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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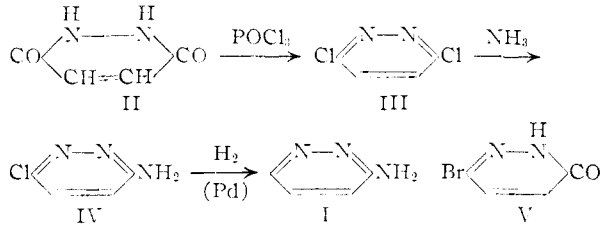
hydride *via* maleic hydrazide, to give a yield of 48% of the hydrochloride of I, in four steps. Since maleic hydrazide (II) is available commercially, it is possible to achieve the preparation in three steps in 56% yield with easily accessible materials in the manner to be described. A less satisfactory procedure involving use of 3,6-dibromopyridazine is also given.

Maleic hydrazide, the tautomer of pyridazine-3,6-diol (II), was first obtained in poor yield from maleic anhydride and hydrazine,[10] but recent improvements in method have increased the yield to 86%.[11,12] Renewed interest in II has been the result of findings on its action on plant growth. The reaction of maleic hydrazide with phosphorus oxychloride has been shown[12] to give 3,6-dichloropyridazine (III) in 87% yield; in large-scale preparations, the yield suffered slightly. Reaction of 3,6-dichloropyridazine with ammoniacal ethanol at 125–130° gave 3-amino-6-chloropyridazine (IV) in 70% yield. Hydrogenolysis of IV with palladium–charcoal catalyst produced 3-aminopyridazine (I), which was isolated as the hydrochloride in 91.5% yield. The compound was further characterized as the base and picrate.

The reaction of maleic hydrazide with phosphorus oxybromide gave a 56% yield of the expected dibromo compound related to III and 4.6% yield of V. It appears that the 6-bromo-3-pyridazone was formed by hydrolysis of 3,6-dibromopyridazine, for a batch which had stood some while after quenching gave a 5.3% yield of V.



Ammonolysis of 3,6-dibromopyridazine produced the aminobromo compound in 96% yield, and hydrogenolysis of the intermediate went equally well. Use of the first-mentioned scheme was preferable for preparation of 3-aminopyridazine.

Experimental[13]

3,6-Dichloropyridazine (III).—The reaction of maleic hydrazide[14] with phosphorus oxychloride (*cf.* ref. 12) gave an 82% yield of crude 3,6-dichloropyridazine when run on a 3.5-mole scale. Excellent recovery of pure III was obtained either by distillation (b.p. 89–91° (1.2 mm.)) or crystallization from hexane, m.p. 69–70° (lit.[12] m.p. 68–69°).

3-Amino-6-chloropyridazine (IV).—A mixture of 7.5 g. (0.05 mole) of 3,6-dichloropyridazine with 8.8 g. (0.52 mole) of ammonia dissolved in 100 cc. of absolute ethanol was heated at 125–130° for ten hours in a shaking autoclave. The brownish residue (8.7 g.) from concentration of the reaction mixture *in vacuo* was extracted in a Soxhlet with ethyl acetate. Crystallization from the extraction solvent gave 4.52 g. (70% yield) of 3-amino-6-chloropyridazine, m.p. 210–212° dec. An additional crystallization from ethyl acetate produced white blades, m.p. 213–214° dec. (in 205°).

Anal. Calcd. for $C_4H_4ClN_3$: C, 37.08; H, 3.11; Cl, 27.37; N, 32.44. Found: C, 37.22, 37.44; H, 3.43, 3.28; Cl, 26.89; N, 32.54, 32.49.

The reaction of 3,5-dichloropyridazine with ammonia in the absence of solvent at 120–125° for 15 hours produced only 7% yield of IV, together with ammonium chloride, and gum.

3-Aminopyridazine (I).—A suspension consisting of 5.18 g. (0.04 mole) of 3-amino-6-chloropyridazine, 1.6 g. (0.04 mole) of sodium hydroxide and 0.1 g. of 7% palladium–charcoal catalyst in 150 cc. of absolute ethanol was subjected to hydrogenation at three atmospheres pressure. The reduction was slow, but an additional 0.5 g. of catalyst aided completion. The mixture was warmed, filtered and then excess of hydrogen chloride was added before concentration of the filtrates (5.4 g. of residue). Two crystallizations from absolute ethanol–pentane produced 4.8 g. (91.5% yield) of 3-aminopyridazine hydrochloride as white microcrystals, m.p. 175.5–176.5°.

Anal. Calcd. for $C_4H_5N_3 \cdot HCl$: N, 31.94; Cl^-, 26.95. Found: N, 31.70; Cl^-, 26.94.

The hydrochloride was converted to the base and the crude product crystallized from ethyl acetate. Transparent blades were obtained, m.p. 170–171° (lit.[2,3] 168–170°; 172°).

Anal. Calcd. for $C_4H_5N_3$: N,[15] 14.73. Found: N,[15] 14.51.

3-Aminopyridazine picrate separated from ethanol as yellow needles, m.p. 249–250° dec. (lit.[3] 248–249° dec.).

Anal. Calcd. for $C_4H_5N_3 \cdot C_6H_3N_3O_7$: C, 37.04; H, 2.49; N,[16] 12.96. Found: C, 37.20; H, 2.35; N,[16] 12.75.

3,6-Dibromopyridazine.—A mixture of 23.0 g. (0.2 mole) of maleic hydrazide and 400 cc. of melted phosphorus oxybromide[3] was stirred and refluxed gently for two hours. The excess reagent was removed *in vacuo* and the residue quenched in ice, basified with aqueous ammonia, collected and dried. A nearly black solid (33 g.) thus obtained was sublimed at 150° (0.5 mm.) to produce 26.6 g. (56% yield) of 3,6-dibromopyridazine, m.p. *ca.* 105°. The sample for analysis was twice crystallized from methanol and resublimed; white blades, m.p. 115–116°.

Anal. Calcd. for $C_4H_2Br_2N_2$: Br, 67.18; N, 11.78. Found: Br, 67.32; N, 11.47.

The residues from the sublimations and the crystallizations were united and twice crystallized from methanol (charcoal), and then from benzene to give 1.65 g. (4.6% yield) of 6-bromo-3-pyridazone (V) in the form of white needles, m.p. 157.5–158.5°.

Anal. Calcd. for $C_4H_3BrN_2O$: C, 27.45; H, 1.73; N, 16.01. Found: C, 27.67; H, 1.51; N, 16.13.

3-Amino-6-bromopyridazine.—Eleven and nine-tenths grams (0.05 mole) of 3,6-dibromopyridazine was shaken with 28 g. (1.65 moles) of ammonia, dissolved in 300 cc. of absolute ethanol, at 140–145° for ten hours. The mixture was taken to dryness *in vacuo*, then leached with water and crystallized from ethanol to give 5.3 g. (96% yield) of yellowish tablets, m.p. 204–206.5° dec. A sample for analysis was obtained by two recrystallizations from ethanol, the 3-amino-6-bromopyridazine formed yellowish tablets, m.p. 205–206.5° dec. No diamino compound was isolable.

Anal. Calcd. for $C_4H_4BrN_3$: Br, 45.92; N,[15] 8.05. Found: Br, 46.31; N,[15] 8.07.

Catalytic dehalogenation of 3-amino-6-bromopyridazine to I was carried out as described for IV. A 94% yield of 3-aminopyridazine hydrochloride, m.p. 174.5–176°, was obtained.

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