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(54) Title: AZA SPIRO ALKANES DERIVATIVES AS THERAPEUTIC AGENTS (I)		
(57) Abstract Compounds of formula (I) and pharmaceutically acceptable salts thereof in which m is an integer from 1 to 3; n is an integer from 2 to 6; R₁ is phenyl optionally substituted by one or more substituents selected from halo, hydroxy, alkoxy, alkanoxy, alkyl, halogenated alkyl, alkylthio, alkylsulphinyl, alkylsulphonyl, cyano, nitro, optionally substituted amino, optionally substituted sulphonyl, optionally substituted carbamoyl or phenyl, or R₁ is naphthyl; R₂ is H, alkyl or phenyl; R₃ is H, alkyl, alkenyl or alkoxyalkyl; R₄ is H or hydroxy; and R₅ is H or together with R₄ represents a bond; have utility in the treatment of obesity and affective disorders such as depression and anxiety.		

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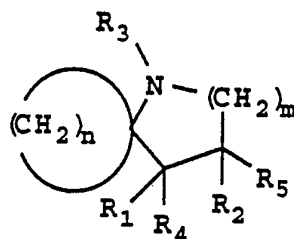
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AZA SPIRO ALKANES DERIVATIVES AS THERAPEUTIC AGENTS

The present invention relates to novel therapeutic agents, to processes for their preparation, to pharmaceutical compositions containing them and to their use in the treatment of obesity and affective disorders such as depression and anxiety.

The present invention provides compounds of formula I



I

and pharmaceutically acceptable salts thereof

in which m is an integer from 1 to 3;

n is an integer from 2 to 6;

R₁ is phenyl optionally substituted by one or more substituents selected from halo, hydroxy, alkoxy containing 1 to 3 carbon atoms, alkanoyl containing 2 or 3 carbon atoms, alkyl containing 1 to 3 carbon atoms, halogenated alkyl containing 1 to 3 carbon atoms, alkylthio containing 1 to 3 carbon atoms, alkylsulphinyl containing 1 to 3 carbon atoms, alkylsulphonyl containing 1 to 3 carbon atoms, cyano, nitro, amino optionally substituted by 1 or 2 alkyl groups each containing 1 to 3 carbon atoms, sulphamoyl optionally substituted by 1 or 2 alkyl groups each containing 1 to 3 carbon atoms, carbamoyl optionally substituted by

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1 or 2 alkyl groups each containing 1 to 3 carbon atoms, or phenyl, or R_1 is naphthyl;

R_2 is H, alkyl containing 1 to 3 carbon atoms or phenyl;

R_3 is H, alkyl containing 1 to 6 carbon atoms, alkenyl
5 containing 3 to 6 carbon atoms, or alkoxyalkyl in which the alkoxy group contains 1 to 4 carbon atoms and the alkyl group contains 2 to 4 carbon atoms;

R_4 is H or hydroxy; and

R_5 is H or together with R_4 represents a bond.

10 In preferred compounds of formula I, n is 4 or 5.

In preferred compounds of formula I, m is 1 or 2.

In preferred compounds of formula I, R_1 is phenyl optionally substituted by one or more substituents selected from halo (for example fluoro, chloro, bromo or
15 iodo), hydroxy, halogenated alkyl containing 1 to 3 carbon atoms in which halo is fluoro, alkoxy containing 1 or 2 carbon atoms or phenyl or R_1 is naphthyl. In more preferred compounds of formula I, R_1 is phenyl optionally substituted by one or more substituents
20 selected from chloro, fluoro, hydroxy, trifluoromethyl, methoxy or phenyl or R_1 is naphthyl. In especially preferred compounds of formula I, R_1 is phenyl, 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 4-fluorophenyl, 3-(trifluoromethyl)phenyl,
25 4-hydroxyphenyl, 4-methoxyphenyl, 4-biphenyl or 2-naphthyl.

In preferred compounds of formula I, R_2 is H.

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In preferred compounds of formula I, R_3 is H, alkyl containing 1 to 3 carbon atoms, alkenyl containing 3 to 6 carbon atoms or alkoxyalkyl in which the alkoxy group contains 1 to 3 carbon atoms and the alkyl group
5 contains 2 or 3 carbon atoms. In more preferred compounds of formula I, R_3 is H, methyl, ethyl, propyl, allyl or 2-methoxyethyl. In especially preferred compounds of formula I, R_3 is H.

In preferred compounds of formula I, R_4 is hydroxy
10 and R_5 is H, R_4 and R_5 are both H, or R_4 and R_5 together represent a bond. In more preferred compounds of formula I, R_4 and R_5 together represent a bond.

Compounds of formula I may exist as salts with pharmaceutically acceptable acids. Examples of such
15 salts include hydrochlorides, hydrobromides, sulphates, methanesulphonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [eg (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures), succinates, benzoates and salts with amino
20 acids such as glutamic acid. Compounds of formula I and their salts may exist in the form of solvates (for example hydrates).

Certain compounds of formula I may exist in more than one crystal form and the present invention includes
25 each crystal form and the mixtures thereof.

Compounds of formula I which contain one or more chiral centres exist in different optically active forms. When compounds of formula I contain one chiral centre, the compounds exist in two enantiomeric forms
30 and the present invention includes both enantiomers and mixtures of enantiomers. The enantiomers may be resolved by methods known to those skilled in the art,

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for example by formation of diastereoisomeric salts which may be separated, for example, by crystallisation; formation of diastereoisomeric derivatives or complexes which may be separated, for example, by crystallisation, 5 gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent, for example enzymatic esterification; or gas-liquid or liquid chromatography in a chiral environment, for example on a chiral support for example silica with 10 a bound chiral ligand or in the presence of a chiral solvent. It will be appreciated that where the active moiety is transformed by the separation procedures described above, a further step is required to convert the product to the active moiety. Alternatively, 15 specific enantiomers may be synthesised by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer to the other by asymmetric transformation.

Specific compounds of formula I are:-

- 20 5-(4-chlorophenyl)-1-azaspiro[5.5]undec-4-ene;
5-(3-chlorophenyl)-1-azaspiro[5.5]undec-4-ene;
5-(3,4-dichlorophenyl)-1-azaspiro[5.5]undec-4-ene;
5-(4-fluorophenyl)-1-azaspiro[5.5]undec-4-ene;
25 5-[3-(trifluoromethyl)phenyl]-1-azaspiro[5.5]undec-4-ene;
5-(2-naphthyl)-1-azaspiro[5.5]undec-4-ene;
5-(4-hydroxyphenyl)-1-azaspiro[5.5]undec-4-ene;
5-(4-chlorophenyl)-1-methyl-1-azaspiro[5.5]undec-4-ene;
30 10-(4-chlorophenyl)-6-azaspiro[4.5]dec-9-ene;
5-(4-chlorophenyl)-5-hydroxy-1-azaspiro[5.5]-undecane;
5-(4-chlorophenyl)-1-ethyl-5-hydroxy-1-azaspiro[5.5]undecane;
35 5-(3-chlorophenyl)-5-hydroxy-1-azaspiro[5.5]-undecane;

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- 5-(3,4-dichlorophenyl)-5-hydroxy-1-azaspiro[5.5]-undecane;
5-(4-chlorophenyl)-1-azaspiro[5.5]undecane;
5-(4-methoxyphenyl)-1-azaspiro[5.5]undecane;
5 5-(4-chlorophenyl)-1-propyl-1-azaspiro[5.5]undec-4-ene;
1-allyl-5-(4-chlorophenyl)-1-azaspiro[5.5]undec-4-ene;
10 5-(4-chlorophenyl)-1-(2-methoxyethyl)-1-azaspiro[5.5]undec-4-ene;
5-phenyl-1-azaspiro[5.5]undec-4-ene;
5-(4-biphenyl)-1-azaspiro[5.5]undec-4-ene;
4-(4-chlorophenyl)-1-azaspiro[4.5]dec-3-ene;

and pharmaceutically acceptable salts thereof.

- 15 The present invention also includes pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I together with a pharmaceutically acceptable diluent or carrier.

- As used hereinafter, the term "active compound"
20 denotes a compound of formula I. In therapeutic use, the active compound may be administered orally, rectally, parenterally or topically, preferably orally. Thus the therapeutic compositions of the present invention may take the form of any of the known
25 pharmaceutical compositions for oral, rectal, parenteral or topical administration. Pharmaceutically acceptable carriers suitable for use in such compositions are well known in the art of pharmacy. The compositions of the invention may contain 0.1-99% by weight of active
30 compound. The compositions of the invention are generally prepared in unit dosage form. Preferably the unit dosage of active ingredient is 1 to 500 mg. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art.

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Compositions for oral administration are the preferred compositions of the invention and these are the known pharmaceutical forms for such administration, for example tablets, capsules, syrups and aqueous or oil suspensions. The excipients used in the preparation of these compositions are the excipients known in the pharmacist's art. Tablets may be prepared by mixing the active compound with an inert diluent such as calcium phosphate in the presence of disintegrating agents, for example maize starch, and lubricating agents, for example magnesium stearate, and tableting the mixture by known methods. The tablets may be formulated in a manner known to those skilled in the art so as to give a sustained release of the compounds of the present invention. Such tablets may, if desired, be provided with enteric coatings by known methods, for example by the use of cellulose acetate phthalate. Similarly, capsules, for example hard or soft gelatin capsules, containing the active compound with or without added excipients, may be prepared by conventional means and, if desired, provided with enteric coatings in a known manner. The tablets and capsules may conveniently each contain 1 to 500 mg of the active compound. Other compositions for oral administration include, for example, aqueous suspensions containing the active compound in an aqueous medium in the presence of a non-toxic suspending agent such as sodium carboxymethyl-cellulose, and oily suspensions containing a compound of the present invention in a suitable vegetable oil, for example arachis oil.

The active compound may be formulated into granules with or without additional excipients. The granules may be ingested directly by the patient or they may be added to a suitable liquid carrier (for example water) before ingestion. The granules may contain disintegrants (for

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example a pharmaceutically acceptable effervescent couple formed from an acid and a carbonate or bicarbonate salt) to facilitate dispersion in the liquid medium.

- 5 Compositions of the invention suitable for rectal administration are the known pharmaceutical forms for such administration, for example, suppositories with cocoa butter or polyethylene glycol bases.

- 10 Compositions of the invention suitable for parenteral administration are the known pharmaceutical forms for such administration, for example sterile suspensions or sterile solutions in a suitable solvent.

- 15 Compositions for topical administration may comprise a matrix in which the pharmacologically active compounds of the present invention are dispersed so that the compounds are held in contact with the skin in order to administer the compounds transdermally. A suitable transdermal composition may be prepared by mixing the pharmaceutically active compound with a topical vehicle, 20 such as a mineral oil, petrolatum and/or a wax, eg paraffin wax or beeswax, together with a potential transdermal accelerant such as dimethyl sulphoxide or propylene glycol. Alternatively the active compounds may be dispersed in a pharmaceutically acceptable cream 25 or ointment base. The amount of active compound contained in a topical formulation should be such that a therapeutically effective amount of the compound is delivered during the period of time for which the topical formulation is intended to be on the skin.

- 30 The compounds of the present invention may also be administered by continuous infusion either from an external source, for example by intravenous infusion or

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from a source of the compound placed within the body. Internal sources include implanted reservoirs containing the compound to be infused which is continuously released for example by osmosis and implants which may
5 be (a) liquid such as a suspension or solution in a pharmaceutically acceptable oil of the compound to be infused for example in the form of a very sparingly water-soluble derivative such as a dodecanoate salt or ester or (b) solid in the form of an implanted support,
10 for example of a synthetic resin or waxy material, for the compound to be infused. The support may be a single body containing all the compound or a series of several bodies each containing part of the compound to be delivered. The amount of active compound present in an
15 internal source should be such that a therapeutically effective amount of the compound is delivered over a long period of time.

In some formulations it may be beneficial to use the compounds of the present invention in the form of
20 particles of very small size, for example as obtained by fluid energy milling.

In the compositions of the present invention the active compound may, if desired, be associated with other compatible pharmacologically active ingredients.

25 The pharmaceutical compositions containing a therapeutically effective amount of a compound of formula I may be used to treat obesity and affective disorders such as depression and anxiety. Whilst the precise amount of active compound administered in such
30 treatment will depend on a number of factors, for example the age of the patient, the severity of the condition and the past medical history, and always lies within the sound discretion of the administering

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physician, the amount of active compound administered per day is in the range 1 to 1000 mg preferably 5 to 500 mg given in a single or in divided doses at one or more times during the day.

5 In yet another aspect, the present invention provides the use of a compound of formula I in the manufacture of a medicament for use in the treatment of obesity and affective disorders such as depression and anxiety.

10 Processes for the preparation of compounds of formula I will now be described. These processes form a further aspect of the present invention.

Compounds of formula I in which R_4 and R_5 together represent a bond may be prepared by dehydration of a
15 compound of formula I in which R_4 is hydroxy and R_5 is H, for example in the presence of (a) sulphuric acid or (b) toluene-4-sulphonic acid and toluene.

Compounds of formula I in which R_3 is alkyl, may be prepared by alkylation of a compound of formula I in
20 which R_3 is H, for example with an alkyl halide, optionally in the presence of a base, for example potassium carbonate, or by reductive alkylation with an aldehyde or a ketone and formic acid or a reducing agent such as sodium cyanoborohydride, or by acylation of a
25 compound of formula I in which R_3 is H with an acylating agent such as an acyl halide, for example, acetyl chloride, or a carboxylic anhydride, for example, acetic anhydride, followed by reaction with a reducing agent, for example, borane-methyl sulphide complex. Compounds
30 of formula I in which R_3 is methyl, may be prepared by methylation of a compound of formula I in which R_3 is H, for example, using formaldehyde and formic acid.

- 10 -

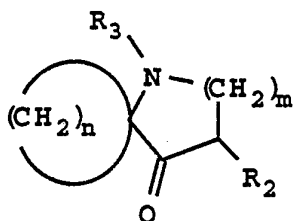
Compounds of formula I in which R_3 is ethyl may be prepared by acylation of a compound of formula I in which R_3 is H, for example, using acetic anhydride, followed by reduction with borane-methyl sulphide
5 complex.

Compounds of formula I in which R_3 is alkenyl, may be prepared by reaction of a compound of formula I in which R_3 is H, for example with an alkenyl halide optionally in the presence of a base, for example
10 potassium carbonate.

Compounds of formula I in which R_3 is alkoxyalkyl, may be prepared by reaction of a compound of formula I in which R_3 is H, for example with an alkoxyalkyl halide optionally in the presence of a base, for example
15 potassium carbonate.

Compounds of formula I in which R_4 and R_5 are both H may be prepared by reduction of a compound of formula I in which R_4 and R_5 together represent a bond with a suitable reducing agent, for example hydrogen in the
20 presence of 10% palladium-on-carbon catalyst, and in a suitable solvent, for example ethanol.

Compounds of formula I in which R_4 is hydroxy and R_5 is H may be prepared by reaction of a compound of formula II



II

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with an organometallic reagent, for example an organolithium compound of formula III



III

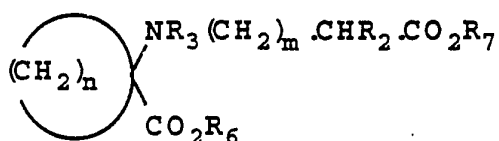
or a Grignard reagent of formula IV



IV

in which X is chloro, bromo or iodo, in a suitable
5 solvent system, followed by hydrolytic work-up.

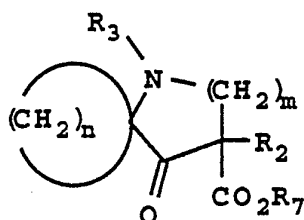
Compounds of formula II may be prepared by reaction
of a compound of formula V



V

in which R_6 and R_7 are the same or different and are
alkyl groups containing 1 to 4 carbon atoms,

10 with a base, for example sodium alkoxide, to give a
compound of formula VI



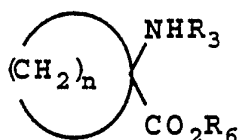
VI

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which is then treated with aqueous acid to give a compound of formula II.

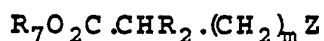
Compounds of formula II may be prepared from compounds of formula V, by addition of a base, for example, sodium alkoxide followed by addition of aqueous acid, without the isolation of compounds of formula VI.

Compounds of formula V may be prepared by reaction of a compound of formula VII



V II

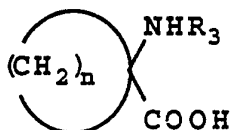
with a compound of formula VIII



V III

10 in which Z is a leaving group, for example chloro, bromo or iodo in the presence of a base, for example potassium carbonate.

Compounds of formula VII may be prepared by esterification of a compound of formula IX



IX

15 with an alcohol of formula R_6OH optionally in the presence of an acid catalyst.

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The therapeutic activity of the compounds of the present invention is illustrated by the following tests performed on standard laboratory animals.

Test 1 - mice

5 The therapeutic activity of the compounds of formula I has been indicated by assessing the ability of the compounds to reverse the hypothermic effects of reserpine in the following manner. Male mice of the Charles River CD1 strain weighing between 18 and 30 g
10 were separated into groups of five and were supplied with food and water ad libitum. After five hours the body temperature of each mouse was taken orally and the mice were injected intraperitoneally with reserpine (10 mg/kg) in solution in deionised water containing
15 ascorbic acid (50 mg/ml). The amount of liquid injected was 10 ml/kg of body weight. Nine hours after the start of the test food was withdrawn but water was still available ad libitum. Twenty-four hours after the start of the test the temperatures of the mice were taken and
20 the mice were given the test compound orally at a dose volume of 10 ml/kg of body weight. The compound was administered in aqueous solution. Three hours later the temperatures of all the mice were again taken. The percentage reversal of the reserpine-induced fall in
25 body temperature was then calculated by the formula:

$$\frac{[(\text{Temp after 27hrs}) - (\text{Temp after 24hrs})] \times 100}{(\text{Temp after 5hrs}) - (\text{Temp after 24hrs})}$$

The percentage reversal value for each group of five mice was determined at more than one dose rate to enable
30 a value of the dose which causes a 50% reversal (ED_{50}) to be obtained. Examples of compounds which gave ED_{50} values of 30 mg/kg or less are given in Table 1. It is

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widely understood by those skilled in the art that this test is indicative of compounds having antidepressant activity in humans.

Test 2 - rats

- 5 The therapeutic activity of the compounds of formula I has been indicated by assessing the ability of the compounds to prevent the ptosis (eye closure) induced by reserpine in the following manner. Male rats of the Charles River CD strain weighing between 140 and
10 180 g were randomly separated into five rats in each cage and supplied with food and water ad libitum. Eighteen hours prior to initiation of the test four of the five rats were marked with a pen such that each rat was individually identifiable; food was then withdrawn.
15 The following morning, two hours before the test, the rats were weighed and a semi-randomised code was used to allocate treatments to rats. The test commenced by orally administering either:
- 20 a) the test compound in solution in deionised water at a dose volume of 10 ml/kg of body weight, followed by immediate intravenous injection of 1 ml/kg of body weight of reserpine (0.75 mg/kg) in solution in deionised water containing 238 mM citric acid, 1.02% v/v Tween 80 and 0.2% v/v benzyl alcohol
25 (treated group);
- 30 b) deionised water at a dose volume of 10 ml/kg of body weight, followed by immediate intravenous injection of 1 ml/kg of body weight of reserpine (0.75 mg/kg) in solution in deionised water containing 238 mM citric acid, 1.02% v/v Tween 80 and 0.2% v/v benzyl alcohol (positive control group); or

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- c) deionised water at a dose volume of 10 ml/kg of body weight, followed by immediate intravenous injection of 1 ml/kg of body weight of deionised water containing 238 mM citric acid, 1.02% v/v Tween 80 and 0.2% v/v benzyl alcohol (negative control group).

Three hours later rats were individually placed in clear perspex boxes (42 x 22 x 22 cm) and observed by a person who was unaware of the treatment received by each animal. The degree of ptosis was scored 45 seconds and 75 seconds later using the following observer rating system: 0 = eye fully open, 1 = eye 1/4 closed, 2 = eye 1/2 closed, 3 = eye 3/4 closed, 4 = eye fully closed. A mean ptosis score was then calculated for all identically treated rats usually comprising a group of eight rats. The mean ptosis score of the negative control group was then subtracted from the mean ptosis score of the positive control group to give the ptosis score induced by reserpine in the absence of the test compound. The mean ptosis score for each group of treated rats was determined at more than one dose of test compound to enable a value for the dose (ED_{50}) which causes a 50% prevention of the reserpine-induced ptosis to be obtained. Examples of compounds which gave ED_{50} values of 30 mg/kg or less are given in Table 1. It is widely understood by those skilled in the art that this test is indicative of compounds having antidepressant activity in humans.

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Table 1

Example No.	Test 1 ED ₅₀ (mg/kg)	Test 2 ED ₅₀ (mg/kg)
5	1	Inactive @ 30
	2	~16
	3	10.7
	4	Inactive @ 30
	5	~20
10	6	14.1
	7, 23	2.0
	8	16.4
	9	~11
	10	~18
15	11	~22
	12	11.9
	13	Inactive @ 30
	14	~12
	15	6.9
20	16	9.4
	17	~23
	18	4.8
	19	~14
	20	~26
	21	Inactive @ 30

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22	~30	10.1
24	~11.5	Inactive @ 30
25	Inactive @ 30	9.9
26	Inactive @ 30	5.6

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The invention is illustrated by the following Examples which are given by way of example only. The final products of each of these Examples were characterised by one or more of the following
5 procedures: gas-liquid chromatography, elemental analysis, nuclear magnetic resonance spectroscopy and infra-red spectroscopy.

Example A

A mixture of 1-aminocyclohexanecarboxylic acid
10 (62.4 g) and saturated ethanolic hydrogen chloride solution (400 ml) was heated under reflux for 7 hours then allowed to stand at ambient temperature for 2 days. The mixture was resaturated with hydrogen chloride and heated under reflux for a further 23 hours. The
15 solvent was removed in vacuo, and the residue diluted with ice-water and basified by the addition of an excess of 5 M aqueous sodium hydroxide solution. The product was extracted into ether, the extracts were washed with water, dried over magnesium sulphate, and the solvent
20 removed in vacuo to give ethyl 1-aminocyclohexanecarboxylate. Yield 50.6 g.

A mixture of ethyl 1-aminocyclohexanecarboxylate (37.1 g, prepared in a similar manner to that described above), potassium carbonate (37 g), and ethyl 4-bromo-
25 butyrate (42.3 g) was stirred at 100°C for 10 hours, cooled to ambient temperature and diluted with ice-water. The product was extracted into ether and the extracts were washed with water, dried over magnesium sulphate, and the solvent removed in vacuo to give an
30 oil (46.6 g). Unreacted ethyl 4-bromobutyrate was removed by distillation (bp 64°C at 1.6 mbar), and the residual ethyl 1-(3-ethoxycarbonylpropylamino)cyclo-

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hexanecarboxylate was used without further purification. Yield 30.5 g.

Sodium (8.9 g) was dissolved in ethanol (175 ml) and the solvent was removed in vacuo. The residue was
5 mixed at ambient temperature with ethyl 1-(3-ethoxy-carbonylpropylamino)cyclohexanecarboxylate (55.2 g, prepared in a similar manner to that described above) and the stirred mixture was heated to 145°C while ethanol formed in the reaction was removed by
10 distillation. When evolution of ethanol ceased, the residue was dissolved in hot propan-2-ol (185 ml). The solution was cooled to ambient temperature, diluted with water and acidified to pH 1 by the addition of concentrated hydrochloric acid. The solution was then
15 basified by the addition of an excess of solid potassium carbonate and the product was extracted into ethyl acetate. The extracts were dried over magnesium sulphate and the solvent removed in vacuo to yield ethyl 5-oxo-1-azaspiro[5.5]undecane-4-carboxylate. Yield
20 30.6 g.

A mixture of ethyl 5-oxo-1-azaspiro[5.5]undecane-4-carboxylate (13.9 g, prepared in a similar manner to that described above), concentrated hydrochloric acid (50 ml) and water (50 ml) was heated at 90-95°C for 5
25 hours. The solvent was removed in vacuo, and the residue diluted with ice-water (50 ml) and basified by the addition of an excess of 5 M aqueous sodium hydroxide solution. The product was extracted into ethyl acetate and the extracts were washed with brine,
30 dried over magnesium sulphate, and the solvent removed in vacuo to give 1-azaspiro[5.5]undecan-5-one as a pale brown solid. Yield 5.9 g, mp 55°C.

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Example B

Sodium (9.4 g) was dissolved in ethanol (185 ml) and the solvent removed in vacuo. The residue was mixed at ambient temperature with ethyl 1-(3-ethoxycarbonyl-
5 propylamino)cyclohexanecarboxylate (52.7 g, prepared in a similar manner to that described in Example A) and the stirred mixture was heated to 160°C while ethanol formed in the reaction was removed by distillation. When evolution of ethanol ceased, the last traces of solvent
10 were removed in vacuo to yield a solid which was cooled to ambient temperature, dissolved in a mixture of water (200 ml) and propan-2-ol (300 ml) and allowed to stand at ambient temperature for 48 hours. The solution was cooled in ice and acidified to pH 1 by the addition of
15 concentrated hydrochloric acid. The mixture was then basified by the addition of an excess of solid potassium carbonate and allowed to stand at ambient temperature for 24 hours. The product was extracted into ethyl acetate, the extracts dried over magnesium sulphate and
20 the solvent removed in vacuo to yield 1-azaspiro[5.5]-undecan-5-one as a pale brown solid. Yield 20.5 g, mp 55°C.

Examples C to I

A compound of formula R_1MgBr in which R_1 is as
25 defined in Table 2 was prepared under nitrogen by the dropwise addition of a solution of a compound of formula R_1Br (a g) in a solvent (b ml) which was ether (k) or tetrahydrofuran (l) or a mixture thereof to magnesium metal (c g) initially at ambient temperature, then, when
30 the exothermic reaction commenced, at reflux temperature. After the addition was complete, the mixture was stirred at ambient temperature for d hours.

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A solution of 1-azaspiro[5.5]undecan-5-one (e g) in a solvent which was ether (f' ml), tetrahydrofuran (f" ml) or a mixture thereof was then added dropwise at 0°C to the stirred solution of R₁MgBr. The mixture was
5 stirred for g hours at ambient temperature in Examples C to G and under reflux in Examples H and I. The reaction mixture (cooled if necessary) was then quenched by cautious addition to a saturated aqueous ammonium chloride solution. The product was extracted into ethyl
10 acetate and the extracts were washed with water, dried over magnesium sulphate and the solvent removed in vacuo.

The crude products were purified by procedures identified in the column headed "Nb" to give compounds
15 of structure I in which R₄ is hydroxy and R₅ is H (h g).

Notes to Table 2

In the column headed mp(°C), the letters "ND" indicate that the melting point was not determined.

2.1 The crude product was triturated with petroleum
20 ether (bp 40-60°C) to yield the free base as a solid.

2.2 The crude product was triturated with ethyl acetate to yield the free base as a solid.

2.3 Low-boiling impurities were removed by distillation
25 in vacuo at 100°C at 0.6 mbar to leave a brown oil. The oil was triturated with ethyl acetate to yield the free base as a solid.

2.4 The crude product was triturated with ethyl acetate to yield a solid which was purified further via preparative scale high performance liquid chromatography

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over silica using methanol as eluent. Appropriate fractions were combined and the solvent removed in vacuo to yield the free base as a solid.

TABLE 2

Ex No	R ₁	a	b	c	d	e	f'	f"	g	h	Nb	mp (°C)
C	4-Chloro-phenyl	39.7	263 (k)	4.98	0.5	14.31	97	0	24	9.62	2.1	143-145
D	3-Chloro-phenyl	14.2	75 (k)	1.78	0.5	5.0	340	100	2.5	4.28	2.2	128-130
E	3,4-Dichloro-phenyl	36.4	180 (l)	3.9	1.5	8.6	0	80	48	3.55	2.2	ND
F	4-Fluoro-phenyl	6.37	35 (l)	0.9	2.5	2.5	0	20	24	1.00	2.2	170-171.5
G	3-(Tri-fluoro-methyl)-phenyl	19.35	100 (k)	2.1	1.0	6.0	20	60	24	3.15	2.2	ND
H	4-Methoxy-phenyl	60.36	170 (k) 100 (l)	3.8	0.5	10.0	0	100	24	3.89	2.3	ND
I	2-Naphthyl	27.8	100 (k) 100 (l)	2.3	1.0	6.6	0	70	24	2.20	2.4	ND

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Example J

4-Chlorophenylmagnesium bromide was prepared under nitrogen by the dropwise addition of a solution of 4-bromochlorobenzene (20.35 g) in ether (160 ml) to
5 magnesium metal (2.6 g) initially at ambient temperature, then, when the exothermic reaction commenced, at reflux temperature. After the addition was complete, the mixture was stirred at ambient temperature for 1 hour.

10 The stirred solution was then heated to reflux temperature and a solution of 1-azaspiro[5.5]undecan-5-one (9.7 g, prepared as described in Example A) in toluene (160 ml) was added dropwise whilst the ether was removed by distillation until the internal temperature
15 rose to approximately 95°C. The mixture was then heated under reflux for 2 hours, allowed to cool to ambient temperature, and then quenched by addition to an excess of saturated aqueous ammonium chloride solution. The product was extracted into ethyl acetate (3 x 300 ml)
20 and the extracts were combined and dried over magnesium sulphate. The solvent was removed in vacuo and the residue triturated with ethyl acetate. The resulting solid was collected by filtration, washed with ethyl acetate, and dried in vacuo at ambient temperature to
25 give 5-(4-chlorophenyl)-5-hydroxy-1-azaspiro[5.5]-undecane as a white solid. Yield 6.7 g, mp 158-164°C.

Examples 1 to 3

The compounds of formula I prepared in Examples C to E were converted into their hydrochloride salts by
30 saturating ethereal solutions of the compounds with hydrogen chloride. The melting points of the resulting hydrochloride salts are given in Table 3.

TABLE 3

Ex No.	Starting Material	mp (°C)
1	C	>250 (dec)
2	D	294-295 (dec)
3	E	307 (dec)

Example 4

A mixture of 5-(4-chlorophenyl)-5-hydroxy-1-azaspiro[5.5]undecane (3 g, prepared as described in Example C) and acetic anhydride (45 ml) was heated at 90-95°C for 16 hours. The excess of acetic anhydride was removed in vacuo and the residue triturated with ether to yield a solid which was collected by filtration. The filtrate was allowed to stand at ambient temperature for 1 hour, facilitating the precipitation of further solid, which was collected by filtration.

A mixture of the combined solids (2.3 g) and tetrahydrofuran (21 ml) was heated to reflux temperature under nitrogen and borane-methyl sulphide complex (2.3 g) was added dropwise over 35 minutes whilst dimethyl sulphide was removed by distillation. After the addition was complete, the mixture was heated under reflux for 4.5 hours then the solvent was removed in vacuo and the residue was heated to 100°C. 5 M hydrochloric acid (1.5 ml) and water (12.4 ml) were added and the solution was heated at 100°C for 45

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minutes. The mixture was then cooled to ambient temperature and 5 M aqueous sodium hydroxide solution (2.3 ml) was added.

The solution was then saturated with solid
5 potassium carbonate and the product was extracted into ether. The extracts were washed with water, dried over magnesium sulphate and the solvent was removed in vacuo to yield an oil (1.7 g). The oil was combined with further oil (0.4 g, prepared in a similar manner) of
10 similar purity, and purified by flash chromatography over silica using a 9:1 mixture of dichloromethane and ethyl acetate as eluent. Appropriate fractions were combined, the solvents removed in vacuo, and the resulting oil (1.9 g) was distilled to give an oil.
15 Yield 1.3 g, bp 150-155°C at 0.4-0.5 mbar.

The oil (1.3 g) was dissolved in ether (20 ml) and the solution saturated with hydrogen chloride. The solvent was removed in vacuo and the residue was triturated with a mixture of dichloromethane and ether.
20 The resulting solid was collected by filtration and dried in vacuo at ambient temperature to give 5-(4-chlorophenyl)-1-ethyl-5-hydroxy-1-azaspiro[5.5]undecane hydrochloride as an off-white solid. Yield 0.6 g, mp 146-148°C.

25 Example 5

5-(4-Chlorophenyl)-5-hydroxy-1-azaspiro[5.5]-undecane (5.9 g, prepared as described in Example C) was dissolved in concentrated sulphuric acid (75 ml) and stirred at ambient temperature for 3 hours. The mixture
30 was then poured slowly into ice-water (300 ml) and the resulting solid collected by filtration, washed with a little water and dried in vacuo at ambient temperature

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over phosphorus pentoxide to give 5-(4-chlorophenyl)-1-azaspiro[5.5]undec-4-ene sulphate as a white solid. Yield 6.2 g, mp 228-233°C.

Example 6

5 A mixture of 5-(4-chlorophenyl)-1-azaspiro-
[5.5]undec-4-ene sulphate (0.5 g, prepared as described
in Example 5) and water (5 ml) was stirred at ambient
temperature to give, initially, a mobile suspension
which rapidly thickened. Water (5 ml) was added to aid
10 mobility and the solid was collected by filtration,
washed with water (5 ml) and dried in vacuo at ambient
temperature to give 5-(4-chlorophenyl)-1-azaspiro[5.5]-
undec-4-ene 0.5 sulphate, 2.1 hydrate as a white solid.
Yield 0.3 g, mp 205-215°C.

15 Example 7

 A suspension of 5-(4-chlorophenyl)-1-azaspiro-
[5.5]undec-4-ene sulphate (13 g prepared in a similar
manner to that described in Example 5) in 1 M aqueous
sodium hydroxide solution (200 ml) was stirred at
20 ambient temperature for 1 hour, then the free base was
extracted into ether (3 x 150 ml). The extracts were
combined, dried over magnesium sulphate, concentrated to
a volume of 150 ml, and filtered. The filtrate was
cooled in ice and saturated with hydrogen chloride. The
25 resulting solid was collected by filtration, washed with
ether, and dried in vacuo at ambient temperature for 24
hours and at 60°C for 8 hours to give 5-(4-chloro-
phenyl)-1-azaspiro[5.5]undec-4-ene hydrochloride as a
white solid. Yield 8.6 g, mp >300°C.

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Example 8

5-(3-Chlorophenyl)-5-hydroxy-1-azaspiro[5.5]-undecane (2.5 g, prepared as described in Example D) was dissolved in concentrated sulphuric acid (35 ml) and stirred at ambient temperature for 2 hours. The mixture was then poured cautiously onto ice (100 ml) and the resulting white precipitate was collected by filtration and suspended in ethyl acetate (300 ml). 5 M Aqueous sodium hydroxide solution (250 ml) was added and the mixture was stirred at ambient temperature for 15 minutes. The aqueous layer was separated and extracted with ethyl acetate (2 x 200 ml), then the combined organic solutions were washed with water, dried over magnesium sulphate and the solvent removed in vacuo. The resulting oil was dissolved in ether (100 ml), charcoal (1 g) was added, and the mixture was heated under reflux for 5 minutes and hot-filtered. The cooled filtrate was saturated with hydrogen chloride and the resulting solid collected, washed with ether and dried in vacuo at ambient temperature to give 5-(3-chlorophenyl)-1-azaspiro[5.5]undec-4-ene hydrochloride as a white solid. Yield 2.1 g, mp 281-282°C (dec).

Example 9

5-(3,4-Dichlorophenyl)-5-hydroxy-1-azaspiro[5.5]-undecane (3.0 g, prepared as described in Example E) was dissolved in concentrated sulphuric acid (35 ml) and stirred at ambient temperature for 4 hours, then the mixture was poured cautiously onto ice (100 ml). The resulting white precipitate was collected by filtration and suspended in 5 M aqueous sodium hydroxide solution (200 ml). The mixture was stirred at ambient temperature for 15 minutes, then the product was extracted into ether (2 x 250 ml). The combined extracts

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were washed with water, dried over magnesium sulphate and filtered. The filtrate was cooled in ice, saturated with hydrogen chloride and the resulting solid collected by filtration, washed with ether and dried in vacuo at
5 ambient temperature to give 5-(3,4-dichlorophenyl)-1-azaspiro[5.5]undec-4-ene hydrochloride as a white solid. Yield 2.5 g, mp 332°C (dec).

Example 10

5-(4-Fluorophenyl)-5-hydroxy-1-azaspiro[5.5]-
10 undecane (1.27 g, prepared in a similar manner to that described in Example F) was dissolved in concentrated sulphuric acid (25 ml) and stirred at ambient temperature for 2 hours, then the solution was carefully poured onto ice (50 ml), and the sticky solid collected
15 by filtration. The solid was triturated with ether (2 x 50 ml), collected by filtration, washed with ether and dried in vacuo at ambient temperature to give a solid which was triturated with hot ether (70 ml), collected by filtration washed with ether and dried in
20 vacuo at 60°C to give 5-(4-fluorophenyl)-1-azaspiro[5.5]undec-4-ene sulphate as a white solid. Yield 1.3 g, mp 195-200°C.

Example 11

5-Hydroxy-5-[3-(trifluoromethyl)phenyl]-1-azaspiro-
25 [5.5]undecane (2.2 g, prepared as described in Example G) was dissolved in concentrated sulphuric acid (25 ml) and stirred at ambient temperature for 4 hours. The mixture was poured cautiously onto ice (100 ml) and the resulting white precipitate was collected by filtration,
30 and suspended in 5 M aqueous sodium hydroxide solution (250 ml). The mixture was stirred at ambient temperature for 15 minutes then the product was

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extracted into ethyl acetate (2 x 125 ml). The combined extracts were washed with water, dried over magnesium sulphate and the solvent removed in vacuo. The resulting oil was dissolved in ether and the solution
5 was filtered. The filtrate was cooled in ice, saturated with hydrogen chloride and the resulting solid collected by filtration, washed with ether and dried in vacuo at ambient temperature to give 5-[3-(trifluoromethyl)-phenyl]-1-azaspiro[5.5]undec-4-ene hydrochloride as a
10 white solid. Yield 1.0 g, mp >250°C (sublimes).

Example 12

A mixture of 5-hydroxy-5-(2-naphthyl)-1-azaspiro[5.5]undecane (2.1 g, prepared as described in Example I), p-toluenesulphonic acid (1.62 g) and toluene
15 (500 ml) was heated under reflux for 20 hours while water evolved in the reaction was removed by azeotropic distillation (Dean-Stark apparatus). More toluene (500 ml) and p-toluenesulphonic acid (2.4 g) were added, and heating under reflux continued for a further 35
20 hours. The cooled mixture was poured into 5 M aqueous sodium hydroxide solution (500 ml) and stirred vigorously for 5 minutes. Ethyl acetate (250 ml) was added and stirring continued for 5 minutes. The aqueous layer was separated and further extracted with ethyl
25 acetate (2 x 500 ml). The organic solutions were combined, washed with water, dried over magnesium sulphate and the solvents removed in vacuo to give an oil. The oil was purified by flash-chromatography over silica using toluene/triethylamine (95:5) as the eluent.
30 Appropriate fractions were combined and the solvents removed in vacuo. The resulting oil was dissolved in ether, the solution was filtered, and the filtrate cooled in ice and saturated with hydrogen chloride. The resulting solid was collected by filtration, washed with

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ether and dried in vacuo at ambient temperature to give 5-(2-naphthyl)-1-azaspiro[5.5]undec-4-ene hydrochloride as a white solid. Yield 1.8 g, mp 297-302°C.

Example 13

5 A mixture of 5-hydroxy-5-(4-methoxyphenyl)-1-azaspiro[5.5]undecane (2.8 g, prepared as described in Example H), p-toluenesulphonic acid (2.3 g) and toluene (150 ml) was heated under reflux for 17 hours while water evolved in the reaction was removed by azeotropic
10 distillation (Dean-Stark apparatus). The cooled mixture was poured onto 5 M aqueous sodium hydroxide solution (500 ml) and stirred vigorously for 5 minutes. Ethyl acetate (250 ml) was added and stirring continued for 5 minutes. The aqueous layer was separated and further
15 extracted with ethyl acetate (2 x 500 ml). The organic solutions were combined, washed with water, dried over magnesium sulphate and the solvents removed in vacuo to give an oil. The oil was dissolved in ether, the solution filtered, and the filtrate cooled in ice and
20 saturated with hydrogen chloride. The resulting solid was collected by filtration, washed with ether and dried in vacuo at ambient temperature to give 5-(4-methoxyphenyl)-1-azaspiro[5.5]undec-4-ene hydrochloride as a white solid. Yield 2.7 g, mp 257-266°C (dec).

25 A mixture of 5-(4-methoxyphenyl)-1-azaspiro[5.5]-undec-4-ene hydrochloride (1.0 g), glacial acetic acid (20 ml) and hydrobromic acid (48%, 20 ml) was heated under reflux for 6.5 hours then allowed to cool. The mixture was neutralised by the addition of saturated
30 aqueous sodium hydrogen carbonate solution and the product extracted into ether (3 x 100 ml). The extracts were combined, dried over magnesium sulphate and the solvent removed in vacuo to give a solid which was

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purified via flash chromatography over silica using toluene/triethylamine (4:1) as eluent. Appropriate fractions were combined, the solvents were removed in vacuo, and the resulting product was dissolved in ether.

5 The solution was filtered, and the filtrate cooled in ice and saturated with hydrogen chloride. The resulting solid was collected by filtration, washed with ether and dried in vacuo at ambient temperature to give 5-(4-hydroxyphenyl)-1-azaspiro[5.5]undec-4-ene hydrochloride

10 as a white solid. Yield 0.7 g, mp 285-295°C.

Example 14

5-(4-Chlorophenyl)-5-hydroxy-1-azaspiro[5.5]-undecane (5.1 g, prepared in a similar manner to that described in Example C) was dissolved in concentrated

15 sulphuric acid (70 ml) and stirred at ambient temperature for 4 hours. The mixture was poured onto ice (300 ml) and the resulting solid was collected by filtration, suspended in water (150 ml) and basified by addition of 5 M aqueous sodium hydroxide solution. The

20 resulting solid, 5-(4-chlorophenyl)-1-azaspiro[5.5]-undec-4-ene, was collected by filtration and dried in vacuo at ambient temperature.

A mixture of the solid (4.5 g) and ethyl formate (300 ml) was heated under reflux for 48 hours. The

25 mixture was concentrated in vacuo to a small volume and the resulting solid collected by filtration and crystallised from ethyl acetate (60 ml) (the hot solution was decolourised by addition of charcoal) to give 5-(4-chlorophenyl)-1-azaspiro[5.5]undec-4-ene

30 formate as a white solid. Yield 1.7 g, mp 136-140°C.

A mixture of 5-(4-chlorophenyl)-1-azaspiro[5.5]-undec-4-ene formate (1.7 g), formic acid (15 ml) and

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37-40% aqueous formaldehyde solution (30 ml) was heated at approximately 95°C for 7.5 hours, then cooled in ice. The mixture was basified by the addition of 5 M aqueous sodium hydroxide solution, and the product extracted into ethyl acetate (2 x 150 ml). The extracts were combined, dried over magnesium sulphate and the solvent removed in vacuo to leave an oil which solidified slowly at ambient temperature. The solid was triturated with ether and the mixture filtered. The filtrate was evaporated to leave an oily residue which was dissolved in ether, dried over magnesium sulphate and the solvent removed in vacuo to leave an oil which solidified slowly at ambient temperature. Yield 1.3 g.

The solid was dissolved in ether (80 ml), the solution was filtered, and the filtrate cooled in ice and saturated with hydrogen chloride. The resulting solid was collected by filtration, washed with ether and dried in vacuo at 70°C to give 5-(4-chlorophenyl)-1-methyl-1-azaspiro[5.5]undec-4-ene hydrochloride as a white solid. Yield 1.2 g, mp 243-248°C (dec).

Example 15

A solution of fumaric acid (0.4 g) in methanol (35 ml) was added to a solution of 5-(4-chlorophenyl)-1-azaspiro[5.5]undec-4-ene (1.0 g, prepared in a similar manner to that described in Example 14) in ether (25 ml). The solvents were removed in vacuo and the residue was triturated with ether to yield a white solid, which was collected by filtration and dried in vacuo at ambient temperature to give 5-(4-chlorophenyl)-1-azaspiro[5.5]undec-4-ene fumarate as a white solid. Yield 1.1 g, mp 175-180.5°C (dec).

Example 16

A solution of methanesulphonic acid (0.3 g) in ether (15 ml) was added dropwise to a cooled solution of 5-(4-chlorophenyl)-1-azaspiro[5.5]undec-4-ene (0.8 g, prepared in a similar manner to that described in Example 14) in ether (25 ml). The resulting solid was collected by filtration, washed with ether and dried in vacuo at ambient temperature to yield 5-(4-chlorophenyl)-1-azaspiro[5.5]undec-4-ene methanesulphonate as a white solid. Yield 1.0 g, mp 226-231.5°C.

Example 17

A mixture of 1-aminocyclopentanecarboxylic acid (50.0 g) and saturated ethanolic hydrogen chloride solution (350 ml) was heated under reflux for 6 hours. The mixture was cooled, the solvent was removed in vacuo and the residue diluted with water (150 ml). The resulting solution was basified by the addition of an excess of 5 M aqueous sodium hydroxide solution and the product was extracted into ether. The extracts were dried over magnesium sulphate and the solvent removed in vacuo to give ethyl 1-aminocyclopentanecarboxylate. Yield 19.6 g.

The aqueous phase was acidified by the addition of 5 M hydrochloric acid and the solvent removed in vacuo. The solid residue was mixed with saturated ethanolic hydrogen chloride solution (230 ml) and the mixture was heated under reflux for 6 hours. The mixture was cooled, the solvent was removed in vacuo and the residue diluted with cold water (100 ml). The mixture was basified by the addition of 5 M aqueous sodium hydroxide solution and the product was extracted into ether. The extracts were washed with water, dried over magnesium

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sulphate and the solvent removed in vacuo to give further ethyl 1-aminocyclopentanecarboxylate. Yield 24.3 g.

5 A mixture of ethyl 1-aminocyclopentanecarboxylate (43.9 g), potassium carbonate (47.8 g) and ethyl 4-bromobutyrate (54.5 g) was stirred at 100°C for 10 hours, cooled to ambient temperature and diluted with ice-water. The product was extracted into ether and the extracts were washed with water, dried over magnesium sulphate and the solvent removed in vacuo to give an oil 10 (61.1 g) which was distilled to give ethyl 1-(3-ethoxycarbonylpropylamino)cyclopentanecarboxylate as a colourless oil. Yield 49.5 g, bp 109-124°C at 0.6 mbar.

15 Sodium (8.4 g) was dissolved in ethanol (170 ml) and the solvent was removed in vacuo. The residue was mixed at ambient temperature with ethyl 1-(3-ethoxycarbonylpropylamino)cyclopentanecarboxylate (49.5 g) and the stirred mixture was heated to 100°C while ethanol formed in the reaction was removed by 20 distillation. When evolution of ethanol ceased, the residue was dissolved in hot propan-2-ol (150 ml). The solution was cooled to ambient temperature, diluted with water and acidified to pH 1 by the addition of concentrated hydrochloric acid. The solution was then 25 basified by the addition of an excess of solid potassium carbonate and the product was extracted into ethyl acetate. The extracts were dried over magnesium sulphate and the solvent removed in vacuo to give ethyl 10-oxo-6-azaspiro[4.5]decan-9-carboxylate. Yield 7.6 g.

30 A mixture of ethyl 10-oxo-6-azaspiro[4.5]decan-9-carboxylate (7.6 g), concentrated hydrochloric acid (35 ml) and water (35 ml) was heated at 90-95°C for 8 hours. The solvent was removed in vacuo and the

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residue diluted with ice-water (35 ml) and basified by the addition of an excess of 5 M aqueous sodium hydroxide solution. The product was extracted into ethyl acetate and the extracts were washed with brine, 5 dried over magnesium sulphate and the solvent removed in vacuo to give 6-azaspiro[4.5]decan-10-one. Yield 3.1 g.

4-Chlorophenylmagnesium bromide was prepared under nitrogen by the dropwise addition of a solution of 4-bromochlorobenzene (9.6 g) in ether (55 ml) to magnesium 10 metal (1.2 g) initially at ambient temperature then, when the exothermic reaction commenced, at reflux temperature. After the addition was complete the mixture was stirred at ambient temperature for 30 minutes. A solution of 6-azaspiro[4.5]decan-10-one 15 (3.1 g, prepared as described above) in ether (25 ml) was added dropwise at 0°C, and the mixture was stirred for 24 hours at ambient temperature. The reaction was quenched by the slow addition of an excess of saturated aqueous ammonium chloride solution, and the resulting 20 solid collected by filtration. The solid was suspended in water and basified by the addition of an excess of 5 M aqueous sodium hydroxide solution. The product was extracted into ethyl acetate (3 x 100 ml), the extracts were dried over magnesium sulphate and the solvent 25 removed in vacuo to give 10-(4-chlorophenyl)-10-hydroxy-6-azaspiro[4.5]decane as an off-white solid. Yield 1.6 g, mp 152-155°C.

10-(4-Chlorophenyl)-10-hydroxy-6-azaspiro-
[4.5]decane (1.6 g) was dissolved in concentrated 30 sulphuric acid (18 ml) and stirred at ambient temperature for 1.5 hours. The mixture was poured cautiously onto ice-water (35 ml), stirred at 0°C for 1 hour and allowed to stand at 4°C for 24 hours. The product was collected by filtration, washed with water

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and dried in vacuo at ambient temperature to give 10-(4-chlorophenyl)-6-azaspiro[4.5]dec-9-ene sulphate as an off-white solid. Yield 1.7 g, mp 184-190°C.

Example 18

5 A mixture of 5-(4-chlorophenyl)-1-azaspiro[5.5]undec-4-ene (2.8 g, obtained by basification of the hydrochloride salt prepared as described in Example 7), 10% platinum-on-carbon catalyst (0.24 g), ethanol (50 ml) and 2.5 M hydrochloric acid
10 (10 ml) was hydrogenated at 1 atmosphere and ambient temperature until hydrogen uptake ceased (2.5 hours), then the mixture was filtered to remove spent catalyst and the solvents were removed in vacuo.

15 The residue was dissolved in ethanol (80 ml) and the solution was added to fresh 10% platinum-on-carbon catalyst (0.23 g). The mixture was hydrogenated at 1 atmosphere and ambient temperature for 4 hours, then spent catalyst was removed by filtration, and the solvent was removed in vacuo. The residue was purified
20 via reduced pressure flash chromatography over silica, using a 9:1 mixture of toluene and triethylamine containing a trace of ethanol as eluent. Appropriate fractions were combined and the solvents removed in vacuo to leave a solid (2.3 g). The solid was suspended
25 in propan-2-ol (25 ml) and the mixture was heated under reflux, filtered while hot, and allowed to cool. The resulting solid was collected by filtration and dried in vacuo to give a white solid (0.24 g). Concentration of the liquor yielded a second crop of white solid
30 (0.46 g).

The solids were combined, dissolved in ether (35 ml) and the solution was saturated with hydrogen

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chloride. The resulting solid was collected by filtration and dried in vacuo at 95°C to give 5-(4-chlorophenyl)-1-azaspiro[5.5]undecane hydrochloride as a white solid. Yield 0.6 g, mp 311-312°C (softens 299°C).

5 Example 19

A mixture of 5-(4-methoxyphenyl)-1-azaspiro[5.5]undec-4-ene hydrochloride, (0.6 g, prepared as described in Example 13), 10% palladium-on-carbon catalyst (0.18 g), ethanol (40 ml) and water (20 ml) was
10 hydrogenated at 1 atmosphere and ambient temperature until hydrogen uptake ceased. The mixture was filtered to removed spent catalyst, then the solvents were removed in vacuo to leave a white solid (0.6 g). The
solid was triturated with ether (25 ml), collected by
15 filtration and dried in vacuo to give 5-(4-methoxyphenyl)-1-azaspiro[5.5]undecane hydrochloride as a white solid. Yield 0.5 g, mp 287-289°C (shrinks 285°C).

Example 20

20 A mixture of 5-(4-chlorophenyl)-1-azaspiro[5.5]undec-4-ene hydrochloride (2.0 g, prepared as described in Example 7), 1-bromopropane (1 ml), potassium carbonate (2.0 g) and dimethylformamide (10 ml) was stirred at ambient temperature for 24 hours,
25 and at 95°C for 24 hours. More bromopropane (1 ml) and a catalytic amount of potassium iodide (10 mg) were added and stirring at 95°C continued for a further 24 hours. More bromopropane (1 ml) was added, and stirring at 95°C continued for a further 24 hours.

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The mixture was cooled to ambient temperature, diluted with 1 M aqueous sodium hydroxide solution (100 ml), and the product extracted into ethyl acetate (3 x 50 ml). The extracts were combined, washed with
5 water (2 x 30 ml), dried over magnesium sulphate, and the solvent removed in vacuo to leave a brown oil. The oil was dissolved in ether (50 ml) and the solution saturated with hydrogen chloride. The resulting solid was collected by filtration, washed with ether, and
10 dried in vacuo at ambient temperature to give 5-(4-chlorophenyl)-1-propyl-1-azaspiro[5.5]undec-4-ene hydrochloride as an off-white solid. Yield 1.9 g, mp 245-246°C, (shrinks 230°C).

Example 21

15 A mixture of 5-(4-chlorophenyl)-1-azaspiro[5.5]undec-4-ene hydrochloride (2.0 g, prepared as described in Example 7), potassium carbonate (2.0 g), allyl bromide (2.9 ml) and dimethylformamide (25 ml) was stirred at 95°C for 17 hours, then allowed to cool to
20 ambient temperature. The mixture was diluted with water (60 ml) and basified by the addition of 5 M aqueous sodium hydroxide solution (50 ml), then the product was extracted into ethyl acetate (3 x 100 ml). The extracts were combined, dried over magnesium sulphate, and the
25 solvent removed in vacuo to leave a brown oil which was purified via flash chromatography over silica using a 99:1 mixture of dichloromethane and industrial methylated spirit as eluent. Appropriate fractions were combined and the solvents removed in vacuo to leave a
30 yellow oil (1.4 g) which was dissolved in ether (50 ml). The solution was filtered and added to an ice-cold solution of maleic acid (0.53 g) in ether (150 ml). The resulting solid was collected by filtration, washed with ether, and dried in vacuo at 50°C to give 1-allyl-5-(4-

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chlorophenyl)-1-azaspiro[5.5]undec-4-ene maleate as a white solid. Yield 1.2 g, mp 130-133°C (shrinks 125°C).

Example 22

A mixture of 5-(4-chlorophenyl)-1-azaspiro[5.5]undec-4-ene (1.5 g, obtained by basification of the hydrochloride salt prepared as described in example 7), potassium carbonate (1.6 g), 2-methoxyethyl bromide (2.7 ml), and dimethylformamide (28 ml) was stirred at 95°C for 67 hours and allowed to cool to ambient temperature. The mixture was diluted with 1 M aqueous sodium hydroxide solution (150 ml), and the product extracted into ethyl acetate (3 x 150 ml). The extracts were combined, washed with water (2 x 100 ml), dried over magnesium sulphate and the solvent removed in vacuo to leave a yellow oil (1.6 g). The oil was combined with another sample (0.2 g, prepared in a similar manner) and purified via flash chromatography over silica using a 95:5 mixture of toluene and triethylamine as eluent. Appropriate fractions were combined and the solvents removed in vacuo to leave an oil which was dissolved in ether (50 ml). The solution was cooled in ice and saturated with hydrogen chloride. The resulting solid was collected by filtration, washed with ether and dried in vacuo at 50°C for 7 hours to give 5-(4-chlorophenyl)-1-(2-methoxyethyl)-1-azaspiro[5.5]undec-4-ene 1.25 hydrochloride as a white solid. Yield 0.7 g, mp 135°C (dec) (softens 95-100°C).

Example 23

Ethanol (4 l) was saturated at 0-5°C over 4 hours with hydrogen chloride. 1-Aminocyclohexanecarboxylic acid (600 g) was added in one portion and the mixture

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was stirred and heated under reflux for 8 hours, then allowed to stand at ambient temperature for 72 hours. The solvent was removed in vacuo and the residue was dissolved in ice-water (1 l) and basified to pH 8-9 at 0-5°C by the addition of 2 M aqueous sodium hydroxide solution. The product was extracted into dichloromethane (4 x 300 ml) and the extracts were combined and dried over sodium sulphate. The aqueous residues were basified to pH 10 by the addition of more 2 M aqueous sodium hydroxide solution and further product was extracted into dichloromethane (4 x 200 ml). The extracts were combined and dried over sodium sulphate. The dried dichloromethane extracts were combined and the solvent was removed in vacuo to leave ethyl 1-aminocyclohexanecarboxylate as a pale yellow oil. Yield 669 g.

A mixture of ethyl 1-aminocyclohexanecarboxylate (669 g), potassium carbonate (683.1 g) and ethyl 4-bromobutyrate (558 ml) was stirred at 130°C for 18 hours, then cooled to ambient temperature and poured onto ice-water (3 l). The product was extracted into dichloromethane and the combined extracts were dried over sodium sulphate and the solvent was removed in vacuo to yield ethyl 1-(3-ethoxycarbonylpropylamino)-cyclohexanecarboxylate as a brown/orange oil. Yield 943.2 g.

Sodium (8.92 g) was dissolved in ethanol (150 ml) and the solvent was removed in vacuo. Ethyl 1-(3-ethoxycarbonylpropylamino)cyclohexanecarboxylate (50 g) was added and the mixture was stirred at 140°C while ethanol formed in the reaction was removed by distillation. When evolution of ethanol ceased the mixture was allowed to cool to ambient temperature to yield an orange foam. A solution of concentrated

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hydrochloric acid (150 ml) in water (150 ml) was added and the mixture was heated at 95°C for 7 hours. Charcoal was added and the mixture was filtered (hot) through "celite", cooled to ambient temperature, washed
5 with ethyl acetate (2 x 150 ml), and basified below 20°C by the addition of 5 M aqueous sodium hydroxide solution. The product was extracted into dichloromethane (5 x 250 ml) and the combined extracts were washed with water (200 ml), dried over sodium
10 sulphate and the solvent removed in vacuo to yield 1-azaspiro[5.5]undecan-5-one as a beige solid. Yield (18.6 g).

The reaction was repeated twice more on the following scale:

15 sodium (159.3 g)
ethanol (1500 ml)
ethyl 1-(3-ethoxycarbonylpropylamino)-
cyclohexanecarboxylate (447 g);
Then
20 concentrated hydrochloric acid (1000 ml)
water (1000 ml).
Overall combined yield 245.11 g.

A solution of 1-azaspiro[5.5]undecan-5-one (132.5 g) in toluene (1900 ml) was added under nitrogen
25 over 45 minutes to stirred 4-chlorophenylmagnesium bromide (1 M solution in ether; 1904 ml) while the ether solvent was removed by distillation at a rate equivalent to the addition of the toluene solution. After the addition was complete the mixture was stirred
30 at 95°C for a further 3 hours, cooled to 20°C and quenched by the dropwise addition of saturated aqueous ammonium chloride solution (1 l). The mixture was filtered through "celite" and the filter bed washed with

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water and ethyl acetate. The filtrate was separated and the aqueous layer extracted with ethyl acetate. The combined organic solutions were washed with water (500 ml) and the product was extracted into 5 M
5 hydrochloric acid (4 x 250 ml). This caused some hydrochloride salt of the product to precipitate; the solid was collected by filtration and washed with ethyl acetate. The filtrate was separated, and the aqueous
10 layer was washed with ethyl acetate, combined with the solid hydrochloride salt and basified by the addition of 5 M aqueous sodium hydroxide solution. The product was extracted into dichloromethane and the combined extracts were washed with water, dried over sodium sulphate and the solvent removed in vacuo to yield a pale yellow
15 solid (136.6 g). The solid was triturated with petroleum ether (bp 40-60°C) (500 ml) to give a solid which was collected by filtration and dried in vacuo to give 5 - (4 - chlorophenyl) - 5 - hydroxy - 1 - azaspiro[5.5]undecane as a pale cream solid. Yield
20 105.2 g.

The reaction was repeated using:

4-Chlorophenylmagnesium bromide (1 M solution in
ether, 1618 ml)
1-azaspiro[5.5]undecan-5-one (112.6 g)
25 Toluene (1.6 l)
Aqueous ammonium chloride solution (1 l).

although the work-up was different: after quenching with ammonium chloride solution, the mixture was filtered through "celite" and the layers separated. The
30 aqueous layer was twice further extracted with ethyl acetate and the combined organic solutions were dried over sodium sulphate and the solvents removed in vacuo to leave an oil. The "celite" filter cake was boiled

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with ethyl acetate and the mixture was hot filtered through "celite". The filtrate was combined with the oil and the solvent was removed in vacuo. The residue was triturated with ice-cold petroleum ether
5 (bp 60-80°C) (1000 ml) to give a solid which was collected by filtration and dried in vacuo to give 5-(4-chlorophenyl)-5-hydroxy-1-azaspiro[5.5]undecane as a beige solid. Yield 129.5 g.

5 - (4 - C h l o r o p h e n y l) - 5 - h y d r o x y - 1 -
10 azaspiro[5.5]undecane (105.1 g) was added in portions to vigorously stirred concentrated sulphuric acid (600 ml) over 20 minutes, then the mixture was stirred at ambient temperature for a further 1 hour and poured carefully onto ice (2 l) causing a white solid to precipitate.
15 The mixture was cooled in ice for 2 hours and the solid was collected by filtration. The solid was basified by addition to an excess of 5 M aqueous sodium hydroxide solution and the product was extracted into ether (4 x 200 ml) followed by dichloromethane (2 x 250 ml).
20 The extracts were combined, dried over sodium sulphate and the solvents removed in vacuo to give 5-(4-chlorophenyl)-1-azaspiro[5.5]undec-4-ene as a cream solid. Yield 98 g.

The reaction was repeated using 5-(4-chlorophenyl)-
25 5-hydroxy-1-azaspiro[5.5]undecane (129.5 g) and concentrated sulphuric acid (600 ml). Yield 122.5 g.

5 M Hydrochloric acid (200 ml) was added slowly to a solution of 5-(4-chlorophenyl)-1-azaspiro[5.5]undec-4-ene (98 g) in ether (1 l) and the mixture was stirred at
30 ambient temperature for 30 minutes. The resulting solid was collected by filtration and washed with cold water followed by dichloromethane to give an off-white solid. The process was repeated using the remainder of 5-(4-

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chlorophenyl)-1-azaspiro[5.5]undec-4-ene to give further off-white solid. The combined solids were stirred in dichloromethane (1 l) for 1 hour, collected by filtration, washed with dichloromethane (200 ml) and
5 dried in vacuo to give 5-(4-chlorophenyl)-1-azaspiro[5.5]undec-4-ene hydrochloride as an off-white solid. Yield 224.3 g, mp >300°C.

Example 24

A solution of 2-bromochlorobenzene (36.7 ml) in
10 ether (260 ml) was added dropwise under nitrogen to magnesium metal (3.8 g) initially at ambient temperature, then, when the exothermic reaction commenced, at reflux temperature. After the addition was complete the mixture was stirred at ambient
15 temperature for 1 hour. A solution of 1-azaspiro[5.5]undecan-5-one (12.5 g, prepared as described in Example B) in tetrahydrofuran (200 ml) was added at ambient temperature, then the mixture was stirred and heated under reflux for 18 hours. The
20 mixture was cooled to ambient temperature and quenched by addition to an excess of saturated aqueous ammonium chloride solution, then the product was extracted into ethyl acetate (2 x 300 ml). The extracts were combined, dried over magnesium sulphate and the solvents removed
25 in vacuo to leave a brown oil (46.7 g). Low-boiling impurities were removed by distillation at <100°C at ~13.3 mbar. The residue, a viscous, brown oil, was triturated in ethyl acetate to give a pale grey solid which was collected by filtration and dried at
30 atmospheric pressure. Yield 0.17 g. The filtrate was allowed to concentrate at atmospheric pressure to give two further crops of pale grey solid (0.11 g + 0.47 g). The three crops of solid were combined to give 5-

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hydroxy-5-phenyl-1-azaspiro[5.5]undecane as a pale grey solid. Yield 0.75 g.

A stirred mixture of 5-hydroxy-5-phenyl-1-azaspiro[5.5]undecane (0.75 g), p-toluenesulphonic acid (1.1 g), and toluene (340 ml) was heated under reflux for 96 hours while water formed in the reaction was removed by azeotropic distillation. Further p-toluenesulphonic acid (2.2 g) was added and heating under reflux was continued for a further 144 hours. The mixture was allowed to cool to ambient temperature and was quenched by addition to an excess of 5 M aqueous sodium hydroxide solution. The product was extracted into toluene and the extracts combined, dried over magnesium sulphate and the solvent removed in vacuo to leave an oil (1 g).

The oil was purified via flash chromatography over silica using a 95:5 mixture of toluene and triethylamine as eluent. Appropriate fractions were combined and the solvents removed in vacuo to leave an oil (0.34 g). The oil was dissolved in ether and the solution saturated with hydrogen chloride to give a solid which was collected by filtration, washed with ether, and dried in vacuo to give 5-phenyl-1-azaspiro[5.5]undec-4-ene hydrochloride as a white solid. Yield 0.36 g, mp 268-275°C(dec).

Example 25

Approximately one quarter of a solution of 4-bromobiphenyl (7.2 g) in ether (80 ml) was added under nitrogen to magnesium metal (0.75 g). A few drops of iodomethane were added and, when the exothermic reaction commenced, the mixture was stirred and allowed to reach reflux temperature. The remainder of the

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4-bromobiphenyl solution was added dropwise at reflux temperature, then the mixture was stirred at reflux temperature for 0.5 hour and the solvent was removed by distillation at atmospheric pressure. A solution of 1-azaspiro[5.5]undecan-5-one (2.1 g, prepared as described in Example B), in toluene (120 ml) was added dropwise at ambient temperature and the mixture was stirred at 95°C for 18 hours. The mixture was quenched by addition to an excess of saturated aqueous ammonium chloride solution (300 ml) and the product was extracted into ether (3 x 300 ml + 1 x 400 ml). The extracts were combined and dried over magnesium sulphate and the solvents removed in vacuo to leave a brown semisolid (6.74 g). The semisolid was triturated with ethyl acetate to give a solid which was collected by filtration and dried in vacuo to give 5-(4-biphenyl)-5-hydroxy-1-azaspiro[5.5]undecane as an off-white solid. Yield 1.3 g.

A stirred mixture of 5-(4-biphenyl)-5-hydroxy-1-azaspiro[5.5]undecane (1.3 g), toluene (200 ml) and p-toluenesulphonic acid (0.9 g) was heated under reflux for 38.5 hours while water formed in the reaction was removed by azeotropic distillation. Further p-toluenesulphonic acid (0.9 g) was added and heating under reflux was continued for a further 18 hours. Further p-toluenesulphonic acid (1.8 g) was added and heating under reflux continued for 72 hours. The mixture was basified by addition to 5 M aqueous sodium hydroxide solution (500 ml) and the product was extracted into ether (200 ml + 300 ml). The extracts were combined, dried over magnesium sulphate and the solvents removed in vacuo to leave a pale brown gum (1.15 g).

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The product was dissolved in a 1:1 mixture of ether and ethyl acetate (150 ml) and the solution was cooled in ice and saturated with hydrogen chloride. The resulting solid was collected by filtration and dried in vacuo at ambient temperature for 16 hours and at 85°C for 8 hours to give 5-(4-biphenylyl)-1-azaspiro[5.5]undec-4-ene hydrochloride as a pale brown solid. Yield 0.9 g, mp 288-292°C(dec) (shrinks 280°C).

Example 26

10 A mixture of ethyl 1-aminocyclohexanecarboxylate (58 g, prepared as described in Example A), potassium carbonate (59 g) and ethyl 3-bromopropionate (61.4 g) was stirred at 110-135°C for 32.5 hours, at 120-145°C for 3.5 hours, and at 145-150°C for a further 3 hours,
15 then poured onto ice-water (600 ml). The product was extracted into ether (2 x 400 ml) and the extracts were combined, dried over magnesium sulphate and the solvent was removed in vacuo to leave a yellow oil (63.75 g). The oil was distilled to give ethyl 1-(2-ethoxycarbonylethylamino)cyclohexanecarboxylate as a
20 colourless oil. Yield 26.3 g, bp 126-135°C at 0.95 mbar.

Sodium (5.0 g) was dissolved in ethanol (280 ml) and the solvent was removed in vacuo. The residue was
25 mixed with ethyl 1-(2-ethoxycarbonylethylamino)cyclohexanecarboxylate (26.3 g), and the stirred mixture was heated to 120°C while ethanol formed in the reaction was removed by distillation. When evolution of ethanol ceased the mixture was allowed to cool slightly and
30 water (100 ml) and concentrated hydrochloric acid (50 ml) were added. The mixture was heated at 95°C for 41 hours, then cooled to ambient temperature and basified by the addition of 5 M aqueous sodium hydroxide

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solution. The product was extracted into ether (3 x 400 ml) and the extracts were combined, dried over magnesium sulphate and the solvent removed in vacuo to leave 1-azaspiro[4.5]decan-4-one as a brown oil. Yield
5 12.8 g.

4-Chlorophenylmagnesium bromide was prepared under nitrogen by the dropwise addition of a solution of 4-bromochlorobenzene (27 g) in ether (220 ml) to magnesium metal (3.4 g) initially at ambient temperature, then
10 when the exothermic reaction commenced, at reflux temperature. After the addition was complete the mixture was stirred at reflux temperature for 1.5 hours. A solution of 1-azaspiro[4.5]decan-4-one (9 g) in toluene (220 ml) was added dropwise while the ether
15 solvent was removed by distillation. When the addition was complete, the mixture was stirred at 100-110°C for 45 minutes, then allowed to stand at ambient temperature for 16 hours. The mixture was heated for a further 2 hours at 140°C, then cooled to ambient temperature and
20 quenched by addition to saturated aqueous ammonium chloride solution (500 ml). The product was extracted into ethyl acetate (2 x 300 ml; 1 x 200 ml) and the extracts were combined, dried over magnesium sulphate and the solvent removed in vacuo to leave an
25 orange/brown semisolid (11.0 g).

The semisolid was triturated with ethyl acetate and the resulting solid was collected by filtration and dried in vacuo at 50°C to give 4-(4-chlorophenyl)-4-hydroxy-1-azaspiro[4.5]decane as a white solid (2.4 g),
30 containing an impurity identified as 4-hydroxy-1-azaspiro[4.5]decan-1,3-diene. This crude product was used in the next stage without purification.

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The crude 4-(4-chlorophenyl)-4-hydroxy-1-azaspiro[4.5]decane (2.2 g) was dissolved in concentrated sulphuric acid (27 ml) and the solution was stirred at ambient temperature for 1 hour. The mixture
5 was poured onto ice to give a white precipitate which was collected by filtration, dissolved in water, and basified by the addition of 5 M aqueous sodium hydroxide solution. The product was extracted into ether (3 x 200 ml) and the extracts were combined, dried over
10 magnesium sulphate, and concentrated in vacuo to 100 ml. The solution was saturated with hydrogen chloride and the resulting solid was collected by filtration and dried in vacuo at 60°C for 7 hours to give 4-(4-chlorophenyl)-1-azaspiro[4.5]dec-3-ene hydrochloride as
15 a white solid. Yield 1.1 g, mp 225-233°C(dec).

Example 27

The use of compounds of the present invention in the manufacture of pharmaceutical compositions is illustrated by the following description. In this
20 description the term "active compound" denotes any compound of the invention but particularly any compound which is the final product of one of the preceding Examples.

a) Capsules

25 In the preparation of capsules, 10 parts by weight of active compound and 240 parts by weight of lactose are de-aggregated and blended. The mixture is filled into hard gelatin capsules, each capsule containing a unit dose of part of a unit dose of active compound.

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b) Tablets

Tablets are prepared from the following ingredients.

Parts by weight

5	Active compound	10
	Lactose	190
	Maize starch	22
	Polyvinylpyrrolidone	10
	Magnesium stearate	3

10 The active compound, the lactose and some of the starch are de-aggregated, blended and the resulting mixture is granulated with a solution of the polyvinylpyrrolidone in ethanol. The dry granulate is blended with the magnesium stearate and the rest of the starch.

15 The mixture is then compressed in a tabletting machine to give tablets each containing a unit dose or a part of a unit dose of active compound.

c) Enteric coated tablets

Tablets are prepared by the method described in

20 (b) above. The tablets are enteric coated in a conventional manner using a solution of 20% cellulose acetate phthalate and 3% diethyl phthalate in ethanol:dichloromethane (1:1).

d) Suppositories

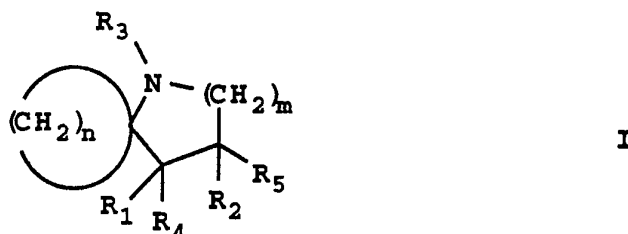
25 In the preparation of suppositories, 100 parts by weight of active compound is incorporated in 1300 parts

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by weight of triglyceride suppository base and the mixture formed into suppositories each containing a therapeutically effective amount of active ingredient.

CLAIMS

1. Compounds of formula I



and pharmaceutically acceptable salts thereof

in which m is an integer from 1 to 3;

5 n is an integer from 2 to 6;

R_1 is phenyl optionally substituted by one or more substituents selected from halo, hydroxy, alkoxy containing 1 to 3 carbon atoms, alkanoyl containing 2 or 3 carbon atoms, alkyl containing 1 to 3 carbon atoms, 10 halogenated alkyl containing 1 to 3 carbon atoms, alkylthio containing 1 to 3 carbon atoms, alkylsulphinyl containing 1 to 3 carbon atoms, alkylsulphonyl containing 1 to 3 carbon atoms, cyano, nitro, amino optionally substituted by 1 or 2 alkyl groups each 15 containing 1 to 3 carbon atoms, sulphamoyl optionally substituted by 1 or 2 alkyl groups each containing 1 to 3 carbon atoms, carbamoyl optionally substituted by 1 or 2 alkyl groups each containing 1 to 3 carbon atoms, or phenyl, or R_1 is naphthyl;

20 R_2 is H, alkyl containing 1 to 3 carbon atoms or phenyl;

R_3 is H, alkyl containing 1 to 6 carbon atoms, alkenyl containing 3 to 6 carbon atoms, or alkoxyalkyl in which

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the alkoxy group contains 1 to 4 carbon atoms and the alkyl group contains 2 to 4 carbon atoms;

R_4 is H or hydroxy; and

R_5 is H or together with R_4 represents a bond.

5 2. Compounds of formula I as claimed in claim 1 wherein R_1 is phenyl optionally substituted by one or more substituents selected from halo, hydroxy, halogenated alkyl containing 1 to 3 carbon atoms in which halo is fluoro, alkoxy containing 1 or 2 carbon
10 atoms or phenyl or R_1 is naphthyl.

3. Compounds of formula I as claimed in any preceding claim wherein R_1 is phenyl optionally substituted by one or more substituents selected from chloro, fluoro, hydroxy, trifluoromethyl, methoxy or phenyl or R_1 is
15 naphthyl.

4. Compounds of formula I as claimed in any preceding claim wherein R_1 is phenyl, 3-chlorophenyl, 4-chlorophenyl, 3,4-dichlorophenyl, 4-fluorophenyl, 3-(trifluoromethyl)phenyl, 4-hydroxyphenyl,
20 4-methoxyphenyl, 4-biphenyl or 2-naphthyl.

5. Compounds of formula I as claimed in any preceding claim wherein R_2 is H.

6. Compounds of formula I as claimed in any preceding claim wherein R_3 is H, alkyl containing 1 to 3 carbon atoms, alkenyl containing 3 to 6 carbon atoms or alkoxyalkyl in which the alkoxy group contains 1 to 3 carbon atoms and the alkyl group contains 2 or 3 carbon
25 atoms.

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7. Compounds of formula I as claimed in any preceding claim wherein R_3 is H, methyl, ethyl, propyl, allyl or 2-methoxyethyl.
8. Compounds of formula I as claimed in any preceding
5 claim wherein R_3 is H.
9. Compounds of formula I as claimed in any preceding claim wherein R_4 is hydroxy and R_5 is H, R_4 and R_5 are both H, or R_4 and R_5 together represent a bond.
10. Compounds of formula I as claimed in any preceding
10 claim wherein R_4 and R_5 together represent a bond.
11. Compounds of formula I as claimed in claim 1 which are:
- 15 5-(4-chlorophenyl)-1-azaspiro[5.5]undec-4-ene;
5-(3-chlorophenyl)-1-azaspiro[5.5]undec-4-ene;
5-(3,4-dichlorophenyl)-1-azaspiro[5.5]undec-4-ene;
5-(4-fluorophenyl)-1-azaspiro[5.5]undec-4-ene;
5-[3-(trifluoromethyl)phenyl]-1-azaspiro[5.5]undec-4-ene;
- 20 5-(2-naphthyl)-1-azaspiro[5.5]undec-4-ene;
5-(4-hydroxyphenyl)-1-azaspiro[5.5]undec-4-ene;
5-(4-chlorophenyl)-1-methyl-1-azaspiro[5.5]undec-4-ene;
- 25 10-(4-chlorophenyl)-6-azaspiro[4.5]dec-9-ene;
5-(4-chlorophenyl)-5-hydroxy-1-azaspiro[5.5]-undecane;
5-(4-chlorophenyl)-1-ethyl-5-hydroxy-1-azaspiro[5.5]undecane;
- 30 5-(3-chlorophenyl)-5-hydroxy-1-azaspiro[5.5]-undecane;
5-(3,4-dichlorophenyl)-5-hydroxy-1-azaspiro[5.5]-undecane;
5-(4-chlorophenyl)-1-azaspiro[5.5]undecane;
5-(4-methoxyphenyl)-1-azaspiro[5.5]undecane;

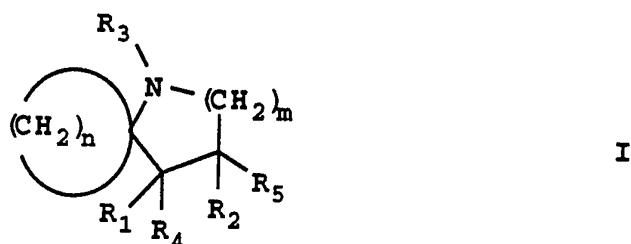
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- 5-(4-chlorophenyl)-1-propyl-1-azaspiro[5.5]undec-4-ene;
1-allyl-5-(4-chlorophenyl)-1-azaspiro[5.5]undec-4-ene;
5 5-(4-chlorophenyl)-1-(2-methoxyethyl)-1-azaspiro[5.5]undec-4-ene;
5-phenyl-1-azaspiro[5.5]undec-4-ene;
5-(4-biphenyl-1-yl)-1-azaspiro[5.5]undec-4-ene;
4-(4-chlorophenyl)-1-azaspiro[4.5]dec-3-ene;
- 10 and pharmaceutically acceptable salts thereof.
12. Pharmaceutical compositions comprising a therapeutically effective amount of a compound of formula I, together with a pharmaceutically acceptable diluent or carrier.
- 15 13. A method of treating obesity which comprises the administration of a therapeutically effective amount of a compound of formula I as claimed in any of claims 1 to 11 to a patient in need thereof.
14. A method of treating affective disorders which
20 comprises the administration of a therapeutically effective amount of a compound of formula I as claimed in any of claims 1 to 11 to a patient in need thereof.
15. A method as claimed in claim 14 for treating depression.
- 25 16. A method as claimed in claim 14 for treating anxiety.
17. The use of a compound of formula I as claimed in any of claims 1 to 11 as a medicament.

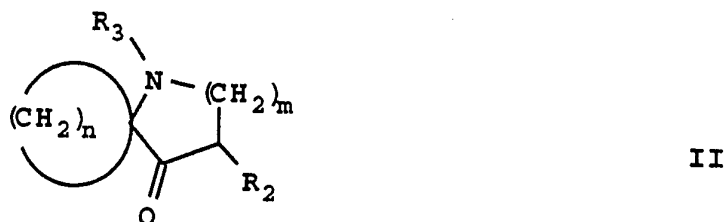
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18. The use of a compound of formula I as claimed in any of claims 1 to 11 as a medicament for treating obesity.
19. The use of a compound of formula I as claimed in
5 any of claims 1 to 11 as a medicament for treating affective disorders.
20. The use of a compound of formula I as claimed in any of claims 1 to 11 as a medicament for treating depression.
- 10 21. The use of a compound of formula I as claimed in any of claims 1 to 11 as a medicament for treating anxiety.
22. The use of a compound of formula I as claimed in any of claims 1 to 11 in the manufacture of a medicament
15 for treating obesity.
23. The use of a compound of formula I as claimed in any of claims 1 to 11 in the manufacture of a medicament for treating affective disorders.
24. The use as claimed in claim 23 in the manufacture
20 of a medicament for treating depression.
25. The use as claimed in claim 23 in the manufacture of a medicament for treating anxiety.
26. A process for the preparation of compounds of formula 1

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in which R_4 is hydroxy and R_5 is H, said process comprising the reaction of a compound of formula II



with an organometallic reagent followed by hydrolytic work-up.

- 5 27. A process as claimed in claim 26 wherein the organometallic reagent is an organolithium compound of formula III



or a Grignard reagent of formula IV



- 10 28. A process for the preparation of compounds of formula I in which R_4 and R_5 together represent a bond,

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said process comprising dehydration of a compound of formula I in which R_4 is hydroxy and R_5 is H.

29. A process for the preparation of compounds of formula I in which R_4 and R_5 are both H, said process
5 comprising the reduction of a compound of formula I in which R_4 and R_5 together represent a bond.
30. A process for the preparation of compounds of formula I in which R_3 is alkyl, said process comprising the alkylation, reductive alkylation or acylation of a
10 compound of formula I in which R_3 is H.
31. A process for the preparation of compounds of formula I in which R_3 is alkenyl, said process comprising the reaction of a compound of formula I in which R_3 is H with an alkenyl halide.
- 15 32. A process for the preparation of compounds of formula I in which R_3 is alkoxyalkyl, said process comprising the reaction of a compound of formula I in which R_3 is H with an alkoxyalkyl halide.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 93/02951

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D221/20 C07D209/96 A61K31/445 A61K31/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,4 430 335 (JOSEPH T. SRRUPCZEWSKI ET AL) 7 February 1984 see the whole document ---	1,12,17
A	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY. vol. 83, no. 5 , 17 March 1961 , GASTON, PA US pages 1128 - 1132 MILTON C. KLOETZEL ET AL 'Heterocyclic compounds.IX Oxygenated pyrrolines from reductive cyclisation of aliphatic gamma-nitro ketones' see page 1129,compound V --- -/--	1

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

17 January 1994

Date of mailing of the international search report

- 3. 02. 94

Name and mailing address of the ISA

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Authorized officer

HENRY, J

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 93/02951

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JOURNAL OF THE AMERICAN CHEMICAL SOCIETY. vol. 114, no. 4 , 12 February 1992 , GASTON, PA US pages 1329 - 1345 WILLIAM H PEARSON ET AL 'Generation of 2-azaallyl anions by the transmetalation of N-(trialkylstannyl)methanimines. Pyrroli dine synthesis by [3+2]cycloaddition with alkenes' see page 1341, preparation of compound 26 -----	1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 93/02951

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 13-16 are directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No

PCT/EP 93/02951

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4430335	07-02-84	EP-A,B 0116347	22-08-84
		JP-T- 60500765	23-05-85
		JP-B- 62016947	15-04-87
		WO-A- 8403090	16-08-84
