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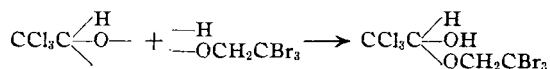
DERIVATIVES OF TRIBROM-ETHANOL: (AVERTIN).

A PRELIMINARY REPORT.

BY S. CHECHIK.

Within the last two or three years, this compound has come into extensive use therapeutically as a local anæsthetic. Its one disadvantage, due to its insolubility in water, is that it must be administered internally in amylene hydrate solution. If this disadvantage can be overcome, the improvement will, no doubt, add materially to the clinical application of this new remedy. Hence, to find a means of introducing avertin into the system in the form of some water-soluble derivative, which at the same time would exert the physiological action of avertin, or which might hydrolyze to liberate avertin itself presents an interesting problem of chemotherapy. However, the writer was not introduced to the study of this compound from this particular point of view.

A systematic study of the readiness with which aliphatic alcohols formed chloral alcoholate addition products with liquid chloral was made in 1930.¹ In connection with the formation of these alcoholates, it seemed of extreme interest to study the possible addition of avertin, which is, structurally, tribrom-ethanol, to chloral, in a manner analogous to that of ethyl alcohol to chloral, namely:



The corresponding bromal compound has also been prepared. Of greater interest, however, are ether-like compounds prepared from tribrom-ethanol. Of these a variety suggested themselves. A preliminary report on some of these is herewith recorded.

EXPERIMENTAL.

Chloral Tribromethylate.—To 1 Gm. of crystalline avertin, a generous quantity of which was supplied by the Winthrop Chemical Research Staff, in 10 cc. of heptane, a mole equivalent of liquid chloral (0.6 Gm.) was added. The reaction mixture was refluxed for half an hour, using an air condenser, allowed to cool, then placed in a refrigerator. Within an hour a crop of glistening white plates was obtained. These were removed by filtration and dried thoroughly on a porous plate. They melted at 68–70°. Recrystallized twice from heptane, the melting point remained constant at 69–70°. This first attempt resulted in a comparatively low yield of 0.92 Gm. or 62 p. c. of the theoretical. Subsequent attempts with 2 and 5 Gm. lots yielded 76 p. c., 83 p. c. and 84 p. c., respectively, of addition compound.

¹ *Jour. A. Ph. A.*, 19 (1930), 320.

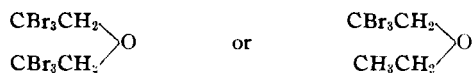
Halogen determinations by the Carius method revealed the presence of 77.9 p. c., 79.7 p. c. and 79.5 p. c., respectively, whereas the theoretical computation calls for 80.2 p. c.

This compound was found to be soluble in water to the extent of 2.5 to 3 p. c. Moreover, when recovered by extraction with ether, its stability in water was demonstrated by the regeneration of the original white crystalline flakes, melting at 70°. Effecting solution in water at 55–60°, however, resulted in its partial hydrolysis yielding a small quantity of chloral hydrate.

Using anhydrous ether as the reaction medium, crystals melting between 67–69° were obtained upon evaporation of the solvent. Recrystallized from heptane, they melted at 68–70°. When carbon tetrachloride was used, crystals with a melting point of 70° resulted. With acetone as reaction medium, crystals were obtained that melted at 68°. Recrystallized from heptane, they melted at 69–70°.

Bromal-Tribrom Ethylate.—Molecular equivalents of avertin (1.5 Gm.) and bromal (1.5 Gm.) suspended and partly dissolved in heptane were refluxed for half an hour. On cooling, crystal sheaths, m. p. 60–62° and 61–62°, were obtained. A bromine determination according to Carius yielded 86.0 p. c. whereas the computed amount of bromine is 85.1 p. c.

Tribrom-Ethanol Ether.—Just as ethyl alcohol, when heated with sulphuric acid yields first ethyl sulphuric acid and subsequently diethyl ether, so tribrom-ethanol may be expected to yield either



according to the conditions under which the experiments are conducted. Substitution of other substances related to alcohol may be expected to yield still different modifications of the ether type, some or all of which may reveal anaesthetic properties. This preliminary report records some of the experiments made in this direction.

Action of Aqueous Sulphuric Acid.—Five grams of avertin crystals were gently heated on the water-bath in 50 cc. of water containing a mole equivalent (2.0 Gm.) of concentrated H₂SO₄ for half an hour. The crystals first went into solution, but after some time a colorless oil settled to the bottom. This oil solidified when the mixture was allowed to cool. When thoroughly dried, it melted at 60–62°, 60–63°, 65–67° and even as high as 67–69°, respectively, in as many experiments. The melting points and bromine contents of these products pointed to a probable mixture of unreacted avertin and some of the ether compound formed. Repeated recrystallizations proved this to be so, as will be shown later on.

The supernatant liquid which was poured off from the solidified oil, on standing yielded a crop of fine, silky needles, m. p. 62–63°, 60–62°, 60–63° as recorded in three experiments.

The yields are herewith tabulated:

| | Avertin. | Solidified Oil. | Needles. |
|-----|----------|-----------------|----------|
| (1) | 5 Gm. | 3.9 Gm. | 0.6 Gm. |
| (2) | 5 Gm. | 3.1 Gm. | 1.2 Gm. |
| (3) | 10 Gm. | 7.0 Gm. | 2.5 Gm. |

Both products gave negative tests for sulphur.

Bromine determinations according to Carius gave the following results:

| | Calc. for $\text{CBr}_3\text{CH}_2\text{OCH}_2\text{CBr}_3$. | Found. |
|----------------|--|--------------------------|
| Solidified oil | | 92.4 p. c. 85.7 p. c. |
| Needles | 87.4 p. c. | 90.6 p. c. 86.5 p. c. |

The solidified oil, having revealed itself as a mixture as already stated, when recrystallized three times from hot heptane yielded 6.5 Gm. of unreacted avertin and 2.0 Gm. of the ether.

This reaction was then repeated using a two-mole equivalent of concentrated H_2SO_4 , in the hope of converting more or all of the avertin into the di-tribrom ethyl ether. This time but a trace of oil solidified, when 5 Gm. of avertin were refluxed with 4 g. H_2SO_4 in 50 cc. water. The supernatant liquor yielded 2.9 Gm. of needles described in the first attempts. The filtrate in turn was diluted with an equal volume of water and shaken out with ether, which procedure yielded 4.0 Gm. of white crystal sheaths, m. p. 61–63° or a total yield of 6.9 Gm. (69.8 p. c.).

Action of Aqueous Nitric Acid.—Five grams of avertin were heated in 50 cc. H_2O with a mole (1.2 Gm.) of concentrated HNO_3 under an air condenser on the water-bath for one hour. The same products were obtained as with H_2SO_4 in aqueous medium. An oil remained insoluble which solidified when the mixture was allowed to cool, while the filtrate on cooling yielded a crop of fine silky needles. The filtrate from the needles was further shaken out with ether.

| Solidified Oil. | Needles. | From Mother Liquor. |
|--------------------------------|---|---------------------------|
| 3.7 Gm. | 0.4 Gm. | 0.6 Gm. |
| M. p. 66–70° | M. p. 62–63° | M. p. 73–76° |
| (Mixture) of avertin and ether | Identical with those described under H_2SO_4 | (Mixture) chiefly avertin |

The first and last products were bulked and recrystallized twice from hot heptane yielding 0.5 Gm. of the ether m. p. 63° and 3.5 Gm. of avertin, m. p. 79–80°.

Action of Alcoholic Sulphuric Acid.—3 Gm. of avertin in 25 cc. of absolute alcohol were heated under reflux for one hour with an excess of one mole of H_2SO_4 (2.0 Gm.). No crystalline substance formed on cooling, but when the mixture had stood in the ice-box for two days a crop of white plates was filtered off and dried between filter paper. They melted sharply at 60–61° and at 60° when recrystallized from heptane. This compound seemed to possess a more aromatic odor than that of the di-tribromethyl ether.

This substance also gave a negative test for sulphur.

Bromine determination according to Carius, revealed the presence of 77.8 p. c. whereas the formula $\text{CBr}_3\text{CH}_2\text{OCH}_2\text{CH}_3$ calls for 77.2 p. c.

The solubility of this compound in water seemed to be greater than that of any of the previous substances described.

To hasten this reaction somewhat, 5 Gm. of avertin and 2 Gm. H_2SO_4 were heated together in heptane, then 6–8 cc. of absolute alcohol were added through the reflux condenser, and the mixture refluxed on the sand-bath at a temperature

of 130–140°. Four grams of the ether, m. p. 60–62°, were obtained from the heptane solution in the following fractions:

- (1) Filmy plates
- (2) Long perfect needles
- (3) Crystal sheaths

To avoid the use of heptane, which is both expensive and not so extensively available, CCl₄ was next employed. The yields (on basis of 5 Gm. of avertin) from the various solvents are tabulated below:

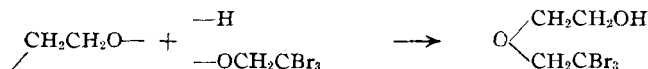
| Medium. | Yield. | % Yield. |
|------------------|---------|------------|
| Abs. alcohol | 3.2 Gm. | 59.2 p. c. |
| | 4.0 Gm. | 74.0 p. c. |
| Heptane | 4.0 Gm. | 74.0 p. c. |
| CCl ₄ | 4.2 Gm. | 77.7 p. c. |

Urethane of Avertin.—To effect the reaction



2.5 Gm. of phenyl isocyanate in heptane were added slowly, with vigorous stirring, to a heptane solution of 6 Gm. of avertin. The mixture was refluxed on the water-bath for one hour. On cooling shiny, white plates m. p. 61–63° formed. Recrystallized twice from hot heptane these melted at 65–67° and 66–67°, respectively.

Action of Ethylene Oxide.—The readiness with which H₂O, HBr, HCl, HI and alcohols react with ethylene oxide led to the assumption that this reagent might add on a molecule of brominated alcohol.



Five grams of avertin dissolved in 150 cc. of dry CCl₄ were poured into a three-necked flask, cooled in an ice-salt mixture to 0–10° C. The ethylene oxide gas was passed through a soda lime tower, while its rate of liberation was gaged by bubbling it in turn through a U-tube containing a small amount of water previously saturated with the gas. It was then cooled in a glass coil, surrounded by an ice-salt mixture, to 0–10° and passed into the reaction flask. The gas was passed into the reaction mixture at the rate of 75–80 bubbles per minute for four hours while the mixture was continually agitated. Any unabsorbed ethylene oxide could be observed bubbling through a second U-tube containing water. By means of a thermometer immersed in the reaction liquid, it was possible to keep the temperature between 0° and 8°, a condition necessary for the maximum absorption of the ethylene oxide.

When the reaction was complete, CCl₄ was distilled off, leaving 20–25 cc. of liquid material. This was allowed to cool and concentrated in an open vessel. A granular crystalline deposit (5.3 Gm.) was obtained, which when dried on a porcelain plate melted at 63–65° C. This, however, was raised to a constant melting point of 70–71° by repeated recrystallization from hot heptane, from

which it was obtained in the form of filmy plates. 4.7 Gm. (= 82.4 p. c.) of this compound were isolated.

Bromine determinations according to Carius yielded 72.8 p. c. and 71.6 p. c., respectively, in two determinations, whereas the formula $\text{CBr}_3\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$ calls for 73.4 p. c.

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SOME CONSTITUENTS OF COMMERCIAL CHERRY GUM.*

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The chemistry of the plant gums (1), as well as of other acid polysaccharides such as pectins, mucilages, hemicelluloses and algins, has not received much detailed attention from research workers until quite recently. This is particularly true of the acidic nuclei of these materials. This problem was attacked long ago by O'Sullivan (2), who believed that gums arabic, gedda and tragacanth contained as acidic nucleus a stable organic acid of the formula $\text{C}_{23}\text{H}_{38}\text{O}_{22}$. Robinson (3) later obtained an acid of similar composition from the gum of *Cochlospermum Gossypium*.

Recent researches in this field have not confirmed the C_{23} acids of O'Sullivan and Robinson as the nucleus of plant gums, since gum arabic (1), (4), mesquite gum (5) and flaxseed mucilage (6) were shown to contain aldobionic acids ($\text{C}_{12}\text{H}_{20}\text{O}_{12}$), which are composed of one uronic acid and one sugar group as stable nuclei. The soluble fraction of gum tragacanth (7) appears to contain a C_{23} acid. This substance, however, differs from the monobasic C_{23} acid of O'Sullivan in that it is composed of one pentose and three uronic acid residues, all three carboxyl groups being free. Aldobionic acids have also been isolated from the hydrolysis products of the serologically specific carbohydrates from bacteria (8) and from hemicellulose of cottonseed hull bran (9).

In the course of our studies on the chemistry of the plant gums, we obtained a number of samples of cherry gum. A report on the composition of a sample collected from wild cherry trees in Indiana will be published elsewhere. In this paper will be found a description of some experiments with material purchased on the open market.

The acidity of cherry gum has been stated by Ehrlich (10) to be due to glucuronic acid. However, no experimental data are given in his report. A few references to investigations showing the presence of *l*-arabinose and *d*-galactose are to be found in the older literature (11). Van der Haar (12) reported the absence of methylpentoses and confirmed the presence of arabinose, galactose and the "glucuronic acid group" without demonstrating which uronic acid was present.

The sample used in the experiments to be described contained 12.8% moisture and 2.8% ash, the constituents of which are shown in Table I.

* Contribution from the Department of Research in Pure Chemistry, Mellon Institute of Industrial Research, Pittsburgh, Pennsylvania.