

PATENT SPECIFICATION

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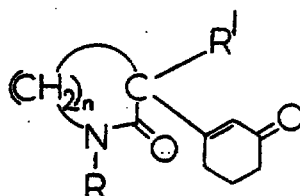


(54) HEXAHYDROAZEPINE, PIPERIDINE AND PYRROLIDINE DERIVATIVES

(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 (I)

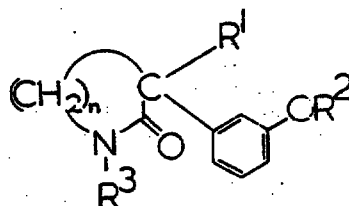


(I)

wherein n is 2, 3 or 4, R is hydrogen, lower alkyl or aryl(lower)alkyl, and R¹ is hydrogen or lower alkyl.

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 when R is lower alkyl, the radical may be, for example, methyl, ethyl, propyl or butyl. Similarly R¹ may be, for example, methyl, ethyl, propyl or butyl. When R is aryl(lower)alkyl, the 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 (I) may be converted by procedure described hereinafter to their aromatised derivatives of general formula (II)



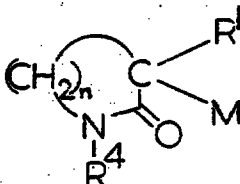
(II)

where n and R^1 are as defined above, 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 compounds of general formula (II) in which R^1 is hydrogen are novel compounds and are claimed, together with a process for their preparation, in our copending application No. 461/80 (Serial No. 1593889 [H-257a] which is a divisional of the present application.

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) 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.

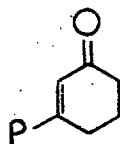
By "N-alkylating" is meant introducing onto the nitrogen atom of the heterocyclic ring a lower alkyl, aryl(lower)alkyl, lower alkenyl or lower alkynyl radical. A compound of formula (I) may be aromatised to a compound of formula (II) in which R^2 is hydrogen by treatment with cupric halide (e.g. cupric bromide or cupric 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.

We have found that the compounds of general formula (I) can be prepared by a novel process from readily available starting materials. Accordingly in a further aspect, the invention provides a process for preparing a compound of general formula (I) which process comprises reacting a compound of general formula (III)



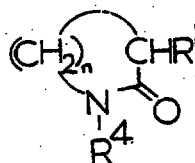
(III)

where n and R^1 are as defined above, R^4 is lower alkyl, aryl(lower)alkyl or trialkyl-, triaryl- or triarylalkylsilyl (e.g. trimethylsilyl), M is $-MgX$ (where X is chlorine, bromine or iodine) sodium, potassium or lithium (preferably M is lithium when R^1 is hydrogen and preferably M is $-MgBr$ when R^1 is lower alkyl) with a cyclohexene derivative of general formula (IV)



(IV)

where P is a hydrolysable protecting group such as lower alkoxy (preferably methoxy, ethoxy or *i*-propyloxy), benzyloxy, tri-alkyl-, tri-aryl- or tri-arylalkylsilyloxy (e.g. trimethylsilyloxy), and subjecting the product to hydrolysis. In a preferred method of carrying out the process the compound of general formula (III) is formed *in situ* by reacting a lactam of general formula (V)

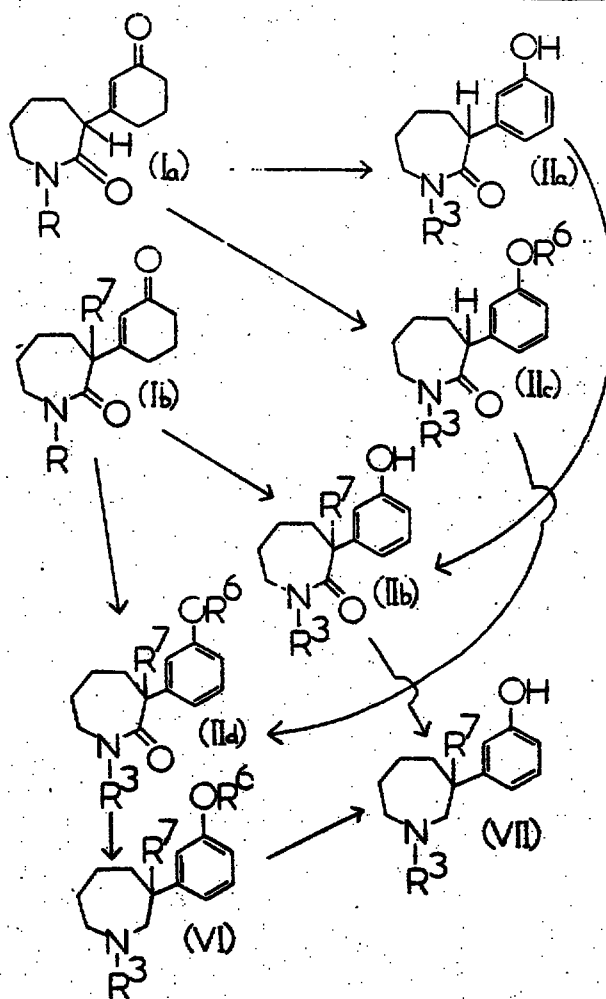


(V)

where n, R¹ and R⁴ are as defined with a compound of general formula MA (where M is as defined above and A is a secondary amine radical). When R¹ is hydrogen M is preferably sodium, potassium or lithium. When M is sodium, potassium or lithium the compound MA is a metal amide and is itself preferably formed *in situ* by reacting a metal compound MR⁵ (where M is sodium, potassium or lithium and R⁵ is alkyl, aryl or aralkyl) with a secondary amine. The secondary amine may be a dialkylamine, e.g. diethylamine, di-isopropylamine, di-tertiarylbutylamine, di-*n*-decylamine, dicyclohexylamine, N-*t*-amyl-N-*t*-butylamine, N-isopropyl-N-cyclohexylamine or N-(1'-ethylcyclohexyl)-1,1,3,3-tetramethylpiperidine or a cyclic compound, e.g. piperidine or 2,2,6,6-tetramethylpiperidine. A preferred metal amide is lithium diisopropylamide. When R¹ in compound (III) is lower alkyl and M is MgBr then the compound of formula (III) is preferably prepared by reacting a corresponding compound of general formula (V) with isopropylmagnesium bromide or bromomagnesiumdiisopropylamide.

The product of the reaction of the compound (III) and the cyclohexene derivative (IV) is preferably not isolated but hydrolysed *in situ* to give the compound of general formula III. If R⁴ in the compound of general formula (V) is a tri-alkyl-, tri-aryl- or tri-aralkylsilyl group, this group is removed by the hydrolysis to give a compound of general formula (I) in which R is hydrogen.

The compounds of formulae (I) and (II) are useful as intermediates for preparing pharmacologically active hexahydroazepine, piperidine and pyrrolidine derivatives. Certain of the reactions described below are claimed in our copending application No. 461/80 (Serial No. 1593889) (H-257a). Compounds (I) can be aromatised (and optionally O-(lower)alkylated or O-aryl(lower)alkylated) as mentioned above, to give compounds (II). The compounds of general formula (II) in which R³ is hydrogen can also be "N-alkylated" as mentioned above; it is preferable to N-alkylate a compound in which R² is lower alkyl or aryl(lower)alkyl. Compounds in which R² is hydrogen can be O-(lower)alkylated or O-aryl(lower)alkylated to give compounds in which R² is lower alkyl or aryl(lower)alkyl. If R¹ in the compounds of formula II is hydrogen the compound can be further 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 and R³ have the meanings given above, R⁶ is lower alkyl and R⁷ is lower alkyl. Compounds (Ia) and (Ib) can be aromatised to compounds (IIa) or (IIb) respectively by the procedures described above or alternatively compounds (Ia) and (Ib) can be aromatised and O-(lower)alkylated to compounds (IIc) and (IId) respectively by the procedures described above. 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 M¹A (where A is as defined above and M¹ 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 R³ 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 VII and VI 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' is methyl and R' 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.

The following Examples illustrate the invention.

EXAMPLE 1

Hexahydro-1-methyl-3-(3-oxocyclohexen-1-yl)-2H-azepin-2-one

Diisopropylamine (12.14 g, 17.0 ml) in dry tetrahydrofuran (THF 20 ml) was added dropwise to a stirred cooled (-10°C) solution of butyl lithium (86 ml of 1.4 molar solution in hexane) under nitrogen. After 10 minutes Gilman test was negative. 1-Methylcaprolactam (14.19 g) in THF (20 ml) was added, also at -10°C . Reaction was stirred for 10 minutes at 0°C and 3-methoxy-2-cyclohexenone (12.6 g, 0.1 mole) in THF (20 ml) was added. The mixture was allowed to warm to room temperature and stirred at room temperature for 1.5 hours, then cooled to -10°C and decomposed by addition of 2N HCl (125 ml) rapidly but not allowing temperature to exceed 0°C . The mixture was stirred at room temperature for 30 minutes. The aqueous layer was separated and extracted with dichloromethane. The combined organic extracts were dried over anhydrous magnesium sulphate and evaporated to an oil which crystallised from toluene-light petroleum (b.p. $60-80^{\circ}\text{C}$) affording the title compound (18.99 g), m.p. $109-110^{\circ}\text{C}$.

Analysis:

Found: C, 70.65; H, 8.6; N, 6.1%.
C₁₃H₁₉NO₂ requires: C, 70.6; H, 8.65; N, 6.3%.

EXAMPLE 2

3-Ethyl-hexahydro-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 15 M 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 3

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

A solution of 3-ethylhexahydro-3-(3-hydroxyphenyl)-1-methyl-2H-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 0.91 g of the title compound, m.p. 127.5–133°C., identical with material prepared by an alternative route.

EXAMPLE 4

1-Methyl-3-(3-oxocyclohexen-1-yl)-2-piperidone

n-Butyllithium (18% in hexane, 120 ml) was treated at 20°C under dry nitrogen with diisopropylamine (27 ml, 19.2 g) in dry ether (25 ml). The mixture was stirred for 10 minutes at 20°C after completion of the addition and then 1-methyl-2-piperidone (20 g) in ether (25 ml) was added dropwise over 10 minutes. The mixture was stirred for a further 10 minutes, and then 3-isopropoxy-2-cyclohexenone (19.4 g) in ether (25 ml) was added dropwise over 10 minutes. The mixture was stirred at 20°C for a further 2 hours and was then hydrolysed by the addition, dropwise at first, of a mixture of conc. hydrochloric acid (50 ml) and water (50 ml). The mixture was cooled in a water bath during the acidification to moderate the reaction. The mixture was cooled to room temperature (from 35°C) and the organic phase was separated and dried (MgSO₄). Removal of the solvent left a mobile yellow oil (0.63 g). The aqueous phase was extracted exhaustively with chloroform (10×40 ml) and the combined extracts were washed with water (100 ml), and saturated aqueous sodium chloride solution (100 ml), and dried (MgSO₄). Evaporation left a pale green oil (25.79 g). The two fractions were combined and distilled, giving two fractions: A, bp <120°C/1 mm (4.6 g), colourless, mobile liquid; and B, bp 150°C/164°C/0.07 mm (14.46 g), yellow oil solidifying to a light yellow mass, mp 41–62°C. Fraction A was identified by IR as slightly impure 1-methyl-2-piperidone (23% recovery), while fraction B was identified by IR and NMR as the title compound.

EXAMPLE 5

3-Ethylhexahydro-1-methyl-3-(3-oxocyclohexen-1-yl)-2H-azepin-2-one

A 2 molar solution of isopropylmagnesium bromide in ether (70 ml) was treated with 3-ethylhexahydro-1-methylazepin-2-one (21.7 g, Aust. J. Chem. 1976, 29, 2651) in THF (20 ml) and the mixture treated dropwise with diisopropylamine (19.6 ml) (exothermic). The reaction mixture was stirred for 2 hours then treated dropwise with 3-methoxy-2-cyclohexenone (12.6 g) in THF (20 ml). After stirring for 2 hours the reaction mixture was poured onto cold 2N HCl (250 ml). After 10 minutes the mixture was extracted with dichloromethane (2×300 ml), the combined organic phases washed with saturated aqueous NaHCO₃ solution and dried (MgSO₄). Removal of the solvents under reduced pressure followed by distillation gave the title compound as a viscous oil (Bpt 155–160°C/0.1 mm) (13 g). Redistillation (154–158°C/0.07 mm) gave analytically pure material.

Analysis:

Found:	C, 72.4; H, 9.6; N, 5.4%
C ₁₅ H ₂₃ NO ₂ requires:	C, 72.25; H, 9.3; N, 5.6%

The product can be aromatised by the procedures described hereinabove.

EXAMPLE 6

Hexahydro-1-methyl-3-(3-oxocyclohexen-1-yl)-2H-azepin-2-one

2-Bromopropane (12.3 g) was added to suspension of magnesium (2.43 g) in ether (50 ml) at such a rate to maintain gentle reflux and the mixture was stirred 1 hour after addition was complete. Diisopropylamine (14 ml) was then added dropwise and the mixture stirred until the Gilman test showed negative (about 1

hour). N-methylcaprolactam (12.7 g) was added dropwise (exothermic). After addition of the N-methylcaprolactam, stirring became difficult due to separation of a sticky solid, which however redissolved on addition of THF (50 ml). After the addition was complete the reaction mixture was stirred $\frac{1}{2}$ hour then treated dropwise with 3 - isopropoxy - 2 - cyclohexenone (16.4 g) (exothermic) and stirred overnight. The reaction mixture was poured onto 2N aq HCl (250 ml) and stirred for $\frac{1}{2}$ hour. Dichloromethane (300 ml) was added and the layers separated. The aqueous layer was extracted with dichloromethane (2x300 ml) and the combined organic phases dried (MgSO₄). Removal of the solvents under reduced pressure followed by recrystallisation of the residue from ethyl acetate gave the title compound (13.2 g) identical with the product of Example 1.

EXAMPLE 7

1-Methyl-3-(3-oxocyclohexen-1-yl)-2-pyrrolidone

n-Butyllithium (15% in hexane, 190 ml) was treated dropwise over 10 minutes under dry nitrogen with diisopropylamine (30.3 g) in dry ether (50 ml), with external water cooling to maintain the reaction temperature below 25°C. After a further 10 minutes, freshly distilled dry 1-methyl-2-pyrrolidone (27.72 g) in dry ether (25 ml) was added dropwise over 15 minutes, and the suspension was stirred for a further 20 minutes at 20°C. 3 - Isopropoxy - 2 - cyclohexenone (31 g) in ether (25 ml) was added to the mixture over 15 minutes, the suspended solid dissolving during the addition. The mixture was stirred for a further 2 hours at 20°C and was then cooled in ice and treated, dropwise at first, with a mixture of conc. hydrochloric acid (100 ml) and water (100 ml). After a further 10 minutes the phases were separated and the organic phase was discarded (only a trace of organic material present in the solvent). The aqueous phase was extracted with chloroform (10x50 ml) and the combined extracts were washed with water (100 ml) and saturated aqueous sodium chloride solution (100 ml) and dried (MgSO₄). Evaporation of the solvent gave an initially colourless oil which darkened in air to a clear red colour (37.82 g). Distillation of the oil gave the title compound as a pale yellow liquid which solidified on seeding to a yellow mass (32.75 g), bp 161°C/0.035 mm—165°C/0.07 mm, m.p. 42—46°C.

EXAMPLE 8

Hexahydro-3-(3-oxocyclohexen-1-yl)-2H-azepin-2-one

Lithium diisopropylamide, prepared by treating diisopropylamine (45.3 ml) with 15% butyl lithium in hexane (231 ml) at -10°C under nitrogen, was treated at -60°C with 1-trimethylsilylhexahydro - 2H - azepin - 2 - one (63.7 g) in dry THF (50 ml). The white suspension was treated after 20 minutes with a solution of 3 - methoxy - 2 - cyclohexenone (40.8 g) in THF (50 ml). The resulting solution was allowed to warm to ambient temperature. After a further 3 hours the cooled solution was treated with concentrated hydrochloric acid (120 ml) and stirred for 18 hours. The THF layer was combined with several chloroform extracts from the aqueous layer. Evaporation of the solvent gave a yellow solid, which recrystallised from ethyl acetate to give hexahydro 3 - (3 - oxocyclohexen - 1 - yl) - 2H - azepin - 2 - one as an off-white solid (45.5 g) m.p. 159—165°C.

Analysis:

Found: C, 68.9; H, 8.74; N, 6.74%
requires: C, 69.54; H, 8.27; N, 6.76%

EXAMPLE 9

Hexahydro-1-phenylmethyl-3-(3-oxocyclohexen-1-yl)-2H-azepin-2-one

A solution of hexahydro-1-phenylmethyl-2H-azepin-2-one (5.68 g) in dry THF was added at -10°C to lithium diisopropylamide prepared from diisopropylamine (4.4 ml) and butyl lithium (22.9 ml of 15% solution in hexane). The mixture was stirred for $\frac{1}{2}$ hour and then treated with a solution of 3 - methoxy - 2 - cyclohexenone (2.53 g) in THF. After 5 hours at ambient temperature the mixture was poured into ice-cold concentrated hydrochloric acid (100 ml). After vigorously stirring for 12 hours the solution was shaken with several portions of chloroform. The combined chloroform layers were evaporated to give the title compound as an orange oil (conc. HCl).

(16)



* C L M S *

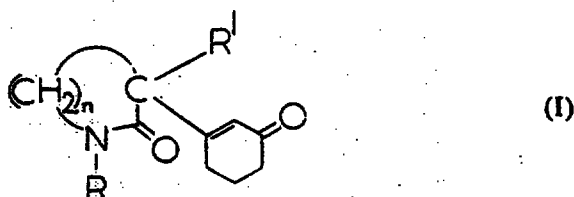
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WHAT WE CLAIM IS:—

1. A compound of general formula (I)



wherein n is 2, 3 or 4, R is hydrogen, lower alkyl or aryl(lower)alkyl and R¹ is hydrogen or lower alkyl.

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 is hydrogen, lower alkyl or benzyl.

4. A compound as claimed in any one of claims 1 to 3 wherein R¹ is hydrogen.

5. Hexahydro - 1 - methyl - 3 - (3 - oxocyclohexen - 1 - yl) - 2H - azepin - 2 - one.

6. 1 - Methyl - 3 - (3 - oxocyclohexen - 1 - yl) - 2 - piperidone.

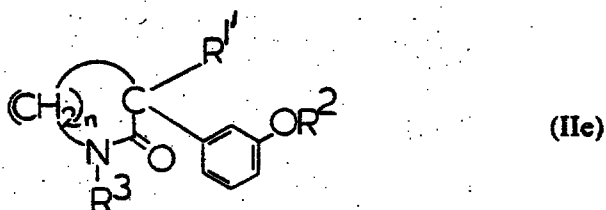
7. 3 - Ethylhexahydro - 1 - methyl - 3 - (3 - oxocyclohexen - 1 - yl) - 2H - azepin - 2 - one.

8. 1 - Methyl - 3 - (3 - oxocyclohexen - 1 - yl) - 2 - pyrrolidone.

9. Hexahydro - 3 - (3 - oxocyclohexen - 1 - yl) - 2H - azepin - 2 - one.

10. Hexahydro - 1 - phenylmethyl - 3 - (3 - oxocyclohexen - 1 - yl) - 2H - azepin - 2 - one.

11. A process for preparing a compound of general formula (IIe)

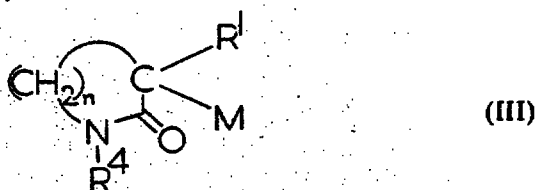


where n is as defined in claim 1, R¹ is lower alkyl, R² is hydrogen, lower alkyl or aryl(lower)alkyl and R³ is hydrogen, lower alkyl, aryl(lower)alkyl, lower alkenyl or lower alkynyl which comprises aromatising, and optionally O-(lower)alkylating or O-aryl(lower)alkylating, a compound of general formula (I) as claimed in claim 1 in which R¹ is alkyl to give a compound of general formula (IIe) in which R³ is hydrogen, lower alkyl or aryl(lower)alkyl and, if desired N-alkylating a compound of general formula (IIe) in which R³ is hydrogen to give a compound of general formula (IIe) in which R³ is lower alkyl, aryl(lower)alkyl, lower alkenyl or lower alkynyl.

12. A process as claimed in claim 11 in which the compound of general formula (I) is aromatised by treatment with cupric halide in the presence or absence of lithium halide.

13. A process as claimed in claim 11 in which the compound of general formula (I) is aromatised by treatment with bromine.

14. A process for preparing a compound claimed in claim 1 which comprises reacting a compound of general formula (III)



where n and R¹ are as defined in claim 1, R⁴ is lower alkyl, aryl(lower)alkyl or trialkyl-, triaryl- or triarylalkylsilyl and M is —MgX (where X is chlorine, bromine



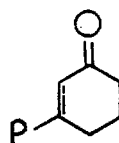
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or iodine), sodium, potassium or lithium, with a cyclohexene derivative of general formula (IV)



(IV)

where P is a hydrolysable protecting group and subjecting the product to hydrolysis.

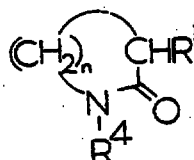
15. A process as claimed in claim 14 wherein R^1 is lower alkyl and M is $-MgX$ (where X is chlorine, bromine or iodine).

16. A process as claimed in claim 15 where X is bromine.

17. A process as claimed in claim 14 wherein R^1 is hydrogen and M is sodium, potassium or lithium.

18. A process as claimed in claim 17 wherein M is lithium.

19. A process as claimed in any one of claims 14 to 18 wherein the compound of general formula (III) is formed *in situ* by reacting a lactam of general formula (V)



(V)

where n and R^1 are as defined in claim 1 and R^4 is as defined in claim 14, with a compound of general formula MA, where M is as defined in claim 14 and A is a secondary amine radical.

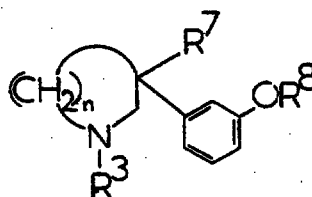
20. A process as claimed in claim 19 wherein R^1 is hydrogen and M is sodium, potassium or lithium.

21. A compound of general formula (IIe) as defined in claim 11 whenever prepared by the process claimed in any one of claims 11 to 13.

22. A compound of general formula (I) as defined in claim 1 whenever prepared by the process claimed in any one of claims 14 to 16 and 19.

23. A compound of general formula (I) as defined in claim 1 whenever prepared by the process claimed in any one of claims 17, 18 and 20.

24. A process for preparing a compound of general formula



where R^3 is hydrogen, lower alkyl, aryl(lower)alkyl, lower alkenyl or lower alkynyl, R^7 is lower alkyl, R^8 is lower alkyl or hydrogen and n is as defined in claim 1 which comprises reducing a compound claimed in claim 21 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.

25. A process as claimed in claim 24 wherein n is 4.

26. A compound whenever prepared by the process claimed in claim 24 or 25.

27. A process for preparing a compound of general formula (I) as defined in claim 1 substantially as hereinbefore described with reference to Example 1.

28. A process for preparing a compound of general formula (I) as defined in claim 1 substantially as hereinbefore described with reference to any one of Examples 4 to 8.

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29. A compound of general formula (I) whenever prepared by the process of claim 27.

30. A compound of general formula (I) whenever prepared by the process of claim 28.

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