PATENT SPECIFICATION

807,835

Date of Application and filing Complete Specification: Sept. 23, 1955.

No. 7467/58.

Application made in Germany on July 1, 1955.

(Divided out of No. 802,723).

Complete Specification Published: Jan. 21, 1959.

Index at acceptance:—Class 2(3), B4(A2:A4:D:K:M), C2A(2:3:5:14), C2B3(A2:B:C:E:G1:G8), C2(R17:R19:S16:T16).

International Classification:—C07c, d.

COMPLETE SPECIFICATION

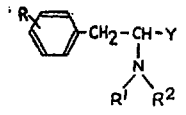
New Tertiary Amines and their Salts and process for their preparation

We, Dr. KARL THOMAE, G.M.B.H., a body Corporate organised under the laws of Germany, of Biberach an der Riss, Germany, 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 present invention is concerned with certain novel tertiary amines and their quaternary salts and with a process for the preparation thereof.

We have found that the new tertiary amines which are the subject of the present invention are valuable therapeutic agents; they are all musculotropic spasmolytics and a number of them possess a high spasmolytic activity, particularly upon the uterus. The new amines also possess marked nicotinolytic properties as well as parasympatholytic activity upon intestines contracted by acetyl choline; they also possess other valuable pharmacological properties which will be more fully described below.

According to the present invention, therefore, we provide as new compounds tertiary amines of the general formula



I

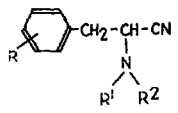
in which R represents a hydrogen atom, a lower alkyl or a lower alkoxy group, R^1 and R^2, which may be the same or different represent lower-alkyl, hydroxy lower-alkyl, cycloalkyl, monocyclic aryl or monocyclic aryl substituted lower alkyl groups or together with the nitrogen atom form a heterocyclic ring containing, if desired, a further heteroatom and Y represents a substituted or unsubstituted aralkyl group or an alkyl group containing from 3—12 carbon atoms, and their acid addition and quaternary salts.

Where R^1 and R^2 together with the nitrogen atom form a heterocyclic ring, a pyrrolidine, piperidine or morpholine ring is preferred. Preferred acid addition salts of the new amines are the hydrochlorides.

The term "lower" where used in this specification in relation to certain substituents is intended to refer to groups containing from 1—6 carbon atoms.

The physical characteristics of certain of the new compounds according to the invention are quoted in the Examples and Table which follow; it should be understood that the characteristics quoted were shown by the purest materials we have been able to prepare and may be liable to variation dependent on the purity of any particular sample of the compounds in question.

According to the present invention we also provide a process for the preparation of the tertiary amines of formula I in which an α-tertiary amino-acetonitrile of the general formula



is condensed with an organomagnesium halide of the general formula

Hal—Mg—Y

where R, R^1, R^2 and Y have the meanings stated above and Hal represents a chlorine, bromine or iodine atom, in the presence of an inert solvent and the resulting condensation product is hydrolytically decomposed to give the desired amine.

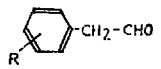
Suitable solvents for the reaction are, for example, ether, dibutyl ether, dioxane and

[*Price 3s. 6d.*]

benzene; solvent mixtures, for example mixtures of benzene and tetrahydrofuran can also be used. The reaction is preferably effected at moderately elevated temperatures, the preferred reaction temperature being the boiling point of the solvent used.

The isolation and purification of the tertiary amines obtained by the reaction may be carried out in any convenient manner and suitable procedures are described in the examples which follow. The resulting tertiary amines may be converted into their acid addition salts by reaction with organic or inorganic acids and may also be converted into their quaternary ammonium salts by reaction with suitable quaternising agents.

A number of the α-tertiary aminopropionitriles required as starting materials in the process according to the invention are known and their preparation has ben described in prior literature. A suitable procedure for the preparation of such aminopropionitriles is described, for instance, in Houben-Weyl " die Methoden der Organischen Chemie," 4th Edition, Vol. 8, pages 279 *et seq*. An alternative process for the production of such compounds, which is both simple and effective, comprises reacting the corresponding aldehyde of the general formula: —



where R has the above stated meaning, which will in general be technically readily available, with potassium cyanide and a secondary amine of the general formula R_1—NH—R_2. This process in conjunction with the process according to the invention, permits the preparation of tertiary amines which, theretofore, could be produced, if at all, only with great difficulty.

Thus, 1-(*p*-methyl phenyl)-2-morpholino-5-phenyl pentane can be readily prepared by first converting *p*-methyl phenyl acetaldehyde into 2-(*p*-methyl phenyl)-1-morpholino propionitrile and then reacting said nitrile with phenyl propyl magnesium halide. The preparation of said compound by reacting *p*-methyl benzyl magnesium halide with 4-phenyl-1-morpholino valeronitrile, in contrast thereto, is much more difficult because the γ-phenyl butyraldehyde which must be used as starting material for said nitrile is not nearly so readily available.

In order that the invention may be well understood the following examples are included by way of illustration only: —

EXAMPLE 1.

1-Phenyl-2-piperidino-5-phenyl pentane

a) 2-Phenyl-1-piperidino propionitrile

52 g. (0.5 mol) of sodium bisulphite, in the form of a 40% aqueous solution, are added, while shaking, to 60 g. (0.5 mol) of phenyl acetaldehyde. Thereafter, 42.5 g. (0.5 mol) of piperidine and 36 g. (0.55 mol) of potassium cyanide are added and the mixture is shaken for 24 hours. The precipitated amino nitrile is dissolved in ether, the ether is evaporated from the resulting ethereal solution, and the residue is recrystallized from petroleum ether. Colorless crystals of 2-phenyl-1-piperidino propionitrile of the melting point 46°C are obtained in a yield of 69% of the theoretical yield.

b) 1-Phenyl-2-piperidino-5-phenyl pentane

10.7 g. of 2-phenyl-1-piperidino propionitrile are dissolved in 70 cc. of anhydrous ether and the solution is added drop by drop, while stirring, to the Grignard reagent prepared in the usual manner from 2.3 g. of magnesium turnings and 19.9 g. of γ-phenyl propyl bromide in 50 cc. of anhydrous ether. The mixture is heated under reflux for 1 to 2 hours. Thereafter the reaction product is decomposed by the addition of ice and dilute hydrochloric acid. The ethereal layer is separated and discarded while the aqueous hydrochloric acid layer is rendered alkaline by the addition of ammonia. The precipitated amine is dissolved in ether. After evaporating the ether, the residue is distilled in a vacuum. The boiling point of the above indicated tertiary amine is 159°C./0.2 mm. The yield amounts to 77% of the theoretical yield.

Its hydrochloride has a melting point of 146°C.

EXAMPLE 2.

1-Phenyl-2-diethylamino undecane

a) 2-Phenyl-1-diethylamino propionitrile

36.5 g. (0.5 mol) of diethylamine are neutralized by the addition of hydrochloric acid while cooling. 60 g. (0.5 mol) of phenyl acetaldehyde and 36 g. (0.55 mol) of potassium cyanide, dissolved in a small amount of water, are added thereto. The mixture is shaken for 24 hours whereby an oil is formed which is dissolved in ether. After evaporating the solvent, the residue is distilled in a vacuum. The nitrile is a yellowish oil of the boiling point 148—150°C./15 mm. The yield is 76% of the theoretical yield.

b) 1-Phenyl-2-diethylamino undecane

10.1 g. of the nitrile, prepared as described hereinabove under a), are dissolved in 50 cc. of ether and the ethereal solution is added drop by drop, while stirring, to the Grignard reagent prepared from 2.3 g. of magnesium turnings and 20.7 g. of *n*-nonyl bromide in 50 cc. of ether. The reaction mixture is heated under reflux for 1 to 2 hours and is then worked up by following the procedure described in example 1 b). The resulting tertiary amine has a boiling point of 134°C./0.3 mm. Yield: 47% of the theoretical yield.

EXAMPLE 3.

1-(4-Methyl phenyl)-2-morpholino-5-phenyl pentane

a) 2-(4-Methyl phenyl)-1-morpholino propionitrile

The nitrile is prepared by following the

procedure described in example 1 a) and using as reactants 33.6 g. of *p*-methyl phenyl acetaldehyde. 26 g. of sodium bisulphite 22 g. of morpholine, and 18 g. of potassium cyanide. The resulting precipitated solid nitrile is recrystallized from petroleum ether. It forms colourless crystals of the melting point 112—113°C. Yield: 63% of the theoretical yield.

b) 1-(4-Methyl phenyl)-2-morpholino-5-phenyl pentane

11.5 g. of the nitrile prepared as described hereinabove under a) are dissolved in 100 cc. of anhydrous benzene and the solution is added drop by drop to the Grignard compound prepared from 19.9 g. of γ-phenyl propyl bromide and 2.3 g. of magnesium in 50 cc. of anhydrous benzene. The reaction mixture is heated, while stirring, to a temperature of about 50°C. for 1 to 2 hours and is then decomposed by the addition of ice and dilute hydrochloric acid. The benzene layer is separated and discarded. Ammonia is added to the aqueous layer in an amount sufficient to render it alkaline. The precipitated oil is dissolved in benzene. Benzene is evaporated from the benzene solution and the residue is distilled in a vacuum. The above indicated tertiary amine is obtained in the form of a viscous oil of the boiling point 173°C./0.06 mm. in a yield of 87% of the theoretical yield.

Its hydrochloride forms colorless crystals which melt at 158°C. after recrystallization from a mixture of ethanol and ether (1:1).

Example 4

1-(4-Isopropyl phenyl)-2-methyl-3-pyrrolidino-4-phenyl butane

a) 3-(4-Isopropyl phenyl)-2-methyl-1-pyrrolidino butyronitrile

This nitrile is prepared from 47.5 g. of cyclamen aldehyde, 26 g. of sodium bisulphite, 17.8 g. of pyrrolidine, and 18 g. of potassium cyanide by following the procedure described in Example 1 a). It is a solid product which, on recrystallization from ethanol, melts at 99°C. The yield is 66% of theoretical.

b) 1-(4-Isopropyl phenyl)-2-methyl-3-pyrrolidino-4-phenyl butane

A solution of 13.5 g. of the nitrile, obtained as described hereinabove under a), in 70 cc. of anhydrous ether is added drop by drop, while stirring to the Grignard compound prepared from 2.3 g. of magnesium and 12.6 g. of benzyl chloride. The resulting mixture is worked up by following the procedure described in Example 1 b). The above indicated amine is obtained in the form of a colorless oil; boiling point 153°C./0.04 mm. The yield is 73% of theoretical. The colorless hydrochloride melts at 172°C.

The new tertiary amines obtained according to the present invention are valuable therapeutic agents; they are all musculotropic spasmolytics and a number of them possess a high spasmolytic activity, especially upon the uterus. They are capable of relieving spasms of the smooth muscles caused by barium chloride, the dose required, in many instances, being smaller than that of papaverine. They also are capable, for instance, of abolishing cardiospasms in the rabbit.

Furthermore, said new compounds possess marked nicotinolytic properties as well as a parasympatholytic activity upon intestines contracted by acetyl choline.

Some of said new compounds have a strong analgetic effect, others have a coronary and vasodilatory effect and can be employed as blood pressure reducing agents while certain other compounds cause an increase in blood pressure.

The new compounds have been successfully administered in veterinary therapy, for instance, to control spasms of the oesophagus, a condition which occurs in the horse, and in other spastic conditions. There are indications that the new compounds are also of value in human therapy in all instances where, for instance, papaverine is employed.

Further compounds within the scope of the present invention, which we have prepared, are listed in the following Table. This Table also contains the physical characteristics, the yield and the method of preparation of these compounds.

TABLE

Example No.	Tertiary Amine produced	Amine B.P. °C. mm	Hydrochloride M.P. °C.	Yield % Th.	Prepared from Nitrile	Grignard Compound of	According to example
5	1-phenyl-2-pyrrolidino pentane	105/0,5		78	2-phenyl-1-pyrrolidino propionitrile	*n*-propyl bromide	2B
6	1-phenyl-2-piperidino pentane	100—101/0,2		70	2-phenyl-1-piperidino propionitrile	*n*-propyl bromide	2b
7	1-phenyl-2-pyrrolidino hexane	108—110/0,6		74	2-phenyl-1-pyrrolidino propionitrile	*n*-butyl bromide	2b
8	1-phenyl-2-pyrrolidino-3-methyl butane	88/0,2		71	2-phenyl-1-pyrrolidino propionitrile	isopropyl bromide	2b
9	1-phenyl-2-di-*n*-butylamino-3-phenylpropane	139/0,08	144—145	51	2-phenyl-1-di-*n*-butyl-amino propionitrile	benzylchloride	3b
10	1-phenyl-2-dimethylamino-4-phenylbutane	115—117/0,2	138—140	75	2-phenyl-1-dimethyl-amino-propionitrile	β-phenylethyl-bromide	1b
11	1-phenyl-2-diethylamino-3-methyl-3-phenyl-propane	116/0,09	210	69	a) 2-phenyl-1-diethyl-amino-propionitrile b) 2-phenyl-2-methyl-1-diethylamino-propionitrile	a) 1-phenyl-1-bromethane b) benzylchloride	1b 4b
12	1-phenyl-2-pyrrolidino-3-methyl-3-phenyl-propane	136—137/0,15	196—197	70	a) 2-phenyl-1-pyrrolidino-propionitrile b) 2-phenyl-2-methyl-1-pyrrolidino-propionitrile	a) 1-phenyl-1-bromethane b) benzylchloride	1b 4b
13	1-phenyl-2-diethylamino-4-phenyl-butane	119—120/0,04	—	82	a) phenyl-2-1-diethyl-aminopropionitrile b) 3-phenyl-1-diethyl-amino-butyronitrile	a) -phenylethylbromide b) benzylchloride	1b 4b

PATENT

TABLE (continued)

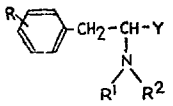
Example No.	Tertiary Amine produced	Amine B.P. °C. mm	Hydrochloride M.P. °C.	Yield % Th.	Prepared from Nitrile	Grignard Compound of	According to example
14	1-phenyl-2-di-*n*-butylamino-4-phenyl-butane	159—160/0,25	133	60	a) 2-phenyl-1-di-n-butylamino-propionitrile	a) -phenylethyl-bromide	1b
					b) 3-phenyl-1-di-*n*-butylamino-butyronitrile	b) benzylchloride	4b
15	1-phenyl-2-pyrrolidino-4-phenyl-butane	142/0,15	—	79	a) 2-phenyl-1-pyrrolidino-propionitrile	a) -phenylethyl-bromide	1b
					b) 3-phenyl-1-pyrrolidino-butyronitrile	b) benzylchloride	4b
16	1-phenyl-2-diethylamino-3-methyl-4-(*p*-isopropyl-phenyl)-butane	144—145/0,1	—	68	3-(*p*-isopropyl-phenyl)-2-methyl-1-diethylamino-butyronitrile	benzylchloride	4b
17	1-phenyl-2-morpholino-3-methyl-4-(*p*-isopropyl-phenyl)-butane	180/0,08	—	69	3-(*p*-isopropyl-phenyl)-2-methyl-1-morpholino-butyronitrile	benzylchloride	4b
18	1-phenyl-2-morpholino-3-methyl-butane	118—120/0,6	178	62	2-phenyl-1-morpholino-propionitrile	isopropylbromide	1b
19	1-phenyl-2-pyrrolidino-3-phenyl-propane	150/0,4	174	71	2-phenyl-1-pyrrolidino-propionitrile	benzylchloride	1b

As stated hereinbefore and set forth in the examples, the new tertiary amines are capable of forming acid addition salts with inorganic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, nitric acid, and others, as well as with organic acids, such as acetic acid, propionic acid, butyric acid, valeric acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, lactic acid, tartaric acid, citric acid, malic acid, benzoic acid, phthalic acid, cinnamic acid, salicylic acid, nicotinic acid, furane-2-carboxylic acid, and others. The hydrochloride, however, has proved to be especially suitable for practical purposes.

The new tertiary amines are also capable of forming quaternary compounds with quaternising agents such as methyl iodide, benzyl bromide, methyl bromide, ethyl iodide, isobutyl bromide, and other alkyl chlorides, bromides, or iodides, dimethyl sulphate, diethyl sulphate, *p*-toluene sulphonic acid alkyl esters, cyclohexyl halides, cyclopentyl halides, and others, whereby quaternization is effected by any convenient procedure.

WHAT WE CLAIM IS:—

1. As new compounds tertiary amines of the general formula



in which R represents a hydrogen atom, a lower alkyl or a lower alkoxy group. R^1 and R^2 which may be the same or different represent lower-alkyl, hydroxy lower-alkyl, cycloalkyl, monocyclic aryl or monocyclic aryl substituted lower alkyl groups or together with the nitrogen atom form a heterocyclic ring containing, if desired, a further heteroatom and Y represents a substituted or unsubstituted aralkyl group or an alkyl group containing from 3—12 carbon atoms, and their acid addition and quaternary salts.

2. Compounds as claimed in claim 1 in which R^1 and R^2 together with the nitrogen atom form a pyrrolidine, piperidine or morpholine ring.

3. 1-phenyl-2-pyrrolidino-pentane.

4. 1-phenyl-2-piperidino-pentane.

5. 1-phenyl-2-pyrrolidino-hexane.

6. 1-phenyl-2-pyrrolidino-3-methyl-butane.

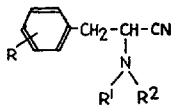
7. 1-phenyl-2-dimethylamino - 4 - phenyl-butane.

8. The tertiary amines as claimed in claim 1 specifically described herein.

9. The quaternary salts of the tertiary amines as claimed in claim 1 specifically described herein.

10. The hydrochlorides of the tertiary amines as claimed in claim 1 specifically described herein.

11. A process for the production of tertiary amines of the general formula stated in claim 1 in which an α-tertiary aminoacetonitrile of the general formula



is condensed with an organomagnesium halide of the general formula

Hal—Mg—Y

where R, R^1, R^2 and Y have the meanings stated in claim 1 and Hal represents a chlorine, bromine or iodine atom, in the presence of an inert solvent and the resulting condensation product is hydrolytically decomposed to give the desired amine.

12. A process as claimed in Claim 11 in which the inert solvent is ether, dibutyl ether, dioxan, benzene or benzene/tetrahydrofuran.

13. A process as claimed in claim 11 or claim 12 in which the reaction is carried out at the boiling point of the solvent employed.

14. A process as claimed in any of claims 11—13 in which the tertiary amine is subsequently reacted with a quaternary agent to form a quaternary salt of the amine.

15. A process for the production of the compounds claimed in claim 1 substantially as herein described with reference to any of the examples.

For the Applicants,
FRANK B. DEHN & CO.,
Chartered Patent Agents,
Kingsway House, 103, Kingsway,
London, W.C.2.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1959.
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

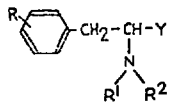
6 AUG 1959

As stated hereinbefore and set forth in the examples, the new tertiary amines are capable of forming acid addition salts with inorganic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, nitric acid, and others, as well as with organic acids, such as acetic acid, propionic acid, butyric acid, valeric acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, lactic acid, tartaric acid, citric acid, malic acid, benzoic acid, phthalic acid, cinnamic acid, salicylic acid, nicotinic acid, furane-2-carboxylic acid, and others. The hydrochloride, however, has proved to be especially suitable for practical purposes.

The new tertiary amines are also capable of forming quaternary compounds with quaternising agents such as methyl iodide, benzyl bromide, methyl bromide, ethyl iodide, isobutyl bromide, and other alkyl chlorides, bromides, or iodides, dimethyl sulphate, diethyl sulphate, *p*-toluene sulphonic acid alkyl esters, cyclohexyl halides, cyclopentyl halides, and others, whereby quaternization is effected by any convenient procedure.

WHAT WE CLAIM IS:—

1. As new compounds tertiary amines of the general formula



in which R represents a hydrogen atom, a lower alkyl or a lower alkoxy group. R^1 and R^2 which may be the same or different represent lower-alkyl, hydroxy lower-alkyl, cycloalkyl, monocyclic aryl or monocyclic aryl substituted lower alkyl groups or together with the nitrogen atom form a heterocyclic ring containing, if desired, a further heteroatom and Y represents a substituted or unsubstituted aralkyl group or an alkyl group containing from 3—12 carbon atoms, and their acid addition and quaternary salts.

2. Compounds as claimed in claim 1 in which R^1 and R^2 together with the nitrogen atom form a pyrrolidine, piperidine or morpholine ring.

3. 1-phenyl-2-pyrrolidino-pentane.

4. 1-phenyl-2-piperidino-pentane.

5. 1-phenyl-2-pyrrolidino-hexane.

6. 1-phenyl-2-pyrrolidino-3-methyl-butane.

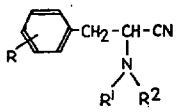
7. 1-phenyl-2-dimethylamino - 4 - phenyl-butane.

8. The tertiary amines as claimed in claim 1 specifically described herein.

9. The quaternary salts of the tertiary amines as claimed in claim 1 specifically described herein.

10. The hydrochlorides of the tertiary amines as claimed in claim 1 specifically described herein.

11. A process for the production of tertiary amines of the general formula stated in claim 1 in which an α-tertiary aminoacetonitrile of the general formula



is condensed with an organomagnesium halide of the general formula

Hal—Mg—Y

where R, R^1, R^2 and Y have the meanings stated in claim 1 and Hal represents a chlorine, bromine or iodine atom, in the presence of an inert solvent and the resulting condensation product is hydrolytically decomposed to give the desired amine.

12. A process as claimed in Claim 11 in which the inert solvent is ether, dibutyl ether, dioxan, benzene or benzene/tetrahydrofuran.

13. A process as claimed in claim 11 or claim 12 in which the reaction is carried out at the boiling point of the solvent employed.

14. A process as claimed in any of claims 11—13 in which the tertiary amine is subsequently reacted with a quaternary agent to form a quaternary salt of the amine.

15. A process for the production of the compounds claimed in claim 1 substantially as herein described with reference to any of the examples.

For the Applicants,
FRANK B. DEHN & CO.,
Chartered Patent Agents,
Kingsway House, 103, Kingsway,
London, W.C.2.

Leamington Spa: Printed for Her Majesty's Stationery Office, by the Courier Press.—1959.
Published by The Patent Office, 25, Southampton Buildings, London, W.C.2, from which copies may be obtained.

6 AUG 1959

* C L M S *