4972.

PATENT SPECIFICATION

773,780

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International Classification:—C07c, d.

COMPLETE SPECIFICATION

Improvements in or relating to the Preparation of Substituted Morpholines

We, ALBERT BOEHRINGER, ERNST BOEHRINGER, ILSE LIEBRECHT and JULIUS LIEBRECHT, all German citizens and all of Ingelheim am Rhein, Germany, trading in partnership as C. H. BOEHRINGER SOHN, 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:—

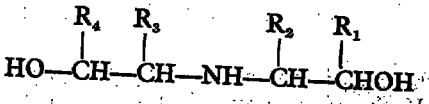
The present invention relates to a process for the production of new substituted morpholines.

Processes for the production of morpholine derivatives are already known in which diethanolamines are treated, for example, by heating to temperatures of 160—180° C. with 70% sulphuric acid, in order to bring about morpholine ring closure.

However, it is particularly necessary when preparing substituted morpholines to use specially mild reaction conditions for the ring closure. In this case the danger of undesired side reactions exists, which can be brought about by the influence of the temperature or the acids employed for the ring closure.

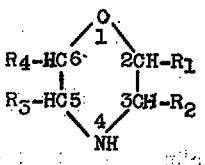
The object of the present invention is, therefore, a process by which ring closure leading to the production of morpholine derivatives can be carried out under particularly mild reaction conditions, e.g. without additional heating or with only slight heating. In specification No. 662,829 a process is described according to which ring closure takes place when the substituted diethanolamine is allowed to stand in solution. However, such an easy ring closure is limited to very definite individual cases, whereas generally vigorous conditions are necessary.

It has now surprisingly been found that a certain group of substituted diethanolamines of the general formula

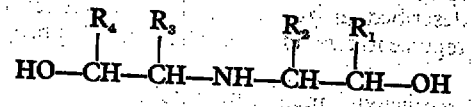


where R_1 is a phenyl residue, which if desired can be substituted by a hydroxyl group or alkyl or alkoxy residue having from 1—5 carbon atoms, R_2 and R_3 are hydrogen atoms or phenyl or alkyl residues and R_4 is a hydrogen atom or a phenyl residue, can be subjected to morpholine ring closure under particularly mild conditions and without disturbing side-reactions.

According to the present invention, therefore, we provide a process for the preparation of substituted morpholines of the general formula



where R_1, R_2, R_3 and R_4 have the above-stated meanings, in which substituted diethanolamines of the general formula



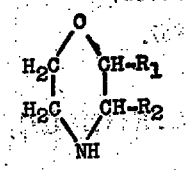
where R_1, R_2, R_3 and R_4 have the above-stated meanings, are treated with acid.

According to a feature of the invention ring closure is brought about with concentrated sulphuric acid without heating.

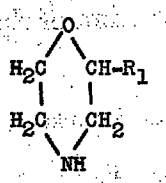
According to a further feature of the inven-

tion ring closure is brought about by treating the substituted diethanolamines with dilute acid at temperatures below 100° C.

This invention also specifically includes, as new compounds, morpholine derivatives of the general formulae



(where R_1 is an unsubstituted phenyl residue and R_2 is an alkyl group having from 1—5 carbon atoms), and

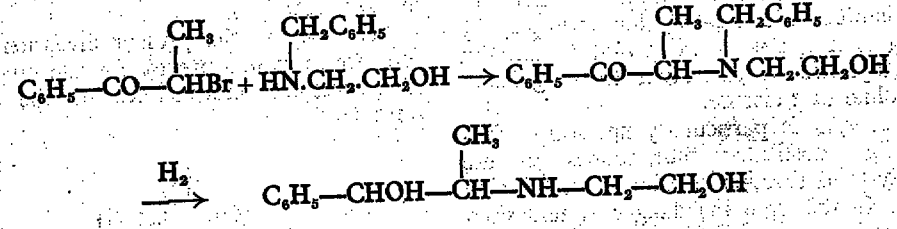


(where R_1 is a mono-hydroxy-phenyl residue).

If the ring closure is brought about with concentrated sulphuric acid without heating, then, using the free base as starting material it will be convenient to work under good cooling conditions in order to remove the liberated heat of neutralization. However, one can also start from a salt of the base, which can be introduced into the concentrated sulphuric acid without special cooling. The desired morpholine derivative is formed after several hours standing and can be worked up in the usual manner, e.g. by pouring on to ice, making alkaline and extracting with ether and purifying the morpholine derivative by crystallization or distillation.

When working with dilute acids the reaction is also carried out, as mentioned above, under relatively mild conditions. In many cases it is sufficient to operate at room temperature. With other derivatives gentle warming or heating to waterbath temperature with an aqueous or alcoholic acid is necessary. This probably depends on the type of substituents. The preferable reaction conditions can readily be ascertained in any given case by simple preliminary tests. As dilute acids, which may be used in the process according to the invention can be mentioned by way of example: sulphuric acid, hydrobromic acid and hydrochloric acid.

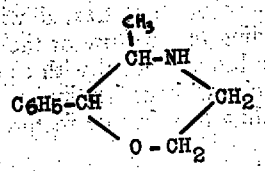
The substituted diethanolamines used as starting materials can be prepared by any suitable method. It has, however, been found preferable, to produce these substituted diethanolamines in the following manner: benzylethanolamine is reacted with a suitable halogenated ketone and the reaction product is subjected to catalytic hydrogenation so that the benzyl residue is split off and the keto group is simultaneously reduced to a carbinol group. These reactions are illustrated by the following reaction scheme:



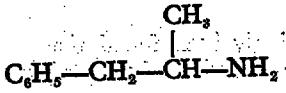
$(R_3 = R_4 = H,\ R_2 = CH_3,\ R_1 = C_6H_5)$

The morpholines produced according to the invention are valuable pharmaceuticals or intermediate products for the production of pharmaceuticals. The pharmacological action of the substances according to invention will be described in greater detail by reference to a representative of this class, i.e. 2-phenyl-3-methyl-morpholine. The principal effect of this substance is shown by a comparison with Benzedrine (Registered Trade Mark) or pervetine, which it surpasses in the particularly desired effect of deferring fatigue, whilst it is less toxic and brings about less stimulation.

2-phenyl-3-methyl-morpholine



Benzedrine



Toxicity: In the case of white mice the LD 50 is 200 mg/kg by subcutaneous injection; the corresponding value for benzedrine is 75 mg/kg. The LD 50 by per oral administration in white mice is 475 mg/kg; for benzedrine it is 95 mg/kg. The LD 50 by intraperitoneal injection in white mice is 200 mg/kg; for benzedrine it is 50 mg/kg.

The stimulation effect on mice and rats, measured by the motility increase, is some 7—10 times weaker than that of benzedrine.

Blood pressure effect: This is approximately 1000—1500 times weaker than that of adrenalin.

Blood sugar effect: 2-phenyl-3-methylmorpholine does not affect the *blood sugar* level on intramuscular injection in dogs in doses of 1.5 to 10 mg/kg. The raising of the blood sugar level by glucose per os is likewise unchanged by this substance.

It was found that the contraction of the nictitating membrane of cats is reduced or cancelled out after administration of 2-phenyl-3-methyl-morpholine with cocaine and anaesthatising. Here too the substance reacts fundamentally like benzedrine.

With human beings doses of up to 25 mg *per os* give no detrimental effects, but cause a definite deferment of fatigue. In such doses the substances produce no stimulation as with pervetine and no irregular thought changes; on the contrary a very good power of concentration is afterwards noticeable. With higher dosages and parenteral application stimulation can be produced as with pervetine, but it is not accompanied by a corresponding rise in blood pressure.

The other substances of this class show similar effects.

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

EXAMPLE 1.

2-phenylmorpholine.

10 g of β-phenyl-β,β^1-dihydroxy-diethylamine-hydrochloride are dissolved in 15 ccs of concentrated sulphuric acid and left to stand overnight at room temperature. The solution is then poured on to ice, made alkaline with caustic soda solution and the base taken up in ether. After drying, the ether residue is fractionally distilled. The 2-phenylmorpholine obtained distills at 145° C. and 14 mm. Yield 83%. The hydrochloride is obtained with alcoholic hydrochloric acid and acetone, Mp. = 151° C.

EXAMPLE 2.

2-phenyl-3-methylmorpholine.

Following the same procedure as in example 1, 2-phenyl-3-methyl-morpholine is obtained in a 92% yield from β-phenyl-α-methyl-β,β^1-dihydroxy-diethylaminehydrochloride. The base is a liquid, b.p. at 12 mm. H_g = 138° C. The hydrochloride crystallizes from alcoholic hydrochloric acid and acetone, Mp. = 182° C.

EXAMPLE 3.

2,3-diphenylmorpholine.

10 g of α,β-diphenyl-β,β^1-dihydroxy-diethylamine-hydrochloride are dissolved in 15 ccs of concentrated sulphuric acid and left to stand overnight at room temperature. The viscous solution is poured on ice and made alkaline with concentrated ammonia, and the 2,3-diphenylmorpholine precipitates in crystalline form, Mp. = 91° C. Further purification is carried out by formation of the hydrochloride, which crystallises out on treatment of the base with alcoholic hydrochloric acid and acetone. Mp. = 265° C., yield 67%.

EXAMPLE 4.

2,6-diphenylmorpholine.

10 g of β,β-diphenyl-β,β^1-dihydroxy-diethylamine-hydrochloride dissolved in 15 ccs of concentrated sulphuric acid are allowed to stand overnight at room temperature. After pouring on to ice, the solution is made alkaline with ammonia. The base precipitates as a tough, sticky mass, which is taken up in chloroform. The solution is dried and the solvent distilled off. The residue, when triturated with ether, produces the crystalline base with Mp. = 108° C. The hydrochloride is obtained with alcoholic hydrochloric acid and acetone. Mp. = ca 200° C. (dec.). Yield 65%.

EXAMPLE 5.

2-phenyl-3-ethylmorpholine.

1-phenyl-1-keto-2-bromobutane is reacted with benzylethanolamine and the aminoketone thus obtained is hydrogenated in the form of its hydrochloride, in methanol and in the presence of palladised charcoal. The resulting 1-phenyl-1-hydroxy-2-ethanolaminobutane was obtained as the hydrochloride of Mp. = 147° C. (dec.). The base recrystallized from benzene melts at 27° C., the bioxalate obtained by addition of an alcoholic solution of oxalic acid and ether is readily soluble in alcohol and melts at 90° C.

1 g of the base was dissolved in 1.5 ccs of concentrated sulphuric acid, the temperature rising to *ca.* 40° C. on account of the heat of neutralization. After standing overnight it was poured over ice, made alkaline, shaken out with ether, and reacted with an excess of an alcoholic solution of oxalic acid; 2-phenyl-3-ethylmorpholine-bioxalate was obtained as crystals of Mp. = 165° C., which are difficultly soluble in alcohol.

EXAMPLE 6.

2-(*p*-tolyl)-morpholine.

67 g of *p*-methyl-acetophenone in 500 ccs of benzene are slowly treated with 25 ccs of bromine and the benzene distilled off after standing for a while. The residue is treated with 150 g of benzylethanolamine in 150 ccs of benzene, care being taken that the temperature does not exceed 55° C. Benzylethanolaminehydrobromide crystallizes out, and is filtered off the next day by suction and washed with benzene. The benzene solution is shaken

2 or 3 times with water, dried over sodium sulphate and the benzene distilled off. The residue crystallizes with alcoholic hydrochloric acid. It is filtered off with suction and washed with acetone. The reaction product 1-(*p*-tolyl)-1-keto-2-benzyl-ethanolaminoethane is obtained in a 60% yield, Mp. = 171° C.

100 g of this product are hydrogenated in 1 litre of methanol in the presence of 30 ccs of 2% palladium chloride solution and charcoal. When 2 mol of hydrogen have been absorbed, the reaction ceases. The catalyst is filtered off with suction, the methanol is removed by distillation and the residue, 1-(*p*-tolyl) - 1 - hydroxy-2-ethanolaminoethane, is heated with 700 ccs of 30% sulphuric acid over a water bath in an open flask. It is allowed to cool, diluted with 700 ccs of water and made alkaline with caustic soda solution. It is then shaken three times with ether, the ethereal solution is dried and the ether evaporated. The residue produces crystals of 2 - (*p*-tolyl)-morpholine-hydrochloride with alcoholic hydrochloric acid, which are filtered off with suction and washed with acetone. Mp. = 181° C. Yield = 73% of theory.

EXAMPLE 7.

3-phenyl-2-(*p*-methoxyphenyl)-morpholine.

50 g of 2-phenyl-1-hydroxy-1-(*p*-methoxyphenyl) - 2-ethanolamino-ethane-hydrochloride produced by hydrogenation in the presence of palladium of 2-phenyl-1-keto-1-(*p*-methoxyphenyl) - 2-benzyl-ethanolaminoethane-hydrochloride obtained from 2-phenyl-1-keto-1-(*p*-methoxyphenyl)-2-bromoethane by reacting with benzylethanolamine, are boiled with 500 ccs of 5% hydrochloric acid for two hours and after cooling, the solution is made alkaline with caustic soda solution, the base taken up in chloroform and the chloroform distilled. The residue when treated with alcoholic hydrochloric acid gives the hydrochloride of 3-phenyl - 2-(*p*-methoxyphenyl)-morpholine of Mp. = 238° C.

EXAMPLE 8.

2-(*p*-hydroxyphenyl)-morpholine.

1 - (*p* - hydroxy-phenyl)-1-keto-2-ethanolaminoethane-hydrochloride obtained from 1-(*p* - hydroxyphenyl)-1-keto-2-bromoethane by reacting with monoethanolamine is hydrogenated in methanol in the presence of palladium at room temperature. The methanol is distilled from the weakly acid reacting solution, and the hydrochloride of 2-(*p*-hydroxyphenyl)-morpholine of Mp. = 220° C. crystallizes out directly.

EXAMPLE 9.

2-phenyl-3-methyl-morpholine.

10 g of β-phenyl-α-methyl-β,β¹-dihydroxydiethylaminehydrochloride, produced from bromopropiophenone by reaction with benzylethanolamine and hydrogenation of the resulting β - phenyl-α-methyl-β-keto-β¹-hydroxy-N - benzyl - diethylaminehydrochloride with palladium and charcoal, are heated on a water-bath for 6 hours in 10% hydrochloric acid. After the usual working up the hydrochloride of 2-phenyl-3-methyl-morpholine crystallizes from methyl-alcoholic hydrochloric acid and acetone. Mp. = 182° C.

EXAMPLE 10.

2,6-diphenyl-3,5-dimethyl-morpholine.

2 mols of 1-phenyl-1-keto-2-bromo-propane produces, on reaction with 1 mol of benzylamine, N - benzyl-β,β¹-diphenyl-β,β¹-diketo-α,α¹-dimethyl-diethylamine, which on catalytic reduction gives β,β¹-diphenyl-β,β¹-dihydroxy-α,α¹-dimethyl-diethylamine.

1 g of this product is dissolved in 1.5 ccs of concentrated sulphuric acid and the product worked up in the normal manner after standing overnight at room temperature. 2,6-Diphenyl - 3,5-dimethyl-morpholine, Mp. = 147° C., is obtained.

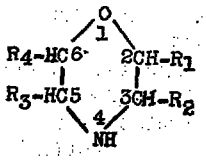
EXAMPLE II.

2-(*m*-hydroxyphenyl)-morpholine.

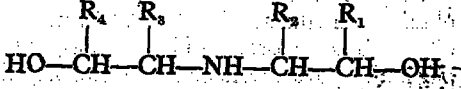
1 - (3-hydroxyphenyl)-1-hydroxy-2-ethanolaminoethane, prepared by the catalytic hydrogenation of 1 - (3-hydroxyphenyl)-1-keto-2-ethanolaminoethane, is heated for 2 hours on a water bath with ten times the quantity of 20% hydrochloric acid, filtered over animal charcoal, and reduced *in vacuo*. The residue is made strongly alkaline with ammonia. The base, 2-(*m*-hydroxyphenyl)-morpholine crystallizes out, is filtered with suction and washed with water, M.pt. = 177° C., yield 35% of the theoretical yield.

What we claim is:—

1. A process for the preparation of substituted morpholines of the general formula



where R_1 is a phenyl residue, which may be substituted by a hydroxyl group or an alkyl or alkoxy residue, having from 1—5 carbon atoms, R_2 and R_3 are hydrogen atoms or phenyl or alkyl residues and R_4 is a hydrogen atom or a phenyl residue, in which substituted diethanolamines of the general formula



wherein R_1, R_2, R_3 and R_4 have the above-stated meanings, are treated with acid.

2. A process as claimed in claim 1, in which ring closure is brought about with concentrated sulphuric acid without heating.

3. A process as claimed in claim 2, in which the starting material is the free substituted diethanolamine and the reaction is carried out with cooling.

2 or 3 times with water, dried over sodium sulphate and the benzene distilled off. The residue crystallizes with alcoholic hydrochloric acid. It is filtered off with suction and washed with acetone. The reaction product 1-(*p*-tolyl)-1-keto-2-benzyl-ethanolaminoethane is obtained in a 60% yield, Mp. = 171° C.

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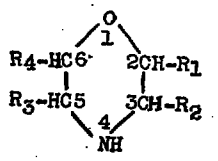
EXAMPLE 11.

2-(*m*-hydroxyphenyl)-morpholine.

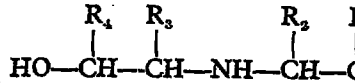
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1. A process for the preparation of substituted morpholines of the general formula



where R_1 is a phenyl residue, which may be substituted by a hydroxyl group or an alkyl or alkoxy residue, having from 1—5 carbon atoms, R_2 and R_3 are hydrogen atoms or phenyl or alkyl residues and R_4 is a hydrogen atom or a phenyl residue, in which substituted diethanolamines of the general formula



wherein R_1, R_2, R_3 and R_4 have the above-stated meanings, are treated with acid.

2. A process as claimed in claim 1, in which ring closure is brought about with concentrated sulphuric acid without heating.

3. A process as claimed in claim 2, in which the starting material is the free substituted diethanolamine and the reaction is carried out with cooling.

* C L M S *

4. A process as claimed in claim 2, in which the starting material is a salt of the substituted diethanolamine and the reaction is carried out at room temperature.

5. A process as claimed in claim 1, in which ring closure is brought about by using dilute acid at temperatures below 100° C.

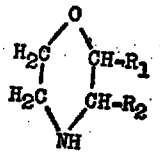
6. A process as claimed in claim 5, in which sulphuric acid, hydrobromic acid or hydrochloric acid are used as the dilute acid.

7. A process as claimed in any of the preceding claims, in which the substituted diethanolamine used as starting material is obtained by reacting benzylethanolamine with a suitable halogenated ketone and catalytic hydrogenation of the reaction product.

8. A process for the preparation of substituted morpholines substantially as herein described.

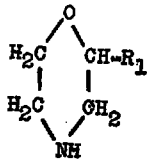
9. A process for the preparation of substituted morpholines substantially as herein described with reference to the examples.

10. As new compounds, morpholine derivatives of the general formula



where R_1 is an unsubstituted phenyl residue and R_2 is an alkyl group having from 1—5 carbon atoms.

11. As new compounds, morpholine derivatives of the general formula



where R_1 is a mono-hydroxy-phenyl residue.

12. 2-(*p*-hydroxy phenyl)-morpholine.

13. 2-phenyl-3-methyl-morpholine.

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

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