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SYNTHESIS OF NEW SUGAR DERIVATIVES HAVING POTENTIAL ANTITUMOUR ACTIVITY

PART XII*. 1,2:5,6-DIEPITHIO-L-IDITOL AND SOME DERIVATIVES THEREOF

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ABSTRACT

The synthesis of 1,2:5,6-diepithio-L-iditol and some of its derivatives, starting from 1,6-dibromo-1,6-dideoxy-D-mannitol, is described.

INTRODUCTION

It is well known that some diepoxides possess cytostatic activity and inhibit the growth of experimental tumours[1]. In the carbohydrate field, 1,2:5,6-dianhydro-D-mannitol[2], in contrast to its 3,4-*O*-isopropylidene derivative[3], shows significant cytostatic activity. Episulphides, which are analogous to epoxides, have been described in the carbohydrate field[4], but diepithio compounds have not been reported. The possibility that diepithio derivatives might show biological and chemical behaviour similar to that of diepoxides prompted the synthesis of 1,2:5,6-diepithiohexitols.

RESULTS AND DISCUSSION

Treatment of 1,6-dibromo-1,6-dideoxy-2,5-di-*O*-methanesulphonyl-D-mannitol[5] (**1**) with potassium thiolbenzoate gave 1,6-di-*S*-benzoyl-2,5-di-*O*-methanesulphonyl-1,6-dithio-D-mannitol (**2**), the structure of which was proved by methanesulphonylation to give 1,6-di-*S*-benzoyl-2,3,4,5-tetra-*O*-methanesulphonyl-1,6-dithio-D-mannitol (**3**), which was also synthesised by another route described below. Treatment of compound **2** with methanolic sodium methoxide gave a mixture of products, from which the desired diepithiohexitol could not be separated. Similarly, the reaction of the diacetate **5** of compound **2** with sodium methoxide gave a mixture, which was shown by t.l.c. [development with 4-(*p*-nitrobenzyl)pyridine] to contain not less than 6 components, indicating the presence of different alkylating agents which could be formed partly by the participation of the hydroxyl groups at C-3 and C-4.

Because of these results, 1,6-dibromo-1,6-dideoxy-3,4-*O*-isopropylidene-2,5-di-*O*-methanesulphonyl-D-mannitol[5] (**6**) was chosen as a starting material in which the hydroxyl groups at positions 3 and 4 are protected by a base-stable group.

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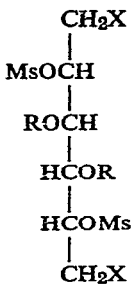
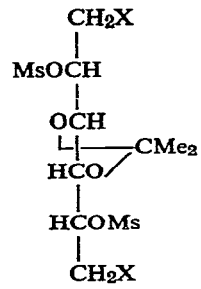


1 X = Br; R = H
2 X = SBz; R = H
3 X = SBz; R = Ms
4 X = Br; R = Ac
5 X = SBz; R = Ac
13 X = Br; R = Ms



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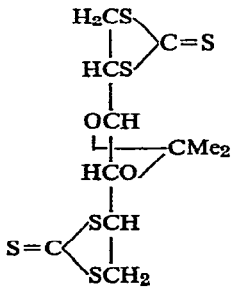
7 X = SBz



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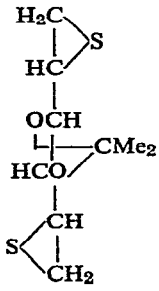

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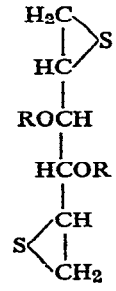


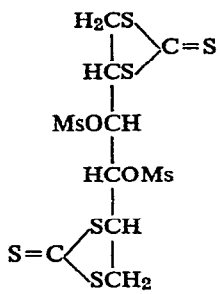
10 R = H
11 R = Ac
12 R = Ms

In this case, the isopropylidene group has to be removed subsequently, without splitting the labile epithio groups. Although the isopropylidene group could not be removed from 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose or 1,2:5,6-dianhydro-3,4-*O*-isopropylidene-D-mannitol without cleavage of the epoxide rings, the formation[6] of a moderate yield of 5,6-epithio-L-idose by mild, acidic hydrolysis of 5,6-epithio-1,2-*O*-isopropylidene-α-L-idofuranose indicated that epithio rings are somewhat more resistant towards acids than are epoxide rings. Confirmation of this supposition has now been obtained.

The bromine atoms could be easily displaced from compound **6** by the benzoylthio group to give 1,6-di-*S*-benzoyl-3,4-*O*-isopropylidene-2,5-di-*O*-methanesulphonyl-1,6-dithio-D-mannitol (**7**). With methanolic sodium methoxide, compound **7** gave crystalline compound **8** in good yield. Compound **8** was identified as 1,2:5,6-diepithio-3,4-*O*-isopropylidene-L-iditol on the basis of analytical data, chemical properties, and the likely mechanism of formation involving Walden inversion at C-2 and C-5. The presence of strained epithio rings, indicated by an infrared band at 3075 cm^{-1}, was proved by conversion of compound **8** into the known 3,4-*O*-isopropylidene-1,2,5,6-tetrathio-L-iditol 1,2:5,6-bis(trithiocarbonate) (**9**).

Compound **8** is very sensitive to bases and acids. In methanol solution, in the presence of sodium methoxide or triethylamine, it rapidly polymerised to an amorphous product having a high optical rotation (−314°) and a molecular weight corresponding to a tetramer. Since the i.r. spectrum of this polymeric product showed no bands for SH or OH groups, its units must be linked by thioether bonds.

The isopropylidene group of compound **8** could be removed, without splitting the epithio rings, by a short treatment with N methanolic hydrogen chloride to give 1,2:5,6-diepithio-L-iditol (**10**) in 70% yield. The structure of compound **10** was verified by its easy polymerisation in aqueous solution, by the positive reaction with 4-(*p*-nitrobenzyl)pyridine, and by the i.r. spectrum which showed a band at 3060 cm^{-1} (strained rings). The n.m.r. data of the di-*O*-acetyl derivative **11** further supported the assigned structure. Methanesulphonylation of compound **10** gave 1,2:5,6-diepithio-3,4-di-*O*-methanesulphonyl-L-iditol (**12**), identical with the product obtained from 1,6-di-*S*-benzoyl-2,3,4,5-tetra-*O*-methanesulphonyl-1,6-dithio-D-mannitol (**3**) by treatment with sodium methoxide. Compound **3** was prepared from 1,6-dibromo-1,6-dideoxy-2,3,4,5-tetra-*O*-methanesulphonyl-D-mannitol (**13**) by displacing the bromine atoms with thiolbenzoate groups. The di-*O*-methanesulphonyl derivative **12** reacts with carbon disulphide in the presence of 2 equivalents of sodium methoxide to give, not the expected bis(trithiocarbonate) **14**, but sodium methanesulphonate (quantitative yield) and a syrupy compound, to which the structure 2,3:4,5-diepithio-1,6-bis[*S*-(methoxythiocarbonyl)]-1,6-dithio-L-mannitol (**15**) was assigned on the basis of analytical data, its alkylating properties, and the probable mechanism of formation, involving compound **16** as an intermediate.



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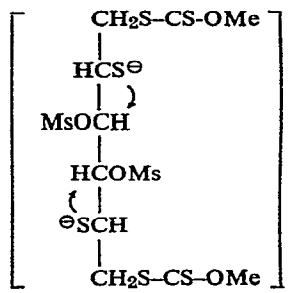

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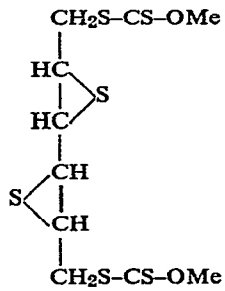

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The epithio derivatives **8**, **10**, and **12** showed no cytostatic activity on Yoshida sarcoma (solid and ascites forms), Walker 256 carcinosarcoma, and Ehrlich ascites sarcoma in doses of $LD_{50}/10$. The absence of *in vivo* activity may be due to the ease of polymerisation of the episulphides.

EXPERIMENTAL

Melting points are uncorrected. Thin-layer chromatography (t.l.c.) was carried out on Kieselgel G with chloroform–ethyl acetate, 3:1 (*A*), 3:2 (*B*), and 5:1 (*C*) as

solvent systems. Detection reagents used were 0.1M potassium permanganate–2N sulphuric acid (1:1), and 4-(*p*-nitrobenzyl)pyridine[8]. I.r. spectra were recorded with a U.R.10 instrument, and n.m.r. spectra with a JEOL J.N.M.-C-60 spectrometer. All evaporations were carried out in a rotary evaporator under diminished pressure. Light petroleum had b.p. 60–80°.

*1,6-Di-*S*-benzoyl-2,5-di-*O*-methanesulphonyl-1,6-dithio-*D*-mannitol* (**2**). — A solution of compound[5] **1** (5 g) and potassium thiolbenzoate (10 g) in acetone (100 ml) was heated on a steam bath for 15 min, cooled, and filtered, and the filtrate was evaporated to a syrup. The residue was dissolved in chloroform, and the solution was washed with 5% aqueous sodium hydrogen carbonate and water, dried (Na_2SO_4), and evaporated. The crystalline residue was triturated with ether and recrystallized from benzene (15 ml); yield, 3.8 g (61.3%); m.p. 106–107°; $[\alpha]_D^{20}$ −107.7° (*c* 1, chloroform); R_F 0.4 (solvent *B*) (Found: C, 45.22; H, 4.73; S, 22.39. $C_{22}H_{26}O_{10}S_4$ calc.: C, 45.66; H, 4.53; S, 22.16%).

Methanesulphonylation of compound **2**. — A solution of compound **2** (0.5 g) in dry pyridine (5 ml) was treated at 0° with methanesulphonyl chloride (0.5 ml). After 24 h at room temperature, the reaction mixture was poured onto ice, and the precipitate was filtered off, dried, and recrystallized from ethanol to yield compound **3** (0.4 g, 63%), m.p. 156–158° alone and in admixture with the compound described below.

*1,6-Di-*S*-benzoyl-2,3,4,5-tetra-*O*-methanesulphonyl-1,6-dithio-*D*-mannitol* (**3**). — A solution of compound **13** (31 g) and potassium thiolbenzoate (18 g) in acetone (500 ml) was heated on a steam bath for 30 min. The precipitate, which formed immediately, was filtered off after cooling, and the filtrate was evaporated to 100 ml, treated with water until turbidity, filtered with charcoal, and diluted with water. The precipitated syrup solidified on storage at 0°, and, after filtration and washing with water and ethanol, gave a crude product (35.5 g). Recrystallization from acetone–ethanol yielded compound **3** (26.5 g, 72%), m.p. 150–152°. This preparation was pure enough for the next step. Further purification was achieved by recrystallization from 150 volumes of ethanol; m.p. 156–158°, $[\alpha]_D^{20}$ +77.5° (*c* 1, chloroform), R_F 0.4 (solvent *A*) (Found: C, 38.96; H, 4.62; S, 25.98. $C_{24}H_{30}O_{14}S_6$ calc.: C, 39.23; H, 4.12; S, 26.18%).

*3,4-Di-*O*-acetyl-1,6-dibromo-1,6-dideoxy-2,5-di-*O*-methanesulphonyl-*D*-mannitol* (**4**). — To a suspension of the dimethanesulphonate **1** (4.65 g) in acetic anhydride (5 ml), one drop of conc. HBr was added. A gentle, exothermic reaction took place, and the solution became clear in a few minutes. Next day, it was poured onto ice, and the precipitate was filtered off, washed with water, dried, and recrystallized from methanol (12 ml) to yield compound **4** (5.2 g, 95%), m.p. 99–100°, $[\alpha]_D^{20}$ +13.7° (*c* 1, chloroform) (Found: C, 26.42; H, 3.85; Br, 28.82; S, 11.53. $C_{12}H_{20}Br_2O_{10}S_2$ calc.: C, 26.28; H, 3.68; Br, 29.16; S, 11.69%).

*3,4-Di-*O*-acetyl-1,6-di-*S*-benzoyl-2,5-di-*O*-methanesulphonyl-1,6-dithio-*D*-mannitol* (**5**). — A solution of compound **4** (5.5 g) and potassium thiolbenzoate (3.6 g) in acetone (50 ml) was treated as described for compound **2**. Evaporation of the

chloroform solution gave an amorphous solid (6 g), $[\alpha]_D^{20}$ +24.0° (*c* 1, chloroform), R_F 0.3 (solvent *C*) (Found: S, 18.61, $C_{26}H_{30}O_{12}S_4$ calc.: S, 19.35%).

*1,6-Di-*S*-benzoyl-3,4-*O*-isopropylidene-2,5-di-*O*-methanesulphonyl-1,6-dithio-*D*-mannitol* (7). — A solution of compound **6** (25.2 g) and potassium thiolbenzoate (17.6 g) in acetone (250 ml) was treated according to the previous procedure. The resulting syrupy **7** (31 g) was pure enough for the next step (Found: S, 20.0%). For further purification, it was eluted from a column of silica gel, first with carbon tetrachloride to remove a contaminant (R_F 0.9, solvent *A*), and then with carbon tetrachloride–ethyl acetate (8:2) to give compound **7** as a colourless syrup, $[\alpha]_D^{20}$ +31.5° (*c* 1, chloroform), R_F 0.45 (solvent A) (Found: S, 19.85. $C_{25}H_{30}O_{10}S_4$ calc.: S, 20.73%).

*1,2:5,6-Diepithio-3,4-*O*-isopropylidene-*L*-iditol* (**8**). — Crude compound **7** (from 25.2 g of compound **6**) was dissolved in dry chloroform (250 ml) and, during 5 min, N sodium methoxide (100 ml) was added, with stirring and cooling, to the solution at 0–10°. The stirring was continued without cooling for 5 min, and then the reaction mixture was washed twice with ice-cold water. The chloroform layer was dried (Na_2SO_4) and evaporated, and methyl benzoate was distilled off at 1 mmHg. The residue was dissolved in methanol (5 ml), and the solution was chilled to −10°. The crystals formed were filtered off and washed with cold methanol; yield, 4.4 g, m.p. 79–80°. The filtrate was evaporated, and the residue was distilled (b.p. 90–92°, 0.05 mm) to yield a further 3.3 g. Recrystallization of the combined crops from methanol (15 ml) afforded compound **8** (7.45 g, 68%), m.p. 80–81°, $[\alpha]_D^{20}$ +89.8° (*c* 1, chloroform), R_F 0.40 (solvent *C*) (Found: C, 49.07; H, 6.40; S, 28.94. $C_9H_{14}O_2S_2$ calc.: C, 49.51; H, 6.46; S, 29.37%). Compound **8** had ν_{max}^{KBr} 3075 (epithio CH and CH_2), 2990, 2980, 1390, 1380, 1180, 1170 (isopropylidene CH_3), 1080, and 870 cm^{-1} (*O*-isopropylidene). N.m.r. data ($CDCl_3$): δ 3.6 (2-proton multiplet, H-3 and H-4), 2.95 (2-proton multiplet, H-2 and H-5), 2.8 (4-proton multiplet, H-1 and H-6), and 1.35 (6-proton singlet, CMe_2).

Polymerization of compound **8**. — A solution of the diepithio compound **8** (1.1 g) in methanol (10 ml) containing N sodium methoxide (1 ml) or triethylamine (1 ml) was refluxed for 2 h. The precipitate was filtered off, after cooling, and washed with methanol, to yield a product (1.1 g), which gradually softened above 160°, $[\alpha]_D^{20}$ −280° (*c* 1, chloroform). The polymer was dissolved in chloroform (5 ml), and the solution was treated with light petroleum until turbidity and then filtered through charcoal into light petroleum (200 ml). The precipitate was filtered off and washed with light petroleum and methanol. The "softening" point increased to 180°; $[\alpha]_D^{20}$ −314° (*c* 1, chloroform). The i.r. spectrum (KBr) had no absorption between 3600–3000 (OH) and 2600–2500 cm^{-1} (SH) (Found: C, 48.97; H, 6.74; S, 28.26; mol. wt. (Rast in borneol), 875. $(C_9H_{14}O_2S_2)_n$ calc.: C, 49.51; H, 6.46; S, 29.37%; mol. wt. (tetramer), 883.

*3,4-*O*-Isopropylidene-1,2,5,6-tetrathio-*L*-iditol 1,2:5,6-bis(trithiocarbonate)* (**9**). — Potassium hydroxide (2.3 g) was dissolved in methanol (10 ml), and carbon disulphide (2.9 ml) and, after cooling, compound **8** (1.5 g) were added. The reaction mixture

was kept for 48 h at room temperature, and the crystalline precipitate was filtered off, and washed with methanol and water to yield a product (0.5 g), m.p. 142–146°. Recrystallization from benzene (6 ml) and light petroleum (3 ml) afforded compound **9** as yellow crystals (0.3 g, 11.6%, m.p. 147–148°), $[\alpha]_D^{20}$ +200° (*c* 1, chloroform); the m.p. was not depressed on admixture with the authentic trithiocarbonate[4].

*1,2:5,6-Diepithio-*L*-iditol* (**10**). — A solution of compound **8** (6.6 g) in N methanolic hydrogen chloride (400 ml) was kept for 10 min at room temperature, and then poured with vigorous stirring and cooling onto an excess (40 g) of solid sodium hydrogen carbonate. The filtered solution was evaporated below 30°, and the residue was treated three times with hot ethyl acetate. The united extracts were evaporated, and the residue was recrystallized from dry chloroform (100 ml) to yield colorless needles of compound **10** (3.2 g). Evaporation of the mother liquor gave a second crop (0.5 g); total yield, 69.3%. On heating, the compound suffered a rearrangement at 118–119° to give material (probably polymeric) having no definite m.p.; a slow decomposition started about 280°. The product had $[\alpha]_D^{20}$ +86.4° (*c* 1, chloroform), R_F 0.15 (solvent *A*), ν_{max}^{KBr} 3500–3300 (OH) and 3060 cm^{-1} (epithio CH) (Found: C, 40.51; H, 5.84; S, 35.67. $C_6H_{10}O_2S_2$ calc.: C, 40.42; H, 5.65; S, 35.97%).

On boiling a solution of compound **10** (0.1 g) in water (5 ml), an insoluble, presumably polymeric material was formed. After 20 min, starting material was not detectable (t.l.c.), and, after cooling, the polymeric material (0.1 g) was filtered off. It had no i.r. absorption in the region of 3000–3100 cm^{-1} (epithio CH) (Found: S, 33.70%).

Acetylation of compound **10**. — A solution of compound **10** (1.8 g) in pyridine (10 ml) and acetic anhydride (3 ml) was kept at room temperature overnight, and then poured onto ice. The solid precipitate was filtered off, washed with water, and dried to yield the crude ester **11** (2 g). This was extracted with hot methanol (20 ml), and water (10 ml) was added to the filtered extract to give compound **11** as needles (1.2 g, 46%), m.p. 124–125°, $[\alpha]_D^{20}$ +35.4° (*c* 1, chloroform), R_F 0.8 (solvent *A*), ν_{max}^{KBr} 3085 (epithio CH), 1725, 1225, 1085, 1060, and 1035 cm^{-1} (ester groups) (Found: C, 45.64; H, 5.44; S, 24.02. $C_{10}H_{14}O_4S_2$ calc.: C, 45.78; H, 5.38; S, 24.45%). N.m.r. data: δ 4.90 (2-proton multiplet, H-3 and H-4), 3.05 (2-proton multiplet, H-2 and H-5), 2.35 (4-proton multiplet, H-1 and H-6), 2.10 (6-proton singlet, acetyl Me).

Methanesulphonylation of compound **10**. — A solution of compound **10** (0.1 g) in dry pyridine (1 ml) was treated with methanesulphonyl chloride (0.1 ml) at 0°. The solution was kept at room temperature for 4 h and was then poured onto ice, and the precipitate was filtered off and washed with water. The crude product (0.15 g, m.p. 109–112°) was recrystallized from ethanol (2 ml) to yield compound **12** (0.1 g, 53.2%), m.p. 114–116° alone and in admixture with the compound described below.

*1,2:5,6-Diepithio-3,4-di-*O*-methanesulphonyl-*L*-iditol* (**12**). — To a stirred solution of compound **3** (14.8 g) in dry chloroform (200 ml), N methanolic sodium methox-

ide (40 ml) was added during a period of 10 min at 0°. The reaction mixture was stirred for 5 min and then poured onto a mixture of 5% aqueous sodium hydrogen carbonate–ice (1:1). The chloroform layer was washed with ice–cold, aqueous sodium hydrogen carbonate and twice with cold water, dried (Na_2SO_4), and evaporated. The semisolid residue was treated with ether to give a crude product (4.8 g, 71.5%). Recrystallization from acetone–light petroleum gave compound **12** (4.4 g), m.p. 114–116°, $[\alpha]_D^{20}$ +36.3° (*c* 1, chloroform), R_F 0.5 (solvent *A*); ν_{max}^{KBr} 3100, 3040, 3025 (epithio CH and CH_2), 3010, and 2935 cm^{-1} (methanesulphonyl CH_3) (Found: C, 28.75; H, 4.50; S, 38.10. $C_8H_{14}O_6S_4$ calc.: C, 28.73; H, 4.22; S, 38.35%). N.m.r. data ($CDCl_3$): δ 4.4 (2-proton multiplet, H-3 and H-4), 3.2 (2-proton multiplet, H-2 and H-5), 2.6 (4-proton multiplet, H-1 and H-6), 3.15 (6-proton singlet, two methanesulphonyl methyl groups).

Treatment of compound **12** *with sodium* O-*methyl dithiocarbonate.* — A solution of compound **12** (3.4 g) in dry chloroform (100 ml) was treated with carbon disulphide (6 ml) and N sodium methoxide (20 ml). The reaction mixture became turbid after a few minutes, and after 3 h, the precipitated sodium methanesulphonate was filtered off. The solution was washed three times with water, dried (Na_2SO_4), and evaporated. Traces of solvent were removed from the syrupy compound **15** at 10^{-2} mmHg and 100°; $[\alpha]_D^{20}$ −31.5° (*c* 1, chloroform), R_F 0.9 (solvent *A*) (Found: S, 51.10; CH_3O, 18.8. $C_{10}H_{14}O_2S_6$ calc.: S, 53.65; CH_3O, 17.28%).

*1,6-Dibromo-1,6-dideoxy-2,3,4,5-tetra-*O*-methanesulphonyl-*D*-mannitol* (**13**). — A solution of 1,6-dibromo-1,6-dideoxy-D-mannitol (MYELOBROMOL®, 30.8 g) in pyridine (200 ml) was treated at 0° with methanesulphonyl chloride (38.5 ml). The reaction mixture was kept at room temperature overnight and then poured onto ice. The precipitated oil solidified on treatment with fresh water, and the product (58.5 g) was dissolved in acetone (50 ml). The solution was treated with charcoal, and diluted with ether (150 ml). The colorless crystals formed were filtered off and washed with ether; yield, 40.7 g. Evaporation of the mother liquor gave a further crop (9.5 g); total yield, 80.5%; m.p. 105–107°, $[\alpha]_D^{20}$ +29.1° (*c* 1, chloroform), R_F 0.15 (solvent A) (Found: C, 19.73; H, 3.67; Br, 25.87; S, 20.88. $C_{10}H_{20}Br_2O_{12}S_4$ calc.: C, 19.36; H, 3.25; Br, 25.78; S, 20.68%).

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REFERENCES

1 W. C. J. Ross, *Biological Alkylating Agents*, Butterworths, London, 1962, p. 107.
2 M. Jarman and W. C. J. Ross, *Chem. Ind.* (London), (1967) 1789.
3 L. Vargha and E. Kasztreiner, *Ber.*, 92 (1959) 2506.
4 A. M. Creighton and L. N. Owen, *J. Chem. Soc.*, (1960) 1024.
5 L. Vargha and T. Horváth, *Acta Unio Intern. Contra Cancrum*, 20 (1964) 76.
6 L. D. Hall, L. Hough, and R. A. Pritchard, *J. Chem. Soc.*, (1961) 1537.
7 S. M. Iqbal and L. N. Owen, *J. Chem. Soc.*, (1960) 1030.
8 D. M. Friedman and E. Boger, *Anal. Chem.*, 33 (1961) 906.