tory. The analyses reported were done by Micro-Tech Laboratories, Skokie, Illinois.

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Synthesis of Acetobromo Sugars

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Acetohalogen derivatives of sugars play an important role in synthetic carbohydrate chemistry and ease of preparation of these compounds is of considerable value. Formerly the classical procedure for preparing acetobromo sugars has involved treatment of the sugar acetate with a solution of hydrogen bromide in either glacial acetic acid or acetic anhydride.[3-5] Acetyl bromide has also been used.[6]

A simplified procedure for making acetobromoglucose has been described[7] in which the brominating agent (HBr) is generated *in situ* by adding water to a mixture of bromine and red phosphorus in glacial acetic acid.

We have been making use of a similar method except that no water was added to the brominating reagent (CH_3COBr). The reaction may be applied to either the free sugars or their acetates. Thus acetobromo derivatives have been prepared from the following: L-arabinose, D-xylose, D-glucose, β-D-glucose pentaacetate and β-cellobiose octaacetate (see Table I).

TABLE I

Compound	Yield, %	Acetobromo derivative M. p., °C.	$[\alpha]^{24}D$ ($CHCl_3$)	Ref.
L-Arabinose	22	137	+284°	8
D-Xylose	63.5[a]	....	....	9
D-Glucose	66	87–89	+195	10
β-D-Glucose pentaacetate	84	88–89	+198	10
β-Cellobiose octaacetate	95–100	185	+ 94	11

[a] This value is based on the yield of methyl β-D-xylopyranosine triacetate (m. p. 112–113°, $[\alpha]^{24}D$ −60° ($CHCl_3$)) derived from the acetobromo compound.

Experimental

Generation of the Brominating Reagent.—Bromine (180 g.) is added dropwise to suspension of red phosphorus (30 g.) in glacial acetic acid (300 ml.) with cooling. After the reaction is complete the mixture is filtered (glass wool) and kept in the cold room if not required for immediate use.

Preparation of Acetobromo Sugars. (a) From the Sugars, *e.g.*, D-Glucose.—The sugar (10 g.) was added with shaking to the brominating reagent (100 ml.), the temperature being kept at or below 40°. After 2 hours at room temperature, the reaction mixture was diluted with chloroform (100 ml.) and poured with stirring into a mixture of ice and water (200 ml.). The chloroform layer was separated and the aqueous layer extracted with chloroform. The chloroform extracts were combined, washed with water then with an aqueous solution of sodium bicarbonate and dried ($CaCl_2$). Removal of solvent *in vacuo* gave α-acetobromo-D-glucose which was crystallized from ether. More material was obtained by adding petroleum ether to the ethereal mother liquors.

(b) From the Sugar Acetates, *e.g.*, β-D-Glucose Pentaacetate.—The acetate (216 g.) was added in portions with shaking to the brominating reagent prepared from bromine (180 g.). After 2 hours at room temperature the reaction mixture was diluted with chloroform (300 ml.) and poured into a mixture of ice and water (800 ml.). The α-acetobromo-D-glucose was isolated as in (a).

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Synthesis of Glycol Bis-(alkyl Sulfites)[1]

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Esters of sulfurous acid of various types are known, simple esters having been prepared long ago.[2] Richter[3] obtained diaryl sulfites while Carre and Libermann[4] prepared many mixed esters, including alkyl aryl sulfites. Some cyclic esters of glycols are known[5] and also the cyclic ester of catechol.[6]

However, no mixed diesters of glycols have been reported. It was the purpose of this work to attempt to prepare mixed glycol bis-(alkyl sulfites) of the type formula: $RO{\cdot}SO{\cdot}O{\cdot}(CH_2)_2{\cdot}X{\cdot}(CH_2)_2{\cdot}O\,SO{\cdot}OR$ where R is ethyl or β-chloroethyl and X is oxygen or sulfur. In addition diesters of tetramethylene glycol were studied.

The compounds were employed in tumor chemotherapy tests in mice. Structures of this type possess a formal analogy to the disulfonic esters of Timmis[7] who showed that the dimethanesulfonate of tetramethylene glycol has activity in causing tumor regression.

The glycol diesters were prepared by reaction of one mole of glycol in inert solvent medium with two moles of an ester chloride of sulfurous acid (alkyl chlorosulfites) in the presence of pyridine.[8] The syntheses were successful with tetramethylene glycol, diethylene glycol, thiodiglycol and butyne diol, when reacted with ethyl or β-chloroethyl chlorosulfites. The products, after appropriate purification, were high boiling oils of little or no odor. Several of the bis-(ethyl sulfites) were distilled but no attempt was made to distil the chloroethyl esters. None of these substances is steam volatile and they did not appear to decompose during short contact with boiling water.

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TABLE I

Compound	B.p. °C.	Mm.	d^{25}_4	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Yield, %
Tetramethylene glycol bis-(ethyl sulfite)	164	5	1.183	35.04	34.86	6.57	6.32	83.9
Diethylene glycol bis-(ethyl sulfite)	178	5	1.237	33.10	33.38	6.21	6.43	75.3
2-Butyne-1,4-diol bis-(ethyl sulfite)	162	3.5	1.219	35.56	35.90	5.19	6.33	74.1
					35.28		6.57	
Thiodiglycol bis-(β-chloroethyl sulfite)	..	..	1.374	25.60	25.78	4.27	4.41	67.0
Tetramethylene glycol bis-(β-chloroethyl sulfite)	..	..	1.343	27.99	28.21	4.66	4.80	74.3

The yields in these preparations vary with the temperature, and at room temperature are very poor. The rate of mixing also influences yields probably by causing local heating during rapid addition of the ester chloride. Since the ester chlorides are known to decompose when warmed with pyridine hydrochloride, and since heating also causes some disproportionation into neutral sulfites and thionyl chloride, the necessity of cold working temperatures for good yields is explained.[8-11]

An attempt to prepare the bis-(β-chloroethyl) ester of ethylene glycol or the bis-(ethyl sulfite) of trimethylene glycol gave little or no product, probably due to the tendency of these glycols to form cyclic sulfites.[5] The possibility that these mixed glycol esters may be obtained by working at lower temperatures should not be excluded, however. The glycols which successfully gave mixed diesters cannot form cyclic sulfites unless 7-membered rings are formed. The bis-(β-chloroethyl sulfite) of diethylene glycol was prepared in a crude state and was not purified. The acetylenic glycol diester was more stable than was expected and distillation proved possible.

The bis-(β-chloroethyl sulfite) of thiodiglycol, which was prepared in this work, shows an analogy to sulfur mustards in addition to a structural resemblance to Timmis' disulfonates. It appeared to be very toxic. The ability of the sulfite ester group to act as a cytotoxic agent is not known, but dialkyl sulfites are known to have some effectiveness as alkylating agents,[12] though inferior in this respect to the sulfates.

Experimental

The ester chlorides were prepared by the methods of Stahler and Schirm[9] or Komisarov.[13] As the β-chloroethyl chlorosulfite is more stable than ethyl chlorosulfite, somewhat higher reaction temperatures could be tolerated with the former.

In general, 1 mole of the glycol was mixed with 2.1 moles of the pyridine in chloroform or ether and a solution of 2.1 moles of the ester chloride in the solvent was added dropwise with good stirring. The reaction flask was maintained in an ice-bath at 5° or lower. The mixture was left for 0.5 to 1.5 hours in the bath and then water added and the mixture worked up. If the glycol was not sufficiently soluble in ether, chloroform was used as the solvent, in which case no pyridine hydrochloride precipitated. The preparation of tetramethylene glycol bis-(ethyl sulfite) is given as an example of the syntheses, other preparations being similar.

A solution of 24 ml. (0.236 mole) of ethyl chlorosulfite in 100 ml. of chloroform was added dropwise with stirring to an ice-cooled solution containing 8.9 ml. of the glycol (0.1 mole) and 20.5 ml. (0.256 mole) of pyridine in 150 ml. of chloroform. The addition took one-half hour and the mixture was left for 1.5 hours in the bath. The light yellow solution was then shaken with water and the layers separated. The chloroform solution was extracted in turn with 1 *N* hydrochloric acid, water, dilute sodium carbonate solution, and finally twice with water. Most of the chloroform was removed and the residue steam distilled under a pressure of 75 mm. for 1 hour. This removes any diethyl sulfite and other volatile material. A heavy oil layer was left which was extracted by ether or chloroform, dried and the solvent removed. The residue was heated in a water-bath for several hours under a pressure of 75 mm. The product weighed 23 g. (83.9%). This contained traces of volatile material and was distilled under a pressure of 5 mm., b.p. 164°. There was obtained a colorless liquid which was somewhat oily and almost odorless.

The bis-(β-chloroethyl sulfites) were steam distilled for several hours longer under vacuum, due to the smaller volatility of the by-product, di-(β-chloroethyl) sulfite. For purification, these chloro esters can be pumped on a high vacuum line with gentle warming for several hours or overnight.

The substances prepared are listed in Table I, together with physical constants, yields and analyses.

High hydrogen values were obtained for the acetylenic glycol diester, probably due to contamination of the glycol with one of its hydrogenated derivatives.

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Pyridazine Derivatives. II.[1] An Improved Synthesis of 3-Aminopyridazine

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3-Aminopyridazine (I) is a simple aminodiazine to which relatively little attention has been paid[2-4] and then chiefly in connection with its use in the preparation of sulfonamides.[2,3,5-8] It is probable that the neglect has resulted from difficulties in its synthesis, including the instability of 3-chloropyridazine (*cf.* ref. 9), a key intermediate. Even based on the best yields, 3-aminopyridazine was obtainable in no more than 11% yield from either diethyl succinate or furoic acid as starting materials.[2-4,9] The present procedure using 3,6-dichloropyridazine as an intermediate renders the preparation of 3-aminopyridazine considerably more satisfactory, proceeding from maleic an-

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