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# THE PREPARATION OF VARIOUS ALIPHATIC HALIDES AND HALOHYDRIN COMPOUNDS

BY MARSTON TAYLOR BOGERT AND EDWARD MARK SLOCUM[1a]

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## Introductory

In the prosecution of investigations which we have had under way recently, it became necessary to prepare sundry reagents and intermediates, and our notes in connection with these preparations may be of service to other organic chemists.

We have found it advantageous to modify somewhat the method of Adams and Voorhees[1b] for the production of alkyl iodides, so as to obviate the necessity of special apparatus and still allow the use of white phosphorus.

For the conversion of trimethylene glycol into the corresponding bromide or iodide, it was ascertained that the phosphorus trihalide could be substituted successfully for the pentahalide.

Differences were observed in the behavior of trimethylene glycol with the hydrogen halides. At 0°, both hydrogen iodide and hydrogen bromide formed solid crystalline addition products with it, which when heated changed nearly quantitatively into halohydrin and water. No such addition product was encountered with hydrogen chloride, and the action of the latter upon the glycol was exceedingly slow even at 150°.

With acetyl halides, like differences were apparent. Acetyl chloride gave mainly trimethylene glycol mono-acetate, with but small amounts of chloropropyl acetate. With acetyl bromide, a 20% yield of bromopropyl alcohol was obtained, together with bromopropyl acetate (about 75%), but no trimethylene glycol mono-acetate, which means that the bromine rather than the acetyl group reacted with the alcoholic hydroxyl.

When the same glycol was treated with a mixture of acetic acid and hydrogen iodide, iodopropyl alcohol was formed together with smaller amounts of iodopropyl acetate, but no detectable amount of the glycol mono-acetate. It would seem, therefore, that our usual explanation of the function of strong mineral acids in bringing about esterification between acetic acid and an alcohol needs some amplification. It is not simply a catalytic effect on the alcohol-ester equilibrium, except possibly in those cases where the acid does not form a stable addition product with the al-

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[1b] Adams and Voorhees, THIS JOURNAL, **41**, 789 (1919).

cohol, but where the ester may,[2] and so the reaction is sent forward in the direction which favors the formation of such an addition compound. But when the alcohol itself forms a stable addition compound with the mineral acid, the alkyl halide may be the major product. The crystalline addition compound of hydrogen iodide and trimethylene glycol may be represented as of oxonium type, (R) (H) O (H) (I), which breaks down into water and iodohydrin (RI) when heated.

## Experimental Part

**Alkyl Iodides.**—The alcohol (3 moles) and red phosphorus (1 atomic weight) were mixed in a flask and the mixture was cooled with tap water. The iodine (3 atomic weights) was weighed in a separate bottle. Some of this iodine was poured into another flask, dissolved by pouring upon it part of the alcohol decanted from the flask containing alcohol-phosphorus, and the mixture cooled to prevent rise of temperature. The resulting alcoholic solution of iodine was then gradually run into the flask containing the rest of the alcohol and the red phosphorus, and this flask likewise cooled if necessary. When the reaction was over, a portion of the supernatant liquid was used to dissolve more of the iodine and the resulting iodine solution was then added gradually to the main flask again. This procedure was continued until all of the iodine had been dissolved and thus brought into the reaction flask. The mixture was kept cool for an hour longer, after which it was left overnight at laboratory temperature suitably protected against loss of product by volatilization.

A receiving flask was filled half full of finely cracked ice and the adapter tube from the condenser buried deeply therein. A small amount ($^1/_3$ atomic weight) of yellow phosphorus was added to the reaction flask and heat applied very gently until minute bubbles began to rise, when the heating was discontinued and the reaction allowed to proceed spontaneously. Usually this followed moderately and satisfactorily; but even in those cases where it began rather violently, the cracked ice in the receiver prevented the loss of much product. The yields were as follows.

| Iodide | B. p. in literature °C. | B. p. of product °C. | Yield % |
|---|---|---|---|
| *n*-Propyl | 102 | 102–103 | 90 |
| *i*-Propyl | 89.5 | 88– 89 | 92 |
| *n*-Butyl | 129.6 | 128–129 | 94 |
| *i*-Butyl | 120 | 119–122 | 80 |
| *i*-Amyl | 147 | 145–148 | 85 |

Adams and Voorhees noted that, in spite of the greater reactivity of the yellow phosphorus as compared with the red variety, some of it always remained unattacked. If the speeds of reaction of the two forms with iodine are a function of the surface exposed, the red variety being finely divided would react more rapidly than the yellow and, since there is an excess of phosphorus present, some of both forms would remain. The value of the yellow phosphorus appears to be that its equilibrium point, in the expression $P + 3I \rightleftharpoons PI_3$, lies much farther to the right than is the case with the red variety. If so, there is no need to add the yellow phosphorus until just before heating begins, for the greater part of the iodine will have already reacted with the red phosphorus, or to add much more than sufficient to combine with the iodine left untouched by the latter.

The iodides obtained by the process described above showed only a slight yellowish

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[2] Kendall and Brakeley, THIS JOURNAL, **43**, 1826 (1921).

tinge. There was no formation of phosphonium iodide or foaming at the end of the distillation, nor were there any explosions when the empty distilling flask was opened. As small amounts of yellow phosphorus are apt to be left, care should be taken in disposing of the flask residues.

*iso*Butyl **Iodide.**—The ordinary commercial *iso*butyl alcohol was found to contain appreciable quantities of *n*-propyl alcohol, and the separation of the two through fractional distillation proved troublesome, because of the presence of constant-boiling mixtures with water. A convenient preliminary separation was effected by washing out the *n*-propyl alcohol with small amounts of water. An *iso*butyl alcohol was obtained thus which gave an 80% yield of iodide, b. p. 119–122°.

**Trimethylene Bromide.**—Phosphorus pentabromide generally has been used[3] for the conversion of the glycol into the bromide. We have found that the tribromide can be used equally well. From 3 moles of the glycol [b. p., 125–127° (25 mm.)] and slightly more than 2 of phosphorus tribromide, the yield was 85%; b. p., 164–168°.

**Trimethylene Iodide.**—The glycol can be converted into the iodide also by use of the phosphorus trihalide, but the yield is not so good (60%) and the product less pure, boiling with decomposition at 210–220°.

**Trimethylene Bromohydrin.**—Both hydrogen bromide and sulfur bromide were employed for the preparation of this bromohydrin from the glycol. The yield by the former method was 74%, by the latter 60%.

During the saturation of the glycol with dry hydrogen bromide at —5° to 0°, some trouble was caused through the clogging of the inlet tube by the solid addition product (m. p., 52°) of the glycol and hydrogen bromide;[4] but the yield and purity of the product were greatly improved by operating at low temperature, and also by freeing the reacting materials as nearly as possible from all moisture. The final product boiled at 80–82° (22 mm.).

**Trimethylene Iodohydrin.**—Half a mole of hydrogen iodide, dried carefully over phosphorus pentoxide, was passed into 1 mole of the glycol at 0°. It was rapidly absorbed and a thick magma formed from the separation of a solid addition product (m. p., about 12°) of the glycol and hydrogen iodide. This magma was thinned with an equal volume of anhydrous ether and the addition of the hydrogen iodide continued until the increase in weight was equivalent to 1 mole of hydrogen iodide. The mixture was left overnight and was then warmed on the water-bath, to remove ether and ethyl iodide. The residue was distilled under diminished pressure (25 mm.) and the crude iodohydrin rectified until it boiled at 110–113° (15 mm.); yield, 68%. Simpson[5] prepared ethylene iodohydrin from the glycol and hydrogen iodide, but in that case no special precautions were necessary, since the two do not unite to give a solid addition product.

In another series of experiments, dry hydrogen iodide was passed into a solution of the glycol in anhydrous benzene at 0°. The yield of iodohydrin was 92%, and this method therefore is preferable to the foregoing.

**Trimethylene Glycol Mono-acetate,** $HO(CH_2)_3OCOCH_3$.—Equal moles of the glycol and acetyl chloride were allowed to interact at low temperature and the mixture was then warmed on the water-bath, as recommended by Lourenco[6] for the preparation of chloro-ethyl acetate. Fractional distillation of the product showed that it was composed of about 15% (of that calculated) of chloropropyl acetate and over 50% of the glycol mono-acetate, b. p., 202–203°.

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[3] Würtz, *Ann.*, **104**, 174 (1857).

[4] Mokiewski, *J. Russ. Phys.-Chem. Soc.*, **30**, 904 (1898).

[5] Simpson, *Ann.*, **113**, 122 (1860).

[6] Lourenco, *Ann.*, **114**, 126 (1860).

*Analysis.* Calc. for $C_5H_{10}O_3$: 1 g. requires 0.474 g. of KOH. Found: 0.489 g.

Palomaa[7] prepared this ester from the glycol and glacial acetic acid, and reported its boiling point as 202.5–204°.

**β-Chloro-ethyl Acetate,** $Cl(CH_2)_2OCOCH_3$.—Ethylene chlorohydrin was treated at low temperature with at least twice the calculated amount of acetyl chloride, following the method used by Derick and Bissell[8] for the preparation of the analogous propyl compound; yield, 90%; b. p., 144–147°; b. p. in the literature, 143–145°.

Henry[9] was the first to use this method of preparation for the chloro-acetate, but did not note the necessity for a large excess of acetyl chloride to acetylate the hydroxyl group completely.

**γ-Chloropropyl Acetate,** $Cl(CH_2)_3OCOCH_3$.—Several methods of obtaining this compound were tested.

1. The action of acetyl chloride upon the glycol at low temperature, followed by warming. As noted above, under trimethylene glycol mono-acetate, this method gave only a 15% yield of the chloropropyl acetate.

2. The addition of acetyl chloride to the glycol at low temperature, in the presence of anhydrous sodium carbonate; yield, 30% (of that calculated) of the chloropropyl acetate and 65% of the crude glycol mono-acetate.

3. The heating of a mixture of acetyl chloride and the glycol in sealed vessels for 8 hours at 100°. This is analogous to the method employed by Simpson[5] for the production of chloro-ethyl acetate. The yield of chloropropyl acetate was 70%.

4. This was similar to Method 3, except that fused zinc chloride also was present. This modification raised the yield of chloropropyl acetate to 80% and, in our opinion, is the best method for the production of this compound.

5. The action of acetyl chloride upon trimethylene chlorohydrin, as described by Derick and Bissell.[8] The acetyl chloride must be in large excess and the heating on the water-bath continued for some time after most of the hydrogen chloride has been driven off; yield, 90%, calculated to the chlorohydrin; or 54%, calculated to the original glycol.

6. The action of phosphorus trichloride upon trimethylene glycol mono-acetate in the presence of fused zinc chloride. Dehn and Davis[10] reported excellent results with this method in the preparation of alkyl chlorides from the corresponding alcohols; but in the case of our product the results were unsatisfactory and the yields poor.

The purified chloropropyl acetate obtained in these experiments boiled at 165–166°. Derick and Bissell[8] reported a boiling point of 162–166°. Henry[11] who prepared it from trimethylene chlorobromide and potassium acetate, gave its boiling point as 163–165°.

**γ-Bromopropyl Acetate.**—Two methods of preparation were applied.

1. The action of an excess of acetyl chloride upon the bromohydrin, along the lines followed by Derick and Bissell[8] for the analogous chlorine compound. As in the case of the latter, heating of the mixture should be continued for some time after the evolution of hydrogen chloride appears to have ceased. The yield by this method was over 90%; b. p., 88–90° (22 mm.)

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[7] Palomaa, *Annal. Acad. Scient. Fenniae,* **4A,** No. 2, 1, Jan., 1913; *Chem. Zentr.,* **1913,** II, 1959.

[8] Derick and Bissell, THIS JOURNAL, **38,** 2478 (1916).

[9] Henry, *Ber.,* **7,** 70 (1874).

[10] Dehn and Davis, THIS JOURNAL, **29,** 1328 (1907).

[11] Henry, *Bull. soc. chim.,* [3] **15,** 1225 (1896); *Bull. Acad. Roy. Belgique,* **32,** 258 (1896).

2. Acetyl bromide was distilled slowly into an equivalent amount of trimethylene glycol kept at 0°. The mixture was allowed to stand overnight, after which it was warmed at 100° for an hour and then distilled under reduced pressure (25 mm.). The crude acetate obtained was contaminated with bromohydrin, and it was therefore digested with acetyl chloride for several hours under a reflux condenser, the mixture neutralized, dried with calcium chloride and fractionated. If the first runnings still showed the presence of bromohydrin, the treatment with acetyl chloride was repeated; yield, 85%. As this compound was not found in the literature, it was analyzed.

*Analysis.* Calc. for $C_5H_9O_2Br$: Br, 44.4. Found: 44.8.

**$\beta$-Iodo-ethyl Acetate** was obtained from the chloro-ethyl acetate and excess of potassium iodide in methyl alcohol solution; yield, 70%; b. p., 108–112° (60 mm.). This is the method which was used by Henry[11] for the preparation of iodopropyl acetate. In a subsequent article, Henry[12] gave the boiling point as 110° (60 mm.).

**$\gamma$-Iodopropyl Acetate.**—An equimolar mixture of trimethylene glycol and glacial acetic acid was cooled below 0° and dry hydrogen iodide passed into it until the increase in weight corresponded to one equivalent of hydrogen iodide. The mixture, after standing overnight, was heated at 100° for an hour and finally distilled at 25 mm. pressure. The crude product was contaminated with iodohydrin, which was changed to acetate by digestion with acetyl chloride as noted above; yield, 88%; b. p., 98–100° (15 mm.). Henry[11] gave the boiling point as 112–115° (38 mm.). This method is similar to that used by Simpson[5] for the preparation of iodo-ethyl acetate. Henry's method consisted in treating the corresponding chlorine derivative with sodium iodide.

*Analysis.* Calc. for $C_5H_9OI$: I, 54.1. Found: 54.7.

**Methylene Ether of Trimethylene Iodohydrin,** $CH_2(OCH_2CH_2CH_2I)_2$.—1. Dry hydrogen chloride was passed into a mixture of 1 mole of trioxymethylene and 2 moles of trimethylene iodohydrin until the trioxymethylene had disappeared. A similar method was used by Stappers[13] for the preparation of the corresponding propylene chlorohydrin ether. We found it unsatisfactory, as the reaction mixture was dark with separated iodine, and on distillation at 14mm. pressure, much formaldehyde and iodohydrin were shown to be present; yield, 35%; b. p., 188–92° (15 mm.).

2. The method used by Henry[14] for the production of the corresponding ether of ethylene chlorohydrin proved to be much more convenient. An equimolar mixture of trimethylene iodohydrin and trioxymethylene was saturated with dry hydrogen chloride, a second mole of the iodohydrin was added, the reaction completed by warming, and the crude product fractionated at 12 mm. pressure; yield, 60%; b. p., 188–193° (12 mm.).

The ether obtained by these methods was a thick, pale yellowish oil, which gave off a slight odor of formaldehyde when heated. It was soluble in alcohol, ether or acetone, but dissolved in water very slightly. When it was boiled with 20% sulfuric acid, it was hydrolyzed to formaldehyde and iodopropyl alcohol. It does not appear to have been described hitherto.

## Summary

1. A modification of the method of Adams and Voorhees for the preparation of alkyl iodides is described.

2. Experiments are recorded in the application of standard reactions

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[12] Henry, *Bull. Acad. Roy. Belgique,* **1901,** 236; *Chem. Zentr.,* **1901,** I, 1356.

[13] Stappers, *Bull. Acad. Roy. Belgique,* **1904,** 1161; *Chem. Zentr.,* **1905,** I, 921.

[14] Henry, *Bull. Acad. Roy. Belgique,* [3] **29,** 355 (1895).

to the preparation of some simple organic compounds not previously produced by the methods employed.

3. Comparative data are supplied in several cases concerning the relative efficiency of various methods of preparation used for the same compound.

4. The compounds studied were the alkyl iodides; trimethylene bromide, iodide, bromohydrin and iodohydrin; trimethylene glycol monoacetate, β-chloro-ethyl acetate, γ-chloropropyl acetate, γ-bromopropyl acetate, β-iodo-ethyl acetate, γ-iodopropyl acetate and the methylene ether of trimethylene iodohydrin.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

# THE ISOMERIC MODIFICATIONS OF METHYLENE AMINO-ACETONITRILE AND THEIR BIOCHEMICAL SIGNIFICANCE

BY TREAT B. JOHNSON AND H. W. RINEHART[1,2]

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In the various biochemical transformations which take place or function in the normal processes of plant growth, the three reagents ammonia, formaldehyde and hydrocyanic acid undoubtedly play a very fundamental part. In fact, we have good reasons for believing that these very reactive and unsaturated substances are the primary constructive chemical units which lead through fundamental and perfectly definite chemical changes to the final synthesis of the naturally occurring compounds containing the elements carbon, nitrogen, oxygen and hydrogen. Support for the assumption that these reagents actually operate in the normal processes of growth is given by the fact that all three compounds have been shown to be present in the free state in the sap or fluids of plants.[3] Hydrocyanic acid occurs widely in nature especially in many of the important glucosides. Formaldehyde may be considered as a primary assimilation product leading by polymerization to the formation of sugar, while ammonia in the form of the base or its salts is known to serve as a nitrogenous food. While the unsaturated nature of these three reagents is favorable

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[1] Constructed from a Dissertation presented by H. W. Rinehart to the Faculty of the Graduate School of Yale University in June, 1922, in Candidacy for the degree of Doctor of Philosophy.

[2] Communicated to the Organic Section of the American Chemical Society at New Haven, Conn., April, 1923.

[3] Hebert, *Bull. soc. chim.*, [3] **19**, 310 (1898). Ravenna and Tonegutti, *Jahresber.*, **1910**, 1672. Stoklasa and Zdobnicky, *Monatsh.*, **32**, 53 (1911). Müntz, *Jahresber.*, **1890**, 2739. Mayer, *ibid.*, **1874**, 892. Curtius and Franzen, *Ber.*, **45**, 1715 (1912). Gentil, *Bull. soc. chim. sucr. dist.*, **27**, 169 (1909); *C. A.*, **3**, 2882 (1909).