

[A COMMUNICATION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

## THE PREPARATION OF NITROMETHANE

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The reaction of a metallic nitrite with an alkyl halide produces varying proportions of the nitroparaffin and alkyl nitrite depending upon the particular metal, alkyl group and halogen involved. In continuing a study of this reaction,<sup>1</sup> the reaction of the salts of halogenated acids with sodium nitrite was investigated. It was found by Bolin in this Laboratory that methyl nitrite was not formed in detectable quantities by the reaction of sodium chloroacetate with sodium nitrite nor ethyl nitrite from sodium  $\alpha$ -chloropropionate. These observations led to attempts to determine what reactions reduced the yield of nitromethane to 35–38% of the theoretical in the standard method for the preparation of nitromethane.<sup>2</sup> Experiments were, therefore, made to ascertain to what extent the low yield of nitromethane was due (1) to mechanical losses, (2) to hydrolysis of chloroacetic acid, (3) to reduction of nitromethane by glycolic acid formed by this hydrolysis, (4) to unreacted sodium nitrite, and (5) to the condensation of nitromethane in the presence of alkali.

\* For the purposes of comparison the following standard procedure slightly modified from that of Whitmore and Whitmore was adopted. A 40% solution of sodium hydroxide (100–105 ml.) was slowly added with vigorous stirring to a mixture of 100 g. of chloroacetic acid and 100 g. of finely crushed ice until the mixture was just alkaline to phenolphthalein, the temperature being kept below 10°. Seventy-three grams of sodium nitrite in 100 ml. of water was added and the mixture slowly heated during twenty-five to thirty minutes to 108–110°. Distillation of nitromethane began when the solution was at a temperature of about 87°. The nitromethane was separated from the water layer and the latter redistilled three to five times until the last distillation yielded approximately 4 ml. of water and 0.3 ml. of nitromethane. The combined fractions of nitromethane was dried over calcium chloride for twelve hours, poured off and distilled, the fraction at 98–101° being saved and weighed as nitromethane. Three successive trials of this method gave yields of 27.5, 26.6 and 26.7 g., the average being 41.6% of the theoretical.

The mechanical loss of nitromethane during the preparation was found to be from 4.9 to 5.1 g. or about 9.0%. This was determined by placing known weights (51 to 64 g.) of the compound in 200 ml. of water and recovering the nitromethane by distillation as in the standard procedure.

The percentage of hydrolysis of sodium chloroacetate under approximately the conditions to which it was subjected during its reaction with sodium nitrite was found to be 14.9%. In this determination 9.5 g. of chloroacetic acid was neutralized as in the standard procedure, and 8.4 g. of sodium bicarbonate and 10 ml. of water added. The mixture was then subjected for a time interval and at temperatures which had previously been determined to be approximately those that occurred in the actual preparation of

<sup>1</sup> Reynolds and Adkins, *THIS JOURNAL*, 51, 279 (1929).

<sup>2</sup> Whitmore and Whitmore, "Organic Syntheses," John Wiley and Sons, Inc., New York, 1923, Vol. III, p. 83.

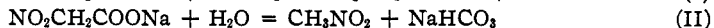
nitromethane. The flask containing the reaction mixture was heated in a water-bath which was raised to a temperature of 90° in eight to nine minutes. The contents of the flask were kept at an average temperature of 90.4° for fifteen minutes, the variation being not more than ±1°. The contents of the flask were then cooled to room temperature in less than one minute. The amount of hydrolysis was calculated from the amount of sodium bicarbonate remaining in the flask. This was determined by the addition of an excess of standard hydrochloric acid, removal of the carbon dioxide by bubbling carbon dioxide-free air through the solution for twenty minutes and then titrating the excess acid. When sodium chloroacetate was subjected to the same conditions except that no sodium bicarbonate was used, the hydrolysis was found to be only 2.3%.

The sodium glycolate formed by hydrolysis apparently has little or no effect upon the preparation except in so far as its formation reduces the amount of sodium chloroacetate available for reaction with sodium nitrite. A reaction mixture to which sodium glycolate had been added gave a yield of 39.6% of nitromethane, which is only 1 or 2% less than the usual yield.

The amount of sodium nitrite remaining in the reaction flask after the distillation of the nitromethane in the standard procedure was found in two analyses to be 18.7 g. and 19.0 g. or an average of 25.8% of the amount originally used. This determination was made by utilizing the fact that ammonium nitrite decomposes to give nitrogen and water. Eighty grams of ammonium chloride and 100 ml. of water were added to the flask containing the residue to be analyzed. The flask was then attached to an apparatus so arranged that the mixture could be subjected to distillation and the evolved gases bubbled through sulfuric acid and sodium hydroxide. Nitrogen was liberated when the reaction flask was at a temperature of 108°. The yields of nitromethane in these two experiments were 45.7 and 41.9% of the theoretical amount. In each of the experiments 800 ± 10 ml. (24°, 740 mm.) of nitrogen was also evolved during the preparation and distillation of the nitromethane.

The method of analysis for sodium nitrite used above was shown to be reliable both for the analysis of solutions containing only sodium nitrite and those containing nitrogenous compounds resulting from the reaction of nitromethane in an alkaline solution. For example, when a solution containing 15.24 g. of sodium nitrite in 75 ml. of water was analyzed the volume of nitrogen obtained was 98.5% of the theoretical amount. In another test of the method of analysis, 15.23 g. of sodium nitrite, 55.5 g. of nitromethane and 84 g. of sodium bicarbonate were placed in 250 ml. of water. The nitromethane was distilled out in the usual way, the recovery being 72.1%. The residue thus containing the condensation products from 15.5 g. of nitromethane and 15.23 g. of sodium nitrite was analyzed for the nitrite. There was found 15.20 g. of nitrite or 99.9% of the amount originally placed in the mixture.

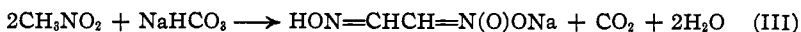
The formation of nitromethane from sodium nitrite and sodium chloroacetate is usually assumed to involve the following reactions as given by Whitmore and Whitmore



These reactions do not explain the vigorous evolution of carbon dioxide that occurs during the preparation nor the highly colored products present during the reaction, nor the nitrogenous tar-like residue. According to Dunstan, Dymond and Goulding<sup>8</sup> nitromethane reacts in the presence of

<sup>8</sup> Dunstan and Dymond, *J. Chem. Soc.*, 59, 430 (1891); Dunstan and Goulding, *ibid.*, 77, 1262 (1900).

sodium bicarbonate to form methazonic acid, water and carbon dioxide, *e. g.*



It seems almost certain that this reaction occurs during the preparation of nitromethane, for the conditions are almost identical with those under which methazonic acid has been prepared. The dry residue was found to explode on heating, which is in accord with the observations of Dunstan and Goulding.

A group of experiments was made to ascertain the extent to which nitromethane reacts in the presence of sodium bicarbonate. The weights of sodium bicarbonate (89 g.) and nitromethane (64.6 g.) which would be formed in the preparation according to Reaction II were placed in 260 ml. of water and distilled as in the actual preparation. An exothermic reaction began at 70°, nitromethane distilled over, and carbon dioxide was evolved. The solution went through the color changes from cherry-red to black which are characteristic of the reaction mixture in the preparation of nitromethane. The solution was gradually heated during twenty or twenty-five minutes up to 105–108° as in the preparation, and the recovery of nitromethane determined. The loss was in three experiments 21.5, 19.6 and 22.1 g., respectively, or an average loss of 32.6%. In this loss there is included the 9% mechanical loss referred to above, so that 23 to 24% of the nitromethane used underwent condensation, presumably to methazonic acid.

The fate of the sodium nitrite was thus completely accounted for in that about 50% was converted into nitromethane, of which about 8 to 9% was lost in manipulation, 23 to 24% was converted into methazonic acid and its condensation products and 25 to 26% remained in the residue. About 10% of the chloroacetic acid was unaccounted for but this is probably due to the impracticability of determining the extent of hydrolysis under exactly the conditions that exist in the reaction mixture. It is possible that some of it reacts with the condensation products of nitromethane.

Upon the basis of these experiments it seemed possible that the yield of nitromethane could be increased by reducing the alkalinity in the zone of reaction either by incompletely neutralizing the chloroacetic acid or by modifying the method of bringing the reactants together. An increase in the yield to 46% was actually obtained if the sodium nitrite solution was heated to 100–110° before the solution of sodium chloroacetate was added by way of a dropping funnel. In another experiment the same yield of 46% was obtained as by this method except that in this latter case the chloroacetic acid was only half neutralized.

The most effective way of increasing the yield of nitromethane was to use the method of adding the reactants described in the preceding paragraph and to increase the ratio of chloroacetic acid to sodium nitrite so as to insure the reaction of all of the sodium nitrite. When the salt from 100 g. of chloroacetic acid was allowed to react with 36.5 g. of sodium nitrite the yield of nitromethane based on the sodium nitrite was 65% of the theoretical amount. Yields up to 70% of the theoretical were obtained by using an excess of chloroacetic acid.

### Summary

The reactions of sodium chloroacetate and sodium nitrite have been studied and it has been ascertained that in using molecular quantities of the reactants approximately 50% of the nitrite is converted into nitromethane, while about 24% of it gives nitromethane which undergoes further condensation to what is presumably the sodium salt of methazonic acid. About 26% of the sodium nitrite does not react, chiefly because 15% or more of the sodium chloroacetate undergoes hydrolysis to sodium glycolate. The formation of nitromethane may be increased to approximately 75% of the theoretical amount if a sufficient excess of sodium chloroacetate is used to insure the complete reaction of the sodium nitrite. The actual yields of nitromethane obtained were about 9% lower than those given above (50 and 75%) because of mechanical losses on the scale of operation used in obtaining them. The weight of nitromethane actually obtained may be increased by about 10% by modifying the standard method so that the sodium chloroacetate is introduced into the nitrite solution after the latter has been heated to the temperature of reaction.

A method is described for the determination of sodium nitrite in the presence of nitrates and methazonic acid and its condensation products.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY IN ORGANOTHERAPEUTICS, ARMOUR AND COMPANY]

## GEOGRAPHIC LOCATION AND THE IODINE CONTENT OF THE THYROID GLAND

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The biochemical literature contains but very limited data regarding seasonal fluctuations in any physiological function. We know that the thyroid gland needs iodine to render its secretion active. The amount of iodine in the gland consequently reveals its potency. Seidell and Fenger<sup>1</sup> have shown that a very marked seasonal variation exists in the percentage of iodine present in the healthy, normal thyroid glands of domestic animals. There is, in general, from two to three times as much iodine present in the glands during the summer and fall months as during the winter and spring seasons. The glands on which these conclusions were based were collected at Chicago and represented principally the middle central states.

As a result of an inquiry from Dr. W. L. Aycock of the Harvard Medical School, it was decided to investigate existing conditions in the northern and southern portions of the United States. Hog glands were selected

<sup>1</sup> Seidell and Fenger, *J. Biol. Chem.*, 13, 517 (1913), and Bulletin 96, Hygienic Laboratory, U. S. Public Health Service, 1914, p. 67.