[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF LOUISVILLE SCHOOL OF MEDICINE]

Reactions of 4-Arsonophenylglycine with Polyalcohols[1]

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This investigation deals with the preparation of organic arsenicals of possible value as trypanocidal agents. Esters of 4-arsonophenylglycine with the polyalcohols, glycerol, α-glycerylmonoamine, α-glycerolmonochlorhydrin and mannitol have been prepared using diacetin and phenol as reaction media. α-4-Arsonophenylglycylmonoglyceride has shown trypanocidal activity.

In the investigation of trypanocidal organic arsenicals, it was found that the methyl and ethyl esters of 4-arsonophenylglycine, previously prepared by Jacobs and Heidelberger,[3] were the only examples of this class of compounds. We have now prepared four additional esters from the polyalcohols, glycerol, α-glycerylmonoamine, α-glycerolmonochlorhydrin and mannitol.

The usual chlorinating agents such as the phosphorus chlorides and thionyl chloride caused extensive decomposition of 4-arsonophenylglycine, hence we were unable to prepare its acid chloride for reaction with the polyalcohols. Similar results have been noted by Hamilton.[4] While 4-arsonophenylglycine reacted with an excess of glycerol, we were unable to separate the product from the excess solvent. However, by using equimolar quantities of these reactants in diacetin as a solvent, the desired ester was obtained in good yields. Similar results were obtained with α-glycerolmonochlorhydrin, but we were unable to obtain a satisfactory monoester from pentaerythritol. In these reactions there seemed to be no tendency for 4-arsonophenylglycine to react with the beta hydroxy group of diacetin.

In the esterification of α-glycerylmonoamine (1-amino-2,3-dihydroxypropane), phenol proved to be a better solvent than diacetin since decomposition of the amine was held to a minimum. In the reaction of mannitol (in phenol) with 4-arsonophenylglycine apparently not only esterification but also internal dehydration to form a mannitan with a 1–5 ether linkage took place. This type reaction has been noted by other investigators.[5,6] The 4-arsonophenylglycylmannitan could not be isolated as the free acid but was precipitated from an alcohol–water mixture as the calcium salt.

The 4-arsonophenylglycine used in this investigation was prepared by the standard procedure[7] but was purified by solution in sodium hydroxide solution, following which the solution was treated with charcoal, filtered and the free acid obtained by acidification to congo red with concentrated hydrochloric acid. In this manner a product was obtained which did not give colored by-products upon esterification with polyalcohols.

Preliminary trials on α-4-arsonophenylglycylmonoglyceride indicate that it has trypanocidal activity against *T. equiperdum* in white rats and mice. The curative dose is about 1000 mg./kg. More details on pharmacological data will be reported elsewhere.

Experimental

α-4-Arsonophenylglycylmonoglyceride.—Fifty-two grams of 4-arsonophenylglycine, 17.4 g. of glycerol and 50 g. of diacetin were heated at 140° under a pressure of 20 mm. for 3 hours. The mixture was cooled, dissolved in 200 ml. of 95% alcohol and cooled in an ice-box for 4 hours to allow separation of unreacted 4-arsonophenylglycine. The solution was charcoaled and filtered, cooled to 20° and poured with vigorous agitation into 400 ml. of ether. The product, a light-brown gum, from which the supernatant fluid was decanted, was purified by solution in 95% alcohol and precipitation upon addition of ether. The final product, dried over concd. sulfuric acid in a vacuum desiccator, was a white crystalline solid that was very hygroscopic. The yield was 54 g. (82%); m.p. 185°.

Anal.[8] Calcd. for $C_{11}H_{16}O_7NAs$: As, 21.4. Found: As, 21.3.

1-(4-Arsonophenylglycyl)-2-hydroxy-3-chloropropane was prepared by a similar procedure using 10 g. of 4-arsonophenylglycine, 4.5 g. of α-glycerolmonochlorohydrin and 30 g. of diacetin. The product was a white crystalline hygroscopic solid weighing 9 g. (58% yield); m.p. 220°.

Anal. Calcd. for $C_{11}H_{15}O_6NClAs$: As, 20.4. Found: As, 20.2.

1-(4-Arsonophenylglycyl)-2-hydroxy-3-aminopropane.—Ten grams of 4-arsonophenylglycine, 5 g. of α-glycerylmonoamine and 30 g. of phenol were heated at 160–170° for 3 hours under reduced pressure just sufficient to cause condensation of phenol at the top of the condenser. The reaction mixture was cooled to 110° and filtered while still hot. The filtrate was poured with vigorous agitation into 100 ml. of cold 95% alcohol, precipitating a white solid. The alcohol–phenol solution was decanted and the product washed with 95% alcohol and dried over concd. sulfuric acid in a vacuum desiccator; yield 8.1 g. (77%). This compound did not melt below 250°.

Anal. Calcd. for $C_{11}H_{17}O_6N_2As$: As, 21.4. Found: As, 21.6.

6-(4-Arsonophenylglycyl)-1,5-mannitan.—Ten grams of 4-arsonophenylglycine, 7 g. of mannitol and 30 g. of phenol were heated in the same manner described in the last procedure. After cooling, 50 ml. of 50% alcohol was added with agitation. Charcoal was added and the solution filtered. The filtrate was neutralized to a *p*H of 7 with 10% sodium hydroxide and 30 ml. of 10% calcium chloride added, precipitating the calcium salt of the product. This white salt was washed with cold 50% alcohol and dried in a vacuum desiccator over anhydrous calcium chloride; yield 6.5 g. (39%).

Anal. Calcd. for $C_{28}H_{38}O_{18}N_2As_2Ca$: As, 17.0. Found: As, 16.9.

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(1) Taken from the M.S. thesis of Robert E. Cox.

(2) Department of Chemistry, University of Oregon, Eugene, Oregon.

(3) W. A. Jacobs and M. Heidelberger, THIS JOURNAL, **41**, 1590 (1919).

(4) C. S. Hamilton, private communication.

(5) R. M. Goepp and K. H. Brown, *Ind. Eng. Chem.*, **30**, 1222 (1938).

(6) W. Frendenberg and E. F. Rogers, THIS JOURNAL, **59**, 1602 (1937).

(7) German Patent 204,664.

(8) A modification of the method of F. E. Cislak and C. S. Hamilton, THIS JOURNAL, **52**, 638 (1930), was used in the arsenic analyses