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2,811,520

IMINODIBENZYL COMPOUNDS

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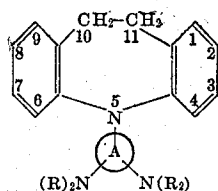
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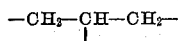
4 Claims. (Cl. 260—239)

This invention relates to new iminodibenzyl compounds and processes for their preparation.

According to the present invention there are provided new iminodibenzyl compounds of the general Formula I:



wherein A represents the trivalent hydrocarbon group



the various nitrogen groups being attached to any of the three free valencies thereof and the groups R are the same or different and represent when taken separately a hydrogen atom or a lower alkyl group and when taken together with the nitrogen atom (i. e. as the group —N(R)_2) represent a residue of a heterocyclic amine such as pyrrolidino, piperidino or morpholino, corresponding compounds in which one or both of the benzene nuclei of the iminodibenzyl carry halogen, lower alkyl or lower alkoxy substituent groups and the acid addition salts, the quaternary ammonium derivatives and the addition compounds (in particular with 8-chlorotheophylline) of any of the aforesaid compounds. By a lower alkyl or lower alkoxy group is meant a group containing not more than 4 carbon atoms.

When the group A contains an asymmetric carbon atom the compounds may exist both in the racemic form and also as optically active isomers and the invention includes the compounds in such various forms.

The aforesaid new iminodibenzyl compounds are of value in human therapy as ganglioplegics, local anaesthetics and, in particular as spasmolytics. Where derivatives of the base of Formula I are concerned the additional groups present should be pharmaceutically acceptable i. e. they should not impart toxicity to the products. Suitable acid addition salts are therefore the hydrochlorides, hydrobromides, citrates and tartrates and suitable quaternary ammonium compounds are the quaternary ammonium iodides and bromides.

According to a feature of the present invention the aforesaid compounds are prepared by introducing into an iminodibenzyl nucleus a grouping



as a substituent on the imino nitrogen atom by methods known per se for the introduction of such a substituent

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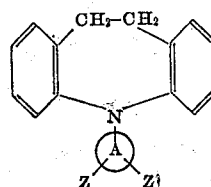
grouping on a nitrogen atom, particularly a heterocyclic nitrogen atom. Such methods include:

(1) Condensation of a halogeno diamine of the type



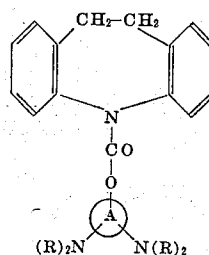
or one of its salts (where A and R have the meanings assigned to them above) with the appropriate iminodibenzyl.

(2) Condensation of a compound HN(R)_2 where R has the meaning set forth above, with an iminodibenzyl derivative of general Formula II:



where one of the two symbols Z represents an acid residue of a reactive ester (such as a halogen atom or a sulphuric or sulphonic ester residue), and the other represents either a said residue of a reactive ester or an —N(R)_2 group, A having the meaning assigned to it above. In this formula and in those following it is, of course, understood that the benzene nuclei of the iminodibenzyl may be substituted as indicated above. It is advantageous to effect the reaction under pressure i. e. in an autoclave or sealed tube, particularly when the compound HN(R)_2 is a volatile amine.

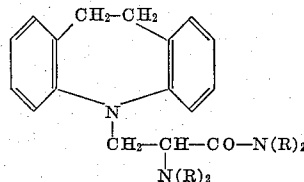
(3) Heating, to effect decarboxylation, a compound of the general Formula III:



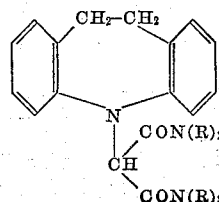
where A and R have the meanings assigned to them above.

(4) To produce compounds of general Formula I where the R groups are lower alkyl groups, alkylation of the corresponding compounds of Formula I where at least one of the R groups is replaced by a hydrogen atom, using methods of alkylation of amines known per se.

(5) Reduction of corresponding amides such as, for example the compounds of the general Formulae IV, V and VI:

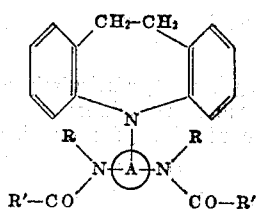


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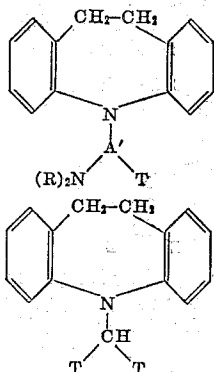
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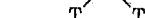
VI

where R' represents a hydrogen atom or an alkyl group containing not more than 3 carbon atoms, and R and A have the meanings assigned to them above.

(6) Reduction in the presence of a compound $\text{HN}(\text{R})_2$ of a derivative of the general Formulae VII or VIII:

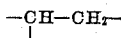


VII



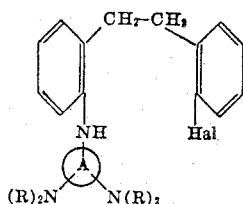
VIII

where R has the meaning assigned to it above, A' represents a



grouping and T represents a $-\text{CHO}$ or $-\text{CN}$ group. When T is a $-\text{CN}$ group, the reaction may be carried out in the absence of the compound $\text{HN}(\text{R})_2$ to give directly the corresponding primary amine.

(7) Cyclisation, preferably in a solvent selected from the class of substituted amides of lower aliphatic acids such as formamides or acetamides, in the presence of a condensing agent (e. g. alkali metal hydroxide or carbonate) and if desired in the presence of a catalyst such as copper powder, of a derivative of the general Formula IX:



IX

where A and R have the meanings assigned to them above and Hal is a halogen atom.

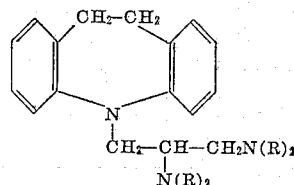
Method 1 is the most advantageous. This reaction may be carried out in the presence or absence of a solvent and in the presence or absence of a condensing agent. It is however convenient to use an aromatic hydrocarbon solvent for example toluene or xylene, in the presence of a condensing agent, preferably selected from alkali metals and their derivatives (such as, for example, hydrides, amides, hydroxides, alcoholates, metal alkyls or aryls) and more particularly metallic sodium, sodamide, powdered sodium or potassium, lithium hydride, sodium tert-butyrate, butyllithium, and phenyllithium. The reaction is preferably carried out at the boiling temperature of the solvent.

It is advantageous to use the halogeno-diamine in the form of the free base in solution in, for example, benzene, toluene or xylene and to add it to the mixture of the other reactants in which the iminodibenzyl may already be present, at least in part, in the form of an alkali

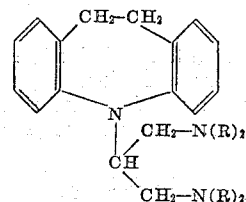
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metal salt. The reaction may also be carried out using a salt of the halogeno-diamine but in this case a larger proportion of the condensing agent is preferably used in order to neutralise the acid of the salt employed.

5 Isomerization may take place during the condensation and there is then obtained a mixture of varying proportions of the two isomers of Formulae X and XI:



X



XI

25 These isomers may be separated, for example by crystallisation of a salt such as the dihydrochloride in alcohol, or by chromatography. It is not, however, essential to carry out this separation, since the two isomers generally have very similar pharmacodynamic properties.

30 The following examples in which the melting points indicated are determined on the Kofler bench, will serve to illustrate the invention but are not to be regarded as limiting it in any way:

Example I

A mixture of iminodibenzyl (6.65 g.), toluene (35 cc.) and sodamide (1.52 g.) is heated under reflux for 1 hour under nitrogen and an 11.5% solution (53 cc.) of 1:3-bis-dimethylamino-2-chloropropane in toluene is then added over 1 hour. After being heated for 10 hours under reflux, the mixture is cooled and washed with water (60 cc.). The toluene solution is extracted with normal hydrochloric acid (70, 30, 20 and 20 cc. successively) and the combined aqueous acid solutions are washed with ether (25 cc.) and then treated with aqueous sodium hydroxide ($d=1.33$; 16 cc.). They are then extracted with ether (3×50 cc.) and the combined ethereal extracts are washed with water (30 cc.) and dried over sodium sulphate. The ether is removed on the water-bath and the residue is distilled in vacuo to give a mixture (6.14 g.) of 5-(2:3-bis-dimethylamino-1-propyl)iminodibenzyl and 5-(1:3-bis-dimethylamino-2-propyl)iminodibenzyl. On dissolving this mixture in isopropanol and treating with ethanolic hydrogen chloride, there is obtained 5-(2:3-bis-dimethylamino-1-propyl)-iminodibenzyl hydrochloride, M. P. about $230-232^\circ \text{C}$.

By the action of methyl iodide on a solution in acetone of the base corresponding to this hydrochloride, the corresponding mono iodomethylate is obtained, M. P. $182-184^\circ \text{C}$. By following the procedure of this example but employing 1:3-bis-diethylamino-2-chloropropane there is obtained a mixture of 5-(2:3-bis-diethylamino-1-propyl)iminodibenzyl and 5-(1:3-bis-diethylamino-2-propyl)iminodibenzyl, the former isomer being in preponderant amount and have B. P. 0.17 $164-168^\circ \text{C}$.

Example II

1:3-bis-dimethylamino-2-propyl-iminodibenzyl-5-carboxylate (3.4 g.), M. P. 72°C , is heated gradually from 185 to 250°C until evolution of carbon dioxide has ceased, which takes about an hour. The oily product obtained is dissolved in diethylether and the ethereal solution extracted with dilute hydrochloric acid. The solution is then made alkaline with dilute caustic soda, extracted with diethyl ether and the ether removed from

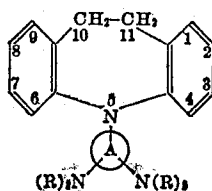
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the extract to yield the product (base) as an oil (1.7 g.) having the correct acidimetric titre. By addition of ethereal hydrogen chloride to an acetone solution of this base there is obtained 5-(2:3-bis-dimethylamino-1-propyl)iminodibenzyl dihydrochloride, M. P. 227–229° C.

The 1:3-bis-dimethylamino-2-propyl-iminodibenzyl-5-carboxylate used as starting material, of which the picrate has M. P. 174–175° C., can be prepared by condensing 1:3-bis-dimethylamino-2-propanol with iminodibenzyl-5-carboxylic acid chloride, M. P. 120–121° C., itself prepared by the action of phosgene on iminodibenzyl.

We claim:

1. A compound selected from the class consisting of iminodibenzyl compounds of the general formula:

**6**

wherein A represents the trivalent hydrocarbon group



the various nitrogen atoms being attached to any of the three free valencies thereof, and the groups R are lower alkyl groups and the acid addition salts, quaternary ammonium derivatives and addition compounds of any of the said compounds where the additional groups are pharmaceutically acceptable.

2. 5-(2:3-bis-dimethylamino-1-propyl)iminodibenzyl.
3. 5-(1:3-bis-dimethylamino-2-propyl)iminodibenzyl.
4. 5-(2:3-bis-diethylamino-1-propyl)iminodibenzyl.

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