

Subst. 0.2729, 0.2238. Cc. 0.1  $N AgNO_3$ ; 14.01, 16.56.

Calc. for  $C_{10}H_4O_4NI_3$ : I, 65.22, Found: 65.08, 65.14.

**Benzoate.**—A sample of pure oxime was dissolved in 4 times its weight of benzoyl chloride at about  $140^\circ$  and the solution held at this temperature for 30 minutes. It was then diluted with alcohol, allowed to stand until the odor of benzoyl chloride disappeared and filtered. The crude benzoate was washed with alcohol and ether and recrystallized from a chloroform alcohol mixture until the melting point of  $224-225^\circ$  (corr.) remained unchanged. Clusters of deep yellow lenticular crystals were obtained.

Subst. 0.3011, 0.2851. Cc. 0.1  $N AgNO_3$ ; 14.35, 13.64.

Calc. for  $C_{15}H_8O_4NI_3$ : I, 59.04. Found: 60.42, 60.65.

PITTSBURGH, PA.

[CONTRIBUTION FROM THE MELLON INSTITUTE OF INDUSTRIAL RESEARCH, UNIVERSITY OF PITTSBURGH.]

## THE PREPARATION OF PIPERAZINE.

BY DAVID S. PRATT AND CHARLES O. YOUNG.

Received June 13, 1918.

Piperazine, or diethylenediamine,  $HN \begin{array}{c} \diagup CH_2 \cdot CH_2 \\ \diagdown CH_2 \cdot CH_2 \end{array} NH$  has been used ex-

tensively in cases of gout and arthritis with such success that its absence from the market justified a rather extended search for methods which might be employed in preparing it.<sup>1</sup> Several important modifications of procedure, as disclosed in the patent literature, have been found which it is believed will materially aid anyone attempting to prepare piperazine commercially.

The ease with which ethylene bromide condenses with aniline to form diphenyl piperazine appears to offer the best starting point in the preparation. This reaction can be carried out under proper conditions to give practically a theoretical yield suitable without further purification for the purpose. Unfortunately, it does not seem possible to replace the two phenyl radicals with hydrogen to give piperazine directly.

However, nitrous acid reacts with diphenyl piperazine, and this derivative can be hydrolyzed. According to German patent No. 60,547, boiling with alkalis accomplishes the desired result.

The conversion of diphenyl piperazine into its dinitroso derivative involves difficulties which are not disclosed in this or other patents. The addition of sodium nitrite to a suspension of diphenyl piperazine in acidulated cold water results in the formation of sticky, green tars which give no traces of piperazine on boiling with aqueous or alcoholic alkali. Many

<sup>1</sup> The value of piperazine in certain types of nephritis has been studied extensively by Dr. E. E. Mayer, who will report his results in the near future.

fruitless attempts to carry out this step in such a way as to avoid decomposition of the desired product were made. It was eventually found possible to obtain good yields of the dinitroso derivative by suspending finely ground diphenyl piperazine in ice-cold conc. hydrochloric acid and adding slowly a saturated aqueous solution of sodium nitrite. The suspension should be stirred vigorously throughout, and the nitrite solution should be added by means of a tube reaching to the bottom of the container. The solution turns red immediately and insoluble diphenyl piperazine is rapidly converted into the hydrochloride of dinitrosodiphenyl piperazine which remains in suspension as a golden-orange precipitate, quite stable while moist.

It may be removed by filtration and washed with cold water without undergoing serious decomposition. The amount of nitrite necessary is only slightly greater than theoretical, and yields are excellent. The use of conc. hydrochloric acid instead of dil. acid is vital. Before this factor was determined, all attempts to prepare the desired base were failures.

Dinitrosodiphenyl piperazine may be hydrolyzed by boiling with alcoholic potash to give free piperazine and nitrosophenol.<sup>1</sup> If this method is employed, the alcohol is removed and piperazine obtained by distillation with superheated steam. We have found low yields rather general, and considerable difficulty in avoiding volatile colored by-products.

Aromatic nitroso amines combine with sodium bisulfite<sup>2</sup> to give sulfonic acid derivatives which readily rearrange with loss of the amine group and hydrolysis. This reaction has been applied<sup>3</sup> to dinitrosodiphenyl piperazine. When these specifications are carried out as outlined, one obtains considerable amounts of ammonia, representing loss of piperazine, and more or less tar. These difficulties have been eliminated to a large extent and at the same time the hydrolysis has been simplified by discarding the addition and subsequent neutralization of a large excess of hydrochloric acid.

The following procedure has proved satisfactory, and can be recommended, although it should be understood that experiments on a larger scale will doubtless disclose other advantageous modifications:

### Experimental.

958 g. of ethylene bromide, 527 g. of aniline, and 575 g. of sodium carbonate (anhydrous) were thoroughly mixed and heated for 5-6 hours to gentle boiling in an oil bath using a reflux condenser. Stirring is decidedly beneficial and probably essential on a large scale, as the reaction product tends to cake. The presence of soda is necessary, otherwise

<sup>1</sup> D. R. P. 60547.

<sup>2</sup> *Ibid.*, 65236.

<sup>3</sup> *Ibid.*, 74628.

ethylene bromide combines with aniline vigorously at about  $95^{\circ}$  to give diphenyl ethylene diamine and hydrobromic acid. The acid so freed unites with aniline to form the salt and liberates sufficient heat to cause charring.

The warm melt was extracted with hot water to remove sodium bromide which can be recovered readily and used as the source of bromine for ethylene bromide. The probability that ethylene chloride will be available soon in large amounts should be noted, and that it can be condensed with aniline similarly, using an autoclave to obtain the necessary temperature. The crude diphenyl piperazine is sufficiently pure for making its dinitroso derivative. Yields of from 90 to 95% are usually obtained.

547 g. of diphenyl piperazine, dried and powdered, was suspended in 2200 cc. of cold conc. hydrochloric acid. With mechanical stirring a saturated solution containing 438 g. of sodium nitrite was slowly added through a tube reaching to the bottom of the acid. In this way, the loss of nitrous fumes is largely prevented and the formation of tar minimized. Cooling is necessary during the addition of nitrite. The resulting product was filtered off with suction and washed once with cold water. It is probably the hydrochloride of dinitrosodiphenyl piperazine, but no effort was made to analyze the material. It decomposes readily on drying, but is quite stable if kept moist.

The moist material was added to a 40% solution containing 1900 g. of sodium bisulfite, and the suspension warmed with stirring to about  $80^{\circ}$ . The reaction proceeds smoothly, giving a deep reddish orange solution and considerable suspended matter that was removed by filtration, and discarded. At this point D. R. P. 74,628 specifies the addition of a large excess of hydrochloric acid and heating to the boiling point before making alkaline with caustic soda. This results in the formation of ammonia due to decomposition, and of sodium chloride in large amounts.

We have omitted the treatment entirely without sacrificing the yield of piperazine. The reddish orange solution obtained above was made strongly alkaline with caustic soda and concentrated by distillation. Some ammonia was liberated at first, but the amount appeared negligible. The distillation was continued with superheated steam, the flask being immersed in an oil bath at  $160^{\circ}$ . Piperazine distilled over rapidly with the steam, and was caught in hydrochloric acid.

Micro tests were found convenient for determining when to stop the distillation. Traces of piperazine give very characteristic light yellow crystals with platinum chloride solution. These vary according to concentration, but in general are square or rectangular. A drop of the condensate on a microscopic slide was run into a drop of platinum chloride solution. The formation of a precipitate at once indicates that the dis-

tillation should be continued. Picric acid may be substituted for platinum chloride, but the resulting crystals are not so characteristic. When no precipitate formed at once, examination under the microscope readily revealed whether more than mere traces of piperazine were coming over.

Another reagent giving characteristic crystals with piperazine is bismuth potassium iodide. The reagent is made by adding enough nitric acid to dissolve suspended bismuth nitrate and sufficient potassium iodide to give a clear red solution. Slight traces of piperazine salt in faintly acid solution give very brilliantly colored garnet crystals with a drop of this reagent. The form of the crystals varies from compact prisms to the more usual clusters of feathery needles. The double salt is very insoluble and it is hoped that it will offer a means of determining piperazine quantitatively.

A less delicate, but very definite, micro test for piperazine is the formation of dinitroso piperazine. A drop containing piperazine is acidified with hydrochloric acid in excess and flowed into a drop of saturated sodium nitrate solution. Slight warming gives characteristic, thin, rhombic, colorless plates.

The aqueous distillate, distinctly acid with hydrochloric acid, gave 366 g. of piperazine hydrochloride on evaporation to dryness. The crude salt may be recrystallized from dil. alcohol or converted into the free base by distilling from sodium hydroxide.

Anhydrous piperazine is a solid with distinctly caustic properties. For this reason it has been marketed in the form of various salts and as the hydrate.

It is sincerely hoped that the information here given may result in the manufacture of this greatly needed medicinal preparation by some American laboratory.

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[CONTRIBUTION FROM THE CHEMICAL DEPARTMENT OF MCGILL UNIVERSITY.]

## THE COMPOUNDS OF PHENOL AND THE CRESOLS WITH PYRIDINE. II.

By F. W. SKIRROW AND T. V. BINMORE.

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In a previous communication<sup>1</sup> by Mr. Hatcher and one of us, it was shown that the effect of excess of phenol in diminishing the extraction of pyridine from benzene solution by dil. sulfuric acid is much more marked than is the effect of excess of pyridine in diminishing the extraction of phenol by means of sodium hydroxide. The subsequent experiments were undertaken in order to elucidate this behavior.

It was shown by means of freezing-point curves that phenol forms two

<sup>1</sup> THIS JOURNAL, 39, 9, 1939 (1917).