corresponding sulfone is inert to these reaction conditions.

Experimental

Typical Chlorination Conditions.—A 500-cc. three-neck flask was fitted with a sealed stirrer, thermometer, a fritted gas inlet tube extending as deep as possible into the flask, and a vent for exit gas. One mole of dimethyl sulfide and an amount of concentrated hydrochloric acid to provide the desired water were placed in the flask and cooled to −10° to −15°. This temperature was maintained while introducing chlorine (up to 2 moles). Subsequent amounts were introduced at +10° to +30° to obtain more complete absorption. When two phases were present at the end of the reaction, the heavy oil layer was fractionally distilled at atmospheric pressure to obtain a chlorinated hydrocarbon cut and mesyl chloride. Both cuts were analyzed by gas chromatography. The dimethyl sulfone was isolated from the still residue or, when no oil phase was present, was obtained by evaporating the acidic aqueous solution under reduced pressure. In either case the dimethyl sulfone was recrystallized from ethanol. The formaldehyde was isolated by treating the aqueous layer with methyl mercaptan and isolating the bis(methylthio)-methane. Some dimethyl disulfide and dimethyl sulfide also are produced at times due to oxidation of the mercaptan by dimethyl sulfoxide, so gas chromatographic assay was required.

Mesyl Chloride.—Two moles of dimethyl sulfide (147 cc.) was placed in the previously described apparatus and chlorine was introduced while maintaining the temperature at 0° to −20° until 3 moles of chlorine was introduced, and at +5° until 3.5 moles was introduced. Water (100 cc.) was then added dropwise and the chlorination continued at 20–28° until 12 moles of chlorine was introduced. The 274-g. lower layer was separated from the 42-g. aqueous layer and distilled in the manner described previously to obtain 174 g. (76%) of mesyl chloride boiling at 161–165° (760 mm).

Chloromethanesulfonyl Chloride.—An excess of chlorine was introduced over 3 hr. into tetrachlorodimethyl sulfide (200 g., 1.00 mole) and water (500 g., 27.8 moles) at 19° to 32°. Distillation of the organic layer at atmospheric pressure yielded 121.1 g. (0.81 mole, 81%) of chloromethanesulfonyl chloride (b.p. 165–175°; $n^{25}\mathrm{D}$ 1.4820) and 127.4 g. (0.83 mole, 83%) of carbon tetrachloride.

Dithiazanes or Methylenediisothiuronium Salts[1]

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During the course of research on isothiuronium salts and derivatives, as part of the doctoral thesis of one of us (C.H.G.), the anomalous behavior of methylene dihalides in the formation of methylenediisothiuronium salts was noted. Most of this work has been published.[3,4] However, details of the reaction of thiourea and N-substituted thioureas with methylene halides have not been published. In view of the continued erroneous references to methylenediisothiuronium salts appearing in the literature, it was felt that our investigations should be published in order to delineate the reactions involved and what actually is obtained.

Dixon and Taylor[5] first reported that they obtained methylenediisothiuronium dihydroiodide by the usual procedure of refluxing methylene iodide and thiourea in alcohol. They gave no melting point for the salt and stated that the base melted at 198°, and gave unreliable analytical data. Based on a sulfur determination on the hydroiodide salt (no melting point given) they assumed the obtention of the methylenediisothiuronium dihydroiodide. The use of isothiuronium picrates as identifying derivatives of alkyl and polymethylene halides is a useful and widely used procedure.[6-8] Jurecek and Vecera[8] prepared a number of such isothiuronium picrates, including the one from methylene iodide, as proposed identifying derivatives. They give a melting point for this picrate of 232° dec.; they state that it is methylenediisothiuronium picrate and give closely corresponding elemental analyses. They also claim to have prepared methylene diisothiuronium dihydroiodide and to have recrystallized it three times from water, giving no melting point, but closely corresponding elemental analyses for four elements therein.

Recently Parham, *et al.*,[9] prepared crude methylenediisothiuronium dihydroiodide (not characterized), which was converted into a picrate, m.p. 232–233° dec. This picrate was compared with the "authentic picrate" prepared according to Jurecek and Vecera and no depression of the melting point was noted.

Underwood and Dains[10] showed that the reaction of methylene dihalides and thiourea, monoarylthioureas and 1,5-diaryldithiobiurets gave rise to 1,3,5-dithiazanes, but that *s*-diarylthioureas gave ill-defined products. They repeated the work of Dixon and Taylor and obtained a base from thiourea and methylene iodide of rather indefinite melting point (202–209°) which gave inconclusive analyses. However, they state that the nitrogen analysis of the hydroiodide salt (no melting point given) corresponded to the 1,3,5-dithiazane structure. Recently Esayan and Oganesyan[11] repeated the work of Dixon and Taylor and obtained a hydroiodide from thiourea and methylene iodide, m.p. 245°, and a picrate, m.p. 228–230°, to which they correctly assigned the 1,3,5-dithiazane structure.

In view of the general confusion and contradiction in the chemical literature on this subject, we have presented conclusive experimental proof of the formation of dithiazanes from thiourea and methylene bromide and, particularly, methylene iodide. The "methylenediisothiuronium picrates" reported in the literature have been shown to be the picrate of 4,6-diimino-1,3,5-dithiazane. This has been confirmed by alternate synthetic routes, conclusive analytical data, and infrared spectra.

Most of the reactions reported in the literature were carried out in ethanol, or higher boiling solvents for pro-

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tracted periods of time, which will favor ring closure of the diisothiuronium salts initially formed. However, we have shown that methylenediisothiuronium dihydroiodide can be obtained under special conditions and that monosubstituted thioureas react normally to give methylenediisothiuronium derivatives in lower boiling solvents and short reflux times.

In closing the literature survey, it also might be pointed out that several references to methylenediisothiuronium salts in the biological and pharmaceutical literature are most likely also erroneous.[12–15] In tests of pressor, depressor effects, amine oxidase inhibition and histaminase inhibition, the methylenediisothiuronium derivatives behaved anomalously, This may be attributed to the first member of the series misbehavior, but, since the preparation and characterization of the compounds are not given, we strongly suspect, on the basis of the experimental data presented herein, that the dithiazane derivative was what was actually tested in these cases.

Experimental

(1) **Methylene Bromide and Thiourea (4,6-Diimino-1,3,5-dithiazine Hydrobromide).** (A).—Proceeding in the customary fashion and refluxing methylene bromide, 10 g. (0.057 mole), with thiourea, 8.8 g. (0.12 mole), for 8 hr. in 60 ml. of ethanol, cooling, and removing the crystalline material by filtration gave 12.4 g. of crystalline product (66% yield for methylenediisothiuronium dihydrobromide), which proved to be mostly thiourea. However, slow heating on the block, permitting the thiourea to sublime away, showed the presence of a material decomposing above 250°. In this experiment it was noted that crystalline material started separating from the boiling reflux after about 1 hr. of refluxing. This was unusual as in the authors' experience isothiuronium and diisothiuronium hydrohalide salt remained in solution until the reflux was cooled. Frequently it was necessary to add ether to the cooled reaction mixture to throw out the salt.

(B).—Repeating experiment A, but filtering after 4 hr. while still boiling when the crystalline material present appeared to have reached a maximum amount under the conditions, and washing with cold alcohol and ether gave 4.4 g. of sparkling perfect hexagonal plates. Heating whole crystals slowly on the block lead to violent decrepitation above 200°, gradual browning up to 280°, and melting with decomposition at 285°. Capillary melting point on pulverized material (put in bath at 250°) was 285° dec. Bromine determination on the material gave an average value of 35.2%, which was far too low for the methylenediisothiuronium dihydrobromide. A complete elemental analysis was performed and compared to those for possible products of the reaction (Table I).

Table I

% Calcd.				
I Bromomethylisothiuronium·HBr	II Methylenediisothiuronium·2HBr	III 4,6-Diimino-1,3,5-dithiazane·HBr	% Found	
9.61	11.05	15.79	15.76; 15.95	C
2.42	3.09	2.65	2.74; 2.79	H
11.21	17.18	18.42	17.99	N
63.94	49.01	35.03	35.2	Br
12.83	19.67	28.11	28.63	S

Elemental analyses gave an empirical formula of $C_3H_6BrN_3S_2$ corresponding to dithiazane derivative, III. Since III is formed by elimination of ammonium bromide from II, an additional experiment was run to search for the ammonium bromide.

(C).—Experiment B was repeated and refluxed for 24 hr. A 4.8-g. sample of the dithiazane were obtained. The filtrate was taken to dryness in a rotary evaporator and residue finely pulverized and repeatedly extracted with small volumes of absolute ethanol. The small residue that remained proved to be ammonium bromide by qualitative tests and quantitative analysis.

(2) **Methylene Iodide and Thiourea (4,6-Diimino-1,3,5-dithiazane Hydroiodide and Methylene Diisothiuronium Dihydroiodide).** (A).—Refluxing methylene iodide, 8 g. (0.03 mole), with thiourea, 4.6 g. (0.06 mole), in 50 ml. of alcohol for 2 hr., cooling, and filtering gave 11 g., m.p. 238–240° dec. Recrystallization from methanol gave material of m.p. 243–245° dec.

(B).—Repeating experiment A in 50 ml. of methanol and refluxing 0.5 hr. gave 10.3 g. of material on cooling. This material was a mixture of crystalline forms. It consisted of long needles and dense pearl-like blocks. The needles were separated by the Pasteur method with a pair of forceps and melted at 186° with gas evolution and resolidification. The material melted again at 240–242° dec. The dense blocks melted at 240–243° dec. If the needles and blocks were pulverized together and heated in the capillary, partial melting with gassing occurred at 182–188°. The whole resolidified and melted at 240–242° dec. If the needles were recrystallized from methanol–ether, they melted at 187–188° with gassing. However, recrystallization from warmed methanol or ethanol gave a mixture of needles and blocks again. Recrystallization of the blocks gave a material with m.p. 243–245° dec., which did not depress the melting point of the material from 2A.

Analysis of the needles showed them to be **methylenediisothiuronium dihydroiodide**.

Anal. Calcd. for $C_3H_{10}I_2N_4S_2$: N, 13.34; I, 60.42. Found: N, 13.18; I, 60.07.

This also could be obtained in mixture with 4,6-diimino-1,3,5-dithiazane hydroiodide by allowing methylene iodide and thiourea to stand in methanol or acetone at room temperature.

Analyses of the blocks from B, or the material from A, showed them to be **4,6-diimino-1,3,5-dithiazane hydroiodide.**

Anal. Calcd. for $C_3H_6IN_3S_2$: N, 15.27; I, 46.13. Found: N, 15.04; I, 46.28.

(3) **Picrates.**—Solution of 0.5 g. of the material from 1B in the minimum of methanol and adding this with rapid stirring to 40 ml. of a saturated aqueous solution of picric acid resulted in the immediate separation of a picrate, m.p. 231–233° dec. Recrystallization from alcohol gave material of m.p. 233–234° dec.

Anal. Calcd. for $C_9H_8N_6O_7S_2$ (**4,6-diimino-13,5-dithiazane picrate**): C, 28.72; H, 2.14; N, 22.33. Found: C, 28.88; H, 2.38; N, 22.50.

Formation of the picrate from the material from 2A gave a material which on recrystallization from alcohol melted at 233–234° dec.

Anal. Calcd. for $C_9H_8N_6O_7S_2$: N, 22.33. Found: 22.46.

A mixture melting point of 1B picrate and 2A picrate showed no depression and showed them to be identical. Their infrared spectra also were identical.

(4) **Methylene Chloride and Thiourea.**—Refluxing methylene chloride with two molar equivalents of thiourea in methanol or ethanol for 1 week resulted, on cooling, in an almost quantitative recovery of thiourea. Refluxing with a crystal of iodine or potassium iodide under similar conditions gave no appreciable reaction.

(5) **Methylene Iodide and Thiosinamine (N-allylthiourea). Methylenedi-N-allylisothiuronium Dihydroiodide.**—Methylene iodide, 8 g. (0.03 mole), and N-allylthiourea, 7 g. (0.06 mole), were refluxed for 3 hr. in 50 ml. of methanol. On cooling and adding four volumes of ether an oil resulted. Repeated slurrying with absolute ether in the freezer (−8°) resulted in solidification in about 1 week, m.p. 127–129°. Recrystallization from methanol–ether (slow) gave large long blocks, m.p. 132.5–134°.

Anal. Calcd. for $C_9H_{18}I_2N_4S_2$: C, 21.61; H, 3.63; I, 50.74; N, 11.20. Found: C, 21.73; H, 3.68; I, 50.88; N, 11.45.

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