PATENT SPECIFICATION

608,208

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No. 5083/46 }

(One Complete Specification left under Section 91 (2) of the Patents and Designs Acts, 1907 to 1942.)

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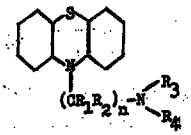
Index at acceptance:—Class 2(iii), C2(a: b3).

COMPLETE SPECIFICATION

Process for the Preparation of Phenthiazine Derivatives

We, SOCIETE DES USINES CHIMIQUES RHONE-POULENC, a French body corporate, of 21 rue Jean Goujon, Paris, 8e, France, do hereby declare the nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

This invention is for improvements in or relating to the preparation of new phenthiazine derivatives, more particularly new amino derivatives of phenthiazine which are substituted on the ring nitrogen atom by a dialkylaminoalkyl group. These new amino derivatives conform to the general formula:—



in which R_1 and R_2 are the same or are different and represent hydrogen atoms or alkyl groups, R_3 and R_4 represent alkyl groups and n is an integer greater than 1. The benzene nuclei may be substituted by alkyl or alkoxy groups. It should be understood that the designation "$(CR_1R_2)_n$" as used in this specification and in the appended claims covers not only straight aliphatic chains in which the successive CR_1R_2 groups are identical, but also branched aliphatic chains in which successive CR_1R_2 groups may be different. For example, the said designation includes the branched chain $—CH_2—C(CH_3)_2—$.

According to the present invention, these new amino derivatives are prepared by the action on phenthiazine, or a phenthiazine in which the benzene nuclei contain alkyl or alkoxy groups, of a dialkylaminoalkyl halide in the presence of a halogen-acid-binding agent, preferably sodamide. Preferably, the reaction is effected at elevated temperature and in the presence of an organic diluent.

The new compounds of the aforesaid general formula possess a marked anti-dyspnoeic and anti-histaminic activity and are therefore of therapeutic value.

The process of the present invention is illustrated by the following non-limitative Examples:—

EXAMPLE I.

60 g. of phenthiazine, 240 g. of xylene and 14 g. of sodamide (85%) are mixed and heated under reflux. 40 g. of diethylaminochloroethane are then added little by little during one hour and thirty minutes while maintaining the temperature of the reaction mixture; heating under reflux is then continued for a further hour. The mixture is cooled, taken up in 800 cc. of water and slightly acidified with hydrochloric acid. The xylene is decanted, and the aqueous layer neutralised with a little caustic soda and filtered. The filtrate is then rendered strongly alkaline and the base which separates extracted with ether. The ether layer is decanted, dried, the ether driven off and the residue rectified under vacuum. There are thus recovered 63 g. of N - diethylaminoethylphenthiazine, which boils at 200—205° C. under 1.1 mm. of mercury. This base gives an hydrochloride melting at 174—175° C. (Maquenne block).

In the same way, there may be prepared N - diethylamino-propyl-phenthiazine which boils at 213—215° C. under 1.5 mm. and N-dimethylamino-ethyl-phenthiazine which boils at 183—187° C. under 1 mm. and the hydrochloride of which melts at 201—201.5° C. (Maquenne block).

[Price 2/-]

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EXAMPLE II.

30 g. of phenthiazine, 120 g. of xylene and 7 g. of sodamide (80%) are mixed and heated under reflux. 23 g. of 3-dimethylamino-1-chloro-propane, diluted with its own weight of xylene, is then added little by little during one hour, while maintaining the temperature of the reaction mixture; heating under reflux is then continued for a further hour. After cooling, the mixture is taken up in 400 cc. of water and rendered slightly acid with hydrochloric acid. The xylene is decanted, the aqueous layer is rendered strongly alkaline with caustic soda and the base which separates is extracted with ether. On rectification of the ether extract, there is obtained N-(3¹-dimethylamino-propyl)-phenthiazine which boils at 208—210° C. under 3 mm. The hydrochloride of this base melts at 181° C. (Maquenne block).

EXAMPLE III.

Following the method of Example II but using an equal quantity of 1-dimethylamino-2-chloro-propane instead of 3-dimethylamino-1-chloro-propane, there is obtained N-(2¹-dimethylamino-2-methyl-ethyl)-phenthiazine which boils at 190—192° C. under 3 mm. The corresponding hydrochloride melts at 204° C. (Maquenne block).

EXAMPLE IV.

A mixture of 20 g. of 2-methoxy-phenthiazine (prepared according to the method of Pumaneret-Gassner, B., *46*, 2325, 1913), 80 g. of xylene and 4.4 g. of sodamide (85%) is heated under reflux. There is added little by little over a period of one hour while maintaining the temperature of the reaction mixture 11.5 g. of dimethylamino-chloroethane, diluted with its own weight of xylene; heating under reflux is then continued for a further period of one hour. The reaction mixture is then treated in accordance with the procedure of Example II where there is obtained N-(2¹-dimethylamino-ethyl)-2-methoxy-phenthiazine which boils at 220—223° C. under 3 mm. The hydrochloride of this base melts at 182° C. (Maquenne block).

EXAMPLE V.

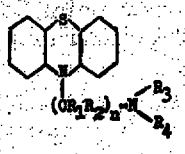
A mixture of 20 g. of 2-methoxy-phenthiazine, 80 g. of xylene and 4.4 g. of sodamide (85%) is heated under reflux. There is then added little by little over a period of one hour 13 g. of 1-dimethylamino-2-chloro-propane diluted with its own weight of xylene; the heating under reflux is then continued for a further period of one hour. The reaction mixture is then treated as described in Example II when there is obtained N-(2¹-dimethylamino-2¹-methyl-ethyl)-2-methoxy-phenthiazine which boils at 218—222° C. under 3 mm.

EXAMPLE VI.

A mixture of 20 g. of phenthiazine, 80 g. of xylene and 5 g. of sodamide (85%) is heated under reflux. There is then added little by little over a period of one hour 17 g. of 1-dimethylamino-2:2-dimethyl-3-chloro-propane, diluted with its own weight of xylene; heating under reflux is then continued for a further period of one hour. On treating the reaction mixture in accordance with the method of Example II there is obtained N-(3¹-dimethylamino-2¹:2¹-dimethyl-propyl)-phenthiazine which boils at 196—199° C. under 3 mm.

Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:—

1. Process for the preparation of new therapeutically valuable amino derivatives of phenthiazine of the general formula:



(in which R_1 and R_2 represent hydrogen atoms or alkyl groups, R_3 and R_4 represent alkyl groups and n is an integer greater than 1) which comprises reacting phenthiazine, or a phenthiazine in which the benzene nuclei contain alkyl or alkoxy groups, with a dialkylaminoalkyl halide in the presence of a halogen-acid-binding agent.

2. Process as claimed in claim 1, wherein the reaction is effected in the presence of sodamide as acid binding agent.

3. Process as claimed in claim 1 or 2, wherein the reaction is effected at elevated temperature and in an organic diluent.

4. Process for the preparation of new amino derivatives of phenthiazine substantially as hereinbefore described.

5. Amino derivatives of phenthiazine having the general formula set forth in claim 1 when prepared by the process claimed in any one of the preceding claims.

EXAMPLE II.

30 g. of phenthiazine, 120 g. of xylene and 7 g. of sodamide (80%) are mixed and heated under reflux. 23 g. of 3-dimethylamino-1-chloro-propane, diluted with its own weight of xylene, is then added little by little during one hour, while maintaining the temperature of the reaction mixture; heating under reflux is then continued for a further hour. After cooling, the mixture is taken up in 400 cc. of water and rendered slightly acid with hydrochloric acid. The xylene is decanted, the aqueous layer is rendered strongly alkaline with caustic soda and the base which separates is extracted with ether. On rectification of the ether extract, there is obtained N-(3¹-dimethylamino-propyl)-phenthiazine which boils at 208—210° C. under 3 mm. The hydrochloride of this base melts at 181° C. (Maquenne block).

EXAMPLE III.

Following the method of Example II but using an equal quantity of 1-dimethylamino-2-chloro-propane instead of 3-dimethylamino-1-chloro-propane, there is obtained N-(2¹-dimethylamino-2-methyl-ethyl)-phenthiazine which boils at 190—192° C. under 3 mm. The corresponding hydrochloride melts at 204° C. (Maquenne block).

EXAMPLE IV.

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EXAMPLE V.

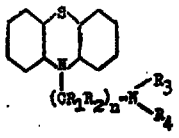
A mixture of 20 g. of 2-methoxy-phenthiazine, 80 g. of xylene and 4.4 g. of sodamide (85%) is heated under reflux. There is then added little by little over a period of one hour 13 g. of 1-dimethylamino-2-chloro-propane diluted with its own weight of xylene; the heating under reflux is then continued for a further period of one hour. The reaction mixture is then treated as described in Example II when there is obtained N-(2¹-dimethylamino-2¹-methyl-ethyl)-2-methoxy-phenthiazine which boils at 218—222° C. under 3 mm.

EXAMPLE VI.

A mixture of 20 g. of phenthiazine, 80 g. of xylene and 5 g. of sodamide (85%) is heated under reflux. There is then added little by little over a period of one hour 17 g. of 1-dimethylamino-2:2-dimethyl-3-chloro-propane, diluted with its own weight of xylene; heating under reflux is then continued for a further period of one hour. On treating the reaction mixture in accordance with the method of Example II there is obtained N-(3¹-dimethylamino-2¹:2¹-dimethyl-propyl)-phenthiazine which boils at 196—199° C. under 3 mm.

Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:—

1. Process for the preparation of new therapeutically valuable amino derivatives of phenthiazine of the general formula:



(in which R_1 and R_2 represent hydrogen atoms or alkyl groups, R_3 and R_4 represent alkyl groups and n is an integer greater than 1) which comprises reacting phenthiazine, or a phenthiazine in which the benzene nuclei contain alkyl or alkoxy groups, with a dialkylaminoalkyl halide in the presence of a halogen-acid-binding agent.

2. Process as claimed in claim 1, wherein the reaction is effected in the presence of sodamide as acid binding agent.

3. Process as claimed in claim 1 or 2, wherein the reaction is effected at elevated temperature and in an organic diluent.

4. Process for the preparation of new amino ~~derivates~~ of phenthiazine substantially as hereinbefore described.

5. Amino derivatives of phenthiazine having the general formula set forth in claim 1 when prepared by the process claimed in any one of the preceding claims.

* C L M S *

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