

ether gave a sample with m.p. 134–135° (lit.,<sup>9</sup> 131–133°); characterized by decarboxylation to  $\alpha$ -L-glutamyl-L-valine (see below).

*Anal.* Calcd. for  $C_{18}H_{24}O_7N_2$ : C, 56.83; H, 6.36; N, 7.37; O, 29.44. Found: C, 56.84; H, 6.40; N, 7.39; O, 29.54.

**$\alpha$ -L-Glutamyl-L-valine.**—N-Carbobenzoxy- $\alpha$ -L-glutamyl-L-valine (300 mg., 0.00079 mole) from the preceding experiment, in 40 ml. of 60% methanol, was hydrogenated over 25 mg. of palladium-charcoal (10%) catalyst at 2 atm. for 1 hr. The catalyst was removed by filtration and washed with 25 ml. of warm water. The combined filtrate and washings were evaporated *in vacuo* and the residue, on crystallization from water-ethanol, yielded 145 mg. (75%) of  $\alpha$ -L-glutamyl-L-valine, m.p. 188°,  $[\alpha]^{25}_D +24.4$  (*c* 2.46 in 0.1 N hydrochloric acid) [lit.,<sup>9</sup> m.p. 189–190°;  $[\alpha]^{25}_D +24.5$  (in dilute hydrochloric acid)].

*Anal.* Calcd. for  $C_{16}H_{20}O_5N_2$ : C, 48.77; H, 7.37; N, 11.38. Found: C, 48.78; H, 7.06; N, 10.93.

**Oxidation of N-Carbobenzoxy- $\alpha$ -L-glutamyl-L-leucine Ethyl Ester  $\gamma$ -Phenylhydrazide (III<sub>d</sub>) with Manganese Dioxide.**—A solution of 1.025 g. (0.002 mole) of III<sub>d</sub> in 50 ml. of 50% acetic acid was stirred with 1.044 g. of activated manganese dioxide<sup>3</sup> for 30 min., more (0.250 g.) manganese dioxide was added and stirring was continued for 15 min. The reaction mixture was worked up as in the preceding oxidation experiments to give 0.663 g. (78%) of N-carbobenzoxy- $\alpha$ -L-glutamyl-L-leucine ethyl ester with m.p. 87–90°. Crystallization from ethyl acetate-hexane afforded a sample with m.p. 92–95° (lit.,<sup>9</sup> 88–94°).

*Anal.* Calcd. for  $C_{27}H_{36}O_7N_2$ : C, 59.70; H, 7.16; N, 6.63. Found: C, 60.02; H, 6.86; N, 6.70.

**Oxidation of N-Carbobenzoxy-L-glutamic Acid  $\gamma$ -Phenylhy-**

**drazide (Ia) with Manganese Dioxide.**—A solution of 1.86 g. (0.005 mole) of Ia in 50 ml. of 50% acetic acid was stirred with 2.18 g. of activated manganese dioxide<sup>3</sup> for 30 min. The solid material was removed by filtration and washed with 25 ml. of 50% acetic acid, 10 ml. of methanol, and finally with 100 ml. of warm ethyl acetate. The combined filtrate and washings were worked up as in the preceding oxidation experiments. The crude product yielded, on crystallization from ethyl acetate-petroleum ether, 1.071 g. (76%) of N-carbobenzoxy-L-glutamic acid with m.p. 118–120° (lit.,<sup>10</sup> 120°), identical to a sample prepared by carbobenzylation of L-glutamic acid (m.p., mixed m.p., and infrared spectrum).

*Anal.* Calcd. for  $C_{13}H_{15}O_6N$ : C, 55.51; H, 5.38; N, 4.98. Found: C, 55.58; H, 5.20; N, 4.94.

**Oxidation of Methionine with Manganese Dioxide.**—A solution of 149 mg. of L-methionine in 5 ml. of 50% acetic acid was stirred with 435 mg. of activated manganese dioxide<sup>3</sup> for 45 min. The mixture was filtered and the solid material washed with 10 ml. of glacial acetic acid and 10 ml. of water. The combined filtrate and washings were saturated with hydrogen sulfide gas then evaporated *in vacuo* at 25–28°. Analysis of the residue on a Beckman/Spinco amino acid analyzer (Model 120) showed that the amino acid content consisted of 67% methionine sulfide and 33% methionine.

**Acknowledgment.**—The author wishes to thank Dr. R. W. Rinehart and associates for analytical data, Dr. A. J. Parcels for amino acid analysis, and R. W. Commins for technical assistance.

(9) W. J. Le Quesne and J. T. Young, *J. Chem. Soc.*, 1954 (1950).

(10) M. Bergman and L. Zervas, *Ber.*, **65**, 1192 (1932).

## Synthesis of Sulfur Analogs of Inositol (Dimercaptocyclohexanetetrols). Nuclear Magnetic Resonance Configurational Proofs<sup>1,2</sup>

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Two stereoisomers of 5,6-dimercapto-1,2,3,4-cyclohexanetetrol have been synthesized and their configurations determined by means of nuclear magnetic resonance spectra and optical rotation calculations. Reaction of dextrorotatory 3,4:5,6-di-*O*-isopropylidene-1,2-anhydro-*allo*-inositol with carbon disulfide gave a mixture of two diastereomeric trithiocarbonate diketals (m.p. 204°, 191°). The 204° diastereomer on reduction gave a tetrolthiol diketal, m.p. 91°, shown by n.m.r. to have the (126/345) configuration. This product was converted to the tetrolthiol, its hexaacetate, and a mercaptole diketal, all of the same configuration. The 191° trithiocarbonate diketal on similar treatment gave a tetrolthiol diketal, tetrolthiol, tetrolthiol hexaacetate, mercaptodithiolane diketal, and mercaptodithiolane pentaacetate, all necessarily having the (125/346) configuration. The trithiocarbonate derivatives give optical rotatory dispersion spectra with well defined Cotton effects and have ultraviolet specific rotations exceeding plus or minus 22,000 degrees. An attempt to predict the monochromatic optical rotations of the two tetrolthiols gave results which were in the right order, but showed large deviations in magnitude from the experimentally found values.

Continuing our studies<sup>2,5</sup> on the stereochemistry and nuclear magnetic resonance spectra of alicyclic type carbohydrates (cyclitols), we wish to report the synthesis and characterization of what appear to be the

first known sulfur analogs of inositol.<sup>5a</sup> Our present products include two optically active diastereomers of 5,6-dimercapto-5,6-dideoxyinositol (XIV, XVII) and corresponding hexaacetate (XV, XVIII), diisopropylidene (X, XII), and trithiocarbonate (VI, VIII) derivatives, and one active diastereomer of a mercaptodiketetal (XI) and of a mercaptodithiolane diketal (XIII) and pentaacetate (XIIIa).

This program of studies on sulfur-containing cyclitols has been initiated, partly in the hope of discovering substances of biological value,<sup>6</sup> and partly in order to expand knowledge in certain relatively unexplored areas of

(1) Presented at Brussels, Belgium, in June, 1962, to the I.U.P.A.C. Symposium International de Chimie Organique consacré à l'Étude des Produits Naturels. Certain aspects of this research were reported to the Division of Carbohydrate Chemistry at the 141st National Meeting of the American Chemical Society, Washington, D. C., March, 1962.

(2) Paper XIII on cyclitol stereochemistry by G. E. McCasland and co-workers; for preceding paper see J. N. Shoolery, L. F. Johnson, Stanley Furuta, and G. E. McCasland, *J. Am. Chem. Soc.*, **83**, 4243 (1961).

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(4) Varian Associates.

(5) G. E. McCasland, Stanley Furuta, L. F. Johnson, and J. N. Shoolery, *J. Am. Chem. Soc.*, **83**, 2335 (1961).

(5a) NOTE ADDED IN SEPTEMBER, 1962: We have recently prepared a monomercaptocyclohexanepentol (hexaacetate m.p. 182°) by reaction of 1,2-anhydro-*cis*-inositol diketal with benzyl mercaptan, reduction and hydrolysis. Details will be given in a subsequent publication.

(6) Biological interest in inositol sulfur analogs arises in part from the fact that *myo*-inositol is essential for growth of isolated normal and malignant human cells in tissue culture [see H. Eagle, *J. Biol. Chem.*, **226**, 191 (1957)] and also for certain microorganisms. There is also some reason to believe that inositol sulfur analogs may show activity as antitoxic agents for metals or as drugs for radiation protection.

carbohydrate and organic sulfur chemistry. In this program special emphasis will be placed on utilization and extension of the newer physical methods of characterization, such as nuclear magnetic resonance and optical rotatory dispersion.

Relatively little is known about carbohydrate sulfur analogs.<sup>7,8</sup> The success of "BAL"<sup>7b</sup> as an antitoxic agent for metals has stimulated a certain amount of work on sulfur analogs of alditols with three or more carbon atoms. The recent work of Owen and co-workers<sup>9</sup> on hexitol analogs is especially relevant to our present research. Goodman, Baker, and co-workers<sup>10</sup> have reported recent intensive work on sulfur and sulfur-nitrogen analogs of monosaccharide derivatives. Pioneering studies on cyclohexanes with (only) one or two sulfur-containing functional groups were reported by Weibull in his 1951 thesis<sup>11</sup> at Stockholm, and followed up by some more recent investigators.<sup>12,13</sup> Previous work on sulfur-containing cyclitols apparently has been limited to sulfonic esters,<sup>14</sup> mercaptols, and sulfones.<sup>15,16</sup>

The starting point in our present investigation was dextrorotatory 3,4:5,6-di-*O*-isopropylidene-1,2-anhydro-*allo*-inositol, previously shown<sup>14b</sup> to have the absolute configuration VII. On treatment with carbon disulfide, this epoxy-cyclohexanetetrol derivative reacts with inversion of configuration at position 1 or 2 (formula VII) to give a mixture of the two diastereomeric trithiocarbonate diketals VI and VIII. Since all subsequent reactions are presumed to occur with retention of configuration, the result (see Chart I) was to produce one configurationally correlated series (X, XI, XIV, XV) having the same configuration as the trithiocarbonate VI, and another series (XII, XIII, XIIIa, XVII, XVIII) having the same configuration as the trithiocarbonate VIII.

Thus by establishing the configuration of any one compound in either series, that series could be assigned one of the two possible configurations, (126/345) or (125/346), and the remaining configuration would automatically correspond to the remaining series. Although the traditional chemical or physical methods offered little hope for characterizing the eleven compounds or even one of them, the more powerful approach of nuclear magnetic resonance has now provided a successful solution to the problem. An attempt was also made to assign configurations by comparing the observed optical rotations of the two tetroldithiols with rotations predicted by the method of

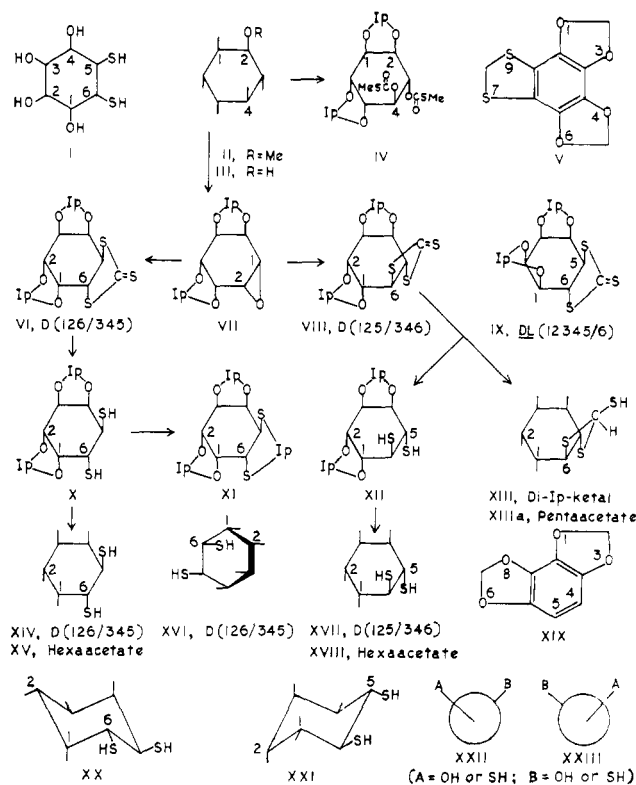


Chart I

Brewster<sup>17</sup>; these assignments were qualitatively in accord with those based on n.m.r. spectra but the quantitative agreement between predicted and found rotations was poor. (Regarding the nomenclature "(126/345)," see below.)

**N.m.r. Configurational Proof.**—The first two compounds examined by n.m.r. were the two trithiocarbonates, VI and VIII; the resulting spectra, however, could not be interpreted in terms of configuration. The next n.m.r. measurements were on the tetroldithiol diketal of m.p. 91° which had been obtained by reduction of the trithiocarbonate, m.p. 204°, and this spectrum has been successfully interpreted.

The high resolution n.m.r. spectrum (Fig. 1) of the tetroldithiol diketal, m.p. 91°, in chloroform-*d* was determined with the Varian HR-60 spectrometer, using a trace of tetramethylsilane as internal reference. Chemical shifts are given in parts per million relative to the reference compound defined as zero, according to the relationship

$$\delta(\text{p.p.m.}) = 10^6 \frac{(\text{H}_{\text{ref}} - \text{H})}{\text{H}_{\text{ref}}}$$

Spin-spin coupling constants, however, are given in cycles per second (c.p.s.).

The spectrum (Fig. 1) shows the following features. A strong sharp line is observed at  $\delta = 1.33$  due to the six protons of two equivalent methyl groups; and a similar line at 1.45 due to the two remaining methyl groups, which are equivalent to each other but not to the first two methyl groups. A complex multiplet centered at  $\delta = 2.13$  can be assigned unequivocally to the signals from the two —SH protons, since these signals disappear if the sample is placed in contact with

(17) J. H. Brewster, *ibid.*, **81**, 5483 (1959); **81**, 5475 (1959); see also D. H. Whiffen, *Chem. Ind. (London)*, 964 (1956).

(7) "Advances in Carbohydrate Chemistry," M. L. Wolfrom, ed., Academic Press, New York, N. Y., 1960: (a) Vol. I, pp. 129-144; (b) Vol. 15, pp. 91-158.

(8) E. Reid, "Organic Chemistry of Bivalent Sulfur," Chemical Publishing Co., New York, N. Y., 1958, Vol. I: (a) pp. 376-402; (b) pp. 385-388.

(9) L. N. Owen, *et al.*, *J. Chem. Soc.*: (a) p. 1024; (b) p. 1030 (1960).

(10) L. Goodman, B. R. Baker, *et al.*, *J. Org. Chem.*, **26**, 3554 (1961), and *J. Am. Chem. Soc.*, **82**, 4738 (1960); and references to previous work there cited.

(11) Bengt Weibull, Inaugural dissertation, University of Uppsala, Sweden, 1951.

(12) *E.g.*, see F. G. Bordwell and H. M. Anderson, *J. Am. Chem. Soc.*, **75**, 4959 (1953); (b) E. Van Tamelen, *ibid.*, **73**, 3444 (1951); (c) L. Miles and L. Owen, *J. Chem. Soc.*, 817 (1952).

(13) T. Taguchi, *et al.*, *J. Am. Chem. Soc.*, **81**, 4322 (1959).

(14) S. J. Angyal, *et al.*: (a) *J. Chem. Soc.*, 3691 (1957); (b) *J. Am. Chem. Soc.*, **77**, 4343 (1955); (c) *J. Chem. Soc.*, 686 (1952).

(15) G. Drummond, J. Aronson, and L. Anderson, *J. Org. Chem.*, **26**, 1601 (1961).

(16) D. MacDonald and H. O. L. Fischer, *J. Am. Chem. Soc.*, **77**, 4348 (1955).

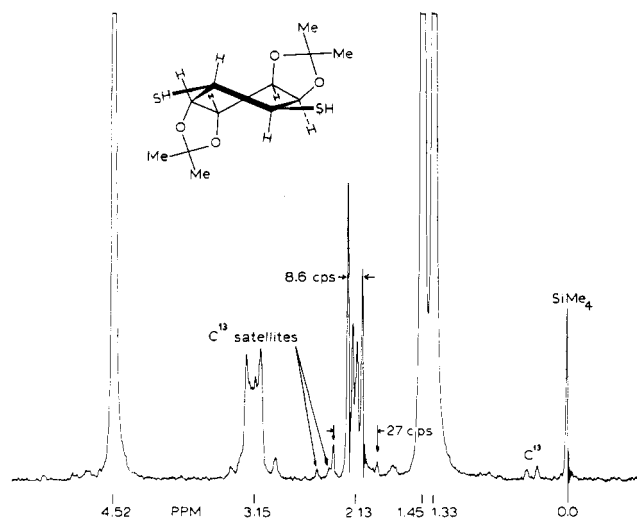


Fig. 1.—Sixty megacycle n.m.r. spectrum in chloroform-*d* of the levorotatory m.p. 91° stereoisomer of 5,6-dimercapto-1,2,3,4-cyclohexanetetrol diacetone ketal (H increases left to right).

deuterium oxide.<sup>18</sup> A pattern with the same general contour as that of the multiplet at 2.13 is observed at  $\delta = 3.15$ , and these signals are assigned to the two protons on C-5 and C-6 (formula X or XII). A single sharp line is observed at  $\delta = 4.52$  and is attributed to the four protons on C-1, C-2, C-3, and C-4. Although the equivalence of H-1 to H-4, and H-2 to H-3, might be anticipated,<sup>19</sup> the equivalence of all four protons is unexpected and may be attributed to accidental degeneracy. At certain locations in the spectrum (Fig. 1) carbon-13 satellite signals are visible, identified by their intensities (1.1% abundance) and spacing of approximately 125 c.p.s. In Fig. 1, only the satellites of the methyl proton signals are clearly visible.

The signals around  $\delta = 2.13$  and 3.15 clearly have the character typical of a group of four nuclei whose chemical shifts and spin-spin coupling constants can be described as an  $A_2X_2$  (or more properly  $A_2B_2$ ) case. For the sake of the analysis, the  $A_2X_2$  approximation<sup>20</sup> is adequate. The line positions and intensities of the pattern centered around  $\delta = 2.13$  fit the theoretical predictions quite well for an  $A_2X_2$  set of nuclei in which  $J_A$ , the coupling constant between the two protons on C-5 and C-6 is 12 c.p.s., and  $J$ , the coupling constant between each —SH proton and the proton on the same carbon atom, is 8.6 c.p.s. The remaining coupling constants,  $J_X$  (between the two —SH protons) and  $J'$  (between H-5 or H-6 and the proton of the nongeminal —SH group), are zero. The pattern at  $\delta = 3.15$  (except for somewhat broader lines) is so similar to the pattern at 2.13 that it is clear the protons H-5 and H-4, or H-6 and H-1, cannot be coupled to one another with a constant greater than one or two c.p.s.

(18) The sample was dissolved in deuterium oxide, the solution allowed to stand for several hours and evaporated to dryness, and the residue dissolved in chloroform-*d*.

(19) The tetroldithiol diketal X, although dissymmetric in all conformations, has in certain conformations a *twofold simple axis of symmetry*. This is true also of the diastereomer XII, and of the tetroldithiol, tetroldithiol hexaacetate, and trithiocarbonate derivatives of X and XII. This symmetry axis tends to produce n.m.r. spectral equivalence of pairs of groups located at positions 2 and 3, or 1 and 4, or 6 and 5. However, the mercaptodithiolane XIII does not have the symmetry axis or the group-equivalence mentioned.

(20) J. Pople, W. Schneider, and H. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, pp. 139-142.

The procedure for calculating the spin-spin coupling constants,  $J$  and  $J_A$ , from the measured frequency differences 8.6 c.p.s. and 27 c.p.s. in the spectrum (Fig. 1) is as follows. The theoretical  $A_2X_2$  spectrum consists of twelve  $X$  lines (of which some are coincident with others) and twelve exactly similar  $A$  lines.<sup>20</sup> In the present calculations only the  $X$  lines are considered (these are located in the multiplet near 2.13 p.p.m.). The two coincident lines (transitions) numbered 1 and 2 (Table 6-18)<sup>20</sup> together with the two coincident lines 3 and 4 form a high intensity doublet, whose center falls at  $\delta = 2.13$ . The measured separation of the doublet lines, 8.6 c.p.s., must be equal to  $\frac{1}{2}N - (-\frac{1}{2}N) = N$ . Since by definition  $J = N - J'$  and  $J'$  is here assumed to be zero, the coupling constant  $J$  between the adjacent  $A$  and  $X$  nuclei is equal to 8.6 c.p.s.

The theoretical lines (transitions) numbered 5 to 12 (Table 6-18)<sup>20</sup> constitute two quartets, which in the present example overlap completely, to form a single quartet of double intensity. The two outermost lines of the resulting quartet have a measured separation of 27 c.p.s. (Fig. 1). This separation can be set equal to the difference between the energy functions 5 and 12 in Table 6-18, so that

$$27 = \frac{1}{2}K + \frac{1}{2}(K^2 + L^2)^{1/2} - [-\frac{1}{2}M - \frac{1}{2}(M^2 + L^2)^{1/2}]$$

Since by definition  $K = J_A + J_X$ ,  $L = J - J'$ ,  $M = J_A - J_X$ ,  $N = J + J'$ , and since in the present case it is assumed that  $J_X = J' = 0$ , it follows that

$$K = M = J_A, L = N = J = 8.6$$

and the above equation becomes

$$27 = \frac{1}{2}J_A + \frac{1}{2}(J_A^2 + 8.6^2)^{1/2} + \frac{1}{2}J_A + \frac{1}{2}(J_A^2 + 8.6^2)^{1/2}$$

so that  $(J_A - 27)^2 = J_A^2 + 8.6^2$ , and  $J_A = 12.1$  c.p.s.

The 12 c.p.s. coupling constant deduced for the two protons at C-5 and C-6 requires that the bonds of these protons must have a dihedral angle<sup>21</sup> in the vicinity of 180°, and thus must have a *trans*-diaxial<sup>22</sup> orientation. Although the favored chair conformation of the (125/346) configuration XII would meet this requirement (making allowance for ring-distortion in the relatively rigid tricyclic structure), this conformation would also have axial protons at C-1 and C-4. The resultant coupling between the two protons at C-1 and C-6, or C-4 and C-5, would be expected to have a constant in excess of 6 c.p.s.<sup>21</sup> Since this coupling constant is observed to be not greater than one or two c.p.s., the (125/346) configuration, XII, is excluded.<sup>23</sup>

The remaining possibility is the (126/345) configuration X. From the inspection of Dreiding stereo-models,<sup>24</sup> it appears that the preferred conformation of

(21) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(22) Because of cyclohexane ring distortion by the relatively rigid tricyclic structure in the tetroldithiol diketal, the terms axial and equatorial are here only approximate, especially when applied to boat conformations.

(23) The (125/346) tetroldithiol diketal can presumably also exist in a twisted boat conformation having a diaxial orientation of the 5,6-ring protons; but here also the neighboring ring protons at positions 1 and 4 would be approximately "axial" in orientation, producing the wrong dihedral angles.

(24) W. Büchi, Glasapparatefabrik Flawil, Switzerland; Scientific Glass Apparatus Co., Inc., Bloomfield, N. J.

this molecule would be a twisted boat conformation<sup>25,26</sup> (Fig. 1) in which the ring protons 5 and 6 are not only *trans* and diaxial, but make dihedral angles of approximately 45° with the neighboring protons at positions 4 and 1, respectively. This dihedral angle would be in accord<sup>21</sup> with the one or two c.p.s. coupling constant mentioned above. The n.m.r. spectrum of the m.p. 91° stereoisomer of the tetrolthiol diketal is thus consistent with the (126/345) configuration, X. The n.m.r. spectrum of the m.p. 103° tetrolthiol diketal has also been obtained and is in qualitative agreement with the (125/346) configuration, but has not been completely analyzed.

Successful evaluation of the n.m.r. spectrum of X thus permitted assignments of the (126/345) configuration to the entire correlated series (see above) of which X is a member (Chart I). The remaining (125/346) configuration then necessarily corresponds to the remaining series.

The n.m.r. spectra tell nothing, of course, about the absolute (enantiomeric) configurations of these compounds. However, from the known configuration, VII, of the starting material used, the compounds in Chart I necessarily have the absolute configurations shown, and not their mirror images.

The n.m.r. spectrum of the trithiocarbonate diketal, VI (m.p. 204°), was also determined. Two strong peaks at  $\delta = 1.37$  and 1.55 indicated the presence of two equivalent methyl groups, and of two other methyl groups equivalent to each other but not to the first two. The six ring protons formed a broad pattern in the neighborhood of  $\delta = 4.66$  which offers no promise of easy interpretation. The spectrum of the stereoisomeric trithiocarbonate diketal, VIII (m.p. 191°) was similar. Neither spectrum appears to be very useful for configurational conclusions.

**Synthetic Routes.**—The preparation of the trithiocarbonate diketals followed the approach which Owen and co-workers<sup>9</sup> had used for alditol and gulitol derivatives. Reaction of the epoxide starting material, VII, with carbon disulfide in methanolic potassium hydroxide yielded a mixture of the two yellow, crystalline trithiocarbonates, VI and VIII.

An interesting procedure was used for separating these diastereomers: Since our reaction product consisted of a conglomerate of two visibly different varieties of crystals (large, well formed pale yellow plates and bright yellow rods), the diastereomers were mechanically separated by handpicking of the crystals.<sup>27</sup>

Although Owen, *et al.*,<sup>9</sup> reported that trithiocarbonates can also be prepared from episulfides, and suggested that episulfides are intermediates in the conversion of epoxides to trithiocarbonates, we have not been able to isolate any episulfides from our reaction mixtures, and as yet our attempts to prepare cyclitol episulfides by other means have not been successful.

The procedures for lithium aluminum hydride reduc-

(25) Inspection of the models suggests that the molecule X could somewhat less easily assume a chair (or semi-chair) conformation, which also would have the requisite 5,6 *trans*-diaxial orientation and dihedral angles. There also may be available to it certain 5,6-diequatorial conformations (chair, semi-chair, or twisted boat), but the n.m.r. spectrum excludes any important contribution by these latter conformations.

(26) It has been shown that such a twist conformation is usually more stable than the traditional planosymmetric "boat." See W. S. Johnson, *J. Am. Chem. Soc.*, **83**, 606 (1961).

(27) In a famous experiment, L. Pasteur used a similar technique for the separation of enantiomers; see *Ann. Chim.*, (3) **24**, 442 (1848).

tion of our trithiocarbonate diketals to tetrolthiol diketals were also similar to those used by Owen, *et al.*<sup>9</sup>

The diisopropylidene derivatives on treatment with boiling 50% aqueous acetic acid were easily hydrolyzed to the free tetrolthiols (XIV, XVII). These inositol sulfur analogs were colorless, crystalline, water-soluble and somewhat hygroscopic substances, melting sharply when heated (but with decomposition). They seem to be stable to air and light, and have only very slight mercaptan odors (perhaps none if completely pure). The tetrolthiols in aqueous solution form a precipitate on addition of dilute lead nitrate solution. Both the —SH and —OH groups are easily acetylated by the usual (for hexols) procedure, giving the colorless, crystalline, water-insoluble, sharp melting hexaacetates.

The dithiol diketal, X, on reaction with acetone gave the mercaptole diketal, XI, in which there is presumably a *trans* fusion between the cyclohexane and dithiolane rings.<sup>28</sup>

An early attempt to reduce the trithiocarbonate diketal VIII (m.p. 191°) gave a colorless crystalline product, m.p. 152°. The n.m.r. spectrum of this product indicated that it is not the expected tetrolthiol diketal, but is actually the mercaptodithiolane diketal, XIII; this was confirmed by microanalysis. With a longer reaction time the complete reduction to the tetrolthiol diketal XII was successfully accomplished.

The mercaptodithiolane spectrum provided the first known chemical shift measurement for a proton on a carbon atom bound to three sulfur atoms. This signal was located at about 5.75 p.p.m. downfield from tetramethylsilane, and here appeared as a 6 c.p.s. doublet due to spin-spin coupling with the single neighboring —SH proton (formula XIII). This coupling also caused the —SH proton signal itself to appear as a doublet. The spectrum also included signals due to the six protons of two equivalent methyl groups; and to the protons of two other methyl groups not equivalent to each other or to the first two groups. Signals were also present corresponding to the two protons with geminal sulfur, and to the four with geminal oxygen (see Experimental).

Hydrolysis and acetylation of the mercaptodithiolane diketal gave the corresponding pentaacetate, XIIIa.

**Attempted Prediction of Optical Rotations.**—Having established the configurations XIV and XVII of the two tetrolthiols by n.m.r., it was of interest to see if their optical rotations calculated by the method of Brewster<sup>17</sup> would be in accord with experimental values, since this method of assigning configurations had proved useful in our previous work.<sup>5</sup> For these calculations we used the previously proposed<sup>17</sup> rotatory parameters for chair form cyclohexane rings:  $k(\text{C—H})$ -(C—H) = 60;  $k(\text{C—H})(\text{O—H})$  = 50;  $k(\text{O—H})$ -(O—H) = 45; and  $k(\text{C—H})(\text{S—H})$  = 174. From these values by simple arithmetic it is found that  $k(\text{S—H})(\text{O—H})$  = 145, and  $k(\text{S—H})(\text{S—H})$  = 505. As before, conformation XXII is assumed to make a positive, and XXIII a negative, contribution. A 1,2-diaxial pair of groups makes zero contribution.

(28) Although *trans*-1,2-cyclohexanedithiol does not form an acetone ketal under the conditions ordinarily used for acetonating the *cis* isomer (but does under special conditions), *trans*-1,2-cyclohexanedithiol reportedly can easily be acetonated at room temperature (S. Iqbal and L. Owen, *J. Chem. Soc.*, 1030 (1960).)

Using these parameters and considering only the favored conformations, the predicted molecular rotations for XX and XXI turn out to be  $-660$  and  $+125^\circ$  (found,  $-192$  and  $-98^\circ$ ). Although not very satisfactory, the calculations would lead one correctly to predict that XIV will be more levorotatory than XVII.

The poor agreement in actual magnitudes suggested that the original parameter<sup>17</sup>  $k(\text{C—H})(\text{S—H}) = 174$  may need revision.<sup>29</sup> To test this possibility, the calculations were repeated with a modified parameter  $k(\text{C—H})(\text{S—H}) = 100$ . The predicted rotations for XX and XXI then turned out to be  $-197$  and  $-90^\circ$  (found  $-192$  and  $-98^\circ$ ). Since the choice of the parameter 100 was somewhat arbitrary, it will be necessary to try it on additional examples of mercapto hydroxy cyclohexanes, which we plan to do, before any firm conclusion can be drawn.

**Optical Rotatory Dispersion Spectra.**—Since the dithiocarbonate (xanthate) derivatives of hydroxy acids give Cotton effect type RD spectra useful for establishing configurations of the hydroxy acids,<sup>30a</sup> it is hoped that the trithiocarbonate derivatives of carbohydrates may give RD spectra useful for characterization of the carbohydrates.

The preliminary results now reported reveal that cyclitol trithiocarbonates do have RD spectra with well defined Cotton effects, and a favorably high ratio of rotation to absorption, characteristic of the chromophore  $-\text{Y}-(\text{C}=\text{S})-\text{Y}-$  where  $\text{Y} = \text{O}$  or  $\text{S}$ . Any attempt to interpret these spectra in terms of configuration will be reserved for a later publication,<sup>31</sup> when it is hoped RD spectra for a larger number of trithiocarbonates will be available.

Although our trithiocarbonates have specific rotations of only about plus or minus  $100^\circ$  at the sodium "D line," their specific rotation maxima in the 280–330- $\mu$  region have magnitudes exceeding plus or minus 22,000 degrees.

The RD spectrum of the monothiolcarbonate, IV, which has no  $\text{C}=\text{S}$  chromophore, was also measured; as expected, this compound gave only a plain dispersion curve. In the course of this work, the RD spectra of several previously known cyclitol intermediates were measured for the first time—see Experimental.

**Other Synthetic Products.**—The actual starting point for our syntheses was natural, levorotatory quebrachitol, II, which had been isolated from rubber latex.<sup>32</sup> This was hydrolyzed to (–)-inositol, III, which was converted to its 1,2:5,6 diacetone ketal.<sup>14b</sup> A portion of this diketal was treated with methanethiol chloroformate,<sup>33</sup> to give the monothiolcarbonate ester, IV. The rest of the diketal was converted to 3,4:5,6-di-*O*-isopropylidene-1,2-anhydro-*allo*-inositol, VII.<sup>14b</sup>

The (12345/6) trithiocarbonate diketal, IX, a racemic substance, m.p.  $204^\circ$ , was prepared by reaction of

1,2:3,4 - di - *O* - isopropylidene - 5,6-anhydro - *allo*-inositol with carbon disulfide. The synthesis and reactions of this diastereomeric trithiocarbonate will be described in a subsequent publication.

**New Ring System.**—A number of the compounds here reported (VI, VIII, IX, XI, XIII) contain a tetracyclic (5,5,5,6) ring system of the type ( $\text{C}_3\text{O}_2$ ,  $\text{C}_3\text{O}_2$ ,  $\text{C}_3\text{S}_2$ ,  $\text{C}_6$ )—see formula V. This ring system is not listed in the "Ring Index,"<sup>34</sup> and we believe has not previously been reported. Its nomenclature is discussed below.

### Explanation of Nomenclature

In this article names based directly on cyclohexane have been used in preference to those based on dideoxyinositol<sup>35</sup> or on heterocyclic systems. However, since *Chemical Abstracts* prefers heterocyclic names (see below) for the tri- and tetracyclic compounds, these names have been given in footnotes.

*Chemical Abstracts'* rules for "precedence of functions" have been followed, e.g., the structure I is numbered as shown and named 5,6-dimercapto-1,2,3,4-cyclohexanetetrol (not 3,4,5,6-tetrahydroxy-1,2-cyclohexanedithiol).

Diastereomeric configurations have been specified by fractional symbols, e.g., (126/345) for XIV. The clockwise or counterclockwise numbering direction, when otherwise ambiguous, is so chosen as to give the lowest numerator numbers, e.g., III is designated (124/356), not (134/256).

Enantiomeric configurations have been specified by "D" or "L" symbols, e.g., for stereoisomer XIV, the symbol "D" signifies that the lowest numbered group is *down* (formula XIV) or to the *right* (formula XVI).<sup>36</sup> For further explanation see previous articles<sup>2,5</sup> or a *Chemical Abstracts* pamphlet.<sup>37</sup>

Heterocyclic names for the tetradithiol diketals are based on the parent system *benzo*[1,2-*d*:3,4-*d'*] *bis*[1,3]dioxole, numbered as in formula XIX. For the tetracyclic intermediates, the parent system is [1,3]dithiolo[5,6]benzo[1,2-*d*:3,4-*d'*] *bis*[1,3]dioxole (V) numbered as indicated. An alternative name<sup>38</sup> for V is 1,3,4,6-tetraoxa-7,9-dithiatrindan.

### Experimental

All melting points have been corrected and were measured with a Nalge-Axelrod micro hot stage. Microanalyses by the Micro-Tech Laboratories, Skokie, Ill. Nuclear magnetic resonance spectra were measured with a Varian Model HR-60, high resolution n.m.r. spectrometer. In a few cases, signals were confirmed by measurements with the new 100-Mc. HR-100 spectrometer. Infrared spectra using potassium bromide pellets were measured with a Perkin-Elmer Model 137 Infracord recording spectrometer. Optical rotatory dispersion spectra were measured on a Rudolph Model 260/655/850 automatic recording photoelectric spectropolarimeter. Monochromatic optical rotations were measured with a Kern Full-Circle polarimeter.

All nonaqueous solutions to be evaporated were dried with an appropriate desiccant and evaporated under reduced pressure. Crystals were washed with an appropriate solvent, and dried *in*

(34) A. Patterson, L. Capell, and D. Walker, "The Ring Index," 2nd ed., American Chemical Society, Washington, D. C., 1960.

(35) The inositol configurational prefixes "neo," "muco," etc., would not be definitive when applied to sulfur analogs unless the locations of replacement of oxygen by sulfur were specified; in some cases, it would also be necessary to distinguish between the two mirror image forms of a dissymmetric sulfur analog molecule derived from a symmetrical (*meso*) inositol molecule.

(36) After the position numbering of the ring is fixed, the perspective formula is so oriented in space that if its plane is horizontal the ring-numbering runs from *right to left around the front* (e.g., formula XIV); or if vertical, from top to bottom around the front (e.g., formula XVI). When this orientation is completed, the configuration may be classified as "D" or "L." (A similar orientation is customary for perspective formulas of pyranose sugars; however, the "D" or "L" classification rule for sugars is different from that used here.)

(37) G. E. McCasland, "A New General System for the Naming of Stereoisomers," 1953, pamphlet available from the Chemical Abstracts Service, c/o Ohio State University, Columbus 10, Ohio.

(38) For example, the *trindan* type name for VI (or VIII) would be hexahydro-2,2,5,5-tetramethyl-1,3,4,6-tetraoxa-7,9-dithiatrindan-8-thione.

(29) Unlike most of Brewster's rotatory parameters, the proposed value 174 was not based on experimental rotation data.

(30) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., Inc., New York, N. Y., 1960: (a) p. 201; (b) p. 230.

(31) The problem of correlating the rotatory dispersion spectra of cyclitol sulfur derivatives with their configurations and conformations is being undertaken by one of us (G.E.M.) in cooperation with Professor Carl Djerassi of Stanford University.

(32) We would like to thank the Plantation Division, U. S. Rubber Co., for a generous supply of quebrachitol.

(33) We would like to thank the Stauffer Chemical Co., Calif., for a sample of methanethiol chloroformate.

*vacuo* to constant weight. Darco G-60 brand of decolorizing charcoal was used.

**New Procedure**<sup>39</sup> for 1,2:5,6-Di-*O*-isopropylidene-3,4-di-*O*-toluenesulfonyl-(−)-inositol [(−)-Inositol Diketetal Ditosylate].—A mixture of 5.7 g. of 3,4-ditosyl-(−)-inositol<sup>14b</sup> (m.p. 185–187°), 9.0 g. of fused zinc chloride, and 40 ml. of anhydrous acetone was stirred at 25° for 3 days. Ether (50 ml.) and a solution of 13.8 g. of potassium carbonate in 14 ml. of water were added, and stirring continued for 1 hr. After filtration, the filtrate was stirred for 1 hr. with a mixture of 14 g. of anhydrous potassium carbonate and 14 g. of anhydrous sodium sulfate. After filtration, the filtrate was evaporated, giving a viscous mass. This was taken up in 35 ml. of absolute ethanol containing a drop of dry pyridine. After 4 hr. at 25°, and 12 hr. at 0°, the crystals were collected, giving 5.2 g. (77%) of colorless needles, m.p. 160–162° [reported,<sup>14b</sup> m.p. 145–146; 161–162° (dimorphic)].

**3,4:5,6-Di-*O*-isopropylidene-1,2-anhydro-*allo*-inositol (VII).**—Quebrachitol [m.p. 190–191°,  $[\alpha]_{25}^{20}$  −81° (water, *c* 1.0)] from rubber latex<sup>32</sup> was successively converted to (−)-inositol, (−)-inositol 1,2:5,6-diacetone ketal, (−)-inositol 1,2:5,6-diacetone ketal 3,4-di-*p*-toluenesulfonate,<sup>39</sup> and the anhydro diketal (m.p. 106–108°,  $[\alpha]_{25}^{20}$  +12° (methanol, *c* 1.0)).

With the spectropolarimeter, the previously unreported optical rotatory dispersion spectra for the following intermediates were measured: *Quebrachitol*.—Negative plain dispersion curve, RD in water (*c* 0.198), 31°:  $[\alpha]_{550}^{20}$  −65°,  $[\alpha]_{589}^{20}$  −74°,  $[\alpha]_{250}^{20}$  −605°. (−)-*Inositol*.—Negative plain dispersion curve, RD in water (*c* 0.250), 31°:  $[\alpha]_{550}^{20}$  −48°,  $[\alpha]_{589}^{20}$  −62°,  $[\alpha]_{255}^{20}$  −439°. (−)-*Inositol* 1,2:5,6-Diacetone Ketal.—Positive plain dispersion curve, RD in dioxane (*c* 0.240), 31°:  $[\alpha]_{550}^{20}$  +5°,  $[\alpha]_{589}^{20}$  +8°,  $[\alpha]_{260}^{20}$  +109°. (−)-*Inositol* 1,2:3,4:5,6-Triacetone Ketal.—Positive plain dispersion curve, RD in dioxane (*c* 0.203) 31°:  $[\alpha]_{550}^{20}$  +25°,  $[\alpha]_{589}^{20}$  +30°,  $[\alpha]_{265}^{20}$  +302°.

#### Neo-inositol or (126/345) Configurational Series

**D(126/345) Stereoisomer of 1,2:3,4-Di-*O*-isopropylidene-5,6-dimercapto-1,2,3,4-cyclohexanetetrol 5,6-Trithiocarbonate [Trithiocarbonate Diketetal, M.p. 204°, VI].**<sup>40</sup>—Five grams of the above anhydro diketal<sup>41</sup> was added to a solution of 6.0 g. of potassium hydroxide and 10 ml. of carbon disulfide in 55 ml. of absolute methanol. The mixture was boiled under reflux (anhydrous conditions) for 24 hr. The orange solution was evaporated to one-third volume, then poured into 250 ml. of water at 0°. After 12 hr., the yellow precipitate was collected, giving 4.8 g. of crude mixed diastereomers.

This material was dissolved in 75 ml. of boiling absolute ethanol (decolorizing charcoal used). The clarified solution at the boiling point was very slowly cooled, so as to favor the formation of large crystals. The resulting product consisted of two visibly different kinds of crystals, pale yellow plates and bright yellow rods, total dry weight, 3.0 g.

This dry conglomerate was mechanically separated by careful hand picking (lens not essential) giving 1.6 g. of pale yellow plates and 1.4 g. of bright yellow rods. The rods were reserved for preparation of the m.p. 190° diastereomer (see below).

The plates after one recrystallization from absolute ethanol weighed 1.2 g., m.p. 201–203°; and after another recrystallization, weighed 0.9 g., m.p. 203–204°.

*Anal.* Calcd. for C<sub>13</sub>H<sub>18</sub>O<sub>4</sub>S<sub>2</sub>: C, 46.68; H, 5.43; S, 28.76. Found: C, 46.81; H, 5.36; S, 29.35.

By concentration of the original ethanolic mother liquor (75 ml.) there was obtained a *second crop* consisting of 0.7 g. of plates and 0.6 g. of rods, separated by hand picking. The rods were reserved for later use. The plates after two recrystallizations weighed 0.38 g., m.p. 203–204°.

(39) Previous preparation of the diketetal ditosylate was by tosylation of the diketetal [S. J. Angyal, *J. Am. Chem. Soc.*, **77**, 4345 (1955)]. In our present work, the diketetal ditosylate was prepared not only by this procedure, but also by acetonation of the ditosylate, since a quantity of the latter compound (see reference mentioned) happened to be available.

(40) The preferred *Chemical Abstracts* name for X (or XII) would be hexahydro-2,2,7,7-tetramethylbenzo[1,2-*d*:3,4-*d'*]bis[1,3]dioxole-4,5-dithiol. The preferred name for VI (or VIII) may be formed by appending "4,5-trithiocarbonate" to this name; and for XIII, by appending "4,5-trithioorthoformate." Alternatively, the compounds VI (or VIII) and XIII might be named hexahydro-2,2,5,5-tetramethyl-1,3]dithiolo[5,6]benzo[1,2-*d*:3,4-*d'*]bis[1,3]dioxole-8-thione, and -8-thiole, respectively.

(41) A qualitative test for sulfur should be performed on each new batch of the anhydro diketetal, since it has been our experience that occasional batches contain some unchanged ditosyl diketetal as impurity.

An additional crop of mixed isomers was obtained by concentrating all of the mother liquors (including those from the m.p. 191° stereoisomer—see below). This crop consisted of 1.3 g. of plates and 1.8 g. of rods, separated by hand picking. The rods were reserved for later use. The plates after two recrystallizations weighed 0.7 g., m.p. 203–204°.

The total yield of purified yellow plates, m.p. 203–204°, was 1.98 g. (30%). This stereoisomer had a rotation  $[\alpha]_{25}^{20}$  −130° (chloroform, *c* 1.0), MR −435°.

The solubility in absolute ethanol at 25° is about 1.5 g./100 ml. for the pure m.p. 204° stereoisomer, and about 2.3 g./100 ml. for the pure m.p. 191° stereoisomer.

With the spectropolarimeter, the m.p. 204° trithiocarbonate diketetal showed a double *negative* Cotton effect; RD in dioxane (*c* 0.00148–0.074), 26°:  $[\alpha]_{550}^{20}$  −27°,  $[\alpha]_{589}^{20}$  −115°,  $[\alpha]_{462}^{20}$  −4440° (trough),  $[\alpha]_{410}^{20}$  +6700° (shoulder),  $[\alpha]_{330}^{20}$  +27,800° (peak),  $[\alpha]_{255}^{20}$  −24,200° (trough),  $[\alpha]_{255}^{20}$  −7220°. (A second peak presumably occurs at a wave length too low for measurement.)

The n.m.r. spectrum of the trithiocarbonate diketetal, m.p. 204°, was determined (see discussion).

**D(126/345) Stereoisomer of 1,2:3,4-Di-*O*-isopropylidene-5,6-dimercapto-1,2,3,4-cyclohexanetetrol<sup>40</sup> [Tetrol-dithiol Diketetal, M.p. 91°, X].**—A solution of 335 mg. of the dry powdered trithiocarbonate diketetal (m.p. 204°) in 30 ml. of dry ether was added dropwise to a suspension of 3.0 g. of lithium aluminum hydride in 25 ml. of dry ether, with stirring. After completion of the addition, stirring was continued until the yellow solution turned colorless,<sup>42</sup> and for 6–12 hr. longer. Then at 0° the excess hydride was carefully decomposed by dropwise addition of ice-cold water.

The mixture was acidified to pH 4 at 0° with ice-cold 6 *M* hydrochloric acid and immediately the mixture was shaken with 50 ml. of ice-cold water and the separated aqueous phase extracted with 20 ml. of ether. The combined ether extracts without delay were washed with ice-cold *M* sodium bicarbonate solution (50 ml.), and with 50 ml. of ice-cold water.

The dried ethereal solution was evaporated, giving a colorless oil, which crystallized on standing. This material was taken up in 2.0 ml. of b.p. 30–60° petroleum ether (decolorizing charcoal used). After standing 12 hr. at 0°, the solution had deposited 250 mg. (85%) of colorless needles, m.p. 90–91°,  $[\alpha]_{25}^{20}$  −185° (chloroform, *c* 1.0), MR −541°. A sample was recrystallized again for analysis.

*Anal.* Calcd. for C<sub>12</sub>H<sub>20</sub>O<sub>4</sub>S<sub>2</sub>: C, 49.29; H, 6.89; S, 21.93. Found: C, 49.19; H, 6.89; S, 21.88.

The infrared spectrum showed typical weak absorption<sup>43</sup> at 2600 cm.<sup>−1</sup> (S—H stretching vibration).

The n.m.r. spectrum of the tetrol-dithiol diketetal, m.p. 91°, is shown in Fig. 1, and has been described in the discussion. The integral curve corresponding to the spectrum was also determined, and it confirmed the presence in the molecule of twenty protons, with steps in the curve corresponding to four, two, two, and twelve protons. The (non-integral) spectrum was also determined in chloroform-*d* after preliminary treatment with deuterium oxide; this caused the signals of the two —SH protons to disappear entirely, and the complex multiplet due to the two S—C—H protons was replaced by a single sharp peak (due to elimination of spin coupling with the —SH protons).

**D(126/345) Stereoisomer of 5,6-Dimercapto-1,2,3,4-cyclohexanetetrol;<sup>44</sup> (−)-1,6-Dimercapto-1,6-dideoxyneoinositol [Tetrol-dithiol, M.p. 218°, XIV].**—The diketetal (0.24 g., m.p. 91°) was heated with 4.0 ml. of 1:1 aqueous acetic acid at 90–100° for 150 min. The solution was evaporated, giving an oil which was taken up in 3.0 ml. of 95% ethanol (decolorizing charcoal used). After 12 hr. standing at 20°, the solution deposited 110 mg. (65%) of colorless needles, m.p. 217–218°,  $[\alpha]_{25}^{20}$  −90° (water, *c* 0.4), MR −192°. A sample was recrystallized for analysis, melting point unchanged.

*Anal.* Calcd. for C<sub>6</sub>H<sub>12</sub>O<sub>4</sub>S<sub>2</sub>: C, 33.95; H, 5.70; S, 30.21. Found: C, 34.17; H, 5.89; S, 29.98.

(42) Disappearance of yellow color indicates only that the first step of the reduction, from trithiocarbonate to mercaptodithiolane, has taken place. Even with a large excess of lithium aluminum hydride, the second step of the reduction, to the tetrol-dithiol, occurs only slowly with the (126/346) diastereomer, somewhat more rapidly with the (126/345) diastereomer.

(43) L. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 350.

(44) Name preferred by *Chemical Abstracts*.

This compound has a melting point similar to that of the D(125/346) diastereomer (see below); however, the hexaacetate melting points are well separated.

When excess of a dilute aqueous solution of the tetroldithiol was added to 0.1 *N* mercuric nitrate, a white precipitate formed, and after filtration, the filtrate gave a negative hydrogen sulfide test for mercuric ion. The precipitate, presumably a mercuric mercaptide,  $\text{HgC}_6\text{H}_{10}\text{O}_4\text{S}_2$ , is being investigated further.

The n.m.r. spectrum of the tetroldithiol, m.p. 218°, in deuterium oxide was measured but has not been fully interpreted.

**D(126/345) Stereoisomer of 5,6-Dimercapto-1,2,3,4-cyclohexanetrol Hexaacetate [Tetroldithiol Hexaacetate, M.p. 223°, XV].**—A mixture of 50 mg. of the D(126/345) stereoisomer of the tetroldithiol (m.p. 218°), 20 mg. of fused sodium acetate, and 3 ml. of redistilled acetic anhydride was boiled under reflux for 4 hr. The mixture was evaporated to dryness, and the residue distributed between water and chloroform. The chloroform extract was washed with 5% sodium bicarbonate solution. The dried chloroform extract was evaporated, and the residue recrystallized from absolute 2-propanol (3 ml.). After cooling the solution below 0° for 12 hr., there was obtained 90 mg. of crystalline product, m.p. 183–187°. Recrystallization from the same solvent gave 70 mg. (64%) of colorless prisms, m.p. 223–224°,  $[\alpha]_D^{25} -36^\circ$  (chloroform, *c* 0.5). A sample was recrystallized again for analysis.

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{24}\text{O}_{10}\text{S}_2$ : C, 46.54; H, 5.21; S, 13.80. Found: C, 46.50; H, 5.21; S, 14.30.

The n.m.r. spectrum of the hexaacetate, m.p. 223°, in chloroform-*d* was measured, but has not been fully interpreted.

**D(126/345) Stereoisomer of 1,2:3,4-Di-*O*-isopropylidene-5,6-(isopropylidenedithio)-1,2,3,4-cyclohexanetrol [Tetroldithiol Mercaptol Diketal, M.p. 152°, XI].**<sup>46</sup>—A mixture of 75 mg. of the tetroldithiol diketal (m.p. 91°), 105 mg. of fused zinc chloride, and 4.0 ml. of acetone was stirred for 3 days at 25°. A solution of 150 mg. of anhydrous potassium carbonate in 0.2 ml. of water was then added to the mixture, and stirring was continued for 1 hr. After filtration, and washing of the precipitated inorganic salts (acetone, 3 ml.), the combined filtrate was dried by stirring with anhydrous potassium carbonate, and then with anhydrous sodium sulfate.

The dry solution was evaporated. The residue was taken up in boiling 2-propanol, and the solution diluted with water to incipient cloudiness. The colorless needles which had separated after 12 hr. at 25° were collected, giving 30 mg. (36%) of product, m.p. 148–150°,  $[\alpha]_D^{25} -55^\circ$  (chloroform, *c* 0.2), MR –183°.

This material was recrystallized from 1 ml. of 2-propanol (2 drops of water added), giving 15 mg. of product, m.p. 151–152°. A sample was recrystallized again for analysis, melting point unchanged.

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{24}\text{O}_4\text{S}_2$ : C, 54.22; H, 7.28; S, 19.29. Found: C, 54.34; H, 7.21; S, 19.41.

#### DL-Inositol or (125/346) Configurational Series

**D(125/346) Stereoisomer of 1,2:3,4-Di-*O*-isopropylidene-5,6-dimercapto-1,2,3,4-cyclohexanetrol 5,6-Trithiocarbonate [Trithiocarbonate Diketal, M.p. 191°, VIII].**<sup>40</sup>—The first crop of bright yellow rods (1.4 g.), separated by hand picking from the m.p. 204° stereoisomer (see above), was recrystallized from absolute ethanol, giving 1.1 g. of rods, m.p. 186–188°, and again recrystallized, giving 0.75 g., m.p. 189–191°. This material was recrystallized once more, giving 0.52 g. of bright yellow rods of constant m.p. 190–191°,  $[\alpha]_D^{25} -104^\circ$  (chloroform, *c* 1.0), MR –348°.

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{18}\text{O}_4\text{S}_3$ : C, 46.68; H, 5.43; S, 28.76. Found: C, 46.89; H, 5.41; S, 29.38.

The second crop of rods (0.6 g.), which had been separated by hand picking from the second crop of the m.p. 204° diastereomer (see above), after two recrystallizations weighed 0.27 g., m.p. 190–191°.

The 1.8 g. third crop of rods (see preparation of m.p. 204° stereoisomer) similarly gave 1.0 g. of product, m.p. 190–191°.

The total yield of purified crystals, m.p. 190–191°, was 1.79 g. (26%). The combined yield for both isomers, based on anhydro diketal, was thus 56%.

With the spectropolarimeter, the m.p. 191° trithiocarbonate diketal showed a double *positive* Cotton effect; RI in dioxane (*c*

0.00725), 26°;  $[\alpha]_{650} +138^\circ$ ,  $[\alpha]_{589} +55^\circ$ ,  $[\alpha]_{475} +3650^\circ$  (peak),  $[\alpha]_{420} -7370^\circ$  (shoulder),  $[\alpha]_{322} -22,000^\circ$  (trough),  $[\alpha]_{250} +19,300^\circ$  (peak),  $[\alpha]_{235} +8980^\circ$ . (A second trough presumably occurs at a wave length too low for measurement.)

The n.m.r. spectrum of the trithiocarbonate diketal, m.p. 191°, was determined (see discussion).

**D(125/346) Stereoisomer of 1,2:3,4-Di-*O*-isopropylidene-5,6-dimercapto-1,2,3,4-cyclohexanetrol [Tetroldithiol Diketal, M.p. 103°, XII].**<sup>40</sup>—A solution of 670 mg. of the trithiocarbonate diketal (m.p. 191°) in 50 ml. of dry ether was added dropwise with stirring to a slurry of 5.0 g. of lithium aluminum hydride in 35 ml. of dry ether. After disappearance of yellow color,<sup>42</sup> the mixture was stirred for at least 12 hr. more. Excess hydride was destroyed at 0° by careful addition of ice-cold water. The mixture was adjusted to pH 4 with ice-cold 6 *M* hydrochloric acid, then immediately shaken with 100 ml. ice-cold water. The aqueous phase was separated and washed with ether (30 ml.). The combined ethereal phases were washed, successively, with ice-cold *M* sodium bicarbonate solution (75 ml.), and ice-cold water (75 ml.).

The dried ethereal solution was evaporated, giving 480 mg. of a colorless oil. A 90-mg. portion of the oil was taken up in 1 ml. of dry cyclohexane, and the solution passed through a column (120 × 6 mm.) of activity grade no. 1 Woelm neutral aluminum oxide. The column was eluted with cyclohexane, and the eluate (70 ml.) evaporated, giving a colorless oil. This oil was taken up in 4.0 ml. of petroleum ether (b.p. 65–110°) (decolorizing charcoal used). This solution, on evaporation, gave a colorless oil which on standing changed into colorless crystals, 75 mg. (13%), m.p. 99–101°,  $[\alpha]_D^{25} -21^\circ$  (chloroform, *c* 0.7), MR –61°.

A 25-mg. portion of this product was recrystallized from the same solvent, for analysis, giving 20 mg. of colorless prisms, m.p. 102–103°.

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{20}\text{O}_4\text{S}_2$ : C, 49.29; H, 6.89; S, 21.93. Found: C, 49.60; H, 6.77; S, 22.05.

The n.m.r. spectrum of the tetroldithiol diketal, m.p. 103°, in chloroform-*d*, was examined on both the HR-60 and HR-100 spectrometers (see comment in discussion).

**D(125/346) Stereoisomer of 5,6-Dimercapto-1,2,3,4-cyclohexanetrol<sup>44</sup>; 3,4-Dimercapto-3,4-dideoxy-(–)-inositol [Tetroldithiol, M.p. 222°, XVII].**—The above diketal (460 mg., m.p. 103°) was dissolved in 15 ml. of aqueous acetic acid (1:1) and the solution boiled under reflux for 4 hr. The solution on evaporation gave a light yellow oil. The oil was taken up in 5 ml. of 2-methyl-1-propanol and the evaporation repeated. The residual sirup was again taken up in 2-methyl-1-propanol (6 ml.; decolorizing charcoal used), and the solution kept at 0° for 2 days. The crystals which then had separated weighed 200 mg., m.p. 215–218°.

This product was recrystallized from the same solvent, giving 120 mg. of colorless crystals, m.p. 221–222°,  $[\alpha]_D^{25} -46^\circ$  (water, *c* 0.8), MR –98°. It was not identical with the above tetroldithiol of similar melting point. The infrared spectrum showed strong O—H absorption at 3470  $\text{cm}^{-1}$ , and a small peak at 2550  $\text{cm}^{-1}$  characteristic of an —SH group.<sup>43</sup> A sample was recrystallized again, for analysis, m.p. 221–222°.

*Anal.* Calcd. for  $\text{C}_6\text{H}_{12}\text{O}_4\text{S}_2$ : C, 33.95; H, 5.70; S, 30.21. Found: C, 34.12; H, 5.64; S, 30.35.

**D(125/346) Stereoisomer of 5,6-Dimercapto-1,2,3,4-cyclohexanetrol Hexaacetate [Tetroldithiol Hexaacetate, M.p. 116°, XVIII].**—A mixture of 20 mg. of the tetroldithiol (m.p. 222°), 10 mg. of fused sodium acetate, and 2.0 ml. of redistilled acetic anhydride was boiled under reflux for 4 hr. Solvent was removed by evaporation, and the residue distributed between chloroform and 5% aqueous sodium bicarbonate (4.0 ml. of each). The chloroform phase was removed and the aqueous phase extracted with 3.0 ml. of additional chloroform. The combined chloroform extracts were dried and evaporated. The residual oil was taken up in 2.0 ml. of absolute ethanol, and evaporation repeated.

The oil was then taken up in 1 ml. of absolute ethanol (decolorizing charcoal used), and the solution kept at 0° for 1 day, giving 20 mg. (43%) of colorless needles, m.p. 114–116°,  $[\alpha]_D^{25} -26^\circ$  (chloroform, *c* 2), MR –121°. This material was analyzed without further purification.

*Anal.* Calcd. for  $\text{C}_{18}\text{H}_{24}\text{O}_{10}\text{S}_2$ : C, 46.54; H, 5.21; S, 13.80. Found: C, 46.35; H, 5.06; S, 13.59.

**D(125/346) Stereoisomer of 1,2:3,4-Di-*O*-isopropylidene-5,6-dimercapto-1,2,3,4-cyclohexanetrol 5,6-Trithioorthoformate [Mercaptodithiolane Diketal, M.p. 152°, XIII].**<sup>40</sup>—A 280-mg. portion of the trithiocarbonate diketal (m.p. 191°) was stirred

(45) The preferred *Chemical Abstracts* name for XI would be hexahydro-2,2,5,5,8,8-hexamethyl[1,3]dithiolo-[5,6]benzo[1,2-*d*:3,4-*d'*]bis[1,3]dioxole.

with 80 mg. of lithium aluminum hydride in 25 ml. of dry ether just until disappearance of the yellow color.<sup>42</sup> (NOTE: The large excess of the hydride can probably be reduced.) Excess hydride was then immediately destroyed, and the reaction mixture processed in a manner similar to that used for the m.p. 103° tetrol-dithiol diketal (see above).

The oil obtained upon evaporation of the ethereal extract was crystallized from 6.0 ml. of petroleum ether, giving 180 mg. of colorless crystals, m.p. 150–152°. This material was again recrystallized, giving 140 mg. (57%) of colorless, fine needles, m.p. 151–152°.

The n.m.r. spectrum (see below) indicated that incomplete reduction had caused formation of mercaptodithiolane instead of tetrol-dithiol diketal. A sample was recrystallized again for analysis, which confirmed the mercaptodithiolane structure.

*Anal.* Calcd. for C<sub>12</sub>H<sub>20</sub>O<sub>4</sub>S<sub>2</sub>: C, 49.29; H, 6.89; S, 21.93. Calcd. for C<sub>13</sub>H<sub>20</sub>O<sub>4</sub>S<sub>3</sub>: C, 46.40; H, 5.99; S, 28.60. Found: C, 46.68; H, 6.01; S, 29.19.

The n.m.r. spectrum of the mercaptodithiolane diketal showed signals for isopropylidene methyl groups at  $\delta = 1.37$  (6 protons), 1.48 (3 protons), and 1.55 (3 protons). A doublet for the -SH proton appeared at  $\delta = 2.98, 3.08$ , and a doublet for the HCS<sub>2</sub> proton at 5.70, 5.80. The signals for the two ring protons on C-5 and C-6 appeared in a series of peaks centered near  $\delta = 3.6$ . The signals for the four ring protons on C-1, C-2, C-3, C-4 appeared in a narrower pattern near  $\delta = 4.5$ . Prior treatment of the sample with deuterium oxide almost eliminated the signals due to the -SH group, and greatly weakened and broadened the signals due to the HCS<sub>2</sub> proton (isotopic exchange was not entirely complete under the conditions employed).

**D(125/346) Stereoisomer of 5,6-Dimercapto-1,2,3,4-cyclohexanetetrol 5,6-Trithioorthoformate Pentaacetate<sup>66</sup>** [Mercaptodithiolane Pentaacetate, M.p. 132°, XIIIa].—The starting material was an oil which had been obtained by successive reduction and hydrolysis (see above) of the trithiocarbonate diketal (m.p. 191°). This oil was believed to consist of impure (125/346) tetrol-dithiol, but due to incomplete reduction, actually consisted mainly of the mercaptodithiolanetetrol (not the diketal).

(46) The preferred *Chemical Abstracts* name for XIIIa would be hexahydro-2-mercapto-1,3-benzodithiole-4,5,6,7-tetrol pentaacetate.

To 100 mg. of this oil was added 40 mg. of fused sodium acetate and 3.0 ml. of redistilled acetic anhydride. The mixture was boiled under reflux 3 hr., evaporated, and the residue distributed between chloroform and water. The washed (5% sodium bicarbonate) and dried chloroform phase was evaporated. The residue was taken up in 3.0 ml. of hot 2-propanol (decolorizing charcoal used). On cooling, the solution deposited 150 mg. of colorless needles, m.p. 126–129°. This material was recrystallized thrice more, giving 50 mg. of product of constant m.p. 131–132°,  $[\alpha]_D^{20} -44^\circ$  (chloroform, *c* 2.7), MR -204°.

*Anal.* Calcd. for C<sub>16</sub>H<sub>24</sub>O<sub>10</sub>S<sub>2</sub>: C, 46.54; H, 5.21; S, 13.80. Calcd. for C<sub>17</sub>H<sub>22</sub>O<sub>9</sub>S<sub>3</sub>: C, 43.76; H, 4.35; S, 20.62. Found: C, 44.37; H, 4.52; S, 20.05.

**L(125/346) Stereoisomer of 5,6-Di-O-(S-methylthiolcarbonyl)-1,2:3,4-di-O-isopropylidene-1,2,3,4-cyclohexanetetrol (IV)**.—A solution of 0.26 g. of (-)-inositol diketal<sup>14b</sup> (m.p. 151°) and 0.50 g. of methanethiol chloroformate<sup>33</sup> in 5 ml. of dry pyridine was kept at 25° for 4 days. The solution was poured into 25 g. of mixed ice and water with stirring. After 30 min. the precipitate was collected, washed with ice-cold water, and dried. The product was recrystallized from absolute ethanol, giving 175 mg. of colorless needles, m.p. 160–163°. This material was again recrystallized from the same solvent, giving 100 mg. of needles, m.p. 166–167°,  $[\alpha]_D -115^\circ$  (chloroform, *c* 1), MR -470°. A sample was again recrystallized for analysis.

*Anal.* Calcd. for C<sub>16</sub>H<sub>24</sub>O<sub>8</sub>S<sub>2</sub>: C, 47.04; H, 5.92; S, 15.70. Found: C, 47.21; H, 6.04; S, 15.78.

With the spectropolarimeter, this compound showed a negative plain dispersion curve, RD in dioxane (*c* 0.103), 26°;  $[\alpha]_{650} -60^\circ$ ,  $[\alpha]_{589} -74^\circ$ ,  $[\alpha]_{255} -546^\circ$ .

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## Further Studies of Schoenberg's Reagent and Sulfur<sup>1</sup>

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The reaction of Schoenberg's reagent with sulfur leads to the formation of a mixture of products, one of which is the previously unreported bis(*p*-methoxyphenyl)methyleneimine. The infrared spectrum of this imine shows ten bands characteristic of one or more aspects of the :C=N—H grouping. Bis(*p*-methoxyphenyl)methyleneimine was observed to react with carbon disulfide and hydrogen sulfide; implications of the latter reaction in analytical applications of Schoenberg's reaction are discussed.

The production of the deep blue *p,p'*-dimethoxythio-benzophenone from a mixture of sulfur and *N*-(4,4'-dimethoxybenzohydrilidene)benzylamine (Schoenberg's reagent) was reported by Schoenberg and Urban<sup>4</sup> in 1934. Ory, Warren, and Williams<sup>1a</sup> utilized this reaction as the basis for a direct quantitative colorimetric determination of free sulfur and cited the first evidence that products other than the thioketone were also formed in the reaction. Attempts by Huddleston<sup>5</sup> to isolate and characterize these products led to the ob-

servation of an acid-soluble fraction in the reaction mixture. This paper reports the purification and identification of the acid-soluble product together with some related observations.

Huddleston<sup>5</sup> reported that the acid-soluble compound, which he obtained in crystalline form from the acid extract of the reaction mixture, was stable in 5% hydrochloric acid at room temperature, but that at reflux temperature hydrolysis took place with the formation of *p,p'*-dimethoxybenzophenone. Subsequent elemental analysis indicated that the acid-soluble component might be bis(*p*-methoxyphenyl)methyleneimine. Independent synthesis of this imine confirmed this identification.

Neely<sup>6</sup> had noted the appearance of five bands in the infrared spectra of samples taken during the course

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(2) National Science Foundation Undergraduate Research Participant, Summer, 1961.

(3) National Science Foundation College Teacher Research Participant, Summer, 1961.

(4) A. Schoenberg and W. Urban, *Ber.*, **67**, 1999 (1934).

(5) G. Huddleston, Ph.D. dissertation, Louisiana State University, 1960.

(6) C. Neely, M.S. thesis, Louisiana State University, 1960.