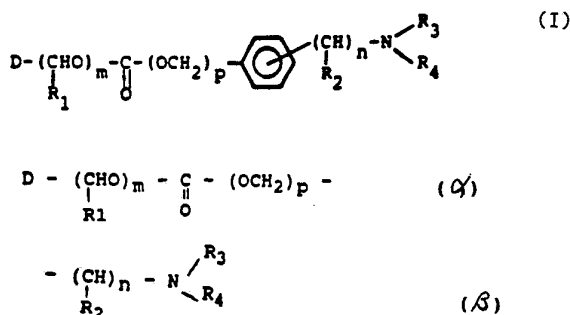




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C07C 229/38, A61K 31/00	A1	(11) International Publication Number: WO 90/08128 (43) International Publication Date: 26 July 1990 (26.07.90)
(21) International Application Number: PCT/DK90/00020 (22) International Filing Date: 19 January 1990 (19.01.90) (30) Priority data: 240/89 20 January 1989 (20.01.89) DK (71)(72) Applicants and Inventors: BUNDGAARD, Hans [DK/DK]; Tjørnevej 36, DK-2970 Hørsholm (DK). FALCH, Erik [DK/DK]; Olgasvej 31, DK-2950 Vedbæk (DK). (74) Agent: PLOUGMANN & VINGTOFT; Sankt Annæ Plads 11, DK-1250 Copenhagen K (DK). (81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), IT (European patent), JP, KR, LU (European patent), NL (European patent), NO, SE (European patent), US.		Published <i>With international search report.</i>

(54) Title: NOVEL PRODRUG DERIVATIVES OF BIOLOGICALLY ACTIVE AGENTS CONTAINING HYDROXYL GROUPS OR NH-ACIDIC GROUPS



(57) Abstract

Compounds of formula (I), wherein D represents the dehydrogenated residue of a hydroxyl group-containing drug or the dehydrogenated residue of an NH-acidic group-containing drug; the substituents in the phenyl ring α and β are in either meta- or para-position to each other; and the phenyl ring additionally may be substituted; m is an integer of 0 or 1; p is an integer of 0 or 1; n is an integer from 1 to 4; R₁ is selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, a group having the formula -COOR₅, wherein R₅ is an alkyl or aralkyl group, or a carbamoyl group of the formula -CONR₆R₇, wherein R₆ and R₇ are the same or different and are hydrogen, an alkyl group, or together with the adjacent nitrogen atom form a 4-, 5-, 6-, or 7-membered heterocyclic ring; R₂ is hydrogen or an alkyl group; R₃ and R₄ are the same or different and are hydrogen, or optionally substituted alkyl, aralkyl, alkenyl or cycloalkyl; or R₃ and R₄ are combined so that -NR₃R₄ forms an optionally substituted 4-, 5-, 6- or 7-membered heterocyclic ring, which in addition to the nitrogen atom may contain one or two further heteroatoms selected from nitrogen, oxygen, and sulfur; with the proviso that m is 0 when D represents the dehydrogenated residue of a hydroxyl group-containing drug and m is 1 when D represents the dehydrogenated residue of an NH-acidic group-containing drug; and the pharmaceutically acceptable acid addition salts or quaternary ammonium salts thereof.

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NOVEL PRODRUG DERIVATIVES OF BIOLOGICALLY ACTIVE AGENTS CONTAINING
HYDROXYL GROUPS OR NH-ACIDIC GROUPS

BACKGROUND OF THE INVENTION

Field of the invention

5 The present invention relates to novel biolabile, in-vitro solution stable and water soluble prodrug forms of drugs containing one or more hydroxyl groups or NH-acidic groups, to methods for preparing the prodrug forms, to pharmaceutical compositions containing such prodrug forms, and to methods for using the prodrug forms.

10 For purposes of this specification, the term "prodrug" denotes a derivative of a known and proven prior art compound which derivative, when administered to warm-blooded animals, e.g. humans, is converted into the proven drug. The enzymatic and/or chemical hydrolytic cleavage of the compounds of the present invention occurs in such a
15 manner that the proven drug form (parent hydroxyl-containing or NH-acidic drug) is released, and the moiety or moieties split off remain non-toxic or are metabolized so that non-toxic metabolic products are produced.

 These novel prodrug forms are esters of certain amino acids.
20 These esters are characterized by possessing a high water solubility and by combining a high susceptibility to undergo enzymatic hydrolysis in-vivo with a high stability in aqueous solution.

Description of the prior art

 It is well-known that a wide variety of compounds containing a
25 hydroxyl group (-OH) or an NH-acidic group (e.g. an imide, uracil or imidazole function) are useful active agents for the treatment or management of various disease states or conditions. It is also well-known that such prior art compounds are characterized by certain inherent disadvantages, notably bioavailability problems upon admini-
30 stration as well as stability or pharmaceutical formulation

problems. Such reduced bioavailability can be attributed in part to poor aqueous solubility and also to metabolic losses during and following conventional administration. Also, the poor water solubility of many such prior art compounds, such as corticosteroids, chloramphenicol, aciclovir, phenytoin, allopurinol and paracetamol, makes it difficult or impossible to prepare formulations suitable for intravenous or intramuscular injection or ophthalmic delivery.

A promising approach to solve such problems may be esterification of the hydroxyl function or N- α -acyloxy-alkylation of the NH-acidic function in the drugs to produce more water soluble prodrug forms. Several types of esters have been described and used to increase the aqueous solubility of hydroxyl-containing agents, e.g. dicarboxylic acid hemiesters, sulfates, phosphates and aminoalkanoyloxy derivatives. However, their use is not without problems, considering the ideal properties of such prodrugs: They should possess adequate aqueous solubility, sufficient aqueous solution stability to allow long-term storage of ready-to-use solutions and yet they should be converted quantitatively and rapidly in-vivo to the active parent drug. For example, succinate esters are not good substrates for hydrolytic enzymes and often show a slow and incomplete regeneration of the parent drug in-vivo as is the case for such esters of several corticosteroids, chloramphenicol and metronidazole (Nahata & Powell, 1981; Bundgaard, 1985, Larsen et al., 1988). Furthermore, such esters have limited solution stability (Bundgaard, 1985). Other ester derivatives which are readily converted to the active drug in-vivo exhibit, on the other hand, poor solution stability. Such derivatives include, for example, various aliphatic amino acid esters of metronidazole (Bundgaard et al., 1984), corticosteroids (Kawamura et al., 1971; Anderson et al., 1985) and paracetamol (Cognacq, 1977; Higasava et al., 1979). Other derivatives may possess the requisite solubility, stability and biolability, but exhibit other disadvantages. Thus, an amine-containing ester prodrug of methylprednisolone apparently fulfilling these requirements was found to cause local toxicity and irritation upon intramuscular or intravenous administration (Anderson et al., 1987). For N- α -acyloxyalkyl prodrug derivatives of NH-acidic drugs, increased water solubility has in the past been achieved by incorporating an ionizable acyl group in the

ester part such as an amino acid residue. For example, amino-containing N-acyloxymethyl allopurinol prodrugs derived from α -amino acids have been disclosed in the US Patent 4,694,006.

Such derivatives exhibit the same disadvantage as similar esters of hydroxyl-containing drugs in possessing a very limited solution stability, making it impossible to formulate ready-to-use solutions (Bundgaard & Falch, 1985). The same applies to similar N-acyloxymethyl derivatives of chlorzoxazone (Johansen & Bundgaard, 1981) and phenytoin (Varia et al., 1984).

Thus, there exists a clear need for new prodrug derivatives of biologically active substances containing a hydroxyl group or an NH-acidic group which derivatives would be devoid of those disadvantages and drawbacks that to date have characterized the prior art compounds.

In accordance with the present invention it has now been discovered that water soluble esters of the formula I below are surprisingly stable in aqueous solution, yet being readily cleaved enzymatically in-vivo, e.g. by plasma enzymes, with release of the parent drug.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a novel water soluble amine-containing prodrug type characterized by possessing a high stability in aqueous solutions in-vitro and at the same time being readily cleaved enzymatically in-vivo to regenerate the parent active drug.

It is another object of this invention to provide novel bioreversible derivatives of drugs or biologically active agents having a hydroxyl group or an NH-acidic function which derivatives, when administered to warm-blooded animals, e.g. humans, elicit the bio-affecting/pharmacological response characterized of the agents from

which they are derived, yet which are characterized by enhanced water solubility and in-vitro stability.

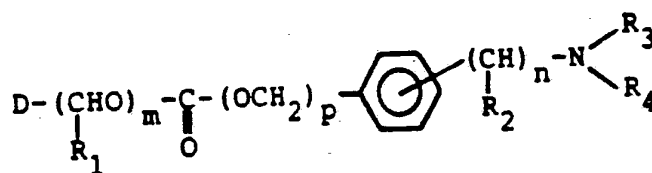
Yet another object of the present invention is to provide pro-
 5 drugs of bio-affecting agents containing a hydroxyl group or an NH-
 acidic function which are capable of making the parent drugs more
 bioavailable from the site of administration such as the gastro-
 intestinal tract, the rectum, the skin or the eye of the human body.

It is a further object of the present invention to provide such
 10 derivatives of conventional bio-affecting agents containing a hy-
 droxyl group or an NH-acidic function which are prodrugs designed to
 cleave in such a manner as to enable the original parent drug form to
 be released at its therapeutic site or sites of activity, while the
 remaining cleaved moiety is non-toxic and/or is metabolized in a non-
 toxic fashion.

15 Other objects, features and advantages of the invention will be
 apparent to those skilled in the art from the detailed description of
 the invention which follows.

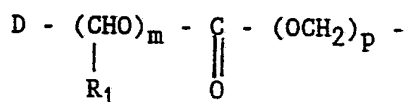
The foregoing objects, features and advantages are provided by
 the novel compounds of the formula I:

20

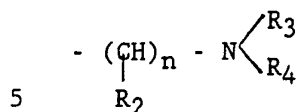


wherein D represents the dehydrogenated residue of a hydroxyl group-
 containing drug or the dehydrogenated residue of an NH-acidic group-
 25 containing drug;

the substituents in the phenyl ring



and



are in either meta- or para-position to each other;

the phenyl ring additionally may be substituted with one, two, three or four substituents selected from the group consisting of an alkyl group, a halogen, a hydroxyl group or an alkoxy group;

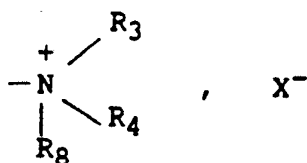
- 10 m is an integer 0 or 1;
 p is an integer of 0 or 1;
 n is an integer from 1 to 4;
 R₁ is selected from the group consisting of hydrogen, an alkyl
 group, an aryl group, an aralkyl group, a group having the
 15 formula -COOR₅, wherein R₅ is an alkyl or aralkyl group, or
 a carbamoyl group of the formula -CONR₆R₇, wherein R₆ and
 R₇ are the same or different and are hydrogen, an alkyl
 group, or together with the adjacent nitrogen atom form a
 20 4-, 5-, 6- or 7-membered heterocyclic ring, which in addi-
 tion to the nitrogen may contain one or two further hetero-
 atoms selected from the group consisting of nitrogen,
 oxygen, and sulfur;
 R₂ is hydrogen or an alkyl group;
- R₃ and R₄ are the same or different and are selected from the group
 25 consisting of hydrogen, an alkyl group, an aralkyl, an
 alkenyl group, a cycloalkyl group, in which the alkyl,
 aralkyl, alkenyl or cycloalkyl group is unsubstituted or
 substituted with one or more substituents selected from:
- 30 - a hydroxyl group
 - a straight or branched-chain alkoxy group
 - a carbamoyl group having the formula -CONR₆R₇ as defined
 above
 - an amino group having the formula -NR₆R₇, wherein R₆ and R₇
 are as defined above; or

- R_3 and R_4 are combined so that $-NR_3R_4$ forms a 4-, 5-, 6- or 7-membered heterocyclic ring, which in addition to the nitrogen atom may contain one or two further heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and which hetero-cyclic ring may be substituted with a hydroxyl group, a carbonyl group, an alkyl group, an alkyl group substituted with a hydroxyl group or an acyloxy group having the formula R_5COO- , wherein R_5 is as defined above, an alkoxy carbonyl group having the formula $-COOR_5$ as defined above, or a carbamoyl group of the formula $-CONR_6R_7$ as defined above;
- with the proviso that m is 0 when D represents the dehydrogenated residue of a hydroxyl group-containing drug and m is 1 when D represents the dehydrogenated residue of an NH-acidic group-containing drug;
- and the pharmaceutically acceptable acid addition salts or quaternary ammonium salts thereof.

In the present context, the dehydrogenated residue of a hydroxyl group-containing drug means the residue attached to the hydroxyl group from which the hydrogen has been removed. Similarly, the dehydrogenated residue of an NH-acidic group containing drug means the residue attached to the NH-acidic moiety from which the hydrogen has been removed.

In the present context, the term "alkyl" designates C_{1-8} alkyl which may be straight or branched, such as methyl, ethyl, propyl, isopropyl, butyl, tert. butyl, pentyl, hexyl, heptyl, or octyl. The term "alkenyl" designates a C_{2-6} -mono-unsaturated aliphatic hydrocarbon group which may be straight or branched, such as propenyl, butenyl or pentenyl. The term "aryl" encompasses aryl radicals such as phenyl and naphthyl and also the corresponding aryl radicals containing one or more substituents, which may be the same or different, such as alkylthio, alkyl, halogen, alkoxy, aryloxy, nitro, alkanoyl, dialkylamino, alkanoyloxy or hydroxy groups. The term "cycloalkyl" designates a radical containing 4 to 7 carbon atoms, e.g. cyclohexyl. The term "aralkyl" designates a radical of the type -alkylene-aryl, wherein aryl is as defined above and the alkylene moiety contains 1 to 6

- carbon atoms and can be straight or branched-chain, e.g. methylene, and the like. When R_3 and R_4 in the formula I and R_6 and R_7 in the formula $-NR_6R_7$ together with the adjacent nitrogen atom form a 4-, 5-, 6- or 7-membered heterocyclic ring which in addition to the nitrogen atom may contain 1 or 2 further hetero atoms selected from the group consisting of nitrogen, oxygen, and sulfur, it may, for instance, be 1-piperidyl, 1-pyrrolidinyl, 1-piperazinyl, 4-methylpiperazin-1-yl, hexamethyleneimino, morpholino, thiomorpholino, 1-pyrazolyl, 1-imidazolyl and 2-methylimidazol-1-yl.
- 10 The term "non-toxic pharmaceutically acceptable acid addition salts" as used herein generally includes the non-toxic acid addition salts of compounds of formula I, formed with non-toxic inorganic or organic acids. For example, the salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulphuric, sulphamic, nitric, phosphoric acid and the like; and the salts with organic acids
- 15 such as acetic, propionic, succinic, fumaric, maleic, tartaric, citric, glycolic, lactic, stearic, malic, pamoic, ascorbic, phenylacetic, benzoic, glutamic, salicylic, sulphuric, sulphanilic acid, and the like.
- 20 The quaternary ammonium derivatives of the compounds of the present invention may be represented by formula I wherein the terminal amino group is substituted by an additional group as depicted below



- wherein R_3 and R_4 alone or taken together with the nitrogen atom to which each is attached have the meanings defined above; R_8 is a lower alkyl group of from 1 to 4 carbon atoms, preferably methyl or ethyl;
- 25 and X^- represents an anion, e.g. X is I, Br, Cl, CH_3SO_3 or CH_3COO .

DETAILED DESCRIPTION OF THE INVENTION

As stated above, D in formula I represents the dehydro-genated residue of any drug or medicament having one or more hydroxyl groups (m=0 in formula I) or D represents the dehydrogenated residue of a
5 drug containing one or more NH-acidic functions (m=1 in formula I). In the present context, an NH-acidic function, group or moiety is defined as a structure with the formula -NH-CO- or -NH-SO₂- or as a heterocyclic nitrogen structure. Examples of NH-acidic structures encompassed within the present invention include the following:

- 10 Secondary carboxamides
- Secondary sulfonamides
- Secondary carbamates
- Imides
- N-alkyl ureas
- 15 N-acyl N'-alkyl ureas
- Cyclic structures containing such moieties like
 - Uracils (2,4-pyrimidinediones)
 - Thiouracils
 - Pyrimidinones
 - 20 Barbituric acids (2,4,6-pyrimidinetriones)
 - Hydantoins (2,4-imidazolidinediones)
 - Oxazolinones
 - Benzoxazolinones
 - Oxazolidinediones
- 25 Imidazoles
- Benzimidazoles
- Pyrazoles
- Benzopyrazoles
- Triazoles
- 30 Benzotriazoles
- Xanthines
- Isatins

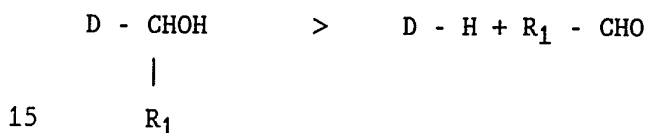
Such structures may contain more than one NH-acidic function. For example, the uracil ring contains two NH-acidic funtions. In such

cases prodrug derivatives formed at both NH-acidic functions are also part of the present invention.

For drugs containing NH-acidic functions it will be appreciated that it is a critical feature of the present invention that $m=1$ in the formula I. If, for example, $m=2$, such compounds would not easily be converted in-vivo to the parent active NH-acidic drug. For compounds with $m=1$ cleavage in-vivo proceeds via two steps, an enzymatic ester hydrolysis to produce D - CHOH



followed by a fast and spontaneous decomposition of this N- α -hydroxy-alkyl derivative as follows:



Examples of drugs or pharmaceuticals from which the instant prodrugs may be derived are listed below. Those skilled in the art will realize that the list is not exhaustive and the invention is applicable to other drugs containing a hydroxyl group or an NH-acidic function as well.

a Drugs containing an OH-group:

Aciclovir
Clavulanic acid
25 Cromolyn and cromolyn esters
Aclarubicin
Doxorubicin
Ivermectin
Benzyl alcohol
30 Alfalcacidol
Erythromycin A
2'-Deoxy-5-trifluoromethyluridine
Amphotericin B

- Cyclocytidine
Arbaprostil
Atropine
Azacitidine
5 Chloramphenicol
Azidamfenicol
Carboprost
Metronidazole
Cefamandole
10 Cetophenicol
Chlorphenesin
Chlorphenesin carbamate
Cycloheximide
Clindamycin
15 Cytarabine
Digoxine
Dinoprostone
Ribavirine
Temazepam
20 Thiamphenicol
Trifluridine
Vidarabine
Doxifluridine
Compactin
25 Mevinolin
Floxuridine
3'-Azido-3'-deoxythymidine (zidovudine)
Cyclaradine
Camptothecin
30 Dipyridamole
Diprophylline
Doxefazepam
Oxazepam
Lorazepam
35 Epirubicine
Ergometrine
Ergotamine
Etofylline

- Etoposide
Fenylramidol
Forskolin
Guaifenesine
5 Idoxuridine
Imipenem
Isometronidazole
Lormetazepam
Mazindol
10 Nandrolone
Naproxol
Nicotiny alcohol
Novobiocin
Oleandomycin
15 Ornidazole
Phenylpropanolamine
Proxiphylline
Pseudoephedrine
Quinidine
20 Retinol
Secnidazole
Budesonide
9 α -Fluorohydrocortisone
Triamcinolone
25 Corticosterone
Prednisone
Prednisolone
6 α -Methylprednisolone
Fluclorolone acetonide
30 Fluocinolone acetonide
Alclometasone
Aldosterone
Alfadolone
Alfaxalone
35 Amcinafal
Beclomethasone
Betamethasone
Betamethasone 17-valerate

- Chlorprednisone
Clobetasol
Clobetasone
Cortisone
5 Hydrocortisone
Dexamethasone
Fludroxycortide
Flumethasone
Flunisolide
10 Fluocortolone
Fluprednisolone
Pregnanolone
Hydroxydione
Paramethasone
15 Prednylidene
Propranolol
Metoprolol
Fluorometholone
Timolol
20 Cetamolol
Celiprolol
Acebutolol
Albuterol
Alprenonol
25 Atenolol
Bucindolol
Levobunolol
Butopamine
Carbuterol
30 Cartelolol
Nadolol
Oxprenolol
Labetalol
Pindolol
35 Pirbuterol
Prenalterol
Sotarol
Metipranolol

	Betaxolol
	Minaxolone
	7-Deacetylforskolin
	Prostacyclin
5	Silybin
	Estramustine
	Ganciclovir
	Bromperidol
	Thymidine
10	Rapamycin
	Sydnocarb
	Digitoxigenin
	Dyphyllin
	4-Acetyl-2-(2-hydroxyethyl)-5,6-bis(4-chlorophenyl)-2H-pyridazin-3-
15	one
	Nystatin
	Aureofacin
	Perimycin
	Testosterone
20	Acenocoumarol
	Paracetamol
	Salicylic acid
	Salicylsalicylic acid
	Tetracycline
25	Bamethan
	Di flunisal
	Dicoumarol
	Carbidopa
	Dienostrol
30	Diethylstilbestrol
	Dithranol
	Dobutamine
	Levodopa
	Methyldopa
35	Estradiol
	Estriol
	Estrone
	Ethinylestradiol

- Etilefrine
- Fenoterol
- Furodazole
- Hydromorphone
- 5 Isoprenaline
- Levallorphan
- Metaraminol
- Metazocine
- Morphine
- 10 Naloxone
- Naltrexone
- Nalorphine
- Nalmexone
- Levorphanol
- 15 Olsalazine
- Orciprenaline
- Adrenaline
- Oxilorphan
- Oximetazoline
- 20 Oxymorphone
- Oxyphenbutazone
- Pentazocine
- Ketobemidone
- Phenprocoumon
- 25 Phenylephrine
- Rimiterol
- Salbutamol
- Salicylamide
- Serotonin
- 30 Terbutaline
- Tocopherol
- Tyrosine
- Warfarin
- 5-aminosalicylic acid and esters thereof
- 35 Dopamine
- Ethylmorphine
- Fenoldopam
- N-t-Butylarterenol

- Isoproterenol
2-Amino-6,7-dihydroxytetrahydronaphthalene (ADTN)
2-(m-Hydroxyphenyl)imidazo[2,1-b]benzothiazole
Isoxsuprine
- 5 Apomorphine
Nalbufine
Cyclazocine
Oxytetracycline
Doxyccline
- 10 Raclopride
Eticlopride
Ethyldeoxyuridine
5-(2-Bromovinyl)-2'-deoxyuridine
Dehydroepiandrosterone
- 15 5-Vinyl-1- β -D-arabinofuranosyluracil
Doxefazepam
Desciclovir
17 β -Hydroxy-11-(4-dimethylaminophenyl)-17 α -prop-1-ynyl-estra-4,9-dien-3-one
- 20 2,3-Dihydro-6-[3-(2-hydroxymethyl)phenyl-2-propenyl]-5-benzofuranol
Levonorgestrel
Propofol
1,3-Dipropyl-8-(p-hydroxyphenyl)xanthine
- b NH-Acidic agents like:
- 25 Allopurinol
5-Fluorouracil
Cimetidine
Theophylline
Phenytoin
- 30 Mephenytoin
Albendazole
Phenobarbital
Alonimide
Aminoglutethimide
- 35 Azathioprine
Mercaptopurine
Bemegride

- Bendazol
Chlorzoxazone
Bromchlorenone
5'-Deoxy-4',5-difluoruridine
5 1,3-Diphenylxanthine
Cambendazole
4-Ethyl-1,3-dihydro-5-[4-(2-methyl-1H-imidazol-1-yl)benzoyl]-2H-imidazol-2-one
N-Methylacetazolamide
10 Pyridoglutethimide
Carbamazepine
Cyclobendazole
Dantrolene
Enprofylline
15 Ethotoin
Fenbendazole
Flubendazole
Flucytosine
Ketoconazole
20 Lobendazole
Methylthiouracil
Methiamide
Miconazole
Mebendazole
25 Niridazole
Nocodazole
Oxfendazole
Oxibendazole
Parbendazole
30 Parconazole
Thiabendazole
Nitrofurantoin
Mifentidine
Mitindomide
35 Domperidone
Ethosuximide
Lixazinone
Spiro-(2-fluoro-9H-fluorene-9,4'-imidazolidine)-2',5'-dione

6-Fluoro-2-methyl-spiro[chroman-4,4'-imidazoline]-2',5'-dione

All of the above compounds are known in the art.

While all of the compounds encompassed by formula I essentially satisfy the objectives of the present invention, preferred compounds
5 include those derived from the following bio-affecting agents (compounds A):

Aciclovir
Cromolyn and cromolyn esters
Erythromycin A
10 Chloramphenicol
Metronidazole
Cefamandole
Cytarabine
Vidarabine
15 Testosterone
Doxifluridine
Floxuridine
Zidovudine
Oxazepam
20 Lorazepam
Etoposide
Forskolin
Idoxuridine
Hydrocortisone
25 Cortisone
5-Aminosalicylic acid and esters thereof
Corticosterone
Prednisone
Prednisolone
30 6 α -Methylprednisolone
Triamcinolone
Dexamethasone
Desciclovir
Flumethasone
35 Chlorprednisone

- Betamethasone
Betamethasone 17-valerate
Fluprednisolone
9 α -Fluorohydrocortisone
5 Pregnanolone
Propranolol
Timolol
Alprenolol
Atenolol
10 Labetalol
Metoprolol
Oxprenolol
Levobunolol
Betaxolol
15 Ganciclovir
Rapamycin
Paracetamol
Levodopa
Methyldopa
20 Dopamine
Dobutamine
Morphine
Naloxone
Naltrexone
25 Nalorphine
Oximetazoline
Ketobemidone
Phenylephrine
Salbutamol
30 Terbutaline
Fenoldopam
Allopurinol
5-Fluorouracil
Theophylline
35 Cimetidine
Phenytoin
Aminogluthethimide
Mercaptopurine

Chlorzoxazone

Mebendazole

Thiabendazole

Mitindomide

5 Domperidone

Ketoconazole

Mifentidine

1,3-Diphenylxanthine

1,3-Dipropyl-8-(p-hydroxyphenyl)xanthine

10 Particularily preferred compounds of the invention include those wherein D in formula I is derived from one of the specific bio-affecting agents named above (compounds A), R_1 is hydrogen or methyl (when $m = 1$), $p = 0$, R_2 is hydrogen, n is 1 or 2, and m and R_3 and R_4 are as defined in connection with the general formula I.

15 In especially preferred compounds of the formula I, D is derived from one of the compounds A above, R_1 is hydrogen (when $m = 1$), $p = 0$, R_2 is hydrogen, $n = 1$, and m and R_3 and R_4 are the same or different and are

- H

20 - CH_3

- C_2H_5

- $CH_2CH_2CH_3$

- CH_2CH_2OH

- CH_2CONH_2

25 - $CH_2CH_2NH_2$

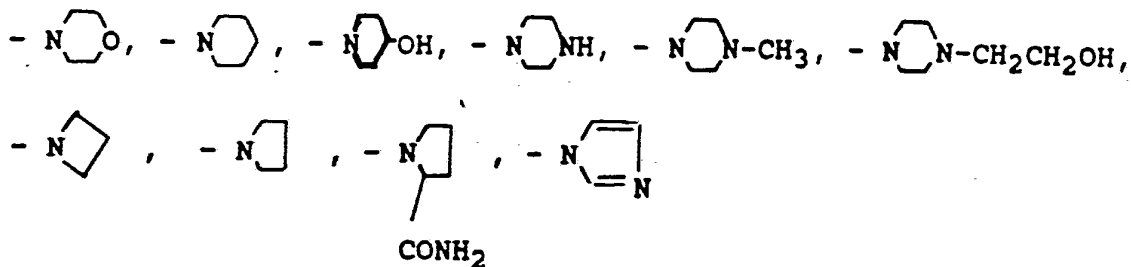
- $CH_2CH_2NHCH_3$

- $CH_2CH_2N(CH_3)_2$

- $CH_2CH_2N(C_2H_5)_2$ or

- $CH_2CH_2OCH_3$

30 or - NR_3R_4 is

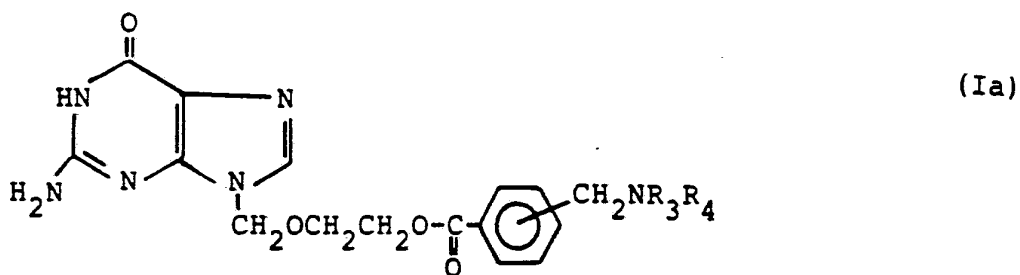


It will be appreciated that in the especially preferred compounds defined immediately above, each and every possible combination between the given examples of R_3 and R_4 in the

formula D - $(\text{CH}_2\text{O})_m - \text{C} \begin{array}{c} | \\ \text{O} \end{array} \text{---} \text{C}_6\text{H}_4 \text{---} \text{CH}_2\text{NR}_3\text{R}_4$ ($m=0$ or 1), may, of

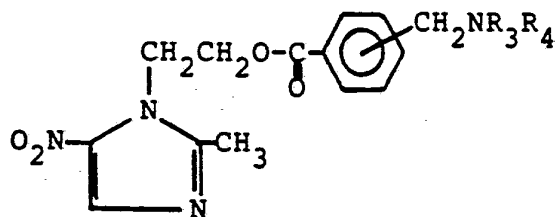
course, be combined with each and every group D derived from the compounds A listed above, and that the above definition is equivalent to listing each and every possible combination of the listed examples of D, m, R_3 and R_4 .

Specific examples of especially preferred compounds of the formula I are the following compounds of formula Ia - Is:



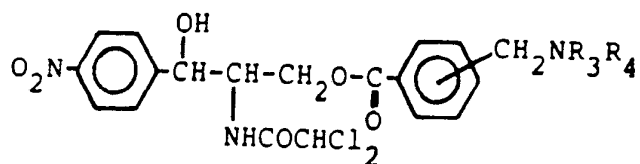
Metronidazole derivatives

(Ib)



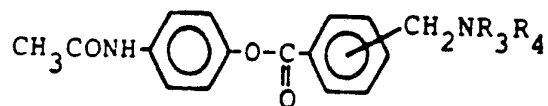
Chloramphenicol derivatives

(Ic)



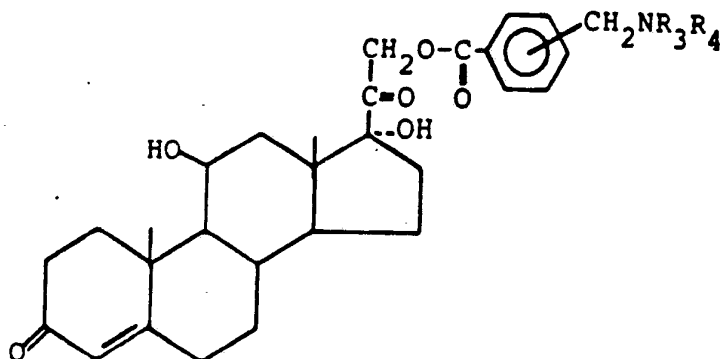
Paracetamol derivatives

(Id)



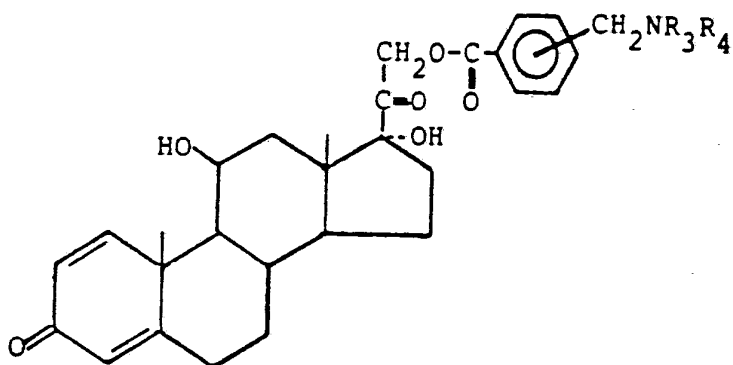
Hydrocortisone derivatives

(Ie)



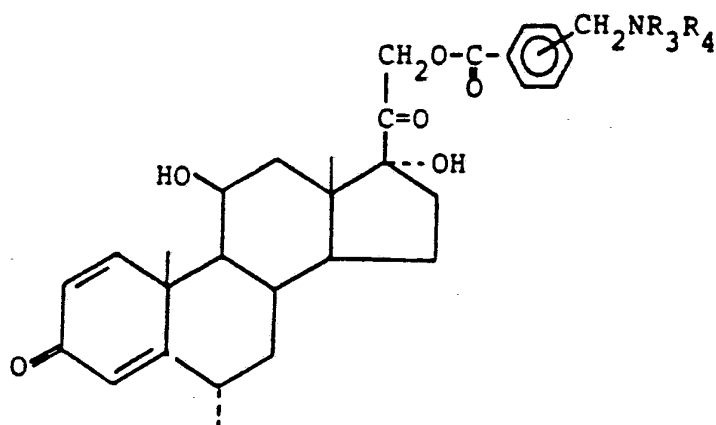
Prednisolone derivatives

(If)



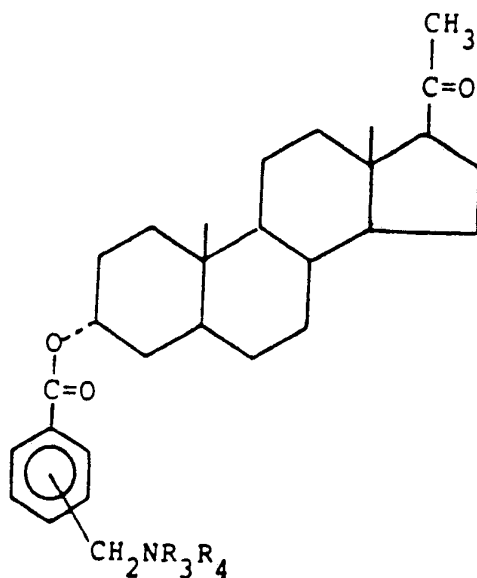
Methylprednisolone derivatives

(Ig)

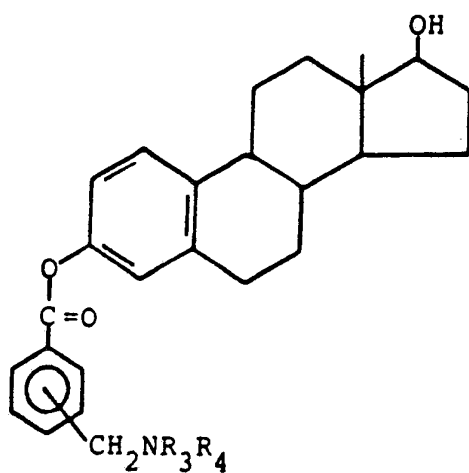


Pregnanolone derivatives

(Ih)

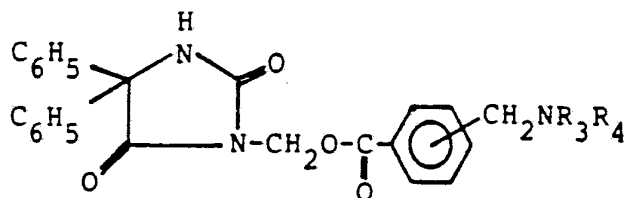
 β -Estradiol derivatives

(Ii)



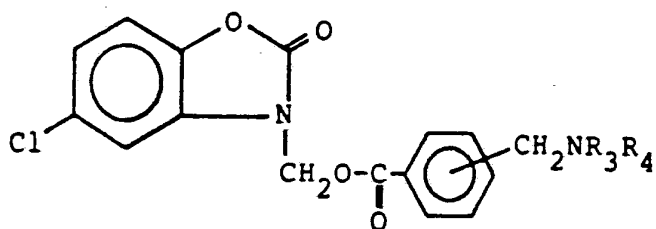
Phenytoin derivatives

(Ij)



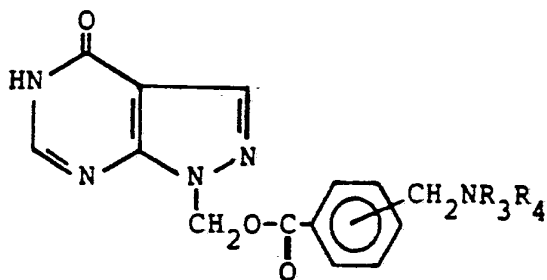
Chlorzoxazone derivatives

(Ik)



Allopurinol derivatives

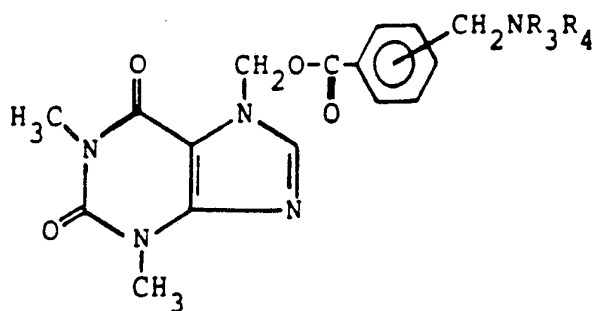
(Il)



and the corresponding 2-substituted, 2,5- and 1,5-disubstituted allopurinol derivatives

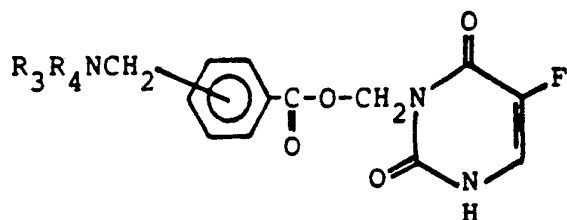
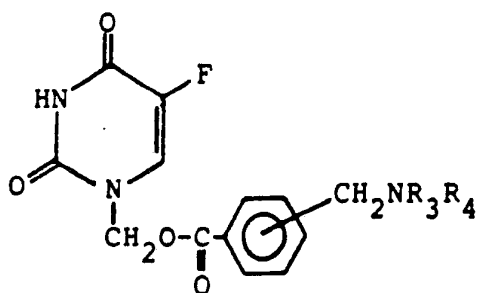
Theophylline derivatives

(Im)



5-Fluorouracil derivatives

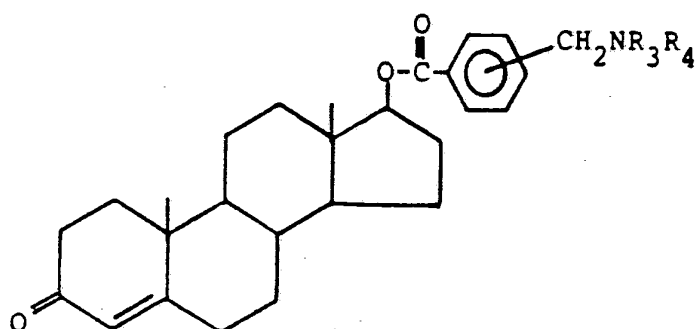
(In)



or the 1,3-disubstituted derivatives

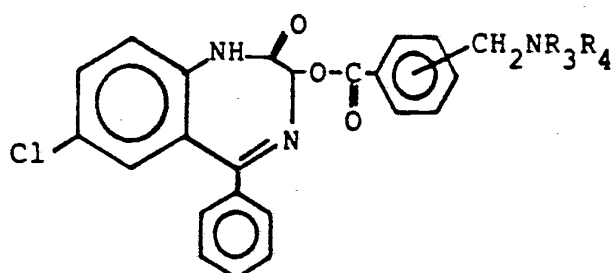
Testosterone derivatives

(Io)



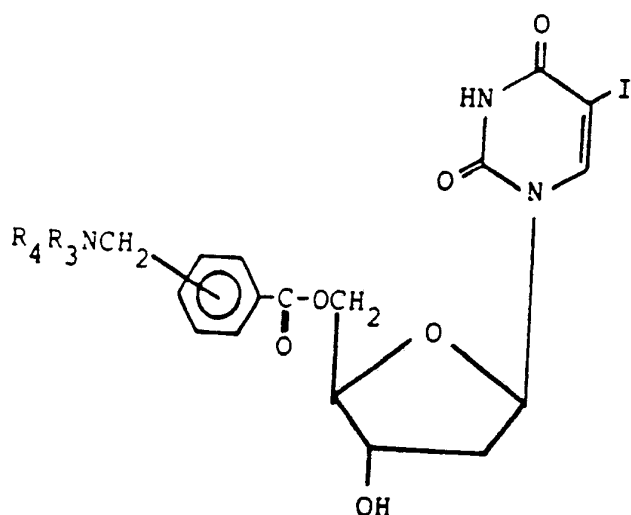
Oxazepam derivatives

(Ip)



Idoxuridine derivatives

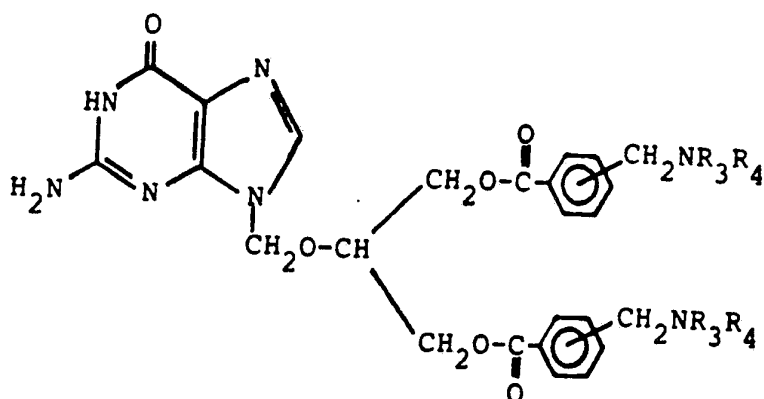
(Iq)



or the corresponding 3',5'-diesters

Ganciclovir derivatives

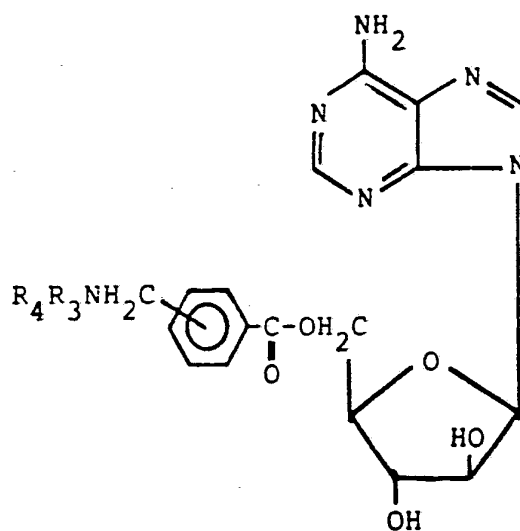
(Ir)



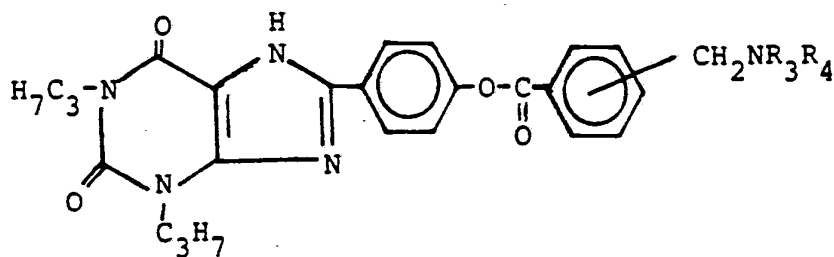
or the corresponding monoesters

Vidarabine (Ara-A) derivatives

(Is)



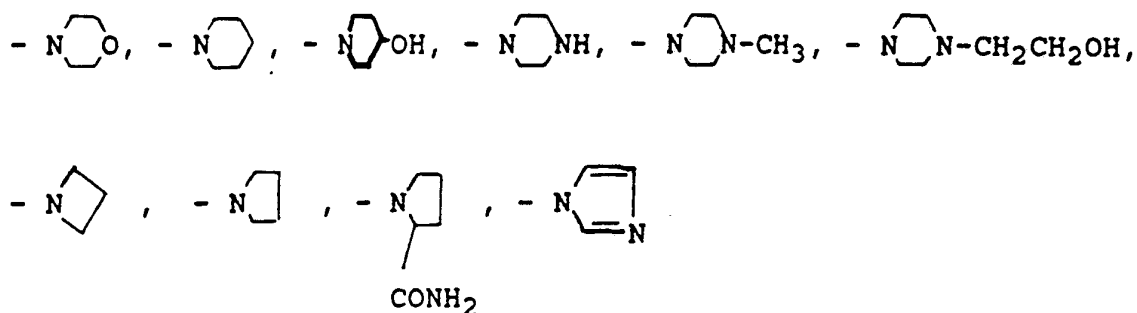
1,3-Dipropyl-8-(p-hydroxyphenyl)xanthine derivatives (It)



wherein the substituents in the phenyl ring of the benzoate ester moiety are in either meta- or para-position to each other and wherein R_3 and R_4 are the same or different and are

- H
- 5 - CH_3
- C_2H_5
- $\text{CH}_2\text{CH}_2\text{CH}_3$
- $\text{CH}_2\text{CH}_2\text{OH}$
- CH_2CONH_2
- 10 - $\text{CH}_2\text{CH}_2\text{NH}_2$
- $\text{CH}_2\text{CH}_2\text{NHCH}_3$
- $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$
- $\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$ or
- $\text{CH}_2\text{CH}_2\text{OCH}_3$

15 or - NR_3R_4 is



A most important characteristic of the novel prodrug derivatives of the formula I is their combination of high water solubility, high stability in aqueous solution at pH values affording the high water solubility (i.e., weakly acidic pH values) and facile enzymatic

20 cleavage in the body with quantitative release of the parent drug. The solution stability of these compounds is markedly higher than that of other amino-containing ester prodrugs such as esters formed

with α -amino acids. Normally, a protonated amino group in the acyl part of an ester strongly activates or catalyzes the ester bond toward hydroxide ion-catalyzed or water-catalyzed hydrolysis (e.g. Bundgaard et al., 1984). In the compounds of formula I the amino group is, however, structurally incapable of exhibiting such catalytic effect on cleavage of the ester bond due to the incorporation of a phenyl group between the ester moiety and the amino group. It can also be said that the phenyl moiety functions as a spacer group hindering any instability-causing interactions between the ester moiety and the solubilizing amino function.

These characteristics of the novel compounds of the present invention make them particularly suitable for administration as sterile aqueous solutions by intravenous injection, intravenous infusion, or intramuscular or subcutaneous injection, or for topical administration to the eye. However, due to their ready solubility at acidic pH values and high chemical stability, the prodrugs of this invention are also highly useful for peroral administration, e.g. to improve the bioavailability of slightly water soluble parent drugs containing a hydroxyl group or an NH-acidic group. Similarly, the solubility and stability characteristics of the novel prodrugs make them highly suitable for rectal or dermal administration.

It will be appreciated that the lipophilicity of the prodrug derivatives of the formula I can be readily modified or controlled by the appropriate selection of the amino group ($-NR_3R_4$ in formula I) in the compounds both in terms of amine basicity, and hence degree of ionization at physiological pH values, and in terms of hydrophobicity of the substituents (R_3 and R_4) on the nitrogen atom. Thus, it is readily feasible to select prodrug derivatives of the formula I which through a combination of improved water solubility and lipophilicity are capable of providing increased biomembrane transport so that the parent drugs are more bioavailable from the site of administration such as the gastro-intestinal tract, the rectum, the skin or the eye of the human body. Likewise, for phenolic drugs, for example, the prodrug derivatization of the present invention makes it feasible to protect the phenolic group in the

parent drug against metabolic inactivation processes during or following e.g. peroral or rectal absorption.

Dosage forms and dose

The prodrug compounds of formula I of the present invention can be used to treat any condition for which the parent hydroxyl or NH-acidic group containing drug, medicament or pharmaceutical is useful. For example, if metronidazol is the parent drug of choice, the ester prodrug can be used for any condition or treatment for which metronidazole would be administered. Thus, the prodrug compounds of formula I may be administered orally, topically, parenterally, rectally or by inhalation spray in dosage forms or formulations containing conventional, non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The formulation and preparation of any of this broad spectrum of dosage forms into which the subject prodrugs can be disposed is well-known to those skilled in the art of pharmaceutical formulation. Specific information can, however, be found in the text entitled "Remington's Pharmaceutical Sciences", Sixteenth Edition, 1980.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous suspensions, or solutions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide a pharmaceutically elegant and palatable preparation.

Formulations for oral use include tablets which contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients. These excipients may be, for example, inert diluents, such as calcium carbonate, sodium chloride, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents,

for example, potato starch, or algi-nic acid, binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example, magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin, or olive oil.

For the rectal application of the compounds of formula I of this invention, typical dosage forms include suppositories, rectal gelatin capsules (solutions and suspensions), and enemas or micro-enemas (solutions and suspensions). Thus, in a typical suppository formulation, any one of the compounds of this invention is combined with any pharmaceutically acceptable suppository base such as cocoa butter, esterified fatty acids (C₁₀-C₁₈), glycerinated gelatin, and various water-soluble or dispersible bases like polyethylene glycols and polyoxyethylene sorbitan fatty acid esters. Various additives like salicylates or surfactant materials may be incorporated. Enemas or micro-enemas of the solution type may simply be prepared by dissolving the water-soluble prodrugs of this invention in water or in water containing e.g. 0.5% methylcellulose or another viscosity-increasing agent.

For topical use, creams, ointments, gels, solutions or the like containing the prodrugs are employed according to methods recognized in the art.

Sterile aqueous solutions of the compounds of Formula I for parenteral administration or ophthalmic use typically will contain

other components such as preservatives, anti-oxidants, chelating agents, buffer substances, or other stabilizers.

Naturally, therapeutic dosage range for the compounds of the present invention will vary with the size and needs of the patient and the particular pain or disease symptom being treated. However, generally speaking, the following dosage guide-lines will suffice. For oral administration, the therapeutic dose required for a compound of the present invention will generally, on a molecular basis, mimic that for the parent hydroxyl- or NH-acidic drug. On a topical basis, application of an 0.01% to 5% concentration of a compound of the present invention (in a suitable topical carrier material) to the affected site should suffice.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration to humans may contain from 5 mg to 5 g of the active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total composition. Other dosage forms such as ophthalmic dosage forms contain less active ingredient such as for example from 0.1 mg to 5 mg. Dosage unit forms will generally contain between from about 0.1 mg to about 500 mg of active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and severity of the particular disease undergoing therapy.

From the foregoing description, one of ordinary skill in the art can easily ascertain the essential characteristics of the present invention and, without departing from the spirit and scope thereof, can make various changes and/or modifications of the invention to adapt it to various usages and conditions. As such, these changes

and/or modifications are properly, equitably and intended to be within the full range of equivalence of the following claims.

Preparation of the prodrugs of formula I

The compounds of the present invention may be prepared by various means, and it will be apparent from the following that the amine-containing ester moiety attached to the OH-group of the parent OH-containing drug or to the -CHOH

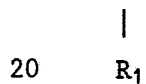


group of the parent NH-acidic drug may be introduced by reaction with an appropriate starting material amino acid which provides the entire moiety, or said ester moiety may be introduced by a sequence of two or more reactions.

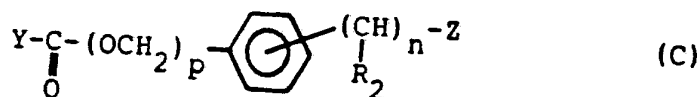
One method (method A) for preparing compounds of the formula I comprises reacting the OH-containing drug of the formula A



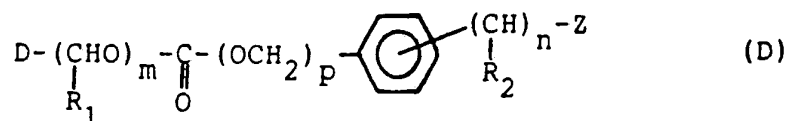
or the N- α -hydroxyalkylated NH-acidic drug of the formula B



wherein D and R_1 are as defined above in connection with formula I, with a compound having the formula C:



wherein p, n, and R_2 are as defined above and Y is a leaving group or a hydroxy group (when p = 0) and Z is a halogen (chlorine, bromide or iodide), and then reacting the so produced compound of the formula D



with an amine of the formula E



wherein R_3 and R_4 are as defined above.

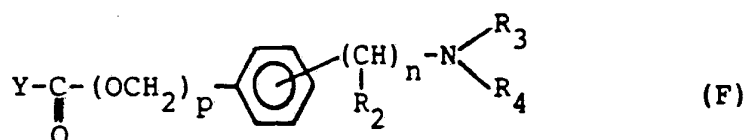
As examples of leaving groups Y may be mentioned chlorine,
 5 bromide and iodine. Group Y may also be an acyloxy group, i.e. the
 reacting compound of formula C may be an anhydride or a mixed an-
 hydride. When Y is a hydroxy group (then $p = 0$ in Formula C), a
 dehydrating agent (e.g. a carbodiimide) has to be present and
 normally, a sulfonic acid or 4-(N,N-dimethylamino)pyridine is added
 10 as a catalyst. The reaction utilizing compound C in which Y is
 hydroxy is conveniently carried out in an inert solvent such as
 dichloromethane, dioxane, pyridine, N,N-dimethylformamide or the
 like, at a temperature of from -10°C to 60°C , for from 1 to 72 h.
 When the reaction utilizes an acid halogenide starting material (e.g.
 15 Y in formula C is chlorine), the process leading to compounds of
 formula D can be conveniently carried out in an inert solvent such as
 benzene, dichloromethane, acetone, N,N- dimethylformamide, dioxane,
 acetonitrile or the like, at from -10°C to reflux temperature, for
 from 1 to 24 h, in the presence of an acid scavenger such as an
 20 alkali metal carbonate, or an organic base such as triethylamine or
 pyridine.

Several compounds of formula C in which $p = 0$, Z is Cl or
 Br and Y is OH, Cl or Br and methods for preparing them are known
 from the literature, see e.g. Blicke & Lilienfeld (1943); Smith &
 25 Menger (1969); Day & Gohil (1976).

The process of reacting a compound of formula D with an amine of
 formula E can be conveniently carried out in the absence of a solvent
 or in an inert solvent such as acetone, acetonitrile, tetrahydro-

furan, ethanol, dichloromethane, N,N-dimethylformamide, or the like, at from -10C° to reflux temperature, for from 1 to 72 h. When Z in a reacting compound of formula D is chlorine, sodium iodide may be added as a catalyst to the reaction mixture.

- 5 Another method (*method B*) for preparing compounds of formula I comprises reacting a compound of formula A or B with a compound having the formula F



- 10 wherein Y, p, n, R₂, R₃ and R₄ are as defined above with the proviso that when Y is hydroxy, p is zero.

- If either R₃ or R₄ is hydrogen, the reaction may preferably be carried out by using a compound of formula F in which the amino group is suitably protected with a protecting group such as a carbobenzyloxycarbonyl or a tert-butyloxycarbonyl group. Deprotection is subsequently performed by known methods, e.g. by hydrogenation or hydrolysis. The reaction is performed under the same conditions as those used to prepare compounds of formula D.

- 20 Several compounds of formula F in which p = 0 and Y is a halogen or hydroxy and methods for preparing them are known from the literature, see e.g. Markwardt et al. (1966); Kasmirowski et al. (1967); Kuhn et al. (1950); Blicke & Lilienfeld (1943); Fujii et al. (1977).

A third method (*method C*) for preparing compounds of the formula I, wherein p = 0, comprises reacting a compound of formula G



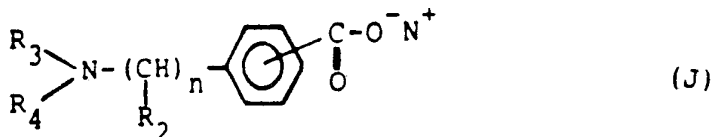
- 25 in which the hydroxy group of the parent drug DH is replaced by Z, so that D' is the dehydroxylated residue of a hydroxyl group-containing drug, or a compound of formula H



|

 R_1

wherein Z is as defined above, with a compound of formula J



- 5 wherein n, R_2 , R_3 and R_4 are as defined above and N^+ is a counter ion such as Na^+ , K^+ , Ag^+ or trialkylammonium. The reaction can be conveniently carried out in an inert solvent such as ethyl acetate, acetone, dimethylformamide or the like, at from room temperature to reflux, for from 0.5 to 48 h. If Z in formula G and H is chlorine, sodium iodide may be added as a catalyst to the reaction mixture.

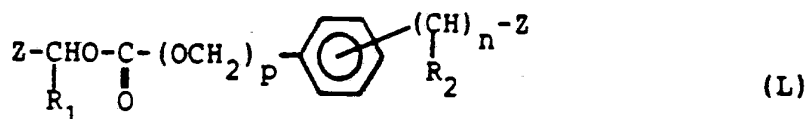
The starting materials of formula B may be prepared by reacting the NH-acidic drug with an aldehyde, preferably formaldehyde, of formula K



- 15 Several N- α -hydroxyalkyl or N-hydroxymethyl derivatives of formula B and methods for their preparation are known in the literature, e.g. for allopurinol (Bansal et al., 1981 b; Bundgaard & Falch, 1987); phenytoin and other hydantoins (Zejc, 1968; Bundgaard & Johansen, 1980); 5-fluorouracil (Buur et al., 1986; Ahmad et al., 1987); benzimidazoles (Hideg & Hanskovsky, 1967; Varma et al., 1980); chlorzoxazone (Varma & Nobles, 1968), theophylline (Bodor & Sloan, 1977); various imides (Vail & Pierce, 1972; Buc, 1947); mitindomide (Deutsch et al., 1986; Haugwitz et al., 1987); barbituric acids (Bansal et al., 1981 b); uracils (Bansal et al., 1981 a); and secondary carboxamides (Böhme et al., 1961). Compounds of formula B derived from other NH-acidic drugs may be prepared by methods similar to those described in these references. Several compounds of formula H and methods for their preparation are also known in the literature, see e.g. Zaugg & Martin (1965) and references cited therein. A convenient method of their preparation is treatment of a compound of

formula B with thionyl chloride, phosphorous pentachloride, phosphorous trichloride or the like.

An alternative method (*method D*) for preparing compounds of the formula I, wherein $m = 1$, comprises reacting a parent NH-acidic drug
5 with a compound of the formula L.



wherein R_1 , R_2 , p , n and Z are as defined above, and then reacting the resultant compound of formula D with an amine of the formula E as described above. Compounds of formula L are prepared by known means e.g. by the procedures described by Bigler et al. (1978), Waranis & Sloan (1987), Binderup & Hansen (1984), Barcelo et al. (1986) and
10 Senet et al. (1988).

An additional method (*method E*) for preparing compounds of the formula I, wherein $p = 1$, comprises reacting a compound of formula M

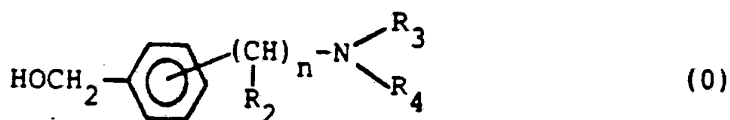


15

or of formula N



20 wherein R_1 and Z are as defined above, with a compound of formula O



wherein n , R_2 , R_3 and R_4 are as defined above. If either R_3 or

R₄ is hydrogen, the reaction is preferably carried out by using a compound of formula O in which the amino group is suitably protected such as described above. Compounds of formula M and N may conveniently be prepared by treating compounds of formula A and B, respectively, with phosgene or a phosgene-releasing agent. Several compounds of formula O and methods for their preparation are known from the literature, see e.g. Lumma et al. (1984).

While the basic methods described above can be used to prepare any of the compounds of the invention, certain conditions and/or modifications therein are made in specific instances. Thus, for example, the basic methods may be modified in the cases where the parent drug contains a free primary or secondary amino group. In such cases, it is preferable to block this amino group before reacting the parent compound as described above. The protected ester prodrug thus obtained is then deprotected by known methods, e.g. by hydrogenation or hydrolysis.

To form acid addition salts of the compounds of formula I said compounds are treated with suitable pharmaceutically acceptable inorganic or organic acids by standard procedures.

The quaternary ammonium salts of the compounds of formula I are formed by reacting said compounds with a suitable alkylating agent such as dimethyl sulphate, diethyl sulphate, methyl bromide, methyl iodide or ethyl iodide.

The present invention is further illustrated by the following examples which, however, are not construed to be limiting. The derivatives described all had spectroscopic properties (IR and ¹H NMR) and elemental analysis in agreement with their structures.

*Brief description of the drawings**Fig. 1*

Time-courses for 1-(4-morpholinomethylbenzoyloxymethyl)-allopurinol (•) and allopurinol (O) during hydrolysis of the prodrug derivative
5 in 80% human plasma at 37°C. The initial prodrug concentration was 10^{-4}M .

Fig. 2

Plots of the first-order kinetics of hydrolysis of various prodrug derivatives in 80% human plasma at 37°C.
10 Key: (O), hydrocortisone 21-(3-[4-methylpiperazin-1-yl]methyl)-benzoate; (•), metronidazole 4-(morpholinomethyl)benzoate; (Δ), 7-(3-morpholinomethylbenzoyloxymethyl)theophylline.

Fig. 3

The pH-rate profile for the degradation of hydrocortisone
15 21-(3-[4-methylpiperazin-1-yl]methyl)benzoate dihydrochloride in aqueous solution at 60°C; k denotes the pseudo-first-order rate constant for the degradation of the ester.

EXAMPLE 1

Hydrocortisone 21-(3-Chloromethyl)benzoate

To a suspension of hydrocortisone (9.05 g, 25 mmol) in dichloromethane (200 ml) was added triethylamine (8.4 ml, 60 mmol) followed by 3-chloromethylbenzoyl chloride (27 mmol, 3.83 ml). The reaction mixture was stirred at room temperature for 4 h. The clear solution obtained was washed with water and a 2% aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulphate and evaporated in vacuo. The residue was recrystallized from methanol-water to give 9.2 g of the title compound as the monohydrate. Mp 175-176°C.

Anal.: Calc. for $C_{29}H_{35}ClO_6$, H_2O :

C, 65.34; H, 6.99; Cl, 6.65.

Found: C, 65.57; H, 7.05; Cl, 6.48.

EXAMPLE 2

Hydrocortisone 21-(4-chloromethyl)benzoate

To a solution of hydrocortisone (9.05 g, 25 mmol) in pyridine (50 ml) was added with stirring 4-chloromethyl-benzoyl chloride (4.61 g, 27 mmol). The reaction mixture was stirred at room temperature for 4 h and concentrated in vacuo. The residue was slurried with water and the solid obtained filtered off and recrystallized from methanol-acetone to give 8.5 g of the title compound as the monohydrate. Mp 189-190°C.

Anal.: Calc. for $C_{29}H_{35}ClO_6$, H_2O :

C, 65.34; H, 6.99; Cl, 6.65.

Found: C, 65.43; H, 7.05; Cl, 6.55.

EXAMPLE 3

Hydrocortisone 21-(4-N,N-diethylaminomethyl)benzoate

A mixture of hydrocortisone 21-(4-chloromethyl)benzoate (533 mg, 1 mmol), sodium iodide (150 mg, 1 mmol) and diethyl-amine (0.83 ml, 8 mmol) in 10 ml of acetone was stirred at 60°C for 5 h. The reaction solution was cooled to about 25°C, filtered and evaporated in vacuo. The residue obtained was stirred with water (30 ml) for about 1 h and the precipitate filtered off, washed with water and recrystallized from acetone-water to give 475 mg of the title compound.

10 Mp 209-211°C.

Anal.: Calc. for $C_{33}H_{45}NO_6$:

C, 71.84; H, 8.22; N, 2.54.

Found: C, 71.88; H, 8.26; N, 2.48.

15 EXAMPLE 4

Hydrocortisone 21-(3-imidazolylomethyl)benzoate

The compound was prepared from hydrocortisone 21-(3-chloromethyl)-benzoate and imidazole by essentially the same procedure as described in Example 3. After recrystallization from ethanol-water, the yield was 80%. Mp 203-205°C (dec.).

20

Anal.: Calc. for $C_{32}H_{38}N_2O_6$, H_2O :

C, 68.05; H, 7.14; N, 4.96.

Found: C, 67.95, H, 7.16; N, 4.85.

EXAMPLE 5

Hydrocortisone 21-[3-(4-methylpiperazin-1-yl)methyl]benzoate, dihydrochloride

A mixture of hydrocortisone 21-(3-chloromethyl)benzoate (2.67 g, 5 mmol), sodium iodide (0.75 g, 5 mmol) and 1-methylpiperazine (5.0 ml, 45 mmol) in 50 ml of acetone was stirred at 60°C for 5 h. Upon cooling to room temperature, the mixture was filtered and evaporated in vacuo. The residue obtained was slurried with 90% ethanol (10 ml) and the precipitate filtered off. Recrystallization from ethanol afforded 2.0 g of the title compound as the monohydrate. Mp 173-175°C.

A dihydrochloride salt was prepared by dissolving 1 g of the free base in a mixture of hot ethanol (40 ml) and acetone (10 ml) and adding an excess of 2.5 M methanolic HCl following by the addition of ether. Upon standing at 4°C overnight the precipitate formed was filtered off and re-crystallized from methanol to give 0.85 g of the title compound as the dihydrochloride. Mp 235-236°C (dec.).

Anal.: Calc. for $C_{34}H_{48}Cl_2N_2O_6 \cdot 2 HCl, 2 H_2O$:

C, 59.38; H, 7.33; Cl, 10.31; N, 4.07.

Found: C, 59.20; H, 7.50; Cl, 10.02; N, 3.95.

EXAMPLE 6

21-[3-(N-ethyl-N[2-diethylaminoethyl]aminomethyl)]benzoate, dihydrochloride

A mixture of hydrocortisone 21-(3-chloromethyl)benzoate (533 mg, 1 mmol), sodium iodide (150 mg, 1 mmol) and N,N,N'-triethylethylenediamine (1 ml) in 10 ml of acetone was stirred at 60°C for 5 h. The mixture was cooled to 20°C and filtered. The filtrate was evaporated in vacuo and the residue taken up in ethyl acetate (50 ml). The solution was washed with water (2 x 25 ml), dried over anhydrous sodium sulphate and evaporated in vacuo to give the title compound as the base. This was dissolved in ether and 2.5 M methanolic HCl (1 ml) added. The precipitate formed upon standing at 4°C for 5 h was fil-

tered off and recrystallized from ethanol to give 390 mg of the title compound.

Anal.: Calc. for $C_{37}H_{54}N_2O_6$, 2 HCl, H_2O :

C, 62.26; H, 8.19; Cl, 9.93; N, 3.92.

5 Found: C, 62.01; H, 8.33; Cl, 9.90; N, 3.87.

EXAMPLE 7

Prednisolone 21-(3-chloromethyl)benzoate

To a solution of prednisolone (5.6 g, 15.5 mmol) in pyridine (40
10 ml) was added with stirring 3-chloromethylbenzoyl chloride (2.41 ml, 17 mmol). The reaction mixture was stirred at room temperature for 4 h and concentrated in vacuo. The residue was slurried with water and the solid obtained filtered off, washed with water and recrystallized from methanol-water to give 6.3 g of the title compound.

15 Mp 226-228°C.

Anal.: Calc. for $C_{29}H_{33}ClO_6$:

C, 67.89; H, 6.48; Cl, 6.91.

Found: C, 67.72; H, 6.62; Cl, 6.81.

20 EXAMPLE 8

Prednisolone 21-[3-(4-methylpiperazin-1-yl)methyl]benzoate, dihydrochloride

The compound was prepared from prednisolone 21-(3-chloromethyl)benzoate and 1-methylpiperazine by essentially the same procedure as
25 described in Example 5. After recrystallization from methanol-ether, the yield was 77%.

Anal.: Calc. for $C_{34}H_{44}N_2O_6$, 2 HCl:

C, 62.86; H, 7.14; Cl, 10.91; N, 4.31.

Found: C, 62.74; H, 7.18; Cl, 10.87; N, 4.28.

30

EXAMPLE 9

Chloramphenicol 3-(3-chloromethyl)benzoate

To a suspension of chloramphenicol (6.46 g, 20 mmol) in dichloromethane (100 ml) was added triethylamine (3.2 ml, 22 mmol) followed
5 by 3-chloromethylbenzoyl chloride (3.14 ml, 22 mmol). The mixture was stirred overnight at room temperature, washed with a 2% aqueous solution of sodium bicarbonate, dried over anhydrous sodium sulphate and evaporated in vacuo. The solid residue obtained was recrystallized from ethanol-water to give 6.5 g of the title compound.

10 *Anal.*: Calc. for $C_{19}H_{17}Cl_3N_2O_6$:

C, 47.97; H, 3.60; Cl, 22.36; N, 5.89.

Found: C, 47.95; H, 3.75; Cl, 22.23; N, 5.80.

EXAMPLE 10

15 *Chloramphenicol 3-(3-N,N-diethylaminomethyl)benzoate, hydrochloride*

A mixture of chloramphenicol 3-(3-chloromethyl)benzoate (0.48 g, 1 mmol), sodium iodide (0.15 g, 1 mmol) and diethylamine (0.83 ml, 8 mmol) in 10 ml of tetrahydrofuran was stirred at 50°C for 16 h. The mixture was filtered and evaporated in vacuo. The residue was taken
20 up in ethyl acetate (50 ml) and water (40 ml) and the organic phase was separated, washed with water, dried and evaporated in vacuo. The residue was dissolved in ether and ethanol and 0.5 ml of a 2.5 M methanolic HCl solution added. Upon standing at 4°C for 20 h the precipitate formed was filtered off and recrystallized from ethanol
25 to yield 0.38 g of the title compound. Mp 210-211°C.

Anal.: Calc. for $C_{23}H_{28}Cl_3N_3O_6$:

C, 50.33; H, 5.14; Cl, 19.38; N, 7.66.

Found: C, 50.31; H, 5.27; Cl, 19.29; N, 7.48.

EXAMPLE 11

Benzyl 4-(N,N-dimethylaminomethyl)benzoate, hydrochloride

To a solution of benzyl alcohol (0.43 ml, 4 mmol) and triethylamine (1.84 ml, 13 mmol) in dichloromethane (25 ml) was added 4-(N,N-dimethylaminomethyl)benzoyl chloride hydrochloride (1.07 g, 4.6 mmol). The mixture was stirred at 20-25°C for 45 h and then washed with water, a 2% aqueous solution of potassium carbonate and water, dried and evaporated in vacuo. The residue obtained was dissolved in a mixture of ether and ethyl acetate. Upon addition of a 2.5 M HCl solution in methanol the title compound precipitated. It was filtered off and recrystallized from acetonitrile-ether to provide 0.85 g. Mp 184-185°C.

Anal.: Calc. for $C_{17}H_{20}ClNO_2$:

C, 66.77; H, 6.59; N, 4.58.

Found: C, 66.42; H, 6.64; N, 4.65.

EXAMPLE 12

Methylprednisolone 21-(3-chloromethyl)benzoate

To a suspension of methylprednisolone (3.74 g, 10 mmol) and triethylamine (3.4 ml, 24 mmol) in dichloromethane (100 ml) was added 3-chloromethylbenzoyl chloride (1.56 ml, 11 mmol). The mixture was stirred at 40°C for 24 h and then washed with water and a 2% aqueous solution of sodium bicarbonate. The dichloromethane phase was dried over anhydrous sodium sulphate and evaporated in vacuo to give the title compound, which was purified by recrystallization from methanol. Mp 214-215°C.

Anal.: Calc. for $C_{30}H_{35}ClO_6$, 0.5 H_2O :

C, 67.22; H, 6.77; Cl, 6.63.

Found: C, 67.34; H, 6.78; Cl, 6.68.

EXAMPLE 13

Methylprednisolone 21-[3-(4-methylpiperazin-1-yl)methyl]benzoate

A mixture of methylprednisolone 21-(3-chloromethyl)-benzoate (527 mg, 1 mmol), sodium iodide (150 mg, 1 mmol) and 1-methylpiperazine (0.89 ml, 8 mmol) in 10 ml of acetone was stirred at 60°C for 5 h. The reaction mixture was filtered and evaporated in vacuo. The residue obtained was triturated with water, filtered off, washed with water and recrystallized from ethanol to yield 470 mg of the title compound. Mp 127-128°C.

Anal.: Calc. for $C_{35}H_{45}N_2O_6$, 2 H_2O :

C, 67.15; H, 7.88; N, 4.48.

Found: C, 67.40, H, 8.00; N, 4.32.

The dihydrochloride salt was obtained as described in Example 10, mp 212-215°C(dec.).

EXAMPLE 14

Methylprednisolone 21-[3-(N-methyl-N-[2-dimethylaminoethyl]-aminomethyl)]benzoate, dihydrochloride

The compound was prepared from methylprednisolone 21-(3-chloromethyl)benzoate and N,N,N'-trimethylethylenediamine by essentially the same procedure as described in Example 6. After recrystallization from acetonitrile-ether, the yield was 81%.

Anal.: Calc. for $C_{35}H_{48}N_2O_6$, 2 HCl:

C, 63.15; H, 7.57; N, 4.21.

Found: C, 63.05; H, 7.66; N, 4.23.

EXAMPLE 15

4-Acetamidophenyl 3-chloromethylbenzoate

To a stirred mixture of paracetamol (4.57 g, 30 mmol) and pyridine (10 ml) was added 3-chloromethylbenzoyl chloride (4.6 ml, 33 mmol) dropwise. The resultant solution was stirred at 20-25°C for 3 h and evaporated in vacuo. The residue obtained solidified by trituration with water and was filtered off and recrystallized from ethanol-acetone to yield 6.5 g of the title compound. Mp 159-160°C.

Anal.: Calc. for $C_{16}H_{14}ClNO_3$:

10 C, 63.27; H, 4.65; N, 4.61.

Found: C, 63.18; H, 4.63; N, 4.71.

EXAMPLE 16

4-Acetamidophenyl 3-[4-methylpiperazin-1-yl)methyl]benzoate, dihydrochloride

A mixture of 4-acetamidophenyl 3-chloromethylbenzoate (1.21 g, 4 mmol), sodium iodide (0.30 g, 2 mmol), 1-methyl-piperazine (1.11 ml, 10 mmol) and 20 ml of acetone was stirred at 40°C for 16 h and filtered. The filtrate was evaporated in vacuo and the residue taken up in ethyl acetate (50 ml) and water (40 ml). The organic phase was separated, washed with water, dried over anhydrous sodium sulphate and evaporated in vacuo. The residue obtained was dissolved in ether and ethyl acetate. A 2.5 M methanolic solution of HCl (4 ml) was added and the mixture allowed to stand at 4°C for 1 h. The crystalline precipitate formed was filtered off and recrystallized from methanol to yield 0.94 g of the title compound as monohydrate. Mp 228-230°C.

Anal.: Calc. for $C_{21}H_{25}N_3O_3$, 2 HCl, H_2O :

C, 55.03; H, 6.37; Cl, 15.47; N, 9.17.

30 Found: C, 55.20; H, 6.40; Cl, 15.53; N, 9.31.

EXAMPLE 17

4-Acetamidophenyl 3-(N,N-diethylaminomethyl)benzoate, fumarate

A mixture of 4-acetamidophenyl 3-chloromethylbenzoate (1.21 g, 4 mmol), sodium iodide (0.30 g, 2 mmol), diethyl-amine (1.04 ml, 10 mmol) and 20 ml of acetone was stirred at 60°C for 5 h and then filtered. The filtrate was evaporated in vacuo and the residue taken up in ethyl acetate (50 ml) and water (40 ml). The ethyl acetate layer was separated, washed with water, dried over anhydrous sodium sulphate and evaporated in vacuo. The residue obtained was dissolved in ether and 2-propanol. A solution of fumaric acid (0.40 g) in 2-propanol (10 ml) was added followed by ether (50 ml). The precipitate formed upon standing at 4°C for 20 h was filtered off and recrystallized from ethanol-ether to give 1.3 g of the title compound. Mp 132-133°C.

Anal.: Calc. for $C_{20}H_{24}N_2O_3$, $C_4H_4O_4$:
C, 63.15; H, 6.18; N, 6.14.
Found: C, 62.99; H, 6.28; N, 6.02.

EXAMPLE 18

N-(3-Chloromethylbenzoyloxymethyl)chlorzoxazone

To a stirred mixture of N-(hydroxymethyl)chlorzoxazone (4.94 g, 30 mmol) [prepared as described by Varma & Nobles (1968)] in 20 ml of pyridine was added 3-chloromethylbenzoyl chloride (4.76 ml, 33 mmol). The mixture was kept at room temperature for 3 h and evaporated in vacuo. The residue obtained was recrystallized twice from ethanol-water, yielding 5.9 g of the title compound. Mp 107-108°C.

Anal.: Calc. for $C_{16}H_{11}Cl_2NO_4$:
C, 54.57; H, 3.15; Cl, 20.13; N, 3.98.
Found: C, 54.47; H, 3.13; Cl, 20.19; N, 3.87.

EXAMPLE 19

N-(3-*N,N*-Diethylaminomethylbenzoyloxymethyl)chlorzoxazone, hydrochloride

A mixture of *N*-(3-chloromethylbenzoyloxymethyl)chlor-zoxazone (0.70 g, 2 mmol), sodium iodide (0.30 g, 2 mmol), diethylamine (1.04 ml, 10 mmol) and 20 ml of acetone was stirred at 60°C for 5 h. Upon cooling to room temperature the mixture was filtered and evaporated in vacuo. The residue obtained was taken up in ethyl acetate. The solution was washed with water, dried and evaporated in vacuo. The residue of evaporation was dissolved in ether whereupon 1 ml of 2.5 M methanolic HCl was added. The precipitate formed was recrystallized from ethanol to give 0.65 g of the title compound. Mp 202-203°C.

Anal.: Calc. for $C_{20}H_{21}ClN_2O_4$, HCl:

C, 56.48; H, 5.21; Cl, 16.67; N, 6.59.

Found: C, 56.35; H, 5.23; Cl, 16.70; N, 6.49.

EXAMPLE 20

Erythromycin 2'-(3-chloromethyl)benzoate

To a solution of erythromycin (2.20 g, 3 mmol) in 10 ml of acetone was added sodium bicarbonate (1.5 g) followed by 3-chloromethylbenzoyl chloride (0.53 ml, 3.75 mmol). The suspension was stirred at room temperature for 4 h and then poured into 100 ml of 0.1 M phosphate buffer (pH 7.0). The precipitate formed was filtered off, washed with water and recrystallized from acetone-water to give 1.8 g of the title compound. Mp 128-131°C.

Anal.: Calc. for $C_{45}H_{72}ClNO_{14}$:

C, 60.97; H, 8.19; N, 1.58.

Found: C, 60.82; H, 8.25; N, 1.65.

EXAMPLE 21

Erythromycin 2'-[3-(4-methylpiperazin-1-yl)methyl]benzoate

A mixture of erythromycin 2'-(3-chloromethyl)benzoate (0.89 g, 1 mmol), sodium iodide (0.15 g, 1 mmol), 1-methyl-piperazine (0.89 ml, 8 mmol) and acetone (10 ml) was stirred at 60°C for 5 h and filtered. The filtrate was evaporated in vacuo and the residue obtained washed with water and recrystallized from ethanol to give 0.62 g of the title compound. Mp 119-121°C.

Anal.: Calc. for $C_{50}H_{83}N_3O_{14}$:

10 C, 63.20; H, 8.80; N, 4.42.

Found: C, 63.43; H, 8.75; N, 4.48.

EXAMPLE 22

7-(3-Chloromethylbenzoyloxymethyl)theophylline

15 To a stirred suspension of 7-(hydroxymethyl)theophylline (4.18 g, 20 mmol), prepared as described by Sloan and Bodor (1982), and triethylamine (4.2 ml, 30 mmol) in 60 ml of di-chloromethane was added 3-chloromethylbenzoyl chloride (3.12 ml, 22 mmol). The mixture was stirred for 5 h at 20-25°C, washed with a 2% aqueous solution of sodium bicarbonate, dried and concentrated in vacuo to yield a white solid which was recrystallized from dichloromethane-petroleum ether, giving 5.5 g of the title product. Mp 150-151°C.

Anal.: Calc. for $C_{16}H_{15}ClN_4O_4$:

C, 52.97; H, 4.17; N, 5.44.

25 Found C, 52.85; H, 4.20; N, 15.33.

EXAMPLE 23

7-(3-N,N-Diethylaminomethylbenzoyloxymethyl)theophylline

A mixture of 7-(3-chloromethylbenzoyloxymethyl)theo-phylline (0.72 g, 2 mmol), sodium iodide (0.30 g, 2 mmol), diethylamine (1 ml) and 20 ml of acetone was stirred at 60°C for 5 h. The mixture was filtered and evaporated in vacuo. The residue obtained was washed with water and recrystallized from ethanol to give 0.51 g of the title compound. Mp 118-119°C.

Anal.: Calc. for $C_{20}H_{25}N_5O_4$:

C, 60.14; H, 6.31; N, 17.53.

Found: C, 60.20; H, 6.28; N, 17.48.

EXAMPLE 24

7-[3-(4-Methylpiperazin-1-yl)methylbenzoyl-oxymethyl]theophylline

The compound was prepared from 7(3-chloromethylbenzoyl-oxymethyl)-theophylline and 1-methylpiperazine by essentially the same procedure as described in Example 23. After recrystallization from water-ethanol, the yield was 60%. Mp 149-151°C.

Anal.: Calc. for $C_{21}H_{24}N_6O_4$:

C, 59.42; H, 5.70; N, 19.80.

Found: C, 59.59; H, 5.65; N, 19.73.

EXAMPLE 25

7-(3-Morpholinomethylbenzoyloxymethyl)theophylline

The compound was prepared from 7-(3-chloromethylbenzoyl-oxymethyl)-theophylline and morpholine by essentially the same procedure as described in Example 23. After recrystallation from ethanol, the yield was 75%. Mp 126-127°C.

Anal.: Calc. for $C_{20}H_{23}N_5O_5$:

C, 58.10; H, 5.61; N, 16.94.

Found: C, 58.15; H, 5.60; N, 16.92.

5 EXAMPLE 26

7-(3-Imidazolylmethylbenzoyloxymethyl)theophylline

The compound was prepared from 7-(3-chloromethyl-benzoyloxymethyl)-theophylline and imidazole by essentially the same procedure as described in Example 23. After recrystallization from ethanol-water, the
10 yield was 71%.

Anal.: Calc. for $C_{19}H_{18}N_6O_4$:

C, 57.86; H, 4.60; N, 21.31.

Found: C, 57.72; H, 4.65; N, 21.21.

The hydrochloride salt was formed with HCl in methanol-ether. Mp 211-
15 212°C (dec.).

EXAMPLE 27

Phenyl 3-chloromethylbenzoate

3-Chloromethylbenzoyl chloride (7.09 ml 50 mmol) was added dropwise
20 with stirring to a solution of phenol (4.7 g, 50 mmol) and pyridine (4.03 ml, 50 mmol) in benzene (30 ml). The mixture was stirred at 60°C for 1 h, cooled to room temperature and filtered. The filtrate was evaporated in vacuo. The residue obtained solidified after storage at -20°C overnight and was recrystallized from dichloromethane-
25 ether to give 9.2 g of the title compound. Mp 59-60°C.

Anal.: Calc. for $C_{14}H_{11}ClO_2$:

C, 68.16; H, 4.49; Cl, 14.37.

Found: C, 68.08; H, 4.48; Cl, 14.39.

EXAMPLE 28

Phenyl 3-(N,N-diethylaminomethyl)benzoate, hydrochloride

A mixture of phenyl 3-chloromethylbenzoate (1.23 g, 5 mmol), sodium iodide (0.38 g, 2.5 mmol), diethylamine (1.04 ml, 10 mmol) and acetone (25 ml) was stirred at 60°C for 5 h. After cooling to room temperature the mixture was filtered and evaporated in vacuo. The residue obtained was dissolved in ethyl acetate (50 ml) and the solution washed with water (2 x 25 ml), dried over anhydrous sodium sulphate and evaporated in vacuo. The residue was dissolved in a mixture of ethyl acetate and ether and a 2.5 M methanolic HCl solution (2.5 ml) was added. The precipitate formed upon storage at 4°C for 4 h was filtered off and recrystallized from ethanol-ether to give 1.2 g of the title compound. Mp 141-142°C.

Anal.: Calc. for $C_{18}H_{21}NO_2$, HCl:

C, 67.60; H, 6.93; Cl, 11.08; N, 4.38.

Found: C, 67.50; H, 6.97; Cl, 11.02; N, 4.36.

EXAMPLE 29

Phenyl 3-[4-methylpiperazin-1-yl)methyl]benzoate, dihydrochloride

The compound was prepared from phenyl 3-chloromethylbenzoate and 1-methylpiperazine by essentially the same procedure as described in Example 28. After recrystallization from methanol, the yield was 75%. Mp 259-261°C.

Anal.: Calc. for $C_{19}H_{22}N_2O_2$, 2 HCl:

C, 59.69; H, 6.33; Cl, 18.55; N, 7.33.

Found: C, 59.57; H, 6.40; Cl, 18.53; N, 7.31.

EXAMPLE 30

 β -Estradiol 3-(3-chloromethyl)benzoate

To a stirred mixture of β -estradiol (2.72 g, 10 mmol) and triethylamine (1.6 ml, 11 mmol) in acetone (50 ml) was added 3-chloromethylbenzoyl chloride (1.57 ml, 11 mmol). The mixture was stirred at 20-25°C for 20 h, filtered and evaporated in vacuo. The solid residue obtained was recrystallized from ethanol-acetone-water to yield 3.2 g of the title compound. Mp 144-145°C.

Anal.: Calc. for $C_{26}H_{29}ClO_3$:

10 C, 73.48; H, 6.88; Cl, 8.34.

Found: C, 73.28; H, 6.86; Cl, 8.45.

EXAMPLE 31

 β -Estradiol 3-(3-N,N-diethylaminomethyl)benzoate, hydrochloride

A mixture of β -estradiol 3-(3-chloromethyl)benzoate (425 mg, 1 mmol), sodium iodide (150 mg, 1 mmol), diethylamine (0.83 ml, 8 mmol) and acetone (10 ml) was stirred at 60°C for 5 h. The reaction solution was cooled to room temperature, filtered and evaporated in vacuo. The residue obtained was taken up in ethyl acetate (50 ml) and the solution washed with water (2 x 25 ml), dried over anhydrous sodium sulphate and evaporated in vacuo. The residue obtained was dissolved in ethyl acetate and ether and a 2.5 M methanolic HCl solution (0.5 ml) was added. The precipitate formed upon storage at 4°C for 4 h was filtered off and recrystallized from ethanol-ether to give 0.38 g of the title compound. Mp 240-241°C.

25 Anal.: Calc. for $C_{30}H_{39}NO_3$, HCl:

C, 72.34; H, 8.09; Cl, 7.12; N, 2.81.

Found: C, 72.44; H, 8.12; Cl, 7.10; N, 2.78.

EXAMPLE 32

β -Estradiol 3-[3-(4-methylpiperazin-1-yl)methyl]benzoate, dihydrochloride

The compound was prepared from β -estradiol 3-(3-chloro-methylbenzoate and 1-methylpiperazine by essentially the same procedure as described in Example 31. After recrystallization from ethanol-ether, the yield was 55%. Mp 254-255°C.

Anal.: Calc. for $C_{31}H_{40}N_2O_3$, 2 HCl:

C, 66.30; H, 7.54; Cl, 12.63; N, 4.99.

Found: C, 66.20, H, 7.60; Cl, 12.55; N, 4.92.

EXAMPLE 33

3-(3-Chloromethylbenzoyloxymethyl)phenytoin

3-Chloromethylbenzoyl chloride (3.12 ml, 22 mmol) was added to a solution of 3-(hydroxymethyl)phenytoin (5.65 g, 20 mmol) (prepared as described by Zejc (1968)) and triethylamine (4.2 ml, 30 mmol) in 60 ml of dichloromethane. The mixture was stirred for 5 h at 20 °C, washed with a 2% aqueous solution of sodium bicarbonate and water, dried over anhydrous sodium sulphate and evaporated in vacuo. The residue was recrystallized from ether-ethanol-petroleum ether to give 6.8 g of the title compound. Mp 117-118°C.

Anal.: Calc. for $C_{24}H_{19}ClN_2O_4$:

C, 66.29; H, 4.40; Cl, 8.15; N, 6.44.

Found: C, 66.28, H, 4.30; Cl, 8.10; N, 6.51.

EXAMPLE 34

3-(3-N,N-Diethylaminomethylbenzoyloxymethyl)phenytoin, hydrochloride

A mixture of 3-(3-chloromethylbenzoyloxymethyl)phenytoin (0.87 g, 2 mmol), sodium iodide (150 mg, 1 mmol), diethylamine (0.83 ml, 10 mmol) and acetone (20 ml) was stirred at 60°C for 6 h. The mixture was cooled to room temperature, filtered and evaporated in vacuo. The residue obtained was dissolved in ethyl acetate (50 ml) and the solution washed with water (2 x 30 ml), dried over anhydrous sodium sulphate and evaporated in vacuo. The residue of the evaporation was dissolved in ethyl acetate and ether and a 2.5 M methanolic HCl solution (0.5 ml) added. The precipitate formed upon storage at -20°C for 20 h was filtered off and recrystallized from acetone-ether to give 0.62 g of the title compound. Mp 113-115°C (dec.).

Anal.: Calc. for $C_{28}H_{29}N_3O_4$, HCl:

C, 66.20; H, 5.95; Cl, 6.98; N, 8.27.

Found: C, 66.22; H, 5.90; Cl, 6.93; N, 8.24

EXAMPLE 35

Pregnanolone 3-(3-N,N-diethylaminomethyl)benzoate, hydrochloride

A mixture of pregnanolone 3-(3-chloromethyl)benzoate (471 mg, 1 mmol), sodium iodide (150 mg, 1 mmol), diethylamine (0.83 ml, 8 mmol) and 10 ml of acetone was stirred at 60°C for 6 h. It was cooled to 25°C, filtered and evaporated in vacuo. The residue obtained was taken up in ethyl acetate (50 ml) and the solution washed with water, dried over anhydrous sodium sulphate and evaporated in vacuo. The residue obtained was dissolved in ethyl acetate and ether and a 2.5 M methanolic HCl solution (0.5 ml) added. The precipitate formed upon storage at -20°C for 24 h was filtered off and recrystallized from ethanol-ether to give 0.37 g of the title compound.

Anal.: Calc. for $C_{33}H_{49}NO_3$, HCl:

C, 72.83; H, 9.26; Cl, 6.51; N, 2.57

Found: C, 72.76; H, 9.35; Cl, 6.48, N, 2.58.

The starting material, pregnanolone 3-(3-chloromethyl)-benzoate was prepared from pregnalonone (pregnan-3 α -ol-20-one) and 3-chloromethylbenzoyl chloride by essentially the same procedure as described in Example 1.

5

EXAMPLE 36

Pregnanolone 3-[3-(4-methylpiperazin-1-yl)methyl]benzoate, dihydrochloride

The compound was prepared from pregnanolone 3-(3-chloromethyl)benzoate and 1-methylpiperazine by essentially the same procedure as described in Example 35. After recrystallization from ethanol-ether, the yield was 67%.

Anal.: Calc. for C₂₈H₅₀N₂O₃, 2 HCl:

C, 62.79; H, 9.79; Cl, 13.24; N, 5.23.

15 Found: C, 62.55, H, 9.89; Cl, 13.20; N, 5.20.

EXAMPLE 37

1-(3-Chloromethylbenzoyloxymethyl)allopurinol

A mixture of 1-(hydroxymethyl)allopurinol (1.6 g, 10 mmol) (prepared as described by Bansal et al. (1981 b)) and 3-chloromethylbenzoyl chloride (1.85 ml, 13 mmol) in pyridine (20 ml) was stirred at room temperature for 3 h. Water (100 ml) was added, and after standing for 3 h at 5°C the precipitate was collected, washed with water and recrystallized from ethanol to give 2.0 g of the title compound. Mp 201-202°C.

25

Anal.: Calc. for C₁₄H₁₁ClN₄O₃:

C, 52.76; H, 3.48; Cl, 11.12; N, 17.58.

Found: C, 52.66, H, 3.49; Cl, 11.12; N, 17.56.

EXAMPLE 38

1-(3-Imidazolylmethylbenzoyloxymethyl)allopurinol

A mixture of 1-(3-chloromethylbenzoyloxymethyl)-allopurinol (319 mg, 1 mmol), sodium iodide (150 mg, 1 mmol), imidazole (340 mg, 5 mmol) and 15 ml of acetone was stirred at 60°C for 5 h. The mixture was cooled to room temperature, filtered and evaporated in vacuo. The residue obtained was stirred with water (20 ml) for 2 h and the precipitate formed filtered off, washed with water and recrystallized from ethanol-water to give 280 mg of the title compound.

Mp 148-150°C.

Anal.: Calc. for $C_{17}H_{14}N_6O_3$:

C, 58.28; H, 4.03; N, 23.99.

Found: C, 58.35; H, 4.04; N, 23.95.

EXAMPLE 39

3-[3-(4-Methylpiperazin-1-ylmethyl)benzoyloxymethyl]phenytoin, dihydrochloride

The compound was prepared from 3-(3-chloromethyl-benzoyloxymethyl)phenytoin and 1-methylpiperazine by essentially the same procedure as described in Example 34.

After recrystallization from ethanol-ether, the yield was 65%. Mp 205-206°C.

Anal.: Calc. for $C_{29}H_{30}N_4O_4$, 2 HCl, H_2O :

C, 59.09; H, 5.81; Cl, 12.03; N, 9.50.

Found: C, 59.11; H, 5.88; Cl, 12.00; N, 9.43

EXAMPLE 40

N-[3-(4-Methylpiperazin-1-ylmethyl)benzoyloxy-methyl]chlorzoxazone, dihydrochloride

The compound was prepared from *N*-(3-chloromethyl-benzoyloxymethyl)chlorzoxazone and 1-methylpiperazine by essentially the same procedure as described in Example 19. After recrystallization from methanol, the yield was 70%.

Mp 240-241°C.

Anal.: Calc. for $C_{21}H_{22}ClN_3O_4$, 2 HCl, H_2O :

10 C, 49.77; H, 5.17; Cl, 20.99; N, 8.29.
Found: C, 49.62; H, 5.32; Cl, 20.90; N, 8.36.

EXAMPLE 41

Metronidazole 3-chloromethylbenzoate

15 A solution of 3-chloromethylbenzoyl chloride (1.42 ml, 10 mmol) in methylene chloride (30 ml) was added dropwise to a mixture of metronidazole (1.71 g, 10 mmol), pyridine (1 ml), and methylene chloride (40 ml). The resulting clear solution was stirred at room temperature for 20 h and evaporated in vacuo. The residue was stirred with 1M sodium carbonate for 15 min and the resulting solid was filtered off
20 and washed with water to give 2.76 g (85%) of the title compound. After recrystallization from ethyl acetate-petroleum ether the compound melted at 78-80°C.

Anal.: Calc. for $C_{14}H_{14}ClN_3O_4$:

25 C, 51.94; H, 4.36; Cl, 10.95; N, 12.98.
Found: C, 51.73; H, 4.38; Cl, 11.14; N, 13.06.

EXAMPLE 42

Metronidazole 4-chloromethylbenzoate

The compound was prepared by a method analogous to that described in Example 41, starting from 2.57 g (15 mmol) of metronidazole and 4-chloromethylbenzoyl chloride (15 mmol). The crude product was purified by flash chromatography on silica gel (eluent: toluene containing ethyl acetate). Yield (from cyclohexane): 3.01 g (62%). Mp 112-115°C.

Anal.: Calc. for $C_{14}H_{14}ClN_3O_4$:

C, 51.94; H, 4.36; Cl, 10.95; N, 12.98.

Found: C, 51.77; H, 4.38; Cl, 11.25; N, 13.13

EXAMPLE 43

Metronidazole 3-(morpholinomethyl)benzoate

To a solution of metronidazole 3-chloromethylbenzoate (0.648 g, 2 mmol) in acetone (25 ml) were added morpholine (0.88 ml, 10 mmol) and sodium iodide (20 mg). The mixture was stirred at room temperature for 20 h, filtered and evaporated in vacuo. Water (10 ml) was added to the residue and the mixture was extracted with methylene chloride (3 x 20 ml). The combined extracts were dried and evaporated in vacuo. Flash chromatography of the residue on silica gel (eluent: methylene chloride containing acetone) gave 0.59 g (79%) of the title compound as an oil. The difumarate was prepared by adding a solution of fumaric acid in 2-propanol and precipitating the salt with ether. Mp (from 2-propanol-ether): 169-170°C.

Anal.: Calc. for $C_{26}H_{30}N_4O_{13}$:

C, 51.49; H, 4.99; N, 9.24.

Found: C, 51.52; H, 4.92; N, 9.22.

EXAMPLE 44

Metronidazole 4-(morpholinomethyl)benzoate

A mixture of metronidazole 4-chloromethylbenzoate (648 mg, 2 mmol), morpholine (0.88 ml, 10 mmol), sodium iodide (20 mg) and acetone (20 ml) was refluxed for 20 h. The reaction mixture was filtered and the filtrate was evaporated in vacuo. Water (20 ml) was added to the residue and the solid formed was collected and washed with water, yielding 625 mg (83%) of the title compound. Mp (from cyclohexane): 98-99°C.

Anal.: Calc. for $C_{18}H_{22}N_4O_5$:

C, 57.74; H, 5.92; N, 14.96

Found: C, 57.93; H, 5.96; N, 14.88.

The fumarate of the title compound melted at 144-146°C.

Anal.: Calc. for $C_{22}H_{26}N_4O_9$:

C, 53.87; H, 5.34; N, 11.42.

Found: C, 53.57; H, 5.51; N, 11.21.

EXAMPLE 45

Metronidazole 3-dimethylaminomethylbenzoate

The compound was prepared by a method analogous to that described in Example 43, from metronidazole 3-chloromethyl-benzoate (456 mg, 1.5 mmol), dimethylamine (0.82 ml of a 33% solution in ethanol, 6 mmol), sodium iodide (20 mg) and acetone (20 ml). Treatment of the title compound with fumaric acid yielded the salt with 1.5 equivalent fumaric acid which crystallized from 2-propanol-ether with 0.25 mole of water: Mp 141-143°C.

Anal.: Calc. for $C_{22}H_{26}N_4O_{10} \cdot 0.25 H_2O$:

C, 51.71; H, 5.22; N, 10.96.

Found: C, 51.64; H, 5.26; N, 10.94.

EXAMPLE 46

Metronidazole 4-dimethylaminomethylbenzoate

The compound was prepared by a method analogous to that described in Example 43. The title compound was recrystallized from ether-
5 petroleum. Mp 73-74°C.

Anal.: Calc. for $C_{16}H_{20}N_4O_4$:

C, 57.82; H, 6.07; N, 16.86.

Found: C, 57.73; H, 6.10; N, 16.75.

10 EXAMPLE 47

Metronidazole 3-[(4-methylpiperazin-1-yl)methyl]benzoate

A mixture of metronidazole 3-chloromethylbenzoate (648 mg, 2 mmol),
N-methylpiperazine (1.12 ml, 10 mmol), sodium iodide (20 mg) and
methylene chloride (25 ml) was refluxed for 20 h. The reaction mix-
15 ture was washed with water (2 x 25 ml), dried and evaporated in
vacuo. To the residue was added a solution of 464 mg (4 mmol) of
fumaric acid in 2-propanol (12 ml) followed by ether precipitating
the difumarate of the title compound with 0.5 equivalent of water.
Yield: 754 mg (60%). Mp 179-182°C.

20 Anal.: Calc. for $C_{27}H_{33}N_5O_{12}$, 0.5 H_2O :

C, 51.59; H, 5.45; N, 11.14;

Found: C, 51.56; H, 5.60; N, 11.15.

EXAMPLE 48

Metronidazole 4-[(4-methylpiperazin-1-yl)methyl]benzoate

The compound was prepared by a method analogous to that described in Example 47. The yield of the difumarate of the title compound was 52%. Mp 193-194°C.

Anal.: Calc. for $C_{27}H_{33}N_5O_{12}$:

C, 52.34; H, 5.37; N, 11.30.

Found: C, 52.10; H, 5.57; N, 11.12.

10 EXAMPLE 49

4-Acetamidophenyl 4-Chloromethylbenzoate

A mixture of 4-chloromethylbenzoic acid (2.6 g, 15 mmol) and thionyl chloride (12 ml) was refluxed for 90 min. The solution was evaporated in vacuo and the residue dissolved in methylene chloride (45 ml). This solution was added dropwise to a mixture of paracetamol (2.27 g, 15 mmol), pyridine (1.5 ml, 19 mmol) and methylene chloride (60 ml). After stirring at room temperature for 20 h, the reaction mixture was evaporated in vacuo. Water (20 ml) was added to the residue and the precipitate collected. Recrystallization from ethyl acetate yielded 2.6 g (57%) of the title compound. Mp 217-218°C.

Anal.: Calc. for $C_{16}H_{14}ClNO_3$:

C, 63.27; H, 4.65; Cl, 11.67; N, 4.61.

Found: C, 63.33; H, 4.79; Cl, 11.63; N, 4.66.

25 EXAMPLE 50

4-Acetamidophenyl 4-(morpholinomethyl)benzoate

A mixture of 4-acetamidophenyl 4-chloromethylbenzoate (304 mg, 1.0 mmol), morpholine (0.44 ml, 5.0 mmol) and acetone was refluxed for 4

h. After filtration, the reaction mixture was evaporated in vacuo. Water (20 ml) was added to the residue and the precipitate collected. Yield of the title compound: 294 mg (83%). Mp (from toluene-cyclohexane): 161-164°C. The hydrochloride of the title compound was prepared by adding a solution of HCl in ethyl acetate to a solution of the title compound in ethyl acetate. Mp (from methanol-ether): 252-256°C (dec.).

Anal.: Calc. for $C_{20}H_{23}ClN_2O_4$:

C, 61.46; H, 5.93; Cl, 9.07; N, 7.17.

Found: C, 61.08; H, 5.86; Cl, 9.06; N, 7.04.

EXAMPLE 51

4-Acetamidophenyl 4-dimethylaminomethylbenzoate

A mixture of 4-acetamidophenyl 4-chloromethylbenzoate (456 mg, 1.5 mmol), dimethylamine (1.0 ml of a 33% solution in ethanol, 7.3 mmol), sodium iodide (20 mg) and acetone (20 ml) was stirred for 20 h at room temperature. The reaction mixture was filtered and the filtrate evaporated in vacuo. Water (10 ml) was added to the residue and the precipitate was collected, dried and suspended in ethyl acetate. A solution of HCl in ethyl acetate was added to give the hydrochloride of the title compound [306 mg (58%)]. Mp (from methanol): 256-259°C.

Anal.: Calc. for $C_{18}H_{21}ClN_2O_3$:

C, 61.98; H, 6.07; Cl, 10.17; N, 8.03.

Found: C, 62.05; H, 6.05; Cl, 10.07; N, 7.98.

The title compound was also prepared by the following method:

A mixture of 4-(N,N-dimethylaminomethyl)benzoic acid hydrochloride (562 mg, 2.6 mmol), paracetamol (395 mg, 2.6 mmol), p-toluenesulfonic acid (40 mg), N,N'-dicyclohexylcarbodiimide (622 mg, 3 mmol) and pyridine (10 ml) was stirred at room temperature for 20 h. Methylene chloride (20 ml) was added to the reaction mixture. The mixture was filtered and the filtrate evaporated in vacuo. Ethyl acetate (20 ml) was added to the residue, and after filtration a solution of HCl in

ethyl acetate was added to the filtrate. The precipitate (348 mg, 37%) was shown to be identical (IR-spectrum and mp) with the compound prepared in the example above.

5 EXAMPLE 52

4-Acetamidophenyl 4-[(4-methylpiperazin-1-yl)methyl]benzoate

The compound was prepared by a method analogous to that described in Example 51 (1st part). The yield of the title compound was 80%, mp (from ethyl acetate-petroleum):

10 181-183°C.

Anal.: Calc. for $C_{21}H_{25}N_3O_3$:

C, 68.64; H, 6.86; N, 11.44.

Found: C, 68.35; H, 6.85; N, 11.31.

15 EXAMPLE 53

4-Acetamidophenyl 4-trimethylammoniomethylbenzoate iodide

A mixture of 4-acetamidophenyl 4-dimethylaminomethyl-benzoate (0.23 g, 0.74 mmol), methyl iodide (0.5 ml, 7 mmol) and methanol (5 ml) was stirred at 50°C for 4 h. After cooling ether (10 ml) was added and
20 the title compound was collected [0.31 g (92%)].

Mp (from ethanol): 231-235°C (dec.).

Anal.: Calc. for $C_{19}H_{23}IN_2O_3$:

C, 50.23; H, 5.10; N, 6.17.

Found: C, 50.36; H, 5.20; N, 6.15.

25

EXAMPLE 54

Metronidazole 4-trimethylammoniomethylbenzoate iodide

The compound was prepared from metronidazole 4-dimethylaminomethylbenzoate (60 mg, 0.18 mmol) by the method described above in Example 53. Yield: 76 mg. Mp 203-206°C (dec.)

EXAMPLE 55

1-(4-Chloromethylbenzoyloxymethyl)allopurinol

A solution of 4-chloromethylbenzoyl chloride (prepared from 4-chloromethylbenzoic acid (5.12 g, 30 mmol) by refluxing with thionylchloride) in methylene chloride (6 ml) was added to a suspension of 1-(hydroxymethyl)allopurinol (3.84 g, 24 mmol) in pyridine (60 ml). The mixture was stirred at room temperature for 3 h and filtered. The filtrate was evaporated in vacuo to half-volume and water (100 ml) was added. The precipitate formed (5.97 g, 62%) was collected and recrystallized from 2-propanol-DMF to give the pure title compound. Mp 245-247°C.

Anal.: Calc. for $C_{14}H_{11}ClN_4O_3$:

C, 52.76; H, 3.48; Cl, 11.13; N, 17.58

Found: C, 52.70; H, 3.63; Cl, 11.00; N, 17.42

EXAMPLE 56

1-(4-Morpholinomethylbenzoyloxymethyl)allopurinol, hydrochloride

A mixture of 4-morpholinomethylbenzoic acid hydrochloride (1.29 g, 5.0 mmol) and thionylchloride (10 ml) was refluxed for 1 h and then evaporated in vacuo. Pyridine (25 ml) and 1-(hydroxymethyl)allopurinol (0.83 g, 5.0 mmol) were added to the residue and the mixture was stirred at room temperature for 30 h. The precipitate was collected

and suspended in water (20 ml). Hydrochloric acid was added to pH 4 and after stir-ring for 30 min. the mixture was filtered and the filtrate evaporated in vacuo. The residue (0.80 g, 38%) was recrystallized from methanol-ethanol (1:1) to give the monohydrate of the title compound. Mp 210-213°C.

Anal.: Calc. for $C_{18}H_{19}N_5O_4 \cdot HCl, H_2O$:

C, 51.01; H, 5.23; Cl, 8.37; N, 16.52

Found: C, 50.68; H, 5.40; Cl, 8.31; N, 16.55.

The title compound was also prepared by the following method:

10 A mixture of 1-(hydroxymethyl)allopurinol (448 mg, 3 mmol), 4-morpholinomethylbenzoic acid hydrochloride (771 mg, 3 mmol), N,N'-dicyclohexylcarbodiimide (618 mg, 3 mmol), p-toluene-sulfonic acid (40 mg) and pyridine (10 ml) was stirred at room temperature for 20 h. Methylene chloride (20 ml) was added to the reaction mixture. After stirring for 2 h the mixture was filtered, and the filtrate evaporated in vacuo. The residue was dissolved in ethanol (10 ml) and excess of hydrochloric acid in ethyl acetate was added, precipitating the title compound (138 mg, 33%). It was identical (IR-spectrum, mp and TLC) with the compound described above.

20 A third method of preparing the title compound is the following:

A mixture of 1-(4-chloromethylbenzoyloxymethyl)allopurinol (478 mg, 1.5 mmol), morpholine (0.53 ml, 6 mmol), sodium iodide (10 mg) and N,N-dimethylformamide (5 ml) was stirred at 50°C for 5 h. The mixture was filtered and the filtrate evaporated in vacuo. The residue was dissolved in methylene chloride (50 ml) and the solution was washed twice with water, dried and evaporated. The residue was recrystallized from ethanol to give the title compound (409 mg, 74%) as the base. Mp 174-176°C.

30 The hydrochloride was prepared by adding a solution of hydrochloric acid in ethyl acetate to a solution of the base in ethanol. The precipitate was shown to be identical (IR-spectrum, mp and TLC) to the compounds prepared by the two other methods above.

EXAMPLE 57

1-(3-Morpholinomethylbenzoyloxymethyl)allopurinol

Morpholine (0.53 ml, 6 mmol) and sodium iodide (10 mg) were added to a solution of 1-(3-chloromethylbenzoyloxymethyl)-allopurinol (478 mg, 1.5 mmol) in N,N-dimethylformamide (5 ml). The mixture was stirred at 50°C for 5 h and left at room temperature for 20 h. After evaporation in vacuo methylene chloride (30 ml) was added to the residue and the solution was washed twice with water, dried and evaporated. The residue was crystallized from ethyl acetate to give the title compound (307 mg, 55%). Mp 126-128°C.

Anal.: Calc. for $C_{18}H_{19}N_5O_4$:

C, 58.53; H, 5.18; N, 18.96.

Found: C, 58.14; H, 5.20; N, 18.72.

EXAMPLE 58

1-[3-(4-Methylpiperazin-1-yl)methylbenzoyloxymethyl]-allopurinol

The compound was prepared from 1-(3-chloromethylbenzoyl-oxymethyl)allopurinol (1.5 mmol) and 1-methylpiperazine (6 mmol) by essentially the same procedure as described in Example 57. The compound crystallized from ethyl acetate with 2/3 mol of ethyl acetate. The yield was 46%. Mp 129-131°C.

Anal.: Calc. for $C_{19}H_{22}N_6O_3$, 2/3 $C_4H_8O_2$:

C, 58.99; H, 6.24; N, 19.05.

Found: C, 59.08; H, 6.25; N, 19.17.

The fumarate was prepared by adding a solution of fumaric acid in 2-propanol. The salt was recrystallized from 2-propanol-ethanol. Mp 212-214°C.

Anal.: Calc. for $C_{23}H_{26}N_6O_7$, 0.25 H_2O :

C, 54.92; H, 5.31; N, 16.71.

Found: C, 55.05; H, 5.39; N, 16.53.

5 EXAMPLE 59

1-[4-(4-Methylpiperazin-1-yl)methylbenzoyloxymethyl]-allopurinol

The compound was prepared from 1-(4-chloromethylbenzoyl-oxymethyl)allopurinol (3 mmol) and 1-methylpiperazine (12 mmol) by essentially the same procedure as described in Example 57. The compound was
10 crystallized from 2-propanol-ethyl acetate. The yield was 29%.
Mp 190-192°C.

Anal.: Calc. for $C_{19}H_{22}N_6O_3$:

C, 59.67; H, 5.80; N, 21.98.

Found: C, 59.42; H, 5.88; N, 21.87.

15

EXAMPLE 60

2,5-[bis-(3-Chloromethylbenzoylmethyl)]allopurinol

A mixture of 2,5-bis(hydroxymethyl)allopurinol (4.0 g, 20 mmol) (prepared as described by Bansal et al. (1981b)) and 3-chloromethylbenzoyl chloride (3.70 ml, 26 mmol) in pyridine (40 ml) was stirred
20 at room temperature for 4 h. Water (200 ml) was added, and after standing for 20 h at 5°C the precipitate was collected, washed with water and recrystallized from ethanol to give 5.9 g of the title compound. Mp 198-199°C.

25 Anal.: Calc. for $C_{23}H_{18}Cl_2N_4O_5$:

C, 55.10; H, 3.62; Cl, 14.14; N, 11.18.

Found: C, 55.15; H, 3.55; Cl, 14.17; N, 11.17.

EXAMPLE 61

2,5-[bis-(3-Morpholinomethylbenzyloxymethyl)]allopurinol

A mixture of 2,5-[bis-(3-chlormethylbenzyloxymethyl)]-allopurinol (501 mg, 1 mmol), morpholine (0.53 ml, 6 mmol), sodium iodide (10 mg) and acetone (20 ml) was refluxed for 6 h. After filtration and evaporation of the filtrate methylene chloride (25 ml) was added to the residue. The solution was washed with water, dried and evaporated. The residue was crystallized from ethyl acetate to give the title compound (371 mg) as the monohydrate. Mp 88-90°C.

Anal.: Calc. for $C_{31}H_{34}N_6O_7 \cdot H_2O$:

C, 60.00; H, 5.85; N, 13.54.

Found: C, 60.24; H, 5.98; N, 13.48.

EXAMPLE 62

9-[[2-(4-Morpholinomethylbenzoyl)oxy]ethoxymethyl]guanine,hydrochloride

To a solution of 4-morpholinomethylbenzoyl chloride hydrochloride (prepared from 4-morpholinomethylbenzoic acid hydrochloride (514 mg, 2.0 mmol)) in pyridine (15 ml) was added aciclovir (480 mg, 2.0 mmol) and the mixture was stirred at room temperature for 20 h. The reaction mixture was filtered and the filtrate evaporated in vacuo. Fractional crystallizations of the residue from methanol containing increasing amounts of acetonitrile afforded the title compound. Thin-layer chromatography on silica gel (Merck):

$R_f = 0.19$ (butanol -acetic acid -water [4:1:1]).

EXAMPLE 63

9-[[2-(4-Morpholinomethylbenzoyl)oxy]ethoxymethyl]guanine

To a mixture of aciclovir (1.92 g, 8 mmol) in 65 ml of pyridine was added 4-morpholinomethylbenzoyl chloride hydrochloride (12 mmol) in four portions over 10 min. The mixture was stirred at room temperature for 20 h and then evaporated in vacuo. The residue obtained was slurried in 25 ml of water and the mixture filtered. Sodium hydroxide (2 M) was added to the filtrate to pH 9±0.2. Upon standing at 4°C for 5 h, the precipitate formed was filtered off, washed with water and recrystallized from ethanol-water to give 1.8 g of the title compound as the monohydrate. Mp 218-220°C.

Anal.: Calc. for $C_{20}H_{24}N_6O_5 \cdot H_2O$:

C, 53.81; H, 5.87; N, 18.82

Found: C, 54.01; H, 5.93; N, 18.92

EXAMPLE 64

9-[[2-(4-Dimethylaminomethylbenzoyl)oxy]ethoxymethyl]guanine

The compound was prepared from aciclovir and 4-dimethylaminomethylbenzoyl chloride hydrochloride by the method described above in Example 63. Yield: 75%. Mp 185-186°C (from ethanol-water).

Anal.: Calc. for $C_{18}H_{22}N_6O_4 \cdot 1.5 H_2O$:

C, 52.30; H, 6.08; N, 20.33

Found: C, 52.48; H, 5.99; N, 20.33

EXAMPLE 65

9-[[2-(3-Dipropylaminomethylbenzoyl)oxy]ethoxymethyl]guanine

The compound was prepared from aciclovir and 3-dipropylaminomethyl-

benzoyl chloride hydrochloride by the method described in Example 63.
Yield: 79%. Mp 195-197°C (from ethanol-water).

Anal.: Calc. for $C_{22}H_{30}N_6O_4$, 0.75 H_2O :

C, 57.94; H, 6.96; N, 18.43

5 Found: C, 57.80; H, 7.02; N, 18.41

EXAMPLE 66

9-[1,3-(Dimorpholinomethylbenzoyloxy)-2-propoxy)methylguanine

To a mixture of ganciclovir (1.18 g, 5 mmol) in 50 ml of pyridine was
10 added 4-morpholinomethylbenzoyl chloride hydrochloride (15 mmol) in
four portions over 10 min. The mixture was stirred at room tempera-
ture for 20 h and then evaporated in vacuo. The residue obtained was
slurried in 50 ml of water and the mixture filtered. Sodium hydroxide
(2 M) was added to the filtrate to pH 8.5. Upon standing at 4°C for 5
15 h the precipitate formed was filtered off, washed with water and
recrystallized from ethanol-water to give 1.4 g of the title compound
as the hemihydrate. Mp 204-205°C.

Anal.: Calc. for $C_{33}H_{39}N_7O_8$, 0.5 H_2O :

C, 59.10; H, 6.01; N, 14.62

20 Found: C, 59.09; H, 6.11; N, 14.70

EXAMPLE 67

9-[(1,3-[4-Dimethylaminomethylbenzoyl)oxy-2-propoxy)methyl]guanine

The compound was prepared from ganciclovir and 4-dimethylaminomethyl-
25 benzoyl chloride hydrochloride by the method described above in
Example 66. Yield: 70%. Mp 109-110°C (from ethanol-water).

Anal.: Calc. for $C_{29}H_{35}N_7O_6$, 2.5 H_2O :

C, 55.94; H, 6.47; N, 15.75

Found: C, 56.04; H, 6.44; N, 15.65

5 EXAMPLE 68

9-[(1,3-(4-Diethylaminomethylbenzoyl)oxy-2-propoxy)methyl]guanine

The compound was prepared from ganciclovir and 4-diethylaminomethylbenzoyl chloride hydrochloride by the method described in Example 66. Yield: 65%. Mp 150-152°C.

10 Anal.: Calc. for $C_{33}H_{43}N_7O_6$, 0.75 H_2O :

C, 61.24; H, 6.93; N, 15.15

Found: C, 61.14; H, 7.02; N, 15.11

EXAMPLE 69

15 *1,3-Dipropyl-8(-p-(4-dimethylaminomethylbenzoyl)oxyphenyl)xanthine*

To a suspension of 1,3-dipropyl-8(p-hydroxyphenyl)xanthine (1.65 g, 5 mmol) in pyridine (30 ml) was added with stirring 4-(N,N-dimethylaminomethyl)benzoyl chloride hydrochloride (7 mmol). The mixture was stirred at room temperature for 20 h and then evaporated in vacuo.

20 The residue was dissolved in water (50 ml) and sodium hydroxide (2 M) was added to pH 8.5-9. Upon standing at 4°C for 4 h the precipitate formed was filtered off, washed with water and recrystallized from acetone-water to give 1.96 g (80% yield) of the title compound. Mp 255-256°C.

25 Anal.: Calc. for $C_{27}H_{31}N_5O_4$:

C, 66.24; H, 6.38; N, 14.31

Found: C, 66.15; H, 6.34; N, 14.24.

The hydrochloride salt of the title compound was prepared as follows:
To a solution of the title compound (490 mg, 1 mmol) in acetone (30 ml) was added 0.5 ml of a 2.5 M methanolic HCl solution. The solution was evaporated in vacuo and the residue obtained recrystallized from ethanol (about 30 ml) with the addition of two drops of water. Mp 247-249°C.

Anal.: Calc. for $C_{27}H_{32}ClN_5O_4$, 0.25 H_2O :

C, 61.13; H, 6.17; N, 13.20

Found: C, 61.15; H, 6.24; N, 13.14

10

EXAMPLE 70

1,3-Dipropyl-8-(p-(3-dipropylaminomethylbenzoyl)oxyphenyl)xanthine

The compound was prepared from 1,3-dipropyl-8-(p-hydroxyphenyl)xanthine and 3(N,N-dipropylaminomethyl)benzoyl chloride hydrochloride by the method described above in Example 69. Yield: 73%. Mp 194-195°C (from N,N-dimethylformamide-ethanol).

Anal.: Calc. for $C_{31}H_{39}N_5O_4$:

C, 68.23; H, 7.20; N, 12.83

Found: C, 68.20; H, 7.12; N, 12.82

20 The hydrochloride salt was prepared as described in Example 69. Mp 151-153°C (from ethanol).

Anal.: Calc. for $C_{31}H_{40}ClN_5O_4$, H_2O :

C, 62.04; H, 7.05; N, 11.67

Found: C, 61.96; H, 7.19; N, 11.51

25

EXAMPLE 71

N-Methyl-N-(4-morpholinomethylbenzoyl)acetazolamide, hydrochloride

To a suspension of N-methylacetazolamide (0.95 g, 4 mmol) in pyridine (10 ml) was added 4-(morpholinomethyl)benzoyl chloride hydrochloride

- (5 mmol). The mixture was stirred at 70°C for 4 h and then evaporated in vacuo. Water (50 ml) was added to the residue followed by sodium hydroxide (2 M) to give a pH of 8-8.5. The precipitate formed was filtered off, washed with water and recrystallized from acetone-water. The compound (0.64 g, 1.45 mmol) was slurried in acetone (30 ml) and 1 ml of 2.5 M methanolic HCl was added. Ether was added to the solution to slight turbidity. Upon standing at -18°C overnight the precipitate formed was filtered off and washed with ether to give 0.59 g of the title compound as the monohydrate. Mp. 116-117°C.
- 10 *Anal.*: Calc. for $C_{17}H_{22}ClN_5O_5S_2 \cdot H_2O$:
C, 41.34; H, 4.89; N, 14.18
Found: C, 41.49; H, 5.01; N, 14.01

EXAMPLE 72

- 15 4-Acetamidophenyl 4-(tert.-butoxycarbonylaminomethyl)benzoate

A mixture of 4-(tert.-butoxycarbonylaminomethyl)benzoic acid (2.58 g, 10 mmol) cf. J.Med.Chem.29 (1986) 448), paracetamol (1.5 g, 10 mmol), p-toluensulfonic acid (150 mg), N,N'-dicyclohexylcarbodiimide (2.06 g, 10 mmol) and pyridine (30 ml) was stirred at room temperature for 24 h. Methylene chloride (60 ml) was added to the reaction mixture. The mixture was filtered and the filtrate evaporated in vacuo. The residue was extracted with two 60 ml portions of warm methylene chloride and the extracts were evaporated. The residue was recrystallized from methanol to give 0.73 g (19%) of the title compound. Mp. 205-208°C.

- 25 *Anal.*: Calc. for $C_{21}H_{24}N_2O_5$:
C, 65.61; H, 6.29; N, 7.29
Found: C, 65.71; H, 6.31; N, 7.23

EXAMPLE 73

4-Acetamidophenyl 4-aminomethylbenzoate, hydrobromide

A mixture of 4-acetamido 4-(tert.-butoxycarbonylaminomethyl)benzoate (190 mg, 0.5 mmol) and a 48% solution of hydrobromic acid in glacial acetic acid (2.0 ml) was stirred at room temperature for 2 min. Ethyl acetate (20 ml) was added and the stirring was continued for 5 min. The mixture was evaporated in vacuo and the residue recrystallized from methanol to give 130 mg (71%) of the title compound. Mp 273-276°C.

10 *Anal.*: Calc. for $C_{16}H_{16}N_2O_3HBr$:
C, 52.62; H, 4.69; N, 7.67; Br 21.88
Found: C, 52.64; H, 4.82; N, 7.65; Br, 21.77

EXAMPLE 74

4-[2-(Morpholino)ethyl]benzoic acid, hydrochloride

15 A mixture of 4-(2-chloroethyl)benzoic acid (1.84 g, 10 mmol), morpholine (4.36 ml, 50 mmol), sodium iodide (0.1 g) and N,N-dimethylacetamide was heated at 125°C for 48 h. The mixture was evaporated in vacuo. The residue was dissolved in 2 M sodium hydroxide (25 ml) and the solution was washed with ether (3 x 25 ml). The aqueous solution
20 was acidified with hydrochloric acid and evaporated. The residue was extracted with boiling ethanol (2 x 50 ml) and the ethanol was evaporated. Recrystallization of the residue from ethanol gave 0.71 g (26%) of the title compound. Mp 267-270°C.

Anal.: Calc. for $C_{13}H_{17}NO_3, HCl$:
25 C, 57.46; H, 6.68; N, 5.16; Cl. 13.05
Found: C, 57.42; H, 6.81; N, 5.15; Cl. 12.93

EXAMPLE 75

4-Acetamidophenyl 4-[2-(morpholino)ethyl]benzoate, hydrochloride

A mixture of 4-[2-(morpholino)ethyl]benzoic acid (544 mg, 2.0 mmol) and thionyl chloride (5 ml) was refluxed for 1 h. The mixture was evaporated in vacuo. Pyridine (15 ml) was added dropwise to the residue followed by paracetamol (302 mg, 2.0 mmol). The mixture was stirred at room temperature for 20 h and evaporated in vacuo. The residue was triturated with 50% aqueous ethanol (5 ml). The insoluble solid was recrystallized from methanol to give 480 mg (59% of the title compound. Mp 273-277°C.

Anal.: Calc. for $C_{21}H_{24}N_2O_4$, HCl:

C, 62.29; H, 6.22; N, 6.92; Cl, 8.76

Found: C, 62.32; H, 6.24; N, 6.88; Cl, 8.65

EXAMPLE 76

N,N-Diethylcarbamoylmethyl 2-hydroxy-5-nitrobenzoate

A mixture of 2-hydroxy-5-nitrobenzoic acid (9.16 g, 50 mmol), 2-chloro-N,N-diethylacetamide (7.55 ml, 55 mmol), triethylamine (7.7 ml, 55 mmol), sodium iodide (0.75 g, 5 mmol) and N,N-dimethylformamide (40 ml) was stirred at 60°C for 20 h. The mixture was poured into water (200 ml) and the precipitate formed filtered off, washed with water and recrystallized from ethyl acetate-light petroleum to give 8.0 g of the title compound. Mp 85-86°C.

Anal.: Calc. for $C_{13}H_{16}N_2O_6$:

C, 52.70; H, 5.44; N, 9.45

Found: C, 52.74; H, 5.47; N, 9.40.

EXAMPLE 77

N,N-Diethylcarbamoylmethyl 2-[4-(morpholinomethyl)benzoyloxy]-5-nitrobenzoate

A mixture of 4-(morpholinomethyl)benzoic acid hydrochloride (1.42 g, 5.5 mmol) and thionyl chloride (10 ml) was refluxed for 1 h. The solution was evaporated in vacuo. Methylene chloride (35 ml), *N,N*-diethylcarbamoylmethyl 2-hydroxy-5-nitro-benzoate (1.48 g, 5.0 mmol) and triethylamine (2.1 ml, 15 mmol) were added to the residue and the resulting solution was stirred at room temperature for 20 h. The reaction mixture was washed with water (30 ml), a 5% aqueous solution of sodium hydrogen carbonate (30 ml) and water (30 ml). After drying, the methylene chloride was evaporated in vacuo. The residue was triturated with ether (20 ml) and the solid compound formed was collected. Recrystallization from ethyl acetate-light petroleum gave 2.23 g (89%) of the title compound. Mp 119-121°C.

Anal.: Calc. for $C_{25}H_{29}N_3O_8$:

C, 60.11; H, 5.85; N, 8.41

Found: C, 60.00; H, 5.88; N, 8.31

20 EXAMPLE 78

N,N-Diethylcarbamoylmethyl 2-[4-(morpholinomethyl)benzoyloxy]-5-aminobenzoate, hydrochloride

To a solution of *N,N*-diethylcarbamoylmethyl 2-[4-(morpholinomethyl)benzoyloxy]-5-nitrobenzoate (500 mg, 1.0 mmol) in 0.05 N hydrochloric acid (20 ml) and ethanol (15 ml) was added platinum oxide (25 mg) and the mixture was hydrogenated for 1 h. The reaction mixture was filtered and evaporated in vacuo. The residue was recrystallized from acetonitrile-ethanol-ether to give 294 mg (57%) of the title compound. Mp 209-213°C.

30 Anal.: Calc. for $C_{25}H_{31}N_3O_6$, HCl, 0.5 H_2O :

C, 58.30; H, 6.46; N, 8.16; Cl, 6.89

Found: C, 58.49; H, 6.44; N, 8.28; Cl, 6.99

EXAMPLE 79

Pregnanolone 3-(3-morpholinomethyl)benzoate, hydrochloride

A mixture of 3-(morpholinomethyl)benzoic acid hydrochloride (445 mg, 1.73 mmol) and thionyl chloride (4 ml) was refluxed for 45 min. The solution was evaporated in vacuo. Pyridine (15 ml) and pregnanolone (500 mg, 1.57 mmol) were added to the residue and the mixture was stirred at room temperature for 20 h. The reaction mixture was evaporated in vacuo. Water (15 ml) was added to the residue and the mixture was extracted with ethyl acetate (3 x 20 ml). The organic extracts were dried and concentrated in vacuo. Ether (25 ml) was added followed by a solution of hydrochloric acid in ethyl acetate to precipitate the title compound. Recrystallization from methanol-ether gave 212 mg (24%) of the title compound. Mp 263-266°C.

Anal.: Calc. for $C_{32}H_{47}NO_4$, HCl:

C, 71.00; H, 8.67; N, 2.51; Cl, 6.35

Found: C, 70.88; H, 8.67; N, 2.50; Cl, 6.15

OTHER EXAMPLES

By following the procedures of the foregoing examples several more esters according to the invention are obtained. The structure of these derivatives are shown in Table 1 and 2.

BIOCONVERSION OF THE PRODRUGS

To demonstrate the bioconversion of the compounds of formula I to the parent drug in plasma, samples of human plasma were diluted to 80% with 0.05 M phosphate buffer (pH 7.4) and warmed to 37°C in a water bath. Aliquots of 100 μ l of aqueous or ethanolic solutions of the prodrug derivatives were added to 5.00 ml of the plasma samples,

the initial concentration of the derivatives being about 10^{-4} M. At various times aliquots of 250 μ l of the solutions were withdrawn and deproteinized by mixing with methanol, acetonitrile or a 1% ZnSO_4 solution (methanol-water 1:1). After centrifugation, the clear supernatant was analyzed by HPLC for remaining derivative as well as for parent drug.

In the HPLC method a reversed-phase Supelcosil LC-8DB column (3.3 x 4.6 mm) was eluted at ambient temperature with mixtures of 0.1% phosphoric acid, methanol and acetonitrile, the composition of the eluent being adjusted for each compound to provide an appropriate retention time and separation of the prodrug and the parent drug. Occasionally, triethylamine was added to the eluent in a concentration of 10^{-4} M in order to improve peak shape. The flow-rate was 1.0 ml/min and the column effluent was monitored spectrophotometrically at an appropriate wavelength. Quantitation of the compounds was done by measurement of the peak heights in relation to those of standards chromatographed under the same conditions.

The various prodrug derivatives were found to be cleaved quantitatively to the parent drugs in human plasma solutions. An example is shown in Fig. 1. In all cases, the cleavage of the derivatives displayed strict first-order kinetics. An example is shown in Fig. 2. The half-lives of hydrolysis of various derivatives in 80% human plasma solutions at 37°C are given in Table 1 and 2. As can be seen from the data the derivatives are readily converted to the parent drugs at conditions similar to those prevailing in-vivo.

A demonstration of the enzymatic conversion of the derivatives in plasma is provided by the fact that the half-lives of hydrolysis of the derivatives in Table 1 and 2 in the absence of plasma, i.e. in a pH 7.4 phosphate buffer at 37°C, exceeded 200-400 h.

The results in Tables 1 and 2 show that it is quite feasible to select prodrug derivatives of the present invention with varying rates of plasma-catalyzed regeneration of a certain parent drug. If the aim is to obtain a very rapid rate of hydrolysis in-vivo for e.g. metronidazole prodrugs, the 4-(morpholinomethyl)benzoate ester of

metronidazole is a preferred derivative since its half-life of hydrolysis in plasma is only 0.4 min.

Stability in aqueous solution

The novel compounds of the present invention were found to exhibit at
5 very high stability in aqueous solutions of pH 3-5, thus affording
long term storage of solutions of said novel compounds. The stability
of the compounds was assessed by keeping aqueous buffer solutions of
the compounds at constant temperatures and analyze the solutions for
10 intact prodrug derivative as well as parent drug formed by the HPLC
methods mentioned above. The pH of the solution was found to have a
marked impact on the stability as seen from the pH-rate profile for a
hydrocortisone prodrug in Fig. 3. Maximal stability for the compounds
of the present invention generally occurs in the pH-range 3-5 at
15 which pH values high solubilities of the compounds also are achieved
due to protonation of their amino function(s).

By performing stability studies at these pH values at different
temperatures shelf-lives in excess of two years at 25°C were predicted.
For example, the hydrocortisone prodrug the pH-rate for degradation
of which is shown in Fig. 3 was to possess a shelf-life in
20 aqueous solutions of pH 4.0 of 6.0 and 10.2 years at 25 and 20°C,
respectively. The stability or shelf-life of solutions of compounds
of the present invention can be prolonged by decreasing the storage
temperature, e.g. to temperatures from 4 to 20°C.

A remarkable feature of the compounds of the present invention with
25 regard to providing highly stable aqueous solutions is the solubilizing
capacity of the compounds for their parent drugs. Thus, whereas
the solubility of hydrocortisone in water is 0.40 mg/ml at 21°C, the
solubility was found to be increased to 3.5 mg/ml in a 10% w/v solution
of the prodrug hydrocortisone 21-[3-(4-methylpiperazin-1-yl-
30 methyl)]benzoate dihydrochloride. This unexpected behaviour greatly
prolongs the shelf-life of aqueous prodrug solutions in cases where
the shelf-life is limited by precipitation of parent drug formed upon
hydrolysis rather than loss in prodrug.

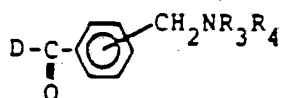
As indicated above, the compounds of Formula I exhibit the highest stability in water when pH of their solution is maintained in the range 3-5. Most advantageously, buffers can be employed to maintain the pH at or near the desired level throughout the shelf-life of the formulation. Suitable buffers are those which are physiologically acceptable and exhibit sufficient buffer capacity in the pH range 3-5, e.g. acetate, citrate, succinate or phthalate buffers. The quantity of buffer used is determined by means known in the art and will depend on the pH desired, the concentration of the solution, and the buffering capacity of the buffer.

*Water solubility and lipophilicity of the prodrugs
of this invention*

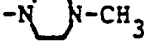
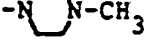
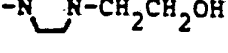
The amine-containing prodrugs of this invention were found to be highly soluble in water when present in salt forms. Solubilities of hydrochloride or fumarate salts were generally found to exceed 15% w/v. The solubilities were assessed by rotating mixtures of excess amounts of the compounds in water for 24-28 h and analyzing an aliquot of the filtered saturated solutions for prodrug derivative by HPLC.

The lipophilicity of the derivatives of the present invention was assessed by measuring the apparent partition coefficients (P) of the compounds between octanol and 0.02M phosphate buffer of pH 7.4. The log P values for some compounds of the present invention are shown in Table 3. The results obtained show clearly that it is readily feasible to obtain prodrug derivatives according to the present invention which at the same time possess both a much higher water solubility and a higher lipophilicity than the parent compound. Such improved properties are quite advantageous for enhanced delivery through various biomenbranes as stated before.

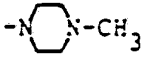
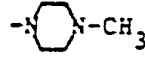
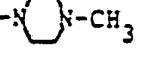
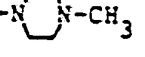
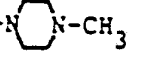
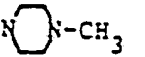
TABLE 1. Half-lives ($t_{1/2}$) of hydrolysis of various compounds of the formula



in 80% human plasma (pH 7.4) at 37°C.

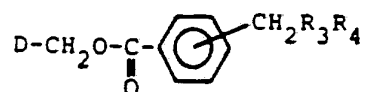
D is the residue of the drug DH	Position of $-\text{CH}_2\text{NR}_3\text{R}_4$	R_3	R_4	$t_{1/2}$ (min)
Hydrocortisone (Formula Ia)	3	H	CH_3	25
	3	H	$\text{CH}_2\text{CH}_2\text{CH}_3$	38
	3	H	CH_2CONH_2	52
	4	H	$\text{CH}_2\text{CH}_2\text{CH}_3$	43
	4	CH_3	$\text{CH}_2\text{CH}_2\text{OH}$	88
	3	CH_3	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	15
	3	C_2H_5	$\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	8
	3	H	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	69
	3	CH_3	CH_3	72
	3	C_2H_5	C_2H_5	34
	4	C_2H_5	C_2H_5	107
	3			62
	4			92
	3			41
	4			76
	3			15
	4			147
	3			15

D- is the residue of the drug DH	Position of $-\text{CH}_2\text{NR}_3\text{R}_4$	R_3	R_4	t_1 (min)
	3			103
	3		$-\text{COOC}_2\text{H}_5$	42
	3	 (L)		75
Prednisolone (Formula If)	3	C_2H_5	C_2H_5	54
	3	C_2H_5	$\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	12
	3			18
Prednisone	3			35
6 α -Methylprednisolone (Formula Ig)	3	CH_3	$\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$	18
	3	C_2H_5	$\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	29
	3			29
Chloramphenicol (Formula Ic)	3	C_2H_5	C_2H_5	8
	3	C_2H_5	$\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	0.9
	3			55
	3			5
Metronidazole (Formula Ib)	4	CH_3	CH_3	4.7
	3	CH_3	CH_3	5
	4		$-\text{N}(\text{CH}_3)_3^+$	51
	3			5

D is the residue of the drug DH	Position of $-\text{CH}_2\text{NR}_3\text{R}_4$	R_3	R_4	t_i (min)
	4			0.4
	3			0.6
	4			2.4
Benzylalcohol	4	CH_3	CH_3	16
Paracetamol (Formula Id)	4	CH_3	CH_3	87
	3	C_2H_5	C_2H_5	70
	3	C_2H_5	$\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$	15
	3			56
	4			57
	3			27
	4			487
	4	$-\text{N}(\text{CH}_3)_3^+$		262
Phenol	3	C_2H_5	C_2H_5	15
	3			0.2
8-Estradiol (Formula Ii)	3	C_2H_5	C_2H_5	7.4 h
	3			10.2 h
Aciclovir (Formula Ia)	4			3.7

D is the residue of the drug DH	Position of -CH ₂ NR ₃ R ₄	R ₃	R ₄	t _{1/2} (min)
Aciclovir (Formula Ia)	4	CH ₃	CH ₃	33
	4	C ₂ H ₅	C ₂ H ₅	25
	4	C ₃ H ₇	C ₃ H ₇	57
	3	C ₃ H ₇	C ₃ H ₇	0.8
	3	C ₂ H ₅	C ₂ H ₅	7.5
	3	CH ₃	CH ₃	7
	3	C ₄ H ₉	C ₄ H ₉	2.3
	4			8.5
	3			4.6
Ganciclovir (Formula Ir)	4	CH ₃	CH ₃	114
	4	C ₂ H ₅	C ₂ H ₅	500
	4	C ₃ H ₇	C ₃ H ₇	69
	4			27
	3			136

TABLE 2. Half-lives ($t_{1/2}$) of hydrolysis of various compounds of the formula



in 80% human plasma (pH 7.4) at 37°C.

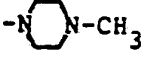
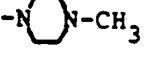
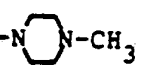
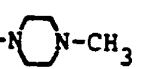
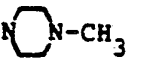
D is the residue >N of an NH-acidic drug (position of NH-derivatization)	Position of $-\text{CH}_2\text{NR}_3\text{R}_4$	R_3	R_4	$t_{1/2}$ (min)
Allopurinol (1) (Formula 1l)	4	CH_3	CH_3	9.4
	4			1.9
	3			8.5
	3			0.5
	4			11
	3			3.6
Chlorzoxazone (Formula 1k)	3	C_2H_5	C_2H_5	28
	3			1.9
Theophylline (7) (Formula 1m)	3	C_2H_5	C_2H_5	0.4
	3			0.4
	3			2.8
	3			0.9
Phenytoin (3) (Formula 1j)	3	C_2H_5	C_2H_5	20
	3			7

TABLE 3.

Water solubilities (S) and partition coefficients (P) for allupurinol, aciclovir and various prodrugs.

5	Compound	S ^a (mg/ml)	log P ^b
	Allopurinol	0.50	- 0.55
10	1-(4-Morpholinomethylbenzoyloxymethyl)allopurinol, fumarate	> 100	1.13
	1-(4-N,N-Dimethylaminomethylbenzoyloxymethyl)allopurinol, fumarate	> 100	0.53
15	1-[3-(4-Methylpiperazin-1-yl)-methyl]benzoyloxymethyl]allopurinol, fumarate	> 100	0.97
20	1-(3-Imidazolylmethylbenzoyloxymethyl)allopurinol	-	0.97
	Aciclovir	1.2	- 1.47
	Aciclovir 4-morpholinomethylbenzoate, hydrochloride	> 100	- 0.05
25	^a At 21°C.		
	Aciclovir 3-dipropylaminomethylbenzoate nitrate	> 50	0.60

^bBetween octanol and phosphate buffer pH 7.4 at 21°C.

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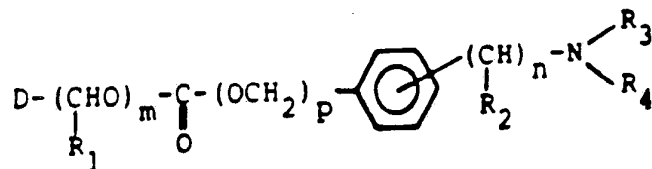
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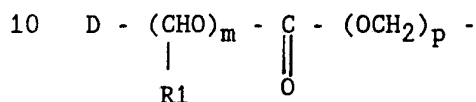
CLAIMS

1. Compounds of the formula I

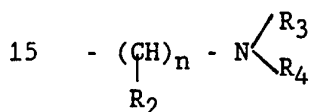


wherein D represents the dehydrogenated residue of a hydroxyl group-containing drug or D represents the dehydrogenated residue of an NH-acidic group-containing drug;

the substituents in the phenyl ring



and



are in either meta- or para- position to each other;

the phenyl ring additionally may be substituted with one, two, three or four substituents selected from the group consisting of an alkyl group, a halogen, a hydroxyl group or an alkoxy group;

m is an integer 0 or 1;

p is an integer of 0 or 1;

n is an integer from 1 to 4;

R₁ is selected from the group consisting of hydrogen, an alkyl group, an aryl group, an aralkyl group, a group having the formula -COOR₅, wherein R₅ is an alkyl or aralkyl group, or a carbamoyl group of the formula -CONR₆R₇, wherein R₆ and R₇ are the same or different and are hydro-gen, an alkyl group, or together with the adjacent nitrogen atom form a 4-, 5-, 6- or 7-membered heterocyclic ring, which in addition to the nitrogen

may contain one or two further hetero-atoms selected from the group consisting of nitrogen, oxygen, and sulfur;

R_2 is hydrogen or an alkyl group;

5 R_3 and R_4 are the same or different and are selected from the group consisting of hydrogen, an alkyl group, an aralkyl, an alkenyl group, a cycloalkyl group, in which the alkyl, aralkyl, alkenyl or cycloalkyl group is unsubstituted or substituted with one or more substituents selected from:

- 10
- a hydroxyl group
 - a straight or branched-chain alkoxy group
 - a carbamoyl group having the formula $-\text{CONR}_6\text{R}_7$ as defined above
 - an amino group having the formula $-\text{NR}_6\text{R}_7$, wherein R_6 and R_7 are as defined above; or

15 R_3 and R_4 are combined so that $-\text{NR}_3\text{R}_4$ forms a 4-, 5-, 6- or 7-membered heterocyclic ring, which in addition to the nitrogen atom may contain one or two further heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur, and which hetero-cyclic ring may be substituted with a hydroxyl group, a carbonyl group, an alkyl

20 group, an alkyl group substituted with a hydroxyl group or an acyloxy group having the formula $\text{R}_5\text{COO}-$, wherein R_5 is as defined above, an alkoxycarbonyl group having the formula $-\text{COOR}_5$ as defined above, or a carbamoyl group of the formula $-\text{CONR}_6\text{R}_7$ as defined above;

with the proviso that m is 0 when D represents the dehydrogenated

25 residue of a hydroxyl group-containing drug and m is 1 when D represents the dehydrogenated residue of an NH-acidic group-containing drug;

and the pharmaceutically acceptable acid addition salts or quaternary ammonium salts thereof.

2. Compounds according to claim 1 wherein D is the dehydrogenated residue of a hydroxyl group-containing drug (m is zero) or of an NH-acidic group-containing drug (m is 1) selected from

- Aciclovir
- 5 Cromolyn and cromolyn esters
- Erythromycin A
- Chloramphenicol
- Metronidazole
- Cefamandole
- 10 Cytarabine
- Vidarabine
- Testosterone
- Doxifluridine
- Floxuridine
- 15 Zidovudine
- Oxazepam
- Lorazepam
- Etoposide
- Forskolin
- 20 Idoxuridine
- Hydrocortisone
- Cortisone
- Corticosterone
- Prednisone
- 25 Prednisolone
- 6 α -Methylprednisolone
- Triamcinolone
- Dexamethasone
- Desciclovir
- 30 Flumethasone
- Chlorprednisone
- Betamethasone
- Betamethasone 17-valerate
- Fluprednisolone
- 35 9 α -Fluorohydrocortisone
- Pregnanolone
- Propranolol

	Timolol
	Alprenolol
	Atenolol
	Labetalol
5	Metoprolol
	Oxprenolol
	Levobunolol
	Betaxolol
	Ganciclovir
10	Rapamycin
	Paracetamol
	Levodopa
	Methyldopa
	Dopamine
15	Dobutamine
	Morphine
	Naloxone
	Naltrexone
	Nalorphine
20	Oximetazoline
	Ketobemidone
	Phenylephrine
	Salbutamol
	Terbutaline
25	Fenoldopam
	Allopurinol
	5-Fluorouracil
	Theophylline
	Cimetidine
30	Phenytoin
	Aminogluthethimide
	Mercaptopurine
	Chlorzoxazone
	Mebendazole
35	Thiabendazole
	Mitindomide
	Domperidone
	Ketoconazole

Mifentidine

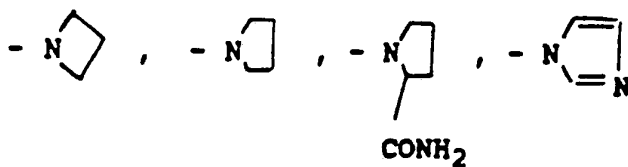
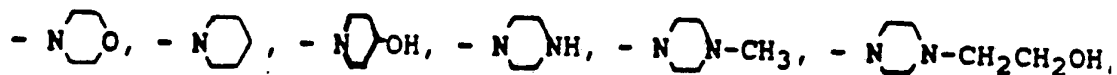
1,3-Diphenylxanthine

3. Compounds according to claim 1 or 2 wherein R_1 is hydrogen or methyl, p is zero, R_2 is hydrogen, m is zero or 1 and n is 1 or 2.

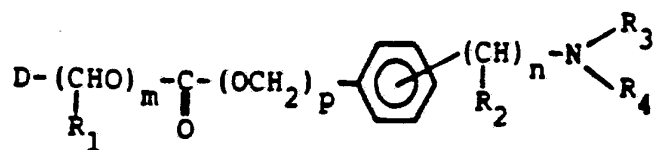
4. Compounds according to claim 2 wherein R_1 is hydrogen, m is zero or 1, p is zero, R_2 is hydrogen, n is 1 and R_3 and R_4 are the same or different and are

- H
- CH_3
- C_2H_5
- $CH_2CH_2CH_3$
- CH_2CH_2OH
- CH_2CONH_2
- $CH_2CH_2NH_2$
- $CH_2CH_2NHCH_3$
- $CH_2CH_2N(CH_3)_2$
- $CH_2CH_2N(C_2H_5)_2$ or
- $CH_2CH_2OCH_3$

or - NR_3R_4 is



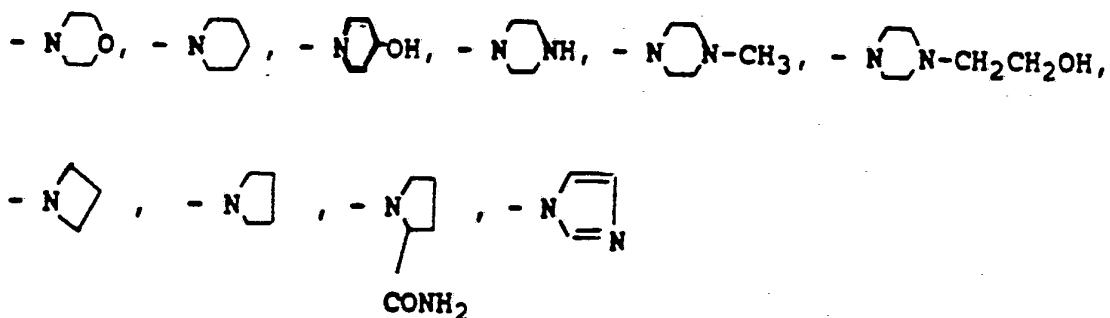
5. Compounds of the formula I



wherein R_1 is hydrogen, R_2 is hydrogen, p is zero, m is zero or 1, n is 1, R_3 and R_4 are the same or different and are

- H
- CH_3
- 5 - C_2H_5
- $\text{CH}_2\text{CH}_2\text{CH}_3$
- $\text{CH}_2\text{CH}_2\text{OH}$
- CH_2CONH_2
- $\text{CH}_2\text{CH}_2\text{NH}_2$
- 10 - $\text{CH}_2\text{CH}_2\text{NHCH}_3$
- $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$
- $\text{CH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$ or
- $\text{CH}_2\text{CH}_2\text{OCH}_3$

or - NR_3R_4 is



- 15 and D is the dehydrogenated residue of a hydroxyl group-containing drug (then m is zero) or of an NH-acidic group-containing drug (then m is 1) selected from aciclovir, metronidazole, chloramphenicol, paracetamol, ganciclovir, hydrocortisone,

prednisolone, methylpred-nisolone, pregnanolone, β -estradiol, phenytoin, chlor-zoxazone, allopurinol, theophylline, 5-fluorouracil, testosterone, oxazepam, idoxuridine and vidarabine.

6. A pharmaceutical composition comprising a pharmaceutically acceptable excipient and a pharmaceutically effective amount of a compound according to any of claims 1-5.

7. A process for preparing a compound of the formula I as defined in claims 1-5 comprising

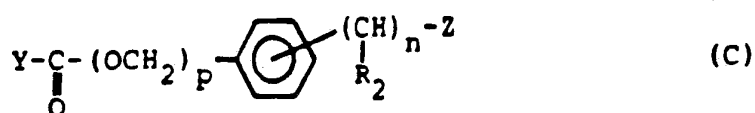
- a) reacting the OH-containing drug of the formula A



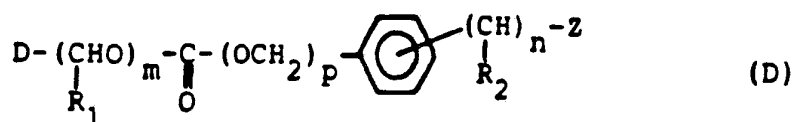
or the N- α -hydroxyalkylated NH-acidic drug of the formula B



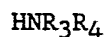
wherein D and R_1 are as defined above in connection with formula I, with a compound having the formula C:



wherein p, n, and R_2 are as defined above and Y is a suitable leaving group, and then reacting the so produced compound of the formula D



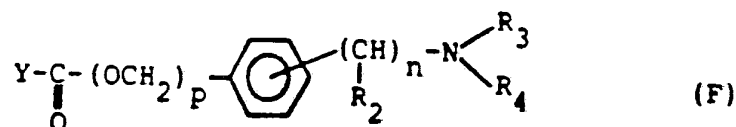
with an amine of the formula E



(E)

wherein R_3 and R_4 are as defined above; or

- b) reacting a compound of formula A or B with a compound having the formula F



- 5 wherein Y, p, n, R_2 , R_3 and R_4 are as defined above with the proviso that when Y is hydroxy, p is zero; or

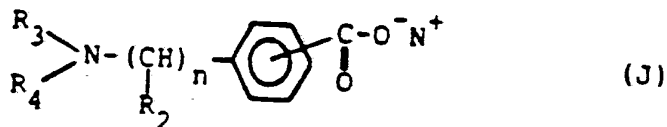
- c) reacting a compound of formula G -



- 10 in which the hydroxy group of the parent drug DH is replaced by Z, so that D' is the dehydroxylated residue of a hydroxyl group-containing drug, or a compound of formula H



- 15 wherein Z is as defined above, with a compound of formula J

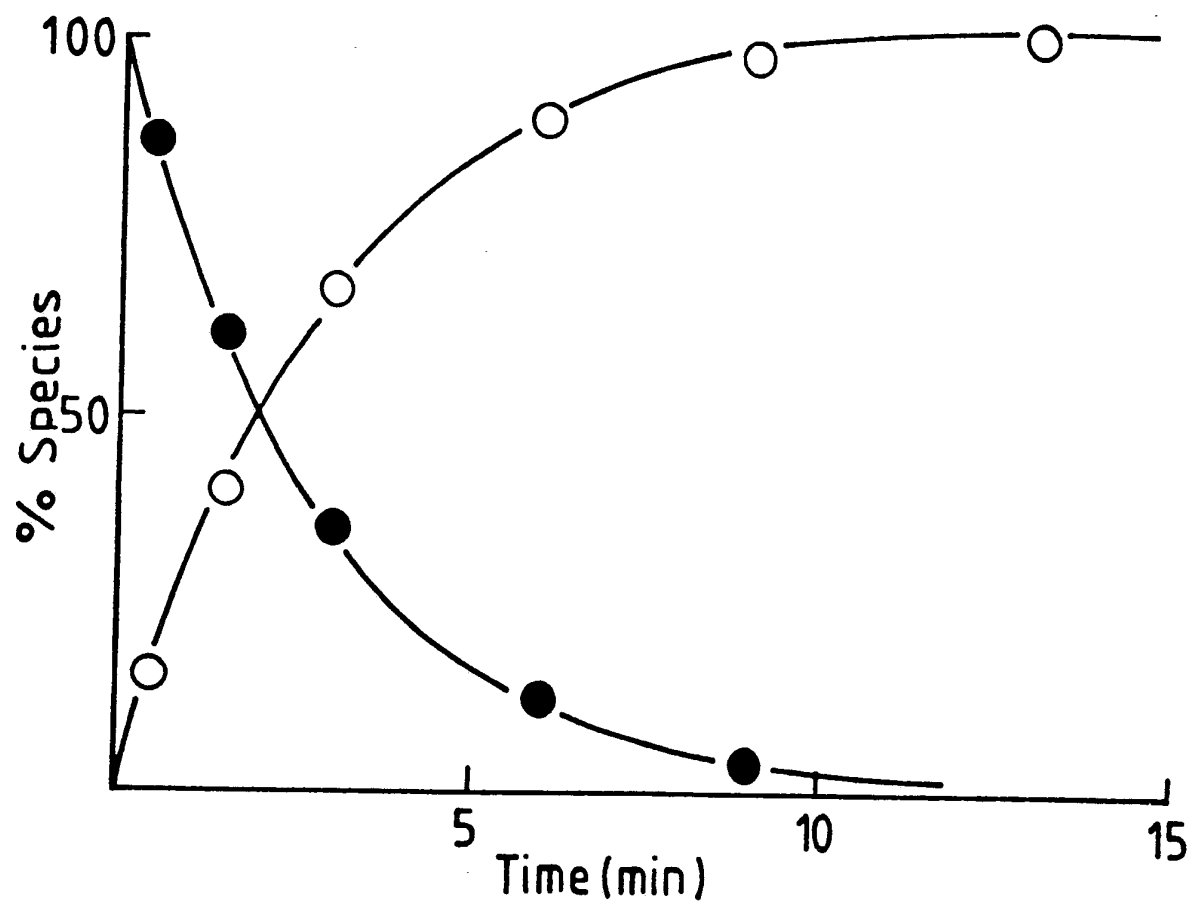


wherein n, R_2 , R_3 and R_4 are as defined above and N^+ is a counter ion such as Na^+ , K^+ , Ag^+ or trialkylammonium.

8. A compound as defined in claims 1-5 for use in therapy.
9. The use of a compound according to any of claims 1-5 for preparing a pharmaceutical composition for use in therapy.

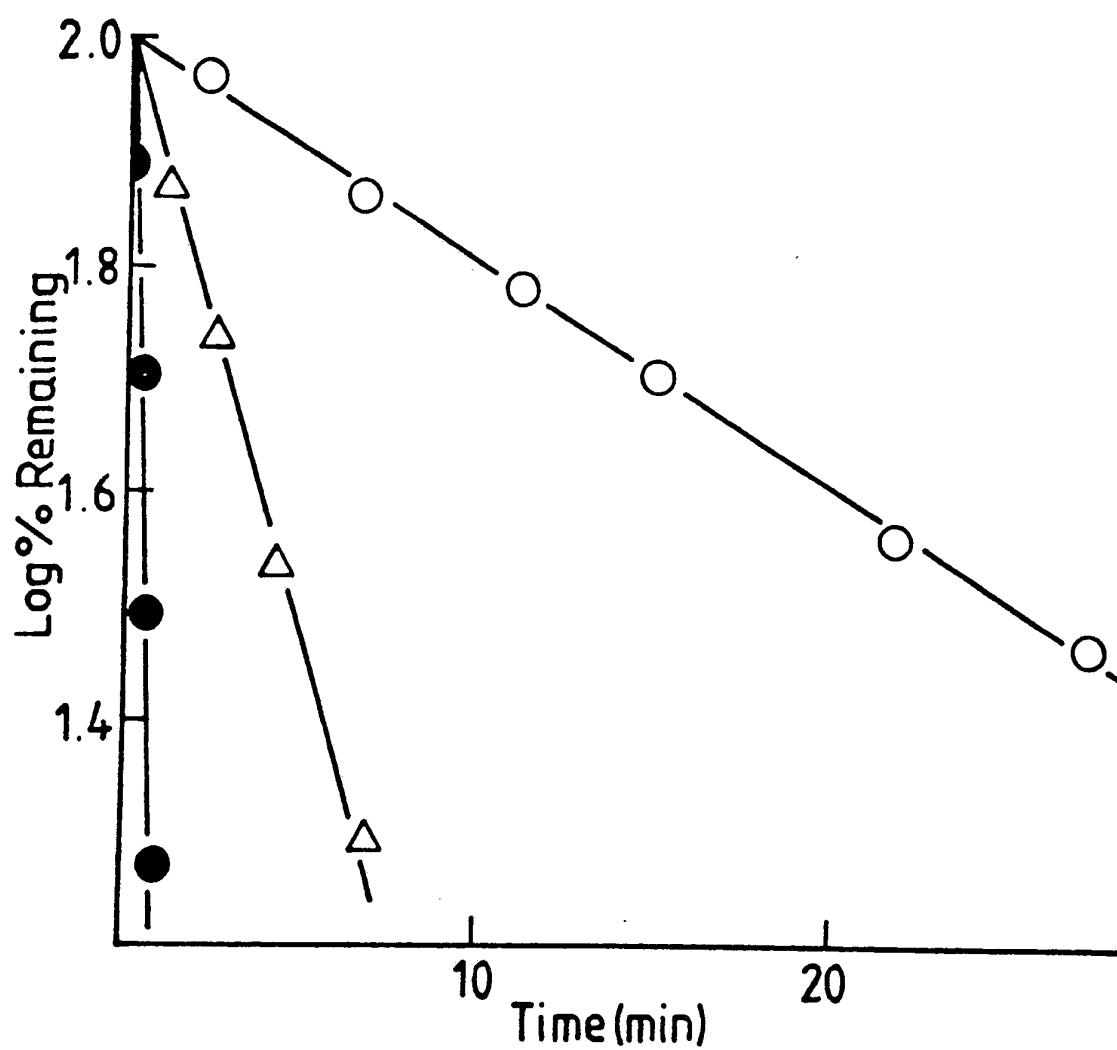
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Figure 1



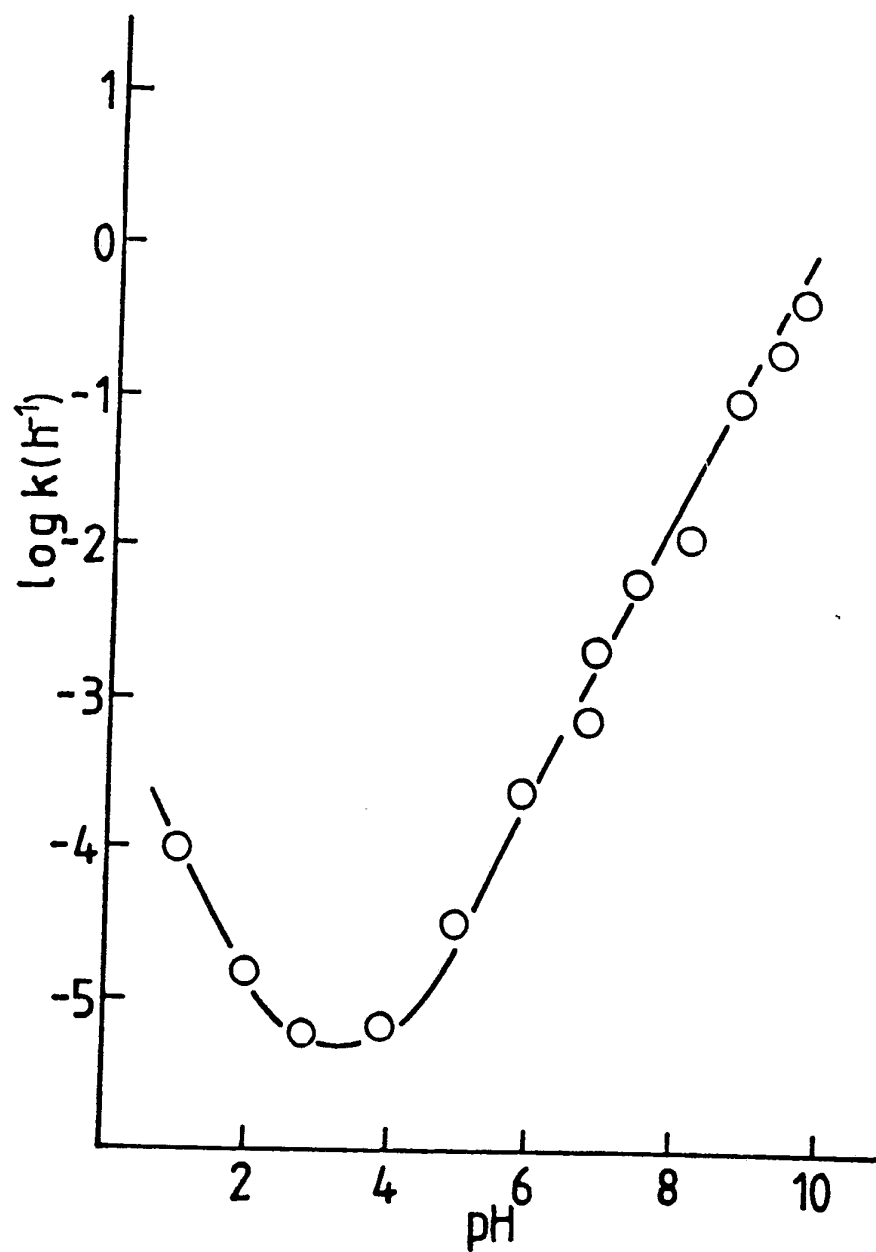
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Figure 2



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Figure 3



INTERNATIONAL SEARCH REPORT

International Application No PCT/DK 90/00020

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) *		
According to International Patent Classification (IPC) or to both National Classification and IPC		
IPC5: C 07 C 229/38, A 61 K 31/00		
II. FIELDS SEARCHED		
Minimum Documentation Searched *		
Classification System	Classification Symbols	
IPC5	C 07 C; A 61 K	
Documentation Searched other than minimum documentation to the extent that such documents are included in the Fields Searched *		
SE,DK,FI,NO classes as above		
III. DOCUMENTS CONSIDERED TO BE RELEVANT *		
Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages **	Relevant to Claim No. **
A	EP, A1, 0221506 (E.I DU PONT DE NEMOURS AND COMPANY) 13 May 1987, see the whole document --	1-7,9
A	EP, A1, 0170090 (E.I. DU PONT DE NEMOURS AND COMPANY) 5 February 1986, see the whole document --	1-7,9
A	WO, A1, 88/01615 (BUNDGAARD HANS ET AL.) 10 March 1988, see the whole document --	1-7,9
A	Chemical Abstracts, volume 110, no. 13, 27 March 1989, (Columbus, Ohio, US), Bundgaard Hans et al : "Timolol prodrugs: preparation and hydrolysis kinetics of N-benzoyl carbamate esters of timolol and related compounds ", see page 11, abstract 107541u, & Acta Pharm. Suec. 1988, 25(6), 293- 306 --	1-7,9
* Special categories of cited documents: 10 "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 "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. "Z" document member of the same patent family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
19th April 1990	1990 -04- 23	
International Searching Authority	Signature of Authorized Officer	
SWEDISH PATENT OFFICE	Anna Hedberg <i>Anna Hedberg</i>	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	Chemical Abstracts, volume 107, no. 6, 10 August 1987, (Columbus, Ohio, US), Buur Anders et al: "Prodrugs of 5-fluorouracil. VIII. Improved rectal and oral delivery of 5-fluorouracil via various prodrugs. Structure-rectal absorption relationships", see page 409, abstract 46157n, & Int. J. Pharm. 1987, 36(1), 41- 49 --	1-7,9
A	Chemical Abstracts, vol. 109, no. 15, 10 October 1988 (Columbus, Ohio, US), Paul William Erhardt et al: "Preparation of prodrug derivatives of the cardio- tonic agent 4-ethyl-1,3-dihydro-5- β -(2-methyl-1H-imidazol-1-yl)benzoyl]-2H-imidazolone", see page 694, abstract 129012d, & Eur. Pat. Appl. EP 264,729 --	1-7,9
A	Chemical Abstracts, volume 110, no. 13, 27 March 1989, (Columbus, Ohio, US), Shanaz M. Tejani-Butt et al : "Evaluation of mono- and dibenzoyl esters of dopamine as potential pro-drugs for dopamine in the central nervous system", see page 132, abstract 108718u, & Naunyn-Schmiedeberg's Arch. Pharmacol. 1988, 338(5), 497- 503 -- -----	1-7,9

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET**V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹**

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers 8 because they relate to subject matter not required to be searched by this Authority, namely:

Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods, see PCT Rule 39.1(iv).

2. ☒ Claim numbers *) 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:

*) Claims 1-7, 9: searched incompletely because the claims are too broadly formulated.

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

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 of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ 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 claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. PCT/DK 90/00020**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A1- 0221506	87-05-13	AU-B- 583160	89-04-20
		AU-D- 6461686	87-05-07
		CA-A- 1255295	89-06-06
		JP-A- 62120398	87-06-01
		US-A- 4757062	88-07-12
EP-A1- 0170090	86-02-05	AU-B- 578391	88-10-20
		AU-D- 4451685	86-01-09
		JP-A- 61063658	86-04-01
		SU-A- 1508960	89-09-15
		US-A- 4668685	87-05-26
WO-A1- 88/01615	88-03-10	NONE	