-143
(E)-N-Cyclopropyl-2-(6-fluoro-3-ethyl-1-indanylidene)acetamide	64;i	143-147

(E)-2-(6-Fluoro-3-ethyl-1-indanylidene)acetamide	like 41;i	163-166
(E)-2-(6-Fluoro-3-ethyl-1-indanylidene)-N-isopropylacetamide	like 64;i	127-130
(E)-2-(6-Fluoro-3-ethyl-1-indanylidene)-N,N-dimethylacetamide	like 64;i	79-82
(E)-2-(6-Fluoro-3-propyl-1-indanylidene)-N-methylacetamide	like 64; i	105-107
(E)-N-Cyclopropyl-2-(6-Fluoro-3-propyl-1-indanylidene)acetamide	like 64;i	94-97
(E)-2-(6-Fluoro-3-propyl-1-indanylidene)-N,N-dimethylacetamide	like 64;i	95-97
(E)-2-(6-Fluoro-3-propyl-1-indanylidene)-N-isopropylacetamide	like 64;i	108-110
(E)-2-(6-Fluoro-3-propyl-1-indanylidene)acetamide	like 41;i	167-169
(E)-N-Cyclopropyl-2-(5-fluoro-1-indanylidene)acetamide	22	137-138
(E)-2-(4-Methyl-1-indanylidene)acetamide	1;k	178-180
(E)-N-Cyclopropyl-2-(4-methyl-1-indanylidene)acetamide		138-140
(E)-2-(5-Chloro-1-indanylidene)-N-cyclopropylacetamide		150-152
(E)-2-(5-Chloro-1-indanylidene)-N-methylacetamide		182-185
(E)-2-(5-Chloro-1-Indanylidene)acetamide		222-224
(E)-2-(4-Chloro-1-indanylidene)-N-cyclopropylacetamide		140-142
(Z)-N-(Cyclopropyl)-2-(2,2-dimethyl-1-indanylidene)acetamide		146-148
(E)-2-(6-Chloro-1-indanylidene)acetamide		174-176
(E)-1-(2-(6-Fluoro-1-indanylidene)acetyl)pyrrolidine	like 5	120-123
(E)-2-(6-Fluoro-1-indanylidene)-N-phenylacetamide	like 5	158-161
(E)-4-(2-(6-Fluoro-1-indanylidene)acetyl)morpholine	like 5	133-136
(E)-1-(2-(6-Fluoro-1-indanylidene)acetyl)azetidine	like 5	123-125
(Z)-2-(6-Fluoro-2-hydroxy-1-indanylidene)acetamide	52	201-202
(E)-2-(6-Fluoro-1-indanylidene)-N-methoxy-N-methylacetamide	like 5	76-78

(Z)-2-(6-Fluoro-2-nitrooxy-1-indanylidene)acetamide	53	162-163
(E)-2-(6-Fluoro-1-indanylidene)-N-(2-hydroxyethyl)acetamide	like 5	146-148
(E)-2-(6-Fluoro-1-indanylidene)-N-isopropylacetamide	like 5	143-145
(Z)-2-(6-Fluoro-2-methoxy-1-indanylidene)acetamide	54	128-130
(Z)-2-(2,3-Dibromo-6-fluoro-1-indanylidene)acetamide	51	158-163
(E)-2-(6-Chloro-1-indanylidene)-N-methylacetamide		220-225
(E)-2-(6-Fluoro-3-hydroxy-1-indanylidene)acetamide	57;g	166-168
(E)-N-cyclopropyl-2-(6-Chloro-1-indanylidene)acetamide		165-168
(E)-2-(6-Fluoro-1-indanylidene)thioacetamide		176-179
(E)-2-(6-Fluoro-1-indanylidene)-N-methylacetamide	like 5	201-205
(E)-N-Cyclopropyl-2-(6-fluoro-1-indanylidene)acetamide	5	124-127
(E)-N-Ethyl-2-(6-fluoro-1-indanylidene)acetamide	3;like 5	125-127
(E)-N-Cyclobutyl-2-(6-fluoro-1-indanylidene)acetamide	like 5	137-139
(E)-N-Cyclopentyl-2-(6-fluoro-1-indanylidene)acetamide	like 5	152-154
(E)-2-(6-Bromo-1-indanylidene)acetamide		179-181
(E)-N-(Cyclopropylmethyl)-2-(6-fluoro-1-indanylidene)acetamide		105-107
(E)-2-(6-Fluoro-1-indanylidene)-N-propylacetamide	like 5	82-84
(E)-2-(6-Fluoro-1-indanylidene)-N,N-dimethylacetamide	like 5	74-77
(E)-N-ethyl-2-(6-fluoro-1-indanylidene)-N-methylacetamide	7; like 5	74-77
(E)-N-Benzyl-2-(6-fluoro-1-indanylidene)acetamide		134-136
(E)-2-(6-Fluoro-3-oxo-1-indanylidene)acetamide	60;g	235
(Z)-2-(2-Acetoxy-6-fluoro-1-indanylidene)acetamide	55	202-203
(Z)-2-(2-Bromo-6-fluoro-1-indanylidene)acetamide	50	162-163

(E)-N-Cyclopropyl-2-(5,6-difluoro-1-indanylidene)acetamide	like 5	169-171
(E)-2-(5,6-Difluoro-1-indanylidene)-N-methylacetamide	like 5	209-211
(E)-2-(5,6-Difluoro-1-indanylidene)acetamide	like 1;k	165-167
(E)-2-(5,7-Difluoro-1-indanylidene)acetamide	like 1;k	161-162
(E)-N-Cyclopropyl-2-(5,7-difluoro-1-indanylidene)acetamide	like 5	145-147
(E)-2-(5,7-Difluoro-1-indanylidene)-N-methylacetamide	like 5	193-195
(E)-2-(6-Methyl-1-indanylidene)acetamide		189-193
(E)-N-Cyclopropyl-2-(4,6-difluoro-1-indanylidene)acetamide	13;like 5	156-158
(E)-2-(4,6-Difluoro-1-indanylidene)acetamide	12;g	178-180
(Z)-2-(1-Indanylidene)acetamide		127
(E)-2-(4,6-Difluoro-1-indanylidene)-N-isopropylacetamide	like 5	167-170
(E)-2-(4,6-Difluoro-1-indanylidene)-N,N-dimethylacetamide	like 5	105-106
(E)-2-(4,6-Difluoro-1-indanylidene)-N-ethylacetamide	like 5	130-132
(E)-2-(4,6-Difluoro-1-indanylidene)-N-(2-hydroxyethyl)acetamide	like 5	152-154
(E)-N-Ethyl-2-(4,6-difluoro-1-indanylidene)-N-methylacetamide	like 5	96-98
(Z)-2-(6-Chloro-1-indanylidene)-N-methylacetamide		110-114
(E)-2-(4,7-Difluoro-1-indanylidene)acetamide	like 12;g	167-169
(E)-2-(4,5-Difluoro-1-indanylidene)acetamide	like 12;g	195-197
(E)-N-Cyclopropyl-2-(4,5-difluoro-1-indanylidene)acetamide	like 5	135-137
(E)-N-Cyclopropyl-2-(4,7-difluoro-1-indanylidene)acetamide	like 5	134-136
(E)-2-(7-Methyl-1-indanylidene)acetamide		198-199
(E)-N-Cyclopropyl-2-(7-methyl-1-indanylidene)acetamide	like 5	142-144.5
(E)-2-(4-Chloro-6-fluoro-1-indanylidene)acetamide		182-184

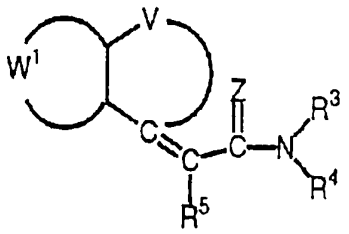
(E)-2-(6-Cyano-1-indanylidene)acetamide	like 1;k	221-223
(E)-2-(4,6-Difluoro-1-indanylidene)-N-methylacetamide	like 5	181-183
(E)-N-Cyclopropyl-2-(4,6-dichloro-1-indanylidene)acetamide		174-176
(E)-2-(4-Chloro-6-fluoro-1-indanylidene)-N-cyclopropylacetamide		147-149
(E)-2-(4,6-Dichloro-1-indanylidene)acetamide		210-212
(E)-2-(4,6-Dichloro-1-indanylidene)-N-methylacetamide		225-227
(Z)-2-(4,6-Difluoro-2-hydroxy-1-indanylidene)acetamide	56	235-237
(E)-2-(4-Chloro-6-fluoro-1-indanylidene)-N-methylacetamide		173-175
(Z)-2-(2-Bromo-4,6-difluoro-1-indanylidene)acetamide	49	187-188
(E)-2-(6-Bromo-1-indanylidene)-N-cyclopropylacetamide	like 5	173-174
(E)-2-(6-Bromo-1-indanylidene)-N-methylacetamide	like 5	225-227
(E)-2-(6-Methoxy-1-indanylidene)acetamide	like 1;k	188-192
(Z)-2-(6-Chloro-1-indanylidene)-N-cyclopropylacetamide		151-153
(Z)-2-(6-Fluoro-1-indanylidene)acetamide	66	175-177
(E)-2-(6-Fluoro-3-isopropyl-1-indanylidene)-N-methylacetamide	like 64;i	
(E)-2-(6-Fluoro-3-isopropyl-1-indanylidene)-N,N-dimethylacetamide	like 64;i	
(E)-N-Cyclopropyl-2-(6-fluoro-3-isopropyl-1-indanylidene)acetamide	like 64;i	
(E)-2-(6-Fluoro-3-isopropyl-1-indanylidene)acetamide	like 64;i	
(E)-2-(6-Chloro-4-Fluoro-1-indanylidene)acetamide		
(E)-2-(6-Chloro-4-Fluoro-1-indanylidene)-N-methylacetamide		
(E)-2-(6-Chloro-4-Fluoro-1-indanylidene)-N-cyclopropylacetamide		
(E)-2-(6-Fluoro-4-methyl-1-indanylidene)acetamide		
(E)-2-(6-Fluoro-4-methyl-1-indanylidene)-N-methylacetamide		

(E)-N-Cyclopropyl-2-(6-Fluoro-4-methyl-1-indanylidene)acetamide		
(E)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-1-naphthylidene)acetamide		134-135
(E)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-5-fluoronaphthylidene)acetamide	37;f	148-149
(E)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide	like 37;f	148-150
(E)-2-(6-Fluoro-3,4-dihydro-2H-1-benzopyran-4-ylidene)acetamide	like 12;g	155-157
(E)-2-(6-Fluoro-3,4-dihydro-2H-1-benzopyran-4-ylidene)-N-methylacetamide	like 5	182-185
(E)-N-Cyclopropyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide	38;like27;d	122.8-123.3
(E)-2-(7-Chloro-1,2,3,4-tetrahydro-1-naphthylidene)-N-cyclopropylacetamide	like 82;c	170.7-171.8
(E)-2-(5-Bromo-1,2,3,4-tetrahydro-1-naphthylidene)-N-cyclopropylacetamide	like 82;c	178.5-180
(E)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N-methylacetamide		115-118
(E)-N-ethyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide		87-89
(E)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-7-methoxy-1-naphthylidene)acetamide	like 82;c	128.3-130.6
(E)-N-Cyclopentyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide	like 82;c	166-167
(E)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N-isopropylacetamide		144-146
(E)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N-propylacetamide		71-74
(E)-N-Cyclobutyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide		159-162
(E)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-6-methoxy-1-naphthylidene)acetamide	like 82;c	179-180.4
(E)-N-Benzyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide	like 82;c	96-98
(E)-4-(2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetyl)morpholine		96-99
(E)-N-Cyclopropyl-2-(5-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)propionamide	like 40;F	161-162
(E)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N-(2-hydroxyethyl)acetamide	like 40;F	120-122
(E)-N-Cyclopropyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide		106-111
(E)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N,N-dimethylacetamide		66-70

(E)-2-(6-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N-methyl-N-methoxyacetamide	like 40;F	67-69
(Z)-N-Cyclopropyl-2-(7-fluoro-1,2,3,4-tetrahydro-2,2-dimethyl-1-naphthylidene)acetamide	like 59	118-121
(E)-N-Cyclopropyl-2-(7-fluoro-1,2,3,4-tetrahydro-2,2-dimethyl-1-naphthylidene)acetamide	like 59	113-115
(E)-N-Ethyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N-methylacetamide		66-68
(E)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetanilide	like 40;F	119-121
(E)-1-(2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetyl)azetidine	like 40;F	58-61
(E)-1-(2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetyl)pyrrolidine	like 82;c	141-143
(E)-2-(5,6,7,8-Tetrahydro-8-quinolinylidene)acetamide		216-218
(E)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-7-methyl-1-naphthylidene)acetamide	like 82;c	151.7-153.9
(E)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-5-methoxy-1-naphthylidene)acetamide	like 82;c	156.8-160.3
(Z)-N-cyclopropyl-2-(1,2,3,4-tetrahydro-1-naphthylidene)acetamide	like 83	106-113
(E)-2-(6-Chloro-1,2,3,4-tetrahydro-1-naphthylidene)-N-cyclopropylacetamide	like 82;c	173-174
(Z)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide		198-201
(E)-N-Cyclopropyl-2-(6-fluoro-3,4-dihydro-2H-1-benzopyran-4-ylidene)acetamide	like 5	146-148
(Z)-N-Ethyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide		117-118
(Z)-2-(7-Chloro-1,2,3,4-tetrahydro-1-naphthylidene)-N-cyclopropylacetamide	like 83	104-105.5
(Z)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-7-methoxy-1-naphthylidene)acetamide	like 83	145-146.1
(Z)-N-Cyclopentyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide	like 83	147-149
(Z)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N-phenylacetamide	like 83	180-184
(E)-2-(6-Chloro-3,4-dihydro-2H-1-benzopyran-4-ylidene)-N-cyclopropylacetamide	like 5	171-172
(E)-2-(6-Chloro-3,4-dihydro-2H-1-benzopyran-4-ylidene)-N-methylacetamide	like 5	204-205
(Z)-N-Cyclopropyl-2-(2,3,4,5-tetrahydro-1-tosyl-1H-1-benzazepin-5-ylidene)acetamide		66-65
(E)-2-(1-acetyl-6-fluoro-1,2,3,4-tetrahydro-4-quinolylidene)-N-cyclopropylacetamide		165-166

(E)-2-(6-Chloro-3,4-dihydro-2H-1-benzopyran-4-ylidene)acetamide	like 5	168-169
(E)-N-Cyclopropyl-2-(3,4-dihydro-2H-1-benzothiopyran-4-ylidene)acetamide	like 5	115-116
(E)-N-2-(3,4-dihydro-2H-1-benzothiopyran-4-ylidene)-N-methylacetamide	like 5	91-93
(E)-2-(3,4-dihydro-2H-1-benzothiopyran-4-ylidene)acetamide	like 5	175-175
(E)-2-(6-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)-N-cyclopropylacetamide		
(E)-2-(6-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)-N-methylacetamide		
(E)-2-(6-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)acetamide		
(E)-2-(5-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)-N-cyclopropylacetamide		
(E)-2-(5-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)-N-methylacetamide		
(E)-2-(5-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)acetamide		
(E)-2-(7-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)acetamide		
(E)-2-(7-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)-N-methylacetamide		
(E)-2-(7-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-Benzopyran-4-ylidene)-N-cyclopropylacetamide		

According to another aspect of the present invention there are provided compounds of formula (I)(as described hereinbefore) and of formula (Ia) for use in medical therapy:



(Ia)

wherein V is

(a) $(CR^7R^8)_mB$,

(b) $B(CR^7R^8)_m$ or

(c) $(CR^7R^8)_mB(CR^7R^8)_m$

wherein B is CR^7R^8, O, NR^6, C=O or $S(O)_m$ and

wherein R^7 and R^8 are the same or different and are

(a) H;

(b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl or C_{1-6}alkylenearyl all optionally substituted with one or more halogen, C_{1-6} alkyl(optionally substituted with one or more halogen, OR^6 or NR^6R^{6a}), $C(O)R^6$, OR^6, N^6R^{6a} or $S(O)_mR^6$; or

R^7R^8 together with the carbon atom to which they are attached form a C_{3-6} ring, or a C_{2-5} heterocyclic ring(comprising one or more heteroatoms selected from the group consisting of O, NR^6, and $S(O)_m$), the carbon atoms of said rings optionally substituted with one or more halogen, C_{1-6} alkyl(optionally substituted with one or more halogen, OR^6 or NR^6R^{6a}), $OC(O)R^6$, OR^6, NR^6R^{6a} or $S(O)_mR^6$;

(c) OR^6;

(d) $OC(O)R^6$;

(e) $NC(O)R^6$; or

(f) halogen(e.g., fluorine) or any combination thereof;

W^1 is an aryl or a heteroaryl ring optionally substituted with one or more

(a) halogen;

(b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkylene(C_{3-6}cycloalkyl), aryl, C_{1-6}alkylenearyl, C_{1-6} alkoxy, aryloxy, or C_{1-6}alkyleneoxyaryl all optionally substituted with one or more halogen, OR^6 or NR^6R^{6a};

(c) OR^6;

(d) NR^6R^{6a}, $NR^6NR^6R^{6a}$, $CONR^6R^{6a}$ or $S(O)_mNR^6R^{6a}$ wherein both of the R^6 and R^{6a} are the same or different and are as described hereinbefore or R^6R^{6a} together with the nitrogen atom to which they are attached denote a C_{2-7} ring optionally substituted with one or more halogen, C_{1-6} alkyl(optionally substituted with one or more halogen, OR^6 or NR^6R^{6a}), OR^6 or NR^6R^{6a};

(e) $C(Y)R^6$ wherein Y is O, NOR^6, NR^6, or S;

(f) CO_2R^6;

(g) OR^6O(cyclic) wherein R^6 is other than H;

(h) $OC(O)R^6$;

(i) $OP(O)(OR^6)_2$;

(j) $OP(O)(R^6)_2$ wherein R^6 is other than H;

(k) $OS(O)(OR^6)$;

(l) $OS(O)_2(OR^6)$;

(m) $S(O)_mR^6$ wherein R^6 is other than H;

(n) $NHS(O)_mR^6$ wherein R^6 is other than H;

(o) $N=NR^6$;

(p) NO;

(q) NO_2;

(r) SCN; or

(s) CN or any combination thereof;

when one m is present, m is 0, 1 or 2;
when more than one m is present, m can be the same or different and is 0, 1 or 2; and

R^3, R^4, R^5, R^6 , R^{6a} and Z are as defined hereinbefore for formula (I);
or salts, solvates or physiologically functional derivatives thereof.

The compounds of formula (I) and (Ia) are particularly suited for use as muscle relaxants and for the treatment or prophylaxis of conditions associated with:

- abnormally raised muscle tone and
- convulsive states.

Other uses of the compounds of formula (I) and (Ia) are for the treatment or prophylaxis of conditions associated with:

- anxiety
- inflammation
- arthritis; and
- pain (algesia)

Preferred compounds of formula (I) for such use include those wherein V is

(a) $(CR^1R^2)_mB$,

(b) $B(CR^1R^2)_m$ or

(c) $(CR^1R^2)_mB(CR^1R^2)_m$

wherein B is CR^1R^2, O, NR^6, or $S(O)_m$

wherein R^1 and R^2 are the same or different and are

(a) H;

(b) C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl all optionally substituted by one or more NR^6R^{6a};

(c) hydroxy;

(d) $OC(O)R^6$; or

(e) halogen(e.g., fluorine) or any combination thereof;

W is aryl or heteroaryl substituted with one or more

(a) halogen(e.g., fluorine or chlorine); or

(b) C_{1-6} alkyl optionally substituted with one or more halogen(e.g., fluorine), OR^6 or CN; or any combination thereof;

when one m is present, m is 1 or 2;

when more than one m is present, m can be the same or different and is1 or 2;

R^3 and R^4 are

(a) H; or

(b) C_{1-6} alkyl, C_{3-6} cycloalkyl(e.g., cyclopropyl, cyclobutyl), C_{1-6} alkylene(C_{3-6} cycloalkyl) or any combination thereof, or together with the nitrogen to which they are attached denote a C_{2-7} ring;

R^5 is H or halogen;

R^6 and R^{6a} are as defined hereinbefore; and

Z is O;
or salts, solvates or physiologically functional derivatives thereof.

More preferred compounds of formula (I) for such use include those wherein V is
(a) $(CR^1R^2)_mB$ or
(b) $B(CR^1R^2)_m$
wherein B is CR^1R^2 or O and
wherein R^1 and R^2 are the same or different and are
(a) H;
(b) CH_3, CH_2 CH_3;
(c) C_{1-6} alkyl substituted by NR^6R^{6a};
(d) hydroxy;
(e) $OC(O)R^6$; or
(f) fluorine or any combination thereof;

W is phenyl or naphthyl substituted with one or more
(a) halogen(e.g., fluorine or chlorine),
(b) CH_3 or
(c) CF_3 or any combination thereof;

when one m is present, m is 1 or 2;
when more than one m is present, m can be the same or different and is 1 or 2;

R^3 and R^4 are
(a) H;
(b) CH_3; or
(c) cyclopropyl or any combination thereof;

R^5 is H or halogen(preferably fluorine);

R^6 and R^{6a} are as defined hereinbefore; and

Z is O;
or salts, solvates or physiologically functional derivatives thereof.

Particularly preferred compounds of formula (I) for such use include those wherein V is $B(CR^1R^2)_m$
wherein B is CR^1R^2 or O and
wherein R^1 and R^2 are the same or different and are selected from H, CH_3, CH_2 CH_3 or OH or any combination thereof;

W is a phenyl ring substituted with halogen, preferably fluoro or chloro or any combination thereof;

m is 1 or 2

R^3 and R^4 are H, CH_3 or cyclopropyl or any combination thereof;

R^5 is H; and

Z is O;
or salts, solvates or physiologically functional derivatives thereof.

Most preferred compounds of formula (I) for such use include those wherein V is $B(CH_2)_m$
wherein B is CR^1R^2 and
wherein R^1 and R^2 are the same or different and are selected from H, CH_3, CH_2 CH_3 or OH; or any combination thereof;

W is a phenyl ring substituted with one or two halogen, preferably fluoro or chloro or any combination thereof;

m is 1 or 2;

R^3 and R^4, are H, CH_3 or cyclopropyl; or any combination thereof;

R_5 is H; and

Z is O;
or salts, solvates or physiologically functional derivatives thereof.

Representative compounds of formula (I) for such use are:

	EXAMPLE	MP °C
(E)-2-(4-Chloro-1-indanylidene)acetamide	1;k	196-198
(E)-2-(6-Fluoro-1-indanylidene)acetamide	l;k	180-183
(E)-N-Cyclopropyl-2-(1-indanylidene)acetamide		115-116
(E)-2-(4-Fluoro-1-indanylidene)acetamide	15;i	198-200
(E)-2-(5-Fluoro-1-indanylidene)acetamide	21;e	191-193
(E)-2-(3-Phenyl-1-indanylidene)acetamide		219-222
(E)-N-Cyclopropyl-2-(3-phenyl-1-indanylidene)acetamide		138-139
(E)-N-Methyl-2-(3-phenyl-1-indanylidene)acetamide		170-172
(E)-2-(1-Indanylidene)acetamide		150-151
(E)-2-(5-Methoxy-1-indanylidene)acetamide		213-216
(E)-N-Cyclopropyl-2-(4-fluoro-1-indanylidene)acetamide	16	121-122
(E)-2-(6-Fluoro-3-methyl-1-indanylidene)acetamide	44;i	149-151
(E)-2-(6-Fluoro-3-methyl-1-indanylidene)-N-methylacetamide	45	168-169
(E)-N-Cyclopropyl-2-(6-fluoro-3-methyl-1-indanylidene)acetamide	46	132-134
(E)-2-(6-Fluoro-3,3-dimethyl-1-indanylidene)acetamide	41;i	167-168
(E)-2-(6-Fluoro-3,3-dimethyl-1-indanylidene)-N-methylacetamide	42	157-158
(E)-N-Cyclopropyl-2-(6-fluoro-3,3-dimethyl-1-indanylidene)acetamide	43	149-150
(E)-2-(6-Fluoro-3-ethyl-1-indanylidene)-N-methylacetamide	like 64;i	141-143
(E)-N-Cyclopropyl-2-(6-fluoro-3-ethyl-1-indanylidene)acetamide	64;i	143-147

(E)-2-(6-Fluoro-3-ethyl-1-indanylidene)acetamide	like 41;i	163-166
(E)-2-(6-Fluoro-3-ethyl-1-indanylidene)-N-isopropylacetamide	like 64;i	127-130
(E)-2-(6-Fluoro-3-ethyl-1-indanylidene)-N,N-dimethylacetamide	like 64;i	79-82
(E)-2-(6-Fluoro-3-propyl-1-indanylidene)-N-methylacetamide	like 64; i	105-107
(E)-N-Cyclopropyl-2-(6-Fluoro-3-propyl-1-indanylidene)acetamide	like 64;i	94-97
(E)-2-(6-Fluoro-3-propyl-1-indanylidene)-N,N-dimethylacetamide	like 64;i	95-97
(E)-2-(6-Fluoro-3-propyl-1-indanylidene)-N-isopropylacetamide	like 64;i	108-110
(E)-2-(6-Fluoro-3-propyl-1-indanylidene)acetamide	like 41;i	167-169
(E)-N-Cyclopropyl-2-(5-fluoro-1-indanylidene)acetamide	22	137-138
(E)-2-(4-Methyl-1-indanylidene)acetamide	1;k	178-180
(E)-N-Cyclopropyl-2-(4-methyl-1-indanylidene)acetamide		138-140
(E)-2-(5-Chloro-1-indanylidene)-N-cyclopropylacetamide		150-152
(E)-2-(5-Chloro-1-indanylidene)-N-methylacetamide		182-185
(E)-2-(5-Chloro-1-Indanylidene)acetamide		222-224
(E)-2-(4-Chloro-1-indanylidene)-N-cyclopropylacetamide		140-142
(Z)-N-(Cyclopropyl)-2-(2,2-dimethyl-1-indanylidene)acetamide		146-148
(E)-2-(6-Chloro-1-indanylidene)acetamide		174-176
(E)-1-(2-(6-Fluoro-1-indanylidene)acetyl)pyrrolidine	like 5	120-123
(E)-2-(6-Fluoro-1-indanylidene)-N-phenylacetamide	like 5	158-161
(E)-4-(2-(6-Fluoro-1-indanylidene)acetyl)morpholine	like 5	133-136
(E)-1-(2-(6-Fluoro-1-indanylidene)acetyl)azetidine	like 5	123-125
(Z)-2-(6-Fluoro-2-hydroxy-1-indanylidene)acetamide	52	201-202
(E)-2-(6-Fluoro-1-indanylidene)-N-methoxy-N-methylacetamide	like 5	76-78

(Z)-2-(6-Fluoro-2-nitrooxy-1-indanylidene)acetamide	53	162-163
(E)-2-(6-Fluoro-1-indanylidene)-N-(2-hydroxyethyl)acetamide	like 5	146-148
(E)-2-(6-Fluoro-1-indanylidene)-N-isopropylacetamide	like 5	143-145
(Z)-2-(6-Fluoro-2-methoxy-1-indanylidene)acetamide	54	128-130
(Z)-2-(2,3-Dibromo-6-fluoro-1-indanylidene)acetamide	51	158-163
(E)-2-(6-Chloro-1-indanylidene)-N-methylacetamide		220-225
(Z)-2-(6-Fluoro-2,3-dihydroxy-1-indanylidene)acetamide	58	224-227
(E)-2-(6-Fluoro-3-hydroxy-1-indanylidene)acetamide	57;g	166-168
(E)-N-cyclopropyl-2-(6-Chloro-1-indanylidene)acetamide		165-168
(E)-2-(6-Fluoro-1-indanylidene)thioacetamide		176-179
(E)-2-(6-Fluoro-1-indanylidene)-N-methylacetamide	like 5	201-205
(E)-N-Cyclopropyl-2-(6-fluoro-1-indanylidene)acetamide	5	124-127
(E)-N-Ethyl-2-(6-fluoro-1-indanylidene)acetamide	3;like 5	125-127
(E)-N-Cyclobutyl-2-(6-fluoro-1-indanylidene)acetamide	like 5	137-139
(E)-N-Cyclopentyl-2-(6-fluoro-1-indanylidene)acetamide	like 5	152-154
(E)-2-(6-Bromo-1-indanylidene)acetamide		179-181
(E)-N-(Cyclopropylmethyl)-2-(6-fluoro-1-indanylidene)acetamide		105-107
(E)-2-(6-Fluoro-1-indanylidene)-N-propylacetamide	like 5	82-84
(E)-2-(6-Fluoro-1-indanylidene)-N,N-dimethylacetamide	like 5	74-77
(E)-N-ethyl-2-(6-fluoro-1-indanylidene)-N-methylacetamide	7; like 5	74-77
(E)-N-Benzyl-2-(6-fluoro-1-indanylidene)acetamide		134-136
(E)-2-(6-Fluoro-3-oxo-1-indanylidene)acetamide	60;g	235
(Z)-2-(2-Acetoxy-6-fluoro-1-indanylidene)acetamide	55	202-203

(Z)-2-(2-Bromo-6-fluoro-1-indanylidene)acetamide	50	162-163
(E)-N-Cyclopropyl-2-(5,6-difluoro-1-indanylidene)acetamide	like 5	169-171
(E)-2-(5,6-Difluoro-1-indanylidene)-N-methylacetamide	like 5	209-211
(E)-2-(5,6-Difluoro-1-indanylidene)acetamide	like 1;k	165-167
(E)-2-(5,7-Difluoro-1-indanylidene)acetamide	like 1;k	161-162
(E)-N-Cyclopropyl-2-(5,7-difluoro-1-indanylidene)acetamide	like 5	145-147
(E)-2-(5,7-Difluoro-1-indanylidene)-N-methylacetamide	like 5	193-195
(E)-2-(6-Methyl-1-indanylidene)acetamide		189-193
(E)-N-Cyclopropyl-2-(4,6-difluoro-1-indanylidene)acetamide	13;like 5	156-158
(E)-2-(4,6-Difluoro-1-indanylidene)acetamide	12;g	178-180
(Z)-2-(1-Indanylidene)acetamide		127
(E)-2-(4,6-Difluoro-1-indanylidene)-N-isopropylacetamide	like 5	167-170
(E)-2-(4,6-Difluoro-1-indanylidene)-N,N-dimethylacetamide	like 5	105-106
(E)-2-(4,6-Difluoro-1-indanylidene)-N-ethylacetamide	like 5	130-132
(E)-2-(4,6-Difluoro-1-indanylidene)-N-(2-hydroxyethyl)acetamide	like 5	152-154
(E)-N-Ethyl-2-(4,6-difluoro-1-indanylidene)-N-methylacetamide	like 5	96-98
(Z)-2-(6-Chloro-1-indanylidene)-N-methylacetamide		110-114
(E)-2-(4,7-Difluoro-1-indanylidene)acetamide	like 12;g	167-169
(E)-2-(4,5-Difluoro-1-indanylidene)acetamide	like 12;g	195-197
(E)-N-Cyclopropyl-2-(4,5-difluoro-1-indanylidene)acetamide	like 5	135-137
(E)-N-Cyclopropyl-2-(4,7-difluoro-1-indanylidene)acetamide	like 5	134-136
(E)-2-(7-Methyl-1-indanylidene)acetamide		198-199
(E)-N-Cyclopropyl-2-(7-methyl-1-indanylidene)acetamide	like 5	142-144.5

(E)-2-(4-Chloro-6-fluoro-1-indanylidene)acetamide		182-184
(E)-2-(6-Cyano-1-indanylidene)acetamide	like 1;k	221-223
(E)-2-(4,6-Difluoro-1-indanylidene)-N-methylacetamide	like 5	181-183
(E)-N-Cyclopropyl-2-(4,6-dichloro-1-indanylidene)acetamide		174-176
(E)-2-(4-Chloro-6-fluoro-1-indanylidene)-N-cyclopropylacetamide		147-149
(E)-2-(4,6-Dichloro-1-indanylidene)acetamide		210-212
(E)-2-(4,6-Dichloro-1-indanylidene)-N-methylacetamide		225-227
(Z)-2-(4,6-Difluoro-2-hydroxy-1-indanylidene)acetamide	56	235-237
(E)-2-(4-Chloro-6-fluoro-1-indanylidene)-N-methylacetamide		173-175
(Z)-2-(2-Bromo-4,6-difluoro-1-indanylidene)acetamide	49	187-188
(E)-2-(6-Bromo-1-indanylidene)-N-cyclopropylacetamide	like 5	173-174
(E)-2-(6-Bromo-1-indanylidene)-N-methylacetamide	like 5	225-227
(E)-2-(6-Methoxy-1-indanylidene)acetamide	like 1;k	188-192
(Z)-2-(6-Chloro-1-indanylidene)-N-cyclopropylacetamide		151-153
(Z)-2-(6-Fluoro-1-indanylidene)acetamide	66	175-177
(E)-2-(6-Fluoro-3-isopropyl-1-indanylidene)-N-methylacetamide	like 64;i	
(E)-2-(6-Fluoro-3-isopropyl-1-indanylidene)-N,N-dimethylacetamide	like 64;i	
(E)-N-Cyclopropyl-2-(6-fluoro-3-isopropyl-1-indanylidene)acetamide	like 64;i	
(E)-2-(6-Fluoro-3-isopropyl-1-indanylidene)acetamide	like 64;i	
(E)-2-(6-Chloro-4-Fluoro-1-indanylidene)acetamide		
(E)-2-(6-Chloro-4-Fluoro-1-indanylidene)-N-methylacetamide		
(E)-2-(6-Chloro-4-Fluoro-1-indanylidene)-N-cyclopropylacetamide		
(E)-2-(6-Fluoro-4-methyl-1-indanylidene)acetamide		

(E)-2-(6-Fluoro-4-methyl-1-indanylidene)-N-methylacetamide		134-135
(E)-N-Cyclopropyl-2-(6-Fluoro-4-methyl-1-indanylidene)acetamide	37;f	148-149
(E)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-1-naphthylidene)acetamide	like 37;f	148-150
(E)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-5-fluoronaphthylidene)acetamide	like 12;g	155-157
(E)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide	like 5	182-185
(E)-2-(6-Fluoro-3,4-dihydro-2H-1-benzopyran-4-ylidene)acetamide	38;like27;d	122.8-123.3
(E)-2-(6-Fluoro-3,4-dihydro-2H-1-benzopyran-4-ylidene)-N-methylacetamide	like 82;c	170.7-171.8
(E)-N-Cyclopropyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide	like 82;c	178.5-180
(E)-2-(7-Chloro-1,2,3,4-tetrahydro-1-naphthylidene)-N-cyclopropylacetamide		115-118
(E)-2-(5-Bromo-1,2,3,4-tetrahydro-1-naphthylidene)-N-cyclopropylacetamide		87-89
(E)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N-methylacetamide	like 82;c	128.3-130.6
(E)-N-ethyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide	like 82;c	166-167
(E)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-7-methoxy-1-naphthylidene)acetamide		144-146
(E)-N-Cyclopentyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide		71-74
(E)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N-isopropylacetamide		159-162
(E)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N-propylacetamide	like 82;c	179-180.4
(E)-N-Cyclobutyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide	like 82;c	96-98
(E)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-6-methoxy-1-naphthylidene)acetamide		96-99
(E)-N-Benzyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide	like 40;F	161-162
(E)-4-(2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetyl)morpholine	like 40;F	120-122
(E)-N-Cyclopropyl-2-(5-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)propionamide		106-111
(E)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N-(2-hydroxyethyl)acetamide		
(E)-N-Cyclopropyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide		

(E)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N,N-dimethylacetamide		66-70
(E)-2-(6-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N-methyl-N-methoxyacetamide	like 40;F	67-69
(Z)-N-Cyclopropyl-2-(7-fluoro-1,2,3,4-tetrahydro-2,2-dimethyl-1-naphthylidene)acetamide	like 59	118-121
(E)-N-Cyclopropyl-2-(7-fluoro-1,2,3,4-tetrahydro-2,2-dimethyl-1-naphthylidene)acetamide	like 59	113-115
(E)-N-Ethyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N-methylacetamide		66-68
(E)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetanilide	like 40;F	119-121
(E)-1-(2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetyl)azetidine	like 40;F	58-61
(E)-1-(2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetyl)pyrrolidine	like 82;c	141-143
(E)-2-(5,6,7,8-Tetrahydro-8-quinolinylidene)acetamide		216-218
(E)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-7-methyl-1-naphthylidene)acetamide	like 82;c	151.7-153.9
(E)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-5-methoxy-1-naphthylidene)acetamide	like 82;c	156.8-160.3
(Z)-N-cyclopropyl-2-(1,2,3,4-tetrahydro-1-naphthylidene)acetamide	like 83	106-113
(E)-2-(6-Chloro-1,2,3,4-tetrahydro-1-naphthylidene)-N-cyclopropylacetamide	like 82;c	173-174
(Z)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide		198-201
(E)-N-Cyclopropyl-2-(6-fluoro-3,4-dihydro-2H-1-benzopyran-4-ylidene)acetamide	like 5	146-148
(Z)-N-Ethyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide		117-118
(Z)-2-(7-Chloro-1,2,3,4-tetrahydro-1-naphthylidene)-N-cyclopropylacetamide	like 83	104-105.5
(Z)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-7-methoxy-1-naphthylidene)acetamide	like 83	145-146.1
(Z)-N-Cyclopentyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide	like 83	147-149
(Z)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N-phenylacetamide	like 83	180-184
(E)-2-(6-Chloro-3,4-dihydro-2H-1-benzopyran-4-ylidene)-N-cyclopropylacetamide	like 5	171-172
(E)-2-(6-Chloro-3,4-dihydro-2H-1-benzopyran-4-ylidene)-N-methylacetamide	like 5	204-205
(Z)-N-Cyclopropyl-2-(2,3,4,5-tetrahydro-1-tosyl-1H-1-benzazepin-5-ylidene)acetamide		66-65

(E)-2-(1-acetyl-6-fluoro-1,2,3,4-tetrahydro-4-quinolylidene)-N-cyclopropylacetamide		165-166
(E)-2-(6-Chloro-3,4-dihydro-2H-1-benzopyran-4-ylidene)acetamide	like 5	168-169
(E)-N-Cyclopropyl-2-(3,4-dihydro-2H-1-benzothiopyran-4-ylidene)acetamide	like 5	115-116
(E)-N-2-(3,4-dihydro-2H-1-benzothiopyran-4-ylidene)-N-methylacetamide	like 5	91-93
(E)-2-(3,4-dihydro-2H-1-benzothiopyran-4-ylidene)acetamide	like 5	175-175
(E)-2-(6-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)-N-cyclopropylacetamide		
(E)-2-(6-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)-N-methylacetamide		
(E)-2-(6-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)acetamide		
(E)-2-(5-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)-N-cyclopropylacetamide		
(E)-2-(5-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)-N-methylacetamide		
(E)-2-(5-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)acetamide		
(E)-2-(7-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)acetamide		
(E)-2-(7-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)-N-methylacetamide		
(E)-2-(7-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-Benzopyran-4-ylidene)-N-cyclopropylacetamide		

Preferred compounds of formula (Ia) for such use include those wherein V is

(a) $(CR^7R^8)_mB$,

(b) $B(CR^7R^8)_m$ or

(c) $(CR^7R^8)_mB(CR^7R^8)_m$

wherein B is CR^7R^8, O, NR^6, or $S(O)_m$ and

wherein R^7 and R^8 are the same or different and are

(a) H;

(b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl optionally substituted by one or more NR^6R^{6a};

(c) hydroxy;

(d) $OC(O)R^6$; or

e) halogen(e.g., fluorine or chlorine) or any combination thereof;

W^1 is aryl or heteroaryl optionally substituted with one or more

(a) halogen(e.g., fluorine or chlorine); or

(b) C_{1-6} alkyl optionally substituted with one or more halogen (e.g., fluorine), OR^6 or CN, or any combination thereof;

when one m is present, m is 1 or 2;

when more than one m is present, m can be the same or different and is 1 or 2;

R^3 and R^4 are

(a) H; or

(b) C_{1-6} alkyl, C_{3-6} cycloalkyl(e.g., cyclopropyl, cyclobutyl), C_{1-6} alkylene (C_{3-6} cycloalkyl) or any combination thereof, or together with the nitrogen to which they are attached denote a C_{2-7} ring;

R^5 is H or halogen;

R^6 and R^{6a} are as defined hereinbefore; and

Z is O;

or salts, solvates or physiologically functional derivatives thereof.

More preferred compounds of formula (Ia) for such use include those wherein V is

(a) $(CR^7R^8)_mB$ or

(b) $B(CR^7R^8)_m$

wherein B is CR^7R^8 or O and

wherein R^7 and R^8 are the same or different and are

(a) H;

(b) CH_3, CH_2CH_3;

(c) C_{1-6} alkyl substituted by NR^6R^{6a};

(d) hydroxy;

(e) $OC(O)R^6$; or

(f) fluorine; or any combination thereof;

W^1 is phenyl or naphthyl optionally substituted with one or more

(a) halogen(e.g., fluorine or chlorine),

(b) CH_3; or

(c) CF_3; or any combination thereof;

when one m is present, m is 1 or 2;

when more than one m is present, m can be the same or different and is 1 or 2;

R^3 and R^4 are

(a) H;

(b) CH_3; or

(c) cyclopropyl; or any combination thereof;

R^5 is H or halogen(preferably fluorine);

R^6 and R^{6a} are as defined hereinbefore; and

Z is O;

or salts, solvates or physiologically functional derivatives thereof.

Particularly preferred compounds of formula (Ia) for such use include those wherein V is

$B(CR^7R^8)_m$

wherein B is CR^7R^8 or O and

wherein R^7 and R^8 are the same or different and are selected from H, CH_3, CH_2 CH_3 or OH or any combination thereof;

W^1 is a phenyl ring optionally substituted with halogen, preferably fluoro;

m is 1 or 2;

R^3 and R^4 are H, CH_3 or cyclopropyl; or any combination thereof;

R^5 is H;

Z is O;
or salts, solvates or physiologically functional derivatives thereof.

Most preferred compounds of formula (Ia) for such use include those wherein V is $B(CH_2)_m$
wherein B is CR^7 R^8 and
wherein R^7 and R^8 are the same or different and are selected from H, CH_3, CH_2 CH_3 or OH; or any combination thereof;

W^1 is a phenyl ring substituted with one or two halogen, preferably fluoro or chloro or any combination thereof;

m is 1 or 2;

R^3 and R^4 are H, CH_3 or cyclopropyl; or any combination thereof; and

R^5 is H; and

Z is O;
or salts, solvates or physiologically functional derivatives thereof.

Especially preferred compound for muscle relaxant or anticonvulsant use are:
(E)-2-(4,6 Difluoro-1-indanylidene)acetamide
(E)-2-(6-Fluoro-1-indanylidene)acetamide

(Z)-2-(6-Fluoro-2-hydroxy-1-indanylidene)acetamide
(E)-2-(6-Fluoro-3,3-dimethyl-1-indanylidene)acetamide
(E)-2-(5,7-Difluoro-1-indanylidene)acetamide
(E)-2-(4,6 Difluoro-1-indanylidene)-N,N-dimethylacetamide
(E)-2-(4,6 Difluoro-1-indanylidene)-N-isopropylacetamide
(E)-2-(7-Fluoro-1,2,3,4-tetrahydro1-naphthylidene)acetamide
(E)-2-(6-Fluoro-3-ethyl-1-indanylidene)-N,N-dimethylacetamide
(E)-2-(6-Fluoro-3-hydroxy-1-indanylidene)acetamide

Especially preferred compounds for anxioloytic use are:
(E)-2-(3-Ethyl-6-fluoro-1-Indanylidene)-N-cyclopropylacetamide
(E)-N-Cyclopropyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide
(E)-N-Cyclopropy 2-(6-fluoro-3,4-dihydro-2H-1-benzopyran-4-ylidene)acetamide
(E)-N-Cyclopropyl-2-(6-fluoro-3-methyl-1-indanylidene)acetamide
(E)-N-Cyclopropyl-2-(4,6 difluoro-1-indanylidene)acetamide
(E)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-1-naphthylidene)acetamide
(E)-2-(4-Chloro-1-indanylidene)-N-cyclopropylacetamide
(E)-N-Cyclopropyl-2-(4-methyl-1-indanylidene)acetamide
(E)-N-Cyclopropy 2-(6-fluoro-1-indanylidene)acetamide
(E)-2-N-Cyclopropyl-(4-fluoro-1-indanylidene)acetamide

Especially preferred compounds for arthritis, antiinflammatory or analgesic use are:
(E)-2-(4-Chloro-6-fluoro-1-indanylidene)-N-methylacetamide
(E)-2-(4-Chloro-6-fluoro-1-indanylidene)acetamide
(E)-2-(4,6 Difluoro-1-indanylidene)acetamide
(E)-2-(6-Fluoro-1-indanylidene)acetamide
(E)-2-(5,7-Difluoro-1-indanylidene)acetamide
(E)-2-(5,6-Difluoro-1-indanylidene)-N-methylacetamide
(E)-2-(4,6-Dichloro-1-indanylidene)acetamide
(Z)-2-(6-Fluoro-2-hydroxy-1-indanylidene)acetamide
(Z)-2-(4,6-Difluoro-2-hydroxy-1-indanylidene)acetamide
(E)-2-(6-Fluoro-3-ethyl-1-indanylidene)-N-methylacetamide

As used herein the term:

a) "C_{1-6} alkyl" as a group or part of a group means a straight or branched chain alkyl group having from 1 to 6 carbon atoms. Such alkyl groups preferably have 1 to 3 carbon atoms and are more preferably methyl, ethyl, propyl, prop-2-yl, butyl, but-2-yl or 2-methylprop-2-yl. Alkyl groups are most preferably methyl or ethyl.

b) "C_{2-6} alkenyl" as a group or part of a group means a straight or branched chain alkenyl group having from 2 to 6 carbon atoms. Such alkenyl groups preferably have 2 to 4 carbon atoms and are more preferably ethenyl or propenyl, most preferably propenyl.

c) "C_{2-6} alkynyl" as a group or part of a group means a straight or branched chain alkynyl group having from 2 to 6 carbon atoms. Such alkynyl groups preferably have 2 to 4 carbon atoms and are more preferably ethynyl or propynyl, most preferably propynyl.

d) "C_{1-6}alkoxy" as a group or part of a group means a monovalent straight or branched chain radical having from 1 to 6 carbon atoms which are attached to the parent moiety through an oxygen atom. Such alkoxy groups preferably have 1 to 4 carbon atoms and are more preferably methoxy or ethoxy, most preferably methoxy.

e) "C_{3-6} cycloalkyl" as a group or part of a group means a cycloalkyl group having from 3 to 6 carbon atoms. Such cycloalkyl groups are preferably cyclopropyl or cyclobutyl, most preferably cyclopropyl.

f) "C_{1-6} alkylene(C_{3-6} cycloalkyl)" as a group or part of a group means a straight or branched chain divalent radical having from 1 to 6 carbon atoms attached at one end to the parent moiety and further having a C_{3-6}cycloalkyl group attached thereto. Such alkylene(cycloalkyl) groups are preferably CH_2(cyclopropyl) or CH_2(cyclobutyl), most preferably CH_2(cyclopropyl).

g) "aryl" as a group or part of a group means phenyl or naphthyl.

h) "C_{1-6}alkylenearyl" as a group or part of a group means a straight or branched chain divalent radical having from 1 to 6 carbon atoms attached at one end to the parent moiety and further having an aryl or substituted aryl group(as defined hereinbefore) attached thereto. Such alkylenearyl groups are preferably CH_2phenyl(i.e., benzyl).

i) "C_{1-6}alkyleneoxyaryl" as a group or part of a group means a straight or branched chain divalent radical having from 1 to 6 carbon atoms attached at one end to an aryl group and further attached to the parent moiety through an oxygen atom. Such alkyleneoxyaryl groups are preferably OCH_2phenyl (i.e, benzyloxy).

j) "heteroaryl" means a monocyclic or bicyclic fused aromatic ring system comprising 5-10 ring atoms wherein 1 or more ring atoms are independently selected from nitrogen, oxygen, or sulfur. Preferred heteroaryl groups are pyridinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyrrolyl, pyridazinyl, quinolinyl, isoquinolinyl, imidazolyl, benzimidazole, furyl, benzofuryl, thienyl, benzthienyl, indazolyl, oxazolyl or thiazolyl. The most preferred heteroaryl group is pyridinyl.

k) "heterocyclic ring" means a saturated monocyclic ring system comprising three to eight ring atoms selected from carbon and at least one atom selected from nitrogen, oxygen or sulfur.

l) "halogen" means fluorine, chlorine, bromine, or iodine.

m) "hydroxy" means OH.

n) "substituted amino" means nitrogen substituted with one or two C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylene(C_{3-6}cycloalkyl), aryl or C_{1-6}alkylenearyl all optionally substituted with one or more halogen, C_{1-6} alkyl(optionally substituted with one or more halogen, OH, C_{1-6}alkoxy, NH_2 or N substituted with one or two C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylene(C_{3-6}cycloalkyl), aryl or C_{1-6}alkylenearyl), OH, C_{1-6}alkoxy, NH_2 or N substituted with one or two C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylene(C_{3-6}cycloalkyl), aryl or C_{1-6}alkylenearyl.

o) "physiologically functional derivatives" means any other physiologically acceptable derivative of a compound of the present invention, for example an ester, which, upon administration to the recipient, such as a human, is capable of providing(directly or indirectly) the said compound or an active metabolite or residue thereof.

p) "salt" means acid addition or base salts as further defined hereinbelow.

q) "solvate" means a combination, in definite proportions, of a compound of the present invention with its solvent.

It will be appreciated that the compounds of formula (I) and (Ia) can exist in various geoisomeric forms and as mixtures thereof in any proportions. The present invention includes within its scope such geoisomeric forms or mixtures of geoisomers, including the individual E and Z isomers of the compounds of formula (I) or (Ia) as well as mixtures of such isomers, in any proportions. Preferred compounds of formulas (I) or (Ia) are those wherein the group adjacent to the exo double bond directly attached to W and the carbon bearing Z are on opposite sides of the exo double bond. The compounds of formulas (I) or (Ia) may exist in forms wherein one or more carbon centers is/are chiral. The present invention includes within its scope each possible optical isomer substantially free, i.e., associated with less than 5%, of any other optical isomer(s), as well as mixtures of one or more optical isomers in any proportion, including racemic mixtures thereof. It will be evident to a skilled person that certain compounds of formulas (I) and (Ia) can exist in enantiomeric forms according to the direction of rotation of plane polarized light when passed through a sample of the compound. Individual optical isomers as well as mixtures of such isomers in any proportion are considered to be within the scope of the invention.

Pharmaceutically acceptable salts are within the scope of the invention and are particularly suitable for medical applications because of their greater aqueous solubility relative to the parent(i.e., basic) compounds. Such salts must clearly have a pharmaceutically acceptable anion or cation. Suitable pharmaceutically acceptable acid addition salts of the compounds of the present invention include those derived from inorganic acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric, sulphonic and sulphuric acids, and organic acids, such as acetic, benzenesulphonic, benzoic, citric, ethanesulphonic, fumaric, gluconic, glycollic, isothionic, lactic, lactobionic, maleic, malic, methanesulphonic, succinic, p-toluenesulphonic, tartaric and trifluoroacetic acids. The chloride salt is particularly preferred for medical purposes. Suitable pharmaceutically acceptable base salts include ammonium salts, alkali metal salts, such as sodium and potassium salts, and alkaline earth salts, such as magnesium and calcium salts.

Salts having a non-pharmaceutically acceptable anion are also within the scope of the invention as useful intermediates for the preparation or purification of pharmaceutically acceptable salts and/or for use in non-therapeutic, for example, in vitro, applications.

For therapeutic use, acid addition and base salts of compounds of formula (I) and (Ia) will be physiologically acceptable(i.e., they will be salts derived from a physiologically acceptable acid or base). However, salts of acids or bases which are not physiologically acceptable may also find use, for example in the preparation or purification of the compound. All acid and base salts whether or not derived from a physiologically acceptable base are to be considered as being within the scope of the present invention.

A further aspect of the present invention is prodrugs of the compounds of formula (I) and (Ia). Such prodrugs can be metabolised in vivo to give a compound of formula (I) or (Ia). These prodrugs may or may not be active in their own right.

The compounds of formula (I) and (Ia) are of particular value in the relaxation of skeletal muscle in spastic, hypertonic and hyperkinetic conditions. In particular the compounds of formula (I) and (Ia) can be used in the treatment and symptomatic relief of exertion-induced skeletal muscle spasm, for example, lower back pain. The compounds of formula (I) and (Ia) can also be used for the treatment of conditions such as spinal cord injury, parkinsonism, chorea, arthritis, athetosis, status epilepticus and tetanus and especially in the relief of muscle spasm in conditions such as spasticity, myositis, spondylitis, cerebral palsy, cerebrovascular disease and multiple sclerosis. The compounds can also be used as pre-surgical muscle relaxants.

Convulsive states for which the compounds of formula (I) or (Ia) can be employed include grand mal, petit mal, psychomotor epilepsy and focal seizure. The compounds of formula (I) and (Ia) can also be used in the treatment of anxiety including generalised anxiety disorders, obsessive compulsive disorder, panic disorder, phobic anxiety, separation anxiety and post-traumatic stress disorder.

The analgesic activity of compounds fo formula (I) and (Ia) make them useful to control pain, e.g., pain associated with inflammation and/or trauma. Accordingly, the compounds of the invention have use as mild and strong analgesics.

The compounds of formula (I) and (Ia) can also be used in the treatment of inflammatory arthritic conditions, including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, as well as non-articular inflammatory conditions, including herniated/ruptured/prolapsed intervertebral disk syndrome, bursitis, tendinitis, tenosynovitis, fibromyalgia syndrome and other inflammatory conditions associated with ligamentous sprain and regional musculoskeletal strain. It is particularly noted that compounds of formula (I) and (Ia) exhibit reduced occurence of ulcerogenicity, as compared with other anti-inflammatory agents, such as ibuprofen, naproxen or asprin.

The compounds of the invention are also useful as anti-anxiety agents.

In a further aspect of the present invention there is included:

(a) compounds of formula (I) and (Ia) or pharmaceutically acceptable salts, solvates or physiologically functional derivatives thereof for use as therapeutic agents, particularly in the prophylaxis or treatment of clinical conditions conditions associated with abnormally raised muscle tone, convulsive states, anxiety, inflammation, arthritis or pain.

(b) pharmaceutical compositions comprising a compound of formula (I) or (Ia) or pharmaceutically acceptable salts, solvates, or physiologically functional derivatives thereof, at least one pharmaceutically acceptable carrier therewith, and optionally one or more other physiologically active agents.

(c) a method for the treatment or prophylaxis of conditions associated with abnormally raised muscle tone, convulsive states, anxiety, inflammation, arthritis or pain in a host, for example, a mammal including a human, comprising administering to the host an effective treatment amount of a compound of formula (I) or (Ia).

(d) use of a compound of formula (I) or (Ia) in the manufacture of a medicament for the treatment or prophylaxis of conditions associated with abnormally raised muscle tone, convulsive states, anxiety, inflammation, arthritis or pain.

(e) processes for the preparation of compounds of formula (I) or (Ia) and intermediates thereof (including salts, solvates or physiologically functional derivatives thereof as defined herein).

(f) compounds of formula (II), (III) or (VI), described hereinafter(including salts or solvates thereof), as well as their use as intermediates in the preparation of compounds according to the invention.

The above compounds can be employed in combination with other therapeutic agents for the treatment of the conditions associated with abnormally raised muscle tone. Examples of such other therapeutic agents include analgesics, such as, codeine, acetaminophen, phenacetin or ibuprofen. The compounds according to the invention can also be employed in combination with other therapeutic agents for the treatment of conditions associated with inflammation, arthritis, and/or pain. Examples of such other therapeutic agents include analgesics, such as codeine, oxycodone, acetaminophen, phenacetin, or ibuprofen; anti-arthritics, such as methotrexate or azathioprine; and decongestants, such as ephedrine or pseudoephedrine.

The present invention further provides pharmaceutical compositions of the compounds of formula (I) or (Ia), also referred to herein as active ingredients, which may be administered for therapy by any suitable route including oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous and intradermal). It will also be appreciated that the preferred route will vary with the conditions and age of the recipient, the nature of the disorder and the chosen active ingredient.

The amount required of the individual active ingredient for the treatment of, for example, increased muscle tone, inflammation, arthritis, and/or pain of course depends upon a number of factors including the severity of the condition to be treated and the identity of the recipient and will ultimately be at the discretion of the attendant physician.

In general, for the foregoing conditions a suitable dose of a compound of formula (I) or (Ia) or salts, solvates or physiologically functional derivatives thereof (estimated as the parent compound) is in the range of 0.05 to 100mg per kilogram body weight of the recipient per day, preferably in the range of 0.1 to 50mg per kilogram body weight per day, most

preferably in the range 0.5 to 20mg per kilogram body weight per day and optimally 1 to 10mg per kilogram body weight per day. The desired dose is preferably presented as two, three, four, five, six or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing 1 to 1500mg, preferably 5 to 1000mg, and most preferably 10 to 700mg of active ingredient per unit dosage form.

While it is possible for the active ingredient to be administered alone it is preferable to present it as a pharmaceutical composition. The compositions of the present invention comprises at least one active ingredient, as defined above, together with one or more acceptable carriers thereof and optionally other therapeutic agents. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not injurious to the recipient.

Compositions include those suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including subcutaneous, intramuscular, intravenous and intradermal) administration. The compositions may conveniently be presented in unit dosage form and may be prepared by any methods well known in the art of pharmacy. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then if necessary shaping the product.

Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder (e.g. povidone, gelatin, hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (e.g. sodium starch glycollate, cross-linked povidone, cross-linked

sodium carboxymethyl cellulose) surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein using, for example hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile. Tablets may optionally be provided with an enteric coating, to provide release in parts of the gut other than the stomach.

Compositions suitable for oral use as described above may also include buffering agents designed to neutralize stomach acidity. Such buffers may be chosen from a variety of organic or inorganic agents such as weak acids or bases admixed with their conjugated salts.

Compositions suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Compositions for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Compositions suitable for parenteral administration include aqueous and non-aqueous isotonic sterile injections solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the compositions isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents, as liposomes or other microparticulate systems which are designed to target the compounds to blood components or one or more organs. The compositions may be presented in unit-dose or multi-dose sealed containers, for example, ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injections, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Compositions suitable for transdermal administration may be presented as discrete patches adapted to remain in intimate contact with the epidermis of the recipient for a prolonged period of time. Such patches suitably contain the active compound as an optionally buffered, aqueous solution of, for example, 0.1 to 0.2M concentration with respect to the said compound. As one particular possibility, the active compound may be delivered from the patch by iontophoresis as generally described in Pharmaceutical Research, 3(6), 318 (1986).

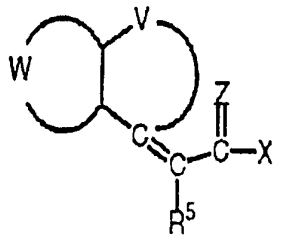
Preferred unit dosage compositions are those containing a daily dose or unit, daily sub-dose, as herein above recited, or an appropriate fraction thereof, of an active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above the compositions of this invention may include other agents conventional in the art having regard to the type of composition in question, for example, those suitable for oral administration may include such further agents as sweeteners, thickeners and flavoring agents.

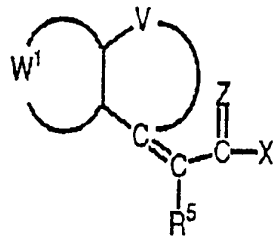
The compounds of the invention can be prepared in any conventional manner and in accordance with the present invention, can, for example, be prepared by any method hereinafter described.

Thus, the present invention further includes a process for the preparation of compounds of formula (I) and (Ia) and acid or base salts, solvates and physiologically functional derivatives thereof which comprises:

reacting a compound of formula (II) or (IIa) respectively



(II)



(IIa)

(wherein V, W, W^1, Z and R^5 are as hereinbefore defined) and X is a suitable leaving group, for example a halogen atom such as chlorine or bromine, activated esters(e.g., N-hydroxysuccinimide, pentafluorophenyl, nitrophenyl, 1-hydroxybenzotriazole), mixed anhydrides(e.g., ethoxycarbonyloxy) or C_{1-6}alkoxy(for example, ethoxy) with NR^3R^4(wherein R^3 and R^4 are as hereinbefore defined) in a suitable organic solvent(e.g., dichloromethane) at a temperature of about 0°C to the reflux temperature.

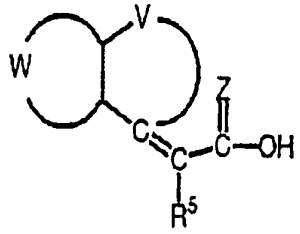
Alternatively, compounds of formula (I) and (Ia) wherein R^3 and R^4 are H can be prepared by reacting compounds of formula (II) and (IIa) respectively wherein X is a halogen atom such as chlorine or bromine with NH_4OH in a suitable organic solvent(e.g., dichloromethane) at a temperature of about 0°C to the reflux temperature.

Compounds of formula(I) or (Ia) wherein R^1 or R^2 are hydroxy can be prepared by reacting compounds of formula (II) or (IIa) respectively wherein X is C_{1-6} alkoxy, for example, ethoxy, and the hydroxy group is suitably protected, for example, as the $SiMe_2$t-Bu, with NH_4Cl and Me_3Al under neutral conditions followed by deprotection underneutral conditions with, for example, pyridinium para-toulenesulfonate(PPTS).

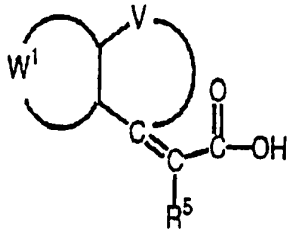
Alternatively, compounds of formula (I) or (Ia) wherein R^1 or R^2 are hydroxy can be prepared from compounds of formula (I) or (Ia) wherein R^1 or R^2 are H by halogenation with, for example, N-bromosuccinamide(NBS) followed by hydrolysis with, for example, silver carbonate($AgCO_3$). Compounds of formula (I) or (Ia) wherein the R^1 or R^2 is/are allylic hydroxy can be prepared from compounds of formula (I) or (Ia) wherein R^1 or R^2 are H by oxidation with, for example selenium dioxide.

Compounds of formula (I) and (Ia) wherein V is SO_2 or SO can be prepared from compounds of formula (II) and (IIa) respectively wherein V is S by controlled oxidation of the sulfur with an oxidizing agent such as hydrogen peroxide in acetic acid, 3-chloroperbenzoic acid in dichloromethane or Oxone®(potassium peroxymonosulfate-Aldrich).

Compounds of formula (II) and (IIa) wherein X is a halogen atom can be prepared from compounds of formula (III) and (IIIa) respectively



(III)



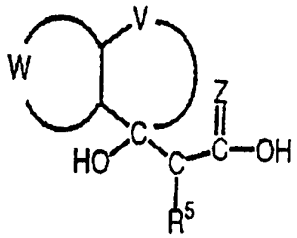
(IIIa)

(wherein V, W, W^1, Z and R^5 are as hereinbefore defined) by reaction with a halogenating agent(e.g., oxalyl chloride, or thionyl chloride) in a suitable organic solvent(e.g., benzene, toluene, dichloromethane) optionally in the presense of a catalyst(for example DMF)at a temperature of about -20°C to the reflux temperature.

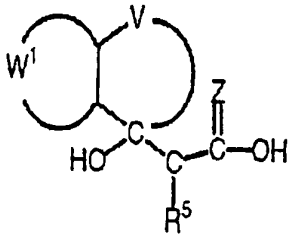
Compounds of formula (II) and (IIa) wherein X is alkoxy(e.g., ethoxy) can be prepared from compounds of formula (III) and (IIIa) respectively by reaction with a suitable polar solvent (e.g., an organic alcohol such as ethanol) optionally in the presence of a catalytic amount of an acid(e.g., tosic acid) at a temperature of about 0°C to the reflux temperature.

Compounds of formula (II) and (IIa) wherein X is an activated ester(as described hereinbefore) can be prepared from compounds of formula (III) and (IIIa) respectively by reaction with the phenol or N-hydroxy compound and a carbodiimide(e.g., dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide) in a solvent such as dimethylformamide(DMF) or dichloromethane at 0°C to 50°C.

Compounds of formula (III) and (IIIa) can be prepared by dehydration of compounds of formula (IV) and (IVa) respectively



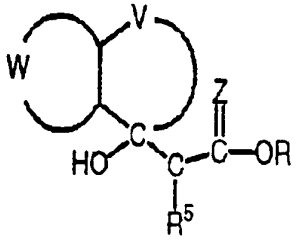
(IV)



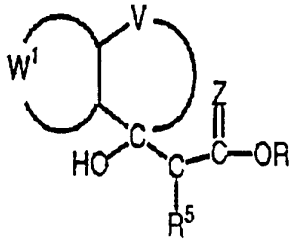
(IVa)

(wherein V, W, W^1, Z and R^5 are as hereinbefore defined) by reaction with an appropriate dehydrating agent(e.g., an acid such as trifluoroacetic acid) in a suitable organic solvent(e.g., dichloromethane) at a temperature of about -20°C to the reflux temperature.

Compounds of formula (IV) and (IVa) can be prepared by saponification of the corresponding ester compounds of formula (V) and (Va) respectively



(V)



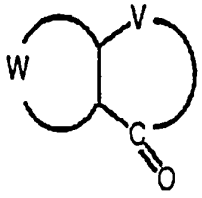
(Va)

(wherein V, W, W^1, Z and R^5 are as hereinbefore defined and wherein R is C_{1-6}alkyl(e.g., ethyl)) with a base(e.g., sodium hydroxide) in a suitable polar solvent(e.g., ethanol) at a temperature of about 0°C to the reflux temperature.

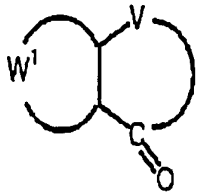
Alternatively, compounds of formula (IV) and (IVa) can be prepared by de-esterification of the corresponding ester compounds of formula (V) and (Va) respectively wherein R is alkyl(e.g., ethyl) with an aqueous acid(e.g., hydrochloric acid) at a temperature of about 0°C to the reflux temperature.

Compounds of formula (V) and (Va) having R^1 or R^2 as protected hydroxy groups, for example, as the $SiMe_2$t-Bu, wherein R is C_{1-6} alkyl(e.g., ethyl) can be dehydrated under neutral conditions(e.g., Martin Sulfurane, bis[α,α-bis(trifluoromethyl)benzenemethanolato]-diphenylsulfur) to give the corresponding protected hydroxy compounds of formula (II) and (Ia) wherein X is C_{1-6} alkoxy(e.g., ethoxy).

Compounds of formula (V) and (Va) can be prepared from compounds of formula (VI) and (VIa) respectively



(VI)



(VIa)

(wherein V, W and W^1 are as hereinbefore defined) by reaction with $XCHR^5C(Z)OR$ (wherein X is a halogen atom such as chlorine, bromine, or iodine(preferably bromine), R is as hereinbefore defined(preferably ethoxy), and Z and R^5 are as hereinbefore defined) in the presence of a metal(e.g., zinc, preferably activated zinc) and a catalytic amount of halogen(e.g., iodine) in a suitable organic solvent(e.g., ethyl ether, benzene) at a temperature of about 0°C to the reflux temperature or by reaction with the lithium salt of ethyl acetate in a suitable solvent(e.g., tetrahydrofuran) at a temperature between -100 °C to room temperature(e.g., -78°C).

Compounds of formula(V) and (Va) having R^1 or R^2 as protected hydroxy groups as defined above can be prepared by reacting the corresponding compounds of formula(VI) and (VIa) by reaction under neutral conditions with $XCHR^5C(Z)OR$ (wherein X is a halogen atom such as chlorine, bromine, or iodine(preferably bromine), R is as hereinbefore defined(preferably ethoxy), and Z and R^5 are as hereinbefore defined) in the presence of a metal(e.g., zinc, preferably activated zinc) and a catalytic amount of halogen(e.g., iodine) in a suitable organic solvent(e.g., ethyl ether, benzene) at a temperature of about 0°C to the reflux temperature or by reaction with the lithium salt of ethyl acetate in a suitable solvent(e.g., tetrahydrofuran) at a temperature between -100 °C to room temperature(e.g., -78°C).

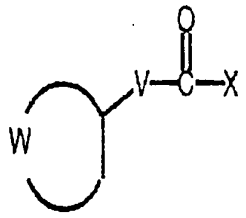
Compounds of formula(VI) and (VIa) having R^1 or R^2 as protected hydroxy groups as defined above can be prepared from the corresponding unprotected hydroxy compound of formula (VI) and (VIa) by suitable protection under neutral conditions with, for example, t-butyl-di-methylsilyl chloride in the presence of a base such as imidazole.

Compounds of formula(VI) and (VIa) having R^1 or R^2 as hydroxy can be prepared from the corresponding halogen(e.g., bromo) compound by hydrolysis under neutral conditions with, for example, silver carbonate($AgCO_3$).

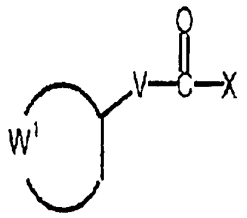
Compounds of formula(VI) and (VIa) having R^1 or R^2 as halogen(e.g., bromo) can be prepared by halogenation of the corresponding compounds wherein R_1 and/or R_2 are H with a suitable halogenating agent, for example, N-bromosuccinamide.

Compounds of formula(VI) and (VIa) having R^1 or R^2 as alpha alkyl(e.g., methyl) can be prepared from the corresponding compounds of formula(VI) or (VIa) wherein R1 and/or R2 are H by reaction with a base(e.g., sodium hydride) followed by alkylation with, for example, methyl iodide(MeI).

Compounds of formula (VI) and (VIa) can be prepared from compounds of formula (VII) and (VIIa) respectively



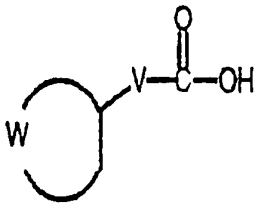
(VII)



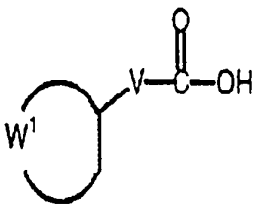
(VIIa)

(wherein V, W, W^1 and X are as hereinbefore defined, preferably X is a halogen atom such as chlorine) by cyclization in the presence of a lewis acid(e.g., aluminum chloride) in a suitable solvent(e.g., dichloromethane) at a temperature of about 0°C to the reflux temperature.

Compounds of formula (VII) and (VIIa) wherein X is a halogen atom(e.g., chlorine, or bromine) can be prepared from compounds of formula (VIII) and (VIIIa) respectively



(VIII)



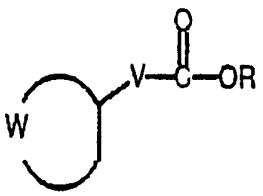
(VIIIa)

(wherein V, W and W^1 are as hereinbefore defined) by reaction with a halogenating agent(e.g., oxalyl chloride or thionyl chloride) either neat or in a suitable organic solvent(e.g. methylene chloride or N,N-dimethylformamide) at a temperature of about 0°C to the reflux temperature.

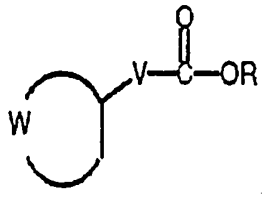
Compounds of formula (VII) and (VIIa) wherein X is alkoxy(e.g., ethoxy) can be prepared from compounds of formula (VIII) and (VIIIa) respectively by reaction with a suitable

organic alcohol (e.g., ethanol) optionally in the presence of a catalytic amount of an acid(e.g., tosic acid) at a temperature of about 0°C to the reflux temperature.

Compounds of formula (VIII) and (VIIIa) can be prepared by saponification of the corresponding ester compounds of formula (IX) and (IXa) respectively



(IX)

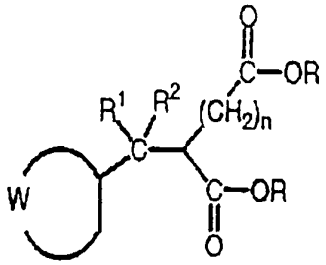


(IXa)

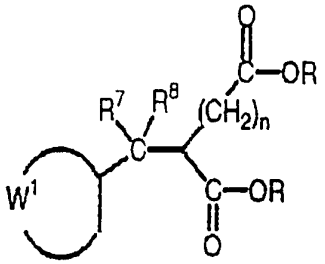
(wherein V, W, W^1 and R are as hereinbefore defined) with a base(e.g., sodium hydroxide) in a suitable polar solvent(e.g., water or ethanol) at a temperature of about 0°C to the reflux temperature.

Alternatively, compounds of formula (VIII) and (VIIIa) can be prepared by saponification of the corresponding ester compounds of formula (IX) and (IXa) respectively wherein R is alkyl(e.g., ethyl) or substituted alkyl with an aqueous acid(e.g., hydrochloric acid) at a temperature of about 0°C to the reflux temperature.

Compounds of formula (VIII) wherein V is $B(CH_2)m$, B is CR^1R^2 and compounds of formula(VIIIa) wherein V is $B(CH_2)m$, B is CR^7R^8, m is 1 or 2 , and W, W^1, R^1, R^2, R^7 and R^8 are as defined hereinbefore can be prepared from compounds of formula (X) and (Xa) respectively



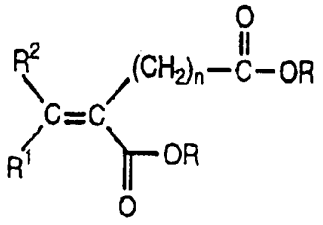
(X)



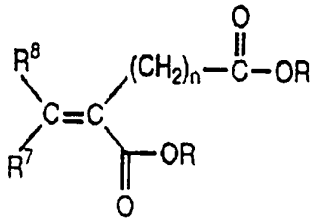
(Xa)

(wherein W, W^1, R, R^1, R^2, R^7 and R^8 are as hereinbefore defined and n is 0 or 1) by mono de-esterification with strong base(e.g., aqueous potassium hydroxide) at the reflux temperature.

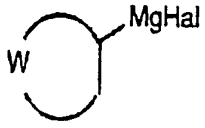
Compounds of formula (X) and (Xa) can be prepared by reacting a compound of formula (XI) or (XIa) respectively with a compound of formula (XIb) and (XIc) respectively



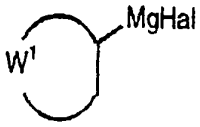
(XI)



(XIa)



(XIb)

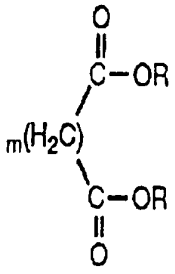


(XIc)

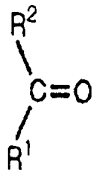
(wherein W, W^1, R, R^1, R^2, R^7, R^8, and n are as hereinbefore defined and Hal is Cl, Br or I preferably Br) in an organic solvent(e.g., anhydrous diethyl ether) and optionally in the

presence of a copper halide(e.g., copper (I) iodide) at a temperature of between -50° C. to the reflux temperature.

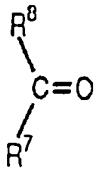
Compounds of formula (XI) and (XIa) can be prepared by reacting a compound of formula (XII) with a compound of formula (XIIa) and (XIIb) respectively



(XII)



(XIIa)



(XIIb)

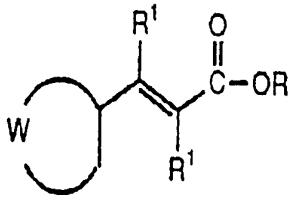
(wherein R, R^1, R^2, R^7 and R^8 are as hereinbefore defined and m is 1 or 2) in an organic solvent(e.g., ethyl ether or dichloromethane) at a temperature of between room temperature and the reflux temperature.

Compounds of formula (XIb) and (XIc) can be prepared from the corresponding halo(e.g., bromo, chloro) compound by standard techniques well known to those skilled in the art. The halo compounds themselves can be obtained commercially or or prepared by methods well known to those skilled in the art or obtainable from the chemical literature.

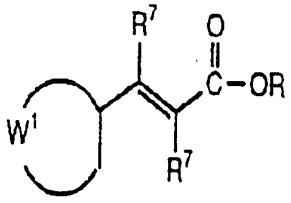
Alternatively, compounds of formula (XI) and (XIa) can be prepared according to the procedure of E.L. Eliel, R.O. Hutchins, and Sr. M. Knoeber, Organic Synthesis Coll. Vol. VI, 442, 1988 with the appropriate modifications readily apparent to those skilled in the art.

Compounds of formula (XII), (XIIa) and (XIIb) can be obtained commercially or by techniques well known to those skilled in the art or readily obtainable from the chemical literature.

Compounds of formula (IX) wherein V is -CHR^1CHR^1- and compounds of formula (IXa) wherein V is -CHR^7CHR^7- can be prepared from compounds of formula (XIII) and (XIIIa) respectively



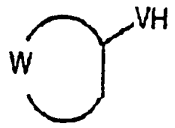
(XIII)



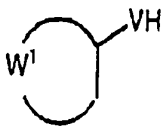
(XIIIa)

(wherein wherein W, W^1, R, R^1, and R^7 are as hereinbefore defined) by reduction of the double bond, e.g., by catalytic reduction with e.g., platinum oxide(PtO_2) and hydrogen, in a suitable organic solvent(e.g., ethanol) at a temperature of about 20°C to 60°C.

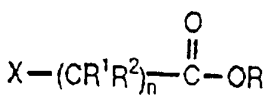
Compounds of formula (IX) wherein V is $(CR^1R^2)_mB$, $B(CR^1R^2)_m$ or $(CR^1R^2)_mB(CR^1R^2)_m$ and compounds of formula (IXa) wherein V is $(CR^7R^8)_mB$, $B(CR^7R^8)_m$ or $(CR^7R^8)_mB(CR^7R^8)_m$ and B is O, S or NR^1 can be prepared by reacting a compound of formula (IXb) and (IXc) respectively with a compound of formula (IXd) and (IXe) respectively



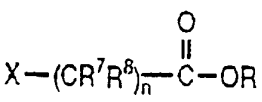
(IXb)



(IXc)



(IXd)

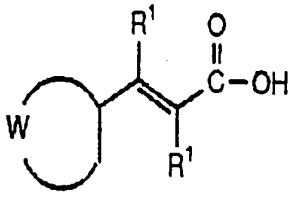


(IXe)

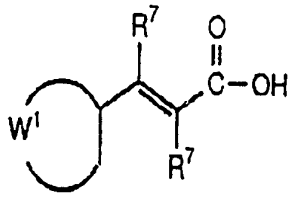
wherein W, W^1, X and R are as hereinbefore defined, V in formula (IXb) is $(CR^1R^2)_mB$ or B, V in formula (IXc) is $(CR^7R^8)_mB$ or B, B is O, S or NR and n is 0, 1 or 2 in a suitable organic solvent in the presence of a base(e.g., sodium hydride).

Compounds of formula (IXb), (IXc) (IXd) and (IXe) can be obtained commercially or by methods well known to those skilled in the art or readily obtainable from the chemical literature.

Compounds of formula (XIII) and (XIIIa) can be prepared from compounds of formula (XIV) and (XIVa)



(XIV)

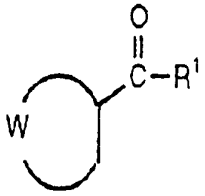


(XIVa)

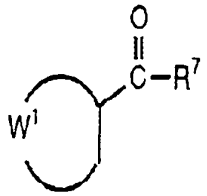
(wherein W, W^1, R^1, and R^7 are as hereinbefore defined) by esterification with an appropriate organic alcohol(e.g., ethanol) optionally in the presense of a catalytic amount of an acid(e.g., HCl, tosic acid, thionyl chloride)at a temperature of about 20°C to 60°C.

Compounds of formula (XIV) and (XIVa) can also be used to directly prepare the corresponding compounds of formula (VIII) and (VIIIa) respectively by reduction of the double bond, e.g., by catalytic reduction with e.g., palladium or platinum oxide(PtO_2) and hydrogen, in a suitable organic solvent(e.g., ethanol) at a temperature of about 0°C to the reflux temperature.

Compounds of formula (XIV) and (XIVa) can be prepared from compounds of formula (XV) and (XVa) respectively



(XV)



(XVa)

(wherein W, W^1, R^1 and R^7 are as hereinbefore defined) by reaction with $HOOCCHR^1COOH$ or $HOOCCHR^7COOH$ respectively in an organic base(e.g., pyridine) optionally in an organic solvent(e.g., dichloromethane) optionally in a catalytic amount of a base(e.g., piperidine) at a temperature of about 0°C to the reflux temperature.

Compounds of formula (XV), (XVa), $HOOCCHR^1COOH$ and $HOOCCHR^7COOH$ can be obtained commercially or by methods well known to those skilled in the art or readily obtainable from the chemical literature.

Alternatively, compounds of formula (I) and (Ia) can be prepared by reacting $R^3R^4NC(Z)CHR^5PO(OR)_2$ (wherein R,R^3,R^4,R^5, and Z are as hereinbefore defined) with a base (e.g., NaH) in a suitable organic solvent (e.g., THF or DMSO) and reacting the resultant anionic species with a compound of formula (VI) or (VIa) respectively at a temperature of about 0°C to the reflux temperature. The addition of a anionic stablizing reagent (e.g., potassium hexamethyldisilizane or a crown ether (e.g., 15-crown-5) can aid the reaction.

The compound $R^3R^4NC(Z)CHR^5PO(OR)_2$ can, depending on R, R^3, R^4, and R^5 be obtained commercially or by methods well known to those skilled in the art or readily obtainable from the chemical literature. Alternatively, these compounds can be prepared by reacting the appropriate $R^3R^4NC(Z)CHR^5X$ (wherein X is as hereinbefore defined) with the appropriate $P(OR)_3$ in a suitable organic solvent (e.g., THF) at a temperature of about 0°C to 50°C.

The compound $R^3R^4NC(Z)CHR^5X$ can be prepared by reacting the appropriate R^3R^4NH with $XCHR^5C(Z)X$ in a suitable organic solvent (e.g., diethyl ether) at a temperature of about 0°C to the reflux temperature.

The compound R^3R^4NH can be obtained commercially or by methods well known to those skilled in the art of preparing amines or readily obtainable from the chemical literature. The compound $XCHR^5C(Z)X$ can be obtained commercially or by methods well known to those skilled in the art of preparing such compounds or readily obtainable from the chemical literature.

Alternatively, compounds of formula (I) and (Ia) can be prepared by reacting $R^3R^4NC(Z)CHR^5P^{(+)}(Ph)_3Cl^{(-)}$(wherein R^3, R^4, R^5, and Z are as hereinbefore defined and Ph is phenyl) with a suitable base (e.g., NaH) in a suitable organic solvent (e.g., dimethoxyethane) at a temperature of about 0°C to 50°C, and reacting the resultant anionic species with a compound of formula (VI) or (VIa) respectively at a temperature of about 0°C to the reflux temperature.

The compound $R^3R^4NC(Z)CHR^5P^{(+)}(Ph)_3Cl^{(-)}$ can be prepared by reacting the appropriate $R^3R^4NC(Z)CHR^5X$ with about a 50% molar excess of $P(Ph)_3$ (triphenylphosphine) in a suitable organic solvent (e.g., THF) at a temperature of about 20°C to the reflux temperature.

$R^3R^4NC(Z)CHR^5X$ can be prepared as defined hereinbefore.

Alternatively, compounds of formula (I) and (Ia) can also be prepared directly from compounds of formula (III) and (IIIa) respectively by reaction with a suitable coupling reagent(e.g., dicyclohexylcarbodiimide(DCC) or ethyl chloroformate) followed by reaction of the activated ester thus formed with the appropriate amine, HNR^3R^4.

The compounds of formula (I) and (Ia) as well as any of the intermediates used in the preparation of these compounds can be effected with one or more of the following optional conversions:

(i) converting a compound of formula (I) or (Ia) or intermediates thereof so formed into base salts, acid addition salts, or other physiologically functional derivatives thereof;

(ii) when a base salt, acid addition salt or other physiologically functional derivative of a compound of formula (I) or (Ia) or an intermediate thereof is formed, converting the said salt or derivative into a compound of formula (I) or (Ia) or an intermediate thereof, or a different derivative thereof.

The present invention further includes the following novel intermediates which are of particular value for the preparation of certain compounds of formula (I) and (Ia):

2-(5-Fluoro-1-hydroxy-1-indanyl)acetic acid,
(E)- 2-(5-Fluoro-1-indanylidene)acetic acid,
(E)- 2-(5-Fluoro-1-indanylidene)acetyl chloride,
2-(6-Fluoro-1-hydroxy-1-indanyl)acetic acid,
(E)- 2-(6-Fluoro-1-indanylidene)acetic acid,
(E)- 2-(6-Fluoro-1-indanylidene)acetyl chloride,
(E)- 2-(6-Fluoro-3-methyl-1-indanylidene)acetic acid,
(E)- 2-(6-Fluoro-3-methyl-1-indanylidene)acetyl chloride,
(E)- 2-(6-Fluoro-3,3-dimethyl-1-indanylidene)acetic acid,
(E)- 2-(6-Fluoro-3,3-dimethyl-1-indanylidene)acetyl chloride,
2-(4,6-Difluoro-1-hydroxy-1-indanyl)acetic acid,
(E)- 2-(4,6-Difluoro-1-indanylidene)acetic acid,
(E)- 2-(4,6-Difluoro-1-indanylidene)acetyl chloride,
2-(4-Chloro-1-hydroxy-1-indanyl)acetic acid,
(E)- 2-(4-Chloro-1-indanylidene)acetic acid,
(E)- 2-(4-Chloro-1-indanylidene)acetyl chloride,
2-(1-hydroxy-4-methyl-1-indanyl)acetic acid,
(E)-2-(4-methyl-1-indanylidene)acetic acid and
(E)-2-(4-methyl-1-indanylidene)acetyl chloride.
2-(4-Chloro-6-fluoro-1-hydroxy-1-indanyl)acetic acid
(E)-2-(4-Chloro-6-fluoro-1-indanylidene)acetic acid
(E)-2-(4-Chloro-6-fluoro-1-indanylidene)acetyl chloride
2-(4,6-Dichloro-1-hydroxy-1-indanyl)acetic acid
(E)-(4,6-Dichloro-1-indanylidene)acetic acid
(E)-2-(4,6-Dichloro-1-indanylidene)acetyl chloride
(E)-2-(3-ethyl-6-fluoro-1-indanylidene)acetic acid

(E)-2-(3-ethyl-6-fluoro-1-indanylidene)acetyl chloride
(E)-2-(6-fluoro-3-propyl-1-indanylidene)acetic acid
(E)-2-(6-fluoro-3-propyl-1-indanylidene)acetyl chloride
2-(6-Fluoro-1-hydroxy-2-iodo-1-indanyl)acetamide
(E)-2-(6-Fluoro-3-ethyl-1-indanylidene) acetic acid
(E)-2-(6-Fluoro-3-ethyl-1-indanylidene)acetyl chloride

The following examples illustrate the present invention but should not be construed as a limitation to the scope thereof.

EXAMPLE 1

Preparation of (E)-2-(6-Fluoro-1-indanylidene)acetamide

a) Preparation of 3-(4-Fluorophenyl)propionic Acid

A mixture of 4-fluorocinnamic acid (300.0 g, 1.8 mol, Aldrich) and 5% palladium on carbon (9.0 g) in ethanol (3 L) was hydrogenated at atmospheric pressure and room temperature for 4.5 h. The mixture was filtered through Celite (diatomaceous earth) and the filtrate was concentrated *in vacuo* to give 275.1 g (91%) of 3-(4-fluorophenyl)propionic acid as a white solid, m.p., 86-88°C; NMR (DMSO-d_6): d12.15 (br s, 1H, COOH), 7.07-7.29 (m, 4H, Ar), 2.81 (t, 2H, CH_2CO), 2.52 (t, 2H, $ArCH_2$).

Anal. Calcd. for $C_9H_9FO_2$: C, 64.28; H, 5.39.
Found: C, 64.23; H, 5.42.

b) Preparation of 3-(4-Fluorophenyl)propionyl Chloride

A mixture of 3-(4-fluorophenyl)propionic acid (275.1 g, 1.6 mol) and thionyl chloride (300 mL, 4.1 mol) was heated to reflux for 3 h, cooled to room temperature and distilled under aspirator vacuum to give 287.6 g (96%) of 3-(4-fluorophenyl)propionyl chloride as a pale pink oil, b.p., 120-122°C/15mm Hg; IR (neat) 1793,1511 cm^{-1}; NMR (DMSO-d_6): d 7.04-7.32 (m, 4H, Ar), 2.50-2.89 (m, 4H, $2XCH_2$).

Anal. Calcd. for C_9H_8ClFO: C, 57.93; H, 4.32; Cl, 19.00.
Found: C, 57.86; H, 4.34; Cl, 18.90.

c) Preparation of 6-Fluoro-1-indanone

A solution of 3-(4-fluorophenyl)propionyl chloride (287.6 g, 1.5 mol) in dichloromethane (1.4 L) was added dropwise during 3 h to an ice-cold, mechanically stirred suspension of aluminum chloride (226.0 g, 1.7 mol, Aldrich) in dichloromethane (2.2 L) under nitrogen. The resulting yellowish-black solution was refluxed for 5 h and allowed to cool to room temperature. The solution was washed successively with water (2 L), 1N sodium hydroxide (2 L), water (2 L) and brine (2 L). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to a tan solid (229.1 g, 99%). The solid was recrystallized from dichloromethane-hexane to give 215.7 g (93%) of 6-fluoro-1-indanone as off-white crystals, m.p., 57-59°C; NMR (DMSO-d_6): d 7.36-7.66 (m, 3H, Ar), 2.65-2.72, 3.06-3.10 (2m's, 4H, $2XCH_2$).

Anal. Calcd. for C_9H_7FO: C, 71.99; H, 4.70.
Found: C, 71.94; H, 4.72.

d) Preparation of Ethyl 2-(6-Fluoro-1-hydroxy-1-indanyl)acetate

A mixture of 6-fluoro-1-indanone (5.0 g, 33.3 mmol), ethyl bromoacetate (8.3 g, 50.0 mmol, Aldrich), activated zinc powder (3.2 g, 50.0 mmol, Mallinckrodt; Org. Synth., Coll. Vol. 6, 290, 1988) and a few crystals of iodine in diethyl ether-benzene (1:1, 100 mL) was heated at reflux under nitrogen for 24 h. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue in diethyl ether was vigorously stirred with excess dilute ammonium hydroxide, dried and concentrated to give ethyl 2-(6-fluoro-1-hydroxy-1-indanyl)acetate as an amber oil (7.6 g, 97%); NMR (DMSO-d_6): d 6.99-7.24 (m, 3H, Ar), 5.38 (s, 1H, OH), 4.00 (q, 2H, $C\underline{H}_2CH_3$), 2.64-2.92 (m, 4H, $2XCH_2$), 2.45-2.54, 2.05-2.14 (2m's, 2H, CH_2CO), 1.08 (t, 3H, CH_3).

Anal. Calcd. for $C_{13}H_{15}FO_3$: C, 65.54; H, 6.35.

Found: C, 65.36; H, 6.39.

e) Preparation of Ethyl 2-(6-Fluoro-1-hydroxy-1-indanyl)acetate

Ethyl acetate (1.8 g, 20 mmol) was added dropwise to a stirred, chilled (dry ice-acetone bath) 1N solution of lithium bis(trimethylsilyl)amide in tetrahydrofuran (20 mL, Aldrich) under nitrogen. After 15 min, a solution of 6-fluoro-1-indanone (3.0 g, 20 mmol) in tetrahydrofuran (20 mL) was added dropwise and the resulting mixture was stirred for 1h (dry ice-acetone bath). A 1N solution of hydrochloric acid (20 mL) was added and the mixture was allowed to warm to room temperature. The organic phase was separated, dried over anhydrous sodium sulfate, filtered and concentrated to a pale yellow oil (5.3 g). The mixture was chromatographed on Silica Gel 60 (silica gel) using a linear gradient of dichloromethane- hexanes (1:1) to dichloromethane as eluent. The fractions containing only ethyl 2-(6-fluoro-1-hydroxy-1-indanyl)acetate were combined and concentrated *in vacuo* to give 3.1g (65%) of a colorless oil; NMR (DMSO-d_6): d 6.98-7.27 (m, 3H, Ar), 5.40 (s, 1H, OH), 4.01 (q, 2H, OCH_2), 2.64-2.96 (m, 4H, $2XCH_2$), 2.44-2.57 (m, 1H, CH), 2.04-2.18 (m, 1H, CH), 1.12 (t, 3H, CH_3).

Anal. Calcd for $C_{13}H_{15}FO_3$: C, 65.54; H, 6.35.
Found: C, 65.44; H, 6.38

f) Preparation of 2-(6-Fluoro-1-hydroxy-1-indanyl)acetic Acid

A mixture of ethyl 2-(6-fluoro-1-hydroxy-1-indanyl)acetate (44.0 g, 0.18 mol), 1N sodium hydroxide (180 mL) and absolute ethanol (280 mL) was stirred for 18 h at room temperature. The mixture was concentrated *in vacuo*, diluted with H_2O and extracted with diethyl ether. The aqueous phase was acidified (pH 3) with dilute hydrochloric acid and extracted with diethyl ether. The diethyl ether layer was washed with brine, dried over sodium sulfate, filtered and concentrated *in vacuo* to give 2-(6-fluoro-1-hydroxy-1-indanyl)acetic acid as an amber oil (37.7 g, 100%; Note: This compound spontaneously dehydrated upon standing at room temperature to a mixture of olefins unless immediately reacted with

trifluoroacetic acid); NMR (DMSO-d_6): d 11.60 (br s, 1H, COOH), 6.75-7.05 (m, 3H, Ar), 5.20 (br s, 1H, OH), 2.22-2.69, 1.77-1.95 (2m's, 6H, $3XCH_2$).

Anal. Calcd. for $C_{11}H_{11}FO_3$: C, 62.85; H, 5.27.
Found: C, 62.57; H, 5.30.

g) Preparation of Lithium 2-(6-Fluoro-1-hydroxy-1-indanyl)acetate.

A mixture of ethyl 2-(6-fluoro-1-hydroxy-1-indanyl)acetate (2.0 g. 8.4 mmol), 1N lithium hydroxide (8.4 mL) and absolute ethanol (13.0 mL) was stirred for 18h at room temperature. The mixture was concentrated *in vacuo*, diluted with H_2O and extracted with diethyl ether. The aqueous phase was concentrated *in vacuo*, diluted with toluene (100 mL) and concentrated *in vacuo* to give lithium 2-(6-fluoro-1-hydroxy-1-indanyl)acetate as a white solid (1.4 g, 77%); NMR (DMSO-d_6): d 8.90 (s, 1H, OH), 6.88-7.18 (m , 3H, Ar), 2.55-2.83 (m, 2H, $ArCH_2$), 2.13 (s, 2H, CH_2CO), 1.88-2.07 (m, 2H, CH_2).

Anal. Calcd. for $C_{11}H_{10}FLiO_3$_0.15 H_2O: C, 60.37; H, 4.74
Found: C, 60.32; H, 4.70

h) Preparation of (*E*)-2-(6-Fluoro-1-indanylidene)acetic Acid

Trifluoroacetic acid (1.5 mL) was added to a stirred, chilled (ice-methanol bath) suspension of lithium 2-(6-fluoro-1-hydroxy-1-indanyl)acetate (0.5 g, 2.3 mmol) in dichloromethane (13.5 mL). After 15 min, the mixture was concentrated *in vacuo* and the resulting white solid was recrystallized from aqueous acetone to give (*E*)-2-(6-fluoro-1-indanylidene)acetic acid as white crystals (0.32 g, 73%) identical to compound of Example 1i by mixed m.p., (203-205°C) and NMR.

Anal. Calcd. for $C_{11}H_9FO_2$: C, 68.75; H, 4.72
Found: C, 68.67; H, 4.75

i) Preparation of (E)-2-(6-Fluoro-1-indanylidene)acetic Acid

Trifluoroacetic acid (100 mL) was added to a stirred, chilled (ice-methanol bath) solution of 2-(6-Fluoro-1-hydroxy-1-indanyl)acetic acid (37.5 g, 0.18 mol) in dichloromethane (900 mL). After 15 min, the mixture was concentrated *in vacuo* to give (E)-2-(6-fluoro-1-indanylidene)acetic acid as a yellowish-tan solid (33.0 g, 95%), m.p., 203-205°C; NMR (DMSO-d_6): d 12.05 (br s, 1H, COOH), 7.16-7.65 (m, 3H, Ar), 6.37 (t, 1H, =CH), 2.94-2.98, 3.15-3.20 (2m's, 4H, $2XCH_2$); steady-state nOe:irradiation at 6.37 d, observed 24% nOe at 7.65 d.

Anal. Calcd. for $C_{11}H_9FO_2$: C, 68.75; H, 4.72.
Found: C, 68.65; H, 4.68.

j) Preparation of (E)-2-(6-Fluoro-1-indanylidene)acetyl Chloride

An ice-cold, stirred suspension of (E)-2-(6-fluoro-1-indanylidene) acetic acid (384 mg, 2 mmol) in benzene (10 mL) was treated with oxalyl chloride (761 mg, 6 mmol) and allowed to warm to room temperature during 1.5 h. The resulting yellow solution was concentrated *in vacuo* to give (E)-2-(6-fluoro-1-indanylidene)acetyl chloride as a pale yellow solid (421 mg, 100%), m.p., 97-99°C; IR (Nujol (high boiling petroleum oil)): 1750, 1600 cm^{-1}; NMR (DMSO-d_6): d 7.18-7.67 (m, 3H, Ar), 6.39 (t, 1H, =CH), 2.96-2.99, 3.16-3.21 (2m's, 4H, $2XCH_2$).

Anal. Calcd. for $C_{11}H_8ClFO$: C, 62.73; H, 3.83; Cl, 16.83.
Found: C, 62.83; H, 3.87; Cl, 16.76.

k) Preparation of (E)-2-(6-Fluoro-1-indanylidene)acetamide

A 29.6% aqueous ammonium hydroxide solution (17.6 mL, 134 mmol) was added dropwise to a stirred, chilled (ice bath) solution of (E)-2-(6-fluoro-1-indanylidene)acetyl chloride (14.1 g, 67 mmol) in dichloromethane (165 mL). After an hour, the resulting white precipitate was collected by filtration, dissolved in ethyl acetate (600 mL) and washed with water (3X300 mL). The ethyl acetate layer was dried over sodium sulfate and concentrated *in vacuo*. The resulting off-white solid was washed with hexane, giving 11.6 g (91%) of (E)-2-(6-fluoro-1-indanylidene)acetamide, m.p., 180-183°C; NMR (DMSO-d_6): d 6.91-7.41 (m,

5H, Ar+NH_2), 6.37 (t, 1H, =CH), 2.92-2.96, 3.16-3.22 (2m's, 4H, 2XCH_2); steady-state nOe:irradiation at 6.37 d, observed 23% nOe at 7.28 d.

Anal. Calcd. for $C_{11}H_{10}FNO$: C, 69.10; H, 5.27; N, 7.33.
Found: C, 69.02; H, 5.33; N, 7.29.

EXAMPLE 2

Preparation of (E)-2-(6-Fluoro-1-indanylidene)acetamide

A stirred suspension of (E)-2-(6-fluoro-1-indanylidene)acetic acid (0.5 g, 2.6 mmol) in dichloromethane (10 mL) at -20°C was successively treated dropwise with ethyl chloroformate (0.3 g, 2.6 mmol, Aldrich) and triethylamine (0.3 g, 2.6 mmol, Eastman). The mixture was stirred at -20°C for 2 h. A solution of anhydrous ammonia in dichloromethane (0.8 M, 12 mL) was added [Note: When aqueous ammonium hydroxide was used, the mixed anhydride was partially hydrolyzed to the acid.], the mixture was stirred for 16 h at room temperature, and subsequently washed successively with water, sodium bicarbonate solution, water and brine. The dichloromethane layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 0.18 g of a 6:1 mixture of (E)-2-(6-fluoro-1-indanylidene)acetamide and 2-(5-fluoro-1H-inden-3-yl)acetamide.

EXAMPLE 3

Preparation of (E)-N-Ethyl-2-(6-fluoro-1-indanylidene)acetamide

This compound was prepared in an analogous manner to that of Example 5 with replacement of cyclopropylamine in Example 5 with ethylamine (70 wt % in water). The chromatography solutions that contained (E)-N-Ethyl-2-(6-fluoro-1-indanylidene)acetamide were concentrated by spin evaporation *in vacuo*. Recrystallization of the residue from dichloromethane-hexanes gave 1.7 g (68%) of (E)-N-ethyl-2-(6-fluoro-1-indanylidene)acetamide, m.p. 125-127°C; NMR (DMSO-d_6): d 7.89 (s, 1H, NH), 7.40-7.13 (m, 3H, Ar), 6.35 (s, 1H, =CH), 3.23-3.11 (m, 4H, 2CH2), 2.95-2.91 (m, 2H, CH2) 1.05 (t, 3H, J=7.15 Hz, CH3); steady state nOe: irradiation at d 6.35, observed 16% nOe at d 7.89 and 21% nOe at d 7.27.

Anal. Calcd for $C_{13}H_{14}FNO$: C, 71.21; H, 6.44; N, 6.39
Found: C, 71.27; H, 6.50; N, 6.44.

EXAMPLE 4

Preparation of (E)-N-Benzyl-2-(6-fluoro-1-indanylidene)acetamide

This compound was prepared in an analogous manner to that of Example 5 with replacement of cyclopropylamine in Example 5 with benzylamine. The residue was chromatographed on silica gel using ethyl acetate-hexanes (1:5) as eluent. The chromatography fractions that contained (E)-N-benzyl-2-(6-fluoro-1-indanylidene)acetamide were concentrated by spin evaporation *in vacuo* . Recrystallization of the residue from dichloromethane-hexanes gave 1.66 g (64%) of (E)-N-benzyl-2-(6-fluoro-1-indanylidene)acetamide, m.p. 134-136°C; NMR (DMSO-d_6): d 8.43 (t, 1H, J=5.85 Hz, NH), 7.42-7.15 (m, 8H, Ar), 6.46 (t, 1H, J=2.35 Hz, =CH), 4.36 (d, 2H, J=5.9 Hz, CH_2), 3.25-3.22 (m, 2H, CH_2), 2.97-2.94 (m, 2H, CH_2); steady state nOe: irradiation at d 6.46, observed 11.7% nOe at d 8.43 and 19.7% nOe at d 7.31.

Anal. Calcd for $C_{18}H_{16}FNO$: C, 76.85; H, 5.69; N, 4.98.
Found: C, 76.87; H, 5.73; N, 5.12.

EXAMPLE 5

Preparation of (E)-N-Cyclopropyl-2-(6-fluoro-1-indanylidene)acetamide

To an ice-cold stirred solution of (E)-2-(6-Fluoro-1-indanylidene)acetyl Chloride in dichloromethane (50 ml) was added cyclopropylamine (1.65 g, 28.86 mmol) and the reaction was warmed to room temperature overnight. The reaction was evaporated *in vacuo* to a solid residue. This residue was dissolved in ethyl acetate (300 ml), washed with water (75 ml), and the organic layer was concentrated by spin evaporation *in vacuo*. The residue was chromatographed on silica gel using ethyl acetate-hexanes (0:1 to 1:1 gradient) as eluent. Fractions containing only the product were combined and concentrated by spin evaporation *in vacuo*. Recrystallization of the residue from

dichloromethane-hexanes gave 1.6 g (76%) of (E)-N-cyclopropyl-2-(6-fluoro-1-indanylidene)acetamide as a white powdery solid, m.p. 124-127°C; NMR (DMSO-d_6): d 8.03 (d, 1H, J=3.9 Hz, NH), 7.45-7.38 (m, 1H, Ar), 7.28-7.14 (m, 2H, Ar), 6.30 (s, 1H, =CH), 3.23-3.21 (m, 2H, CH_2), 2.99-2.96 (m, 2H, CH_2), 2.72 (m, 1H, NCH), 0.71-0.39 (2ms, 4H, CH_2-CH_2); steady state nOe: irradiation at d6.30, observed 15% nOe at d 8.03 and 20% nOe at d 7.23.

Anal. Calcd for $C_{14}N_{14}FNO$: C, 72.71; H, 6.10; N, 6.06.
Found: C, 72.54; H, 6.13; N, 6.01.

EXAMPLE 6

Preparation of (E)-N-(Cyclopropylmethyl)-2-(6-fluoro-1-indanylidene)acetamide

This compound was prepared in an analogous manner to that of Example 5 with replacement of cyclopropylamine in Example 5 with aminomethylcyclopropane. The residue was chromatographed on silica gel using ethyl acetate-hexanes (1:4) as eluent. The chromatography fractions that contained (E)-N-(cyclopropylmethyl)-2-(6-fluoro-1-indanylidene)acetamide were concentrated by spin evaporation *in vacuo*. Recrystallization of the residue from dichloromethane-hexanes gave 1.42 g (63%) pure (E)-N-(cyclopropylmethyl)-2-(6-fluoro-1-indanylidene)acetamide, m.p. 105-107°C; NMR (DMSO-d_6): d 8.0 (t, 1H, NH), 7.45-7.14 (m, 3H, Ar), 6.43 (t, 1H, J=2.4 Hz, =CH), 3.27-3.19 (m, 2H, CH_2), 3.07-2.93 (br m, 4H, 2 CH_2), 0.98-0.88 (m, 1H, CH), 0.48-0.39 (m, 2H, CH_2), 0.23-0.15 (m, 2H, CH_2); steady state nOe: irradiation at d 6.43, observed 13.1% nOe at d 8.0 and 16.5% nOe at d 7.34.

Anal. Calcd for $C_{15}H_{16}FNO$: C, 73.44; H, 6.58; N, 5.71.
Found: C, 73.40; H, 6.63; N, 5.68.

EXAMPLE 7

Preparation of (E)-N-Ethyl-2-(6-fluoro-1-indanylidene)-N-methylacetamide

This compound was prepared in an analogous manner to that of Example 5 with replacement of cyclopropylamine in Example 5 with N-ethylmethylamine (3.5 mL,

0.025 mol, Aldrich). The residue was chromatographed on silica gel using ethyl acetate-hexanes (1:5 to 1:2 gradient) as eluent. The chromatography fractions that contained (E)-N-ethyl-2-(6-fluoro-1-indanylidene)-N-methylacetamide were concentrated by spin evaporation *in vacuo*. Recrystallization of the residue from ethyl acetate-hexanes gave 1.32 g (61%) of (E)-N-ethyl-2-(6-fluoro-1-indanylidene)-N-methylacetamide as a white solid, m.p. 74-77-°C, NMR (DMSO-d_6): d 7.73 (t, 1H, J=9.7 Hz, Ar), 7.39-7.35 (m, 1H, Ar), 7.19-7.12 (m, 1H, Ar), 6.86 (t, 1H, J=2.4 Hz, =CH), 3.51 (q, 1H, 1/2 CH_2), 3.37 (q, 1H, 1/2 CH_2), 3.16-3.11 (m, 2H, CH_2), 3.08 (s, 1.5 H, 1/2 CH_3), 2.95-2.91 (m, 2H, CH_2), 2.87 (s, 1.5H, 1/2 CH_3), 1.12 (t, 1.5 H, J=7.1 Hz, 1/2 CH_3), 1.04 (t, 1.5 H, J=7.1 Hz, 1/2 CH_3). Steady state nOe: irradiation at d 6.86, observed 22.2% nOe at d 7.73.

Anal. Calcd for $C_{14}H_{16}FNO$: C, 72.08, H, 6.91, N, 6.00.
Found: C, 71.94; H, 6.88; N, 5.98.

EXAMPLE 8

Preparation of (E)-2-(1-indenylidene)acetamide

a) Preparation of (E)-2-(1-Indenylidene)acetic acid

This compound was prepared by the method described by Shuman, et al[1] for the preparation of (E)-2-(1-indenylidene)acetic acid, which was erroneously referred to in that reference as (Z)-1-indenylidene-acetic acid. To indene (13.5 g, 0.116 mol) under nitrogen was added tetramethylammonium hydroxide (93 ml of 2.81 M in methanol, 0.261 mol) and glyoxylic acid (19.65 ml of 50% solution in water, 0.174 mol). The reaction mixture was stirred at 55°C for 70 min. Water (150 ml) and toluene (150 ml) were added, the pH was adjusted to 2 with H_2SO_4, and the layers were separated. The water layer was extracted with 2 x 50 ml of 1,2-dichloroethane, and the toluene and 1,2-dichloroethane extracts were combined. After washing with water (50 ml) the organic extracts were stripped to dryness under vacuum. The solid residue (10.4 g, 52%) crystallized from ethyl acetate (110 ml) and was dried at 50°C under vacuum to give 4.8 g (24%) of (E)-2-(1-indanylidene)acetic acid; m.p. 198-201°C dec; UV max 259 nm (0.1 M HCl in CH_3OH, e 27 850); TLC, single component on silica gel

(9 C_6H_6-1 CH_3OH), R_f 0.35; ^1H NMR (Me_2SO-d_6) d 6.75 (s, 1, vinyl H), 7.0-7.5 (m, 5, aromatic H and indenyl H), 7.7-7.9 (m, 1, aromatic H).

Anal. Calcd for $C_{11}H_8O_2$: C, 76.73; H, 4.68.
Found: C, 76.81; H, 4.87.

[1]Shuman, Pines, Shearin, Czaja, Abramson, Tull, *J.Org.Chem* 42, 1977, 1918.

The product obtained from the reaction was identical to that prepared by Shuman et al. (m.p.>200° (dec)). However, based on nuclear Overhauser effect NMR measurements, the compound was determined to be (E)-2-(1-indenylidene)acetic acid and not its Z isomer as reported by Shuman; NMR (DMSO-d_6) steady state nOe: irradiation at d 6.75, observed significant nOe at d 7.75.

(b) Preparation of (E)-2-(1-indenylidene)acetamide

A mixture of (E)-2-(1-indenylidene)acetic acid (5.03 g, 29.22 mmol) and thionyl chloride (25 ml, 40.78 g, 342.73 mmol) was heated at reflux for 1.5 h. The mixture was coevaporated with dichloromethane (2 x 250 ml) to give crude (E)-2-(1-indenylidene)acetyl chloride as a rust-colored solid. To a solution of the acid chloride in dichloromethane (200 ml) was added ammonium hydroxide (150 ml) and the resulting heterogeneous mixture was stirred at ambient temperature for 0.75 h. The aqueous phase was extracted with dichloromethane (2 x 75 ml). The organic phases were combined, washed with water (50 ml) and concentrated by evaporation *in vacuo*. The residue was chromatographed twice on silica gel using ethyl acetate as eluent. The fractions containing the product were combined and concentrated by spin evaporation *in vacuo*. Recrystallization of the residue from hot water gave 2.34 g (46.8%) of (E)-2-(1-indenylidene)acetamide as a shiny yellow crystalline solid, m.p. >200° dec., NMR (DMSO-d_6): d 7.80 (bs, 1H, NH), 7.56 (d, 1H, J=7.23 Hz, Ar), 7.39 (d, 1H, J=5.67 Hz, =CH), 7,.35 (bs, 1H, NH), 7.32-7.15 (m, 3H, Ar), 7.03 (d, 1H, J=5.62 Hz, =CH), 6.79 (s, 1H, =CH), nOe: irradiation at d 6.79 observed nOe at d 7.80 and d 7.56.

Anal. Calcd for $C_{11}H_9NO$: C, 77.17; H, 5.3; N, 8.18.

Found: C, 77.15; H, 5.30; N, 8.12.

EXAMPLE 9

Preparation of (E)-N-cyclopropyl-2-(4-methyl-1-indanylidene)acetamide

a) Preparation of 2-Methylcinnamic Acid

This compound was prepared by a method analogous to that described in Example 10a substituting 2-tolualdehyde (50.0 g, 0.42 mol, Aldrich) for 2-chlorobenzaldehyde to give 53.7 g (80%) of 2-methylcinnamic acid as a white solid. This material was used without further purification.

b) Preparation of 3-(2-Methylphenyl)propanoic Acid

This compound was prepared in a similar manner as that described for the preparation of ethyl 3-(2-chlorophenyl)propionate in Example 10c substituting 2-methylcinnamic acid (44.9 g, 0.28 mol) for ethyl 2-chlorocinnamate to give 45.5g (99%) of 3-(2-methyl-phenyl)propanoic acid as an off-white solid. Recrystallization of 1.5g from acetone: water mixtures gave 0.96g of 3-(2-methylphenyl)propanoic acid as a white solid: m.p., 99-102°C; NMR (DMSO-d_6) ; d 12.15 (br, 1H, COOH), 7.04-7.12 (m, 4H, Ar), 2.80 (t, 2H, CH_2), 2.48 (t, 2H, CH_2), 2.26 (s, 3H, CH_3).

Anal. Calcd. for $C_{10}H_{12}O_2$ (mw 164.20): C, 73.14; H, 7.37.
Found : C, 73.01; H, 7.38.

c) Preparation of 4-Methyl-1-indanone

This material was prepared in a similar manner to that described for 4-chloro-1-indanone in Example 10e substituting 3-(2-methylphenyl)propanoic acid (44.0 g, 0.27 mol) for 3-(2-chlorophenyl)propanoic acid to give 29.6 g of crude 4-methyl-1-indanone. Chromatography on silica gel with hexanes: ethyl acetate (8:2) as eluent gave 26.5 g of a slightly yellow solid. Recrystallization of 1.0 g from acetone: water mixtures gave 0.59 g of 4-methyl-1-indanone as a white solid: m.p., 95-96°C; (Lit.[a] 98-101°C); NMR ($CDCl_3$) : d 7.25-7.61 (m, 3H, Ar), 3.02 (t, 2H, CH_2), 2.70 (m, 2H, CH_2), 2.36 (s, 3H. CH_3).

Anal. Calcd. for $C_{10}H_{10}O$ (mw 146.2): C, 82.16; H , 6.90.
Found: C, 81.94; H , 7.00.

[a] J. Chem.Soc. **1961**, 3958.

d) Preparation of Ethyl 2-(1-hydroxy-4-methyl-1-indanyl)acetate

This compound was prepared in an analogous manner to that described in Example 10f for ethyl 2-(4-chloro-1-hydroxy-1-indanyl)acetate substituting 4-methyl-1-indanone (25.5 g, 0.17 mol) for 4-chloro-1-indanone to give 39.3 g of crude ethyl 2-(1-hydroxy-4-methyl-1-indanyl)acetate. Chromatography on silica gel with dichloromethane as eluent gave 21.4g (53%) of an amber oil ; NMR ($CDCl_3$): d 7.06-7.20 (m, 3H, Ar), 4.21 (q, 2H, $C\underline{H}_2CH_3$), 4.08 (br, 1H, OH), 2.84 (2m's, 4H, $CH_{2's}$), 2.25 (m, 5H, CH_2 and CH_3),1.28 (t, 3H, CH_3).

Anal. Calcd. for $C_{14}H_{18}O_3$ (mw 234.28): C, 71.77; H, 7.74.
Found: C, 71.64; H, 7.78.

e) Preparation of 2-(1-hydroxy-4-methyl-1-indanyl)acetic Acid

This compound was prepared in a similar manner to that described for 2-(4-chloro-1-hydroxy-1-indanyl)acetic acid in Example 10 g by substituting ethyl 2-(1-hydroxy-4-methyl-1-indanyl)acetate (20.4 g , 0.09 mol) for ethyl 2-(4-chloro-

1-hydroxy-1-indanyl)acetate to give a quantitative yield of crude 2-(1-hydroxy-4-methyl-1-indanyl)acetic acid. This material was used immediately without further purification.

f) Preparation of (E)-2-(4-methyl-1-indanylidene)acetic Acid

This compound was prepared in an analogous manner to (E)-2-(4-chloro-1--indanylidene)acetic acid Example 10h by substituting 2-(1-hydroxy-4-methyl-1-indanyl)acetic acid (18.9 g, 0.09 mol) for 2-(4-chloro-1-hydroxy-1-indanyl)acetic acid to give 9.45g of crude (E)-2-(4-methyl-1-indanylidene)acetic acid. Recrystallization of 1.0 g from acetonitrile: acetone: water mixtures gave 0.68 g of (E)-2-(4-methyl-1-indanylidene)acetic acid as a white solid: m.p., 233-235°C; NMR (DMSO-d_6): d11.95 (br , 1H, COOH), 7.16-7.60 (m, 3H, Ar), 6.30 (s, 1H, =CH), 2.88-2.94, 3.12-3.19(2m's, 4H, 2XCH_2), 2.25 (s, 3H, CH_3) ; steady-state nOe: irradiation at 6.30 d, observed 14% nOe at 7.58 d.

Anal. Calcd. for $C_{12}H_{12}O_2$ (mw 188.22): C, 76.57; H, 6.43.
Found: C, 76.59; H, 6.46.

g) Preparation of (E)-2-(4-methyl-1-indanylidene)acetyl Chloride

This compound was prepared in a similar manner to (E)-2-(4-chloro-1-indanylidene)acetyl Chloride in Example 10i by substituting (E)-2-(4-methyl-1-indanylidene)acetic Acid (8.45g, 0.04mol) for (E)-2-(4-chloro-1-indanylidene)acetic Acid. The resulting solution was concentrated *in vacuo* and the residue used without further purification.

h) Preparation of (E)-N-cyclopropyl-2-(4-methyl-1-indanylidene)acetamide

This compound was prepared in a similar manner to that described for (E)-2-(4-chloro-1-indanylidene)-N-cyclopropylacetamide Example in 10j by substituting (E)-2-(4-methyl-1-indanylidene)acetyl chloride (3.2g, 0.015 mol) for (E)-2-(4-chloro-1-indanylidene)acetyl chloride to give 3.3g of crude product. Chromatography on silica gel with ethyl acetate: hexanes (6:4) as eluent and trituration of the resulting solid with pentane gave 2.69g (79%) of (E)-N-

cyclopropyl-2-(4-methyl-1-indanylidene)acetamide as a white solid: m.p., 138-140°C; NMR (DMSO-d_6): d 8.02 (d, 1H, NH), 7.18-7.36 (m, 3H, Ar), 6.27 (t, 1H, =CH), 2.82-2.92, 3.17-3.32 (2m's, 4H, 2XCH_2), 2.72 (m,1H,CH), 0.38-0.46,0.61-0.70 (2m's,4H, 2XCH_2), 2.25 (S, 3H, CH_3); steady-state nOe: irradiation at 6.27 d, observed 16% nOe at 7.34d.

Anal. Calcd. for $C_{15}H_{17}NO$ (mw 227.29): C, 79.26; H, 7.54; N, 6.16. Found: C, 79.34; H, 7.59; N, 6.21.

EXAMPLE 10

Preparation of (E)-2-(4-Chloro-1-indanylidene)-N-cyclopropylacetamide

a) Preparation of 2-Chlorocinnamic Acid

To a mixture of 2-chlorobenzaldehyde (100.0g, 0.71 mol, Aldrich) and malonic acid (148.1g, 1.42 mol, Aldrich) in pyridine (300 mL) at 50°C was added dropwise piperidine (20 mL). After 18h the mixture was poured into an ice cold solution of concentrated HCl (700 mL) and water (500 mL). The resulting solid was filtered and washed repeatedly with water to give 122.9g (95%) of 2-chlorocinnamic acid as a white solid: m.p., 208- 209°C (Lit.[a] 208-210°C). This material was used without further purification.

[a]Beilstein **9**, 594.

b) Preparation of Ethyl 2-Chlorocinnamate

A mixture of 2-chlorocinnamic acid (90.0g, 0.49 mol) and 1.0M HCl in diethyl ether (20 mL, Aldrich) in ethanol (800 mL) was heated to reflux for 18h. The mixture was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with $NaHCO_3$ (5% aqueous) and dried (Na_2SO_4). Filtration and concentration gave 97.7g (95%) of ethyl 2-chlorocinnamate as an orange oil. This material was used without further purification.

c) Preparation of Ethyl 3-(2-Chlorophenyl)propionate

A mixture of ethyl 2-chlorocinnamic acid (60.0g, 0.28 mol) and platinum oxide hydrate (1.0g, EM Scientific) in 95% ethanol (300 mL) was placed on a Parr hydrogenation apparatus. After the appropriate amount of hydrogen was taken up, the catalyst was filtered and the mixture was concentrated *in vacuo* to give 46.2g (76%) of ethyl 3-(2-chlorophenyl)propionate as a yellow oil. This material was used without further purification.

d) Preparation of 3-(2-Chlorophenyl)propanoic Acid

A mixture of ethyl 3-(2-chlorophenyl)propionate (46.2g, 0.22 mol) and sodium hydroxide (9.6g, 0.24 mol) in water (500 mL) was refluxed for 2h. After cooling the mixture was washed with diethyl ether. The aqueous phase was chilled in an ice bath and concentrated hydrochloric acid was added until the mixture was acidic. The resulting solid was filtered and washed repeatedly with water. Recrystallization from acetonitrile/water mixtures gave 31.0 g (76%) of 3-(2-chlorophenyl)propanoic acid as a white solid. This material was used without further purification.

e) Preparation of 4-Chloro-1-indanone

To a mixture of 3-(2-chlorophenyl)propanoic acid (30.6 g, 0.17 mol) and dimethylformamide (5 drops) at room temperature was added dropwise oxalyl chloride (120 mL). The mixture was stirred at room temperature until gas evolution had ceased. The excess oxalyl chloride was removed by distillation to give 3-(2-chlorophenyl) propionyl chloride. A solution of the 3-(2-chlorophenyl)propionyl chloride in dichloromethane (300 mL) was added dropwise to a mixture of aluminum chloride (25.3 g, 0.19 mol, Aldrich) in dichloromethane (300 mL) at ice bath temperature. After the addition was completed, the mixture was refluxed for 3.5h. The reaction mixture was poured into ice water (1500 mL). The two phases were separated and the dichloromethane phase was washed with 0.1N aqueous sodium hydroxide, dried (Na_2SO_4), and concentrated to give 23.8g of crude 4-chloro-1-indanone. Chromatography on silica gel with hexane:ethyl acetate (9:1) as eluent afforded

18.2 g (66%) of 4-chloro-1-indanone. Recrystallization of 1.0g from acetone/water mixtures gave 0.63g of 4-chloro-1-indanone as an off-white solid: m.p., 88-90°C; NMR ($CDCl_3$) : d 7.32-7.68 (m, 3H, Ar), 3.13 (t, 2H, CH_2), 2.74 (t, 2H, CH_2).

Anal. Calcd. for C_9H_7ClO (mw 166.6): C, 64.88; H 4.24.
Found: C, 64.82; H 4.28.

f) Preparation of Ethyl 2-(4-chloro-1-hydroxy-1-indanyl)acetate

A mixture of 4-chloro-1-indanone (17.2 g, 0.10 mol), ethyl bromoacetate (26.1 g, 0.16 mol, Aldrich), activated zinc powder (10.2 g, 0.16 mol, Aldrich ; Org. Synth., Coll. Vol. 6, 290, 1988) and a few crystals of iodine in diethyl ether-toluene (1:1, 350 mL) was heated at reflux under nitrogen for 24h. A few more crystals of iodine were added and the mixture was refluxed for an additional 24h. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue in diethyl ether was vigorously stirred with excess dilute ammonium hydroxide, dried (Na_2SO_4) and concentrated to give 24.7 g of an orange oil. Chromatography on silica gel with dichloromethane:hexanes (8:2) gave 13.5 g (52%) of ethyl 2-(4-chloro-1-hydroxy-1-indanyl)acetate as a yellow oil ; NMR ($CDCl_3$): d 7.15-7.27 (m, 3H, Ar), 4.29 (s, 1H, OH), 4.20 (q, 2H, $C\underline{H_2}CH_3$), 3.06 (m, 1H, CH_2), 2.78 (2m's, 3H, CH_2's), 2.30 (t, 2H, CH_2),1.27 (t, 3H, CH_3).

Anal. Calcd. for $C_{13}H_{15}ClO_3$ (mw 254.71): C, 61.30; H, 5.94.
Found: C, 61.21; H, 5.94.

g) Preparation of 2-(4-Chloro-1-hydroxy-1-indanyl)acetic Acid

A mixture of ethyl 2-(4-chloro-1-hydroxy-1-indanyl)acetate (12.5 g, 0.05 mol), 1N sodium hydroxide (50 mL) and absolute ethanol (100 mL) was stirred for 18h at room temperature. The mixture was concentrated *in vacuo*, diluted with H_2O and extracted with diethyl ether. The aqueous phase was neutralized with 1.0N hydrochloric acid (50 mL) and extracted with diethyl ether. The diethyl ether layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to give

10.4 g (94%) of the product as a yellow solid. This material was used immediately without further purification.

h) Preparation of (E)-2-(4-chloro-1-indanylidene)acetic Acid

Trifluoroacetic acid (25.1 mL) was added to a stirred, chilled (ice-methanol bath) solution of 2-(4-chloro-1-hydroxy-1-indanyl)acetic acid (10.4 g, 0.05 mol) in dichloromethane (230 mL). After 30 min, the mixture was concentrated *in vacuo*. Dichloromethane was added to the residue and the mixture was concentrated *in vacuo* to give 6.5 g (68%)of a white solid. Recrystallization of 0.98 g from acetonitrile: 2-propanol mixtures gave 0.62 g of a white solid: m.p., 233-234°C; NMR (DMSO-d_6): d12.15 (br , 1H, COOH), 7.30-7.81 (m, 3H, Ar), 6.41 (s, 1H, =CH), 3.00-3.06, 3.19-3.22 (2m's, 4H, 2XCH_2); steady-state nOe: irradiation at 6.41 d, observed 19.7% nOe at 7.79 d.

Anal. Calcd. for $C_{11}H_9ClO_2$ (mw 208.64): C, 63.32; H, 4.35.
Found: C, 63.25; H, 4.39.

i) Preparation of (E)-2-(4-chloro-1-indanylidene)acetyl Chloride

A suspension of (E)-2-(4-chloro-1-indanylidene)acetic acid (5.5 g, 0.03 mol) in a mixture of dimethylformamide: dichloromethane (5 drops: 50 mL) was treated with oxalyl chloride (6.6 g, 0.05 mol) and allowed to stir at room temperature for 18h. The resulting solution was concentrated *in vacuo* and the residue used without further purification.

j) Preparation of (E)-2-(4-chloro-1-indanylidene)-N-cyclopropylacetamide

An ice cold solution of (E)-2-(4-chloro-1-indanylidene)acetyl chloride (2.95 g, 0.013 mol) in dichloromethane (30 mL) was treated with cyclopropylamine (1.48 g, 0.026 mol, Aldrich) and the mixture was stirred for 4h. The mixture was concentrated *in vacuo* and the residue was taken up in a mixture of ethyl acetate and 5% aqueous sodium bicarbonate. The ethyl acetate phase was washed with 5% aqueous sodium bicarbonate, saturated aqueous NaCl and dried (Na_2SO_4). Filtration and concentration gave 3.5g of crude product.

Chromatography on Silica gel with ethyl acetate:hexanes (1:1) as eluent and trituration of the resulting solid with hexanes gave 2.46 g (76%) of (E)-2-(4-chloro-1-indanylidene)-N-cyclopropylacetamide as an off-white solid: m.p., 140-142_C; NMR (DMSO-d_6): d 8.1 (d, 1H, NH), 7.29-7.51 (m, 3H,Ar), 6.34 (t, 1H, =CH), 2.93-3.07, 3.18-3.31 (2m's, 4H, 2XCH_2), 2.72 (m,1H,CH), 0.62-0.72, 0.39-0.47 (2m's,4H, 2XCH_2); steady-state nOe: irradiation at 6.34 d, observed 20.3% nOe at 7.46 d.

Anal. Calcd. for $C_{14}H_{14}ClNO$ (mw 247.72): C, 67.88; H, 5.70; N, 5.65.
Found: C, 67.86; H, 5.74; N, 5.58.

EXAMPLE 11

Preparation of (E)-2-(6 -Bromo-1-indanylidene)acetamide

a) Preparation of Diethyl 2-(4-bromobenzyl)malonate

To a mixture of sodium hydride (4.8g, 0.20 mol, 88% dispersion in mineral oil, Aldrich) in dimethoxyethane (50 mL) under a nitrogen atmosphere was added dropwise a solution of diethylmalonate (33.6 g, 0.21 mol, Aldrich) in dimethoxyethane (100 mL). After stirring at room temperature for 2h, a solution of 4-bromobenzylbromide (50.0g, 0.20 mol, Aldrich) in dimethoxyethane (100 mL) was added dropwise. The resulting mixture was refluxed for 18h, concentrated *in vacuo* and the residue treated with a mixture of water (300 mL) and dichloromethane (300 mL). The aqueous phase was extracted with dichloromethane and the combined extracts were dried (Na_2SO_4), and concentrated *in vacuo* to give 79.2 g of a crude mixture of diethyl 2-(4-bromobenzyl)malonate and diethyl 2,2-bis-(4--bromobenzyl)malonate. Chromatography on silica gel with hexanes: dichloromethane (1:1) as eluent gave 37.6g (57%) of diethyl 2-(4-bromobenzyl)malonate as a colorless oil; NMR ($CDCl_3$) d 7.06-7.42 (m, 4H, Ar), 4.16 (2Xq's, 4H, 2X CH_2's), 3.59 (t, 1H, CH), 3.15 (d, 2H, CH_2), 1.21 (2Xt's, 6H, 2X CH_3's).

Anal. Calcd. for $C_{14}H_{17}BrO_4$ (mw 329.20): C, 51.08; H , 5.21.
Found: C, 51.18; H , 5.19.

b) Preparation of 3-(4-Bromophenyl)propanoic Acid

A mixture of diethyl 2-(4-bromobenzyl)malonate (36.6g, 0.11 mol) and potassium hydroxide (12.5 g, 0.22 mol) in water (200 mL) was refluxed for 4.5h. The mixture was concentrated *in vacuo* to remove the ethanol, a solution of concentrated sulfuric acid (18.7 mL) and water (51.3 mL) was added and the mixture was refluxed for 18h. The reaction mixture was chilled in an ice bath, and the resulting solid was filtered and washed with water to get 24.8 g (72%) of 3-(4-bromophenyl)propanoic acid as a white solid: m.p., 131-133°C; NMR (DMSO-d_6) d 12.15 (br, 1H, COOH), 7.18-7.48 (m, 4H, Ar), 2.79 (t, 2H, CH_2), 2.52 (t, 2H, CH_2).

Anal. Calcd. for $C_9H_9BrO_2$(mw 229.08): C, 47.18; H , 3.96.
Found: C, 47.25; H , 3.97.

c) Preparation of 6-Bromo-1-indanone

This material was prepared in a similar manner to that described for 4-chloro-1-indanone in Example 10e substituting 3-(4-bromophenyl)propanoic acid (31.0g, 0.14 mol) for 3-(2-chlorophenyl) propanoic acid to give 30.5 g of crude 6-bromo-1-indanone . Recrystallization of 1.0 g from acetone: water mixtures gave 0.55 g of 6-bromo-1-indanone as an off-white solid: m.p., 108-110°C; NMR ($CDCl_3$) : d 7.35-7.89 (m, 3H, Ar), 3.07-3.13 (m, 2H, CH_2), 2.70- 2.76 (m, 2H, CH_2).

Anal. Calcd. for C_9H_7BrO (mw 211.06): C, 51.21; H , 3.34.
Found: C, 51.14; H , 3.39.

d) Preparation of Ethyl 2-(6-bromo-1-hydroxy-1-indanyl)acetate

This compound was prepared in an analogous manner to that described in Example 10f for ethyl 2-(4-chloro-1-hydroxy-1-indanyl)acetate substituting 6-

bromo-1-indanone (29.0 g, 0.14 mol) for 4-chloro-1-indanone to give 37.7 g of crude ethyl 2-(6- bromo-1-hydroxy-1-indanyl)acetate. Chromatography on silica gel with dichloromethane: hexanes (8:2) as eluent gave 29.2 g (70%) of a yellow oil ; NMR ($CDCl_3$): d 7.08-7.47 (m, 3H, Ar), 4.24 (overlapping br and q, 3H, CH_2CH_3 and OH), 2.64-3.03 (m, 4H, 2X CH_2's), 2.28 (t, 2H, CH_2), 1.29 (t, 3H, CH_3).

Anal. Calcd. for $C_{13}H_{15}BrO_3$ (mw 299.17): C, 52.19; H, 5.05.
Found: C, 52.24; H, 5.07.

e) Preparation of 2-(6-Bromo-1-hydroxy-1-indanyl)acetic Acid

This compound was prepared in a similar manner to that described for 2-(4-chloro-1-hydroxy-1-indanyl)acetic acid in Example 10g by substituting ethyl 2-(6-bromo-1-hydroxy-1-indanyl)acetate (28.2 g , 0.09 mol) for ethyl 2-(4-chloro--1-hydroxy-1-indanyl) acetate to give a quantitative yield of crude 2-(6-bromo-1-hydroxy-1-indanyl)acetic acid. This material was used immediately without further purification.

f) Preparation of (E)-2-(6-Bromo-1-indanylidene)acetic Acid

This compound was prepared in an analogous manner to (E)-2-(4-chloro-1-indanylidene)acetic acid in Example 10h by substituting 2-(6-bromo-1-hydroxy-1-indanyl)acetic acid (25.9 g, 0.09 mol) for 2-(4-chloro-1-hydroxy-1-indanyl)acetic acid to give 14.7 g of crude (E)-2-(6-bromo-1-indanylidene)acetic acid. Recrystallization of 1.0 g from acetonitrile: 2-propanol mixtures gave 0.65g of (E)-2-(6-bromo-1-indanylidene)acetic acid as a white solid: m.p., 252-253°C; NMR (DMSO-d_6): d 7.35-8.05 (m, 3H, Ar), 6.44 (t, 1H, =CH), 3.15-3.24, 2.95-3.01(2m's, 4H, 2XCH_2); steady-state nOe ($CDCl_3$): irradiation at 6.30 d, observed 19% nOe at 7.75 d.

Anal. Calcd. for $C_{11}H_9BrO_2$ (mw 253.10): C, 52.20; H, 3.58.
Found: C, 52.11; H, 3.62.

g) Preparation of (E)-2-(6-bromo-1-indanylidene)acetyl Chloride

This compound was prepared in a similar manner to (E)-2-(4-chloro-1-indanylidene)acetyl chloride Example in 10i by substituting (E)-2-(6-bromo-1-indanylidene)acetic acid (4.5 g, 0.02 mol) for (E)-2-(4-chloro-1-indanylidene)acetic acid. The resulting solution was concentrated *in vacuo* and the residue used without further purification.

h) Preparation of (E)-2-(6-Bromo-1-indanylidene)acetamide

This compound was prepared in a similar manner to that described for (E)-2-(6-fluoro-1-indanylidene)acetamide Example in 1k by substituting (E)-2-(6-bromo-1-indanylidene)acetyl chloride (4.9 g, 0.02 mol) for (E)-2-(6-fluoro-1-indanylidene)acetyl chloride. Chromatography on silica gel with ethyl acetate: hexanes (1:1) as eluent and trituration of the resulting solid with hexanes gave 2.71 g (60%) of (E)-2-(6-bromo-1-indanylidene)acetamide as a white solid: m.p., 179- 181°C; NMR ($CDCl_3$): d 7.21-7.69 (m, 3H, Ar), 6.25 (s, 1H, =CH), 5.63 (br, 2H, NH_2), 2.98-3.09, 3.33-3.40 (2m's, 4H, $2XCH_2$); steady-state nOe: irradiation at 6.25 d, observed 8% nOe at 7.69d.

Anal. Calcd. for $C_{11}H_{10}BrNO$ (mw 252.11): C, 52.40; H, 4.00; N, 5.58. Found: C, 52.34; H, 4.02; N, 5.56.

EXAMPLE 12

Preparation of (E)-2-(4,6 Difluoro-1-indanylidene)acetamide

a) Preparation of 3-(2, 4-Difluorophenyl)propanoic Acid

A mixture of 2,4-difluorocinnamic acid (30.0g, 0.16 mol, Aldrich) and platinum oxide hydrate (0.5g, EM Scientific) in 95% ethanol (140 mL) was placed on a Parr hydrogenation apparatus. After the appropriate amount of hydrogen was taken up, the catalyst was filtered and the filtrate was concentrated *in vacuo* to give 29.7g (98%) of 3-(2,4-difluorophenyl)propanoic acid as a white solid. Recrystallization of 1.0g from acetonitrile: water mixtures gave 0.61g of 3-(2,4-

difluorophenyl)propanoic acid as a white solid: mp 104-106°C; NMR (DMSO-d_6) ; d 12.2 (br, 1H), 6.98-7.40 (m, 3H), 2.81 (t, 2H), 2.51 (t, 2H).

Anal. Calcd. for $C_9H_8F_2O_2$ (mw186.15): C, 58.06; H, 4.33.
Found : C, 57.94; H, 4.36.

b) Preparation of 4,6-Difluoro-1-indanone

To a mixture of 3-(2,4-difluorophenyl) propanoic acid (28.7g, 0.15 mol) and dimethylformamide (5 drops) at ambient temperature was added dropwise oxalyl chloride (50 mL, Aldrich) . The mixture was stirred at ambient temperature for 18h. The excess oxalyl chloride was removed by distillation *in vacuo* to give 3-(2,4-difluorophenyl)propionyl chloride. A solution of the 3-(2,4-difluorophenyl)propionyl chloride in dichloromethane (300 mL) was added dropwise to a mixture of aluminum chloride (23.4g, 0.18 mol, Aldrich) in dichloromethane (300 mL) at ice bath temperature. After the addition was completed, the mixture was refluxed for 3.5h and allowed to come to ambient temperature overnight. The reaction mixture was poured into ice water (1500 mL), the two phases were separated and the aqueous phase was extracted with dichloromethane. The combined organic phase was washed successively with 0.1N aqueous sodium hydroxide and saturated sodium chloride solution , dried over sodium sulfate and concentrated *in vacuo* to give 21.7g of crude 4,6-difluoro-1-indanone . Chromatography on silica gel with hexanes: dichloromethane (3:1) as eluent gave 10.1g of a light yellow solid. Recrystallization of 0.5g from acetone: water mixtures gave 0.2g of 4,6-difluoro-1-indanone as a white solid: mp 97-99°C; NMR ($CDCl_3$) : d 7.02-7.27 (m, 2H), 3.12 (t, 2H), 2.76 (m, 2H).

Anal. Calcd. for $C_9H_6F_2O$ (mw 168.14): C, 64.29; H , 3.60.
Found: C, 64.18; H , 3.61.

c) Preparation of Ethyl 2-(4,6-Difluoro-1-hydroxy-1-indanyl)acetate

A mixture of 4,6-difluoro-1-indanone (12.6g, 0.08 mol), ethyl bromoacetate (19.0g, 0.11 mol, Aldrich), activated zinc powder (7.5g, 0.11 mol, Aldrich; Org.

Syn., Coll. Vol. 6, 290, 1988) and a few crystals of iodine in diethyl ether:toluene (1:1, 300 mL) was heated at 30-35°C under a nitrogen atmosphere for 24h. A few more crystals of iodine were added, the temperature was adjusted to 40-45°C, and the mixture was kept at that temperature for an additional 24h. The reaction mixture was filtered and concentrated *in vacuo*. The residue was treated with a mixture of diethyl ether (450 mL), concentrated ammonium hydroxide (135 mL) and water (135 mL). The aqueous phase was separated and extracted with diethyl ether. The combined organic phase was washed with saturated aqueous sodium chloride solution, dried over sodium sulfate, filtered and concentrated *in vacuo* to give 22.7g of crude Ethyl 2-(4,6-difluoro-1- hydroxy-1-indanyl)acetate. Chromatography on silica gel with dichloromethane:hexanes (9:1) as eluent gave 12.7g (66%) of a yellow oil ; NMR ($CDCl_3$): d 6.67-6.88 (m, 2H), 4.22 (q, 2H), 3.02 (m, 1H), 2.75 (2m's, 3H), 2.31 (m, 2H), 1.28 (t, 3H).

Anal. Calcd. for $C_{13}H_{14}F_2O_3$ (mw 256.24): C, 60.93; H, 5.51.
Found: C, 60.68; H, 5.50.

d) Preparation of 2-(4,6-difluoro-1-hydroxy-1-indanyl)acetic Acid

A mixture of ethyl 2-(4,6-difluoro-1-hydroxy-1-indanyl)acetate (12.0g , 0.047 mol) and 1.0N sodium hydroxide (48 mL, 0.048 mol, Universal Scientific Supply Co.) in ethanol (75 mL) was stirred for 18h at ambient temperature. The reaction mixture was concentrated *in vacuo*, diluted with water and washed with diethyl ether. The aqueous phase was neutralized with 1.0N hydrochloric acid (48 mL, 0.048 mol, Universal Scientific Supply Co.) and extracted with diethyl ether . The diethyl ether extract was dried over sodium sulfate, filtered and concentrated *in vacuo* to give a quantitative yield of crude 2-(4,6-difluoro-1-hydroxy-1-indanyl)acetic acid. This material was used immediately without further purification.

e) Preparation of (E)-2-(4,6-difluoro-1-indanylidene)acetic Acid

Trifluoroacetic acid (39.9g, 0.35 mol) was added dropwise to a stirred , chilled (ice-methanol bath) mixture of 2-(4,6-difluoro-1-hydroxy-1-indanyl)acetic acid (11.3g, 0.05 mol) in dichloromethane (250 mL). After 35 min. the mixture was

concentrated *in vacuo*. Dichloromethane was added to the residue and the mixture was concentrated *in vacuo* . This procedure was repeated once more to give 6.4g of crude (E)-2-(4,6- difluoro-1-indanylidene) acetic acid. Recrystallization of 0.9g from acetone: water mixtures gave 0.15g of (E)-2-(4,6-difluoro-1-indanylidene) acetic acid as a white solid: mp 238-239°C; NMR (DMSO-d_6): d12.25 (br , 1H), 7.23-7.65 (m, 2H), 6.46 (t, 1H), 3.20-3.28, 2.97-3.20(2m's, 4H); steady-state nOe: irradiation at 6.46 d, observed 21.6% nOe at 7.63 d.

Anal. Calcd. for $C_{11}H_8F_2O_2$ (mw 210.17): C, 62.86; H, 3.84.
Found: C, 62.76; H, 3.86.

f) Preparation of (E)-2-(4,6-difluoro-1-indanylidene)acetyl Chloride

A suspension of (E)-2-(4,6-difluoro-1-indanylidene)acetic Acid (5.49g, 0.026mol) in a mixture of dichloromethane: dimethylformamide (50 mL: 5 drops) was treated with oxalyl chloride (6.6g 0.052 mol, Aldrich) and allowed to stir at ambient temperature for 18h. The resulting solution was concentrated *in vacuo* and the residue used without further purification.

g) Preparation of (E)-2-(4,6-difluoro-1-indanylidene)acetamide

A 30% aqueous ammonium hydroxide solution (1.7 mL, 0.026 mol) was added dropwise to a stirred ,chilled (ice bath) solution of (E)-2-(4,6-difluoro-1-indanylidene)acetyl chloride (2.97g, 0.013 mol) in dichloromethane (50 mL). After 4.5h the mixture was concentrated *in vacuo* and the residue was partitioned between 5% aqueous sodium bicarbonate solution and ethyl acetate. The ethyl acetate solution was washed with saturated aqueous sodium chloride, dried over sodium sulfate, filtered and concentrated *in vacuo*. Chromatography on silica gel with ethyl acetate: hexanes (7:3)as eluent and trituration of the resulting solid with pentane gave 1.63g (60%) of (E)-2-(4,6-difluoro-1-indanylidene)acetamide as a white solid: mp 178-180°C; NMR (DMSO-d_6): d 6.94-7.45 (m, 4H), 6.46 (s, 1H), 2.94-3.00, 3.21-3.27 (2m's, 4H); steady-state nOe: irradiation at 6.46 d, observed 19% nOe at 7.26d.

Anal. Calcd. for $C_{11}H_9F_2NO$ (mw 209.19): C, 63.15; H, 4.34; N, 6.70.
Found: C, 63.07; H, 4.36; N, 6.67.

EXAMPLE 13

Preparation of (E)-N-Cyclopropyl-2-(4,6 difluoro-1-indanylidene)acetamide

This compound was prepared in a similar manner to that described for (E)-2-(4-chloro-1-indanylidene)-N-cyclopropylacetamide in Example 10j by substituting (E)-2-(4,6-difluoro-1-indanylidene) acetyl chloride (2.97 g, 0.013 mol) for (E)-2-(4- chloro- 1-indanylidene)acetyl chloride. Chromatography on silica gel with ethyl acetate: hexanes (1:1) as eluent and trituration of the resulting solid with pentane gave 1.92 g (59%) of (E)-N-cyclopropyl-2-(4,6-difluoro-1-indanylidene)acetamide as a white solid: m.p., 156-158°C; NMR (DMSO-d_6): d 8.08 (d,1H,NH), 7.16-7.26 (m, 2H, Ar), 6.33 (t, 1H, =CH), 2.94-3.00, 3.22-3.30 (2m's, 4H, 2XCH_2), 2.67-2.76 (m, 1H, CH), 0.44-0.47, 0.62-0.68 (2m's, 4H, CH_2's); steady-state nOe ($CDCl_3$): irradiation at 6.10 d, observed 9.8% nOe at 6.98d.

Anal. Calcd. for $C_{14}H_{13}F_2NO$ (mw 249.25): C, 67.46; H, 5.26; N, 5.62.
Found: C, 67.41; H, 5.25; N, 5.58.

EXAMPLE 14

Preparation of (Z)-N-(Cyclopropyl)-2-(2,2-dimethyl-1-indanylidene)acetamide

a) Preparation of 2,2-Dimethyl-1-indanone[a]

To a suspension of NaH (2.7g, 0.11 mol, 80% dispersion in mineral oil, Aldrich) in dimethoxyethane (75 mL) under a nitrogen atmosphere at room temperature was added dropwise 1-indanone (5.0 g, 0.04 mol, Aldrich) in dimethoxyethane (20 mL). After 1h methyl iodide (16.2 g. 0.11 mol, Mallinckrodt) in dimethoxyethane (20 mL) was added in a dropwise fashion over a 0.25h period. The mixture was stirred at room temperature for 18h. Water (120 mL) was added and the mixture was extracted with diethyl ether. The diethyl ether extracts were washed with water, dried ($MgSO_4$), and concentrated to give

7.9 g of crude product. Chromatography on silica gel with dichloromethane as eluent gave 3.3g (54%) of 2,2-dimethyl-1-indanone as an orange oil; NMR (DMSO-d_6) d 7.41-7.73 (m, 4H, Ar), 3.01 (s, 2H, CH_2), 1.14 (s, 6H, 2X CH_3's).

[a] J. Org. Chem., 55 (6), 1874-1881 (1990)

b) Preparation of (Z)-Ethyl 2-(2,2-Dimethyl-1-indanylidene)acetate

To a suspension of NaH (1.4 g, 0.06 mol, 80% dispersion in mineral oil, Aldrich) in dimethoxyethane (50 mL) under a nitrogen atmosphere at room temperature was added dropwise a solution of triethylphosphonoacetate (13.0 g, 0.06 mol, Aldrich) in dimethoxyethane (50 mL). After the evolution of hydrogen had ceased a solution of 2,2-dimethyl-1-indanone (4.6 g, 0.03 mol) in dimethoxy ethane (50 mL) was added dropwise and the mixture was refluxed for 18h. The reaction mixture was poured into 1L of ice water and the aqueous phase was extracted with diethyl ether. The diethyl ether extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give 7.4 g of an orange oil. Chromatography on silica gel with hexanes: dichloromethane (1:1) as eluent gave 1.97 g (29%) of (Z)-ethyl- 2-(2,2-dimethyl-1-indanylidene)acetate as a yellow oil; NMR ($CDCl_3$) d 7.24-8.76 (m, 4H Ar), 5.80 (s, 1H, =CH), 4.24 (q, 2H, $\underline{CH_2}CH_3$), 2.87 (s, 2H, CH_2), 1.34 (t, 3H, $CH_2\underline{CH_3}$), 1.26 (s, 6H, 2X CH_3).

c) Preparation of (Z)-2-(2,2-Dimethyl-1-indanylidene)acetic Acid

A mixture of (Z)-ethyl 2-(2,2-dimethyl-1-indanylidene)acetate (1.97 g, 0.009 mol) and potassium hydroxide (1.0 g, 0.018 mol) in absolute ethanol (20 mL) was refluxed for 2h. The mixture was concentrated *in vacuo* and the residue was dissolved in water. The aqueous phase was chilled in an ice bath and concentrated hydrochloric acid was added until the mixture was acidic. The resulting solid was filtered and washed with water to give 1.6 g (88%) of (Z)-2-(2,2-dimethyl-1-indanylidene)acetic acid as an off-white solid: m.p., 117-121°C. This material was used without further purification.

d) Preparation of (Z)-N-(Cyclopropyl)-2-(2,2-dimethyl-1-indanylidene)acetamide

To a mixture of (Z)-2-(2,2-dimethyl-1-indanylidene)acetic acid (1.6 g, 0.008 mol) and triethylamine (0.8 g, 0.008 mol, Eastman) in tetrahydrofuran (20 mL) at ice bath temperature was added dropwise a solution of ethyl chloroformate (0.9 g, 0.008 mol, Eastman) in tetrahydrofuran (5 mL). After 1.5h the triethylamine hydrochloride was filtered off and the filtrate was added dropwise to a solution of cyclopropylamine (0.5 g, 0.008 mol, Aldrich) in tetrahydrofuran (10 mL) and the mixture was stirred at room temperature for 18h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with 5% aqueous $NaHCO_3$ (2X 50 mL), 1.0N hydrochloric acid (2X 50 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give 1.61g of an off-white solid. Recrystallization from dichloromethane: hexanes mixtures gave 0.88 g (46%) of (Z)-N-(cyclopropyl)-2-(2,2-dimethyl-1-indanylidene)acetamide as a white solid: m.p., 146-148°C; NMR (DMSO-d_6) d 7.15-7.31 and 8.66-8.69 (m's, 4H, Ar), 8.12 (d, 1H, NH), 5.80 (s, 1H, =CH), 2.81 (s, 2H, CH_2), 2.71-2.77 (m, 1H, CH), 1.17 (s, 6H, 2X CH_3's), 0.41-0.47, 0.63-0.69 (2X m's, 4H, 2X CH_2's).

Anal. Calcd. for $C_{16}H_{19}NO$ (mw 241.32): C, 79.63; H, 7.94; N, 5.80.
Found: C, 79.48; H, 7.97; N, 5.83.

EXAMPLE 15

Preparation of (E)-2-(4-Fluoro-1-indanylidene)acetamide

a) Preparation of Ethyl 2-Fluorocinnamate

A solution of 2-fluorocinnamic acid (48.4 g, 0.29 mol, Aldrich) and thionyl chloride (5 mL) in ethanol (650 mL) was heated to reflux for 48h. The mixture was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed successively with a 5% aqueous sodium bicarbonate solution, water and brine, and dried (Na_2SO_4). Filtration and concentration gave 54.25 g (96%) of crude ethyl 2-fluorocinnamate. This material was used without further purification.

b) Preparation of Ethyl 3-(2-fluorophenyl)propionate

A mixture of ethyl 2-fluorocinnamate (29.25 g, 0.176 mol) and platinum oxide hydrate (0.25, EM Scientific) in 95% ethanol (150 mL) was placed on a Parr hydrogenation apparatus and shaken under 2-4 atm at hydrogen pressure. After the appropriate amount of hydrogen was consumed, the catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to give 29.39 g (99%) of crude ethyl 3-(2-fluorophenyl)propionate. This material was used without further purification.

c) Preparation of 3-(2-Fluorophenyl)propionic acid

A mixture of ethyl 3-(2-fluorophenyl)propionate (25.54 g, 0.130 mol) and a 50% aqueous solution of sodium hydroxide (30 mL) in water (130 mL) was refluxed for 2h. After cooling the mixture was washed with diethyl ether (2x100 mL). The aqueous phase was chilled in an ice bath, and the pH was adjusted to 3 with hydrochloric acid . The white precipitate which formed was collected by filtration, washed repeatedly with water, and dried in a vacuum at 60°C for 18 h to give 18.66g (85%) of 3-(2-fluorophenyl)propionic acid as a white solid; m.p., 72-74°C. This material was used without further purification.

d) Preparation of 4-fluoro-1-indanone

To a mixture of 3-(2-fluorophenyl)propionic acid (18.64 g, 0.111 mol) and dimethylformamide (5 drops) at room temperature was added dropwise oxalyl chloride (60 mL). The mixture was stirred at room temperature until gas evolution had ceased. The excess oxalyl chloride was removed by distillation to give 3-(2-fluorophenyl)propionyl chloride. A solution of the 3-(2-fluorophenyl)propionyl chloride in dichloromethane (230 mL) was added dropwise to a mixture of aluminum chloride (16.25 g, 0.12 mol) in dichloromethane (230 mL), and the mixture was refluxed for 3.5h. The reaction mixture was poured into ice water (1200 mL), and the two phases were separated. The dichloromethane phase was washed successively with 0.1N aqueous sodium hydroxide (2x100 mL), water (200 mL), and brine (200 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residual oil

was chromatographed on silica gel eluting with hexane:dichloromethane (9:1) to give 11.0 g of crude 4-fluoro-1-indanone as a yellow solid. Recrystallization from acetone : water mixtures gave 8.02 g (48%) of 4-fluoro-1-indanone as a pale yellow solid: m.p., 71-72°C; NMR (DMSO-d_6): d 7.51 (m, 3H, Ar), 3.13 (t, 2H, CH_2), 2.74 (t, 2H, CH_2).

Anal. Calcd. for C_9H_7FO (mw 150.152): C, 71.99; H, 4.70.
Found: C, 71.86; H, 4.79.

e) Preparation of Ethyl 2-(4-fluoro-1-hydroxy-1-indanyl)acetate

This compound was prepared in an analogous manner to that described in Example 10f for ethyl 2-(4-chloro-1-hydroxy-1-indanyl) acetate substituting 4-fluoro-1-indanone (15.53 g, 0.103 mol) for 4-chloro-1-indanone. Chromatography on silica gel with ethyl acetate:hexanes (19:1) as eluent gave 19.11 g (78%)of ethyl 2-(4-fluoro-1-hydroxy-1-indanyl)acetate which was used without further purification.

f) Preparation of 2-(4-fluoro-1-hydroxy-1-indanyl)acetic Acid

This compound was prepared in a similar manner to that described for 2-(6-chloro-1-hydroxy-1-indanyl)acetic acid in Example 10g by substituting ethyl 2-(4-fluoro-1-hydroxy-1-indanyl)acetate (17.35 g , 0.0728 mol) for ethyl 2-(6-chloro- 1-hydroxy-1-indanyl) acetate to give a quantitative yield of crude 2-(4-fluoro-1-hydroxy-1-indanyl)acetic acid. This material was used immediately without further purification.

g) Preparation of (E)-2-(4-fluoro-1-indanylidene)acetic Acid

This compound was prepared in an analogous manner to (E)-2-(4-chloro-1-indanylidene)acetic acid in Example 10h by substituting 2-(4-fluoro-1-hydroxy-1-indanyl)acetic acid (14.6 g, 0.069 mol) for 2-(4-chloro-1-hydroxy-1-indanyl)acetic acid to give crude (E)-2-(4-fluoro-1-indanylidene)acetic acid. Recrystallization from acetonitrile : 2-propanol mixtures gave 6.85 g (52%) of (E)-2-(4-fluoro-1-indanylidene)acetic acid as a white solid; m.p., 249-251°C;

NMR (DMSO-d_6): d12.15 (br , 1H, COOH), 7.19-7.68 (m, 3H, Ar), 6.41 (t, 1H, =CH), 3.25 and 3.05 (2m, 4H, $ArCH_2CH_2$); steady-state nOe: irradiation at 6.46 d, observed 20.6% nOe at 7.66 d.

Anal. Calcd. for $C_{11}H_9FO_2$ (mw 192.19): C, 68.74; H, 4.72.
Found: C, 68.67; H, 4.74.

h) Preparation of (E)-2-(4-fluoro-1-indanylidene)acetyl Chloride

This compound was prepared in a similar manner to (E)-2-(4-chloro-1-indanylidene)acetyl chloride in Example 10i by substituting (E)-2-(4-fluoro-1-indanylidene)acetic acid (5.77 g, 0.03 mol) for (E)-2-(4-chloro-1-indanylidene)acetic acid. The resulting solution was concentrated *in vacuo*, and the residue was used without further purification.

i) Preparation of (E)-2-(4-fluoro-1-indanylidene)acetamide

An ice cold solution of (E)-2-(4-fluoro-1-indanylidene)acetyl chloride (2.11g, 0.01 mol) in dichloromethane (65 mL) was treated with a 30% aqueous solution of ammonium hydroxide (2.63 ml, 0.02 mol), and the mixture was stirred for 18h. Hexane was added to the mixture, and the solids were collected by filtration to give 1.63 g of crude product. Recrystallization from acetonitrile : water mixtures gave 1.11 g (58%) of (E)-2-(4-fluoro-1-indanylidene)-acetamide as a white solid; m.p., 198-200°C; NMR (DMSO-d_6): d 6.86-7.44 (m, 5H, Ar and NH_2), 6.43 (t, 1H, =CH), 2.99 and 3.21 (2m, 4H, $ArCH_2CH_2$); steady-state nOe: irradiation at 6.43 d, observed 15% nOe at 7.39 d.

Anal. Calcd. for $C_{11}H_{10}FNO$ (mw 191.198): C, 69.10; H, 5.27; N, 7.33.
Found: C, 69.14; H, 5.29; N, 7.31.

EXAMPLE 16

Preparation of (E)-2-N-cyclopropyl-(4-fluoro-1-indanylidene)acetamide

An ice cold solution of (E)-2-(4-fluoro-1-indanylidene)acetyl chloride (2.11 g, 0.010 mol) in dichloromethane (65 mL) was treated with cyclopropylamine (1.39 mL, 0.02 mol), and the mixture was stirred for 18h. Hexane was added to the mixture, and the solids were collected by filtration and washed successively with water and hexane to give 1.22 g of crude product. Recrystallization from acetonitrile : water mixtures gave 0.83 g (36%) of (E)-2-N-cyclopropyl-(4-fluoro-1-indanylidene)acetamide as a white solid; m.p., 121-122°C; NMR (DMSO-d_6): d 8.07 (d, 1H, NH), 7.13-7.37 (m, 3H, Ar), 6.34 (t, 1H, =CH), 2.99 and 3.24 (2 m, 4H, $ArCH_2CH_2$), 2.71 (m, 1H, NCH), 0.66 and 0.43 (m, 4H, CH_2CH_2); steady-state nOe: irradiation at 6.34 d, observed 17% nOe at 7.35 d.

Anal. Calcd. for $C_{14}H_{14}FNO$ (mw 231.314): C, 72.71; H, 6.10; N, 6.06.
Found: C, 72.54; H, 6.15; N, 6.01.

EXAMPLE 17

Preparation of (E)-2-(5-methoxy-1-indanylidene)acetamide

a) Preparation of (E)-Ethyl 2-(5-methoxy-1-indanylidene)acetate

A mixture of 5-methoxy-1-indanone (20.0 g, 0.123 mol, Aldrich), ethyl bromoacetate (31.63 g, 0.19 mol, Aldrich), activated zinc powder (12.0 g, 0.18 mol, Aldrich ; Org. Synth., Coll. Vol. 6, 290, 1988) and a few crystals of iodine in diethyl ether : benzene (1:1, 350 mL) was heated at reflux under nitrogen for 24h. The mixture was concentrated *in vacuo*, and the residue in diethyl ether was stirred vigorously with excess dilute ammonium hydroxide for 2h. The layers were separated, and the aqueous layer was extracted with additional diethyl ether (3x100 mL). The extracts were combined, washed with water, and chromatographed on Silica gel, eluting with ethyl acetate : hexane (1 : 19) to give 18.96 g (64%) of (E)-ethyl 2-(5-methoxy-1-indanylidene)acetate as a clear oil which solidified upon standing at room temperature. This compound was used without further purification. NMR (DMSO-d_6): d 6.80-7.65 (m, 3H, Ar), 6.17 (t, 1H, =CH), 4.15 (q, 2H, CH_2CH_3), 3.80 (s, 3H, OCH_3), 3.18 and 3.02 (2m, 4H, CH_2CH_2), 1.22 (t, 3H, CH_3); steady-state nOe: irradiation at 6.17 d, observed 18% nOe at 7.63 d.

b) Preparation of (E)-2-(5-methoxy-1-indanylidene)acetic Acid

A mixture of (E)-ethyl 2-(5-methoxy-1-indanylidene)acetate (18.53 g, 0.080 mol), 1N sodium hydroxide (70 mL) and absolute ethanol (145 mL) was stirred for 18h at room temperature. Dichloromethane was added to dissolve the solids, and the solution was stirred for 3 days. Additional 1N sodium hydroxide (10 mL) was added, and the solution was stirred for 18h. The mixture was diluted with water (200 mL), concentrated *in vacuo* to 250 mL, and filtered to remove unreacted starting material. The pH of the filtrate was adjusted to 3 with 1 N hydrochloric acid (50 mL). The precipitate which formed was collected by filtration, washed with water and diethyl ether, and dried *in vacuo* to give (10.65 g, 67%) of (E)-2-(5-methoxy-1-indanylidene)acetic acid as a beige solid. This material was used without further purification; NMR (DMSO-d_6): d 12.25 (s, 1H, CO_2H), 6.84-7.64 (m, 3H, Ar), 6.26 (s, 1H, =CH), 3.79 (s, 3H, OCH_3), 3.18 and 2.97 (2m, 4H, CH_2CH_2); steady-state nOe: irradiation at 6.26 d, observed 12% nOe at 7.64 d.

c) Preparation of (E)-2-(5-methoxy-1-indanylidene)acetyl Chloride

A suspension of (E)-2-(5-methoxy-1-indanylidene)acetic acid (10.00 g, 0.049 mol) in dichloromethane (240 mL) was treated with oxalyl chloride (17.46 g, 0.14 mol) and allowed to stir at room temperature for 1.5 h. The resulting solution was concentrated *in vacuo*, and the residue was used without further purification.

d) Preparation of (E)-2-(5-methoxy-1-indanylidene)acetamide

An ice cold solution of (E)-2-(5-methoxy-1-indanylidene)acetyl chloride (3.63 g, 0.016 mol) in dichloromethane (80 mL) was treated with a 30% aqueous solution of ammonium hydroxide (4.3 mL, 0.033 mol), and the mixture was stirred for 18h. The solids were collected by filtration and chromatographed on Silica gel eluting with ethyl acetate : hexane (1 : 9) to give an orange solid. Treatment of the solid in ethyl acetate with decolorizing carbon gave 1.03 g (31%) of (E)-2-(5-methoxy-1-indanylidene)acetamide as a pale orange solid; m.p., 213-216°C; NMR (DMSO-d_6): d 6.95-7.50 (m, 5H, Ar and NH_2), 6.24

(t, 1H, =CH), 3.80 (s, 3H, CH_3), 2.95 and 3.18 (2 m, 4H, $ArCH_2CH_2$); steady-state nOe: irradiation at 6.24 d, observed 11% nOe at 7.50 d.

Anal. Calcd. for $C_{12}H_{13}NO_2$ (mw 203.23): C, 70.91; H, 6.45; N, 6.89.
Found: C, 70.92; H, 6.46; N, 6.88.

EXAMPLE 18

Preparation of (E)-2-(3-phenyl-1-indanylidene)acetamide

a) Preparation of Ethyl 2-(3-phenyl-1-hydroxy-1-indanyl)acetate

This compound was prepared in an analogous manner to that described in Example 10f for ethyl 2-(4-chloro-1-hydroxy-1-indanyl) acetate substituting 3-phenyl-1- indanone (22.15 g, 0.106 mol, Lancaster) for 4-chloro-1-indanone. Chromatography on silica gel with ethyl acetate: hexanes (9:1) as eluent gave 21.61 g (66%) of crude ethyl 2-(3-phenyl-1-hydroxy-1-indanyl)acetate as an oil. Rechromatography of 2.00 g followed by recrystallization from hexane gave 1.03 g of ethyl 2-(3-phenyl-1-hydroxy-1-indanyl)acetate as a white solid: m.p., 53-54°C; NMR (DMSO-d_6): d 6.74-7.45 (m, 9H, Ar), 5.58 (s, 1H, OH), 4.25 (t, 1H, ArCH), 4.08 (q, 2H, CH_2CH_3), 3.07 and 2.12 (2m, 2H, CH_2), 2.71 (s, 2H, CH_2CO_2), 1.12 (t, 3H, CH_3).

Anal. Calcd. for $C_{19}H_{20}O_3$ (mw 296.36): C, 77.00; H, 6.80.
Found: C, 77.12; H, 6.79.

b) Preparation of 2-(3-phenyl-1-hydroxy-1-indanyl)acetic Acid

This compound was prepared in a similar manner to that described for 2-(4-chloro-1-hydroxy-1-indanyl)acetic acid Example 10 g by substituting ethyl 2-(3-phenyl-1-hydroxy-1-indanyl)acetate (19.61 g , 0.067 mol) for ethyl 2-(4-chloro-1-hydroxy-1-indanyl) acetate to give 11.43 g (87%) of crude 2-(3-phenyl-1-hydroxy-1-indanyl)acetic acid as a white solid: m.p., 92-95°C. This material was used immediately without further purification.

c) Preparation of (E)-2-(3-Phenyl-1-indanylidene)acetic Acid

This compound was prepared in an analogous manner to (E)-2-(4-chloro-1-indanylidene)acetic acid in Example 10h by substituting 2-(3-phenyl-1-hydroxy-1-indanyl)acetic acid (15.23 g, 0.057 mol) for 2-(4-chloro-1-hydroxy-1-indanyl) acetic acid to give 9.83 g (69%) of crude (E)-2-(3-phenyl-1-indanylidene) acetic acid as a white solid. Recrystallization of 0.50 g from acetonitrile : 2-propanol mixtures gave 0.31 g of analytically pure (E)-2-(3-phenyl-1-indanylidene)acetic acid as a white solid: m.p., 233°C; NMR (DMSO-d_6): d12.15 (br s, 1H, COOH), 7.10-7.89 (m, 9H, Ar), 6.44 (s, 1H, =CH), 4.56 (m, 1H, ArCH), 3.83 and 3.05 (2m, 2H, CH_2); steady-state nOe: irradiation at 6.44 d, observed 18.5% nOe at 7.79 d.

Anal. Calcd. for $C_{17}H_{14}O_2$ (mw 250.28): C, 81.58; H, 5.63.
Found: C, 81.55; H, 5.69.

d) Preparation of (E)-2-(3-phenyl-1-indanylidene)acetyl Chloride

This compound was prepared in a similar manner to (E)-2-(4-chloro-1-indanylidene)acetyl chloride in Example 10i by substituting (E)-2-(3-phenyl-1-indanylidene)acetic acid (9.33g, 0.037 mol) for (E)-2-(4-chloro-1-indanylidene)acetic acid. The resulting solution was concentrated *in vacuo*, and the residue was used without further purification.

e) Preparation of (E)-2-(3-phenyl-1-indanylidene)acetamide

This compound was prepared in a similar manner to that described for (E)-2-(6-fluoro-1-indanylidene) acetamide in Example 1k by substituting (E)-2-(3-phenyl-1-indanylidene)acetyl chloride (3.33 g, 0.012 mol) for (E)-2-(6-fluoro-1-indanylidene)acetyl chloride. Two recrystallizations from 2-propanol : water mixtures gave 1.43 g (46%) of (E)-2-(3-phenyl-1-indanylidene)acetamide as a white solid; m.p., 219-222°C; NMR (DMSO-d_6): d 6.90-7.66 (m, 11H, Ar and NH_2), 6.47 (s, 1H, =CH), 4.50 (m, 1H, ArCH), 3.78 and 3.16 (2m, 2H, CH_2); steady-state nOe: irradiation at 6.47 d, observed 14% nOe at 7.65 d.

Anal. Calcd. for $C_{17}H_{15}NO$ (mw 249.30): C, 81.90; H, 6.06; N, 5.62.
Found: C, 81.68; H, 6.03; N, 5.56.

EXAMPLE 19

Preparation of (E)-N-Cyclopropyl-2-(3-phenyl-1-indanylidene)acetamide

This compound was prepared in a similar manner to that described for (E)-2-(6-fluoro-1-indanylidene)acetamide in Example 1k by substituting (E)-2-(3-phenyl-1-indanylidene)acetyl chloride (3.33 g, 0.012 mol) for (E)-2-(6-fluoro-1-indanylidene)acetyl chloride and cyclopropylamine (1.72 mL, 0.025 mol) for ammonium hydroxide. Recrystallization from acetonitrile : water mixtures gave 1.83 g (51%) of (E)-N-cyclopropyl-2-(3-phenyl-1-indanylidene)acetamide as a white solid; m.p., 138-139°C; NMR (DMSO-d_6): d 8.08 (d, 1H, NH), 7.06-7.62 (m, 9H, Ar), 6.34 (s, 1H, =CH), 4.51 (m, 1H, ArCH), 3.76 and 3.18 (2m, 2H, CH_2), 2.70 (m, 1H, NCH), 0.53 (m, 4H, CH_2CH_2); steady-state nOe: irradiation at 6.34 d, observed 16% nOe at 8.08 d.

Anal. Calcd. for $C_{20}H_{19}NO$ (mw 289.36): C, 83.01; H, 6.62; N, 4.84.
Found: C, 83.06; H, 6.64; N, 4.90.

EXAMPLE 20

Preparation of (E)-2-N-methyl-(3-Phenyl-1-indanylidene)acetamide

This compound was prepared in a similar manner to that described for (E)-2-(6-fluoro-1-indanylidene)acetamide in Example 1k by substituting (E)-2-(3-phenyl-1-indanylidene)acetyl chloride (3.33 g, 0.012 mol) for (E)-2-(6-fluoro-1-indanylidene)acetyl chloride and a solution of methylamine in benzene (1.8 M, 14.8 mL, 0.025 mol, Aldrich) for ammonium hydroxide. Recrystallization from acetonitrile : water mixtures gave 1.73g (53%) of (E)-2-N-methyl-(3-phenyl-1-indanylidene)acetamide as a white solid; m.p., 170-172°C; NMR (DMSO-d_6): d 7.93 (m, 1H, NH), 7.04-7.65 (m, 9H, Ar), 6.44 (s, 1H, =CH), 4.50 (m, 1H, ArCH), 3.77 and 3.17 (2m, 2H, CH_2), 2.65 (d, 3H, CH_3); steady-state nOe: irradiation at 6.44 d, observed 16% nOe at 7.63 d.

Anal. Calcd. for $C_{18}H_{17}NO$ (mw 263.33): C, 82.09; H, 6.51; N, 5.32.

Found: C, 82.11; H, 6.48; N, 5.38.

EXAMPLE 21

Preparation of (E)-2-(5-fluoro-1-indanylidene)acetamide

a) Preparation of Ethyl 2-(5-fluoro-1-hydroxy-1-indanyl)acetate

This compound was prepared in an analogous manner to that described in Example 10f for ethyl 2-(4-chloro-1-hydroxy-1-indanyl) acetate substituting 5-fluoro-1-indanone (14.77 g, 0.098 mol, Fairfield) for 4-chloro-1-indanone. Chromatography on silica gel with ethyl acetate: hexanes (9:1) as eluent gave 19.56 g (83%) of analytically pure ethyl 2-(5-fluoro-1-hydroxy-1-indanyl)acetate as a pale yellow oil; NMR ($CDCl_3$): d 6.88-7.30 (m, 3H, Ar), 5.30 (s, 1H, OH), 4.20 (q, 2H, $C\underline{H_2}CH_3$), 2.66-3.08 (m, 4H, $2CH_2$), 2.30 (t, 2H, CH_2Ar),1.28 (t, 3H, CH_3).

Anal. Calcd. for $C_{13}H_{15}FO_3$ (mw 238.25): C, 65.54; H, 6.35.
Found: C, 65.39; H, 6.33.

b) Preparation of 2-(5-fluoro-1-hydroxy-1-indanyl)acetic Acid

This compound was prepared in a similar manner to that described for 2-(4-chloro-1-hydroxy-1-indanyl)acetic acid in Example 10g by substituting ethyl 2-(5-fluoro-1-hydroxy-1-indanyl) acetate (19.55 g , 0.082 mol) for ethyl 2-(4-chloro-1-hydroxy-1-indanyl) acetate to give 14.70 g (84%) of crude 2-(5-fluoro-1-hydroxy-1-indanyl) acetic acid as a white solid. This material was used immediately without further purification.

c) Preparation of (E)-2-(5-Fluoro-1-indanylidene)acetic Acid

This compound was prepared in an analogous manner to (E)-2-(4-chloro-1-indanylidene)acetic acid in Example 10h by substituting 2-(5-fluoro-1-hydroxy-1-indanyl)acetic acid(14.70 g, 0.069 mol) for 2-(4-chloro-1-hydroxy-1-indanyl)acetic acid. Recrystallization from acetonitrile : 2-propanol mixtures

gave 9.05g (68%) of (E)-2-(5-fluoro-1-indanylidene)acetic acid as a white solid: m.p., 240-242°C; NMR (DMSO-d_6): d12.15 (s, 1H, COOH), 7.05-7.81 (m, 3H, Ar), 6.30 (s, 1H, =CH), 3.00 and 3.20 (2m, 4H, $2CH_2$); steady-state nOe: irradiation at 6.30 d, observed 19.6% nOe at 7.79 d.

Anal. Calcd. for $C_{11}H_9FO_2$ (mw 192.19): C, 68.74; H, 4.72.
Found: C, 68.56; H, 4.79.

d) Preparation of (E)-2-(5-fluoro-1-indanylidene)acetyl Chloride

This compound was prepared in a similar manner to (E)-2-(4-chloro-1-indanylidene)acetyl chloride in Example 10i by substituting (E)-2-(5-fluoro-1-indanylidene)acetic acid (5.77 g, 0.03 mol) for (E)-2-(4-chloro-1-indanylidene)acetic acid. The resulting solution was concentrated *in vacuo*, and the residue was used without further purification.

e) Preparation of (E)-2-(5-fluoro-1-indanylidene)acetamide

This compound was prepared in a similar manner to that described for (E)-2-(6-fluoro-1-indanylidene)acetamide Example 1k by substituting (E)-2-(5-fluoro-1-indanylidene)acetyl chloride (3.16 g, 0.015 mol) for (E)-2-(6-fluoro-1-indanylidene)acetyl chloride. Recrystallization from acetonitrile : water mixtures gave 1.28 g (44%) of (E)-2-(5-fluoro-1-indanylidene)acetamide as a white solid; m.p., 191-193°C; NMR (DMSO-d_6): d 6.90-7.78 (m, 5H, Ar and NH_2), 6.35 (s, 1H, =CH), 3.21 and 2.99 (2m, 4H, $2CH_2$); steady-state nOe: irradiation at 6.35 d, observed 13% nOe at 7.76 d.

Anal. Calcd. for $C_{11}H_{10}FNO$ (mw 191.198): C, 69.10; H, 5.27; N, 7.33.
Found: C, 69.01; H, 5.23; N, 7.33.

EXAMPLE 22

Preparation of (E)-N-Cyclopropyl-2-(5-fluoro-1-indanylidene)acetamide

A solution of (E)-2-(5-fluoro-1-indanylidene)acetic acid (0.97 g, 0.005 mol), 1-hydroxybenzo-triazole (0.68 g, 0.005 mol, Fluka), cyclopropylamine (0.35 mL, 0.005 mol, Aldrich) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.96 g, 0.005 mol, Sigma), which was added last, in dimethylformamide (15 mL) was stirred at room temperature for 18h, and the solution was concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed successively with a 5% aqueous solution of citric acid (3x50 mL), a saturated aqueous sodium bicarbonate solution (2 x 50 mL) and brine, and dried over sodium sulfate. The solution was concentrated *in vacuo* to give crude (E)-N-cyclopropyl-2-(5-fluoro-1-indanylidene)acetamide. Chromatography on Silica gel eluting with hexane : ethyl acetate (1 : 1) gave 0.52 g (44%) of (E)-N-cyclopropyl-2-(5-fluoro-1-indanylidene)acetamide as a white solid: m.p., 137-138°C; NMR (DMSO-d_6): d 8.00 (d, 1H, NH), 7.10-7.55 (m, 3H, Ar), 6.24 (s, 1H, =CH), 3.21 and 2.98 (2 m, 4H, $ArCH_2CH_2$), 2.70 (m, 1H, NCH), 0.65 and 0.42 (2 m, 4H, CH_2CH_2); steady-state nOe: irradiation at 6.24 d, observed 20% nOe at 7.55 d.

Anal. Calcd. for $C_{14}H_{14}FNO$ (mw 231.314): C, 72.71; H, 6.10; N, 6.06.
Found: C, 72.55; H, 6.13; N, 6.03.

EXAMPLE 23

Preparation of (E)-2-(5-chloro-1-indanylidene)acetamide

a) Preparation of Ethyl 2-(5-chloro-1-hydroxy-1-indanyl)acetate

This compound was prepared in an analogous manner to that described in Example 10f for ethyl 2-(4-chloro-1-hydroxy-1-indanyl) acetate substituting 5-chloro-1-indanone (31.35 g, 0.188 mol, Fairfield) for 4-chloro-1-indanone. Chromatography on silica gel with hexane : dichloromethane (1 : 2) as eluent gave 32.76 g (68%) of ethyl 2-(5-chloro-1-hydroxy-1-indanyl)acetate as a pale yellow oil. This compound was used without further purification.

b) Preparation of 2-(5-Chloro-1-hydroxy-1-indanyl)acetic acid

This compound was prepared in a similar manner to that described for 2-(4-chloro-1-hydroxy-1-indanyl)acetic acid in Example 10 g by substituting ethyl 2-(5-chloro-1-hydroxy-1-indanyl) acetate (32.75 g , 0.129 mol) for ethyl 2-(4-chloro-1-hydroxy-1-indanyl) acetate to give 23.76 g (81%) of crude 2-(5-chloro-1-hydroxy-1-indanyl) acetic acid as a pale yellow solid. This material was used immediately without further purification.

c) Preparation of (E)-2-(5-Chloro-1-indanylidene)acetic Acid

This compound was prepared in an analogous manner to (E)-2-(4-chloro-1-indanylidene)acetic acid in Example 10h by substituting 2-(5-chloro-1-hydroxy-1-indanyl)acetic acid (23.74 g, 0.104 mol) for 2-(4-chloro-1-hydroxy-1-indanyl)acetic acid to give 18.42 g (84%) of crude (E)-2-(5-chloro-1-indanylidene) acetic acid as a white solid. Recrystallization of 2.00 g from acetonitrile : 2-propanol mixtures gave 1.12 g of analytically pure (E)-2-(5-chloro-1-indanylidene) acetic acid as a white solid: m.p., 275-277_C; NMR (DMSO-d_6): d12.05 (s, 1H, COOH), 7.25-7.80 (m, 3H, Ar), 6.35(s, 1H, =CH), 3.00 and 3.20 (2m, 4H, $ArCH_2CH_2$); steady-state nOe: irradiation at 6.35 d, observed 18% nOe at 7.80 d.

Anal. Calcd. for $C_{11}H_9ClO_2$ (mw 208.63): C, 63.32; H, 4.35.
Found: C, 63.27; H, 4.33.

d) Preparation of (E)-2-(5-Chloro-1-indanylidene)acetyl Chloride

This compound was prepared in a similar manner to (E)-2-(4-chloro-1-indanylidene)acetyl chloride in Example 10i by substituting (E)-2-(5-chloro-1-indanylidene)acetic acid (2.11 g, 0.010 mol) for (E)-2-(4-chloro-1-indanylidene)acetic acid. The resulting solution was concentrated *in vacuo*, and the residue was used without further purification.

e) Preparation of (E)-2-(5-chloro-1-indanylidene)acetamide

This compound was prepared in a similar manner to that described for (E)-2-(6-fluoro-1-indanylidene)acetamide Example 1k by substituting (E)-2-(5-chloro-1-indanylidene)acetyl chloride (2.29 g, 0.010 mol) for (E)-2-(6-fluoro-1-indanylidene)acetyl chloride. Recrystallization from ethyl acetate : hexane mixtures gave 1.03g (50%) of (E)-2-(5-chloro-1-indanylidene)acetamide as a white solid; m.p., 222-224°C; NMR (DMSO-d_6): d 6.86-7.61 (m, 5H, Ar and NH_2), 6.40 (m, 1H, =CH), 3.20 and 2.86 (2m, 4H, $ArCH_2CH_2$); steady-state nOe: irradiation at 6.40 d, observed 22% nOe at 7.61 d.

Anal. Calcd. for $C_{11}H_{10}ClNO$ (mw 207.71): C, 63.60; H, 4.85; N, 6.77.
Found: C, 63.53; H, 4.89; N, 6.73.

EXAMPLE 24

Preparation of (E)-N-Cyclopropyl-2-(5-chloro-1-indanylidene)acetamide

This compound was prepared in a similar manner to that described for (E)-2-N-cyclopropyl-(5-fluoro-1-indanylidene)acetamide in Example 22 by substituting (E)-2-(5-chloro-1-indanylidene) acetic acid (5.00 g, 0.024 mol) for (E)-2-(5-fluoro-1-indanylidene) acetic acid. Chromatography on Silica gel eluting with hexane : ethyl acetate (3 : 1) gave 3.52 g (60%) of (E)-N-cyclopropyl-2-(5-chloro-1-indanylidene)acetamide as a white solid; m.p., 150-152°C; NMR (DMSO-d_6): d 8.05 (d, 1H, NH), 7.31-7.54 (m, 3H, Ar), 6.30 (s, 1H, =CH), 3.21 and 2.99 (2m, 4H, $ArCH_2CH_2$), 2.71 (m, 1H, NCH), 0.67 and 0.44 (2 m, 4H, CH2CH2); steady-state nOe: irradiation at 6.30 d, observed 20% nOe at 7.54 d.

Anal. Calcd. for $C_{14}H_{14}ClNO$ (mw 247.71): C, 67.88; H, 5.70; N, 5.66.
Found: C, 67.76; H, 5.75; N, 5.61.

EXAMPLE 25

Preparation of (E)-2-N-methyl-(5-Chloro-1-indanylidene)acetamide

This compound was prepared in a similar manner to that described for (E)-2-N-cyclopropyl-(5-fluoro-1-indanylidene)acetamide in Example 22 by substituting (E)-2-(5-chloro-1-indanylidene) acetic acid (5.00 g, 0.024 mol) for (E)-2-(5-fluoro-1-indanylidene) acetic acid and methylamine hydrochloride (1.62 g, 0.024 mol, Aldrich) for cyclopropylamine and with the addition of N-methylmorpholine (2.6 mL, 0.024 mol) to neutralize the methylamine hydrochloride. Recrystallization from ethyl acetate : ethanol mixtures gave 1.01 g (48%) of (E)-2-N-methyl-(5-chloro-1-indanylidene)acetamide as a white solid; m.p., 182-185°C; NMR (DMSO-d_6): d 7.89 (m, 1H, NH), 7.30-7.55 (m, 3H, Ar), 6.36 (s, 1H, =CH), 3.19 and 2.99 (2m, 4H, $ArCH_2CH_2$), 2.65 (d, 3H, CH_3); steady-state nOe: irradiation at 6.36 d, observed 16% nOe at 7.63 d.

Anal. Calcd. for $C_{12}H_{12}ClNO$ (mw 221.71): C, 65.00; H, 5.46; N, 6.34.
Found: C, 64.96; H, 5.48; N, 6.29.

EXAMPLE 26

Alternative Preparation of (E)-2-(6-Fluoro-1-indanylidene)acetamide

To an ice-cold stirred suspension of NaH (60% dispersion in mineral oil, 12.41 g, 60.25 mmoles, Aldrich) in tetrahydrofuran (30 ml) with 15-crown-5 (3.96 g, 17.98 mmoles, Aldrich) was added under N_2, diethyl carbamoylmethylphosphonate (11.7 g, 59.97 mmoles, K&K-ICN) and 6-fluoro-1-indanone (9.0 g, 59.96 mmol) respectively in tetrahydrofuran (80 ml). The mixture was allowed to warm to room temperature overnight. The mixture was poured into 200 ice-cold water and extracted with three 600 ml portions of diethyl ether. One organic phase was washed successively with 200 ml portions of aqueous sodium bisulfite (10%) and a saturated sodium chloride solution. The organic phase was dried over potassium carbonate, filtered, spin evaporated *in vacuo* and coevaporated with 200 ml dichloromethane to yield a tacky solid residue. The residue was chromatographed on Silica Gel 60 using ethyl

acetate:hexane (2:1). Fractions containing (E)-2-(6-fluoro-1-indanylidene)acetamide were combined and spin evaporated *in vacuo* to give 2.38 g of a yellow solid. Dilution of a dichloromethane solution of the crude material with hexane gave 2.16 g (18.8%) of (E)-2-(6-fluoro-1-indanylidene)acetamide, m.p., 178-182° C; NMR (DMSO-d_6); d 7.4-7.1 (m, 4H, Ar and NH), 6.88 (br s, 1H, NH), 6.37 (t, 1H, J=2.54 Hz, =CH), 3.22-3.14 (m, 2H, CH_2), 2.95-2.89 (m, 2H, CH_2); steady-state nOe: irradiation at d 6.37, significant observed nOe at d 7.33-7.28.

Anal. Calcd for $C_{11}H_{10}FNO$: C, 69.10; H, 5.27; N, 7.33
Found: C, 69.01; H, 5.29; N, 7.28.

EXAMPLE 27

Preparation of (E)-2-(6-Chloro-1-indanylidene)acetamide

a) Preparation of 3-(4-Chlorophenyl)propionic acid

This compound was prepared in an analogous manner to that of Example 1 with the replacement of 4-fluorocinnamic acid in Example 1a with 4-chlorocinnamic acid (27.43 g, 0.15 mol, Aldrich) and a change in solvent to ethyl acetate:glacial acetic acid (6:1) (175 ml). Filtration and spin evaporation *in vacuo* gave 29.45 g of a white solid. The solid was recrystallized from hexanes-dichloromethane to give 26.88 g (91%) of 3-(4-chlorophenyl)propionic acid, m.p., 118-122°C; NMR (DMSO-d_6): d 12.12 (br s, 1H, OH), 7.33-7.21 (m, 4H, Ar), 2.82-2.74 (m, 2H, CH2) 2.54-2.47 (m, 2H, CH_2).

b) Preparation of 3-(4-Chlorophenyl)propionyl chloride

This compound was prepared in an analogous manner to that of Example 1b with the replacement of 3-(4-fluorophenyl)propionic acid in Example 1b with 3-(4-chlorophenyl)propionic acid (24.88 g, 0.135 mol). Fractional distillation under aspirator pressure gave 24.9 g (91%) of 3-(4-chlorophenyl)propionyl chloride as a pale yellow liquid, b.p. 145-148°C at 9-10 Torr, NMR (DMSO-d_6): d 7.33-7.26 (m, 4H, Ar), 2.78-2.74 (m, 2H, $CH_2C(O)$), 2.54-2.47 (m, 2H, Ar CH_2).

c) Preparation of 6-Chloro-1-indanone

This compound was prepared in an analogous manner to that of Example 1c with the replacement of 3-(4-fluorophenyl)propionyl chloride in Example 1C with 3-(4-chlorophenyl)propionyl chloride. The resulting organic layer was filtered through glass wool and spin evaporated *in vacuo* to give 21.07 g, (98%) of 6-chloro-1-indanone, m.p. 73-78°C; NMR (DMSO-d_6): d 7.68-7.58 (m, 3H, Ar), 3.1-3.04 (m, 2H, CH_2), 2.69-2.63 (m, 2H, CH_2).

d) Preparation of (E)-2-(6-Chloro-1-indanylidene)acetamide

To a stirred suspension of NaH (60% dispersion in mineral oil, 3.11 g, 77.75 mmoles, Aldrich) in dimethyl sulfoxide (225 ml) at room temperature under N_2 was added diethyl carbamoylmethylphosphonate (14.97 g, 76.71 mmoles, K&K-ICN). The reaction was slightly exothermic. To the resulting solution was added 6-chloro-1-indanone in dimethyl sulfoxide (175 ml). The reaction was stirred overnight at room temperature. The reaction was poured into ice-cold water (800 ml) and extracted with four 500 ml portions dichloromethane. The organic phase was washed with eight 500 ml portions of water, filtered and spin evaporated *in vacuo*. This residue was chromatographed on Silica Gel 60 using ethyl acetate:hexane (2:1). Fractions containing (E)-6-chloro-2-(1-indanylidene)acetamide were combined and spin evaporated *in vacuo* to give 3.5 g of a yellow solid. Dilution of a dichloromethane solution of the crude material with hexane gave 2.63 g (17%) of (E)-chloro-2-(1-indanylidene)acetamide, m.p., 174-176°C; NMR (DMSO-d_6): d 7.54 (s, 1H, Ar), 7.37 (s, 2H, Ar), 7.24-6.88 (br s, 2H, NH_2), 6.42 (t, 1H, J=2.6 Hz, =CH), 3.20-3.11 (m, 2H, CH_2), 2.98-2.90 (m, 2H, CH_2); steady-state nOe: irradiation at d 6.42, significant nOe observed at 7.54.

Anal. Calcd. for $C_{11}H_{10}ClNO$ 7/200 CH_2Cl_2: C, 62.93; H, 4.82; N, 6.65; Cl, 18.01.
Found: C, 62.92; H, 4.81; N, 6.66; Cl, 18.08.

EXAMPLE 28

Preparation of (E)-2-(6-Methyl-1-indanylidene)acetamide

a) Preparation of 3-(4-Methylphenyl)propionic acid

This compound was prepared in an analogous manner to that of Example 1 with the replacement of 4-fluorocinnamic acid in Example 1a with 4-methylcinnamic acid (Aldrich) and the replacement of palladium on carbon (5%) with platinum oxide (Englehard). Filtration and spin evaporation *in vacuo* gave 28.98 g of a white solid. The solid was recrystallized from hexanes-methanol to give 22 g, (87%) of 3-(4-methylphenyl)propionic acid, m.p. 112-115°C; NMR (DMSO-d_6): d 12.07 (br s, 1H, COOH), 7.07 (s, 4H, Ar) 2.75 (t, 2H, J=7.5 Hz, CH_2CO), 2.51-2.43 (m, 2H, CH_2Ar), 2.23 (s, 3H, $ArCH_3$).

b) Preparation of 3-(4-Methylphenyl)propionyl chloride

This compound was prepared in an analogous manner to that of Example 1b with the replacement of 3-(4-fluorophenyl)propionic acid in Example 1b with 3-(4-methylphenyl)propionic acid. Fractional distillation under aspirator pressure gave 19.5 g (75%) of 3-(4-methylphenyl)propionyl chloride, b.p.=121-124°C at 9 Torr, NMR (DMSO-d_6): d 7.07 (s, 4H, Ar), 2.78-2.71 (m, 2H, CH_2CO), 2.47-2.43 (m, 2H, CH_2Ar), 2.23 (s, 3H, CH_3).

c) Preparation of 6-Methyl-1-indanone

This compound was prepared in an analogous manner to that of Example 1c with the replacement of 3-(4-fluorophenyl)propionyl chloride in Example 1C with 3-(4-methylphenyl)propionyl chloride. The organic layer was filtered through glass wool and spin evaporated *in vacuo* to a liquid which solidified to give 8.56 g (99.7%) of 6-methyl-1-indanone, m.p., 53-58°C; NMR (DMSO-d_6): d 7.43 (d, 3H, Ar), 3.06-3.0 (m, 2H, CH_2) 2.62-2.56 (m, 2H, CH_2), 2.35 (s, 3H, CH_3).

d) Preparation of (E)-2-(6-Methyl-1-indanylidene)acetamide

This compound was prepared in an analogous manner to Example 27d with the replacement of 6-chloro-1-indanone in Example 27d with 6-methyl-1-indanone. The crude product was chromatographed using C_{18} cartridges in a Waters Associates Prep 500 system with 0.1N aqueous ammonium acetate:methanol / 1:1. Fractions containing (E)-2-(6-methyl-1-indanylidene)acetamide were combined and evaporated to a small volume. This solution was extracted with four 500 ml portions of dichloromethane. The organic layer was washed with water (300 ml), filtered and spin evaporated *in vacuo* to give 2.1 g of an off-white solid residue. Dilution of a solution of the crude product in dichloromethane with hexanes gave 1.47 g (21.2%) of (E)-2-(6-methyl-1-indanylidene)acetamide, m.p. 189-193°C; NMR (DMSO-d_6): d 7.33-7.13 (m, 4H, Ar + NH), 6.77 (br s, 1H, NH), 6.35 (t, 1H, J=2.56 Hz, =CH), 3.19-3.11 (m, 2H, CH_2), 2.93-2.87 (M, 2H, CH_2), 2.31 (s, 1H, CH_3).

Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48
Found: C, 76.92; H, 7.01; N, 7.46.

EXAMPLE 29

Preparation of (E)-2-(6-Chloro-1-indanylidene)-N-methylacetamide

a) Preparation of 2-Chloro-N-methylacetamide

Chloroacetyl chloride (45 g, 398 mmoles, Aldrich) was added dropwise to aqueous methylamine (40%, 30.7 g, 1.31 mol) in 300 ml of water originally at -20C_ with stirring. The temperature of the reaction was raised to 0C_ and stirring was continued until the reaction was no longer exothermic. The resulting solution was acidified with concentrated hydrochloric acid (7 ml) and extracted with dichloromethane (4x250 ml). The organic layer was washed with H_2O (250 ml) and spin evaporated *in vacuo* to give a clear liquid residue. This residue was diluted with pentane (300 ml) and spin evaporated *in vacuo* to give 15.62 g (37%) of 2-chloro-N-methylacetamide as a white solid; NMR (DMSO-d_6): d 8.13 (br s, 1H, NH), 4.02 (s, 2H, CH_2), 2.60 (d, 3H, J=4.69 Hz, CH_3)

b) Preparation of ((N-Methylcarbamoyl)methylene)triphenylphosphonium chloride.

A solution of 2-chloro-N-methylacetamide (15.6 g, 145 mmoles) and triphenylphosphine (55.2 g, 210 mmole, Aldrich) in tetrahydrofuran (200 ml) was refluxed for 72 hours under N_2. The reaction solution was cooled and diluted with diethyl ether (250 ml). The resulting suspension was stirred at ambient temperature for 0.5 hours. Filtration gave 39.95 g (74%) of ((N-methylcarbamoyl)methylene)triphenylphosphonium chloride as a white solid; m.p. 255-267°C; NMR (DMSO-d_6): d (br m, 1H, NH), 7.91-7.7 (m, 15H, Ar), 5.00 (d, 2H, J=15.0 Hz, PCH_2), 2.48 (d, 3H, J=3.69 Hz, $HNCH_3$).

c) Preparation of (E)-2-(6-Chloro-1-indanylidene)-N-methylacetamide

To an ice-cold stirred suspension of sodium hydride (60% dispersion in mineral oil, 3.87 g, 96.8 mmoles, Aldrich) in dimethoxyethane (250 ml, Kodak) was added ((N-methylcarbamoyl)methylene)triphenylphosphonium chloride in dimethoxyethane (50 ml). After 0.5 hours, 6-chloro-1-indanone (8.03 g, 43.2 mmoles) was added, and the reaction was refluxed overnight. The reaction mixture was poured into a stirring mixture of dichloromethane:water (1:1) (800 ml). The aqueous phase was extracted with dichloromethane (3x500 ml) and the organic extracts were combined and washed with H_2O (2x250 ml), passed through a silica gel pad, and spin evaporated *in vacuo*. The residue was dissolved in dichloromethane (50 ml) and diluted with hexanes (50 ml) to give crude (E)-2-(6-chloro-1-indanylidene)-N-methylacetamide (4.6 g). An analytical sample was obtained by dissolving the crude sample in absolute ethanol (500 ml), passing the solution through a silica gel pad and spin evaporating the filtrates *in vacuo* to give 4.48 g (42%) of (E)-(6-chloro-1-indanylidene)-N-methylacetamide; m.p., 220-225°C, NMR (DMSO-d_6): d 7.8-7.78 (br m, 1H, NH), 7.53 (s, 1H, Ar), 7.36 (s, 2H, Ar), 6.38 (t, 1H, J=2.54 Hz, =CH), 3.22-2.9 (m, 4H, CH_2CH_2), 2.65 (d, 3H, CH_3).

Anal. Calcd. for $C_{12}H_{12}ClNO$: C, 65.02; H, 5.46; N, 6.32; Cl, 15.99.
Found: C, 64.93; H, 5.47; N, 6.27; Cl, 16.07.

EXAMPLE 30

Preparation of (Z)-2-(6-Chloro-1-indanylidene)-N-methylacetamide

The filtrate from Example 29c was concentrated and chromatographed on Silica Gel 60 using ethyl acetate-hexane (1:1) as eluent. Fractions containing only (Z)-6-chloro-2-(1-indanylidene)-N-methylacetamide were combined and spin evaporated *in vacuo* to give 0.41 g (4%) of (Z)-6-chloro-2-(1-indanylidene)-N-methylacetamide, m.p., 110-114_C; NMR (DMSO-d_6): d 8.98 (s, 1H, Ar), 8.02-8.00 (br m, 1H, NH), 7.34 (s, 2H, Ar), 5.99 (s, 1H, =CH), 2.86 (br s, 4H, CH_2CH_2), 2.64 (d, 3H, J=4.53 Hz, CH_3).

Anal. Calcd for $C_{12}H_{12}ClNO$: C, 65.02; H, 5.46; N, 6.32; Cl, 15.99.
Found: C, 65.07; H, 5.51; N, 6.30; Cl, 15.96.

EXAMPLE 31

Preparation of (E)-N-cyclopropyl-2-(6-Chloro-1-indanylidene)acetamide

a) Preparation of 2-Chloro-N-cyclopropyl-acetamide

Cyclopropylamine (21.5 g, 376 mmole Aldrich) was added dropwise over one hour to a solution of chloroacetyl chloride (21.3 g, 188 mmole, Aldrich) in diethyl ether (300 ml) at 0_C. The reaction was diluted with chloroform (300 ml) and cyclopropylamine hydrochloride was removed by filtration. The filtrate was evaporated *in vacuo* to give an off-white solid residue. This residue was dissolved in dichloromethane (500 mL), washed with H_2O (175 ml), filtered through glass wool and spin evaporated *in vacuo* to give 24.4 g (97%) of 2-chloro-N-cyclopropylacetamide, m.p. 74-78°C; NMR (DMSO-d_6): d 8.27 (br s, 1H, NH), 3.95 (s, 2H, CH_2), 2.65-2.59 (m, 1H, CH), 0.67-0.37 (m, 4H, CH_2CH_2).

b) Preparation of [(N-Cyclopropylcarbamoyl)methylene]triphenylphosphonium chloride.

This compound was prepared in an analogous manner to that of Example 29 with the replacement of 2-chloro-N-methylacetamide in Example 29b with 2-chloro-N-cyclopropylacetamide. The refluxing time was shortened to 48 hours. Product was collected from the ethereal suspension and further washed with diethyl ether (300 ml) to give 48.5 g,(68%) of (N-cyclopropylcarbamolyl)-methylene)triphenylphosphonium chloride as an off-white solid, m.p. 245-249_C, NMR (DMSO-d_6): d 8.88 (br s, 1H, NH), 7.90-7.77 (m, 15H, Ar), 4.9 (d, 2H, J=14.83 Hz, PCH_2), 2.51 (br s, 1H, CH), 0.56-0.19 (m, 4H, CH_2CH_2).

c) Preparation of (E)-N-cyclopropyl-2-(6-Chloro-1-indanylidene)acetamide

This compound was prepared in an analogous manner as Example 29 with the replacement of [(N-methylcarbamoyl)methylene]triphenylphosphonium chloride in Example 29c with [(N-cyclopropyl-carbamoyl)methylene]triphenylphosponium chloride. After the addition of 6-chloro-1-indanone, the reaction was refluxed 48 hours. The combined organic phases were flushed through a silica gel pad and spin evaporated *in vacuo*. This residue was chromatographed on Silica Gel 60 using ethyl acetate-hexane (1:1) as eluent. Fractions containing (E)-6-chloro-N-cyclopropyl-2-(1-indanylidene)acetamide were combined and spin evaporated *in vacuo* to give 5.75 g of an off-white solid. Dilution of a dichloromethane solution of the crude material with hexanes gave 3.7 g (39%) of (E)-N-cyclopropyl-2-(6-chloro-1-indanylidene)acetamide, m.p., 165-168°C; NMR (DMSO-d_6): d 8.01-7.99 (m, 1H, NH), 7.50 (s, 1H, Ar), 7.39-7.38 (m, 2H, Ar), 6.33 (t, 1H, J=2.48 Hz, =CH), 3.23-2.94 (m, 4H, CH_2CH_2), 2.8-2.65 (m, 1H, CH), 0.67-0.4 (m, 4H, CH_2CH_2).

Anal. Calcd for $C_{14}H_{14}ClNO$: C, 67.88; H, 5.70; N, 5.65; Cl, 14.31.
Found: C, 67.87; H, 5.75; N, 5.59; Cl, 14.27.

EXAMPLE 32

Preparation of (Z)-2-(6-Chloro-1-indanylidene)-N-cyclopropylacetamide

Method A

Other fractions obtained from the chromatography of the residue from Example 31c contained only (Z)-2-(6-chloro-1-indanylidene)-N-cyclopropylacetamide. These fractions were combined and spin evaporated *in vacuo* to give 0.375 g (4%) of (Z)-2-(6-chloro-1-indanylidene)-N-cyclopropylacetamide as a white solid, m.p., 147-152°C; NMR (DMSO-d_6): d 9.98 (s, 1H, Ar), 8.15-8.13 (m, 1H, NH), 7.33 (s, 2H, Ar), 5.94 (br s, 1H, =CH), 2.93-2.8 (m, 4H, CH_2CH_2), 2.75-2.65 (m, 1H, CH), 0.70-0.37 (m, 4H, CH_2CH_2)

Method B

a) Preparation of Bis(2,2,2-trifluoroethyl) (cyclopropylcarbamoyl)methyl)phosphonate

A solution of 2-chloro-N-cyclopropylacetamide (12.2 g, 91.5 mmole) in tetrahydrofuran (75 ml) was added dropwise to a cold (0C°), stirring mixture of bis(2,2,2-trifluoroethyl) phosphonate (25 g, 102 mmole, Aldrich) and potassium hexamethyldisilazane (101.37 g, 102 mmol, 20% by weight in tetrahydrofuran, Callery) in tetrahydrofuran (50 ml) under N_2. The reaction was stirred at 0C_ for 1 hour and warmed to ambient temperature for 0.5 hours. The reaction was poured into a mixture of saturated ammonium chloride solution-dichloromethane (1:1) (800 ml). The aqueous phase was extracted with dichloromethane (2 x 350 ml). The organic layers were combined and washed with water (2 x 250 ml), filtered with silicone treated filter paper (Whatman 1PS Phase Separator) and spin evaporated *in vacuo*. The residue was chromatographed on Silica Gel 60 using ethyl acetate-hexane (1:1). Fractions containing bis(2,2,2-trifluoroethyl) ((cyclopropylcarbamoyl)methyl)phosphonate were combined and spin evaporated *in vacuo* to give 15 g (51.3%) of bis(2,2,2-trifluoroethyl) (cyclopropylcarbamoyl)methyl)phosphonate, m.p. 89-92°C; NMR (DMSO-d_6):

d 8.24 (br s, 1H, NH), 4.73-4.62 (m, 4H, $2CF_3CH_2O$), 3.13 (d, 2H, J=21.5 Hz, $P(O)CH_2$), 2.64-2.58 (m, 1H, CH), 0.67-0.35 (m, 4H, CH_2CH_2).

Anal. Calcd. for $C_9H_{12}F_6NO_4P$: C, 31.5; H, 3.53, N, 4.08.
Found: C, 31.59; H, 3.56; N, 4.06.

b) Preparation of (Z)-2-(6-Chloro-1-indanylidene)-N-cyclopropylacetamide

A solution of 6-chloro-1-indanone (4.86 g, 29 mmoles) in tetrahydrofuran (160 ml) was added to a cold (-60C°), stirring solution of potassium hexamethyldisilazane (24 g, 24 mmole, 20% by weight in tetrahydrofuran), bis (2,2,2-trifluoroethyl)((cyclo-propylcarbamoyl)methyl) phosphonate (10 g, 29 mmole) and 18-crown-6 (7.7 g, 29 mmoles, Aldrich) in tetrahydrofuran (200 ml). After 1.5 hours at -60°C, the reaction was poured into a mixture of saturated aqueous ammonium chloride-dichloromethane (1:2). The aqueous phase was extracted with dichloromethane (2x500 ml). The organic phases were combined and washed with H_2O (350 ml), filtered through glass wool and spin evaporated *in vacuo* a light beige semi-solid residue. Crude (Z)-2-(6-chloro-1-indanylidene)-N-cyclopropylacetamide (3.4 g) was collected from the partial dissolution of the beige residue. An analytical sample was obtained by dilution of a solution of this residue in dichloromethane with hexanes to give 3.1 g (43%) of (Z)-2-(6-chloro-1-indanylidene)-N-cyclopropylacetamide as a white solid, m.p. 151-153°C, which was structurally consistent to the sample prepared using Method A as determined by NMR data.

EXAMPLE 33

Preparation of (E)-2-(1-Indanylidene)acetamide

To a stirred solution of diethyl carbamoylmethylphosphonate (14.6 g, 75 mmoles, K&K-ICN) in tetrahydrofuran (200 ml) at 15°C under a nitrogen atmosphere was added n-butyl lithium (1.6 M in hexanes, 14.6 ml, 75 mmoles, Aldrich) dropwise. The solution was stirred for 20 min. A solution of 1-indanone (9.9 g, 75 mmoles, Aldrich) in tetrahydrofuran (20 ml) was added. The solution was stirred for 1 hour at room temperature, 1 hour at 50°C, and 18 hours at room temperature. The solution was

poured into ice water (600 ml) and extracted with dichloromethane (700 ml in 3 portions). The dichloromethane extracts were combined and washed with a small amount of water. The dichloromethane layer was concentrated by spin evaporation *in vacuo*. The residue was chromatographed on Silica Gel 60, eluting with methanol:dichloromethane (1:19). The fractions containing (E)-2-(1-indanylidene)acetamide were combined, concentrated, and the residue was recrystallized from dichloromethane/hexanes to give 2.132 g (16%) of (E)-2-(1-indanylidene)acetamide; m. p., 151-152°C; NMR (DMSO-d_6): d 7.54 (d, 1 H, J = 6.8 Hz, Ar), 7.4 - 7.2 (m, 4 H, Ar and NH), 6.80 (br s, 1 H, NH), 6.37 (t, 1 H, J = 2.5 Hz, =CH), 3.2 - 3.10 (m, 2 H, CH2), 3.00-2.92 (m, 2 H, CH_2).

Anal: Calcd. for $C_{11}H_{14}NO$: C, 76.28; H, 6.40; N, 8.09.
Found: C, 76.19; H, 6.44; N, 8.01.

EXAMPLE 34

Preparation of (E)-N-cyclopropyl-2-(1-indanylidene)acetamide

a) Preparation of Diethyl((cyclopropylcarbamoyl)methyl)phosphonate

2-Chloro-N-cyclopropylacetamide (20 g, 0.15 moles) was added in portions with stirring to triethyl phosphite (28 g, 0.17 moles, Aldrich) at 110°C. The solution was then heated to 155°C for 30 minutes , cooled to 125°C, and the volatiles were removed by distillation under aspirator vacuum (15 mm Hg) at this temperature. The residual oil was stirred with pentane (200 mL) while cooling in an ice bath to induce crystallization. Filtration gave 5.2 g (14%) of diethyl((cyclopropylcarbamoyl)methyl)phosphonate as white crystals; m.p. 51-56°C. The liquor was concentrated and cooled to give 25.3 g (71%) of a second crop; m.p. 50-56°C. Recrystallization from dichloromethane/hexanes gave the analytical sample, m.p. 55-57°C.

Anal. Calcd. for $C_9H_{18}NO_4P$: C, 45.96; H, 7.71; N, 5.95.
Found. C, 45.85; H, 7.76; N, 5.90.

b) Preparation of (E)-N-cyclopropyl-2-(1-indanylidene)acetamide

This compound was prepared in an analogous manner to that in Example 33 with the replacement of diethyl carbamoylmethylphosphonate with diethyl (cyclopropyl-carbamoyl)methylphosphonate. The reaction of diethyl ((cyclopropylcarbamoyl)methyl-phosphonate with n-butyl lithium was conducted initially at -50°C, followed by stirring at -20°C for 10 min. The solution was cooled to -45°C prior to the addition of the solution of 1-indanone in tetrahydrofuran. The stirring at room temperature in the final reaction period was done for 2 hours instead of 18 hours. The chromatography column was eluted with ethyl acetate:hexanes (1:2) instead of methanol:dichloromethane. The chromatography fraction containing (E)-N-cyclopropyl-2-(1-indanylidene)acetamide were combined, concentrated, and the residue was recrystallized from dichloromethane/hexanes to give 3.422 g (32%) of (E)-N-cyclopropyl-2-(1-indanylidene)acetamide; m.p., 115-116°C; NMR (DMSO-d_6): d 7.96 (br d, 1 H, NH), 7.50 (d, 1 H, J = 7.4 Hz, Ar), 7.45-7.21 (m, 3 H, Ar), 6.29 (br s, 1 H, =CH), 3.25-3.10 (m, 2 H, CH_2), 3.05-2.85 (m, 2 H, CH_2), 2.78-2.60 (m, 1 H, CH), 0.70 - 0.55 (m, 2 H, CH_2), 0.48 - 0.37 (m, 2 H, CH2); steady state nOe: irradiation at d 6.29, significant nOe at d 7.50 and d 7.96.

Anal: Calcd. for $C_{14}H_{15}NO$: C, 78.84; H, 7.04; N, 6.57.
Found: C, 78.74; H, 7.14; N, 6.52.

EXAMPLE 35

Preparation of (Z)-2-(1-Indanylidene)acetamide

Other fractions from the chromatographic purification of a reaction performed according to the procedure described in Example 33 except on a 0.114 mmole scale contained the (Z)-2-(1-indanylidene)acetamide. These were combined, concentrated, and the residue was recrystallized from dichloromethane:hexanes to give 0.112 g (6 %) of (Z)-2-(1-indanylidene)acetamide; m.p., 127°C (dec.); NMR (DMSO-d_6): d 8.76 (d, 1 H, Ar), 7.39 (br s, 1 H, NH), 7.3 - 7.1 (m, 3 H, Ar), 6.86 (br s, 1 H, NH), 5.96 (s, 1 H, =CH), 3.00 - 2.85 (m, 2 H, CH_2), 2.85 - 2.70 (m, 2 H, CH_2).

Anal: Calcd. for $C_{11}H_{11}NO \cdot 1/20\ C_6H_{14}\ \ 3/25\ H_2O$: C, 75.53; H, 6.70; N, 7.80.
Found: C, 75.66; H, 6.30; N, 7.40.

EXAMPLE 36

Preparation of (E)-N-cyclopropyl-2-(1,2,3,4-tetrahydro-1-naphthylidene)acetamide

This compound was prepared in an analogous manner to that of Example 27d with the replacement of 6-chloro-1-indanone and diethyl carbamoylmethylphosphonate with 1-tetralone and diethyl (cyclopropylcarbamoyl)methylphosphonate. Recrystallization from ethyl acetate : hexane mixtures of the residue obtained from the chromatography gave a crude product. A final recrystallization from ethyl acetate gave 5.9 g (13%) of (E)-N-cyclopropyl-2-(1,2,3,4-tetrahydro-1-naphthylidene)acetamide; m.p., 136.0-136.5°C; NMR (DMSO-d_6): d 8.01 (br d, 1H, J=4.2 Hz, NH), 7.58-7.53 (m, 1H, aromatic H), 7.30-7.10 (m, 3H, aromatic H), 6.31 (s, 1H, =CH), 3.09 (t, 2H, J=6 Hz, CH_2), 2.80-2.60 (m, 3H, CH_2 and NCH), 1.71 (quintet, 2H, J=6 Hz, CH_2), 0.66-0.61 (m, 2H, 2 x cyclopropyl CH), 0.44-0.38 (m, 2H, 2 x cyclopropyl CH); steady-state nOe: irradiation at d 6.31, significant nOe observed at d 8.14 and d 7.55.

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16.
Found: C, 79.12; H, 7.59; N, 6.13.

EXAMPLE 37

Preparation of (E)-N-Cyclopropyl-2-(5-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide

a) Preparation of 2-(2-Fluorophenyl)ethylbromide

To a mixture of aqueous hydrobromic acid (48%, 360 mL) and concentrated sulfuric acid (103.6 mL) at room temperature was added dropwise 2-(2-fluorophenyl)ethanol (250 g, 1.78 mol, Aldrich). The reaction mixture was refluxed for 7 h, poured onto 600 ml of ice and the mixture was extracted with diethyl ether. The diethyl ether extracts were washed successively with saturated sodium carbonate and brine. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give 359.9 g (99%) of 2-(2-fluorophenyl)-ethylbromide as a brown oil. This product was used without further purification. NMR ($CDCl_3$: d 7.6-6.9 (m, 4H, ArH), 3.6 (t, 2H, CH_2), 3.2 (t, 2H, CH_2).

b) Preparation of Diethyl 2-(2-(2-fluorophenyl)ethylmalonate

To absolute ethanol (1.5 L) at room temperature under a nitrogen atmosphere was added sodium metal (61.1 g, 2.66 mol) in small pieces over several hours. After stirring for 24 h at room temperature, the mixture was warmed to 40°C, and dimethyl malonate (525.4 g, 3.28 mol) was added dropwise followed by 2-(2-fluorophenyl)ethylbromide (359.9 g, 1.77 mol). The mixture was refluxed for 8 h. The crude material was purified by vacuum distillation at 85-130°C and 0.60 mm Hg to give 312.6 g (62%) of diethyl 2-(2-(2-fluorophenyl)ethyl)malonate as a clear oil. NMR ($CDCL_3$): d 7.6-7.0 (m, 4H, ArH), 4.2 (q, 4H, 2X CH_2) 3.4 (t, 1H, CH), 2.6 (q, 2H, CH_2), 2.2 (t, 2H, CH_2), 1.2 (t, 6H, 2X CH_3).

c) Preparation of 2-[2-(2-Fluorophenyl)ethyl]malonic acid

A mixture of diethyl 2-(2-(2-fluorophenyl)ethyl)malonate (381.8 g, 1.35 mol) and potassium hydroxide (227.3 g, 4.1 mol) and potassium hydroxide (227.3 g, 4.1 mol) in ethanol (500 mL) and water (500 mL) was refluxed for 24 h. The

reaction mixture was placed in an ice bath and hydrochloric acid (6N, 442 mL) was added. The ethanol was removed *in vacuo* and the aqueous residue was extracted with diethyl ether. The extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give 309.3 g (100%) of 2-(2-(2-fluorophenyl)ethyl)malonic acid as an off-white solid. This product was used without further purification. NMR (DMSO-d_6): d 6.8-6.2 (m, 4H, ArH), 2.4 (t, 1H, CH), 1.9 (q, 2H, CH_2), 1.3 (t, 2H, CH_2). IR (KBr) 1691 CM^{-1}.

d) Preparation of 4-(2-Fluorophenyl)butyric acid

The 2-(2-(2-fluorophenyl)ethyl)malonic acid (147 g, 0.65 mol) was heated in an oil bath at 170°C for 2.5 h. On cooling, 4-(2-fluorophenyl)butyric acid (117.3 g, 99%) crystallized as a tan solid. This product was used without further purification. NMR ($CDCl_3$): d 7.6-7.0 (m, 4H, ArH), 3.0-1.8 (m, 6H, 3X CH_2). IR (neat) 1709 cm^{-1}.

e) Preparation of 5-Fluorotetralone

A mixture of 4-(2-fluorophenyl)butyric acid (100 g, 0.55 mol) and thionyl chloride (418.8 g, 3.51 mol) was refluxed for 3 h. The excess thionyl chloride was removed *in vacuo* to give 110.1 g (100%) of 4-(2-fluorophenyl)butyryl chloride.

To the 4-(2-fluorophenyl)butyryl chloride in carbon disulfide (1.0 L) at -78°C was added aluminum chloride (93.2 g, 0.7 mol) portionwise over a 30 min period. The mixture was warmed to room temperature for 30 min, then refluxed for 2 h. The reaction mixture was poured into a mixture of ice (500 mL) and HCl (6N, 500 mL). The carbon disulfide layer was separated, washed with saturated sodium bicarbonate and extracted with ethyl acetate. The aqueous phase was extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give 84.2 g (93%) of 5-fluorotetralone as a tan solid. NMR ($CDCl_3$): d 7.7 (m, 1H, ArH), 7.1 (m, 2H, ArH), 2.9 (t, 2H, CH_2), 2.6 (t, 2H, CH_2), 2.1 (q, 2H, CH_2).

f) Preparation of (E)-N-Cyclopropyl-2-(5-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide

This compound was prepared in an analogous manner to Example 27d with the replacement of 6-chloro-1-indanone and diethyl carbamoylmethylphosphonate with 5-fluoro-1-tetralone (13.7 g, 0.08 mol) and diethyl(cyclopropylcarbamoyl)methylphosphonate (21.5 g, 0.09 mol). Chromatography on Silica gel using 35% to 50% ethyl acetate:hexanes as eluent followed by trituration of the resulting solid with pentane at room temperature gave 5.07 g (25%) of (E)-N-cyclopropyl-2-(5-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide, m.p., 148-149_C; NMR (DMSO-d_6): d 8.11 (br d, 1H), 7.43 (dd, 1H), 7.10-7.31 (m, 2H), 6.39 (s, 1H), 3.05-3.13 (m,2H), 2.65-2.78 (m, 3H), 1.71-1.83 (m, 2H), 0.62- 0.72 (m, 2H), 0.38-0.47 (m, 2H); steady-state nOe: irradiation at 6.39 d, observed 24% nOe at 7.4d.

Anal. Calcd. for $C_{15}H_{16}FNO$ (mw 245.30): C, 73.45; H, 6.57; N, 5.71.
Found: C, 73.38; H, 6.58; N, 5.68.

EXAMPLE 38

Preparation of
(E)-N-Cyclopropyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide

a) Preparation of 3-(4-fluorobenzoyl)propionic acid

A mixture of fluorobenzene (104.4 g, 1.09 mol, Aldrich) and succinic anhydride (93.5 g, 0.93 mol) in 1,2-dichlorobenzene (530 mL) was heated to 50°C. Aluminum chloride (245 g, 1.84 mol) was added portionwise keeping the temperature below 60°C. After 4 h at 60_C followed by 5 h at 80°C, the reaction mixture was poured into a mixture of concentrated HCl (200 mL) and ice water (2 L). The organic layer was separated and the aqueous phase was extracted with dichloromethane. The combined organic phase was dried and concentrated *in vacuo*. The residue was poured into hexane (2 L) and the resulting solid was filtered and washed with pentane to give 164.1 g (89%) of 3-

(4-fluorobenzoyl)propionic acid as a white solid. m.p., 102-104.5°C (lit *J. Org. Chem.* 26, 2667, 1961; m.p., 102.5-103.5°C)

b) Preparation of 4-(4-fluorophenyl)butyric acid

A mixture of 3-(4-fluorobenzoyl)propanoic acid (42.3 g, 0.22 mol) and 10% Palladium on carbon (3 g) in acetic acid (250 mL) was hydrogenated at 50 psi and 25°C for 6 h. The mixture was filtered and concentrated *in vacuo*. The residue was distilled at 0.02 mm Hg and the product crystallized to give 4-(4-fluorophenyl)butyric acid as a white solid (97%). m.p., 44-46.2°C (lit. *J. Am. Chem. Soc.* 89, 386, 1967; m.p., 45.5-46.5°C).

c) Preparation of 7-Fluoro-1-tetralone

A mixture of 4-(4-fluorophenyl)butyric acid (68.2 g, 0.37 mol) and thionyl chloride (155 g, 1.3 mol) was refluxed for 1.25 h. The mixture was concentrated *in vacuo* to give 75.3 g (100%) of 4-(4-fluorophenyl)butyryl chloride)

To a mixture of aluminum chloride (66 g, 0.50 mol) in carbon disulfide (600 mL) was added dropwise a solution of 4-(4-fluorophenyl)butyryl chloride (75.3 g, 0.37 mole) in carbon disulfide (260 mL) keeping the internal temperature below 10_C. After refluxing for 0.5 h, the reaction mixture was poured into a mixture of concentrated HCl (50 mL) and ice water (800 mL). The mixture was filtered and extracted with diethyl ether. The diethyl ether extracts were dried and concentrated *in vacuo* to give crude 7-fluoro-1-tetralone. Vacuum distillation gave pure 7-fluoro-1-tetralone b.p., 83°C at 0.3 mm Hg which solidified to a white solid (94%). m.p., 62-64°C (lit, *J. Am. Chem. Soc.*, 89, 386, 1967; m.p., 63.5-65.0°C)

d) Preparation of (E)-N-Cyclopropyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide

This compound was prepared in an analogous manner to Example 27d with the replacement of 6-chloro-1-indanone and diethyl carbamoylmethylphosphonate with 7-fluoro-1-tetralone (7.76 g, 0.05 mol) and

diethyl(cyclopropylcarbamoyl)methylphosphonate (11.1 g, 0.05 mol). Chromatography on Silica gel using ethyl acetate:hexanes (1:2) as eluent gave 4.38 g (37%) of (E)-N-Cyclopropyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene) acetamide, m.p., 122.8-123.3°C; NMR (DMSO-d_6): d 8.00 (d, J=4.0 Hz,1H), 7.32 (dd, J= 11.2 Hz,1H), 7.04-7.23 (m, 2H), 6.33 (s, 1H), 3.06 (m,2H), 2.69 (m, 3H), 1.70 (m, 2H), 0.66 (m, 2H), 0.40 (m, 2H); steady-state nOe: irradiation at 6.39 d, observed significant nOe at 7.32 d.

Anal. Calcd. for $C_{15}H_{16}FNO$ (mw 245.30): C, 73.45; H, 6.57; N, 5.71. Found: C, 73.38; H, 6.64; N, 5.67.

EXAMPLE 39

Preparation of 2-(1-Indanyl)acetamide

a) Preparation of 2-(1H-inden-3-yl)acetamide

A mixture of 1-indanone (23.0 g, 0.17 mol, Aldrich) and diethyl carbamoylmethyl-phosphonate (33.9 g, 0.17 mol, K&K-ICN) in anhydrous tetrahydrofuran (300 mL) was added under a nitrogen atmosphere to a stirred, cold (ice bath) suspension of a 50% (w/w) oil dispersion of sodium hydride (8.35 g, 0.17 mol,) and 15-crown-5 (1.04 g, 0.005 mol, Aldrich) in anhydrous tetrahydrofuran (700 mL) at a rate that maintained the temperature below 4°C. The mixture was stirred at ambient temperature for 18h and subsequently diluted with water (2L). The aqueous phase was extracted with diethyl ether (4L total). The combined extracts were concentrated *in vacuo* to give 24.1 g of crude product as an isomeric mixture. Chromatography on silica gel using ethyl acetate:hexanes (2:1) as eluant gave 10.7g of 2-(1H-inden-3-yl)acetamide. NMR analysis indicated a small amount of (E)-2-(1-indanylidene)acetamide (Example 33). This isomeric mixture was used without further purification.

b) Preparation of 2-(1-Indanyl)acetamide

A solution of 2-(1H-inden-3-yl)acetamide (4.4 g, 25.4 mmol) in 95% ethanol (125 mL) with 10% palladium on carbon (0.12 g, Aldrich) was hydrogenated on

a Parr apparatus. The catalyst was filtered off and the solution was concentrated *in vacuo*. The residue was recrystallized from ethyl acetate:hexanes (2:7) to give 3.83 g, (86%) of 2-(1-indanyl) acetamide; m.p. 92-96°; NMR (DMSO-d_6) d 7.33 (br s, 1H, NH), 7.21- 7.08 (m, 4H, Ar), 6.82 (br s, 1H, NH), 3.50-3.38 (m, 1H, ArC<u>H</u>), 2.92-2.71 (m, 2H, Ar C<u>H</u>$_2$) , 2.58-2.47 (m, 1H, 1/2 C(O)C<u>H</u>$_2$), 2.28-2.09 (m, 2H, 1/2 C(O)C<u>H</u>$_2$ and 1/2 $CH_2C\underline{H}_2$), 1.71-1.57 (m, 1H, 1/2 $CH_2C\underline{H}_2$).

Anal. Calcd. for $C_{11}H_{13}NO$ (mw 175.23): C, 75.40; H, 7.48; N, 7.99. Found: C, 75.31; H, 7.51; N, 8.00.

EXAMPLE 40

Preparation of (*E*)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetic acid

a) Preparation of Ethyl 2-(7-Fluoro-1,2,3,4-tetrahydro-1-hydroxy-1-naphthyl)acetate

Ethyl acetate (5.4 g, 61 mmol) was added dropwise to a stirred, chilled (dry ice-acetone bath) solution of 1M lithium bis(trimethylsilyl)amide in tetrahydrofuran (61 mL, 0.061 mol, Aldrich) under nitrogen. After 15 min, a solution of 7-fluoro-1-tetralone (10.0 g, 61 mmol) in tetrahydrofuran (25 mL) was added dropwise and the resulting mixture was stirred for 1h (dry ice-acetone bath). A 1N solution of hydrochloric acid (61 mL) was added and the mixture was allowed to warm to room temperature. The organic phase was separated, dried over anhydrous sodium sulfate, filtered and concentrated to a pale yellow oil (15.0 g, 100%). An analytical sample was obtained by chromatographing a 1.5 g portion on Silica Gel 60 using dichloromethane-hexanes (1:1) as eluent. The fractions containing only ethyl 2-(7-fluoro-1,2,3,4-tetrahydro-1-hydroxy-1-naphthyl)acetate were combined and concentrated *in vacuo* to give 1.2 g (80%) of a colorless oil; NMR (DMSO-d_6): d 6.93-7.31 (m, 3H, Ar), 5.28 (s, 1H, OH), 3.98 (m, 2H, CH_2OOC), 2.60-2.87 (m, 4H, CH_2CO, CH_2), 2.12-2.28 (m, 1H, CH), 1.78-1.86 (m, 3H, CH, CH_2), 1.09 (t, 3H, CH_3).

Anal. Calcd. for $C_{14}H_{17}FO_3$: C, 66.65; H, 6.79.

Found: C, 66.64; H, 6.82.

b) Preparation of Ethyl 2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthyl)acetate

Trifluoroacetic acid (20 mL) was added to a stirred, chilled (ice-methanol bath) solution of crude ethyl 2-(7-fluoro-1,2,3,4-tetrahydro-1-hydroxy-1-naphthyl)acetate (10.0 g, 35.8 mmol) in dichloromethane (180 mL). After 4h, the mixture was concentrated *in vacuo* to a clear oil (8.3 g, 100%); NMR (DMSO-d_6): d 6.94-7.65 (m, 3H, Ar), 6.45 (br s, 0.2 H, =CH */E*), 6.10 (t, 0.8H, =CH/*endo*), 4.08 (m, 2H, CH_2OOC), 3.67, 3.51 (s's, 2.2H, H_2O, CH_2/*endo*), 3.08, 2.70, 2.25, 1.77 (m's, 4.4H, 5xCH_2), 1.26 (t, 0.6H, CH_3 */E*), 1.17 (t, 2.4H, CH_3 */endo*).

Anal. Calcd. for $C_{14}H_{15}FO_2 \cdot 0.3\ H_2O$: C, 70.16; H, 6.56.
Found: C, 70.03; H, 6.34.

A portion of the above mixture of *E* and *endo* esters (2.3g, 10 mmol), sodium hypophosphite hydrate (1.8g, 20 mmol, Aldrich) and 10% palladium on carbon (0.2 g) in 75% aq ethanol (20 mL) was heated to reflux for 2h. The mixture was filtered through celite and the filtrate was concentrated *in vacuo*. The residue in dichloromethane was washed successively with water (100 mL) and brine (50 mL), dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo* and chromatographed on Silica Gel 60 using ethyl acetate-hexane (3:97) as eluent. The fractions containing only ethyl 2-(7-fluoro-1,2,3,4-tetrahydro- 1-naphthyl)acetate were combined and concentrated *in vacuo* to give 1.9g (78%) of a pale yellow oil; NMR (DMSO-d_6): d 6.89-7.14 (m, 3H, Ar), 4.11 (q, 2H, CH_2OOC), 3.15-3.27 (m, 1H, CH), 2.44-2.82 (m, 4H, 2xCH_2), 1.52-1.90 (m, 4H, 2xCH_2), 1.20 (t, 3H, CH_3).

Anal. Calcd. for $C_{14}H_{17}FO_2$: C, 71.17; H, 7.25.
Found: C, 71.25; H, 7.26.

c) Preparation of Ethyl 2-Bromo-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthyl)acetate

To a stirred, chilled (dry ice-acetone bath) solution of diisopropylamine (0.3 mL, 1.9 mmol, Aldrich) in tetrahydrofuran (3 mL) under nitrogen was successively added 2.5N *n*-butyl lithium in hexane (0.8 mL, Aldrich), chlorotrimethylsilane (0.2 mL, 1.8 mmol, Aldrich) and ethyl 2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthyl)acetate (236 mg, 1.0 mmol). The resulting clear solution was stirred for 1h, treated with N-bromosuccinimide (180 mg, 1.0 mmol, Aldrich) and stirred for an additional 0.5h before the dry ice-acetone bath was removed. The reddish cloudy solution was stirred for 2h at room temperature, treated with dilute aq hydrochloric acid (4 meq) and extracted with diethyl ether (30 mL). The ether layer was dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo* and chromatographed on Silica Gel 60 using dichloromethane-hexane (1:9) as eluent. Fractions containing only ethyl 2-bromo-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthyl)acetate as a 1:4 isomeric mixture were combined and concentrated *in vacuo* to a clear oil (171mg, 54%); NMR (DMSO-d_6): d 7.00-7.18 (m, 3H, Ar), 5.20 (d, J=6.2 Hz, 0.8H, BrCHCO), 5.17 (d, J=6.2 Hz, 0.2H, BrCHCO), 4.19 (q, 1.6H, CH_2OOC), 4.14 (q, 0.4H, CH_2OOC), 3.49 (m, 1H, ArCH), 2.69 (m, 2H, $ArCH_2$), 1.81-1.97 (m, 3H, CH, CH_2), 1.61-1.67 (m, 1H, CH), 1.21 (t, 2.4H, CH_3), 1.07 (t, 0.6H, CH_3).

Anal. Calcd. for $C_{14}H_{16}BrFO_2$: C, 53.35; H, 5.12; Br, 25.35.
Found: C, 53.44; H, 5.09; Br, 25.32.

d) Preparation of (*E*)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetic Acid

A mixture of ethyl 2-bromo-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthyl)acetate (2.2 g, 7.0 mmol), 1N potassium *tert*-butoxide in tetrahydrofuran (14mL, Aldrich) and *tert*-butanol (140 mL) was stirred for 5h at room temperature. The resulting suspension was concentrated *in vacuo*, diluted with water (200 mL) and washed with diethyl ether. The aqueous layer was acidified by adding 1N hydrochloric acid (14 mL) and extracted with diethyl ether. The ether extract was dried over anhydrous sodium sulfate, filtered, concentrated *in vacuo* and chromatographed on Silica Gel 60 using ethyl acetate-hexane (1:1) as eluent. The fractions containing only (*E*)-2-(7-fluoro-1,2,3,4-tetrahydro-1-

naphthylidene)acetic acid were combined and concentrated *in vacuo* to give a white solid (0.8g, 55%); NMR (DMSO-d_6): d 12.22 (br s, 1H, COOH), 7.57 (d of d, J_m=2.6 Hz, J_o=11.0 Hz, 1H, Ar), 7.12-7.28 (m, 2H, Ar), 6.36 (s, 1H, =CH, *E*), 3.04 (t, 2H, $ArCH_2$), 2.74 (t, 2H, CH_2), 1.74 (m, 2H, CH_2); steady-state nOe: irradiation at 6.36, observed 25% nOe at 7.57.

Anal Calcd. for $C_{12}H_{11}FO_2$: C, 69.89; H, 5.38.
Found: C, 69.88; H, 5.38.

Example 41

Preparation of (E)-2-(6-Fluoro-3,3-dimethyl-1-indanylidene)acetamide

a) Preparation of Diethyl Isopropylidenemalonate.

Diethyl isopropylidenemalonate was prepared according to the procedure of E. L. Eliel, R. O. Hutchins, and Sr. M. Knoeber, Organic Synthesis Coll. Vol. VI, 442, 1988, with following modifications. A mixture of acetone (54 g, 0.93 mol, Mallinckrodt), diethyl malonate (100 g, 0.62 mol, Aldrich), acetic anhydride (80 g, 0.78 mol, Mallinckrodt), and zinc chloride (12.5 g, 0.78 mol, Aldrich) was refluxed (90°C oil bath) for 18 h while protected from moisture. The reaction solution was diluted with dichloromethane (500 ml) and washed with cold water (3 x 50 ml). The aqueous washes were combined and extracted with dichloromethane. All dichloromethane layers were combined and concentrated by spin evaporation *in vacuo*. The residual oil was distilled under vacuum and the fractions boiling at 102 - 138°C at 12 Torr were combined with the pot residue and heated for 6 h with a 200°C oil bath. The dark oil was redistilled to give 40.1 g (32%) of diethyl isopropylidenemalonate as a clear oil: b.p., 110 - 115° C/12 mmHg: NMR (DMSO-d_6): d 4.19 (q, 4 H, J = 7.2 Hz, OCH_2), 2.03 (s, 6 H, $=C(CH_3)_2$), 2.25 (t, 6 H, J = 7.2 Hz, CH_2).

b) Preparation of Diethyl 2-(2-(4-Fluorophenyl)-2-methylethyl)malonate

A mixture of 4-fluorophenylmagnesium bromide (82 ml of a 2 N solution in ethyl ether, 0.164 mol, Aldrich) and copper(I) iodide (0.310 mg, 1.63 mmol, Aldrich) was stirred for 15 min at -10° C while blanketed with a nitrogen atmosphere. To this mixture was added a solution of diethyl isopropylidenemalonate (29.6 g, 0.148 mol) in anhydrous diethyl ether (250 ml) in a thin stream with rapid stirring. The resulting solution was stirred at -10° C for 2 h, at 25° C for 30 min and then poured with rapid stirring into 0.5 kg of crushed ice containing 30 ml of 12 N hydrochloric acid. The layers were separated and the aqueous layer was extracted with ethyl ether (3 x 400 ml). All ether layers were combined and washed with deionized water (2 x 25 ml), saturated aqueous sodium bicarbonate (25 ml), and deionized water (25 ml). The etheral layer was concentrated by spin evaporation *in vacuo* and the residue was distilled to give 25.9g (59%) of diethyl 2-(2-(4-fluorophenyl)-2-methylethyl)malonate as a clear oil (b.p., 140-145° C/0.01 mmHg): NMR (DMSO-d_6): d 7.55 - 7.40 (m, 2 H , Ar), 7.11 (t, 2 H, J = 8.8 Hz, Ar), 3.99 (q, 4 H, J = 7.0 Hz, 2 x CH_2), 3.89 (s, 1 H, CH), 1.50 (s, 6 H, 2 x CH3), 1.04 (t, 6 H, J = 0.7 Hz, 2 x CH_3).

Anal: Calcd. for $C_{16}H_{21}FO_2$ (mw 296.339): C, 64.85; H, 7.14.
Found: C, 64.82; H, 7.21.

c) Preparation of 3-(4-Fluorophenyl)-3-methylbutyric Acid

A solution of diethyl 2-(2-(4-fluorophenyl)-2-methylethyl)malonate (41 g, 0.138 mol) and potassium hydroxide 85% (18.25 g, 0.277 mol, Mallinkrodt) in 250 ml of deionized water was vigorously refluxed for 4 hours with an 150° C oil bath. After cooling with an ice bath, the solution was neutralized with 18 N sulfuric acid (23 ml, 0.414 mol, Mallinkrodt), and extracted with dichloromethane (4 x 250 ml). The dichloromethane extracts were combined, washed with water, and concentrated by spin evaporation *in vacuo*. The residue was slurried with water and the crystalline product was collected by filtration to give 24.3 g (90 %) of 3-(4-fluorophenyl)-3-methylbutyric acid, m.p., 45 - 57_ C: NMR (DMSO-d_6): d

11.9 (br s, 1 H, CO_2H), 7.50 - 7.45 (m, 2 H, Ar), 7.09 (t, 2 H, J = 9.0 Hz, Ar), 2.57 (s, 2 H, CH_2), 1.36 (s, 6 H, $C(CH_3)_2$).

d) Preparation of 3-(4-Fluorophenyl)-3-methylbutyryl Chloride

Oxalyl chloride (46.5 g, 0.367 mol, Aldrich) was added to a solution of 3-(4-fluorophenyl)-3-methylbutyric acid (24 g, 0.122 mol) at -10°C while protected from moisture by a nitrogen atmosphere. The stirring mixture was allowed to warm to 25°C and was stirred for 2 h. Fractional distillation gave 26.6 g (76%) of 3-(4-fluorophenyl)-3-methylbutyryl chloride as a clear oil, b.p., 132 - 138°C: NMR (DMSO-d_6): d 7.40 - 7.20 (m, 2 H, Ar), 7.02 (t, 2 H, J = 8.7 Hz, Ar), 3.27 (s, 2 H, CH_2), 1.47 (s, 6 H, $C(CH_3)_2$).

e) Preparation of 6-Fluoro-3,3-dimethyl-1-indanone.

A solution of 3-(4-fluorophenyl)-3-methylbutyryl chloride (19.0 g, 0.0815 mol) in dichloromethane (100 ml) was added dropwise over 2.5 h to a stirring mixture of aluminum chloride (13.57 g, 0.102 mol, Aldrich) in dichloromethane (200 ml) while protected from moisture by a nitrogen atmosphere. After stirring 18 h at 25°C, the reaction solution was poured over ice (400 g) and the resulting solution was extracted with dichloromethane (2 x 200 ml). The dichloromethane layers were combined, washed with deionized water (50 ml), and concentrated by spin evaporation *in vacuo*. The residue was dissolved in ethyl acetate and washed through a pad of silica gel. The pad was washed with additional ethyl acetate. Removal of the volatiles from the combined washes by spin evaporation *in vacuo* gave 15.2 g (99%) of 6-fluoro-3,3-dimethyl-1-indanone as a light yellow oil which crystallized on standing, m.p., 57 - 62°C: NMR (DMSO-d_6): d 7.75 (dd, 1 H, J_{HF} = 4.7 Hz, J_{HH} = 8.5 Hz, Ar), 7.55 (ddd, 1 H,J_{HF} = 8.6 Hz, J_{HH} = 8.4 and 2.6 Hz, Ar), 7.32 (dd, 1 H,J_{HF} = 7.7 Hz, J_{HH} = 2.6 Hz, Ar), 2.61 (s, 2 H, CH_2), 1.37 (s, 6 H, $C(CH_3)_2$).

Anal. Calcd. for $C_{11}H_{11}FO$ (mw 187.206): C, 74.14; H, 6.22.
Found: C, 74.02; H, 6.23.

f) Preparation of Ethyl 2-(6-Fluoro-1-hydroxy-3,3-dimethyl-1-indanyl)acetate.

This compound was prepared in a similar manner to ethyl 2-(6-fluoro-1-hydroxy-1-indanyl)acetate in Example 1d by substituting 6-fluoro-3,3-dimethyl-1-indanone for 6-fluoro-1-indanone and preparing the activated zinc by heating zinc dust (Aldrich) with iodine (Aldrich) without solvent. Removal of the volatiles from the workup solution by spin evaporation *in vacuo* gave 16.2 g (82%) of ethyl 2-(6-fluoro-1-hydroxy-3,3-dimethyl-1-indanyl)acetate as a light yellow oil: NMR (DMSO-d_6): d 7.30 - 7.18 (m, 1 H, Ar), 7.16-7.00 (m, 2 H, Ar), 5.22 (br s, 1 H, OH), 4.10 - 3.90 (m, 2 H, OCH_2), 2.89 (d, 1 H, J = 14.0 Hz, C(O)C<u>H</u>H), 2.69 (d, 1 H, J = 14.0 Hz, C(O)CH<u>H</u>), 2.42 (d, 1 H, J = 14.0 Hz, C(OH)C<u>H</u>H), 2.07 (d, 1 H, J = 14.0 Hz, C(OH)CH<u>H</u>), 1.29 (s, 3 H, CH_3), 1.23 (s, 3 H, CH_3), 1.12 (t, 3 H, J = 7.1 Hz, CH_3).

Anal. Calcd. for $C_{15}H_{19}FO_3$ (mw 266.312): C, 67.65; H, 7.19;.
Found: C, 67.72; H, 7.19.

g) Preparation of (E)-2-(6-Fluoro-3,3-dimethyl-1-indanylidene)acetic Acid.

A solution of ethyl 2-(6-fluoro-1-hydroxy-3,3-dimethyl-1-indanyl)acetate (16 g, 0.0601 mol) in 1N sodium hydroxide (60.1 ml, 0.0601 mol) and ethanol (60 ml) was stirred for 20 h. The solution was concentrated to a small volume by spin evaporation *in vacuo*, diluted with deionized water (100 ml), and acidified to pH 3 with 1N hydrochloric acid This biphasic solution was extracted with dichloromethane (2 x 100 ml). The extracts were combined, washed with deionized water (20 ml), dried with magnesium sulfate (Mallinckrodt), and concentrated by spin evaporation *in vacuo*. The residue was dissolved in dichloromethane (30 ml), cooled to 0°C, and diluted with 400 ml of a cold (0° C) solution of trifluoroacetic acid (45 g, Aldrich) in dichloromethane (400 ml). After 15 min, the solution was concentrated by spin evaporation *in vacuo* and the residue was crystallized by adding hexanes to give 9.23 g (70%) of (E)-2-(6-fluoro-3,3-dimethyl-1-indanylidene)acetic acid as a white crystalline solid, m.p.,

202 - 203.5°C: NMR (DMSO-d_6): d 7.36 (dd, 1 H, J_{HF} = 9.4 Hz, J_{HH} = 2.3 Hz, Ar), 7.45 (dd, 1 H, J_{HF} = 5.3 Hz, J_{HH} = 8.5 Hz), 7.25 (ddd, 1 H, J_{HF} = 8.5 Hz, J_{HH} = 8.5 and 2.3 Hz, Ar), 6.42 (t, 1 H, J = 2.4 Hz, vinyl H), 3.08 (d, 2 H, J = 2.4 Hz, CH_2), 1.27 (s, 6 H, $C(CH_3)_2$.

Anal. Calcd. for $C_{13}H_{13}FO_2$ (mw 220.243): C, 70.90; H, 5.95;.
Found: C, 70.95; H, 5.90

h) Preparation of (E)-2-(6-Fluoro-3,3-dimethyl-1-indanylidene)acetyl Chloride.

To an ice cold, stirred suspension of (E)-2-(6-fluoro-3,3-dimethyl-1-indanylidene)acetic acid (9.0 g, 0.0409 mol) in dichloromethane (200 ml) was added oxalyl chloride (15.6 g, 0.123 mol, Aldrich). The stirring suspension was allowed to warm to 25°C during 2 h. The resulting solution was concentrated by spin evaporation *in vacuo* with the addition of dichloromethane (4 x 75 ml) to give (E)-2-(6-fluoro-3,3-dimethyl-1-indanylidene)acetyl chloride as an uncharacterized oil. Dichloromethane (approximately 70 g) was added to dissolve this residual oil and the resulting solution was divided equally and used without other purification in Examples 41i, 42, and 43.

i) Preparation of (E)-2-(6-Fluoro-3,3-dimethyl-1-indanylidene)acetamide

A solution of 30% aqueous ammonium hydroxide (10 ml, 76 mmol, Mallinckrodt) was added to the solution of (E)-2-(6-fluoro-3,3-dimethyl-1-indanylidene)acetyl chloride (0.01363 mol) obtained from Example 41h diluted with dichloromethane (200 ml) and cooled to 0°C. The biphasic solution was stirred rapidly and allowed to warm to room temperature over 18 h. The reaction solution was concentrated by spin evaporation *in vacuo*, diluted with dichloromethane (200 ml), and washed with 1N aqueous hydrochloric acid (McIntosh), a solution of 5% aqueous sodium bicarbonate (Mallinckrodt), dried with magnesium sulfate (Mallinckrodt), and concentrated by spin evaporation *in vacuo*. The residue was chromatographed on Silica Gel 60 using ethyl acetate-hexanes (1:1), and then ethyl acetate. Fractions containing (E)-2-(6-fluoro-3,3-

dimethyl-1-indanylidene) acetamide were combined and concentrated by spin evaporation *in vacuo*. Recrystallization from dichloromethane-hexanes gave 2.85 g (95%) of (E)-2-(6-fluoro-3,3-dimethyl-1-indanylidene)acetamide as a white crystalline solid, m.p., 167 - 168°C: NMR (DMSO-d_6): d 7.40 (dd, 1 lH, J_{HF} = 5.2 Hz, J_{HH} = 8.4 Hz, Ar), 7.34 (br s, 1 H, NH), 7.26 (dd, 1 H, J_{HF} = 9.4 Hz, J_{HH} = 2.4 Hz, Ar), 7.19 (ddd, 1 H, J_{HF} = 8.6 Hz, J_{HH} = 8.4 and 2.4 Hz, Ar), 6.94 (br s, 1 H, NH), 6.39 (t, 1 H, J = 2.3 Hz, vinyl H), 3.07 (d, 2 H, J = 2.3 Hz, CH_2), 1.23 (s, 6 H, $C(CH_3)_2$; steady-state nOe: irradiation at d 6.40, observed 20.7% nOe at d 7.25.

Anal. Calcd. for $C_{13}H_{14}FO$ (mw 219.259): C, 71.21; H,6.44; N, 6.39. Found: C, 71.13; H, 6.46; N, 6.31.

Example 42

Preparation of (E)-2-(6-Fluoro-3,3-dimethyl-1-indanylidene)-N-methylacetamide

This compound was prepared in an analogous manner to Example 41i with the replacement of the solution of 30% aqueous ammonium hydroxide with a 40% aqueous solution of methylamine (10 ml, Aldrich). Recrystallization from dichloromethane-hexanes gave 2.89 g (91%) of (E)-2-(6-fluoro-3,3-dimethyl-1-indanylidene)-N-methylacetamide as a white crystalline solid, m.p., 157 - 158_ C: NMR (DMSO-d_6): d 7.87 (br q, 1 H, J = 4.6 Hz, NH) 7.38 (dd, 1 H, J_{HF} = 4.3 Hz, J_{HH} = 8.4 Hz, Ar), 7.25 (dd, 1 H, J_{HF} = 9.2 Hz, J_{HH} = 2.2 Hz, Ar), 7.17 (ddd, 1 H, J_{HF} = 9.1 Hz, J_{HH} = 8.4 and 2.2 Hz, Ar), 6.37 (s, 1 H, vinyl H), 3.08 (s, 2 H, CH_2), 2.66 (d, 3 H, J = 4.6 Hz, NCH_3), 1.22 (s, 6 H, $C(CH_3)_2$; steady-state nOe: irradiation at d 6.37, observed 15% nOe at d 7.86 and 21% nOe at d 7.25.

Anal. Calcd. for $C_{14}H_{16}FNO$ (mw 233.285): C, 72.08; H, 6.91; N, 6.00. Found: C, 71.92; H, 6.93; N, 5.96.

Example 43

Preparation of (E)-N-Cyclopropyl-2-(6-fluoro-3,3-dimethyl-1-indanylidene)acetamide

This compound was prepared in an analogous manner to Example 41i with the replacement of the solution of 30% aqueous ammonium hydroxide with cyclopropyl amine (4 ml, Aldrich). Recrystallization from dichloromethane-hexanes gave 2.86 g (81%) of (E)-N-cyclopropyl-2-(6-fluoro-3,3-dimethyl-1-indanylidene)acetamide as a white crystalline solid, m.p., 149 - 150°C: NMR (DMSO-d_6): d 8.04 (br d, 1 H, J = 4.2 Hz, NH), 7.39 (dd, 1 H, J_{HF} = 5.2 Hz, J_{HH} = 8.0 Hz, Ar), 7.19 (d, 1 H, J_{HH} = 8.9 Hz, Ar), 7.20 - 7.10 (m, 1 H, Ar), 6.3 (t, 1 H, J = 2.3 Hz, vinyl H), 3.09 (d, 2 H, J = 2.3 Hz, CH_2), 2.77 - 2.60 (m, 1 H, cyclopropyl CH), 1.23 (s, 6 H, $C(CH_3)_2$), 0.68 - 0.61 (m, 2 H, cyclopropyl CHHCHH), 0.46 - 0.41 (m, 2 H, cyclopropyl CHHCHH); steady-state nOe: irradiation at d 6.29, observed 14% nOe at d 8.04 and 22% nOe at d 7.19.

Anal. Calcd. for $C_{16}H_{18}FNO$ (mw 259.323): C, 74.11; H, 7.00; N, 5.40.
Found: C, 73.98; H, 7.03; N, 5.31.

Example 44

Preparation of (E)-2-(6-Fluoro-3-methyl-1-indanylidene)acetamide

a) Preparation of Ethyl 4-Fluorocinnamate

A solution of butyl lithium, 2.5 M in hexanes (159 ml, 0.3975 mol, Aldrich), was added dropwise over 0.25 hr, with rapid mechanical stirring, to a solution of triethyl phosphonoacetate (89.2 g, 0.389 mol, Aldrich) in tetrahydrofuran (800 ml, anhydrous, Aldrich) at <5°C while blanketed with a nitrogen atmosphere. This solution was stirred for an additional 0.25 hr and cooled to 0°C with an ice bath and a solution of 4'-fluoroacetophenone (50g, 0.362 mol, Aldrich) in tetrahydrofuran (50 ml) was then added in one portion. Stirring was continued for 18 hr without additional cooling. The solution was then concentrated to ~100ml by spin evaporation *in vacuo* and diluted to 500 ml with ethyl acetate. After washing with deionized water (3 x 50 ml) this solution was concentrated by spin evaporation *in vacuo*. Distillation at reduced pressure gave

48 g (63%) of ethyl 4-fluorocinnamate as a mixture of (E) to (Z) isomers (ratio 3:1) contaminated with 16% of triethyl phosphonacetate as a clear oil, b.p., 138-143°C at 14 Torr: NMR ($CDCl_3$): d7.52-7.41 (m, 1.5 H, (E)-ArH), 7.27-7.11 (m, 0.5 H, (Z)-ArH), 7.10-6.97 (m, 2H, (E)-&(Z)-ArH), 6.10 (s, 0.75 H, (E)-=CH), 6,.91 (s, 0.25 H, (Z)-=CH), 4.27-4.10 (m, 2.64 H, (E)-&(Z)-OCH_2) and $P(OCH_2)_2$), 2.96 (d, 0.32 H, J_{PH}=21.5 Hz, CH_2P), 2.56 (s, 2.25 H, (E)-=CCH_3), 2.16 (s, 0.25 H, (Z)-=CCH_3), 1.50-1.20 (m, 3H, (E)-&(Z)-$OCCH_3$), 1.12 (t, 0.48H, J=7.1 Hz, $COCCH_3$).

b) Preparation of Ethyl 3-(4-Fluorophenyl)butyrate

A mixture of ethyl 4-fluorocinnamate (47.5 g, 0.228 mol) and 10% palladium on carbon (0.85 g, Aldrich) in 95% ethanol was shaken in a Parr hydrogenator under 2-3 atm of H_2 pressure for 1 h. The mixture was filtered and concentrated by spin evaporation *in vacuo*. Fractional distillation gave 46.5 g (97%) of ethyl 3-(4-fluorophenyl)butyrate as a clear oil, b.p., 122 - 128° C: NMR (DMSO-d_6): d 7.31 - 7.25 (m, 2 H, Ar), 7.12 - 7.04 (m, 2 H, Ar), 3.97 (q, 2 H, J = 7.1 Hz, OCH_2), 3.24 - 3.10 (m, 1 H, CH), 2.62 - 2.52 (m, 2 H, $C(O)CH_2$), 1.20 (d, 3 H, J = 7.1 Hz, CH_3), 1.08 (t, 3 H, J = 7.1 Hz, CH_3).

Anal. Calcd. for $C_{12}H_{15}FO_2$ 0.2 H_2O (mw 213.855): C, 67.40; H, 7.26. Found: C, 67.25; H, 7.26.

c) Preparation of 3-(4-Fluorophenyl)butanoic Acid.

A solution of ethyl 3-(4-fluorophenyl)butyrate (45.3 g, 0.215 mol), 85% potassium hydroxide (14.22 g, 0.215 mol, Mallinckrodt) in 200 ml of deionized water was refluxed for 2 h, concentrated by spin evaporation in vacuo, made acidic (pH 3) with 12 N hydrochloric acid (Mallinckrodt), and extracted with dichloromethane (4 x 200 ml). The dichloromethane layers were combined, washed with deionized water (50 ml), and concentrated by spin evaporation in vacuo. The residue was crystallized from dichloromethane-hexanes to give 34.5 g (88%) of 3-(4-fluorophenyl)butyric acid as a white crystalline solid: NMR (DMSO-d_6): d 12.7 (s, 1 H, CO_2H), 7.32 - 7.25 (m, 2 H, Ar), 7.14 -7.03 (m, 2

H, Ar), 3.21 - 3.07 (m, 1 H, CH), 2.49 (d, 2 H, J = 7.6 Hz, CH_2), 1.19 (d, 3 H, J = 7.0 Hz, CH_3).

Anal. Calcd. for $C_{10}H_{11}FO_2$ 0.1 H_2O (mw 183.996): C, 65.28 ; H, 6.14.

Found: C, 65.11; H, 6.07.

d) Preparation of 3-(4-Fluorophenyl)butyryl Chloride

Oxalyl chloride (71 g, 48.8 ml, 0.560 mol, Aldrich) was added to a mixture of 3-(4-fluorophenyl)butyric acid (34 g, 0.187 mol) in 200 ml of dichloromethane at -5°C. After stirring for 20 min at this temperature, the solution was allowed to warm to 25°C and stirring was continued for 2 h. The volatiles were removed by spin evaporation *in vacuo* with the addition of dichloromethane (4 x) during concentration to give 35.1 g (94%) of 3-(4-fluorophenyl)butyryl chloride as a light yellow oil: NMR (DMSO-d_6): d 7.24 - 7.14 (m, 2 H, Ar), 7.05 - 6.95 (m, 2 H, Ar), 3.40 - 3.30 (m, 1 H, CH), 3.21 - 3.05 (m, 2 H, CH_2), 1.34 (d, 3 H, J = 7.0 Hz, CH_3).

Anal. Calcd. for $C_{10}H_{10}ClFO$ (mw 200.640): C, 59.86; H, 5.02; Cl, 17.67.
Found: C, 59.98; H, 5.07; Cl, 17.57.

e) Preparation of 6-Fluoro-3-methyl-1-indanone.

This compound was prepared in an analogous manner to Example 41e with the replacement of 3-(4-fluorophenyl)-3-methyl-butyryl chloride with 3-(4-fluorophenyl)butyryl chloride. Removal of the volatiles from the combined washes by spin evaporation *in vacuo* gave 26.3g (92%) of 6-fluoro-3-methyl-1-indanone as an oil which formed low melting crystals on standing: NMR (DMSO-d_6): d 7.72 (dd, 1 H, J_{HF} = 4.7 Hz, J_{HH} = 8.2 Hz, Ar), 7.56 (ddd, 1 H, J_{HF} = 8.6 Hz, J_{HH} = 8.2 and 2.3 Hz, Ar), 7.35 (dd, 1 H, J_{HF} = 7.9 Hz, J_{HH} = 2.3 Hz), 2.45-2.27 (m, 1 H, indanylidene CH), 2.96 (dd, 1 H, J = 19.2 and 7.3 Hz, Ar), 2.29 (dd, 1 H, J = 19.2 and 2.3 Hz, Ar), 1.34 (d, 3 H, J = 7.1 Hz, CH_3).

f) Preparation of Ethyl 2-(6-Fluoro-1-hydroxy-3-methyl-1-indanyl)acetate.

This compound was prepared in an analogous manner to Example 41f with the replacement of 6-fluoro-3,3-dimethyl-1-indanone with 6-fluoro-3-methyl-1-indanone. Removal of the volatiles from the workup solution gave 15.0 g (45%) of ethyl 2-(6-fluoro-1-hydroxy-3-methyl-1-indanyl)acetate as a light tan oil: NMR (DMSO-d_6): d 7.25 - 7.15 (m, 1 H, Ar), 7.11 - 7.00 (m, 2 H, Ar), 5.47 (s, 1 H, OH), 3.98 (q, 2 H, J = 7.0 Hz, OCH_2), 3.03 - 2.95 (m, 1 H, CH), 2.83 - 2.74 (m, 1 H, CH), 2.66 - 2.53 (m, 1 H, CH), 1.70 - 1.71 (m, 1 H, CH), 1.25 (d, 3 H, J= 6.8 Hz, CH_3), 1.10 (t, 3 H, J = 7.1 Hz, CH_3).

g) Preparation of (E)-2-(6-Fluoro-3-methyl-1-indanylidene)acetic Acid.

This compound was prepared in an analogous manner to Example 41g with the replacement of ethyl 2-(6-fluoro-1-hydroxy-3,3-dimethyl-1-indanyl)acetate with ethyl 2-(6-fluoro-1-hydroxy-3-methyl-1-indanyl)acetate. Removal of the volatiles from workup gave 9.3 g (76%) of (E)-2-(6-fluoro-3-methyl-1-indanylidene)acetic acid as a tan solid, m.p., 175 - 177°C: NMR (DMSO-d_6): d 12.1 (v br s, 1 H, COOH), 7.65 (dd, 1 H, J_{HF} = 9.6 Hz, J_{HH} = 2.3 Hz, Ar), 7.45 (dd, 1 H, J_{HF} = 5.1 Hz, J_{HH} = 8.4 Hz, Ar), 7.25 (ddd, 1 H, J_{HF} = 9.0 Hz, J_{HH} = 8.4 and 2.3 Hz, Ar), 6.40 (t, 1 H, J = 2.5 Hz, vinyl H), 3.53 (ddd, 1 H, J = 2.2, 7.6, and 19.4 Hz; indanylidene C<u>H</u>H), 3.4 - 3.2 (m, 1 H, indanylidene CH), 2.70 (dt, 1 H, J = 3.0 and 19.4 Hz, indanylidene CH<u>H</u>), 1.26 (d, 3 H, J = 6.9 Hz, CH_3).

h) Preparation of (E)-2-(6-Fluoro-3-methyl-1-indanylidene)acetyl Chloride.

This compound was prepared in an analogous manner to Example 41h with the replacement of (E)-2-(6-fluoro-3,3-dimethyl-1-indanylidene)acetic acid with (E)-2-(6-fluoro-3-methyl-1-indanylidene)acetic acid. The product residue was dissolved in dichloromethane and used, without purification, in Example 44i, 45, and 46.

i) Preparation of (E)-2-(6-Fluoro-3-methyl-1-indanylidene)acetamide

This compound was prepared in an analogous manner to Example 41i with the replacement of (E)-2-(6-fluoro-3,3-dimethyl-1-indanylidene)acetyl chloride with (E)-2-(6-fluoro-3-methyl-1-indanylidene)acetyl chloride. Recrystallization from dichloromethane-hexanes gave 2.39 g (77%) of (E)-2-(6-fluoro-3-methyl-1-indanylidene)acetamide as a white crystalline solid, m.p., 149 - 151°C: NMR (DMSO-d_6): d 7.43 - 7.37 (m, 1 H, Ar), 7.33 (br s, 1 H, NH), 7.28 (m, 1 H, Ar), 7.25 - 7.15 (m, 1 H, Ar), 6.38 (br s, 1 H, NH), 6.38 (s, 1 H, vinyl H), 3.57 - 3.47 (m, 1 H, CHH), 3.26 - 3.17 (m, 1 H, CH), 2.72 - 2.64 (m, 1 H, CHH), 1.22 (d, 3 H, J = 6.9 Hz, CH_3); steady-state nOe: irradiation at d 6.38: observed 20.5% nOe at d 7.26.

Anal. Calcd. for $C_{12}H_{12}FNO$ (mw 205.232): C, 70.23; H, 5.89; N, 6.86. Found: C, 70.08; H, 5.86; N, 6.80.

Example 45

Preparation of (E)-2-(6-Fluoro-3-methyl-1-indanylidene)-N-methylacetamide

This compound was prepared in an analogous manner to Example 42 with the replacement of (E)-2-(6-fluoro-3,3-dimethyl-1-indanylidene)acetyl chloride with (E)-2-(6-fluoro-3-methyl-1-indanylidene)acetyl chloride. Recrystallization from dichloromethane-hexanes gave 2.27 g (71%) of (E)-2-(6-fluoro-3-methyl-1-indanylidene)-N-methylacetamide as a white crystalline solid, m.p., 168 - 169°C: NMR (DMSO-d_6): d 7.85 (br d, 1 H, J = 4.4 Hz, NH), 7.40 (dd, 1 H, J_{HF} = 5.2 Hz, J_{HH} = 8.3 Hz, Ar), 7.28 (dd, 1 H, J_{HF}= 9.3 Hz, J_{HH} = 2.3 Hz, Ar), 7.18 (ddd, 1 H, J_{HF} = 8.5 Hz, J_{HH} = 8.3 and 2.3 Hz, Ar), 6.35 (d, 1 H, J = 2.2 Hz, vinyl H), 3.58 - 3.46 (m, 1 H, indanylidene CHH), 3.30-3.5 (m, 1 H, indanylidene CH), 2.75 - 2.59 (m, 1 H, indanylidene CHH), 2.66 (d, 3 H, J = 4.4 Hz, NCH_3), 1.72 (d, 3 H, J = 7.0 Hz, CH_3); steady-state nOe: irradiation at d 6.34, observed 15.3% nOe at d 7.85 and 21.9% nOe at d 7.27.

Anal. Calcd. for $C_{13}H_{14}FNO$ (mw 219.258): C, 71.21; H, 6.48 N, 6.44.
Found: C,71.07; H, 6.47; N, 6.40.

Example 46

Preparation of (E)-N-Cyclopropyl-2-(6-fluoro-3-methyl-1-indanylidene)acetamide

This compound was prepared in an analogous manner to Example 43 with the replacement of (E)-2-(6-fluoro-3,3-dimethyl-1-indanylidene)acetyl chloride with (E)-2-(6-fluoro-3-methyl-1-indanylidene)acetyl chloride. Recrystallization from dichloromethane-hexanes gave 2.30 g (67%) of (E)-N-cyclopropyl-2-(6-fluoro-3-methyl-1-indanylidene)acetamide as a white crystalline solid, m.p., 132 - 134° C: NMR (DMSO-d_6): d 8.03 (br d, 1 H, J = 4.2 Hz, NH), 7.42 - 7.37 (m, 1 H, Ar), 7.24 - 7.10 (m, 2 H, Ar), 6.27 (d, 1 H, J = 2.3 Hz, vinyl H), 3.57 (dd, 1 H, J=2.1 and 7.9 Hz, indanylidene C<u>H</u>H), 3.28 -3.17 (m, 1 H, indanylidene CH), 2.75 - 2.65 (m, 2 H, indanylidene CH<u>H</u> and cyclopropyl CH), 1.22 (d, 3 H, J = 6.9 Hz, CH_3), 0.68 - 0.61 (m, 2 H, cyclopropyl C<u>H</u>HC<u>H</u>H), 0.51 - 0.40 (m, 2 H, cyclopropyl CH<u>H</u>C<u>H</u>H); steady-state nOe: irradiation at d 6.21, observed 16% nOe at d 8.03 and 22% nOe at d 7.21.

Anal. Calcd. for $C_{15}H_{16}FNO$ (mw 245.296): C, 73.45; H, 6.57; N, 5.71.
Found: C, 73.31; H, 6.58; N, 5.72.

Example 47

Preparation of 2-(6-Fluoro-1-hydroxy-1-indanyl)acetamide

A mixture of 2-(6-fluoro-1-hydroxy-1-indanyl)acetic acid (5.0 g, 24 mmol), 1-hydroxybenzotriazole hydrate (3.2 g, 24 mmol, Aldrich), 1,3-dicyclohexylcarbodiimide (5.0 g, 24 mmol, Aldrich) and 29.6% aqueous ammonium hydroxide solution (4.1 mL, 31 mmol) in dimethylformamide-dichloromethane (1:4, 100 mL) was stirred for 18 h at room temperature. The resulting suspension was filtered and the filtrate was washed successively with sodium bicarbonate solution, brine, 5% aqueous citric acid and brine. The organic layer was dried over sodium sulfate, filtered and concentrated *in vacuo* to give a tan semi-solid (3.57 g). Recrystallization from dichloromethane-methanol-hexanes gave 1.34 g (27%) of off-white crystals of the product, m.p., 109-111°C; NMR

(DMSO-d_6): d 6.97-7.37 (m, 5H, Ar+NH_2), 5.78 (s, 1H, OH), 2.00-2.71 (m, 6H, 3XCH_2).

Anal. Calcd. for $C_{11}H_{12}FNO_2$: C, 63.15; H, 5.78; N, 6.69.
Found: C, 63.03; H, 5.79; N, 6.71.

Example 48

Preparation of 2-(5-Fluoro-1H-inden-3-yl)acetamide

1,1'-Carbonyldiimidazole (324 mg, 2 mmol, Aldrich) was added to an ice-cold, stirred solution of (E)-2-(6-fluoro-1-indanylidene)acetic acid (192 mg, 1 mmol) in tetrahydrofuran (10 mL) under nitrogen. The resulting solution was stirred for 1.5 h at room temperature and chilled (ice-methanol bath) before anhydrous ammonia was bubbled into the solution for 5 min. The resulting suspension was stirred for 1 h at room temperature and concentrated *in vacuo*. The residue was washed with water, leaving the product as a white water-insoluble solid (150 mg, 78%), m.p., 168-171°C; NMR (DMSO-d_6): d 6.94-7.53 (m, 5H, Ar+NH_2); 6.48 (s, 1H, =CH), 3.20-3.39 (m, 4H, 2XCH_2).

Anal. Calcd. for $C_{11}H_{10}FNO$: C, 69.10; H, 5.27; N, 7.33.
Found: C, 68.83; H, 5.33; N, 7.31.

Example 49

(Z)-2-(2-Bromo-4,6-difluoro-1-indanylideneacetamide

N-bromosuccinimide (17.2g, 0.096 mol, Aldrich) was added in three portions over a one hour period to a mixture of (E)-2-(4,6-difluoro-1-indanylidene) acetamide (19.4g, 0.093 mol, prepared as in Example 12g), and benzoyl peroxide (1.5g, 0.006 mol, Aldrich) in carbon tetrachloride:benzene (1:1) (600 mL) and the mixture was stirred at ambient temperature while illuminating with an infrared lamp (250w). After two hours, the mixture was filtered and the solid was washed with carbon tetrachloride. Column chromatography twice on silica gel with ethyl acetate:hexanes (1:1) as eluent and trituration of the resulting solid with pentane gave 1.93g of crude (Z)-2-(2-bromo-4,6-

difluoro-1-indanylideneacetamide. Recrystallization from ethyl acetate:pentane mixtures gave 1.01g as a yellow solid m.p. 187-188°C. NMR (DMSO-d_6): d 7.63 (br s, 1H), 7.32-7.38 (m, 3H), 6.51(d, 1H, J=1.1), 6.33 (m, 1H), 3.69 (dd, 1H, J= 5.5 Hz, J= 18.1 Hz), 3.30 (d, 1H, J= 18.4 Hz); steady-state nOe: irradiation at 6.51 d, observed 26.4% nOe at 7.35d.

Anal. Calcd. for $C_{11}H_8BrF_2NO$ (mw 288.10): C, 45.86; H, 2.80; N, 4.86.
Found: C, 45.98; H, 2.78; N, 4.85.

Example 50

Preparation of (Z)-2-(2-bromo-6-fluoro-1-indanylidene)acetamide

N-Bromosuccinimide (22.57 g, 126.8 mmoles, Aldrich) and benzoyl peroxide (1.89 g, 7.8 mmoles, Aldrich) were added to a suspension of (E)-2-(6-fluoro-1-indanylidene)acetamide (21.00 g, 109.8 mmoles) in carbon tetrachloride (400 mL) and benzene (400mL). The mixture was refluxed under a calcium chloride drying tube while shining an infrared lamp on it for two hours, after which time an orange solution formed. The heat and light were removed, and the solution was stirred at ambient temperature for 18 hours. The mixture was filtered, and the solids were washed with ethyl acetate. The washings and filtrate were combined and evaporated *in vacuo*. The residue was dissolved in ethyl acetate (800 mL) and washed with water (3 x 200 mL) and brine (200 mL), dried over sodium sulfate, filtered and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting first with hexane : ethyl acetate (2 : 1) gradually increasing the polarity to hexane : ethyl acetate (1 : 1). The fractions containing the major spot were combined and evaporated *in vacuo* to give a yellow solid which was dried in a vacuum at 70°C for 18 hours to give 1.022 g (3%) of (Z)-2-(2-bromo-6-fluoro-1-indanylidene)acetamide as a yellow solid, mp 162-163 °C. ^{1}H-NMR (DMSO-d_6): d7.19-7.85 (m, 5H), 6.46 (s, 1H), 6.32 (d, 1H, J = 5.7 Hz), 3.64 (dd, 1H, J = 5.6 Hz, 18.4 Hz) and 3.27 (d, 1H, J = 18.5 Hz); steady-state nOe: irradiation at 6.46 d, observed 21% nOe at 7.39 d.

Anal. Calcd. for $C_{11}H_9BrFNO$ (mw 270.095): C, 48.91; H, 3.36; N, 5.19; Br, 29.58.
Found: C, 49.02; H, 3.35; N, 5.16; Br, 29.50.

Example 51

Preparation of (Z)-2-(2,3-dibromo-6-fluoro-1-indanylidene)acetamide

N-Bromosuccinimide (49.37 g, 277.4 mmoles, Aldrich) and benzoyl peroxide (1.60 g, 6.6 mmoles, Aldrich) were added to a suspension of (E)-2-(6-fluoro-1-indanylidene)acetamide (17.68 g, 92.5 mmoles) in carbon tetrachloride (335 mL) and benzene (335 mL). The mixture was refluxed under a calcium chloride drying tube for four hours, after which time an orange solution formed. The heat was removed, and the solution was stirred at ambient temperature for 18 hours. The mixture was filtered, and the solids were washed with ethyl acetate. The washings and filtrate were combined and evaporated *in vacuo*. The residue was dissolved in ethyl acetate (800 mL) and washed with water (3 x 200 mL) and brine (200 mL), dried over sodium sulfate, filtered and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with hexane : ethyl acetate (2 : 1). The fractions containing the compound with Rf = 0.4 in hexane : ethyl acetate (1 : 1) were combined and chromatographed again on silica gel eluting with hexane : ethyl acetate (2 : 1). The fractions containing the compound with Rf = 0.4 in hexane : ethyl acetate (1 : 1) were combined and evaporated *in vacuo* to give a solid which was washed with hexane and dried in a vacuum at 50°C for 18 hours to give 1.35 g (4%) of (Z)-2-(2,3-dibromo-6-fluoro-1-indanylidene)acetamide as a yellow solid, mp 158-163°C (decomposed). ^{1}H-NMR (DMSO-d6): d 7.35-7.70 (m, 5H), 6.68 (s, 1H), 6.53 (s, 1H), 5.99 (s, 1H).

Anal. Calcd. for $C_{11}H_8Br_2FNO$ (mw 348.985): C, 37.85; H, 2.31; N, 4.01.
Found: C, 37.98; H, 2.26; N, 4.03.

Example 52

Preparation of (Z)-2-(6-fluoro-2-hydroxy-1-indanylidene)acetamide (Method A)

A mixture of (Z)-2-(2-bromo-6-fluoro-1-indanylidene)acetamide (5.30 g, 19.25 mmoles) and silver nitrate (10.40 g, 61.18 mmoles, Aldrich) in dimethoxyethane (265 mL) and water (100 mL) was refluxed for 18 hours. The mixture was filtered, and the filtrate was diluted with water (700 mL) and extracted with ethyl acetate (6 x 100 mL). The combined extracts were washed with water (200 mL) and brine (200 mL), dried over

magnesium sulfate, filtered, and evaporated *in vacuo*. The residue was chromatographed on silica gel, eluting with hexane : ethyl acetate (2 : 1), gradually increasing the polarity to hexane : ethyl acetate (1 : 1). The fractions containing the compound with Rf = 0.18 were combined and evaporated *in vacuo* to give 1.13 g (28%) of crude (Z)-2-(6-fluoro-2-hydroxy-1-indanylidene)acetamide as an orange solid. Recrystallization from ethyl acetate : hexane mixtures gave 0.49 g (12%) of (Z)-2-(6-fluoro-2-hydroxy-1-indanylidene)acetamide as an off-white solid, mp 201-202°C; ^{1}H-NMR (DMSO-d_6): d 7.73 (d, 2H), 7.19-7.39 (m, 3H), 6.53 (m, 1H), 6.47 (m, 1H), 5.23 (m, 1H), 3.33 (dd, 1H, J = 9.6 Hz, 17.0 Hz), and 2.81 (dd, 1H, J = 1.6 Hz, 16.3 Hz); steady-state nOe: irradiation at 6.47 d, observed 20% nOe at 7.38 d.

Anal. Calcd. for $C_{11}H_{10}FNO_2$ (mw 207.20): C, 63.76; H, 4.86; N, 6.76.
Found: C, 63.77; H, 4.89; N, 6.73.

Preparation of (Z)-2-(6-fluoro-2-hydroxy-1-indanylidene)acetamide (Method B)

A suspension of (E)-2-(6-fluoro-1-indanylidene)acetamide (12.00 g, 62.8 mmoles) in dichloromethane (250 mL) was added to a solution of selenium dioxide (5.20 g, 46.9 mmoles, Aldrich) and tert-butyl hydroperoxide (25 mL, 260.8 mmoles, Aldrich) in dichloromethane (500 mL). The suspension was stirred at ambient temperature for 3 days. Additional tert-butyl hydroperoxide (10 mL, 104.3 mmoles) was added, and the mixture was stirred at ambient temperature for 18 hours. Additional selenium dioxide (5.00 g, 45.1 mmoles) was added, and the mixture was stirred at ambient temperature for 18 hours. Additional tert-butyl hydroperoxide (15 mL, 156.5 mmoles) was added, and the mixture was stirred at ambient temperature for 18 hours. The mixture was filtered to remove about one gram of impure product, and the filtrate was dried over magnesium sulfate, filtered, and evaporated *in vacuo*. Additional selenium dioxide (5.00 g, 45.1 mmoles) was added, and the mixture was stirred at ambient temperature for 18 hours. The mixture was concentrated *in vacuo* to 300 mL, hexane was added, and the precipitate was collected by filtration, washed with hexane, and combined with the solids collected previously. The combined solids were dissolved in ethyl acetate (700 mL), washed successively with water (3x100 mL) and brine (100 mL), concentrated *in vacuo* to 100 mL, and cooled in an ice bath. The solids were collected by filtration, and the filtrate was concentrated *in vacuo* to give a second crop of solids. All of the solids were combined and chromatographed on silica gel, eluting with hexane : ethyl acetate (1 : 1).

The fractions containing the major spot were combined and evaporated *in vacuo* to give 5.80 g of an off-white solid, which was washed with chloroform (3x50 mL) to give 5.43 g (42%) of (Z)-2-(6-fluoro-2-hydroxy-1-indanylidene)acetamide as a white solid; mp 202-204°C; ^{1}H-NMR (DMSO-d_6): d 7.76 (d, 1H), 7.19-7.43 (m, 3H), 6.53 (m, 1H), 6.48 (m, 1H), 5.25 (m, 1H), 3.33 (dd, 1H, J = 7.8 Hz, 17.0 Hz), and 2.81 (dd, 1H, J = 3.2 Hz, 16.8 Hz).

Anal. Calcd. for $C_{11}H_{10}FNO_2$ (mw 207.20): C, 63.76; H, 4.86; N, 6.76.
Found: C, 63.82; H, 4.83; N, 6.79.

Example53

Preparation of (Z)-2-(6-fluoro-2-nitrooxy-1-indanylidene)acetamide

A mixture of (Z)-2-(2-bromo-6-fluoro-1-indanylidene)acetamide (5.20 g, 19.25 mmoles) and silver nitrate (10.40 g, 61.18 mmoles, Aldrich) in dimethoxyethane (265 mL) and water (100 mL) was refluxed for 18 hours. The mixture was filtered, and the filtrate was diluted with water (700 mL) and extracted with ethyl acetate (6 x 100 mL). The combined extracts were washed with water (200 mL) and brine (200 mL), dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was chromatographed on silica gel, eluting with hexane : ethyl acetate (2 : 1). The fractions containing the compound with Rf = 0.50 were combined, evaporated *in vacuo*, and dried in a vacuum at 80°C for 18 hours to give 0.50 g (10%) of (Z)-2-(6-fluoro-2-nitrooxy-1-indanylidene)acetamide as a pale orange solid, mp 162-163°C; ^{1}H-NMR (DMSO-d_6): d 7.23-7.71 (m, 5H), 6.93 (d, 1H), 6.72 (s, 1H), 3.54 (dd, 1H, J = 6.6 Hz and 18.4 Hz), and 3.29 (d, 1H, J = 18.4 Hz); steady-state nOe: irradiation at 6.72 d, observed nOe at 7.41 and 7.71 d.

Anal. Calcd. for $C_{11}H_9FN_2O_4$ (mw 252.20): C, 52.38; H, 3.60; N, 11.11.
Found: C, 52.43; H, 3.65; N, 11.03.

Example 54

Preparation of (Z)-2-(6-fluoro-2-methoxy-1-indanylidene)acetamide

A mixture of (Z)-2-(2-bromo-6-fluoro-1-indanylidene)acetamide (2.60 g, 9.60 mmoles) and silver nitrate (5.10 g, 27.43 mmoles, Aldrich) in methanol (200 mL) was refluxed for 8 hours. Additional silver nitrate (5.10 g, 27.43 mmoles) was added and the mixture was refluxed for 18 hours. The mixture was filtered, and the filtrate was evaporated *in vacuo*. The residue was chromatographed on silica gel, eluting with hexane : ethyl acetate (1 : 4), gradually increasing the polarity to 100% ethyl acetate. The fractions containing the compound with Rf = 0.15 with hexane : ethyl acetate (1 : 1) as the eluant were combined and evaporated *in vacuo* and dried in a vacuum at 50°C for 18 hours to give 0.68 g (32%) of crude (Z)-2-(6-fluoro-2-methoxy-1-indanylidene)acetamide as a tan solid. Recrystallization from ethyl acetate : hexane mixtures gave 0.49 g (23%) of (Z)-2-(6-fluoro-2-methoxy-1-indanylidene)acetamide as an off-white solid, mp 128-130°C; ^{1}H-NMR (DMSO-d_6): d 7.13-7.48 (m, 5H), 6.54 (s, 1H), 5.34 (d, 1H), 3.25 (s, 3H), 3.05 (dd, 1H, J = 5.7 Hz, 17.3 Hz), and 2.87 (d, 1H, J = 17.1 Hz).

Anal. Calcd. for $C_{12}H_{12}FNO_2$ (mw 221.225): C, 65.14; H, 5.47; N, 6.33.
Found: C, 65.08; H, 5.54; N, 6.26.

Example 55

Preparation of (Z)-2-(2-acetoxy-6-fluoro-1-indanylidene)acetamide

A mixture of (Z)-2-(2-bromo-6-fluoro-1-indanylidene)acetamide (0.51 g, 1.90 mmoles), potassium acetate (0.37 g, 3.80 mmoles), and 18-crown-6 (0.06 g, 0.24 mmoles, Aldrich) in acetonitrile (20 mL) and ethanol (10 mL) was sonicated using a Sonicor ultrasonicator for 2 hours, allowing the temperature to rise to 35°C. The mixture was stirred overnight at ambient temperature. Glacial acetic acid (3 mL) was added and the mixture was sonicated for 1.5 hours allowing the temperature to rise to 50°C. The mixture was stirred overnight at ambient temperature and evaporated *in vacuo*. The residue was dissolved in dichloromethane (100 mL), washed with water (2 x 50 mL) and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with hexane : ethyl acetate (3 : 1) gradually increasing the polarity to 100% ethyl acetate.

The fractions containing the compound with Rf = 0.3 in hexane : ethyl acetate (1 : 1) were combined and evaporated *in vacuo* to give a solid which was washed with hexane and dried in a vacuum at 50°C for 18 hours to give 0.22 g (46%) of (Z)-2-(2-acetoxy-6-fluoro-1-indanylidene)acetamide as a white solid, mp 202-203°C; ^{1}H-NMR (DMSO-d_6): d 7.49 and 7.08 (d, 2H), 7.19-7.38 (m, 3H), 6.57 (s, 1H), 6.42 (d, 1H), 3.39 (dd, 1H, J = 6.9 Hz, 17.7 Hz), and 2.82 (d, 1H, J = 18.0 Hz), 1.91 (s, 3H); steady-state nOe: irradiation at 6.57 d, observed 22% nOe at 7.35 d.

Anal. Calcd. for $C_{13}H_{12}FNO_3$ (mw 249.24): C, 62.64; H, 4.85; N, 5.62.
Found: C, 62.75; H, 4.85; N, 5.66.

Example 56

(Z)-2-(4,6-Difluoro-2-hydroxy-1-indanylidene)acetamide

A suspension of (E)-2-(4,6-difluoro-1-indanylidene)acetamide (10.0g, 0.05 mol, prepared as in Example 12g) in dichloromethane (250 mL) was added portionwise over a 10 min. period to a mixture of 70% aqueous t-butylhydroperoxide (19.8 mL, 0.15 mol, Aldrich) and selenium dioxide (3.7g, 0.03 mol, Aldrich) in dichloromethane (500 mL) at ambient temperature. After 18h, additional t-butylhydroperoxide (10 mL of a 5.0M solution in 2,2,4-trimethylpentane , 0.05 mol, Aldrich) and selenium dioxide (1.8g, 0.02 mol) were added and the mixture was stirred at ambient temperature. After 18h, additional t-butylhydroperoxide (10 mL of 70% aqueous solution, 0.08 mol) and selenium dioxide (3.7g, 0.05 mol) were added and the mixture was stirred at ambient temperature for 8 days. The resulting solid was filtered off and washed with dichloromethane to give 5.85g of crude (Z)-2-(4,6-difluoro-2-hydroxy-1-indanylidene)acetamide. After 7 days at ambient temperature a second crop of crude (Z)-2-(4,6-difluoro-2-hydroxy-1-indanylidene)acetamide was obtained from the filtrate. Column chromatography on silica gel using ethyl acetate as the eluent followed by a second column chromatography on silica gel using ethyl acetate:hexanes (3:2) as eluent and trituration of the resulting solid with pentane gave 2.38g of (Z)-2-(4,6-difluoro-2-hydroxy-1-indanylidene)acetamide as a pink solid: m.p. 235-237°C. NMR (DMSO-d_6): d 7.94 (br s, 1H), 7.60 (br s, 1H), 7.21-7.29 (m, 2H), 6.56(d, 1H, J= 1.9), 6.35 (d, 1H, J= 2.1), 5.27 (m, 1H), 3.33 (dd, 1H, J= 7.7 Hz, J= 17.3 Hz), 2.73 (d, 1H, J= 17.0 Hz); steady-state nOe: irradiation at 6.56 d, observed 25.1% nOe at 7.26d.

Anal. Calcd. for $C_{11}H_9F_2NO_2$ (mw 225.19): C, 58.67; H, 4.03; N, 6.22.
Found: C, 58.59; H, 3.99; N, 6.19.

Example 57

Preparation of (E)-2-(6-fluoro-3-hydroxy-1-indanylidene)acetamide

a) Preparation of 3-bromo-6-fluoro-1-indanone

A mixture of N-bromosuccinimide (2.76 g, 15.51 mmoles, Aldrich), benzoyl peroxide (0.01 g, 0.04 mmoles, Aldrich) and 6-fluoro-1-indanone (2.29 g, 15.25 mmoles) in carbon tetrachloride (20 mL) was refluxed under nitrogen for two hours. The mixture was cooled to ambient temperature, filtered, and the solids were washed with dichloromethane. The washings and filtrate were combined, washed successively with 1.0 N sodium hydroxide (2 x 30 mL), water (2 x 30 mL) and brine (30 mL), and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting first with hexane, gradually increasing the polarity to hexane : ethyl acetate (95 : 5). The fractions containing the major spot were combined and evaporated *in vacuo* to give a 2.30 g (66%) of 3-bromo-6-fluoro-1-indanone as a yellow oil which was used without further purification. ^{1}H-NMR ($CDCl_3$): d7.23-7.74 (m, 3H), 5.56 (d, 1H), 3.64 (dd, 1H, J = 7.0 Hz, 19.9 Hz) and 3.10 (dd, 1H, J = 19.9 and 2.7 Hz).

b) Preparation of 3-hydroxy-6-fluoro-1-indanone

A mixture of 3-bromo-6-fluoro-1-indanone (2.50 g, 10.0 mmoles) and silver carbonate (4.19 g, 15.2 mmoles, Aldrich) in dimethoxyethane (85 mL) and water (65 mL) was stirred overnight at ambient temperature. The mixture was filtered through a pad of celite, and the filtrate was diluted with water (500 mL) and extracted with ethyl acetate (4 x 100 mL). The combined extracts were washed with water (100 mL) and brine (75 mL), dried over sodium sulfate, filtered, and evaporated *in vacuo* to give 2.80 g (quantitative) of crude 3-hydroxy-6-fluoro-1-indanone which was used without further purification. Chromatography of 0.41 g on silica gel, eluting with hexane : ethyl acetate (3 : 4) gave 0.050 g of

analytically pure 3-hydroxy-6-fluoro-1-indanone as a tan solid, mp 73-76°C; ^{1}H-NMR (DMSO-d6): d7.36-7.74 (m, 3H), 5.43 (m, 1H), 3.18 (dd, 1H, J = 6.7 Hz, 18.9 Hz), 2.65 (dd, 1H, J = 2.8 Hz, 19.1 Hz) and 2.09 (bs, 1H).

Anal. Calcd. for C9H7FO (mw 166.146): C, 65.06; H, 4.25.
Found: C, 64.84; H, 4.27.

c) Preparation of 3-((tert-butyldimethylsilyl)oxy)-6-fluoro-1-indanone

A solution of 3-hydroxy-6-fluoro-1-indanone (4.09 g, 24.6 mmoles) in dimethylformamide (10 mL) was added to a solution of tert-butyldimethylsilyl chloride (4.60 g, 30.5 mmoles, Aldrich) and imidazole (4.22 g, 62.0 mmoles, Aldrich) in dimethylformamide (20 mL). The solution was stirred at ambient temperature for 18 hours and evaporated *in vacuo*. The residue was dissolved in dichloromethane (200 mL) and washed with water (6 x 75 mL) and brine (100 mL), dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with hexane : ethyl acetate (95 : 5). The fractions containing the major spot were combined and evaporated *in vacuo*, and the residue was dried in a vacuum at ambient temperature for 18 hours to give 4.14 g (60%) of 3-((tert-butyldimethylsilyl)oxy)-6-fluoro-1-indanone as a white solid, mp 56-58°C; ^{1}H-NMR (DMSO-d6): d7.41-7.68 (m, 3H), 5.47 (m, 1H), 3.16 (dd, 1H, J = 6.6 Hz, 18.5 Hz), 2.65 (dd, 1H, J = 3.2 Hz, 18.3 Hz), 0.92 (s, 9H), 0.22 (s, 3H), 0.18 (s, 3H).

Anal. Calcd. for $C_{15}H_{21}FO_2Si$ (mw 280.41): C, 64.25; H, 7.56.
Found: C, 64.13; H, 7.52.

d) Preparation of Ethyl 2-(3-((tert-butyldimethylsilyl)oxy)-6-fluoro-1-hydroxy-1-indanyl) acetate

A solution of ethyl acetate (1.00 mL, 10.3 mmoles) and lithium diisopropylamine [This salt was prepared from diisopropylamine (1.41 mL, 10.0 mmoles, Aldrich) and n-butyl lithium (4.00 mL of a 2.5 M hexane solution, 10.0 mmoles, Aldrich)], in tetrahydrofuran (15 mL) was stirred at -78°C under nitrogen for 15 minutes. A solution of 3-((tert-butyldimethylsilyl)oxy)-6-fluoro-1-indanone

(2.80 g, 10.0 mmoles) in tetrahydrofuran (15 mL) was added dropwise over a 7 minute period, and the solution was stirred at -78°C under nitrogen for 1.5 hours. A solution of ammonium chloride (1.60 g, 30.0 mmoles) in water (9 mL) was added, and the resulting suspension was allowed to warm to ambient temperature. The layers were separated, and the aqueous layer was extracted with ether (2 x 100 mL). The organic extracts were combined and washed successively with water (100 mL) and brine (100 mL), dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with hexane : ethyl acetate (98 : 2), gradually increasing the polarity to hexane : ethyl acetate (4 : 1). The fractions containing the major spot were combined and evaporated *in vacuo*, and the residue was dried in a vacuum at ambient temperature for 18 hours at 60°C to give 2.86 g (78%) of ethyl 2-(3-((tert-butyldimethylsilyl)oxy)-6-fluoro-1-hydroxy-1-indanyl) acetate as a clear oil; ^{1}H-NMR (DMSO-d$_6$): d7.11-7.27 (m, 3H), 5.69 (s, 1H), 3.97 (q, 2H), 5.07 (t, 1H), 3.03 and 1.93 (m, 2H), 2.63 (d, 2H), 1.09 (t, 3H), 0.93 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H).

Anal. Calcd. for $C_{19}H_{29}FO_4Si$ (mw 368.521): C, 61.92; H, 7.93.
Found: C, 61.93; H, 7.77.

e) Preparation of (E)-Ethyl 2-(3-((tert-butyldimethylsilyl)oxy)-6-fluoro-1-indanylidene) acetate

A solution of ethyl 2-(3-((tert-butyldimethylsilyl)oxy)-6-fluoro-1-hydroxy-1-indanyl) acetate (2.80 g, 7.6 mmoles) was added to a solution of bis[2,2,2-trifluoro-1-phenyl-1-(trifluoromethyl)-ethoxy]diphenylsulfurane (6.30 g, 9.4 mmoles, Fluka) in dichloromethane (50 mL) under a nitrogen atmosphere. The solution was stirred at ambient temperature for 35 minutes and poured into water (500 mL). The organic layer was separated, washed with brine (250 mL), dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with hexane : ethyl acetate (99 : 1). The fractions containing the major spot (and also a minor impurity) were combined and evaporated *in vacuo* to give 2.68 g (quantitative) of crude (E)-ethyl 2-(3-((tert-butyldimethylsilyl)oxy)-6-fluoro-1-indanylidene) acetate as a yellow oil which was used without further purification; ^{1}H-NMR ($CDCl_3$): d7.05-7.52 (m,

3H), 6.22 (m, 1H), 5.25 (m, 1H), 4.22 (q, 2H), 3.82 and 2.98 (m, 2H), 1.25 (t, 3H), 0.93 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H).

f) Preparation of (E)-2-(3-((tert-butyldimethylsilyl)oxy)-6-fluoro-1-indanylidene acetamide

A solution of dimethylaluminum amide was prepared by adding trimethyl aluminum (6.5 mL of a 2.0 M toluene solution, 13.0 mmoles, Aldrich) to a solution of ammonium chloride (0.695 g, 13.0 mmoles) in dichloromethane (25 mL) under a nitrogen atmosphere and stirring for 45 minutes at ambient temperature. This solution of dimethylaluminum amide (13.0 mmoles) was added to a solution of (E)-ethyl 2-(3-((tert-butyldimethylsilyl)oxy)-6-fluoro-1-indanylidene) acetate (1.190 g, 3.4 mmoles) in dichloromethane (60 mL) under a nitrogen atmosphere. The mixture was stirred at ambient temperature for 30 minutes and refluxed for 18 hours. After cooling to ambient temperature and then in an ice bath, the mixture was quenched by dropwise addition of 0.5 N hydrochloric acid until gas evolution ceased. The solution was diluted with water (50 mL), the layers were separated, and the aqueous layer was extracted with dichloromethane (75 mL). The organic layers were combined, washed successively with water (75 mL) and brine (75 mL), dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was recrystallized from dichloromethane : hexane mixtures to give 0.321 g (29%) of (E)-2-(3-((tert-butyldimethylsilyl)oxy)-6-fluoro-1-indanylidene) acetamide as a white solid, mp 160-165°C; ^{1}H-NMR (DMSO-d_6): d7.02-7.45 (m, 5H), 6.44 (m, 1H), 5.30 (m, 1H), 3.68 and 2.82 (m, 2H), 0.91 (s, 9H), 0.18 (s, 3H), 0.16 (s, 3H).

Anal. Calcd. for $C_{17}H_{24}FNO_2Si$ (mw 321.467): C, 63.51; H, 7.52; N, 4.36. Found: C, 63.23; H, 7.50; N, 4.32.

g) Preparation of (E)-2-(6-fluoro-3-hydroxy-1-indanylidene)acetamide

A solution of (E)-2-(3-((tert-butyldimethylsilyl)oxy)-6-fluoro-1-indanylidene) acetamide (1.80 g, 5.6 mmoles) and pyridinium p-toluenesulfonate (0.85 g, 3.4 mmoles, Aldrich) in ethanol (65 mL) was heated at 55-68°C for 3.5 hours under a nitrogen atmosphere and evaporated *in vacuo*. The residue was dissolved in

ethyl acetate (150 mL) and washed successively with water (2 x 150 mL) and brine (150 mL), dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residue was chromatographed on silica gel eluting with ethyl acetate, gradually increasing the polarity to ethyl acetate : ethanol (95 : 5). The fractions containing the major spot were combined and evaporated *in vacuo*, and the residue was dried in a vacuum at 80°C for 18 hours to give 0.72 g (62%) of (E)-2-(6-fluoro-3-hydroxy-1-indanylidene)acetamide as a white solid, mp 166-168°C; ^{1}H-NMR (DMSO-d_6): d6.98-7.56 (m, 5H), 6.43 (s, 1H), 5.49 (d, 1H), 5.09 (m, 1H), 3.61 (dd, 1H, J = 7.6 Hz, 19.1 Hz), 2.85 (dd, 1H, J = 2.6 Hz, 19.0 Hz).

Anal. Calcd. for $C_{11}H_{10}FNO_2$ (mw 207.204): C, 63.76; H, 4.86; N, 6.76. Found: C, 63.51; H, 4.96; N, 6.62.

Example 58

Preparation of (Z)-2-(2,3-dihydroxy-6-fluoro-1-indanylidene) acetamide

A mixture of (Z)-2-(2,3-dibromo-6-fluoro-1-indanylidene)acetamide (0.54 g, 1.55 mmoles) and silver carbonate (0.56 g, 2.03 mmoles, Aldrich) in dimethoxyethane (15 mL) and water (30 mL) was refluxed for 6 hours. The mixture was stirred overnight at ambient temperature and refluxed again for 6 hours. The mixture was diluted with water (100 mL) and extracted with ethyl acetate (6 x 30 mL). The combined extracts were washed with water (100 mL) and brine (100 mL), and evaporated *in vacuo*. The residue was chromatographed on silica gel, eluting with hexane : ethyl acetate (2 : 1). The fractions containing the compound with Rf = 0.15, eluting with ethyl acetate, were combined and evaporated *in vacuo* to give 0.12 g (35%) of crude (Z)-2-(2,3-dihydroxy-6-fluoro-1-indanylidene) acetamide as a beige solid. Recrystallization from ethyl acetate : hexane mixtures gave 0.037 g (11%) of (Z)-2-(2,3-dihydroxy-6-fluoro-1-indanylidene)acetamide as an off-white solid which was shown by ^{1}H-NMR to be a mixture (85 : 15) of diastereomers, mp 212-220°C; ^{1}H-NMR (DMSO-d_6): d 7.82 (d, 2H), 7.28-7.76 (m, 3H), 6.96 (s, 1H), 6.80 (s, 0.15H), 6.54 (s, 0.85H), 6.51 and 6.12 (m, 0.3H), 5.92 (d, 1H), 4.81 (m, 1.7H); steady-state nOe: irradiation at 6.47d, observed 20% nOe at 7.38d.

Anal. Calcd. for $C_{11}H_{10}FNO_3$ (mw 223.13): C, 59.21; H, 4.49; N, 6.28.

Found: C, 59.28; H, 4.54; N, 6.23.

EXAMPLE 59

Preparation of (E)-2-(6-Fluoro-2-hydroxy-1-indanylidene)acetamide

A solution of (Z)-2-(6-fluoro-2-hydroxy-1-indanylidene)acetamide (5.456 g, 0.026 mol) in dichloromethane:methanol/9:1 (1000ml) was irradiated by an Canrad-Hanovia quartz, mecury-vapor photochemical immersion lamp, 450 wattts (Ace Glass, 7825-35) for 1h. The volitiles were removed by spin evaporation *in vacuo* to give a light brown solid residue. This residue was chromatographed on Silica Gel 60 using a step gradient going from ethyl acetate:hexanes/1:1 to ethyl acetate:ethanol/1:1. Fractions containing (E)-2-(6-fluoro-2-hydroxy-1-indanylidene)acetamide were combined and concentrated by spin evaporation *in vacuo*. The resulting residue was recrystallized from ethanol-hexanes to give 1.31g (24%) of (E)-2-(6-fluoro-2-hydroxy-1-indanylidene)acetamide as an off-white crystalline solid, m.p., 159-163°C, NMR(DMSO-d_6): d 8.56 (dd, 1H, J_{HF}= 11.0 Hz, J_{HH}= 2.9 Hz), 7.67 (br s, 1H), 7.34-7.30 (m, 1H), 7.2-7.13 (m, 1H), 7.06 (br s, 1H),6.18 (s, 1H), 5.69 (d,1H, J=6.8 Hz), 4.74 (q, 1H, J=12.1 Hz, J= 6.0 Hz), 3.21-3.13 (m, 1H) 2.73-2.66(m,1H); steady state nOe: irradiation at d6.19,observed 5.4% nOe at d4.74, 4.3% at d7.67 and 1.5% at d 5.69.

Anal. Calcd. for $C_{11}H_{10}FNO_2$ 0.5 H_2O (mw 216.212): C, 61.11; H, 5.13; N, 6.48. Found: C, 61.20; H, 5.17; N, 6.44.

EXAMPLE 60

Preparation of (E)-2-(6-Fluoro-3-oxo-1-indanylidene)acetamide

a) Preparation of (E)-Ethyl 3-fluorocinnamate

This compound was prepared in an analogous manner to Example 44a with the replacement of 4'-fluoroacetophenone with 3-fluorobenzaldehyde (Aldrich). Distillation gave 32.85g (56%) of (E)-ethyl 3-fluorocinnamate in 5 fractions (b.p., 140 - 155°C at 15 Torr) which were equally contaminated with

approximately 13% of triethyl phosphonoacetate. This material was used without additional purification. ^{1}H NMR (DMSO-d_6): d 7.66 - 7.47 (m, 2H), 7.45 - 7.40 (m, 1H), 7.27 - 7.20 (m, 1H), 6.70 (d, 1H, J_{HH} = 16 Hz), 4.18 (q, 2H, J_{HH} = 7.2 Hz), 4.10 - 3.96 (m, 0.78H), 3.77 (d, 0.26H, J_{PH} = 21.3 Hz), 1.24 (t, 3H, J_{HH} = 7.0 Hz), 1.24 - 1.14 (m, 1.17H).

b) Preparation of Diethyl 2-carbethoxy-3-(3-fluorophenyl)glutarate

Sodium metal (0.388g, 0.0169 mol) was stirred in diethyl malonate (15.28 g, 0.0953 mol, Aldrich) under a nitrogen atmosphere at 120°C for 0.33 hr. To the resulting solution was added (E)-ethyl 3-fluorocinnamate (16.4g, 0.0845 mol) and stirring was continued for 7 hrs at the same temperature. The dark solution was cooled, dissolved in dichloromethane (500 ml) and made acidic with 30 ml of 1N aqueous hydrochloric acid (Macintosh). The volatiles were removed from the resulting froth by spin evaporation *in vacuo* and the residue was dissolved in ethyl acetate. This solution was washed with 5% aqueous sodium bicarbonate until neutral, water, and the volatiles were removed by spin evaporation *in vacuo*. Distillation gave 20 g of a material boiling between 130 - 185°C at 0.150 Torr. Redistillation gave 14.72 g (44%) of diethyl 2-carbethoxy-3-(3-fluorophenyl)glutarate as a clear liquid: b.p., 155 - 160°C at 0.1 Torr; ^{1}H NMR (DMSO-d_6): d 7.38 - 7.00 (m, 4H), 4.18 (q, 2H, J_{HH} = 7.1 Hz), 4.01 (d, 2H, J_{HH} = 10.8 Hz), 3.96 - 3.81 (m, 4H), 3.79 - 3.63 (m, 1H), 2.76 (d, 2H, J_{HH} = 7.7 Hz), 1.20 (t, 3H, J_{HH} = 7.1 Hz), 1.01 (t, 3H, J_{HH} = 7.1 Hz), 0.889 (t, 3H, J_{HH} = 7.0 Hz).

Anal. Calcd. for $C_{18}H_{23}FO_6$ (mw 354.378): C, 61.01; H, 6.54.
Found: C 61.04; H, 6.62.

c) Preparation of 3-(3-Fluorophenyl)glutaric acid

To a hot solution of sodium hydroxide (19.15 g, 0.479 mol) in water (50 ml) was added a solution of diethyl 2-carbethoxy-3-(3-fluorophenyl)glutarate (18.8g, 0.0532 mol) in ethanol (36 ml). The resulting slurry was refluxed for 5 hrs. The mixture was poured into icewater and the ethanol was removed by spin evaporation *in vacuo*. The residual aqueous solution was acidified with

concentrated hydrochloric acid (12 N) and the solution (200 ml) was extracted with ethyl acetate (3 x 300 ml). The ethyl acetate layers were combined, washed with water (50 ml) and the volatiles were removed by spin evaporation *in vacuo* to give a solid that was recrystallized from dichloromethane and hexanes to give 9.3 g (77%) of 3-(3-fluorophenyl)glutaric acid a white solid; m.p., 126 - 127.5°C; ^{1}H NMR (DMSO-d_6): d 12.15 (b s, 2H), 7.38 - 7.26 (m, 1H), 7.14 - 6.98 (m, 3H), 3.47 - 3.35 (m, 1H), 2.73 - 2.47 (m, 4H).

Anal. Calcd. for $C_{11}H_{11}FO_4$ (mw 226.205): C, 58.41; H, 4.90.
Found: C 58.20; H, 4.99.

d) Preparation of 2-(6-Fluoro-3-oxo-1-indanyl)acetic acid

Polyphosphoric acid (39.6g, Aldrich) and 3-(3-fluorophenyl)glutaric acid (6.6g, 0.0292 mol) were combined and the mixture heated with an oil bath at 120°C for 10 min. The now red solution was cooled to approximately 60°C and water (approximately 100 ml) was added dropwise, with efficient stirring. The resulting precipitate was collected and washed with water. Recrystallization from dichloromethane and hexanes gave 5.3g (87%) of 2-(6-fluoro-3-oxo-1-indanyl)acetic acid: m.p.,150 - 151°C; ^{1}H NMR (DMSO-d_6): d 12.31 (b s, 1H,), 7.65 - 7.69 (m, 1H), 7.52-7.56 (m, 1H), 7.23 - 7.29 (m, 1H), 3.69 - 3.61 (m, 1H), 2.96 - 2.84 (m, 2H), 2.61 - 2.36 (m, 2H).

Anal. Calcd. for $C_{11}H_9FO_3$ (mw 208.190): C, 63.46; H, 4.63.
Found: C 63.46; H, 4.41.

e) Preparation of 2-(6-Fluoro-3-oxo-1-indanyl)acetyl chloride

Oxalyl chloride (4.5 g, 0.035 mol, Aldrich) was added to an ice cold stirring mixture of 2-(6-fluoro-3-oxo-1-indanyl)acetic acid (5.0 g, 0.024 mol) in dichloromethane (200 ml) under a nitrogen atmosphere. The mixture was allowed to warm to room temperature and stirring was continued for 48 hrs. The volatiles were removed from the solution by spin evaporation *in vacuo* with the addition of dichloromethane (3 x 50 ml) to give 2-(6-fluoro-3-oxo-1-indanyl)acetyl chloride which was used without purification or analysis.

f) Preparation of 2-(6-Fluoro-3-oxo-1-indanyl)acetamide

A solution of 2-(6-fluoro-3-oxo-1-indanyl)acetyl chloride (prepared from 0.024 mol of 2-(6-fluoro-3-oxo-1-indanyl)acetic acid) in dichloromethane (150 ml) was cooled to 0_C and stirred rapidly while 50 ml of ammonium hydroxide, 28-30%, was added. The resulting mixture was allowed to warm to room temperature and stirring was continued for 18 hr. The volatiles from this mixture were removed by spin evaporation *in vacuo* and the residue was dissolved in dichloromethane (250 ml) and washed with water (3 x 50 ml). The dichloromethane phase was then slurried with Silica Gel 60 and the volatiles were removed by spin evaporation *in vacuo*. This silica was then applied to a column of Silica Gel 60 (51 x 400 mm) wet with dichloromethane and the product was removed by elution with methanol:dichloromethane (3:97) to give, after recrystallization from methanol, 2.4 g (48%) of 2-(6-fluoro-3-oxo-1-indanyl)acetamide as a yellow solid: m.p., 150-152°C : ^{1}H NMR (DMSO-d6): d 7.74 - 7.66 (m, 1H), 7.54 - 7.49 (m, 1H), 7.40 (b s, 1H), 7.36 - 7.24 (m, 1H), 6.95 (b s, 1H), 3.79 - 3.66 (m, 1H), 2.89 (dd, 1H, J_{HH} = 19.1 and 7.6 Hz), 2.69 (dd, 1H, J_{HH} = 14.8 and 5.4 Hz), 2.47 - 2.29 (m, 2H).

Anal. Calcd. for $C_{11}H_{10}FNO_2$ (mw 207.205): C, 63.76; H, 4.86; N, 6.76. Found: C 63.76; H, 4.86; N, 6.73.

g) Preparation of (E)-2-(6-Fluoro-3-oxo-1-indanylidene)acetamide

A mixture of 2-(6-fluoro-3-oxo-1-indanyl)acetamide (0.750g, 0.0036 mol), N-bromosuccinimide (0.750g, 0.0042 mol, Aldrich), benzoyl peroxide (0.270g, 0.0011 mol, Aldrich) in tetrachloromethane (37 ml) and benzene (37 ml) was stirred while heating with an oil bath at 120°C for 20 min. This reaction was combined with a similarly run reaction (except 0.0024 mol scale). The solution was slurried with Silica Gel 60 and the volatiles were removed by spin evaporation *in vacuo*. This silica gel was then applied to a column of Silica Gel 60 (51 x 450mm) wet with dichloromethane and the product was removed by elution with methanol:dichloromethane (3:97). After the volatiles were removed from the combined fractions containing product by spin evaporation *in vacuo*, the

residue was recrystallized from methanol to give 0.810g (58%) of (E)-2-(6-fluoro-3-oxo-1-indanylidene)acetamide: m.p., 235°C (dec.); ^{1}H NMR (DMSO-d6): d 7.82 - 7.77 (m, lH), 7.73 - 7.70 (m, 1H), 7.55 (b s, 1H,), 7.47 - 7.40 (m, 1H), 7.22 (b s, 1H), 6.67 (s, 1H), 3.63 (s, 2H); steady-state nOe: irradiation at d 6.67, observed 21% nOe at d 7.73 - 7.70, 3.3% nOe at d 7.55, and 1.3% nOe at d 7.22.

Anal. Calcd. for $C_{11}H_8FNO_2$ (mw 205.190): C, 64.39; H, 3.93; N, 6.83.
Found: C 64.36; H, 3.94; N, 6.85.

EXAMPLE 61

Preparation of (E)-2-(4-Chloro-6 -fluoro-1-indanylidene)-N-Methylacetamide

a) Preparation of 2-Chloro-4-Fluorocinnamic acid

This compound was prepared in an analogous manner to that described for the preparation of 2-Chlorocinnamic acid in Example 10a substituting 2-chloro-4-fluorobenzaldehyde (20.0g, 0.13 mol, Aldrich) for 2-chlorobenzaldehyde to give 24.4g (96%) of 2-chloro-4-fluorocinnamic acid as a white solid.
Recrystallization of 1.5g from acetone:water mixtures gave 1.1g of 2-chloro-4-fluorocinnamic acid as a white solid: mp 243-245°C; NMR (DMSO-d6); d 12.7 (br, 1H), 7.25-8.02 (m, 3H), 7.79 (d, 1H, J= 15.8 Hz), 6.58 (d, 1H, J= 16.0 Hz).

Anal. Calcd. for $C_9H_6ClFO_2$ (mw 200.60): C, 53.88; H , 3.02.
Found: C, 53.91; H , 3.03.

b) Preparation of 3-(2-Chloro- 4-fluorophenyl)propanoic Acid

This compound was prepared in a similar manner as that described for the preparation of ethyl 3-(2-chlorophenyl)propionate in Example 10c substituting 2-chloro-4-fluorocinnamic acid (22.9g, 0.11 mol) for ethyl 2-chlorocinnamate to give 22.6g (98%) of 3-(2-chloro-4-fluorophenyl) propanoic acid as a purple solid. This material was used without further purification.

c) Preparation of 4-Chloro-6-fluoro-1-indanone

This material was prepared in a similar manner to that described for 4-choro-1-indanone in Example 10e substituting 3-(2-chloro-4-fluorophenyl) propanoic acid (21.6g, 0.11 mol) for 3-(2-chlorophenyl) propanoic acid. Chromatography on silica gel with hexanes: dichloromethane (1:1) as eluent gave 11.1g (55%)of 4-choro-6-fluoro-1-indanone a white solid: mp 94-96°C ; NMR (DMSO-d_6) : d 7.41-7.83 (m, 2H), 3.01 (m, 2H), 2.73 (m, 2H).

Anal. Calcd. for C_9H_6ClFO (mw 184.60): C, 58.56; H , 3.28.
Found: C, 58.38; H , 3.34.

d) Preparation of Ethyl 2-(4-Chloro-6-fluoro-1-hydroxy-1-indanyl)acetate

Ethyl acetate (5.9g, 0.07 mol) was added dropwise to a stirred , chilled (dry ice-acetone bath) solution of lithium diisopropylamide (prepared by dropwise addition of a 2.5M solution of n-butyllithium (26.8 mL, 0.07 mol) in hexane to a chilled (dry ice-acetone bath) solution of diisopropylamine (6.8g, 0.07 mol) in tetrahydrofuran (35 mL)) . After 30 min, a solution of 4-chloro-6-fluoro-1-indanone (12.4g, 0.07 mol) in tetrahydrofuran (100 mL) was added dropwise and the mixture was stirred for 1h (dry ice-acetone bath). A solution of ammonium chloride (10.6g, 0.20 mol) in water (80 mL) was added and the mixture was allowed to come to ambient temperature. The aqueous phase was separated and extracted with diethyl ether. The combined organic phase was dried (sodium sulfate), filtered and concentrated *in vacuo* to give 19.5g of crude ethyl 2-(4-chloro-6-fluoro-1-hydroxy-1-indanyl)acetate. Chromatography on silica gel with hexanes: ethyl acetate (8:2) as eluent gave 15.2g (83%) of a yellow oil ; NMR (DMSO-d_6): d 7.13- 7.28 (m, 2H), 5.55 (s, 1H), 3.98 (m, 2H), 2.79 (2m's, 4H), 2.50 (m, 1H), 2.11 (m, 1H), 1.08 (t, 3H).

Anal. Calcd. for $C_{13}H_{14}ClFO_3$ (mw 272.70): C, 57.25; H, 5.17.
Found: C, 57.17; H, 5.18.

e) Preparation of 2-(4-Chloro-6-fluoro-1-hydroxy-1-indanyl)acetic Acid

This compound was prepared in a similar manner to that described for 2-(4-chloro-1-hydroxy-1-indanyl)acetic acid in Example 10g by substituting ethyl 2-(4-chloro-6-fluoro-1-hydroxy-1-indanyl)acetate (14.5g , 0.05 mol) for ethyl 2-(6-chloro- 1-hydroxy-1-indanyl) acetate to give 12.5g (96%) of crude 2-(4-chloro-6-fluoro-1-hydroxy-1-indanyl)acetic acid. This material was used immediately without further purification.

f) Preparation of (E)-2-(4-Chloro-6-fluoro-1-indanylidene)acetic Acid

This compound was prepared in an analogous manner to (E)-2-(4-chloro-1-indanylidene) acetic acid in Example 10h by substituting 2-(4-chloro-6-fluoro-1-hydroxy-1-indanyl)acetic acid (12.5g, 0.05 mol) for 2-(4-chloro-1-hydroxy-1-indanyl)acetic acid to give 10.6g of crude (E)-2-(4-chloro-6-fluoro-1-indanylidene)acetic acid. Chromatography of a 1.0g sample on silica gel with ethyl acetate: hexanes (1:1) as eluent gave 0.32g of (E)-2-(4-chloro-6-fluoro-1-indanylidene)acetic acid as a white solid: mp 229-230°C; NMR (DMSO-d6): d12.20 (br , 1H), 7.44-7.73 (m, 2H), 6.44 (t, 1H), 3.21 (m, 2H), 2.97 (m, 2H); steady-state nOe: irradiation at 6.44 d, observed 15.4% nOe at 7.71 d.

Anal. Calcd. for $C_{11}H_8ClFO_2$ (mw 226.63): C, 58.29; H, 3.56.
Found: C, 58.32; H, 3.60.

g) Preparation of (E)-2-(4-Chloro-6-fluoro-1-indanylidene)acetyl Chloride

This compound was prepared in a similar manner to (E)-2-(4-chloro-1-indanylidene)acetyl Chloride in Example 10i by substituting (E)-2-(4-chloro-6-fluoro-1-indanylidene)acetic Acid (9.6g, 0.04mol) for (E)-2-(4-chloro-1-indanylidene)acetic Acid. The resulting solution was concentrated *in vacuo* and the residue used without further purification.

h) Preparation of (E)-2-(4-Chloro-6-fluoro-1-indanylidene)-N-Methylacetamide

A solution of (E)-2-(4-chloro-6-fluoro-1-indanylidene)acetyl chloride (4.0g, 0.015 mol) in dichloromethane (36 mL) was added dropwise to an ice-cold mixture of 40% aqueous methylamine (2.6 mL, 0.03 mol) and dichloromethane (100 mL) and the mixture was stirred at ambient temperature for 18 h. The reaction mixture was concentrated in vacuo and the residue was partitioned between 5% aqueous sodium bicarbonate and ethyl acetate. The ethyl acetate solution was dried over sodium sulfate, filtered and concentrated in vacuo. The residue was purified by column chromatography on silica gel using ethyl acetate:hexanes (1:1) as eluent to give 1.59g (44%) of (E)-2-(4-chloro-6-fluoro-1-indanylidene)-N-Methylacetamide as a white solid: mp 173-175°C; NMR ($CDCl_3$): d 7.10-7.30 (m, 2H),6.16 (s, 1H), 5.64 (br, 1H), 3.42-3.48 (m, 2H), 3.01-3.07 (m, 2H) 2.95 (s, 3H); steady-state nOe: irradiation at 6.16 d, observed 10.3% nOe at 7.16d.

Anal. Calcd. for $C_{12}H_{11}ClFNO$ (mw 239.67): C, 60.13; H, 4.63; N, 5.84. Found: C, 60.08; H, 4.65; N, 5.84.

Example 62

(E)-2-(4-Chloro-6-fluoro-1-indanylidene)acetamide

A solution of (E)-2-(4-chloro-6-fluoro-1-indanylidene)acetyl chloride (4.0g, 0.015 mol) [as prepared in example 61g] in dichloromethane (36 mL) was added dropwise to an ice-cold mixture of 30% aqueous ammonium hydroxide (2.0 mL, 0.03 mol) and dichloromethane (100 mL) and the mixture was stirred at ambient temperature for 18 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between 5% aqueous sodium bicarbonate and ethyl acetate. The ethyl acetate solution was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with ethyl acetate: hexanes (2:1) as eluent. Trituration of the resulting solid with pentane gave 1.47g (43%) of (E)-2-(4-chloro-6-fluoro-1-indanylidene)acetamide as a white solid: m.p. 182-184°C; NMR ($CDCl_3$): d 7.12-7.18 (m, 2H), 6.26 (t, 1H), 5.73 (br s, 2H), 3.43 (m, 2H), 3.07 (m, 2H,); steady-state nOe: irradiation at 6.26 d, observed 10% nOe at 7.16d.

Anal. Calcd. for $C_{11}H_9ClFNO$ (mw 225.65): C, 58.55; H, 4.02; N, 6.21.
Found: C, 58.63; H, 4.06; N, 6.28.

EXAMPLE 63

Preparation of (E)-2-(4,6-dichloro-1-indanylidene)acetamide

a) Preparation of 3-(2,4-dichlorophenyl)propanoic Acid

This compound was prepared in a similar manner as that described for the preparation of ethyl 3-(2-chlorophenyl)propionate in Example 10c substituting 2,4-dichlorocinnamic acid (25.0g, 0.12 mol, Aldrich) for ethyl 2-chlorocinnamate. After filtering off the catalyst and concentrating *in vacuo*, the residue was taken up in a mixture of ethyl acetate and dichloromethane and dried over sodium sulfate. The mixture was filtered and concentrated *in vacuo* to give 25.3g (quantitative yield) of crude 3-(2,4-dichlorophenyl)propanoic acid. This material was used without further purification.

b) Preparation of 4,6-dichloro-1-indanone

This material was prepared in a similar manner to that described for 4-chloro-1-indanone in Example 10e substituting 3-(2,4-dichlorophenyl) propanoic acid (24.3g, 0.11 mol) for 3-(2-chlorophenyl)propanoic acid. Chromatography on silica gel with hexanes: dichloromethane (1:1) as eluent gave 12.2g (55%) of 4,6-dichloro-1-indanone as a white solid. Recrystallization of 1.0g from hexanes gave 0.7g of 4,6-dichloro-1-indanone as a white solid: mp 118-120°C; NMR ($CDCl_3$) : d 7.59-7.63 (m, 2H), 3.10 (m, 2H), 2.77 (m, 2H).

Anal. Calcd. for $C_9H_6Cl_2O$ (mw 201.05): C, 53.76; H , 3.01.
Found: C, 53.67; H , 3.05.

c) Preparation of Ethyl 2-(4,6-Dichloro-1-hydroxy-1-indanyl)acetate

Ethyl acetate (4.9g, 0.06 mol) was added dropwise to a stirred , chilled (dry ice-acetone bath) solution of lithium diisopropylamide (prepared by dropwise addition of a 2.5M solution of n-butyllithium (22.4 mL, 0.06 mol) in hexane to a chilled (dry ice-acetone bath) solution of diisopropylamine (5.7g, 0.06 mol) in tetrahydrofuran (40 mL)) . After 30 min, a solution of 4,6-dichloro-1-indanone (11.2g, 0.06 mol) in tetrahydrofuran (50 mL) was added dropwise and the mixture was stirred for 1h (dry ice-acetone bath). A solution of ammonium chloride (9.0g, 0.18 mol) in water (80 mL) was added, and the mixture was allowed to warm to ambient temperature overnight. The aqueous phase was separated and extracted with diethyl ether. The combined organic phase was dried (sodium sulfate), filtered and concentrated *in vacuo* to give 15.5g of crude Ethyl 2-(4,6-dichloro-1-hydroxy-1-indanyl)acetate. Chromatography on silica gel with hexanes: ethyl acetate (8:2) as eluent gave 10.6g (65%) of a yellow oil ; NMR ($CDCl_3$): d 7.22- 7.27 (m, 2H), 4.28 (br, 1H), 4.21 (m, 2H), 3.03 (m, 1H), 2.75 (m, 3H), 2.30 (m, 2H), 1.28 (t, 3H).

Anal. Calcd. for $C_{13}H_{14}Cl_2O_3$ (mw 289.16): C, 54.00; H, 4.88.
Found: C, 53.96; H, 4.91.

d) Preparation of 2-(4,6-Dichloro-1-hydroxy-1-indanyl)acetic Acid

This compound was prepared in a similar manner to that described for 2-(4-chloro-1-hydroxy-1-indanyl)acetic acid in Example 10g by substituting ethyl 2-(4,6-dichloro-1-hydroxy-1-indanyl)acetate (9.9g , 0.03 mol) for ethyl 2-(6-chloro-1-hydroxy-1-indanyl)acetate to give 8.6g (96%) of crude 2-(4,6-dichloro-1-hydroxy-1-indanyl)acetic acid. This material was used immediately without further purification.

e) Preparation of (E)-2-(4,6-Dichloro-1-indanylidene)acetic Acid

This compound was prepared in an analogous manner to (E)-2-(4-chloro-1-indanylidene)acetic acid in Example 10h by substituting 2-(4,6-dichloro-1-hydroxy-1-indanyl)acetic acid (8.6g, 0.03 mol) for 2-(4-chloro-

1-hydroxy-1-indanyl)acetic acid to give 6.31g of crude (E)-2-(4,6-dichloro-1-indanylidene)acetic acid. A 1.0g sample was recrystallized from isopropanol: water mixtures to give 0.6g of (E)-2-(4,6-dichloro- 1-indanylidene)acetic acid as a white solid: mp 245-247°C; NMR (DMSO-d_6): d12.26 (br s , 1H), 7.96 (d, 1H), 7.62 (d, 1H), 6.50 (t, 1H), 3.22 (m, 2H), 2.98 (m, 2H); steady-state nOe: irradiation at 6.50 d, observed 26.5% nOe at 7.96 d.

Anal. Calcd. for $C_{11}H_8Cl_2O_2$ (mw 243.09): C, 54.35; H, 3.32.
Found: C, 54.40; H, 3.33.

f) Preparation of (E)-2-(4-Chloro-6-fluoro-1-indanylidene)acetyl Chloride

This compound was prepared in a similar manner to (E)-2-(4-chloro-1-indanylidene)acetyl chloride in Example 10i by substituting (E)-2-(4,6-dichloro-1-indanylidene)acetic acid (5.3g, 0.02mol) for (E)-2-(4-chloro-1-indanylidene)acetic acid. The resulting solution was concentrated *in vacuo* and the residue used without further purification.

g) Preparation of (E)-2-(4,6-Dichloro-1-indanylidene)acetamide

A solution of (E)-2-(4,6-dichloro-1-indanylidene)acetyl chloride (2.09g, 0.008 mol) in dichloromethane (37 mL) was added dropwise to an ice-cold mixture of 30% aqueous ammonium hydroxide (1.04 mL, 0.016 mol) and dichloromethane (50 mL), and the mixture was stirred at ambient temperature for 18 h. The reaction mixture was concentrated *in vacuo* , and the residue was partitioned between 5% aqueous sodium bicarbonate and ethyl acetate. The ethyl acetate solution was dried over sodium sulfate, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel with ethyl acetate: hexanes (3:2) as eluent. Trituration of the resulting solid with pentane gave 1.01g (52%) of (E)-2-(4,6-dichloro-1-indanylidene)acetamide as a white solid: m.p. 210-212°C; NMR (DMSO-d_6): d 7.57-7.59 (m, 2H), 7.33 (br, 1H), 7.02 (br, 1H), 6.49 (t, 1H), 3.23 (m, 2H), 2.97 (m, 2H); steady-state nOe: irradiation at 6.49 d, observed 33.7% nOe at 7.58d, 3.8% nOe at 7.33d and 2.26% nOe at 7.02d.

Anal. Calcd. for $C_{11}H_9Cl_2NO$ (mw 242.10): C, 54.57; H, 3.75; N, 5.79. Found: C, 54.52; H, 3.82; N, 5.74.

Example 64

Preparation of (E)-N-Cyclopropyl-2-(6-fluoro-3-ethyl-1-indanylidene)acetamide

a) Preparation of Ethyl 3-(4-fluorophenyl)pentenoate

A solution of butyllithium, 1.6M in hexanes (230ml,0.368 mol, Aldrich) was added dropwise over 0.5 hr, with rapid mechanical stirring, to a solution of triethyl phosphonoacetate (78.9g, 0.351 mol, Aldrich) in tetrahydrofuran (800ml, anhydrous, Aldrich) at <5°C while blanketed with a nitrogen atmosphere. This solution was stirred for an additional 0.25 hr and cooled to -5°C with a methanol:ice bath and a solution of 4'-fluoropropiophenone (50g,0.328 mol, Aldrich) in tetrahydrofuran (50ml) was then added in one portion. Stirring was continued for 18 hr without additional cooling. The solution was concentrated to a golden yellow sludge by spin evaporation *in vacuo* and diluted to 1000ml with ethyl acetate. After washing with deionized water (3 x 100ml) this solution was concentrated by spin evaporation *in vacuo*.. Distillation at reduced pressure gave 45.65g (63%) of ethyl 3-(4-fluorophenyl)pentenoate as a mixture of (E) and (Z) isomers (ratio 1:1) contaminated with 30% of triethyl phosphonoacetate as a clear liquid, b.p. 140-146°C at aspirator pressure: NMR ($CDCl_3$): d 7.44-6.97 (m, 4H) , 5.96 and 5.87 (2 s, 1H), 4.23- 3.96 (m, 3.8 H, 3.11-3.04 (q, 1H, J= 14.7 Hz, J= 7.2 Hz), 2.96 (d, 0.6 H, J= 21.6), 2.43 (q, 1H, J=14.7 Hz , J=7.5 Hz), 1.42- 1.01 (m, 8.7 H).

b) Preparation of Ethyl 3-(4-Fluorophenyl)valerate

A mixture of ethyl 3-(4-fluorophenyl)pentenoate (45.65 g,0.137 mol) and 10% palladium on carbon (0.86 g, Aldrich) in 95 % ethanol was shaken under 4 atm hydrogen pressure in a Parr hydrogenator for 1.5 hr. The mixture was filtered and concentrated by spin evaporation *in vacuo* . Fractional distillation gave 38.95g (63%) of ethyl 3-(4-fluorophenyl)valerate as a clear oil contaminated with 29% triethyl phosphonoacetate , b.p., 133-142°C at 17 mm Hg: NMR (DMSO-

d_6): d 7.25- 7.2 9 m, 2H), 7.11-7.05 (m, 2H), 4.11-3.97 (m, 1.7H), 3.91 (q, 2H, J= 6.9 Hz), 3.08 (d,0.58 H, J= 21.6 Hz), 2.91- 2.85 (m, 1H), 2.68 -2.45 (m, 2H), 1.66-1.44 (m, 2H), 1.24- 1.14 (m, 2.6 H), 1.02 (t, 3H, J= 7.2 Hz), 0.68 (t, 3H, J= 7.2 Hz).

c) Preparation of 3-(4-Flurophenyl)valeric acid

This compound was prepared in an analogous manner to Example 44c with the replacement of 3-(4-fluorophenyl)butyrate with ethyl 3-(4-fluorophenyl)valerate (38.95 g 0.144 mol, containing 29% triethyl phosphoneacetate) and using an excess of 85% potassium hydroxide (18.05 g, 0.273 mol, Mallinckrodt). The dichloromethane layers were combined, washed with deionized water (50 ml) and concentrated by spin evaporation *in vacuo*. The residue was crystallized from hexanes to give 23.47 g (83%) of 3-(4-flurophenyl)valeric acid as a white crystalline solid: NMR (DMSO-d_6): d 12 (s, 1H), 7.28-7.24 (m, 2H), 7.14-7.08 (m, 2H), 2.91-2.89 (m, 1H), 2.64-2.41 (m, 2H), 1.66-162 (m, 1H), 1.56-1.51 (m, 1H), 0.71 (t, 3H, J=7.3 Hz).

Anal. Calcd. for $C_{11}H_{13}FO_2$ (mw 196.221): C, 67.33; H, 6.68.
Found: C, 67.19; H, 6.76.

d) Preparation of 3-(4-Fluorophenyl)valeroyl chloride

This compound was prepared in an analogous manner to Example 44d with the replacement of 3-(4-fluorophenyl)butyric acid with 3-(4-fluorophenyl)valeric acid (23.47g, 0.120 mol). The volatiles were removed by spin evaporation *in vacuo* with the addition of dichloromethane (6 x 250 ml) during concentration to give 25.25 g (98%) of 3-(4-fluorphenyl)valeroyl chloride as a golden yellow liquid: NMR (DMSO-d_6): d 7.3-7.22 (m, 2H), 7.15-7.06 (m, 2H), 2.98-2.73 (m, 1H), 2.66-2.38 (m, 2H), 1.74-1.37 (m,2H), 0.70 (t, 3H, J=7.2 Hz).

e) Preparation of 3-Ethyl-6-fluoro-1-indanone

This compound was prepared in an analogous manner to Example 44e with the replacement of 3-(4-fluorophenyl)butyryl chloride with 3-(4-

fluorophenyl)valeroyl chloride(25.27g, 0.118 mol). The dichloromethane extractions were combined, washed with deionized water (100 ml) and concentrated by spin evaporation *in vacuo* The residue was chromatographed on Silica Gel 60 using a step gradient going from hexanes to ethyl acetate:hexanes/1:1. Fractions containing 3-ethyl-6-fluoro-1-indanone were combined and concentrated by spin evaporation *in vacuo* with dichloromethane (2 x 150 ml) added during concentration to give 17.48g (83%) of 3-ethyl-6-fluoro-1-indanone as a canary yellow syrup: NMR (DMSO-d_6): d 7.74-7.7 (dd, 1H, J_{HF}=8.4 Hz, J_{HH}=4.8 Hz), 7.6-7.53 (ddd, 1H, J_{HF}=9.0 Hz, J_{HH}=9.0 Hz and 2.7 Hz), 7.37 (dd, 1H,J_{HF}=7.8 Hz, J_{HH}= 2.4 Hz), ~3.3(m, 1H, partially obscured by water), 2.88 (dd,1H, J_{gem}=19.2 Hz, J =7.6 Hz), 2.39 (dd, 1H, J_{gem}=19.2 Hz, J =2.4 Hz), 1.98-1.90 (m, 1H), 1.54-1.44 (m, 1H), 0.90 (t, 3H, J=7.3 Hz).

Anal. Calcd. for $C_{11}H_{11}FO$ (mw 178.2): C, 74.14; H, 6.22.
Found: C,74.06; H, 6.21.

f) Preparation of *cis* and *trans* Ethyl 2-(3-ethyl-6-fluoro-1-hydroxy-1-indanyl)acetate.

This compound was prepared in an analogous manner to Example 44f with replacement of 6-fluoro-3-methyl-1-indanone with 3-ethyl-6-fluoro-1-indanone (17.3 g, 0.097 mol). Removal of the volatiles from the workup solution gave 25.17g (97%) of *cis* and *trans* ethyl 2-(3-ethyl-6-fluoro-1-hydroxy-1-indanyl)acetate as a golden yellow oil: NMR (DMSO-d_6): d 7.23-7.21 (m,1H), 7.13-7.06 (m, 2H), 5.48 (s, 1H), 4.0 (q, 2H, J = 7.2 Hz), 2.90-2.82 (m, 1H), 2.80-2.73 (m, 1H), 2.70-2.55 (m, 2H), 2.04-1.9 (m,1H), 1.83-167 (m, 1H), 1.46-1.28 (m,1H), 1.11 (t,3H, J=7.1 Hz), 0.95 (t, 3H, J=7.3 Hz).

Anal. Calcd. for $C_{15}H_{19}FO_3$ (mw 266.3): C, 67.65; H, 7.19.
Found: C, 67.40; H, 7.25.

g) Preparation of (E)-2-(3-Ethyl-6-fluoro-1-indanylidene)acetic acid

This compound was prepared in an analogous manner with Example 44g with the replacement of ethyl 2-(6-fluoro-1-hydroxy-3-methyl-1-indanyl)acetate with ethyl 2-(3-ethyl-6-fluoro-1-hydroxy-1-indanyl)acetate (24.85g, 0.093 mol). Removal of the volatiles from the workup gave a beige residue. Recrystallization from dichloromethane-hexanes gave 12.91g (63%) of (E)-2-(3-ethyl-6-fluoro-1-indanylidene)acetic acid as a white crystalline solid, m.p., 145-148°C: NMR (DMSO-d_6): d 12.1 (s, 1H), 7.65 (dd, 1H, J_{HF}=9.5 Hz, J_{HH}=2.5 H), 7.42 (ddd, 1H, J_{HF}= 5.2 Hz, J_{HH}= 8.4 Hz and 0.8 Hz), 7.22 (ddd, 1H, J_{HF}= 9.1 Hz, J_{HH}= 8.4 and 2.5 Hz), 6.4 (t, 1 H, J=2.4 Hz), 3.37 (ddd, 1 H, J= 19.5 Hz, 7.9 Hz, and 2.6 Hz), 3.16 (m, 1H), 2.81 (ddd, 1H, J=19.5 Hz, 3.6 Hz, and 2.7 Hz), 1.86-1.73 (m, 1H), 1.46-1.132 (m, 1H), 0.89 (t, 3H, J= 7.2 Hz).

Anal. Calcd. for $C_{13}H_{13}FO_2$ (mw 220.23): C,70.90; H,5.95.
Found: C,70.93; H,5.95.

h) Preparation of (E)-2-(3-ethyl-6-fluoro-1-indanylidene)acetyl chloride.

This compound was prepared in an analogous manner to Example 44h with replacement of (E)-2-(6-fluoro-3-methyl-1-indanylidene)acetic acid with (E)-2-(3-ethyl-6-fluoro-1-indanylidene)acetic acid. The product residue was dissolved in dichloromethane and used without purification in Example 64i.

i) Preparation of (E)-N-Cyclopropyl-2-(6-fluoro-3-ethyl-1-indanylidene)acetamide.

This compound was prepared in an analogous manner to Example 46 with the replacement of (E)-2-(6-fluoro-3-methyl-1-indanylidene)acetyl chloride with (E)-2-(3-ethyl-6-fluoro-1-indanylidene)acetyl chloride. Recrystallization from dichloromethane-hexanes gave 2.24g (65%) of (E)-N-cyclopropyl-2-(6-fluoro-3-ethyl-1-indanylidene)acetamide as a white crystalline solid, m.p.,143-147°C: NMR(DMSO-d_6): d 8.05 (br d, 1H, J=4.2 Hz), 7.45-7.40 (m, 1H), 7.26-716 (m, 2H), 6.29 (t, 1H, J=2.4 Hz), 3.47 -3.37 (m, 1H), 3.16-3.12 (m, 1H), 2.91-2.83 (m, 1H), 2.76-2.70 (m, 1H), 1.85-1.77 (m, 1H), 1.43-1.33 (m, 1H), 0.89 (t, 3H, J=7.3 Hz), 0.66 (dd, 2H, J = 4.8 Hz and 2.1 Hz), 0.44 (dd, 2H, J = 2.4 Hz

and 1.8 Hz); steady state nOe: irradiation at d 6.29, observed 15% nOe at d 8.05 and 22% nOe at d 7.24.

Anal. Calcd. for $C_{16}H_{18}FNO$ 0.1 H_2O (mw 261.125): C,73.60; H, 7.02; N, 5.36.
Found: C, 73.51; H, 7.04; N, 5.34.

Example 65

Preparation of (E)-N-Cyclopropyl-2-(6-fluoro-3-propyl-1-indanylidene)acetamide.

a) Preparation of 4' fluorobutyrophenone

Aluminum chloride (139 g, 1.04 mol) was added to a solution of butyryl chloride (55.45g, 0.520 mol, Aldrich) in dichloromethane (500ml) stirring under a nitrogen atmosphere at 25°C. A solution of fluorobenzene (50.1 g, 0.521 mol, Aldrich) in dichloromethane was added and stirring was continued for 18h. The reaction solution was poured over ice and extracted with dichloromethane (3 x 400ml) . The combined dichloromethane extractions were washed with deionized water (2 x 250 ml), 1.0 N hydrochloric acid (500ml), saturated sodium bicarbonate solution (2 x 500ml) and deionized water (4 x 250 ml),concentrated by spin evaporation *in vacuo*. This material was combined with material from a similar preparation (using 0.26 mol of fluorobenzene) for distillation. Distillation at reduced pressure gave 69.27g (53%) of 4'-fluorobutyrophenone as a pale yellow liquid which later partially crystallized, b.p. 108-112°C at 30 millitorr: NMR (DMSO-d_6): d 8.03 (q, 2H, J= 9.0 Hz and 5.6 Hz), 7.31 (t, 2H, J= 8.9 Hz), 2.97 (t, 2H, J= 7.0 Hz), 1.65-1.55 (m, 2H), 0.91 (t, 3H, J= 7.3 Hz).

Anal. Calcd. for $C_{10}H_{11}FO$ (mw 166.19): C, 72.27; H, 6.67.
Found: C, 72.34; H, 6.65.

b) Preparation of Ethyl 3-(4-fluorophenyl)hexenoate

A solution of butyllithium, 2.5M in hexanes (166 ml, 0.416 mol, Aldrich) was added dropwise over 0.5 hr, with rapid mechanical stirring, to a solution of

triethyl phosphonoacetate (93.2g, 0.416 mol, Aldrich) in tetrahydrofuran (700ml, anhydrous,Aldrich) at <5°C while blanketed with a nitrogen atmosphere. This solution was stirred for an additional 0.25 hr and cooled to -5°C with a methanol:ice bath and a solution of 4'-fluorobutyrophenone (69 g, 0.416 mol, Aldrich) in tetrahydrofuran (150ml) was then added in one portion. Stirring was continued for 18 hr without additional cooling. The solution was concentrated to a dark camel sludge by spin evaporation *in vacuo* and diluted to 600 ml with deionized water. The aqueous solution was extracted with dichloromethane (5 x 500 ml) and the dichloromethane was concentrated by spin evaporation *in vacuo*. Distillation at reduced pressure gave 58.5g (60%) of ethyl 3-(4-fluorophenyl) hexenoate as a mixture of (E) and (Z) isomers (ratio 1:1) as clear liquid, b.p. 140-150°C at aspirator pressure: NMR ($CDCl_3$): d 7.43-7.40 (m, 1H), 7.15-6.99 (m, 3H), 5.98 (s, 0.5H), 5.87 (s, 0.5 H), 4.2 (q,1H, J= 14.1 Hz and 7.2 Hz), 3.99 (q, 1H, J= 14.1 Hz and 6.8 Hz), 3.07-3.02 (m, 1H), 2.39 (t, 1H, J= 7.2 Hz), 1.45-1.36 (m, 2H), 1.31 (t, 1.5 H, J= 7.2 Hz), 1.1 (t, 1.5 H, J= 7.2 Hz), 0.91 (m, 3H).

Anal. Calcd. for $C_{14}H_{17}FO_2$ (mw 236.28): C, 71.16; H, 7.25.
Found: C, 71.26; H, 7.30.

c) Preparation of Ethyl 3-(4-Fluorophenyl)hexanoate

A mixture of ethyl 3-(4-fluorophenyl)hexenoate (58.12 g, 0.246 mol) and 10% palladium on carbon (1.1 g, Aldrich) in 95 % ethanol was shaken in a Parr hydrogenator under a pressure of 2-4 atm of hydrogen for 0.75 hr. The mixture was filtered and concentrated by spin evaporation *in vacuo* to give 58.4 g (99.6%) of ethyl 3-(4-fluorophenyl)hexanoate as a clear liquid, NMR (DMSO-d_6): d 7.27- 7.20 (m, 2H), 7.12-7.04 (m, 2H), 3.91 (q, 2H, J= 7.2 Hz), 2.99 (m, 1H), 2.66- 2.59 (m, 1H), 2.52-2.44 (m, 1H, partially obscured by DMSO), 1.59-1.46 (m, 2H), 1.13-1.07 (m, 2H), 1.02 (t, 3H, J= 7.2 Hz), 0.78 (t, 3H, J= 7.5 Hz).

Anal. Calcd. for $C_{14}H_{19}FO_2$ (mw 238.29): C, 70.56; H, 8.04.
Found: C, 70.29; H, 7.98.

d) Preparation of 3-(4-Fluorophenyl)hexanoic acid

This compound was prepared in an analogous manner to Example 65c with the replacement of 3-(4-fluorophenyl)valerate with ethyl 3-(4-fluorophenyl)hexanoate (58 g, 0.243 mol). The dichloromethane layers were combined, washed with deionized water (250 ml) and concentrated by spin evaporation *in vacuo*. The residue was coevaporated with hexanes (200 ml) to give 46.81 g (92%) of 3-(4-fluorophenyl)hexanoic acid as a pale yellow oil: NMR (DMSO-d_6): d 12 (s, 1H), 7.25-7.21 (m, 2H), 7.10-7.04 (m, 2H), 3.02-2.92 (m, 1H), 2.58-2.37 (m, 2H), 1.61-1.40 (m, 2H), 1.10- 1.01 (m,2H), 0.78 (t, 3H, J=7.2 Hz).

Anal. Calcd. for $C_{12}H_{15}FO_2$ (mw 210.24): C, 68.55; H, 7.19.
Found: C, 68.65; H, 7.20.

e) Preparation of 3-(4-Fluorophenyl)hexanoyl chloride

This compound was prepared in an analogous manner to Example 44d with the replacement of 3-(4-fluorophenyl)butyric acid with 3-(4-fluorophenyl)hexanoic acid (46.5g, 0.222 mol). The volatiles were removed by spin evaporation *in vacuo* with the addition of dichloromethane (5 x 250 ml) during concentration to give 50.01 g (99%) of 3-(4-fluorophenyl)hexanoyl chloride as a golden yellow liquid: NMR ($CDCl_3$): d 7.17-7.12 (m, 2H), 7.04-6.98 (m, 2H), 3.21- 3.05 (m, 3H), 1.71-1.52 (m, 2H), 1.26-1.11 (m,2H), 0.87 (t, 3H, J=7.2 Hz).

f) Preparation of 6-fluoro-3-propyl-1-indanone

This compound was prepared in an analogous manner to Example 44e with the replacement of 3-(4-fluorophenyl)butyryl chloride with 3-(4-fluorophenyl)hexanoyl chloride (49.95 g, 0.218 mol). The dichloromethane extractions were combined, washed with deionized water (250 ml) and concentrated by spin evaporation *in vacuo* . The residue was coevaporated with dichloromethane (100 ml) to give 41.26 g (98%) of 6-fluoro-3-propyl-1-indanone as a golden yellow syrup: NMR (DMSO-d_6): d 7.70-7.66 (dd, 1H, J_{HF}= 9.0 Hz, J_{HH}= 3.9Hz),7.56-7.47 (m, 1H), 7.34 (dd, 1H, J_{HF}=7.8 Hz,

J_{HH}= 2.7 Hz), 3.4-3.25 (m, 1H, partially obscured by water), 2.86 (dd, 1H, J_{gem}= 19.2, J= 7.5 Hz), 2.36(dd, 1H, J_{gem}= 18.9 Hz, J=3.0 Hz), 1.88-1.78 (m, 1H), 1.46- 1.22 (m , 3H), 0.90 (t, 3H, J= 7.2 Hz).

Anal. Calcd. for $C_{12}H_{13}FO$ (mw 192.22): C, 74.98; H, 6.82.
Found: C,74.86; H, 6.80.

g) Preparation of *cis* and *trans* Ethyl 2-(6-fluoro-1-hydroxy-3-propyl-1-indanyl)acetate.

This compound was prepared in an analogous manner to Example 44f with replacement of 6-fluoro-3-methyl-1-indanone with 6-fluoro-3-propyl-1-indanone (40.75 g, 0.212 mol). Removal of the volatiles from the workup solution gave 57.48 g (97%) of *cis* and *trans* ethyl 2-(6-fluoro-1-hydroxy-3-propyl-1-indanyl)acetate as a golden yellow oil: NMR (DMSO-d_6): d 7.22-7.17 (m, 1H), 7.09-6.98 (m, 2H), 5.44 (s, 1H), 3,96 (q, 2H, J= 6.9 Hz), 2.92-2.80 (m, 1H), 2.77-2.6 (dd , 1H, J=7.5 Hz and J= 12.9 Hz), 2.59 (dd, 2H, J=13.8 Hz, J=6.6 Hz), 1.89-1.79 (m, 1H), 1.67 (dd, 1H, J= 8.7 Hz, J=4.2 Hz), 1.41-1.26 (m, 3H), 1.07 (t, 3H, J= 7.2 Hz), 0.92 (t, 3H, J= 7.2 Hz).

Anal. Calcd. for $C_{16}H_{21}FO_3$ (mw 280.33): C, 68.55; H, 7.55.
Found: C, 68.39; H, 7.59.

h) Preparation of (E)-2-(6-Fluoro- 3-propyl-1-indanylidene)acetic acid

This compound was prepared in an analogous manner with Example 44g with the replacement of ethyl 2-(6-fluoro-1-hydroxy-3-methyl-1-indanyl)acetate with ethyl 2-(6-fluoro-1-hydroxy-3-propyl-1-indanyl)acetate (57.12 g, 0.204 mol). Removal of the volatiles from the workup gave a golden yellow residue. The residue was slurried in hexanes to give 24.49 g (51%) of (E)-2-(6-fluoro-3-propyl-1-indanylidene)acetic acid as a white crystalline solid, m.p., 141- 144 °C: NMR (DMSO-d6): 12.1 (b s, 1H), 7.61 (dd, 1H, JHF= 9.6 Hz, JHH= 2.4 Hz), 7.41 (dd, 1H, JHF= 8.4 Hz, JHH= 5.2 Hz), 7.20 (ddd, 1H, JHF=10.8 Hz, JHH= 8.8 Hz and 2.4 Hz), 6.36 (t, 1H, J=2.8 Hz), 3.41-3.34 (m, 1H), 3.20- 3.17 (m,

1H), 2.83-2.76 (m, 1H), 1.73- 1.70 (m, 1H), 1.35-1.28 (m, 3H), 0.89 (t, 3H, J= 6.8 Hz), steady state nOe: irradiation at d 6.36, observed 16% nOe at d 7.61.

Anal. Calcd. for $C_{14}H_{15}FO_2$ (mw 234.26): C,71.77; H,6.45.
Found: C,71.72; H,6.45.

i) Preparation of (E)-2-(6-Fluoro-3-propyl-1-indanylidene)acetyl chloride.

This compound was prepared in an analogous manner to Example 44h with replacement of (E)-2-(6-fluoro-3-methyl-1-indanylidnene)acetic acid with (E)-2-(6-fluoro-3-propyl-1-indanylidene)acetic acid. The product residue was dissolved in dichloromethane and used without purification in Example 65j.

j) Preparation of (E)-N-Cyclopropyl-2-(6-fluoro-3-propyl-1-indanylidene)acetamide.

This compound was prepared in an analogous manner to Example 46 with the replacement of (E)-2-(6-fluoro-3-methyl-1-indanylidene)acetyl chloride with (E)-2-(6-fluoro-3-propyl-1-indanylidene)acetyl chloride (3.26 g, 0.013 mol). The volatiles were removed by spin evaporation *in vacuo* to give a golden yellow oil. The oil was chromatographed on Silica Gel 60 with a step gradient of hexanes to ethyl acetate-hexanes (1:1). Fractions containing (E)-N-cyclopropyl-2-(6-fluoro-3-propyl-1-indanylidene)acetamide were combined and concentrated by spin evaporation *in vacuo* with hexanes (4 x 250ml) added during concentration to give 2.09 g (59%) of (E)-N-Cyclopropyl-2-(6-fluoro-3-propyl-1-indanylidene)acetamide as a white powdery solid, m.p. 94-97°C: NMR(DMSO-d6): d 8.0 (d, 1H), 7.38 (dd, 1H, J_{HF}=8.1 Hz and J_{HH}= 5.3 Hz), 7.22- 7.13 (m, 2H), 6.25 (t, 1H, J=2.4 Hz), 3.42-3.35 (ddd, 1H, J_{gem}=19.2, J= 7.8 Hz and 2.5 Hz), 3.20-3.10 (m, 1H), 2.83 (ddd, 1H, J_{gem}=19.2 Hz and J= 3.0 Hz and 3.0 Hz), 2.7-2.6 (m, 1H), 1.7-1.6 (m, 1H), 1.35-1.28 (m, 3H), 0.89 (t, 3H, J= 7.2 Hz), 0.64-0.60 (m, 2H), 0.42-0.38 (m, 2H); steady state nOe: irradiation at d 6.25, observed 12.1% nOe at d 8.0 and 18.7% nOe at d 7.2.

Anal. Calcd. for $C_{17}H_{20}FNO$ (mw 273.338): C,74.70; H, 7.38; N, 5.12.
Found: C, 74.66; H, 7.36; N, 5.09.

Example 66

Preparation of (Z)-2-(6-Fluoro-1-indanylidene)acetamide

A solution of (E)-2-(6-fluoro-1-indanylidene)acetamide (20g,104.6 mmol) in dichloromethane:methanol(3:1) (1000ml) was irradiated by an Canrad-Hanovia quartz, mercury-vapor photochemical immersion lamp, 450 wattts (Ace Glass, 7825-35) for 0.5h. The volatiles were removed by spin evaporation *in vacuo* to give a beige residue. This residue was chromatographed on Silica Gel 60 using a step gradient going from ethyl acetate: hexanes(1:1) to ethyl acetate:ethanol(1:1). Fractions containing (Z)-2-(6-fluoro-1-indanylidene)acetamide were combined and concentrated by spin evaporation *in vacuo*. The resulting solid was slurried in hexanes to give 7.52g (37%) of (Z)-2-(6-fluoro-1-indanylidene)acetamide as a white crystalline solid, m.p.,175-177 °C: NMR (DMSO-d_6): d 8.7 (dd, 1H, J_{HF}=9.0 Hz, J_{HH}=11.3 Hz), 7.48 (br s, 1H) 7.3 (dd, 1H, J_{HF}=8.1Hz,J_{HH}=2.3 Hz), 7.14 (ddd, 1H, J_{HF}=8.7 Hz, J_{HH}=2.5 Hz), 6.97 (br s, 1 H), 6.03 (s, 1H), 2.87 (br s, 4H) ; steady-state nOe: irradiation at d 6.03, observed 4.4% nOe at d 7.49, 2.5% nOe at d 6.97, and 8.7% nOe at d 2.9.

Anal. Calcd. for $C_{11}H_{10}FNO$ (mw 191.205): C,69.10; H,5.27; N,7.33.
Found: C, 68.97; H,5.30; N,7.30.

Example 67

Preparation of (E)-2-(4,6-Difluoro-3-oxo-1-indanylidene)acetamide

a) Preparation of 2,4-Dicarbethoxy-3-(3,5-difluorophenyl)-5-hydroxy-5-methyl-1-cyclohexanone

Slightly warm, liquid 3,5-difluorobenzaldehyde (5.0g, 0.0352 mol, Aldrich), 95% ethanol (1.75 ml), and piperidine (0.7 ml) were added, with stirring, to ethyl acetoacetate (9.2g, 0.0704 mol, Aldrich). The solution was stirred until homogeneous and was then placed in a water bath to control the slightly exothermic reaction. After 4 hrs, the crystalline mass was dissolved in warm

dichloromethane (100 ml). Dilution with hexanes (300 ml) gave a turbid solution. After standing for 24 hrs, the crystalline product was collected by filtration and washed with hexanes to give 8.0g (59%) of 2,4-dicarbethoxy-3-(3,5-difluorophenyl)-5-hydroxy-5-methyl-1-cyclohexanone: m.p., 185 - 186°C; ^{1}H NMR (DMSO-d_6): d 7.18 - 7.02 (m, 3H), 5.09 (s, 1H), 4.07 - 3.84 (m, 6H), 3.38 (d, 1H, J_{HH} = 11.2 Hz), 2.89 (d, 1H, J_{HH} = 13.6 Hz), 2.38 (d, 1H, J_{HH} = 13.6 Hz), 1.28 (s, 3H), 1.00 (t, 3H, J_{HH} = 7.0 Hz), 0.92 (t, 3H, J_{HH} = 7.0 Hz).

Anal. Calcd. for $C_{19}H_{22}F_2O_6$ (mw 384.377): C, 59.37; H, 5.77.
Found: C, 59.30; H, 5.84.

b) Preparation of 3-(3,5-Difluorophenyl)glutaric acid

To a hot (95°C) solution prepared from sodium hydroxide (322g, 8.1 mol) and deionized water (322 ml) was added a mixture of 2,4-diacetyl-3-(3,5-difluorophenyl)-5-hydroxy-5-methyl-1-cyclohexanone (43g, 0.112 mol) in ethanol (322 ml) with rapid stirring. The resulting mixture was refluxed for 4 hrs using an oil bath at 140°C. The ethanol was removed by spin evaporation *in vacuo* and the resulting slurry was cooled with an ice bath, and concentrated hydrochloric acid (12N) was added to adjust the pH to approximately 1. The precipitate was dissolved by the addition of water, and this aqueous solution was extracted with ethyl acetate (total volume 1500 ml). The ethyl acetate extracts were combined, washed with water, dried with $MgSO_4$, and the volatiles were removed by spin evaporation *in vacuo*. Recrystallization of the residue from dichloromethane and hexanes gave 9.10g (33%) of 3-(3,5-difluorophenyl)glutaric acid: m.p., 170 - 172°C; ^{1}H NMR (DMSO-d_6): d 12.2 (b s, 2H), 7.10 - 7.02 (m, 3H), 3.52 - 3.30 (m, 1H), 3.02-2.70 (m, 2H), 2.40 - 2.66 (m, 2H).

Anal. Calcd. for $C_{11}H_{10}F_2O_4$ (mw 244.196): C, 54.10; H, 4.13.
Found: C 53.85; H, 4.18.

c) Preparation of 2-(4,6-Difluoro-3-oxo-1-indanyl)acetic acid

This compound was prepared in an analogous manner to that of Example 60d with the replacement of 3-(3-fluorophenyl)glutaric acid with 3-(3,5-

difluorophenyl)glutaric acid and an increase of the heating time from 10 min to 30 min. Chromatography of the collected product on a column of Silica Gel 60 (51 x 450 mm) with methanol: dichloromethane (4:96) gave a material which was recrystallized from water to give 1.93 g (23%) of 2-(4,6-difluoro-3-oxo-1-indanyl)acetic acid: m.p., 170 - 172°C; ^{1}H NMR (DMSO-d_6): d 12.67 (b s, 1H), 7.45 (d, 1H, J_{HF} = 8.6 Hz), 7.27 (t, 1H, J_{HF} = 9.7 Hz), 3.73 - 3.62 (m, 1H), 3.02 - 2.85 (m, 2H), 2.70 - 2.39 (m, 2H).

Anal. Calcd. for $C_{11}H_8F_2O_3$ (mw 226.181): C, 58.41; H, 3.57.
Found: C 58.36; H, 3.58.

d) Preparation of 2-(4,6-difluoro-3-oxo-1-indanyl)acetyl chloride

This compound was prepared in an analogous manner to that of Example 60e with the replacement of 2-(6-fluoro-3-oxo-1-indanyl)acetic acid with 2-(4,6-difluoro-3-oxo-1-indanyl)acetic acid (3.85g, 0.017 mol). The 2-(4,6-difluoro-3-oxo-1-indanyl)acetyl chloride thus prepared was used without additional purification or analysis.

e) Preparation of 2-(4,6-Difluoro-3-oxo-1-indanyl)acetamide

This compound was prepared in an analogous manner to that of Example 60f with the replacement of 2-(3-fluoro-3-oxo-1-indanyl)acetyl chloride with 2-(4,6-difluoro-3-oxo-1-indanyl)acetic acid. After chromatography, recrystallization twice from dichloromethane:hexanes gave 2.8g (77%) of 2-(4,6-Difluoro-3-oxo-1-indanyl)acetamide: m.p., 155 - 157°C; ^{1}H NMR (DMSO-d_6): d 7.30 - 7.43 (m, 2H), 7.27 - 7.19 (m, 1H), 6.91 (b s, 1H), 3.72 - 3.64 (m, 1H), 2.85 (dd, 1H, J_{HH} = 10.1 and 7 .7 Hz), 2.76 (dd, 1H, J_{HH} = 15.0 and 5.2 Hz), 2.46 - 2.32 (m, 2H).

Anal. Calcd. for $C_{11}H_9F_2NO_2$ 0.1 H_2O (mw 226.997): C, 58.20; H, 4.09; N, 6.07.
Found: C 58.09; H, 4.01; N, 5.97.

f) Preparation of (E)-2-(4,6-Difluoro-3-oxo-1-indanylidene)acetamide

A mixture of 2-(4,6-difluoro-3-oxo-1-indanyl)acetamide (1.0g, 0.0044 mol), N-bromosuccinimide (0.950g, 0.00533 mol), 2,2'-azobis(2-methylpropionitrile) (0.350g, 0.00213 mol, Kodak), tetrachloromethane (50 ml) and benzene (50 ml) was heated with an oil bath at 120°C for 1 hr. The reaction solution was diluted with dichloromethane, slurried with Silica Gel 60, and the volatiles were removed by spin evaporation *in vacuo*. This silica was then applied to a column of Silica Gel 60 (51 x 450 mm) wet with dichloromethane and the product was removed by elution with methanol:dichloromethane (2:98). The volatiles were removed by spin evaporation *in vacuo* to give 0.613g of a residue. This residue was recrystallized from methanol to give 0.302g (31%) of (E)-2-(4,6-difluoro-3-oxo-1-indanylidene)acetamide: m.p., 250°C (dec.); ^{1}H NMR (DMSO-d6): d 7.72 - 7.58 (m, 1H), 7.57 (b s, 1H), 7.48 - 7.40 (m, 1H), 7.27 (b s, 1H), 6.70 (t, 1H, J_{HH} = 1.8 Hz), 3.64 (d, 1H, J_{HH} = 1.8 Hz); steady-state nOe: irradiation at d 6.70, observed 27% nOe at d 7.72 - 7.58.

Anal. Calcd. for $C_{11}H_7F_2NO_2$ (mw 223.178): C, 59.2; H, 3.16; N, 6.28. Found: C 59.12; H, 3.20; N, 6.28.

Pharmaceutical Compositions

In the following composition Examples, the "Active Ingredient" may be any compound of formula (I) or (Ia) or base salt, acid addition salt, or other physiologically functional derivative thereof, for example, compounds of Examples 1 to 67.

Example 68

Tablet Compositions

The following compositions A, B and C are prepared by wet granulation of the ingredients with a solution of povidone, followed by addition of magnesium stearate and compression.

Composition A

	mg/tablet	mg/tablet

(a)	Active ingredient	250	250
(b)	Lactose B.P.	210	26
(c)	Povidone B.P.	15	9
(d)	Sodium Starch Glycollate	20	12
(e)	Magnesium Stearate	5	3
		500	300

Composition B

		mg/tablet	mg/tablet
(a)	Active ingredient	250	250
(b)	Lactose	150	-
(c)	Avicel PH 101	60	26
(d)	Povidone B.P.	15	9
(e)	Sodium Starch Glycollate	20	12
(f)	Magnesium Stearate	5	3
		500	300

Composition C

	mg/tablet
Active ingredient	100
Lactose	200
Starch	50
Povidone	5
Magnesium Stearate	4
	359

The following compositions, D and E, are prepared by direct compression of the admixed ingredients. The lactose in composition E is of the direct compression type (Dairy Crest - "Zeparox").

Composition D

mg/tablet

Active ingredient	250
Pregelatinized Starch NF15	150
	400

Composition E

	mg/tablet
Active ingredient	250
Lactose	150
Avicel	100
	500

Composition F (Controlled Release Formulation)

The composition is prepared by wet granulation of the ingredients (below) with a solution of povidone followed by the addition of magnesium stearate and compression.

		mg/tablet
(a)	Active ingredient	500
(b)	Hydroxypropylmethylcellulose (Methocel K4M Premium)	112
(c)	Lactose B.P.	53
(d)	Povidone B.P.	28
(e)	Magnesium Stearate	7
		700

Example 69

Capsule Compositions

Composition A

A capsule composition is prepared by admixing the ingredients of Composition D in Example 68 above and filling into a two-part hard gelatin capsule. Composition B (infra) is prepared in a similar manner.

Composition B

		mg/capsule
(a)	Active ingredient	250
(b)	Lactose B.P.	143
(c)	Sodium Starch Glycollate	25
(d)	Magnesium Stearate	2
		420

Composition C

		mg/capsule
(a)	Active ingredient	250
(b)	Macrogol 4000 B.P.	350
		600

Composition D

	mg/capsule
Active ingredient	250
Lecithin	100
Arachis Oil	100
	450

Capsules of composition D are prepared by dispersing the active ingredient in the lecithin and arachis oil and filling the dispersion into soft, elastic gelatin capsules.

Composition E

		mg/capsule
(a)	Active ingredient	100
(b)	Lactose	300
(c)	Magnesium Stearate	2
(d)	Sodium Lauryl Sulfate	2

(e)	Sodium Starch Glycollate	50
(f)	Talc, USP	25
		479

A capsule composition is prepared by micronizing the active ingredient using a GEM-T Type 1047 Jet Mill and admixing with the remaining ingredients of Composition E and filling into a two-part hard gelatin capsule.

Composition F (Controlled Release Capsule)

The following controlled release capsule composition is prepared by extruding ingredients a, b and c using an extruder, followed by spheronization of the extrudate and drying. The dried pellets are then coated with release-controlling membrane (d) and filled into a two-piece, hard gelatin capsule.

		mg/capsule
(a)	Active ingredient	250
(b)	Microcrystalline Cellulose	125
(c)	Lactose B.P.	125
(d)	Ethyl Cellulose	13
		513

Example 70

Injectable Composition

Active ingredient	0.200 g
95% Ethanol and PEG 400, 1:1 ratio	
Sterile water	q.s. to 10 mL

The active ingredient is dissolved in 95% Ethanol and PEG 400 (1:1). The batch is then made up to volume with the water and filtered through a sterile micropore filter into a sterile 10 mL amber glass vial (type 1) and sealed with sterile closures and overseals.

Example 71

Syrup

Active ingredient	0.25 g
Sorbitol Solution	1.50 g
Glycerol	2.00 g
Sodium Benzoate	0.005 g
Flavor, Peach 17.42.3169	0.0125 mL
Purified Water	q.s. to 5.00 mL

The active ingredient is dissolved in a mixture of the glycerol and most of the purified water. An aqueous solution of the sodium benzoate is then added to the solution, followed by addition of the sorbitol solution and finally the flavor. The volume is made up with purified water and mixed well.

Example 72

Suppository

	mg/suppository
Active ingredient	250
Hard Fat, B.P. (Witepsol H15 - Dynamit NoBel)	1770
	2020

One-fifth of the Witepsol H15 is melted in a steam-jacketed pan at 45°C maximum. The active ingredient is sifted through a 200 μM sieve and added to the molten base with mixing, using a Silverson fitted with a cutting head, until smooth dispersion is achieved. Maintaining the mixture at 45°C, the remaining Witepsol H15 is added to the suspension and stirred to ensure a homogenous mix. The entire suspension is passed through a 250 μM stainless steel screen and, with continuous stirring, is allowed to cool to 40°C. At a temperature of 38°C to 40°C, 2.02 g of the mixture is filled into suitable, 2 mL plastic molds. The suppositories are allowed to cool to room temperature.

Example 73

Pessaries

	mg/pessary
Active ingredient	250
Anhydrate Dextrose	380
Potato Starch	363
Magnesium Stearate	7
	1000

The above ingredients are mixed directly and pessaries prepared by direct compression of the resulting mixture.

Example 74

Muscle Relaxant Activity

Muscle relaxant activity of compounds of formula (I) or (Ia) was determined using a Straub tail test based on that described by K.O. Ellis and J.F. Carpenter Neuropharmacol, 13, 211 (1974).

The Straub tail test result is reported as an ED_{50} in mg/kg. The ED_{50} is defined as the dose of compound administered, which prevents Straub tail in 50% of mice. The compound is administered by oral gavage (po) 60 min. prior to scoring.

The side effect potential of these compounds was determined using the mouse rotorod test as described by G.D. Novak and J.M.-Zwolshei, J.Pharmacological. Methods, 10, 175 (1983). Rotorod result is reported as ED_{50} in mg/kg. The ED_{50} is the dose which causes 50% of the animals to fail to maintain position on a cylinder rotating at 11 r.p.m.

Antagonism of morphine-induced Straub tail reflects muscle relaxant efficacy while failure in the rotorod test reflects sedation and incoordination. Determination of the ratio of rotorod failure to antagonism of morphine-induced Straub tail is a means of assessing side effect liability of muscle relaxants (G.D. Novak, Drug Dev. Res., 2, 383 (1982).

Compound of	Straub Tail	Rotorod	Rotorod/Straub Tail

Example No.	p.o. ED_{50}, mg/kg.	p.o. ED_{50}, mg/kg.	
1	51	88	1.7
12	54	79	1.5

Example 75

Anticonvulsant Activity

Anticonvulsant activity of compounds of formula (I) or (Ia) was determined using a method described by Mehta et al., J.Med.Chem., 24, 465 (1981).

The anticonvulsant activity is reported as an ED_{50} in mg/kg. The ED_{50} for protection against maximal electroshock-induced convulsions was the dose which prevented hind limb extension in 50% of the animals. The ED_{50} for protection against Metrazol-induced convulsions was the dose which prevented convulsions in 50% of the animals.

Compound of Example No.	i.p. ED_{50}, mg/kg (rat)	
	MES	MET
38	25 i.p.	5.2 p.o.

MES - maximal electroshock
MET - metrazol

Example 76

Anxiolytic Activity

Anxiolytic activity of the compounds of formula (I) or (Ia) was measured using method of Geller and Seifter, J.Psychopharmacolgia, 1, 482 (1960) as modified by Pollard and Howard, Psychopharmacology, 62, 117 (1979). Clinically efficacious anxiolytics increase punished responding. The anxiolytic activity of the compound is reported as the lowest dose necessary to produce a significant increase in punished responding in rats(MED).

Compound of Example No.	p.o. MED, mg/kg

38	3.13 p.o.

MED - Mean Effective Dose

Example 77

Antiinflammatory Activity

The compounds of formula (I) and (Ia) possess anti-inflammatory activity as demonstrated using a modification of the standard carrageenan pleurisy assay as described by R. Vinegar, J.F., Traux, and J.L. Selph(*Pro. Soc. Exp. Biol. Med.* 143:711-714, 1973). The rats used in these experiments were Lewis males, weighing 160-180 g, assigned to groups consisting of 5 animals. Test compounds were given to fasted rats by oral gavage 0.5 hr prior to intrapleural injection of 50 mg carrageenan. After 4 hr, the pleural exudate was collected and the edema volume and cell number were determined. ED_{50} values were estimated by linear regression analysis, and represent the doses at which a given drug produced 50% inhibition of carrageenan-induced cell accumulation and edema formation within the rat pleura.

Compound of Example No.	p.o. ED_{50}, mg/kg	
	Cells	Edema
1	21	20

Example 78

Established Adjuvant Arthritis

The compounds of formula (I) and (Ia) also exhibit chronic anti-inflammatory activity as evidenced by inhibition of established adjuvant-induced polyarthritis in the rat. The procedures for this test have been described in detail by R. Vinegar, J.F. Truax, J. L. Selph, A. Lea, and P.R. Johnston (*J. Immunopharmacol.* 1:497-520, 1979). The rats used in these studies were female Lewis rats whose starting weight was 190 ± 10 g. Arthritic rats were assigned to treatment groups consisting of six animals each. Fed rats were dosed by oral gavage starting on day 21 post adjuvant injection; therapy was continued until day 28. The incidence and severity of arthritic lesions were assessed

using a modification of the scoring procedure described by H.L.F. Currey and M. Ziff (*J. Exp. Med.* 121:185-203, 1968). Briefly, the bilateral joints were scored for erythema, edema, and ankylosis as outlined below:

Joint Evaluated	Arbitrary Joint Score (range)	
	Right	Left
Wrist	0-4	0-4
Ankle	0-4	0-4
Tarsus	0-4	0-4
Metacarpals	0-4	0-4
Metatarsals	0-4	0-4

The maximal possible score per rat was 40. Experimental results were analyzed by one-way ANOVA, followed by post hoc comparisons of treatment effects versus untreated arthritic control using the Newman-Keuls test. The percent inhibition of each drug-treated group was calculated from the mean relative to the arthritic control. Compound of Example No. 12 significantly ($p<0.01$) lowered arthritic scores on days 22, 25, and 27 in rats with established adjuvant arthritis dosed b.i.d. with 50 mg/kg. Spleen weight and plasma fibrinogen were measured postmortem on day 27 and were also significantly reduced ($p<0.01$).

Example 79

Mild Analgesia

The compounds of formula (I) and (Ia) possess mild analgesic activity as demonstrated using a modification of the trypsin -induced rat hind limb hyperalgesia assay as described by R. Vinegar, J.F. Truax, J.L. Selph and P.R. Johnston (*J. Pharmacol. Meth.*, 23:51-61, 1990). The rats used in these studies were Lewis male, weighing 160-180 g. and assigned to groups consisting of 5-6 animals. Test compounds were given to fasted rats by oral gavage 0.5 hours prior to the subplantar injection of 250 mg trypsin in one hind limb. One hour later the rats were evaluated for hyperalgesia using a F-shaped mechanical force clamp on the injected hind limb metatarsal area. Latency (seconds) to the algesic response (vocalization or flight) was determined, with 4 seconds being the maximum latency allowed. ED_{50} values were estimated by linear regression analysis and

represent the dose at which a given drug extended the latency response to produce 50% inhibition using the formula: (4 sec. - Control Latency) - (4 sec. - Test Latency)/4 sec. - Control Latency X 100.

Compound of Example No.	p.o. ED_{50}, mg/kg
12	4.0

Example 80

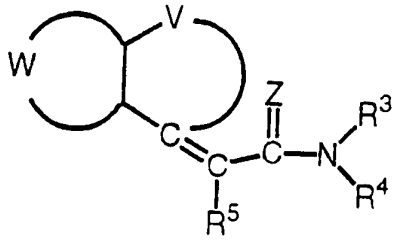
Strong Analgesia

The compounds of formula (I) and (Ia) possess strong analgesic activity as demonstrated using the phalanges algesic assay [a modification of the trypsin -induced rat hind limb hyperalgesia assay as described by R. Vinegar, J.F. Truax, J.L. Selph and P.R. Johnston (*J. Pharmacol. Meth.* 23: 51-61, 1990)]. The rats used in these studies were Lewis male weighing 160-180 g and assigned to groups of 5-6 animals. The phalanges algesic assay is an algesic test (no hyperalgesia) in which test compounds were given to fasted rats by oral gavage. One hour later an F-shaped mechanical force clamp was applied to the phalanges of one hind limb which initiated an algesic response(vocalization or flight). Latency (seconds) to the algesic response was determined with 3 seconds maximum allowed time. ED_{50} values were estimated by linear regression analysis and represent the dose at which a given compound extended the latency response to produce 50% inhibition using the formula: (3 sec. - Control Latency) - (3 sec. - Test Latency)/3 sec. - Control Latency X 100.

Compound of Example No.	p.o. ED_{50}, mg/kg
12	22

CLAIMS

1. The compounds comprising Formula (I):



(I)

wherein V is

(a) $(CR^1R^2)_mB$,

(b) $B(CR^1R^2)_m$ or

(c) $(CR^1R^2)_mB(CR^1R^2)_m$

wherein B is CR^1R^2, O, NR^6, C=O or $S(O)_m$ and

wherein R^1 and R^2 are the same or different and are

(a) H;

(b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl or C_{1-6}alkylenearyl all optionally substituted with one or more halogen, C_{1-6} alkyl(optionally substituted with one or more halogen, OR^6 or NR^6R^{6a}), $OC(O)R^6$, OR^6, NR^6R^{6a} or $S(O)_mR^6$; or

R^1R^2 together with the carbon atom to which they are attached form a C_{3-4} ring, or a C_{2-5} heterocyclic ring (comprising one or more heteroatoms of O, NR^6, and $S(O)_m$), the carbon atoms of said rings optionally substituted with one or more halogen, C_{1-6} alkyl(optionally substituted with one or more halogen, OR^6 or NR^6R^{6a}), $OC(O)R^6$, OR^6, NR^6R^{6a} or $S(O)_mR^6$;

(c) OR^6;

(d) $OC(O)R^6$;

(e) $NC(O)R^6$; or

(f) halogen(e.g., fluorine);

wherein R^6 and R^{6a} are the same or different and are H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylene (C_{3-6} cycloalkyl), aryl or C_{1-6} alkylenearyl all optionally substituted with one or more halogen, C_{1-6}

alkyl(optionally substituted with one or more halogen, OH, C_{1-6}alkoxy, NH_2 or substituted amino(as defined hereinafter)); or any combination thereof;

W is an aryl or a heteroaryl ring substituted with one or more

(a) halogen;

(b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkylene(C_{3-6}cycloalkyl), aryl, C_{1-6}alkylenearyl, C_{1-6} alkoxy, aryloxy, or C_{1-6} alkyleneoxyaryl all optionally substituted with one or more halogen, OR^6, or NR^6R^{6a};

(c) OR^6;

(d) NR^6R^{6a}, $NR^6NR^6R^{6a}$, $CONR^6R^{6a}$ or $S(O)_mNR^6R^{6a}$ wherein both of the R^6 and R^{6a} are the same or different and are as described hereinbefore or R^6R^{6a} together with the nitrogen atom to which they are attached denote a C_{2-7} ring optionally substituted with one or more halogen, C_{1-6} alkyl(optionally substituted with one or more halogen, OR^6 or NR^6R^{6a}), OR^6 or NR^6R^{6a};

(e) $C(Y)R^6$ wherein Y is O, NOR^6, NR^6 or S;

(f) CO_2R^6;

(g) OR^6O(cyclic) wherein R^6 is other than H;

(h) $OC(O)R^6$;

(i) $OP(O)(OR^6)_2$;

(j) $OP(O)(R^6)_2$ wherein R^6 is other than H;

(k) $OS(O)(OR^6)$;

(l) $OS(O)_2(OR^6)$;

(m) $S(O)_mR^6$ wherein R^6 is other than H;

(n) $NHS(O)_mR^6$ wherein R^6 is other than H;

(o) $N=NR^6$;

(p) NO;

(q) NO_2;

(r) SCN; or

(s) CN or a combination thereof;

when one m is present, m is 0,1 or 2;

when more than one m is present, m can be the same or different and is 0,1 or 2;

R^3 and R^4 are the same or different and are

(a) H; or

(b) C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkylene(C_{3-6}cycloalkyl), aryl or C_{1-6}alkylenearyl all optionally substituted with one or more halogen, C_{1-6} alkyl(optionally substituted with one or more halogen, OR^6 or NR^6R^{6a}), OR^6 or NR^6R^{6a}; or

R^3 and R^4 together with the nitrogen atom to which they are attached denote a C_{2-7} ring or a C_{1-4} heterocyclic ring (comprising one or more heteroatoms selected from the group consisting of O, NR^6, and $S(O)_m$) the carbon atoms of said rings optionally substituted with one or more halogen, C_{1-6} alkyl (optionally substituted with one or more halogen, OR^6 or NR^6R^{6a}), OR^6 or NR^6R^{6a} or any combination thereof;

R^5 is

(a) H;

(b) halogen;

(c) CN;

(d) $C(O)OR^6$;

(e) $C(O)NR^3R^4$;

(f) C_{1-6} alkyl, aryl or C_{1-6} alkylenearyl all optionally substituted with one or more halogen, $OC(O)R^6$, OR^6, NR^6R^{6a} or SR^6;

(g) OR^6; or

(h) SR^6 or any combination thereof; and

Z is O or S;

or salts, solvates or physiologically functional derivatives thereof.

2. The compounds of Claim 1 wherein V is

(a) $(CR^1R^2)_mB$,

(b) $B(CR^1R^2)_m$ or

(c) $(CR^1R^2)_mB(CR^1R^2)_m$

wherein B is CR^1R^2, O, NR^6, or $S(O)_m$ and

wherein R^1 and R^2 are the same or different and are selected from

(a) H;

(b) C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl all optionally substituted by one or more NR^6R^{6a};

(c) hydroxy;

(d) $OC(O)R^6$; or

(e) halogen(e.g., fluorine) or any combination thereof;

W is aryl or heteroaryl substituted with one or more

(a) halogen (e.g., fluorine or chlorine); or

(b) C_{1-6} alkyl optionally substituted with one or more halogen (e.g., fluorine), OR^6 or CN or any combination thereof;

when one m is present, m is 1 or 2;

when more than one m is present, m can be the same or different and is 1 or 2;

R^3 and R^4 are the same or different and are

(a) H; or

(b) C_{1-6} alkyl, C_{3-6} cycloalkyl(e.g., cyclopropyl, cyclobutyl), C_{1-6} alkylene(C_{3-6} cycloalkyl) or any combination thereof; or together with the nitrogen to which they are attached denote a C_{2-7} ring;

R^5 is H or halogen;

R^6 and R^{6a} are as defined hereinbefore; and

Z is O;

or salts, solvates or physiologically functional derivatives thereof.

3. The compounds of Claim 1 wherein V is

(a) $(CR^1R^2)_mB$ or

(b) $B(CR^1R^2)_m$

wherein B is CR^1R^2 or O and

wherein R^1 and R^2 are the same or different and are selected from

(a) H;

(b) CH_3, CH_2 CH_3;
(c) C_{1-6} alkyl substituted by NR^6R^{6a};
(d) hydroxy;
(e) $OC(O)R^6$; or
(f) fluorine, or any combination thereof;

W is phenyl or naphthyl substituted with one or more
(a) halogen(e.g., fluorine or chlorine),
(b) CH_3;
(c) CF_3, or any combination thereof;

when one m is present, m is 1 or 2;
when more than one m is present, m can be the same or different and is 1 or 2;

R^3 and R^4 are the same or different and are
(a) H;
(b) CH_3;or
(c) cyclopropyl, or any combination thereof;

R^5 is H or halogen(preferably fluorine);

R^6 and R^{6a} are as defined hereinbefore; and

Z is O;

or salts, solvates or physiologically functional derivatives thereof.

4. The compounds of Claim 1 wherein V is $B(CR^1R^2)_m$ wherein B is CR^1R^2 or O and wherein R^1 and R^2 are the same or different and are selected from H, CH_3 or OH or any combination thereof;

W is a phenyl ring substituted with one or more halogen (preferably fluoro or chloro or any combination thereof);

when one m is present, m is 1 or 2;

when more than one m is present, m can be the same or different and is 1 or 2;

R^3 and R^4 are H, CH_3 or cyclopropyl or any combination thereof;

R^5 is H; and

Z is O;
or salts, solvates or physiologically functional derivatives thereof.

5. The compounds of Claim 1 wherein V is

$B(CH_2)_m$
wherein B is CR^1R^2 and

wherein R^1 and R^2 are the same or different and are H, CH_3, CH_2 CH_3 or OH or any combination thereof;

W is a phenyl ring substituted with one or two halogen (preferably fluoro or chloro) or any combination thereof;

when one m is present, m is 1 or 2;
when more than one m is present, m can be the same or different and is 1 or 2;

R^3 and R^4 are the same or different and are H, CH_3 or cyclopropyl or any combination thereof;

R^5 is H; and

Z is O;
or salts, solvates or physiologically functional derivatives thereof.

6. The compounds of Claim 1 comprising:

(E)-2-(4-Chloro-1-indanylidene)acetamide
(E)-2-(6-Fluoro-1-indanylidene)acetamide
(E)-N-Cyclopropyl-2-(1-indanylidene)acetamide

(E)-2-(4-Fluoro-1-indanylidene)acetamide
(E)-2-(5-Fluoro-1-indanylidene)acetamide
(E)-2-(3-Phenyl-1-indanylidene)acetamide
(E)-N-Cyclopropyl-2-(3-phenyl-1-indanylidene)acetamide
(E)-N-Methyl-2-(3-phenyl-1-indanylidene)acetamide
(E)-2-(1-Indanylidene)acetamide
(E)-2-(5-Methoxy-1-indanylidene)acetamide
(E)-N-Cyclopropyl-2-(4-fluoro-1-indanylidene)acetamide
(E)-2-(6-Fluoro-3-methyl-1-indanylidene)acetamide
(E)-2-(6-Fluoro-3-methyl-1-indanylidene)-N-methylacetamide
(E)-N-Cyclopropyl-2-(6-fluoro-3-methyl-1-indanylidene)acetamide
(E)-2-(6-Fluoro-3,3-dimethyl-1-indanylidene)acetamide
(E)-2-(6-Fluoro-3,3-dimethyl-1-indanylidene)-N-methylacetamide
(E)-N-Cyclopropyl-2-(6-fluoro-3,3-dimethyl-1-indanylidene)acetamide
(E)-2-(6-Fluoro-3-ethyl-1-indanylidene)-N-methylacetamide
(E)-N-Cyclopropyl-2-(6-fluoro-3-ethyl-1-indanylidene)acetamide
(E)-2-(6-Fluoro-3-ethyl-1-indanylidene)acetamide
(E)-2-(6-Fluoro-3-ethyl-1-indanylidene)-N-isopropylacetamide
(E)-2-(6-Fluoro-3-ethyl-1-indanylidene)-N,N-dimethylacetamide
(E)-2-(6-Fluoro-3-propyl-1-indanylidene)-N-methylacetamide
(E)-N-Cyclopropyl-2-(6-Fluoro-3-propyl-1-indanylidene)acetamide
(E)-2-(6-Fluoro-3-propyl-1-indanylidene)-N,N-dimethylacetamide
(E)-2-(6-Fluoro-3-propyl-1-indanylidene)-N-isopropylacetamide
(E)-2-(6-Fluoro-3-propyl-1-indanylidene)acetamide
(E)-N-Cyclopropyl-2-(5-fluoro-1-indanylidene)acetamide
(E)-2-(4-Methyl-1-indanylidene)acetamide
(E)-N-Cyclopropyl-2-(4-methyl-1-indanylidene)acetamide
(E)-2-(5-Chloro-1-indanylidene)-N-cyclopropylacetamide
(E)-2-(5-Chloro-1-indanylidene)-N-methylacetamide
(E)-2-(5-Chloro-1-Indanylidene)acetamide
(E)-2-(4-Chloro-1-indanylidene)-N-cyclopropylacetamide
(Z)-N-(Cyclopropyl)-2-(2,2-dimethyl-1-indanylidene)acetamide
(E)-2-(6-Chloro-1-indanylidene)acetamide
(E)-1-(2-(6-Fluoro-1-indanylidene)acetyl)pyrrolidine
(E)-2-(6-Fluoro-1-indanylidene)-N-phenylacetamide

(E)-4-(2-(6-Fluoro-1-indanylidene)acetyl)morpholine
(E)-1-(2-(6-Fluoro-1-indanylidene)acetyl)azetidine
(E)-2-(6-Fluoro-1-indanylidene)-N-methoxy-N-methylacetamide
(Z)-2-(6-Fluoro-2-nitrooxy-1-indanylidene)acetamide
(E)-2-(6-Fluoro-1-indanylidene)-N-(2-hydroxyethyl)acetamide
(E)-2-(6-Fluoro-1-indanylidene)-N-isopropylacetamide
(Z)-2-(6-Fluoro-2-methoxy-1-indanylidene)acetamide
(Z)-2-(2,3-Dibromo-6-fluoro-1-indanylidene)acetamide
(E)-2-(6-Chloro-1-indanylidene)-N-methylacetamide
(Z)-2-(6-Fluoro-2,3-dihydroxy-1-indanylidene)acetamide
(E)-2-(6-Fluoro-3-hydroxy-1-indanylidene)acetamide
(E)-N-cyclopropyl-2-(6-Chloro-1-indanylidene)acetamide
(E)-2-(6-Fluoro-1-indanylidene)thioacetamide
(E)-2-(6-Fluoro-1-indanylidene)-N-methylacetamide
(E)-N-Cyclopropyl-2-(6-fluoro-1-indanylidene)acetamide
(E)-N-Ethyl-2-(6-fluoro-1-indanylidene)acetamide
(E)-N-Cyclobutyl-2-(6-fluoro-1-indanylidene)acetamide
(E)-N-Cyclopentyl-2-(6-fluoro-1-indanylidene)acetamide
(E)-2-(6-Bromo-1-indanylidene)acetamide
(E)-N-(Cyclopropylmethyl)-2-(6-fluoro-1-indanylidene)acetamide
(E)-2-(6-Fluoro-1-indanylidene)-N-propylacetamide
(E)-2-(6-Fluoro-1-indanylidene)-N,N-dimethylacetamide
(E)-N-ethyl-2-(6-fluoro-1-indanylidene)-N-methylacetamide
(E)-N-Benzyl-2-(6-fluoro-1-indanylidene)acetamide

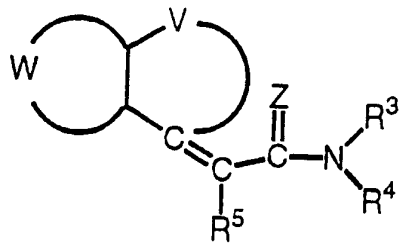
(Z)-2-(2-Acetoxy-6-fluoro-1-indanylidene)acetamide
(Z)-2-(2-Bromo-6-fluoro-1-indanylidene)acetamide
(E)-N-Cyclopropyl-2-(5,6-difluoro-1-indanylidene)acetamide
(E)-2-(5,6-Difluoro-1-indanylidene)-N-methylacetamide
(E)-2-(5,6-Difluoro-1-indanylidene)acetamide
(E)-2-(5,7-Difluoro-1-indanylidene)acetamide
(E)-N-Cyclopropyl-2-(5,7-difluoro-1-indanylidene)acetamide
(E)-2-(5,7-Difluoro-1-indanylidene)-N-methylacetamide
(E)-2-(6-Methyl-1-indanylidene)acetamide
(E)-N-Cyclopropyl-2-(4,6-difluoro-1-indanylidene)acetamide

(E)-2-(4,6-Difluoro-1-indanylidene)acetamide
(Z)-2-(1-Indanylidene)acetamide
(E)-2-(4,6-Difluoro-1-indanylidene)-N-isopropylacetamide
(E)-2-(4,6-Difluoro-1-indanylidene)-N,N-dimethylacetamide
(E)-2-(4,6-Difluoro-1-indanylidene)-N-ethylacetamide
(E)-2-(4,6-Difluoro-1-indanylidene)-N-(2-hydroxyethyl)acetamide
(E)-N-Ethyl-2-(4,6-difluoro-1-indanylidene)-N-methylacetamide
(Z)-2-(6-Chloro-1-indanylidene)-N-methylacetamide
(E)-2-(4,7-Difluoro-1-indanylidene)acetamide
(E)-2-(4,5-Difluoro-1-indanylidene)acetamide
(E)-N-Cyclopropyl-2-(4,5-difluoro-1-indanylidene)acetamide
(E)-N-Cyclopropyl-2-(4,7-difluoro-1-indanylidene)acetamide
(E)-2-(7-Methyl-1-indanylidene)acetamide
(E)-N-Cyclopropyl-2-(7-methyl-1-indanylidene)acetamide
(E)-2-(4-Chloro-6-fluoro-1-indanylidene)acetamide
(E)-2-(6-Cyano-1-indanylidene)acetamide
(E)-2-(4,6-Difluoro-1-indanylidene)-N-methylacetamide
(E)-N-Cyclopropyl-2-(4,6-dichloro-1-indanylidene)acetamide
(E)-2-(4-Chloro-6-fluoro-1-indanylidene)-N-cyclopropylacetamide
(E)-2-(4,6-Dichloro-1-indanylidene)acetamide
(E)-2-(4,6-Dichloro-1-indanylidene)-N-methylacetamide
(Z)-2-(4,6-Difluoro-2-hydroxy-1-indanylidene)acetamide
(E)-2-(4-Chloro-6-fluoro-1-indanylidene)-N-methylacetamide
(Z)-2-(2-Bromo-4,6-difluoro-1-indanylidene)acetamide
(E)-2-(6-Bromo-1-indanylidene)-N-cyclopropylacetamide
(E)-2-(6-Bromo-1-indanylidene)-N-methylacetamide
(E)-2-(6-Methoxy-1-indanylidene)acetamide
(Z)-2-(6-Chloro-1-indanylidene)-N-cyclopropylacetamide
(Z)-2-(6-Fluoro-1-indanylidene)acetamide
(E)-2-(6-Fluoro-3-isopropyl-1-indanylidene)-N-methylacetamide
(E)-2-(6-Fluoro-3-isopropyl-1-indanylidene)-N,N-dimethylacetamide
(E)-N-Cyclopropyl-2-(6-fluoro-3-isopropyl-1-indanylidene)acetamide
(E)-2-(6-Fluoro-3-isopropyl-1-indanylidene)acetamide
(E)-2-(6-Chloro-4-Fluoro-1-indanylidene)acetamide
(E)-2-(6-Chloro-4-Fluoro-1-indanylidene)-N-methylacetamide

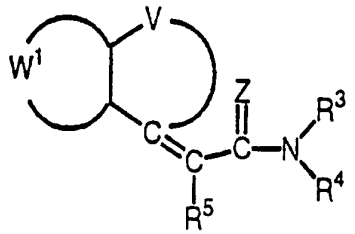
(E)-2-(6-Chloro-4-Fluoro-1-indanylidene)-N-cyclopropylacetamide
(E)-2-(6-Fluoro-4-methyl-1-indanylidene)acetamide
(E)-2-(6-Fluoro-4-methyl-1-indanylidene)-N-methylacetamide
(E)-N-Cyclopropyl-2-(6-Fluoro-4-methyl-1-indanylidene)acetamide
(E)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-1-naphthylidene)acetamide
(E)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-5-fluoronaphthylidene)acetamide
(E)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide
(E)-2-(6-Fluoro-3,4-dihydro-2H-1-benzopyran-4-ylidene)acetamide
(E)-2-(6-Fluoro-3,4-dihydro-2H-1-benzopyran-4-ylidene)-N-methylacetamide
(E)-N-Cyclopropyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide
(E)-2-(7-Chloro-1,2,3,4-tetrahydro-1-naphthylidene)-N-cyclopropylacetamide
(E)-2-(5-Bromo-1,2,3,4-tetrahydro-1-naphthylidene)-N-cyclopropylacetamide
(E)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N-methylacetamide
(E)-N-ethyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide
(E)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-7-methoxy-1-naphthylidene)acetamide
(E)-N-Cyclopentyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide
(E)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N-isopropylacetamide
(E)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N-propylacetamide
(E)-N-Cyclobutyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide
(E)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-6-methoxy-1-naphthylidene)acetamide
(E)-N-Benzyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide
(E)-4-(2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetyl)morpholine
(E)-N-Cyclopropyl-2-(5-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)propionamide
(E)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N-(2-hydroxyethyl)acetamide
(E)-N-Cyclopropyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide
(E)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N,N-dimethylacetamide
(E)-2-(6-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N-methyl-N-methoxyacetamide
(Z)-N-Cyclopropyl-2-(7-fluoro-1,2,3,4-tetrahydro-2,2-dimethyl-1-naphthylidene)acetamide
(E)-N-Cyclopropyl-2-(7-fluoro-1,2,3,4-tetrahydro-2,2-dimethyl-1-naphthylidene)acetamide
(E)-N-Ethyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N-methylacetamide
(E)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetanilide
(E)-1-(2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetyl)azetidine
(E)-1-(2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetyl)pyrrolidine

(E)-2-(5,6,7,8-Tetrahydro-8-quinolinylidene)acetamide
(E)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-7-methyl-1-naphthylidene)acetamide
(E)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-5-methoxy-1-naphthylidene)acetamide
(Z)-N-cyclopropyl-2-(1,2,3,4-tetrahydro-1-naphthylidene)acetamide
(E)-2-(6-Chloro-1,2,3,4-tetrahydro-1-naphthylidene)-N-cyclopropylacetamide
(Z)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide
(E)-N-Cyclopropyl-2-(6-fluoro-3,4-dihydro-2H-1-benzopyran-4-ylidene)acetamide
(Z)-N-Ethyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide
(Z)-2-(7-Chloro-1,2,3,4-tetrahydro-1-naphthylidene)-N-cyclopropylacetamide
(Z)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-7-methoxy-1-naphthylidene)acetamide
(Z)-N-Cyclopentyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide
(Z)-2-(7-Fluoro-1,2,3,4-tetrahydro-1-naphthylidene)-N-phenylacetamide
(E)-2-(6-Chloro-3,4-dihydro-2H-1-benzopyran-4-ylidene)-N-cyclopropylacetamide
(E)-2-(6-Chloro-3,4-dihydro-2H-1-benzopyran-4-ylidene)-N-methylacetamide
(Z)-N-Cyclopropyl-2-(2,3,4,5-tetrahydro-1-tosyl-1H-1-benzazepin-5-ylidene)acetamide
(E)-2-(1-acetyl-6-fluoro-1,2,3,4-tetrahydro-4-quinolylidene)-N-cyclopropylacetamide
(E)-2-(6-Chloro-3,4-dihydro-2H-1-benzopyran-4-ylidene)acetamide
(E)-N-Cyclopropyl-2-(3,4-dihydro-2H-1-benzothiopyran-4-ylidene)acetamide
(E)-N-2-(3,4-dihydro-2H-1-benzothiopyran-4-ylidene)-N-methylacetamide
(E)-2-(3,4-dihydro-2H-1-benzothiopyran-4-ylidene)acetamide
(E)-2-(6-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)
-N-cyclopropylacetamide
(E)-2-(6-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)
-N-methylacetamide
(E)-2-(6-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)acetamide
(E)-2-(5-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)
-N-cyclopropylacetamide
(E)-2-(5-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)
-N-methylacetamide
(E)-2-(5-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)acetamide
(E)-2-(7-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)acetamide
(E)-2-(7-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-benzopyran-4-ylidene)
-N-methylacetamide
(E)-2-(7-Fluoro-2,2-dimethyl-3,4-dihydro-2H-1-Benzopyran-4-ylidene)
-N-cyclopropylacetamide

7. A method for the treatment or prophylaxis of conditions associated with abormally raised muscle tone, convulsive states, anxiety, inflammation, arthritis or pain in a host, comprising administering to the host an effective treatment amount of a compound of formula (I) or (Ia).



(I)



(Ia)

wherein V is

(a) $(CR^7R^8)_mB$,

(b) $B(CR^7R^8)_m$ or

(c) $(CR^7R^8)_mB(CR^7R^8)_m$

wherein B is CR^7R^8, O, NR^6, C=O or $S(O)_m$ and

wherein R^7 and R^8 are the same or different and are

(a) H;

(b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl or C_{1-6}alkylenearyl all optionally substituted with one or more halogen, C_{1-6} alkyl(optionally substituted with one or more halogen, OR^6 or NR^6R^{6a}), $C(O)R^6$, OR^6, N^6R^{6a} or $S(O)_mR^6$; or

R^7R^8 together with the carbon atom to which they are attached form a C_{3-6} ring, or a C_{2-5} heterocyclic ring(comprising one or more heteroatoms of O, NR^6, and $S(O)_m$), the carbon atoms of said rings optionally substituted with one or more halogen, C_{1-6} alkyl(optionally substituted with one or more halogen, OR^6 or NR^6R^{6a}), $OC(O)R^6$, OR^6, NR^6R^{6a} or $S(O)_mR^6$;

(c) OR^6;

(d) $OC(O)R^6$;

(e) $NC(O)R^6$; or

(f) halogen(e.g., fluorine); wherein R^6 and R^{6a} are the same or different and are H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkylene (C_{3-6} cycloalkyl), aryl or C_{1-6} alkylenearyl all optionally substituted with one or more halogen, C_{1-6} alkyl (optionally substituted with one or more halogen, OH, C_{1-6} alkoxy, NH_2 or substituted amino(as defined hereinafter)); or any combination thereof;

W^1 is an aryl or a heteroaryl ring optionally substituted with one or more

(a) halogen;

(b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkylene(C_{3-6}cycloalkyl), aryl, C_{1-6}alkylenearyl, C_{1-6} alkoxy, aryloxy, or C_{1-6}alkyleneoxyaryl all optionally substituted with one or more halogen, OR^6 or NR^6R^{6a};

(c) OR^6;

(d) NR^6R^{6a}, $NR^6NR^6R^{6a}$, $CONR^6R^{6a}$ or $S(O)_mNR^6R^{6a}$ wherein both of the R^6 and R^{6a} are the same or different and are as described hereinbefore or R^6R^{6a} together with the nitrogen atom to which they are attached denote a C_{2-7} ring optionally substituted with one or more halogen, C_{1-6} alkyl(optionally substituted with one or more halogen, OR^6 or NR^6R^{6a}), OR^6 or NR^6R^{6a};

(e) $C(Y)R^6$ wherein Y is O, NOR^6, NR^6, or S;

(f) CO_2R^6;

(g) OR^6O(cyclic) wherein R^6 is other than H;

(h) $OC(O)R^6$;

(i) $OP(O)(OR^6)_2$;

(j) $OP(O)(R^6)_2$ wherein R^6 is other than H;

(k) $OS(O)(OR^6)$;

(l) $OS(O)_2(OR^6)$;

(m) $S(O)_mR^6$ wherein R^6 is other than H;

(n) $NHS(O)_mR^6$ wherein R^6 is other than H;

(o) $N=NR^6$;

(p) NO;

(q) NO_2;

(r) SCN; or

(s) CN or any combination thereof;

when one m is present, m is 0, 1 or 2;

when more than one m is present, m can be the same or different and is 0, 1 or 2;

R^3 and R^4 are the same or different and are

(a) H; or

(b) C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkylene (C_{3-6} cycloalkyl), aryl or C_{1-6} alkylenearyl all optionally substituted with one or more halogen, C_{1-6} alkyl (optionally substituted with one or more halogen, OR^6 or NR^6R^{6a}), OR^6 or NR^6or NR^6R^{6a}; or R^3 and R^4 together with the nitrogen atom to which they are attached denote a C_{2-7} ring or a C_{1-4} heterocyclic ring (comprising one or more heteroatoms selected from the group consisting of O, NR^6, and $S(O)_m$) the carbon atoms of said rings optionally substituted with one or more halogen, C_{1-6} alkyl (optionally substituted with one or more halogen, OR^6 or NR^6R^{6a}), OR_6 or NR^6R^{6a}; or any combination thereof;

R^5 is

(a) H;

(b) halogen;

(c) CN;

(d) $C(O)OR^6$;

(e) $C(O)NR^3R^4$;

(f) C_{1-6} alkyl, aryl or C_{1-6} alkylenearyl all optionally substituted with one or more halogen, $OC(O)R^6$, OR^6, NR^6R^{6a}or SR^6;

(g) OR^6; or

(h) SR^6; or any combination thereof: and

Z is O or S;

or salts, solvates or physiologically functional derivatives thereof.

8. The method of Claim 7 wherein the condition is abnormally raised muscle tone or convulsive states and the compound of formula (I) or (Ia) is:

(E)-2-(4,6 Difluoro-1-indanylidene)acetamide
(E)-2-(6-Fluoro-1-indanylidene)acetamide
(Z)-2-(6-Fluoro-2-hydroxy-1-indanylidene)acetamide
(E)-2-(6-Fluoro-3,3-dimethyl-1-indanylidene)acetamide
(E)-2-(5,7-Difluoro-1-indanylidene)acetamide
(E)-2-(4,6 Difluoro-1-indanylidene)-N,N-dimethylacetamide
(E)-2-(4,6 Difluoro-1-indanylidene)-N-isopropylacetamide
(E)-2-(7-Fluoro-1,2,3,4-tetrahydro1-naphthylidene)acetamide
(E)-2-(6-Fluoro-3-ethyl-1-indanylidene)-N,N-dimethylacetamide
(E)-2-(6-Fluoro-3-hydroxy-1-indanylidene)acetamide

9. The method of Claim 7 wherein the condition is anxiety and the compound of formula (I) or (Ia) is:

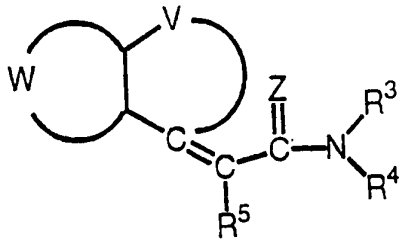
(E)-2-(3-Ethyl-6-fluoro-1-Indanylidene)-N-cyclopropylacetamide
(E)-N-Cyclopropyl-2-(7-fluoro-1,2,3,4-tetrahydro-1-naphthylidene)acetamide
(E)-N-Cyclopropy 2-(6-fluoro-3,4-dihydro-2H-1-benzopyran-4-ylidene)acetamide
(E)-N-Cyclopropyl-2-(6-fluoro-3-methyl-1-indanylidene)acetamide
(E)-N-Cyclopropyl-2-(4,6 difluoro-1-indanylidene)acetamide
(E)-N-Cyclopropyl-2-(1,2,3,4-tetrahydro-1-naphthylidene)acetamide
(E)-2-(4-Chloro-1-indanylidene)-N-cyclopropylacetamide
(E)-N-Cyclopropyl-2-(4-methyl-1-indanylidene)acetamide
(E)-N-Cyclopropy 2-(6-fluoro-1-indanylidene)acetamide
(E)-2-N-Cyclopropyl-(4-fluoro-1-indanylidene)acetamide

10. The method of Claim 7 wherein the condition is inflammation, arthritis or pain and the compound of formula (I) or (Ia) is:

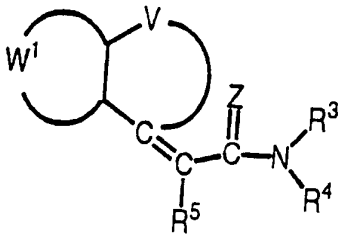
(E)-2-(4-Chloro-6-fluoro-1-indanylidene)-N-methylacetamide
(E)-2-(4-Chloro-6-fluoro-1-indanylidene)acetamide
(E)-2-(4,6 Difluoro-1-indanylidene)acetamide
(E)-2-(6-Fluoro-1-indanylidene)acetamide

(E)-2-(5,7-Difluoro-1-indanylidene)acetamide
(E)-2-(5,6-Difluoro-1-indanylidene)-N-methylacetamide
(E)-2-(4,6-Dichloro-1-indanylidene)acetamide
(Z)-2-(6-Fluoro-2-hydroxy-1-indanylidene)acetamide
(Z)-2-(4,6-Difluoro-2-hydroxy-1-indanylidene)acetamide
(E)-2-(6-Fluoro-3-ethyl-1-indanylidene)-N-methylacetamide

11. A pharmaceutical composition comprising a compound of Formula (I) or (Ia)



(I)



(Ia)

wherein V is
(a) $(CR^1R^2)_mB$,
(b) $B(CR^1R^2)_m$ or
(c) $(CR^1R^2)_mB(CR^1R^2)_m$
wherein B is CR^1R^2, O, NR^6, C=O or $S(O)_m$ and
wherein R^1 and R^2 are the same or different and are
(a) H;
(b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, aryl or C_{1-6}alkylenearyl all optionally substituted with one or more halogen, C_{1-6} alkyl(optionally substituted with

one or more halogen, OR^6 or NR^6R^{6a}), $OC(O)R^6$, OR^6, NR^6R^{6a} or $S(O)_mR^6$; or

R^1R^2 together with the carbon atom to which they are attached form a C_{3-4} ring, or a C_{2-5} heterocyclic ring (comprising one or more heteroatoms of O, NR^6, and $S(O)_m$), the carbon atoms of said rings optionally substituted with one or more halogen, C_{1-6} alkyl(optionally substituted with one or more halogen, OR^6 or NR^6R^{6a}), $OC(O)R^6$, OR^6, NR^6R^{6a} or $S(O)_mR^6$;

(c) OR^6;

(d) $OC(O)R^6$;

(e) $NC(O)R^6$; or

(f) halogen(e.g., fluorine);

wherein R^6 and R^{6a} are the same or different and are H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6}cycloalkyl, C_{1-6}alkylene (C_{3-6} cycloalkyl), aryl or C_{1-6} alkylenearyl all optionally substituted with one or more halogen, C_{1-6} alkyl(optionally substituted with one or more halogen, OH, C_{1-6}alkoxy, NH_2 or substituted amino(as defined hereinafter)); or any combination thereof;

W is an aryl or a heteroaryl ring substituted with one or more

(a) halogen;

(b) C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkylene(C_{3-6}cycloalkyl), aryl, C_{1-6}alkylenearyl, C_{1-6} alkoxy, aryloxy, or C_{1-6} alkyleneoxyaryl all optionally substituted with one or more halogen, OR^6, or NR^6R^{6a};

(c) OR^6;

(d) NR^6R^{6a}, $NR^6NR^6R^{6a}$, $CONR^6R^{6a}$ or $S(O)_mNR^6R^{6a}$ wherein both of the R^6 and R^{6a} are the same or different and are as described hereinbefore or R^6R^{6a} together with the nitrogen atom to which they are attached denote a C_{2-7} ring optionally substituted with one or more halogen, C_{1-6} alkyl(optionally substituted with one or more halogen, OR^6 or NR^6R^{6a}), OR^6 or NR^6R^{6a};

(e) $C(Y)R^6$ wherein Y is O, NOR^6, NR^6 or S;

(f) CO_2R^6;

(g) OR^6O(cyclic) wherein R^6 is other than H;

(h) $OC(O)R^6$;

(i) $OP(O)(OR^6)_2$;

(j) $OP(O)(R^6)_2$ wherein R^6 is other than H;

(k) $OS(O)(OR^6)$;

(l) $OS(O)_2(OR^6)$;

(m) $S(O)_mR^6$ wherein R^6 is other than H;

(n) $NHS(O)_mR^6$ wherein R^6 is other than H;

(o) $N=NR^6$;

(p) NO;

(q) NO_2;

(r) SCN; or

(s) CN or a combination thereof;

when one m is present, m is 0,1 or 2;
when more than one m is present, m can be the same or different and is 0,1 or 2;

R^3 and R^4 are the same or different and are

(a) H; or

(b) C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{1-6} alkylene(C_{3-6}cycloalkyl), aryl or C_{1-6}alkylenearyl all optionally substituted with one or more halogen, C_{1-6} alkyl(optionally substituted with one or more halogen, OR^6 or NR^6R^{6a}), OR^6 or NR^6R^{6a}; or

C_{2-7} R^3 and R^4 together with the nitrogen atom to which they are attached denote a ring or a C_{1-4} heterocyclic ring (comprising one or more heteroatoms selected from the group consisting of O, NR^6, and $S(O)_m$) the carbon atoms of said rings optionally substituted with one or more halogen, C_{1-6} alkyl (optionally substituted with one or more halogen, OR^6 or NR^6R^{6a}), OR^6 or NR^6R^{6a} or any combination thereof;

R^5 is

(a) H;

(b) halogen;

(c) CN;

(d) $C(O)OR^6$;

(e) $C(O)NR^3R^4$;

(f) C_{1-6} alkyl, aryl or C_{1-6} alkylenearyl all optionally substituted with one or more halogen, $OC(O)R^6$, OR^6, NR^6R^{6a} or SR^6;

(g) OR^6; or

(h) SR^6 or any combination thereof; and

Z is O or S;

or salts, solvates or physiologically functional derivatives thereof, in admixture with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Interr ıal Application No
PCT/GB 94/01002

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07C233/11 C07D295/18 C07D311/58 C07D215/12 C07D223/16
A61K31/16 A61K31/35 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SYNTHESIS. no. 2 , February 1974 , STUTTGART DE pages 116 - 7 Y. ANGHELOVA ET. AL. 'Conversion of 5-Aryl-3-phenyl-2,4-pentadienoic Acids and Their Amides into Indane Derivatives' see whole document, especially compound 2a ---	1,6
X	FR,A,2 177 929 (AKTIEBOLAGET KABI) 9 November 1973 see example 3 ---	1-5,11
A	EP,A,0 218 373 (BEECHAM) 15 April 1987 see claims; examples ---	1,11
A	DE,B,12 41 438 (DIPL.-CHEM. EMIL FRESE) 1 June 1967 see example 4 ---	1
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 July 1994	22.07.94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Helps, I

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF HETEROCYCLIC CHEMISTRY vol. 10, no. 1 , February 1973 , PROVO US pages 137 - 8 K. D. PAULL ET. AL. 'A New Class of Sultones and Related Compounds' see whole document -----	1

INTERNATIONAL SEARCH REPORT

ternational application No.
PCT/GB94/01002

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 7 and 8 are drawn to a method of treatment of the human or animal body by therapy (Rule 39.1(iv)-PCT), the search has been carried out and based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Due to the broad scope of claims a complete search was not possible on economic grounds. The search has been limited to examples (Guidelines B-III 3.7)
Claims searched incompletely: 1-3,7

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter ıal Application No
PCT/GB 94/01002

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
FR-A-2177929	09-11-73	SE-B-	371190	11-11-74
		AT-A,B	333743	10-12-76
		AT-A,B	333744	10-12-76
		AT-B-	329045	26-04-76
		CA-A-	1032165	30-05-78
		CH-A-	626044	30-10-81
		CH-A-	622769	30-04-81
		CH-A-	626045	30-10-81
		CH-A-	621110	15-01-81
		DE-A,C	2314636	04-10-73
		GB-A-	1421208	14-01-76
		JP-C-	1237357	31-10-84
		JP-A-	49005957	19-01-74
		JP-B-	59009540	03-03-84
		US-A-	4172093	23-10-79
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		US-A-	4987138	22-01-91
DE-B-1241438		NONE		