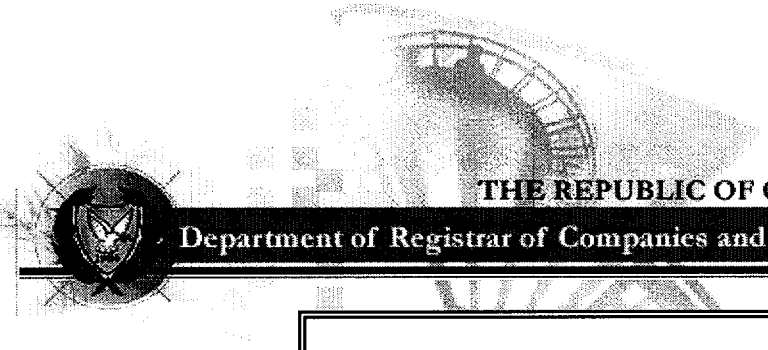

ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ

THE PATENT OFFICE OF CYPRUS

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PUBLICATION NUMBER

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Το έγγραφο που παρουσιάζεται πιο κάτω καταχωρήθηκε στο «Γραφείο Διπλωμάτων Ευρεσιτεχνίας» στην Αγγλία σύμφωνα με το Νόμο Κεφ. 266 πριν την 1η Απριλίου 1998. Δημοσίευση έγινε μετέπειτα από το Γραφείο Διπλωμάτων Ευρεσιτεχνίας του Ηνωμένου Βασιλείου μόνο στην Αγγλική γλώσσα.

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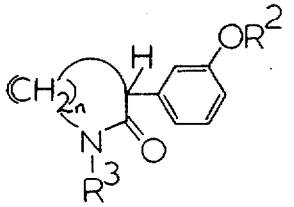
(72) Inventors JOHN FREDERICK CAVALLA and ALAN CHAPMAN WHITE

(54) HEXAHYDROAZEPINE, PIPERIDINE AND PYRROLIDINE DERIVATIVES

(71) We, JOHN WYETH & BROTHER LIMITED, a British Company of Huntercombe Lane South, Taplow, Maidenhead, Berkshire SL6 0PH, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to hexahydroazepine, piperidine and pyrrolidine derivatives. More particularly the invention relates to certain novel 2 - oxo - hexahydroazepine, -piperidine and -pyrrolidine derivatives, to a novel process for preparing the novel derivatives and to the use of the novel derivatives in preparing 2 - unsubstituted - 3,3 - disubstituted - hexahydroazepine, -piperidine, and - pyrrolidine derivatives.

The novel compounds provided by the invention are 2 - oxo - hexahydroazepine, -piperidine and -pyrrolidine derivatives of the general formula (II)

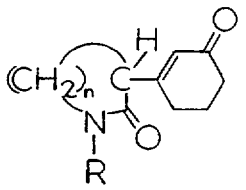


(II)

wherein n is 2, 3 or 4, R^2 is hydrogen, lower alkyl or aryl(lower)alkyl and R^3 is hydrogen, lower alkyl, aryl(lower)alkyl, lower alkenyl or lower alkynyl.

The term "lower" as used herein means that the radical referred to contains 1 to 6 carbon atoms. The radical preferably contains 1 to 4 carbon atoms. For example a lower alkyl radical may be, for example, methyl, ethyl, propyl or butyl. An aryl(lower)alkyl radical is preferably a phenyl(lower)alkyl radical such as phenethyl or benzyl; the phenyl group may be substituted by, for example, one or more substituents such as halogen, alkoxy, trifluoromethyl or other substituents common in medicinal chemistry.

The compounds of general formula (II) may be prepared by aromatising and optionally O - (lower) - alkylating or O - aryl(lower)alkylating the compounds of general formula (I)



(I)

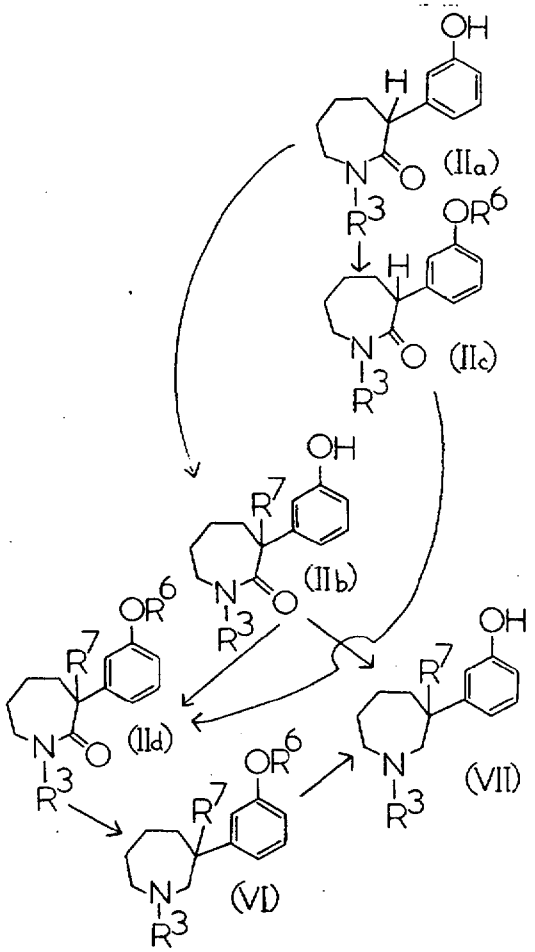
where n is as defined above and R is hydrogen, lower alkyl or aryl(lower)alkyl to give a compound of general formula (II) in which R^3 is hydrogen, lower alkyl or

aryl(lower)alkyl and, if desired "N - alkylating" a compound of general formula (II) in which R^3 is hydrogen to give a compound of general formula (II) in which R^3 is lower alkyl, aryl(lower)alkyl, lower alkenyl or lower alkynyl.

By "N - alkylating" is meant introducing onto the nitrogen atom of the heterocyclic ring a lower alkyl, aryl(lower)alkyl, lower alkenyl or lower alkynyl radical. A compound of formula (I) may be aromatised to a compound of formula (II) in which R^2 is hydrogen by treatment with cupric halide (e.g. cupric bromide or curpric chloride), in the presence or absence of lithium halide. The reaction may be carried out in a solvent such as tetrahydrofuran or, preferably, acetonitrile. Alternatively a compound of general formula (I) may be aromatised to a compound of general formula (II) by treatment with bromine, for example, in a solvent such as chloroform, methylene dichloride or carbon tetrachloride. Preferably not more than about 1 mole of bromine is used per mole of compound of general formula (I). Alternatively, a compound of formula (I) may be aromatised and O - (lower)alkylated to a compound of formula (II) in which R^2 is lower alkyl by treatment with bromine in presence of a lower alkanol (for example, in a solvent such as benzene, cyclohexane or acetonitrile) or by treatment with a brominating agent such as N - bromosuccinimide in, for example, a solvent such as chloroform, methylene dichloride or carbon tetrachloride containing a lower alkanol.

The compounds of general formula (I) and processes for their preparation are described and claimed in UK Application No. 53370/77 (Serial No. 1593888) from which the present application is divided.

The compounds of formula (II) are useful as intermediates for preparing pharmacologically active hexahydroazepine, piperidine and pyrrolidine derivatives. For example, the compounds of general formula (II) in which R^3 is hydrogen can be "N - alkylated" as mentioned above; it is preferable to N-alkylate a compound in which R^2 is lower alkyl or aryl(lower)alkyl. Compounds in which R^2 is hydrogen can be O - (lower)alkylated or O - aryl(lower)alkylated to give compounds in which R^2 is lower alkyl or aryl(lower)alkyl. The compounds of formula II can be substituted in the 3-position by, for example, a lower alkyl group. The 3,3 - disubstituted compound can be reduced to give a 2 - unsubstituted - 3,3 - disubstituted - hexahydroazepine, piperidine or pyrrolidine derivative. An embodiment of this route for preparing 2 - unsubstituted - 3,3 - disubstituted - hexahydroazepines is illustrated, by way of example, in the reaction scheme below:—



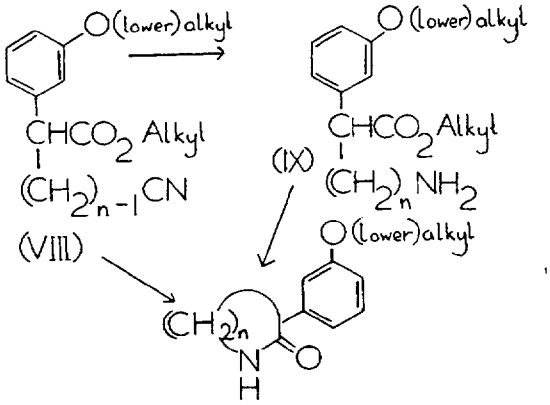
In this reaction scheme R^3 has the meaning given above, R^6 is lower alkyl and R^7 is lower alkyl. If desired compounds (IIa) and (IIb) can be etherified to compounds (IIc) and (IId) respectively by treatment with a (lower)alkylating agent, e.g. dimethylsulphate or with an aryl(lower)alkylating agent such as benzyl chloride. Either compound IIa or compound IIc can be C - (lower)alkylated to compound IIb or compound IId respectively. The C - (lower)alkylation can, for example, be carried out by reacting compound IIa or IIc with an alkyl halide (e.g. an alkyl bromide) in presence of a strong base, such as sodium hydride, sodamide or a metal amide M^1A (where A is a secondary amine radical and M^1 is sodium, potassium or lithium). The metal amide, such as lithium diisopropylamide may be formed *in situ*. Under some conditions compound IIa may be both C- and O - alkylated to a compound of formula IId. If R^3 in the compounds IIa and IIc is hydrogen then it is preferable to alkylate (using a base such as for example sodium hydride in toluene) or benzylate the N-atom selectively before carrying out the C - (lower)alkylation process. The compounds IIb and IId can be reduced to the compounds VI and VII respectively as disclosed in our UK Patent Specification No. 1,285,025. For example, the reduction can be carried out with a hydride transfer agent, e.g. lithium aluminium hydride. If desired compound VI can be converted to compound VII by ether cleavage, e.g. with hydrogen bromide or boron tribromide, as described in the above mentioned UK Specification No. 1,285,025.

Compounds VI and VII are disclosed in UK Specification No. 1,285,025 as having pharmacological activity, particularly analgesic activity. A particularly important analgesic compound is that of formula VII in which R^3 i.e. methyl and R^7 is ethyl. This compound is meptazinol. The present invention provides a novel process for preparing such compounds in good yield from readily available

starting materials. For example, the starting materials of formula V in which n is 3 are readily available derivatives of caprolactam.

The processes shown in the reaction scheme can be subject to various modifications. For example, the alkyl halides used in the C-alkylation of compounds IIa and IIc can be replaced by other active halogen compounds to give compounds corresponding to VI and VII in which the 3 - (lower)alkyl radical is replaced by an alkyl radical containing a functional group; if this functional group is reducible it may be further modified during the subsequent reduction step. In a further modification the group in the 1-position of the intermediate compounds may be removed to give a 1 - H - derivative which may subsequently be alkylated, as for example, described in Specification 1,285,025, to give a product having a different 1-substituent. Analogous reactions to those described above in connection with the Reaction Scheme and the modifications can be carried out with compounds I and II in which n is 2 or 3 to give analogous 2 - unsubstituted - 3,3 - disubstituted - piperidines and -pyrrolidines having pharmacological activity such as profadol and related pyrrolidines described in J. Med. Chem., 1965, *8*, 316 and Belgian Patent Specification No. 850777 and myfadol and related piperidines described in J. Med. Chem., 1965, *8*, 313.

Compounds of general formula II can be prepared by alternative methods. One method is illustrated below:—



(X)

In the above formulae n has the meaning given hereinbefore. In this process a nitrile ester of general formula VIII is reduced either directly to the cyclised compound of formula X or to the open chain compound IX which can be cyclised to the compound X. The reduction can be carried out by catalytic hydrogenation, e.g. at a temperature up to about 80°C (for example with hydrogen in presence of palladium on charcoal at about room temperature in a solvent such as methanol containing sulphuric acid and under a pressure of about 60 p.s.i.) or at a temperature above about 100°C (e.g. with hydrogen in the presence of Raney nickel at temperatures of about 100 to 150°C in a solvent such as cyclohexane and under pressures of about 800 to 1200 p.s.i.). Low temperature reduction tends to give the open chain compound IX while higher temperature reduction tends to give compound X. The open chain compound IX may be cyclised to the compound X, e.g. by heating in a solvent (e.g. refluxing xylene or toluene). The compounds X are compounds of formula II in which R^3 is hydrogen. Compounds X can be converted into the compounds II in which R^3 is lower alkyl or aryl(lower)alkyl by selectively N - alkylating (including N - arylalkylating) them with alkylating agents such as alkyl halides in the presence of a base or for example, by reductive methylation.

The following examples illustrate the invention:

EXAMPLE 1

Hexahydro-3-(3-methoxyphenyl)-2H-azepin-2-one

2 - (3 - Methoxyphenyl) - 5 - cyanopentanoic acid methyl ester (10 g) was reduced at 60 p.s.i. in methanol (100 ml) containing conc. sulphuric acid (7.2 ml) and 10% palladium charcoal (2.2 g). Uptake ceased when 2 moles of hydrogen had been taken up. The catalyst was filtered off, methanol removed under reduced

pressure affording an oil. The oil was poured into water, basified with conc. ammonium hydroxide, extracted into ether, the combined ether washings dried over magnesium sulphate and evaporated to an oil.

The oil (11 g) was heated under reflux in xylene for six days. The xylene was removed under reduced pressure affording an oil which gave pale yellow crystals of the title product from ethylacetate (2.72 g), m.p. 116—117°C. A further 894 mg of crystals were obtained by distilling the residue and crystallizing the resulting oil from ethylacetate.

Analysis:

Found: C, 71.35; H, 7.94; N, 6.7%.
$C_{13}H_{17}NO_2$ requires: C, 71.2; H, 7.8; N, 6.4%.

EXAMPLE 2

Hexahydro-3-(3-methoxyphenyl)-1-methyl-2H-azepin-2-one

Hexahydro - 3 - (3 - methoxyphenyl) - 2H - azepin - 2 - one (2.2 g) in dry toluene (40 ml) was added dropwise to a stirred suspension of sodium hydride (0.62 g, 0.015 mole of 50% dispension in oil) pre-washed with dry light petroleum (b.p. 40—60°). After stirring and heating at 60° for 1 hour the reaction was cooled to 5°C and methyl iodide (1.9 ml, 2.5 g, 0.02 mole) was added rapidly. After stirring at ambient temperature for 20 hours acetic acid and water were added. The aqueous layer was separated and washed with toluene. Toluene extracts were washed with water, dried over anhydrous magnesium sulphate and evaporated to an oil. Oil was recrystallised from ethylacetate/light petroleum (b.p. 60—80°) affording 1.95 g (83%) of hexahydro - 3 - (3 - methoxyphenyl - 1 - methyl - 2*H* - azepin - 2 - one, in several crops, m.p. 74—5°C.

Analysis:

C, 72.4; H, 8.5; N, 5.7%.
$C_{14}H_{19}NO_2$ requires: C, 72.1; H, 8.2; N, 6.0%.

EXAMPLE 3

Hexahydro-3-(3-hydroxyphenyl)-1-methyl-2H-azepin-2-one

Hexahydro - 1 - methyl - 3 - (3 - oxocyclohexen - 1 - yl - 2H - azepin - 2 - one (11.1 g) in acetonitrile (250 ml) was stirred overnight with a mixture of copper (II) bromide (22.3 g) and lithium bromide (4.3 g). The acetonitrile was removed under reduced pressure and the dark residue suspended in sodium hydroxide solution (2N, 200 ml). The solution was filtered, the precipitate washed with water and the filtrate acidified with conc. hydrochloric acid. The precipitated title phenol was filtered and washed with water affording 8.62 g of off-white powder m.p. 185—187°C. A second crop of 900 mg, m.p. 188—191°C was obtained by extracting the mother liquors with chloroform. The product was purified by recrystallising from ethyl acetate or ethyl acetate/methanol to give pure product, m.p. 192—193°C.

Analysis:

Found: C, 71.1; H, 8.0; N, 6.4%.
$C_{13}H_{17}NO_2$ requires: C, 71.2; H, 7.8; N, 6.4%.

EXAMPLE 4

Hexahydro-3-(3-methoxyphenyl)-1-methyl-2H-azepin-2-one

Hexahydro - 3 - (3 - hydroxyphenyl) - 1 - 2*H* - azepin - 2 - one (21.9 g) was dissolved in 2M sodium hydroxide solution (100 ml) and dimethyl sulphate (18.3 g, 14.5 ml) added. The reaction mixture was stirred at room temperature for 10 minutes then seeded. The product crystallised after leaving at 0°C for 3 hours. The product was filtered, washed with water and dried affording 16.99 g of title compound as off-white powder m.p. 73—74°C, identical to that obtained in Example 2.

A further 1.69 g of the required material was obtained by treating the aqueous mother liquors with 2M sodium hydroxide (50 ml) and dimethyl sulphate (7.25 ml).

EXAMPLE 5

3-Ethyl-hexahydro-3-(3-methoxyphenyl-1-methyl-2H-azepin-2-one

Hexahydro - 3 - (3 - methoxyphenyl) - 1 - methyl - 2H - azepin - 2 - one (4.66 g) in dry toluene (25 ml) was added dropwise to a stirred suspension of sodium amide (1.0 g) in dry toluene (50 ml). The reaction mixture was heated to reflux, ammonia was evolved and the reaction mixture became red. After refluxing for 2 hours dry tetrahydrofuran (20 ml) was added, the mixture cooled and ethyl iodide (3.7 g) added. A white precipitate was formed and the red colour rapidly disappeared. The reaction mixture was heated under reflux for 2 hours, cooled and decomposed by the addition of water. The aqueous phase was separated and the organic layer washed with saturated sodium chloride solution, dried over anhydrous magnesium sulphate and evaporated affording an oil which crystallised from diisopropyl ether to give the title compound (3.29 g), m.p. 62—64°C.

Analysis:

Found: C, 73.5; H, 9.0; N, 5.15%.
$C_{16}H_{23}NO_2$ requires: C, 73.5; H, 8.9; N, 5.4%.

EXAMPLE 6

3-Ethylhexahydro-3-(3-methoxyphenyl)-1-methyl-1H-azepine

3 - Ethyl - 3 - (3 - methoxyphenyl) - 1 - methylhexahydro - 2H - azepin - 2 - one (5.52 g) in anhydrous ether (100 ml) was added dropwise to a stirred suspension of aluminium lithium hydride (1.5 g) in anhydrous ether (50 ml). The reaction was heated under reflux for 3 hours.

A further portion of aluminium lithium hydride (1.0 g) was added and heating continued for a further 2 hours. After cooling, the reaction mixture was decomposed by the successive addition of water (3 ml), 15% sodium-hydroxide (3 ml) and water (6 ml). The granular precipitate was filtered and the precipitate washed with ether. The combined filtrate and ether washings were extracted with 2M hydrochloric acid (3x25 ml). The combined acid washings were basified with 15M aqueous ammonium hydroxide and extracted with ether. After drying over anhydrous magnesium sulphate the solvent was removed to leave 3.98 g of title compound as a colourless oil 98% pure by gas/liquid chromatography and identical to the material prepared by an alternative route. [The product is converted to 3 - ethyl - hexahydro - 3 - (3 - hydroxyphenyl) - 1 - methyl - 1H - azepine by the procedure described in UK Specification No. 1,285,025].

EXAMPLE 7

3-Ethylhexahydro-3-(3-hydroxyphenyl)-1-methyl-2H-azepin-2-one

Butyl lithium (77 ml of a 15% w/w solution in hexane) was added to a solution of diisopropylamine (14.8 ml) in dry tetrahydrofuran (20 ml) at −10°C under nitrogen. The mixture was stirred at −10°C for ten minutes and finely powdered hexahydro - 3 - (3 - hydroxyphenyl) - 1 - methyl - 2H - azepin - 2 - one (11 g) was added. Tetrahydrofuran (500 ml) was added and the mixture heated under reflux for 3 hours. After cooling, ethyl iodide (8.2 g) was added and the mixture again heated under reflux for 3 hours. Water (20 ml) was then cautiously added to the cooled solution and the mixture evaporated to a brown residue. After dissolving in water the mixture was extracted with dichloromethane and the dichloromethane extracted in turn with 2M sodium hydroxide. The aqueous and sodium hydroxide washings were combined and acidified with concentrated hydrochloric acid. The precipitated solid was filtered, washed with water, dried and recrystallised from ethyl acetate, affording 8.72 g of the title compound as white crystals, m.p. 178—180°C.

Analysis:

Found: C, 72.55; H, 8.6; N, 5.3%.
$C_{15}H_{21}NO_2$ requires: C, 72.8; H, 8.6; N, 5.7%.

EXAMPLE 8

3-Ethyl-Hexahydro-3-(3-hydroxyphenyl)-1-methyl-2H-azepine

A solution of 3 - ethylhexahydro - 3 - (3 - hydroxyphenyl) - 1 - methyl - 2*H* - azepin - 2 - one (1.5 g) in dry tetrahydrofuran was added to a stirred

suspension of aluminium lithium hydride (0.48 g) and heated under reflux for 5 hours. The reaction mixture was cooled and decomposed by the addition of water and the precipitate filtered. The precipitate was washed with tetrahydrofuran and the combined filtrate and washings evaporated to a solid. The solid was dissolved in water and ammonium chloride added. The precipitated oil was extracted with dichloromethane, dried over anhydrous magnesium sulphate and evaporated to leave a solid which was recrystallised from acetonitrile to give 0.81 g of the title compound, m.p. 127.5—133°C., identical with material prepared by an alternative route.

EXAMPLE 9

3-(3-Hydroxyphenyl)-1-methyl-2-piperidone

1 - Methyl - 3 - [3 - oxocyclohexen - 1 - yl] - 2 - piperidone (3.5 g) was refluxed in acetonitrile (100 ml) in the presence of lithium bromide (1.4 g) and cupric bromide (7.6 g) for 0.5 hours. The acetonitrile was evaporated to give a gum, to which 2N sodium hydroxide (100 ml) was added, the solution filtered, conc. HCl (30 ml) added to the filtrate, the aqueous extracted with chloroform, dried ($MgSO_4$) and evaporated to give an oil, which on standing overnight, at 0°C, in hexane gave a yellow solid. This was collected, washed with ether then acetone to give the title compound as the quarter hydrate, a colourless solid (0.50 g) m.p. 111—114°C.

Analysis:

Found: C, 69.1; H, 7.27; N, 7.11%.
$C_{12}H_{15}NO_2.H_2O$ requires: C, 68.7; H, 7.45; N, 6.68%.

EXAMPLE 10

3-(3-Hydroxyphenyl)-1-methyl-2-pyrrolidone

1 - Methyl - 3 - (3 - oxocyclohexen - 1 - yl) - 2 - pyrrolidone (9.24 g), cupric bromide (21.39 g) and lithium bromide (4.16 g) were heated to reflux in acetonitrile (50 ml) for 1 hour. The resulting dark solution was evaporated to dryness and the residue was treated with 2N sodium hydroxide solution (100 ml). The resulting orange precipitate was removed by filtration and washed with 2N sodium hydroxide (10 ml) and water (25 ml). The alkaline filtrate and washings were combined and extracted with dichloromethane (3×50 ml) to remove unreacted starting material. The dark aqueous phase was then acidified with conc. hydrochloric acid (25 ml) and extracted with chloroform (4×50 ml). The combined, dried ($MgSO_4$) extracts were evaporated, leaving a dark gum (8.85 g) which crystallised on seeding and dilution with a little ethyl acetate to a brown crystalline mass (7.8 g, 86.1%), m.p. 95—115°C. This material was crystallised from ethyl acetate/80—100° petrol, giving the title compound as pale buff crystals (5.12 g), m.p. 123—124°C (decomp.).

EXAMPLE 11

3-(3-Hydroxyphenyl)-1-methyl-3-(1-propyl)-2-pyrrolidone

Lithium diisopropylamide was prepared under nitrogen at room temperature from n - butyllithium (1.6M in hexane, 16 ml) and diisopropylamine (2.8 ml, 2.02 g). A solution of 3 - (3 - hydroxyphenyl) - 1 - methyl - 2 - pyrrolidone (1.71 g) in THF (50 ml) was added and the resulting suspension was stirred for 1 hour at room temperature. 1 - Iodopropane (0.95 ml, 1.63 g) was then added in one lot, when the solid immediately dissolved. The mixture was warmed over 2 hours to reflux, held at reflux for ½ hour, cooled, and treated with water (20 ml). Organic solvents were removed under reduced pressure and the residual aqueous phase was diluted with water (20 ml), and extracted with dichloromethane (2×50 ml). The lower emulsion phases were separated, combined, and back-extracted with water (3×10 ml). The dichloromethane phase was dried ($MgSO_4$) and evaporated, leaving impure title compound as a brown gum which partially crystallised (0.3 g). The aqueous phases were combined with the original aqueous phase (pH>12) and acidified with conc. hydrochloric acid to pH<1. The precipitated yellow gum was extracted into dichloromethane (4×25 ml) and the combined extracts were dried ($MgSO_4$) and evaporated, leaving a brown gum which crystallised on trituration with a little ethyl acetate (2.04 g). This material was crystallised, after charcoal treatment in ethyl acetate and removal of the solvent, from cyclohexane-toluene

(about 1:1 v/v) to give 3 - (3 - hydroxyphenyl) - 1 - methyl - 3 - (1 - propyl) - 2 - pyrrolidone as ochre crystals (0.91 g), m.p. 75.5—76.5°C.

Analysis:

Found: C, 72.2; H, 8.4; N, 6.2%.
$C_{14}H_{19}NO_2$ requires: C, 72.1; H, 8.2; N, 6.0%.

EXAMPLE 12

3-(3-Hydroxyphenyl)hexahydro-2H-azepin-2-one

A mixture of hexahydro - 3 - (3 - oxocyclohexen - 1 - yl) - 2H - azepin - 2 - one (20.73 g), cupric bromide (44.9 g) and lithium bromide (8.8 g) was refluxed in acetonitrile (1000 ml) for 1 hour. Evaporation of the solvent left a black gum which was triturated with an excess of 2N sodium hydroxide solution. The resulting orange suspension was filtered through Kieselguhr, and the filtrate acidified (conc. HCl). The white suspension was extracted several times with chloroform, and the residue left on evaporation of the organic layers was crystallised from ethyl acetate to give 3 - (3 - hydroxyphenyl) hexahydro - 2*H* - azepin - 2 - one (11.18 g) m.p. 175—178°C.

Analysis:

Found: C, 70.1; H, 7.6; N, 6.6%.
$C_{12}H_{15}NO_2$ requires: C, 70.22; H, 7.37; N, 6.82%.

EXAMPLE 13

3-(3-Benzyloxyphenyl)hexahydro-2H-azepin-2-one

A solution of 3 - (3 - hydroxyphenyl)hexahydro - 2H - azepin - 2 - one (2.05 g) in dry DMF was added dropwise to a suspension of sodium hydride (0.3 g). After ½ hour at ambient temperature, benzyl chloride (1.3 g) was added. The mixture was stirred for a further 2 hours and then cooled, and treated with water. The resulting solution was extracted several times with toluene, and the combined toluene layers washed thoroughly with water. The solvent was evaporated to give an oil that crystallised from ethyl acetate to give the title compound as a white solid (1.4 g) m.p. 119—122°C.

Analysis:

Found: C, 77.42; H, 7.37; N, 4.64%.
$C_{19}H_{21}NO_2$ requires: C, 77.26; H, 7.17; N, 4.74%.

EXAMPLE 14

3-Ethyl-hexahydro-3-(methoxyphenyl)-2H-azepin-2-one

Lithium diisopropylamide, prepared by adding 15% butyl lithium in hexane (15.7 ml) to diisopropylamine (3.15 ml) at −10°C under nitrogen, was treated with a solution of hexahydro - 3 - (3 - methoxyphenyl) - 1 - methyl - 2H - azepin - 2 - one in THF. After 30 minutes, ethyl bromide (1.0 ml) was added. The mixture was allowed to warm to ambient temperature. After a further 2 hours the reaction was quenched with water. The organic layer was evaporated to give an oil that crystallised on scratching. The solid was recrystallised from ethyl acetate to give the title compound (1.68) m.p. 85—87°C.

Analysis:

Found: C, 72.88; H, 8.91; N, 5.39%.
$C_{15}H_{21}NO_2$ requires: C, 72.84; H, 8.56; N, 5.66%.

EXAMPLE 15

Hexahydro-3-(3-hydroxyphenyl)-1-phenylmethyl-2H-azepin-2-one

Hexahydro - 1 - phenylmethyl - 3 - (3 - oxocyclohexen - 1 - yl) - 2*H* - azepin - 2 - one, the product of Example 9 of Application No. 53370/77 was refluxed with cupric bromide (8.95 g) and lithium bromide (1.74 g; 0.02 m) in acetonitrile for 1 hour. Removal of the solvent left a black oil that was triturated with excess 2N sodium hydroxide solution. The filtrate, after removal of the orange precipitate, was extracted with methylene chloride. The organic layer was acidified (conc. HCl) and the white suspension shaken with several portions of

chloroform and were evaporated to leave a dark red oil (1.2 g) that crystallised from ethyl acetate to give the title compound (0.35 g) m.p. 160—166°C.

Analysis:

Found: C, 75.31; H, 7.48; N, 4.36%.
$C_{19}H_{21}NO_2\frac{1}{2}H_2O$ requires: C, 74.97; H, 7.28; N, 4.6%.

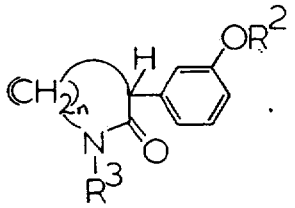
EXAMPLE 16

Hexahydro-3-(3-hydroxyphenyl)-1-methyl-2*H*-azepin-2-one

A solution of hexahydro - 1 - methyl - 3 - (3 - oxocyclohexen - 1 - yl) - 2H - azepin - 2 - one (150 g) in dichloromethane (750 ml) was warmed to 25°C. Bromine (97.5 g) was added over 40 minutes at 25—32°C (occasional water cooling being applied) and the mixture stirred for 1 hour at 25—32°C. A further quantity of bromine (11.0 g) was added over 5 minutes and the mixture stirred for 2 hours at about 25°C. Water (200 ml) was added and the dichloromethane layer washed with water (100 ml). The aqueous phases were combined and extracted into dichloromethane (2x100 ml). The dichloromethane extracts were combined and the solvent distilled off and replaced with ethyl acetate to keep temperature of 72°C (750 ml ethyl acetate added; 900 ml distillate collected). The mixture was cooled to room temperature and filtered. The product was washed with 100 ml ethyl acetate and dried to give the title compound (134.3 g) as a crystalline fawn powder, m.p. 184—189°C. Identical to product of Example 3.

WHAT WE CLAIM IS:—

1. A compound of general formula



(II)

where n is 2, 3 or 4, R^2 is hydrogen, lower alkyl or aryl(lower)alkyl and R^3 is hydrogen, lower alkyl, aryl(lower)alkyl, lower alkenyl or lower alkynyl.

2. A compound as claimed in Claim 1 wherein n is 4.

3. A compound as claimed in Claim 1 or Claim 2 wherein R^3 is hydrogen, lower alkyl or aryl(lower)alkyl.

4. Hexahydro - 3 - (3 - methoxyphenyl) - 2*H* - azepin - 2 - one.

5. Hexahydro - 3 - (3 - methoxyphenyl) - 1 - methyl - 2*H* - azepin - 2 - one.

6. Hexahydro - 3 - (3 - hydroxyphenyl) - 1 - methyl - 2*H* - azepin - 2 - one.

7. 3 - (3 - Hydroxyphenyl) - 1 - methyl - 2 - piperidone.

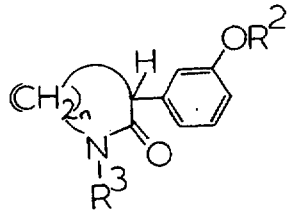
8. 3 - (3 - Hydroxyphenyl) - 1 - methyl - 2 - pyrrolidone.

9. 3 - (3 - Hydroxyphenyl)hexahydro - 2*H* - azepin - 2 - one.

10. 3 - (3 - Benzyloxyphenyl)hexahydro - 2*H* - azepin - 2 - one.

11. Hexahydro - 3 - (3 - hydroxyphenyl) - 1 - phenylmethyl - 2H - azepin - 2 - one.

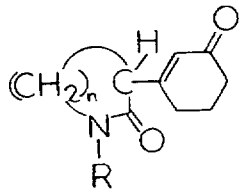
12. A process for preparing a compound of general formula (II)



(II)

where n, R^2 and R^3 are as defined in Claim 1 which comprises aromatising and

optionally O - (lower)alkylating or O - aryl(lower)alkylating, a compound of general formula (I)



(I)

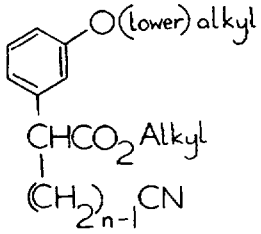
where n is as defined above and R is hydrogen, lower alkyl or aryl(lower)alkyl to give a compound of general formula (II) in which R^3 is hydrogen, lower alkyl or aryl(lower)alkyl and, if desired N-alkylating a compound of general formula (II) in which R^3 is hydrogen to give a compound of general formula (II) in which R^3 is lower alkyl, aryl(lower)alkyl, lower alkenyl or lower alkynyl.

13. A process as claimed in Claim 12 in which the compound of general formula (I) is aromatised by treatment with cupric halide in the presence or absence of lithium halide.

14. A process as claimed in Claim 12 in which the compound of general formula (I) is aromatised by treatment with bromine.

15. A process as claimed in any one of Claims 12 to 14 in which a compound of general formula (I) is aromatised and optionally O - (lower)alkylated or O - aryl(lower)alkylated to a compound of general formula (II) in which R^3 is hydrogen, lower alkyl or aryl(lower)alkyl.

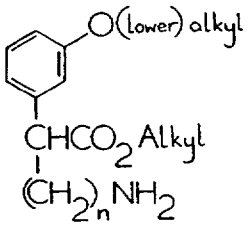
16. A process for preparing a compound claimed in Claim 1 which comprises reducing and cyclising a compound of general formula (VIII)



(VIII)

where n has the meaning given in Claim 1 and, if desired, N - alkylating a compound of formula (II) in which R^3 is hydrogen to give a compound in which R^3 is lower alkyl, aryl(lower)alkyl, lower alkenyl or lower alkynyl or etherifying a compound of formula (II) in which R^2 is hydrogen to give a compound in which R^2 is lower alkyl or aryl(lower)alkyl.

17. A process for preparing a compound claimed in Claim 1 which comprises cyclising a compound of general formula (IX)

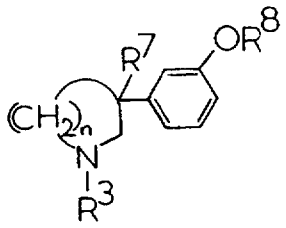


(IX)

where n has the meaning given in Claim 1, and if desired, N - alkylating a compound of formula (II) in which R^3 is hydrogen to give a compound in which R^3 is lower alkyl, aryl(lower)alkyl, lower alkenyl or lower alkynyl or etherifying a compound of formula (II) in which R^2 is hydrogen to give a compound in which R^2 is lower alkyl or aryl(lower)alkyl.

18. A process as claimed in Claim 16 or 17 wherein in the product R^2 is lower alkyl and R^3 is hydrogen, lower alkyl or aryl(lower)alkyl.

19. A process for preparing a compound of general formula



where R^7 is lower alkyl and R^8 is lower alkyl or hydrogen and n and R^3 are as defined in Claim 1 which comprises C-lower alkylating and reducing a compound claimed in Claim 1 and if desired either cleaving a product in which R^8 is lower alkyl to give a product in which R^8 is hydrogen or N-alkylating a product in which R^3 is hydrogen to give a product in which R^3 is lower alkyl, aryl(lower)alkyl, lower alkenyl or lower alkynyl.

20. A process as claimed in Claim 19 wherein n is 4.

21. A process for preparing a compound of general formula II as defined in Claim 1 substantially as hereinbefore described with reference to any one of Examples 1 to 4.

22. A process for preparing a compound of general formula II as defined in Claim 1 substantially as hereinbefore described with reference to any one of Examples 9, 10, 12, 13, 15 and 16.

23. A compound of formula (II) whenever prepared by the process claimed in any one of Claims 12 to 14, 16, 17 and 22.

24. A compound of formula (II) whenever prepared by the process claimed in any one of Claims 15, 18 and 21.

25. A compound whenever prepared by the process claimed in Claim 19 or 20.

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