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N-NITROSOPIPERAZINE

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This invention relates to an improved process for producing N-mono-substituted piperazines and N,N'-unsymmetrically disubstituted piperazines, as well as to a novel intermediate for their production and the method of producing this intermediate.

In accordance with the prior art, a number of methods have been suggested for blocking one of the imino groups of piperazine in order to permit the introduction of a desired substituent at the other nitrogen atom while avoiding the undesired production of N,N'-symmetrically disubstituted piperazine. These blocking methods for the production of mono-substituted piperazines have a number of common difficulties. For example, carbethoxylation with ethylchloroformate involves the use of an expensive reagent, is a difficult reaction, and subsequent removal of the blocking group with acid is difficult. When acetylation is employed, the yields are poor and it is difficult to isolate the monoacetylated product. Benzylation necessitates the use of an expensive reagent, affords low yields and requires catalytic hydrogenation for removal of the blocking group.

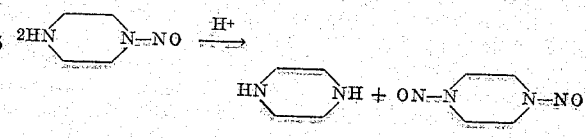
In accordance with the present invention, it has been unexpectedly discovered that a nitroso group may be introduced to obtain N-nitrosopiperazine in substantially high yields providing certain conditions are fulfilled, and that this compound is an exceedingly useful intermediate for the production of pure N-mono-substituted and N,N'-unsymmetrically disubstituted piperazines. The advantages of N-nitrosopiperazine as an intermediate are manifold: for instance, yields of the order of from 80 to 90% N-nitrosopiperazine are obtained in accordance with the process of the present invention; the reagents, preferably a mineral acid, an alkali metal nitrite and an alkali metal hydroxide, are relatively cheap and easily obtained; control of reaction conditions is neither difficult nor is expensive equipment required; the yields of desired N-mono substituted piperazines are of the order of 90% or more; and the nitroso blocking group may be easily removed, e.g., by hydrolyzing with an inexpensive acid, such as hydrochloric acid, or such acid and urea.

In accordance with the process of the present invention for producing N-nitrosopiperazine, this valuable intermediate may be prepared by treating an aqueous solution of piperazine with nitrous acid while maintaining the solution at a temperature in the range of from about −30° to about 35° C., adjusting the acidity of the medium to a pH of at least 4 by the addition of a base, such as an alkali metal or alkaline earth metal hydroxide, preferably sodium hydroxide, separating the relatively minor amount of insoluble N,N'-dinitrosopiperazine by-product and then recovering N-nitrosopiperazine. Recovery of the latter is most conveniently accomplished by organic solvent extraction of the resulting aqueous filtrate which had been made strongly alkaline, concentration of the organic extract if desired, and subsequent distillation under reduced pressure.

A variation of this process relates to the separation of the insoluble N,N'-dinitrosopiperazine at any pH before the N-nitrosopiperazine oils out; or it may be found equally desirable to separate the desired product from the by-product by vacuum distillation. Furthermore, the small amount of insoluble N,N'-dinitrosopiperazine present can even be allowed to remain in the reaction mixture without causing any difficulty in subsequent steps of the process.

A preferred embodiment of the process of this invention involves utilization of an aqueous solution of piperazine which is acidified with a mineral acid, such as nitric acid, sulfuric acid, phosphoric acid, hydrofluoric acid, hydrochloric acid or hydrobromic acid, while maintaining the solution at a temperature below about 50° C. to obtain a solution of a piperazine diacid salt. In order to obtain a high yield in this step, an excess of mineral acid is, of course, preferably employed. This solution is then treated with a water-soluble inorganic nitrite salt, preferably an alkali metal or alkaline earth metal nitrite, and most desirably sodium nitrite in view of its availability and cheapness, while maintaining the solution at a temperature in the range of from about −30° to about 35° C.; the preferred optimum temperature is in the range of from about −15° to about 25° C. The amount of water-soluble inorganic nitrite salt employed is not critical, but a stoichiometrically equivalent amount is, of course, preferred in order to convert a maximum amount of the piperazine diacid salt to the desired N-nitrosopiperazine without production of substantial amounts of N,N'-dinitrosopiperazine by-product.

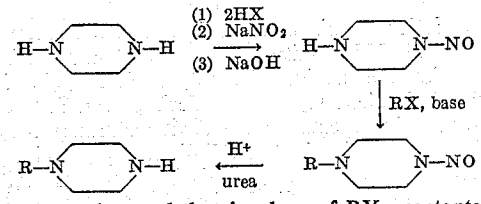
Following treatment with the nitrite salt and, preferably immediately thereafter, the solution is adjusted to a pH in the range of from about 4 to about 7 by the addition of any suitable base, i.e., alkali metal or alkaline earth metal hydroxides, carbonates and bicarbonates; and, preferably, sodium hydroxide because of its relative availability and low cost. The reason for adjustment of pH within a minimum time period after the end of the nitrosation is to avoid disproportionation of the desired product to piperazine and N,N'-dinitrosopiperazine as indicated by the following equation:



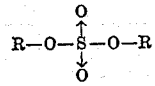
Following pH adjustment, the insoluble N,N'-dinitrosopiperazine by-product is preferably removed, and N-nitrosopiperazine recovered from the combined aqueous filtrate and washings by the method outlined above after said filtrate has been first made strongly alkaline, although any pH value over 7 is sufficient. A preferred solvent for extraction is chloroform, but other halogenated hydrocarbon solvents, such as methylene chloride, carbon tetrachloride, ethylene dichloride and trichloroethylene, are satisfactory.

The following equations illustrate the process described herein for the production of N-nitrosopiperazine, the subsequent introduction of a substituent group, such as alkyl, aryl, aralkyl, cycloalkyl and acyl, etc., and finally, the removal of the nitroso group to afford a corresponding N-mono-substituted piperazine. In this instance, R represents the substituent group and X represents a halogen atom such as chlorine, bromine and iodine; examples of RX include m-xylylbromide, p-chlorobenzhydrylchloride, benzyl chloride, ethyl bromide, hexylbromide, propyl iodide, cyclopentyl iodide, acetyl chloride, etc., or any of the many substituents referred

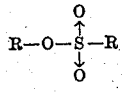
to and specifically illustrated in U.S. Patent No. 2,415,785 of February 11, 1947:



It will be understood that in place of RX, reactants such as



and



may be employed, R being the substituent group as set forth above; examples of these compounds include dimethyl sulfate, dimethyl sulfite, etc.

For the purpose of introducing the substituent group R at the other imino nitrogen of N-nitrosopiperazine, the reactant containing the desired R substituent is introduced into a solution of said intermediate, the solvent for this solution being inert and one in which both reactant and N-nitrosopiperazine are soluble. Preferred solvents include dioxane, lower alkanols, e.g., methanol, ethanol, isobutanol, etc., lower aliphatic ketones, e.g., acetone, methyl ethyl ketone, etc., and water, and mixtures thereof. For the purpose of neutralizing the by-product acid produced during condensation, a base such as an alkali metal hydroxide, an alkaline earth metal hydroxide, an alkali metal carbonate or an alkali metal bicarbonate is present in the reaction mixture.

Subsequent to formation of the N'-substituted-N-nitrosopiperazine, the nitroso group may be removed by treatment with concentrated hydrochloric acid or hot, strong hydrochloric acid in the presence of urea. Removal of the nitroso group by means of hydrogenation in the presence of Raney Nickel catalyst may also be employed, except in the case where an aralkyl group is present at the other N-position, e.g., a benzyl group would be removed during the hydrogenation.

For the purpose of producing an N,N'-unsymmetrically disubstituted piperazine, the N-mono-substituted piperazine produced as above is treated in accordance with the method described in the aforementioned patent.

The foregoing description of the present invention and the examples hereinafter are for the purpose of illustration only and not limiting to the scope thereof.

Example I

To 540 ml. of water in a five liter, three-necked flask equipped with a stirrer, thermometer, dropping funnel and vent to the atmosphere were added 1,163 g. (6.0 moles) of piperazine hexahydrate. Stirring was then initiated and the temperature held below 50° C. while 1.14 liters (13.8 equivalents) of concentrated hydrochloric acid were added. The mixture was then cooled to 0° by means of an ice-salt-water bath and a solution of 436.2 g. (approximately 6.0 moles) of approximately 95% pure sodium nitrite in 840 ml. of water was added during the course of about 55–70 minutes, the temperature being maintained at 0–5° C. throughout the addition; the reaction mixture was then subsequently stirred for about another 15 minutes at this same temperature.

Upon completion of this reaction, the mixture was treated with 120 ml. of commercial 50% aqueous sodium hydroxide without any further cooling (resulting pH about 5.2). At this point, the insoluble N,N'-dinitrosopiperazine by-product was filtered from the reaction mixture, and the resulting cake washed with about 150 ml. of water. The filtrate and washings were then combined and made strongly alkaline by slowly adding 1.86 liters of 50% aqueous sodium hydroxide. The desired product was then extracted from the aqueous solution with two 1.5 liter portions and one 600 ml. portion of chloroform. The separated chloroform layers were then combined and subsequently filtered through a film of diatomateous earth in order to remove suspended aqueous droplets. The organic filtrate was then concentrated by evaporating the solvent on a steam cone under reduced pressure, and the residual liquid was distilled in vacuo. The yield of product boiling at 85–95° C./1.0±0.4 mm. amounted to 572 g. (82%). N-nitrosopiperazine is a liquid having characteristic yellow color, λ max at 214 mu ($e_{max=357}$); $n_D^{25°}$ 1.5000±0.0005. It is almost odorless, and it is completely miscible with water and polar organic solvents.

Analysis.—Calcd. for $C_4H_9N_3O$: C, 41.73; H, 7.88; neut. equiv., 115.1. Found: C, 41.11; H, 7.11; neut. equiv., 115.8.

Example II

The same procedure as described in Example I was followed here except that the nitrosation was carried out at —15° C., whereby an 81% yield of N-nitrosopiperazine was obtained; when the nitrosation was conducted at 25° C., a 65% yield of product was obtained. In a similar manner, the reaction was conducted at various other temperatures in the range of from about —30° C. to about 35° C., and N-nitrosopiperazine was produced in each instance.

Example III

To a solution of 117.5 g. of N-nitrosopiperazine in 700 ml. of methyl alcohol and 108 ml. of water containing 86 g. of sodium bicarbonate was added 192.6 g. of m-xylyl bromide during the course of one hour, the temperature being maintained at 25–30° C. throughout the addition. The reaction mixture was then stirred for an additional two hours at this temperature and subsequently refluxed for four hours. After the excess methanol solvent had been removed by evaporation under reduced pressure, the cooled residue was treated with four equivalents of 2.34 N hydrochloric acid. The strongly acidic medium containing the intermediate N-nitroso-N'-xylylpiperazine was then contacted with two equivalents of urea which were added at 40–50° C. during the course of 30 minutes; a vigorous evolution of gas was observed throughout the addition. The resulting solution was then refluxed for four hours, cooled, and the pH adjusted to 6.2 with 50% sodium hydroxide. The desired product was then extracted from the aqueous alkaline solution with benzene; the resultant aqueous phase was then readjusted to pH 12.5 with 50% sodium hydroxide and twice extracted with benzene to obtain further product. The benzene extracts were then combined and dried over anhydrous sodium sulfate. After removal of the drying agent by filtration, the benzene was removed from the filtrate by evaporation under reduced pressure. The residual liquid was then subjected to distillation in vacuo and there was obtained an 82% yield of m-xylylpiperazine, B.P. 122–128° C. at 3 mm.; $n_D^{20°}$ 1.5431.

Example IV

The same procedure as described in Example III was followed up to the point where the methanol was removed from the reaction mixture. Then 400 ml. of water and four equivalents of concentrated hydrochloric acid were added, and the resulting mixture boiled until the evolution of gas ceased. The pH was then adjusted to 6.2 and the procedure described in Example III was again followed.

Example V

The procedures described in Examples III and IV were

employed here except that the alkylating agent used was p-chlorobenzhhydrylchloride and the product obtained was N-p-chlorobenzhydrylpiperazine. In a similar manner, the alkating agent employed was benzyl chloride, ethyl bromide, hexyl bromide, propyl iodide, cyclopentyl iodide, acetyl chloride, dimethyl sulfite and dimethyl sulfate; in each case, the corresponding N-substituted piperazine was obtained.

Example VI

An N-monosubstituted piperazine of this invention prepared as described above, such as N-xylylpiperazine and N-p-chlorobenzhydrylpiperazine, was alkylated according to the procedure of Clarke, Gillespie and Wiesshauss (J. Amer. Chem Soc. 55, 4571 (1933)), employing any of the alkylating agents previously mentioned. After liberation of the base, the reaction mixture was treated with benzoylchloride to remove any N-mono-substituted piperazine that had remained unreacted. The basic material was again liberated by alkali and the desired product distilled in vacuo. Further purification of the resulting N,N'-unsymmetrically disubstituted piperazine was achieved by crystallizing the dihydrochloride salt from an absolute alcohol-ether solution.

Similarly, the same products may be obtained by treating the N-mono-substituted piperazine according to the same procedure described in Example III.

What is claimed is:

1. The process for the production of an intermediate useful in the synthesis of N-mono-substituted and N,N'-unsymmetrically disubstituted piperazine compounds, which comprises treating an aqueous solution of piperazine with nitrous acid while maintaining the solution at a temperature in the range of from about −30° to about 35° C. and immediately thereafter adjusting the solution to a pH in the range of from about 4 to 7.

2. The process for the production of N-nitrosopiperazine, which comprises contacting an aqueous piperazine solution with a mineral acid while maintaining the solution at a temperature below about 50° C., treating the resulting piperazine diacid salt containing solution with a water-soluble inorganic nitrite salt while maintaining the solution at a temperature in the range of from about −30° to about 35° C., immediately thereafter adjusting the solution to a pH in the range of from about 4 to about 7 and finally recovering the N-nitrosopiperazine.

3. The process as claimed in claim 2 wherein the water-soluble inorganic nitrite salt is chosen from the group consisting of alkali metal nitrites and alkaline earth metal nitrites.

4. The process as claimed in claim 2 wherein N-nitrosopiperazine is recovered by separating the insoluble N,N'-dinitrosopiperazine, adjusting the aqueous filtrate to a pH of at least 7 and subsequently extracting with a halogenated hydrocarbon solvent.

5. In the process for the production of a N-nitroso-N'-mono-substituted piperazine from piperazine, the improvement which comprises treating an aqueous solution of piperazine with nitrous acid while maintaining the solution at a temperature in the range of from about −30° to about 35° C. and immediately thereafter adjusting the solution to a pH in the range of from about 4 to 7 to thereby block one piperazine imino nitrogen with a nitroso group and then introducing the desired mono substituent at the other imino nitrogen of the piperazine molecule.

6. In the process for the production of a N-mono-substituted piperazine from piperazine, the improvement which comprises treating an aqueous solution of piperazine with nitrous acid while maintaining the solution at a temperature in the range of from about −30° to about 35° C. and immediately thereafter adjusting the solution to a pH in the range of from about 4 to 7 to thereby block one piperazine imino nitrogen with a nitroso group, then introducing the desired mono-substituent at the other imino nitrogen of the piperazine molecule, and subsequently removing the nitroso blocking group.

7. In the process for the production of a N,N'-unsymmetrically disubstituted piperazine, the improvement which comprises treating an aqueous solution of piperazine with nitrous acid while maintaining the solution at a temperature in the range of from about −30° to about 35° C. and immediately thereafter adjusting the solution to a pH in the range of from about 4 to 7 to thereby block one piperazine imino nitrogen with a nitroso group, then introducing a desired mono substituent at the other imino nitrogen of the piperazine molecule, subsequently removing the nitroso blocking group, and then substituting another and different substituent group for the active hydrogen atom of the remaining free imino group.

References Cited in the file of this patent

FOREIGN PATENTS

529,491	Canada	Aug. 21, 1956
59,222	Germany	Dec. 8, 1891

OTHER REFERENCES

Roy et al.: Jour. Chem. Soc. (London), vol. 103, pp. 2–3 (1903).

Beilstein: vol. 23, p. 7, 1st supplement (1936).