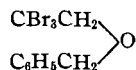


DERIVATIVES OF TRIBROMETHANOL: (AVERTIN) II.*

BY S. CHECHIK.

In a continued study of the formation of ethers of this compound, inability to use the very convenient Williamson reaction, namely, the interaction of the sodium alcoholate and an alkyl or acyl halide with the production of an ether, proved somewhat of a handicap. This method had to be avoided, because of the readiness with which tribromethanol goes to pieces in even dilute alkaline solutions. Willstätter and Duisberg,¹ in their original investigation of this compound, reported that when heated in NaOH solution, tribromethanol decomposes, accompanied by the evolution of carbon dioxide. Hence all reactions had to be carried out in neutral hydrocarbon media, which are by no means satisfactory if one has to resort to the sulphuric acid method for the production of ethers. The method has one distinct advantage, however, in that the reaction product can be thoroughly extracted free of the acid. The dry HCl method was also used with satisfactory results.

Tribromethanol-benzyl ether—

(a) *Sulphuric Acid Method.*—Five grams of avertin were dissolved in 50 cc. of freshly distilled anhydrous CCl_4 (b. p. 76–77°). To this solution were added, dropwise with vigorous stirring, 2.2 Gm. of sulphuric acid and the mixture refluxed for 20 minutes. The acid layer settles to the bottom and becomes tinged a faint yellowish brown. A mole (2.0 Gm.) of benzyl alcohol, freshly distilled, and boiling constantly at 204°, dissolved in 25 cc. of CCl_4 was then added slowly from a dropping funnel, after which the contents were refluxed for one hour. The upper, clear CCl_4 layer was then poured off, leaving a small light brown acid residue. The latter was thoroughly extracted with hot heptane, which solution, on strong chilling, yielded 1.0 Gm. of unreacted avertin crystals, m. p. 79–80°, when recrystallized twice from hot heptane.

The CCl_4 layer was distilled under vacuum until all the CCl_4 had been removed. The remaining viscous, straw-colored liquid was taken up in ether, the latter evaporated, and the oil refluxed in heptane, then chilled to 0° C., to crystallize any free avertin held in solution. Since this precaution yielded none, the heptane solution of the oil was then fractionated under a column. After all the heptane had been recovered at 97–98°, the oil was distilled over between 164–174°. 3.9 Gm. (59 p. c. yield) of the crude benzyl ether were obtained.

(b) *Dry HCl Method.*—A CCl_4 solution containing 5 Gm. of avertin was saturated with absolutely dry HCl gas, while the contents were held at the boiling point of the CCl_4 . A CCl_4 solution of a mole of benzyl alcohol was then gradually added while the reaction mixture was being further saturated with HCl gas, and kept at a temperature of 75–77° C. After refluxing for two hours, strong cooling produced no excess avertin. By fractionation, 5.2 Gm. (78 p. c. yield) of the ether were obtained. The products of three preparations, the third yielding 12.2 Gm.

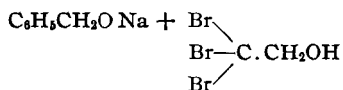
* For the first report see JOUR. A. PH. A., 21 (1932), 20.

¹ Ber., 56 (1924), 2283–2286.

(90 p. c. yield), were then bulked and carefully fractionated, yielding a colorless oil, b. p. 172–174°. This ether is very irritating and lachrymating, not unlike the effect produced by benzyl bromide and other exceedingly offensive benzyl derivatives.

Bromine determinations by the Carius method revealed this compound to contain 63.6 p. c. and 63.0 p. c. Br, whereas the theory calls for 64.2 p. c. Its specific gravity, as determined by the pycnometer method, was found to be 1.703 and 1.708, respectively, at 20° C.

Dibenzyl Monobrom Ethyl Alcohol.—The penetrating irritability of the benzyl ether seemed to be a reasonable basis for predicting its pharmacological value as being out of the question. It seemed, therefore, of further interest to study the effect of introducing one or more benzyl ether groups on the opposite side of the tribromethanol molecule, as brought about by the reaction



From the above formulas it becomes apparent that a mono benzyl ether dibromethanol, a dibenzyl ether monobromethanol, and a tribenzyl ether of ethanol are theoretically possible.

Experimental.—To 40 Gm. of freshly distilled benzyl alcohol (204°), were added cautiously, accompanied by gentle heat, 8.0 Gm. of metallic sodium, to produce sufficient sodium benzylate equal to a three-mole equivalent. This mixture was heated until all the sodium had completely dissolved, whereby a thick white pasty mass formed, which when heated somewhat more changed to a yellow oil. To this were added 20 Gm. of avertin in 20 cc. of anhydrous ether, and the mixture refluxed under a spiral condenser on an oil-bath between 170–180° for 3 hours.

The mixture was allowed to cool, a liter of distilled water added, and the contents of the flask thoroughly agitated with a mechanical stirrer for an hour. The lower oily layer was then shaken out with ether, the ethereal solution filtered free of some flocculent resinous material, then fractionated to yield the following:

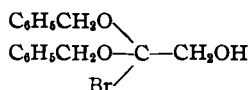
(1)	40–68°	—	2.5 Gm.—chiefly ether
(2)	195–200°	—	18.3 Gm.
(3)	203–204°	—	7.2 Gm.—benzyl alcohol
(4)	215–218°	—	8.2 Gm.
(5)	270–280°	—	2.9 Gm.—dibenzyl

All the fractions were colorless, possessing the characteristic sharp benzyl alcohol odor in varying degrees, but much milder than that of the previously described benzyl ether of tribromethanol.

The above procedure was repeated using half of the previous quantities with the following results:

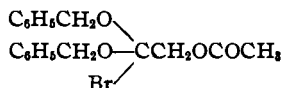
(1)	195–198°	—	6.0 Gm.
(2)	204°	—	2.4 Gm.—benzyl alcohol
(3)	214–217°	—	7.3 Gm.
(4)	230–240°	—	7.6 Gm.

Fraction 195-200°.—Both yields were bulked and carefully refractionated, collecting the portion distilling between 194-196°. This fraction contained 21.1 p. c. and 22.4 p. c. bromine. The theoretical for



is 23.6 p. c. bromine.

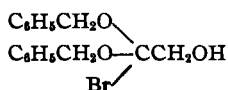
This oil was acetylated, forming a very penetrating liquid acetate which, when analyzed for bromine, was found to contain 19.9 p. c. in contrast to the theoretical for



which is 21.1 p. c. bromine.

Fraction 215-218°.—The bulked oil from both experiments was carefully refractionated, collecting the distillate between 216-218°.

This fraction contained 21.5 p. c. and 22.3 p. c. bromine, respectively, corresponding also to the configuration



This compound was also acetylated, yielding an equally sharp, somewhat lachrymating liquid acetate. Its bromine content was not determined.

Fraction 230-240°.—This was redistilled, but again came over between 230-240°, and judging from the low bromine contents (8 to 12.5 p. c.) is very probably a mixture of several substances, hence was not investigated any further.

Fraction 270-280°.—This oil distilled over very sharply between 285-286°. It contained no bromine and refused to acetylate. Dibenzyl boils at 284° C.

The pharmacological investigation of the derivatives of avertin described thus far will be reported elsewhere.

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QUININE HYDROBROMIDE WITH CHLOROFORM AND BROMOFORM OF CRYSTALLIZATION.

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During our work on the solubilities of the U. S. P. chemicals, the solubility of quinine hydrobromide in chloroform was to be checked. The U. S. P. states that one Gm. quinine hydrobromide dissolves in 0.6 cc. of chloroform. Quinine hydrobromide contains 1 mol of water, or 4.26%. The material we used substantially contained this amount of water. When it was treated with the proportion of chloroform given in the U. S. P. a turbid solution resulted. This turbidity was attributable to the water in the quinine hydrobromide. Upon allowing the turbid