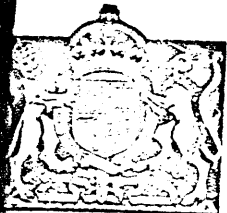


PATENT SPECIFICATION

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COMPLETE SPECIFICATION SCIENCE REFERENCE LIBRARY

Method for the Production of Substituted Benzyl Carbinamines and Product thereof

Communication from FRED P. NABENHAUER, a citizen of the United States of America, and residing at Overhill Road near County Line, in Somerton, County of Philadelphia, State of Pennsylvania, United States of America, Chemist.

I, LEONARD MELLERSH-JACKSON, a subject of the King of Great Britain, of the firm of Haseltine, Lake & Co., Chartered Patent Agents, 28, Southampton Buildings, London, W.C.2, in the County of Middlesex, 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 relates to a method for the production of substituted benzyl carbinamines having the formula $C_6H_5CH_2CHX.NH_2$, in which X is an alkyl or alhyl group and to the products produced in accordance with the method. More particularly, this invention relates to a method for producing benzyl methyl carbinamine and to the product produced in accordance with the method.

Heretofore various methods have been known for the production of substituted benzyl carbinamines, but variously they have been open to objections from the standpoint of economy, facility in practice, low yield and from the standpoint of lack of purity of product.

The method in accordance with this invention will be found to be economic, readily carried out in practice on a commercial scale, productive of a high yield and directly of products of a high degree of purity.

The method in accordance with this invention involves in essence the production of a substituted benzyl carbinamine by electrolytic reduction of a benzyl ketone oxime to a corresponding benzyl carbinamine. Thus, more specifically, the method in accordance with this invention involves the electrolytic reduction of benzyl methyl ketone oxime to benzyl methyl carbinamine.

In the practical adaptation of the method in accordance with this invention the benzyl ketone oxime used may be ob-

tained from any suitable source or prepared in any suitable or well known manner. Thus, for example, with reference more specifically to benzyl methyl ketone oxime, the oxime may be prepared by first heating a mixture of the calcium salts of phenylacetic acid and of acetic acid for the production of benzyl methyl ketone and then after separating the ketone, converting it into its oxime by treatment with hydroxylamine in alkaline solution. Similar procedure may be followed for the production of various benzyl ketone oximes for use in the preparation of the substituted benzyl carbinamines by the method in accordance with this invention.

In proceeding in accordance with this invention having at hand the benzyl ketone oxime, the oxime is subjected to electrolytic reduction in the presence of sulphuric acid with the production of the corresponding acid amine sulphate. The acid amine sulphate produced is then treated with alkali to free the amine. The free amine is then neutralized by dissolving in hydrochloric acid and the resultant neutral amine hydrochloride extracted. Finally, the neutral amine hydrochloride is treated with alkali to free the amine, which will desirably be distilled in vacuo for recovery in pure form.

The products in accordance with this invention, and especially benzyl methyl carbinamine, have been found to possess therapeutic value to a high degree and they, and especially benzyl methyl carbinamine, have been found to have a high remedial affect in cases of common colds and in such connection to be highly advantageous in treatment of the mucosa and respiratory passages, for the treatment of which they, and particularly benzyl methyl carbinamine, are especially adaptable in view of their volatility, which permits their application by inhalation.

Having indicated in a general way the procedure in accordance with this invention, it will now be exemplified in detail with reference to practical procedure for the preparation of benzyl methyl carbinamine, all with reference to the

accompanying drawing by which is diagrammatically illustrated a suitable form of apparatus for carrying out the essential procedure embodying this invention.

5 With reference to the drawing, A indicates a bath containing brine *b*. Within the bath A is positioned a glass jar C containing a layer of mercury *h* and a supply of electrolyte, as, for example, 10 battery acid *d* comprising, for example, sulphuric acid solution having a specific gravity of 1.4. In the jar C enough mercury is added to cover the bottom completely. This is connected by wire E and 15 a suitable lead wire *f* to a source of direct current G, which may, for example, be a motor generator. Within the jar C and submerged in the battery acid is a stirring device, as, for example, a paddle 20 *i* adapted to be operated in any suitable manner to effect agitation of the electrolyte.

Within the jar C and submerged in the electrolyte contained therein is positioned a porous porcelain cup J, in which 25 is contained a supply of electrolyte *k*, as, for example, battery acid comprising sulphuric acid having a specific gravity of 1.4. Within the cup J and immersed in the electrolyte is suspended a lead anode 30 L connected with the source of current by a suitable lead wire *f'*.

In carrying out the method in accordance with this invention, for example, 35 150cc. of sulphuric acid, specific gravity 1.4, will be placed in the cup J, sufficient mercury, and sulphuric acid, specific gravity 1.4, are placed in jar C, and brine is placed in brine bath A. The brine 40 is suitably cooled to maintain a temperature in jar C of about 25°C. or lower. To the sulphuric acid in the jar C there will then be added 150 grams of benzyl methyl ketone oxime obtained from any 45 suitable source or produced as indicated above. A current of about 6 to 10 volts and about 36 amperes corresponding to a current density of about 11 to 14 amperes per square decimeter will then be maintained as the reaction proceeds. At the 50 end of four hours a further addition of 150 grams of benzyl methyl ketone oxime will be made to the jar C.

The benzyl methyl ketone oxime will be 55 dissolved in the sulphuric acid solution in the jar C and as a result of the electrolytic action hydrogen will be discharged from the solution at mercury cathode *h*. The hydrogen will combine 60 with the oxime to form amine in the form of acid amine sulphate in solution in the sulphuric acid.

When the reduction of the total of 1500 65 grams of benzyl methyl ketone oxime added to the jar C is complete, the jar C

will contain acid benzyl methyl amine sulphate in concentrated solution.

On completion of the reduction, the concentrated solution of acid benzyl methyl amine sulphate will be diluted 70 with water and oily impurities permitted to separate. The oily impurities having been removed, an alkali, as caustic soda, will be added to the solution to neutralize 75 the acid and free the amine, which will float out as an oily layer which may be separated from the aqueous solution by decantation or other means. The oily layer or free amine, which is strongly basic, 80 is then neutralized by dissolving it in hydrochloric acid, which converts the amine into a neutral hydrochloride. Oily impurities are then removed from the resultant solution of neutral amine hydrochloride by extraction of the solution 85 with an organic solvent, as, for example, isopropyl ether.

The amine hydrochloride in solution is then converted to free amine by the addition of alkali. The free amine, which 90 is the benzyl methyl carbinamine product, will settle from the solution as an oily layer, which may be readily separated. The separated benzyl methyl carbinamine is then desirably distilled in vacuo for 95 recovery of the pure product. The distillation in vacuo may be carried out within a wide range of temperatures and under varying pressures. By way of 100 example, the distillation will desirably be carried out at a temperature of about 80°-90°C. and under a pressure of about one mm. mercury.

It will now be noted that the method 105 in accordance with this invention involves, from the broad standpoint, electrolytic reduction of a benzyl ketone oxime, more particularly benzyl methyl ketone oxime, to the corresponding amine sulphate and freeing the amine. More 110 specifically, the purity of the final product is assured by the separation of by-products from the original solution of amine sulphate obtained, freeing the amine, as by the addition of alkali, the 115 formation of amine hydrochloride by dissolving the amine in hydrochloric acid, extracting the amine hydrochloride solution with an organic solvent, converting the amine hydrochloride to free amine 120 and finally distilling in vacuo.

As will be appreciated, the unit of apparatus described above with reference to the accompanying drawing may be duplicated and the units arranged in batteries. 125 As will be obvious, the precise arrangement and capacity of the unit as described for illustrative purposes may be widely varied.

The method in accordance with this in- 130

vention will be found to be readily carried out on a commercial scale and will be found to be highly efficient and economic, it having been found that the yield obtained from the oxime runs in the neighborhood of 60% of theoretical. Economy in commercial practice will further be obtained from the fact that the oily impurities removed in connection with recovery of the substituted benzyl carbinamine may readily be reoxidized to ketone, which in turn may be readily converted to oxime for use in carrying out the method of this invention. Thus, for example, in carrying out the method in accordance with this invention for the production of benzyl methyl carbinamine one may readily recover benzyl methyl carbinol from the oily impurities and such may be readily oxidized to benzyl methyl ketone, which in turn may be readily converted into benzyl methyl ketone oxime.

The method in accordance with this invention will further be found to be distinctly advantageous over methods heretofore known for the production of substituted benzyl carbinamines in that, for example, it will display increased safety in that no sodium is used. The method affords easy control and will give uniform yields. Objectible impurities are not formed and side products may be readily recovered and re-used.

Having now particularly described and ascertained the nature of my said invention and in what manner the same is to be performed, as communicated to me by my foreign correspondents, I declare that what I claim is:—

1. The method of producing a substituted benzyl carbinamine which includes effecting electrolytic reduction of a

benzyl ketone oxime to the corresponding amine.

2. The method in accordance with claim 1 characterized by the fact that the benzyl ketone oxime treated is a benzyl methyl ketone oxime.

3. The method in accordance with claims 1 and 2, characterized by the fact that the benzyl ketone oxime is subjected to electrolytic reduction in solution in aqueous sulphuric acid having a specific gravity of about 1.4.

4. The method in accordance with claims 1 and 2, characterized by the fact that the benzyl ketone oxime is electrolytically reduced to the corresponding acid amine sulphate, that the acid amine sulphate is neutralized with alkali to free the amine, that the amine is treated with hydrochloric acid to form neutral amine hydrochloride and that the neutral amine hydrochloride is treated with alkali to free the amine.

5. Benzyl methyl carbinamine whenever produced by electrolytic reduction of benzyl methyl ketone oxime.

6. The method for the production of substituted benzyl carbinamines by electrolytic reduction of a benzyl ketone oxime substantially as described herein.

7. Benzyl methyl carbinamine when prepared in accordance with the method substantially as described herein.

Dated this 11th day of March, 1935.

HASELTINE, LAKE & CO.,
28, Southampton Buildings, London,
England, and
19, West 44th Street,
New York, N.Y., U.S.A.,
Agent for the Applicant.

[This Drawing is a reproduction of the Original on a reduced scale.]

