Sulfur-Containing Carbohydrates. Synthesis of 1,3,4,6-Tetrathio-D-iditol[1,2]

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Received August 1, 1975

A series of analogues of D-iditol and its derivatives have been prepared, in which two, or four, of the hexitol oxygen atoms are replaced by sulfur. The 1,2;5,6-di-*O*-isopropylidene-3,4-*S*-thiocarbonyldithio derivative (formula **1**, mp 127 °C) of 3,4-dithio-D-iditol was oxidized to the corresponding dithiocarbonate (**2**). The trithiocarbonate **1** was also reduced to the dithiol diketal (**7**) which was characterized by conversion to the di-*S*-acetate (**8**) and the *O,O,S*-triketal (**9**). The trithiocarbonate diketal (**1**) on reaction with anhydrous hydrogen bromide–acetic acid was converted to the 1,6-dibromide 2,5-di-*O*-acetate (**10**). The dithiocarbonate diketal (**2**) similarly was transformed into the dibromide diacetate **5**. The trithiocarbonate dibromide (**10**) on prolonged heating with potassium thiolacetate surprisingly gave the dithiocarbonate tetraacetate derivative (**6**) of 1,3,4,6-tetrathio-D-iditol; this was confirmed by preparation of **6** from the dithiocarbonate dibromide (**5**) and potassium thiolacetate. The dithiocarbonate di-*O*-acetate di-*S*-acetate (**6**) on reduction gave free 1,3,4,6-tetrathio-D-iditol (**11**), mp 87 °C, which was converted to its hexaacetate **12**, mp 97 °C. The above di-*O*-isopropylidene dithiol (**7**) was also used to prepare its di-*S*-benzyl derivative, **15**, and the related tetrol (**13**) and tetraacetate (**14**). The tetrol **13** was also converted to the 1,6-di-*O*-trityl-2,5-di-*O*-acetyl derivative **16**. Since the trityl, acetyl, and *S*-benzyl protective groups can easily be removed when desired, the compound **16** should be a useful intermediate for preparation of pentathio- and hexathiohexitols.

For two decades, one of the most rapidly expanding fields of organic chemistry has been the preparation of sulfur analogues of organic oxygen compounds, and in particular of carbohydrates. Since most reported sulfur analogues of carbohydrates have contained only one or two sulfur atoms, we have in recent years concentrated our attention on efforts to prepare analogues in which most or all of the oxygen atoms of well-known carbohydrates would be replaced by sulfur (polythio- and perthiocarbohydrates). Most of the carbohydrates we have chosen for emulation have been hexitols or cyclohexitols (inositols).[2,4]

In the present article, we describe the preparation of dithio and tetrathio analogues of D-iditol and many of its derivatives. Each product reported has been extensively characterized, and we are hopeful that some of these compounds will have valuable physical, chemical, and especially biological properties.

The starting material for our present studies was the diisopropylidene trithiocarbonate derivative (formula **1**) of 3,4-dithio-D-iditol.[2b] This yellow, crystalline compound, mp 126–127 °C, on permanganate oxidation gave the corresponding, colorless dithiocarbonate, **2**, which has very nearly the same melting point, but differs markedly in its optical rotation and infrared spectrum (C=O vs. C=S).

The trithiocarbonate **1** was also converted, by lithium aluminum hydride reduction, to the di-*O*-isopropylidene derivative, **7**, of 3,4-dithio-D-iditol, mp 138 °C. This product was transformed in the usual manner to its di-*S*-acetate **8**, mp 116 °C, and to the triisopropylidene derivative, **9**, mp 80 °C. The ^{1}H NMR spectrum of **9** revealed sharply different chemical shifts for the *O*- and *S*-isopropylidene methyl singlets (δ 1.35 and 1.92 ppm, respectively).

Attempted mild acid hydrolysis of **7** (and presumably of **9**) to the free dithiohexitol surprisingly gave instead the mono-*S*-isopropylidene derivative, **17**, mp 105 °C. Isotopic studies using acetone-d_6 showed that this result, in the case of **7**, is due to fast reaction of the SH groups with (hydrolytically liberated) acetone in the reaction mixture, to form the more stable dithiolane ring. The product structure was established by the NMR methyl group chemical shifts mentioned above.[4d]

Our purpose was next to transform one of these intermediates, e.g., **7**, having C–S bonds at positions 3 and 4, to a polythio or preferably hexathiohexitol, having C–S bonds at some or all of the remaining positions 1, 2, 5, and 6. It appeared that this might best be accomplished by introduction of a suitable bivalent substituent, such as thiocarbonyldithio, epithio, epoxy, or even a carbon–carbon double bond, at 1,2 and/or at 5,6.

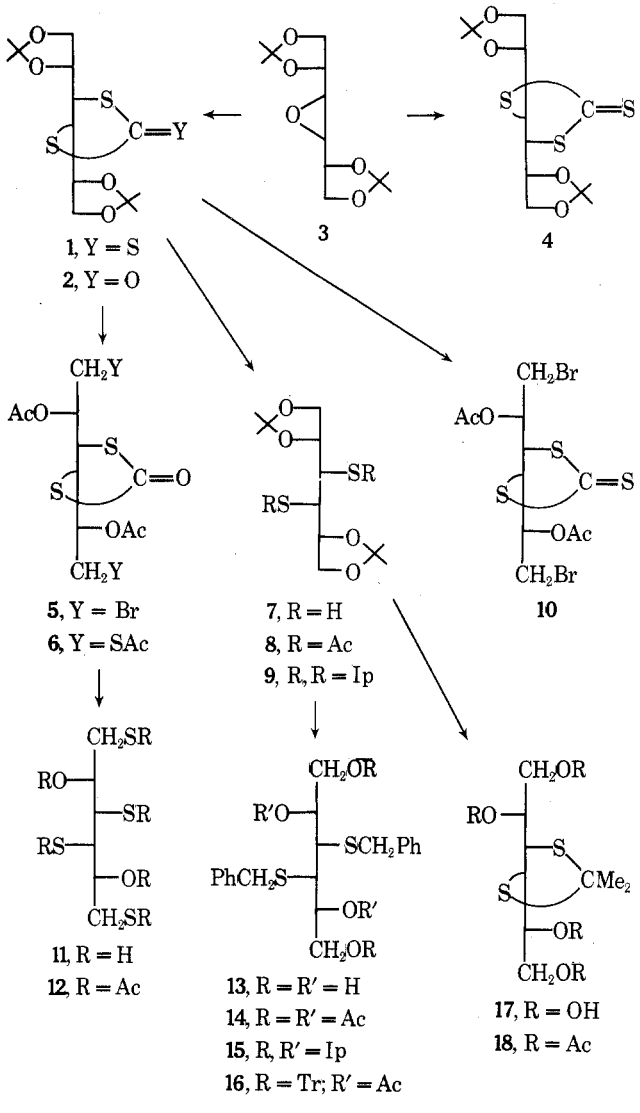
As a first step in this direction, the trithiocarbonate diketal, **1**, was converted by direct reaction with anhydrous hydrogen bromide–acetic acid to a 1,6-dibromide, isolated in the form of its 2,5-diacetate **10**, mp 102 °C, yellow crystals. The corresponding dithiocarbonate dibromide diacetate, **5**, colorless crystals, mp 108 °C, was prepared from the dithiocarbonate **2** in the same manner. (In previous work, we have found that dithiocarbonates sometimes crystallize more easily, and give better yields in subsequent reactions.)

The dithiocarbonate dibromide, **5**, on prolonged heating with potassium thiolacetate in acetone, gave the expected dithiocarbonate tetraacetate derivative, **6**, of 1,3,4,6-tetrathio-D-iditol, colorless plates, mp 116 °C. Similar reaction of the trithiocarbonate dibromide **10** gave a brown syrup, which was purified by chromatography using silica gel. The crystalline product then isolated, mp 116 °C, surprisingly was identical with the above dithiocarbonate tetraacetate, **6**. The oxygen atom in the carbonyldithio group conceivably may be derived from the thiolacetate, acetone, water, ethyl acetate, or silica gel used in the procedure (see Experimental Section); however, no really good explanation is yet available.

In order to obtain one of the desired polythioalditol final products, the tetrathiohexitol dithiocarbonate tetraacetate **6** was reduced with lithium aluminum hydride under dry nitrogen (to prevent oxidation of free SH groups). The product, 1,3,4,6-tetrathio-D-iditol (**11**), was obtained as colorless, almost odorless plates, mp 87 °C, specific rotation −153°. This tetrathiohexitol appears to be somewhat less polar than ordinary hexitols, as indicated by its solubility in boiling (but not cold) isopropyl ether. The di-*O*-acetate tetra-*S*-acetate derivative **12**, mp 97 °C, was prepared in the usual manner.

We next attempted to introduce mercapto (or other suit-

Chart I



able sulfur) groups into the two remaining positions, 2 and 5. For this purpose, the 1,6-dibromide (**5** or **10**), or 1,6-di(acetylthio) derivative (**6, 11,** or **12**) seemed especially suitable. However, we have not yet been able to prepare the 1,2 (and/or 5,6) epithio, thiocarbonyldithio, etc., intermediates which presumably could be transformed easily into pentathio- or hexathiohexitols.

Some preliminary work has been done on an alternative approach. This involves using *S*-benzyl groups as temporary protective groups for the two SH groups at positions 3 and 4, e.g., in the intermediate **7**. The *S*-benzyl group is easily removed when desired, by reductive fission, for example in our previously reported preparation of a mercaptodeoxyinositol.[4c]

The di-*O*-isopropylidene derivative **7** of 3,4-dithio-D-iditol accordingly was treated with benzyl bromide and sodium hydride in dimethylformamide. The di-*S*-benzyl product **15** was obtained as colorless needles, mp 106 °C. By mild acid hydrolysis, this intermediate was converted to the di-*S*-benzyl dithiohexitol **13**, mp 101 °C. This compound was converted to its tetraacetate, **14**, mp 110 °C, in the usual manner.

The di-*S*-benzyl tetrol **13** was next converted, in the usual manner, to its 1,6-bis(triphenylmethyl) derivative, isolated as the 2,5-diacetate **16**, mp 160 °C. This should be a useful intermediate, since either the trityl or acetyl protective group is easily removed under mild conditions, permitting synthetic operations on the corresponding free hydroxyl groups. After introduction of sulfur at positions 1, 2, 5, and 6, the *S*-benzyl protective groups could be removed.

Since, unfortunately, our laboratory has had to discontinue research on sulfur-containing carbohydrates, we are making these preliminary results on *S*-benzyl derivatives available, for possible use by others working in this field.

Experimental Section

All melting points (corrected) were measured on a Nalge-Axelrod micro hot stage. Microanalyses were performed by the Micro-Tech Laboratories, Skokie, Ill. NMR spectra were recorded and integrated with Varian A-60D and/or HR-100 spectrometers. Chemical shifts are given as parts per million (δ). Field sweep was used for 60-MHz and frequency sweep for 100-MHz NMR spectra. Infrared spectra were measured on a Perkin-Elmer Model 337 spectrometer. Evaporations were performed under reduced pressure. Acetone used was reagent grade.

1,2;5,6-Di-*O*-isopropylidene-3,4-*S*-thiocarbonyldithio-D-iditol (1). The crude product previously reported[2b] was recrystallized from *n*-hexane, giving yellow crystals: mp 126.5–127.5 °C; $[\alpha]^{23}D$ −328° (*c* 2.1, $CHCl_3$); NMR (100 MHz, $CDCl_3$) δ 1.37 (s, 6, isopropylidene methyl), 1.48 (s, 6, isopropylidene methyl); ir (KBr) 1060 (C=S), 1150, 1060, and 1040 cm^{-1} (1,3-dioxolane).

Anal. Calcd for $C_{13}H_{20}O_4S_3$: C, 46.40; H, 5.99; S, 28.59. Found: C, 46.29; H, 5.84; S, 28.42.

1,2;5,6-Di-*O*-isopropylidene-3,4-*S*-carbonyl-3,4-dithio-D-iditol (2). To a solution of 2.0 g of the above trithiocarbonate, mp 126–127 °C, in 60 ml of acetone, 5.2 g of powdered potassium permanganate was added in small portions, with cooling and stirring, during 2 h. After an additional 1 h, the mixture was filtered, and the residue washed with three 15-ml portions of acetone.

The combined filtrates were evaporated, and the solid residue extracted with three 15-ml portions of boiling benzene. The benzene extract was evaporated, giving 1.23 g (62%) of colorless plates: mp 126–127 °C; $[\alpha]^{23}D$ −196° (*c* 1.5, $CHCl_3$); ir (KBr) 1610 (C=O), 1155, 1060, and 1040 cm^{-1} (1,3-dioxolane); NMR ($CDCl_3$) δ 1.43 (s, 6, isopropylidene methyl), 1.53 (s, 6, isopropylidene methyl).

Anal. Calcd for $C_{13}H_{20}O_5S_2$: C, 48.73; H, 6.29; S, 20.01. Found: C, 48.53; H, 6.21; S, 19.93.

1,2;5,6-Di-*O*-isopropylidene-3,4-dithio-D-iditol (7). The procedure was similar to one of Iqbal and Owen.[5] Reduction of 12.8 g of the above trithiocarbonate (formula **1**, mp 126–127 °C) with lithium aluminum hydride gave 7.80 g (74%) of colorless needles (crystallized from *n*-hexane), mp 136–138 °C. A sample was recrystallized: mp 137.5–138 °C; $[\alpha]^{23}D$ −38° (*c* 1.4, $CHCl_3$); NMR (100 MHz, $CDCl_3$) δ 1.38 (s, 6, isopropylidene methyl), 2.12 (d, 2, –SH), 1.47 (s, 6, isopropylidene methyl).

A similar preparation reported by Iqbal and Owen,[5] mp 133–135 °C, $[\alpha]^{23}D$ −10° (*c* 3.6, $CHCl_3$), presumably contained some D-manno impurity.

1,2;5,6-Di-*O*-isopropylidene-3,4-di-*S*-acetyl-3,4-dithio-D-iditol (8). A 107-mg portion of the above dithiol (**7**) was acetylated with acetic anhydride in pyridine, in the usual manner, giving 125 mg of crude product, mp 101–104 °C. This was crystallized from 5 ml of *n*-hexane, giving 74 mg (54%) of colorless needles, mp 115.5–116 °C. A sample was recrystallized: mp 115.5–116 °C; $[\alpha]^{23}D$ +4.0° (*c* 1.6, $CHCl_3$); ir (KBr) 1690 (C=O), 1150, 1070, and 1060 cm^{-1} (1,3-dioxolane); NMR (100 MHz, $CDCl_3$) δ 1.32 (s, 6, isopropylidene methyl), 1.40 (s, 6, isopropylidene methyl), 2.37 (s, 6, $-SCOCH_3$).

Anal. Calcd for $C_{16}H_{26}O_6S_2$: C, 50.77; H, 6.92; S, 16.94. Found: C, 50.90; H, 6.91; S, 16.84.

1,2;5,6-Di-*O*-isopropylidene-3,4-*S*-isopropylidene-3,4-dithio-D-iditol (9). A mixture of 500 mg of the above dithiol **7** with 10 ml of acetone (dried with Drierite, and containing 0.01% sulfuric acid) and 1.2 g of fresh Drierite was stirred for 2 days and filtered. The filtrate was poured into 5% sodium bicarbonate solution, and the resulting mixture extracted repeatedly with chloroform. The extract was washed with water, dried, and evaporated, giving a solid residue. By two recrystallizations from *n*-hexane, there was obtained 100 mg of colorless crystals, mp 72–80 °C; then 35 mg, mp 76–79 °C.

A somewhat purer product was obtained from the combined mother liquors by chromatography (Woelm silica gel, 25 × 1 cm column, eluted with 1:2 isopropyl ether–*n*-hexane). The resulting material (280 mg, 55%, mp 79–80 °C) was recrystallized, giving a

sample of mp 79.5–80 °C; $[\alpha]^{23}D$ −110° (*c* 1.8, $CHCl_3$); NMR ($CDCl_3$) δ 1.42 (s, 6, *O*-isopropylidene), 1.53 (s, 6, *O*-isopropylidene), 1.92 (s, 6, *S*-isopropylidene).

Anal. Calcd for $C_{15}H_{26}O_4S_2$: C, 53.86; H, 7.84; S, 19.17. Found: C, 54.16; H, 8.03; S, 19.14.

1,6-Dibromo-1,6-dideoxy-2,5-di-*O*-acetyl-3,4-*S*-thiocarbonyldithio-D-iditol (10). A 1.0-g portion of the trithiocarbonate diketal (1) was dissolved in 10 ml of an anhydrous 32% solution of hydrogen bromide in acetic acid. After 1 h at 25 °C, the solution was poured with stirring into 10 ml of saturated sodium bicarbonate solution. The resulting syrup was separated by decantation and washed twice with water, causing it to crystallize: dry weight 1.20 g, mp 96–99 °C. The product was recrystallized from benzene–*n*-hexane, giving 1.0 g (77%) of yellow plates, mp 100–102 °C.

A sample recrystallized from benzene had mp 101–102 °C; $[\alpha]^{24}D$ −265° (*c* 1.5, $CHCl_3$); ir (KBr) 1715 (C=O), 1070 cm^{-1} (C=S); NMR ($CDCl_3$) δ 2.18 (s, 6, $-OCOCH_3$).

Anal. Calcd for $C_{11}H_{14}O_4Br_2S_3$: C, 28.33; H, 3.03; Br, 34.28; S, 20.62. Found: C, 28.36; H, 3.08; Br, 32.38; S, 19.72.

1,6-Dibromo-1,6-dideoxy-2,5-di-*O*-acetyl-3,4-*S*-carbonyldithio-D-iditol (5). Similar reaction of the dithiocarbonate diketal (**2**, 300 mg) gave a syrup. This syrup was taken up in 10 ml of chloroform, and the solution washed twice with water, dried, and evaporated. The resulting syrup was crystallized from benzene–*n*-hexane, giving 250 mg of colorless crystals, mp 105–106.5 °C. A sample was again recrystallized: mp 107.5–108 °C; $[\alpha]^{24}D$ −124° (*c* 0.6, $CHCl_3$); ir (KBr) 1720 (acetate ester C=O), 1640 cm^{-1} (carbonyldithio C=O); NMR ($CDCl_3$) δ 2.15 (s, 6, acetate methyl).

Anal. Calcd for $C_{11}H_{14}Br_2O_5S_2$: C, 29.35; H, 3.13; Br, 35.50; S, 14.24. Found: C, 29.56; H, 3.14; Br, 35.63; S, 14.13.

2,5-Di-*O*-acetyl-1,6-di-*S*-acetyl-3,4-*S*-carbonyl-1,3,4,6-tetrathio-D-iditol (6). A. From the Trithiocarbonate. A mixture of 320 mg of the trithiocarbonate dibromide (**10**), 350 mg of potassium thiolacetate, and 15 ml of acetone was boiled under reflux for 24 h. The cooled, filtered mixture was evaporated. The residual syrup was taken up in chloroform, and the solution washed, dried, and evaporated. The residual brown syrup was taken up in ethyl acetate (decolorized with charcoal) and the solution evaporated.

The resulting syrup was purified by chromatography, using a 60 × 1.5 cm column of Woelm silica gel. The column was eluted with *n*-hexane containing increasing concentrations (5–40%) of ethyl acetate. The "40%" eluate on evaporation yielded 35 mg of colorless needles, mp 114–115 °C. A sample recrystallized from isopropyl ether had mp 114.5–115.5 °C; ir (KBr) 1750 (acetate C=O), 1700 (*S*-acetyl C=O), 1650 cm^{-1} (*S*-carbonyl); NMR ($CDCl_3$) δ 2.11 (s, 6, *O*-acetate methyl), 2.40 (s, 6, *S*-acetate methyl); $[\alpha]^{23}D$ −104° (*c* 0.6, $CHCl_3$).

This compound, prepared from the trithiocarbonate **10**, surprisingly was found to be the dithiocarbonate (**6**), as confirmed by preparation from the dithiocarbonate **5**, see procedure B below.

Anal. Calcd for $C_{15}H_{20}O_6S_5$: C, 39.46; H, 4.42; O, 21.02; S, 35.11. Calcd for $C_{15}H_{20}O_7S_4$: C, 40.89; H, 4.58; O, 25.42; S, 29.11. Found: C, 40.77; H, 4.54; (O, 25.09); S, 29.60.

B. From the Dithiocarbonate. The reaction of 1.50 g of the dithiocarbonate dibromide was conducted by a procedure similar to procedure A; however, chromatography was not employed. A 630-mg (43%) yield of once-crystallized (from benzene–*n*-hexane) product was obtained, mp 114–115 °C. A sample recrystallized from benzene melted at 114.5–115.5 °C.

Anal. Found: C, 41.04; H, 4.67; S, 28.64.

The product was identical with that from the above procedure A.

1,3,4,6-Tetrathio-D-iditol (11). A 250-mg portion of the dithiocarbonate tetraacetate (**6**) was reduced with lithium aluminum hydride in ether, and the product isolated, in the usual manner. The crude product, a syrup, was crystallized from isopropyl ether, giving 75 mg (60%) of colorless, almost odorless plates, mp 85–86 °C. A sample was recrystallized: mp 86.5–87 °C; $[\alpha]^{23}D$ −153° (*c* 2.7, methanol); ir (KBr) 3150 (broad, –OH), 2545 cm^{-1} (–SH). (The usually weak –SH chromophore was strong here, because four –SH groups are present.)

Anal. Calcd for $C_6H_{14}O_2S_4$: C, 29.24; H, 5.73; S, 52.05. Found: C, 29.41; H, 5.64; S, 50.67.

2,5-Di-*O*-acetyl-1,3,4,6-tetra-*S*-acetyl-1,3,4,6-tetrathio-D-iditol (12). A 45-mg portion of the tetrathiohexitol **11** was treated with acetic anhydride and pyridine, in the usual manner. The crude product, a syrup, was crystallized from *n*-hexane, giving 72 mg (82%) of colorless needles, mp 94–95.5 °C. A sample was recrystallized: mp 96–96.5 °C; $[\alpha]^{23}D$ +86° (*c* 1.9, $CHCl_3$); ir (KBr) 1750 (*O*-acetate C=O), 1700 cm^{-1} (*S*-acetate C=O); NMR ($CDCl_3$) δ 2.08 (s, 6, *O*-acetate methyl), 2.32 (s, 6, $-CH_2SCOCH_3$ methyl), 2.37 (s, 6, $=CHSCOCH_3$ methyl).

Anal. Calcd for $C_{18}H_{26}O_8S_4$: C, 43.36; H, 5.26; S, 25.72. Found: C, 43.58; H, 5.21; S, 25.80.

1,2;5,6-Di-*O*-isopropylidene-3,4-di-*S*-benzyl-3,4-dithio-D-iditol (15). To 1.24 g of the dithiol **7** and 570 mg of sodium hydride in 40 ml of dry *N,N*-dimethylformamide, under dry nitrogen, with stirring, at 0 °C, 8.5 g of benzyl bromide was added dropwise during 10 min. The mixture was stirred at 25 °C for 4 h.

Excess hydride was cautiously destroyed by addition of methanol, and the mixture evaporated at 1.2 Torr, 70 °C (bath).

The residual syrup was processed with chloroform and water in the usual manner. The solid residue from evaporation of the chloroform extract was recrystallized from *n*-hexane, giving 1.40 g (83%) of colorless crystals, mp 100–103 °C.

A sample was recrystallized: mp 105–105.5 °C; $[\alpha]^{24}D$ +217° (*c* 0.6, $CHCl_3$); ir (KBr) 1580 and 700 cm^{-1} (phenyl); NMR ($CDCl_3$) δ 1.32 and 1.43 (s, 6 and s, 6, isopropylidene methyl).

Anal. Calcd for $C_{26}H_{34}O_4S_2$: C, 65.80; H, 7.22; S, 13.49. Found: C, 65.74; H, 7.30; S, 13.46.

3,4-Di-*S*-benzyl-3,4-dithio-D-iditol (13). A 900-mg portion of the diketal **15** was treated with warm ethanol containing a little 12 M hydrochloric acid, and the product isolated in the usual manner. The crude product, a syrup, was crystallized from benzene–petroleum ether (bp 30–60 °C), giving 730 mg of colorless needles, mp 98–99 °C. A sample was recrystallized from benzene: 660 mg (87%); mp 99.5–100.5 °C; $[\alpha]^{24}D$ −91° (*c* 1, methanol); ir (KBr) 1590 and 700 cm^{-1} (phenyl).

Anal. Calcd for $C_{20}H_{26}O_4S_2$: C, 60.90; H, 6.64; S, 16.24. Found: C, 60.86; H, 6.87; S, 16.14.

1,2,5,6-Tetra-*O*-acetyl-3,4-di-*S*-benzyl-3,4-dithio-D-iditol (14). A 70-mg portion of the tetrol **13** was treated with acetic anhydride–pyridine in the usual manner, giving 101 mg of crude solid product, mp 106–108.5 °C. This material was recrystallized from 1-butanol–petroleum ether (bp 50–60 °C), giving 68 mg (68%) of colorless plates: mp 109.5–110 °C; $[\alpha]^{23}D$ −75° (*c* 1.1, $CHCl_3$); ir (KBr) 1750 (C=O), 700 cm^{-1} (phenyl); NMR ($CDCl_3$) δ 1.98 and 2.04 (s, 6 and s, 6, primary and secondary acetate methyl), 3.80 (s, 4, *S*-benzyl methylene).

Anal. Calcd for $C_{28}H_{34}O_8S_2$: C, 59.76; H, 6.09; S, 11.39. Found: C, 59.91; H, 6.25; S, 11.51.

2,5-Di-*O*-acetyl-1,6-di-*O*-trityl-3,4-di-*S*-benzyl-3,4-dithio-D-iditol (16). A 100-mg portion of the tetrol **13** was treated with excess triphenylmethyl chloride in dry pyridine for 2 days at 25 °C. Excess acetic anhydride was then added, and the mixture kept for 1 more day, then poured into water with stirring.

The crude solid product (220 mg) so obtained was purified by chromatography, using a 20 × 1 cm column of Woelm silica gel. The column was eluted with 50 ml of 1:3 acetone–*n*-hexane, giving 96 mg of solid product, on evaporation, mp 155–159 °C. Recrystallization from 95% ethanol afforded 72 mg of colorless plates, mp 159–160 °C. A sample was recrystallized: mp 159.5–160 °C; $[\alpha]^{23}D$ +34° (*c* 2.1, $CHCl_3$); ir (KBr) 1720 (C=O), 1580 and 700 cm^{-1} (phenyl).

Anal. Calcd for $C_{62}H_{58}O_6S_2$: C, 77.31; H, 6.07; S, 6.66. Found: C, 76.70; H, 6.13; S, 6.22.

Acknowledgment. This research was made possible by a grant (AM-11433) from the National Institute of Arthritis and Metabolic Diseases, U.S. Public Health Service. We are grateful to the National Science Foundation for an Instruments Grant for purchase of a Varian A-60D nuclear magnetic resonance spectrometer and spin decoupler.

Registry No.—**1**, 51051-69-5; **2**, 57900-55-7; **5**, 57900-56-8; **6**, 57900-57-9; **7**, 32860-91-6; **8**, 57866-81-6; **9**, 57866-82-7; **10**, 57900-58-0; **11**, 57900-59-1; **12**, 57900-60-4; **13**, 57866-83-8; **14**, 57866-84-9; **15**, 57866-85-0; **16**, 57866-86-1.

References and Notes

(1) Presented to the Division of Carbohydrate Chemistry at the 169th National Meeting of the American Chemical Society, Philadelphia, Pa., April 1975.

(2) For preceding publication, see (a) A. B. Zanlungo and G. E. McCasland, *Carbohydr. Res.*, **38**, 352 (1974); see also (b) G. E. McCasland, A. B. Zanlungo, and L. J. Durham, *J. Org. Chem.*, **39**, 1462 (1974), and references cited therein.

(3) (a) To whom any communications should be addressed, at the University of San Francisco; (b) Stanford University.

(4) For earlier publications on sulfur analogues of alditols and cyclitols, see (a) G. E. McCasland, A. Furst, L. F. Johnson, J. N. Shoolery, and S. Furuta, *J. Org. Chem.*, **28**, 456 (1963); (b) G. E. McCasland, A. Furst, and S. Furuta, *J. Am. Chem. Soc.*, **85**, 2866 (1963); (c) *J. Org. Chem.*, **29**, 724 (1964); (d) G. E. McCasland and A. B. Zanlungo, *Carbohydr. Res.*, **17**, 475 (1971); (e) G. E. McCasland, A. K. M. Anisuzzaman, S. R. Naik, and L. J. Durham, *J. Org. Chem.*, **37**, 1201 (1972); (f) *Chem. Eng. News*, 51 (April 9, 1962).

(5) S. M. Iqbal and L. N. Owen, *J. Chem. Soc.*, 1030 (1960). It now appears that the dithiol product reported by these authors (and its trithiocarbonate precursor) may actually have been a mixture of the D-manno and D-ido isomers.

Alkane Diazotates. XXI. Ethanolysis and Thioethanolysis of Octane-2-diazotate[1]

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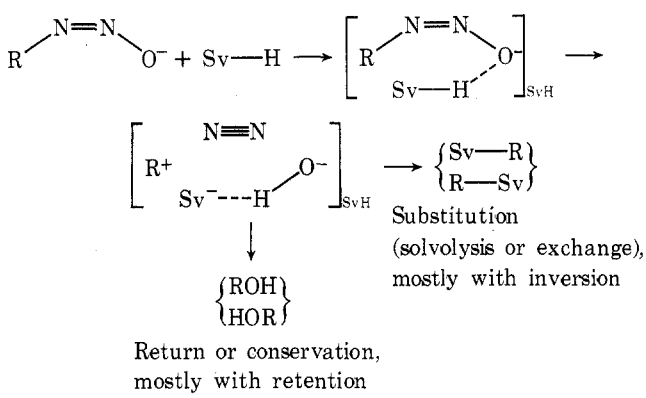
Received October 7, 1975

Optically active 2-aminooctane was converted to octane-2-diazotate and solvolyzed in either ethanol or thioethanol. In the ethanolysis reaction, 2-octyl ethyl ether and 2-octanol were formed with 74% overall inversion and 79% overall retention, respectively. In the thioethanolysis, 2-octyl ethyl sulfide and 2-octanol were formed with 73% overall inversion and 74% overall retention, respectively. The similarity of the results is discussed in relation to the stereochemical courses of other diazotate solvolysis reactions.

We have extensively studied the solvolysis of alkane diazotates,[3] RN=NO$^-$, paying particular attention to the hydrolysis,[4] ammonolysis,[5] and lithium ion catalyzed decomposition[6] of octane-2-diazotate (**1**). Scheme I has been found useful in rationalizing the results of the solvolysis reactions.[3]

Scheme I

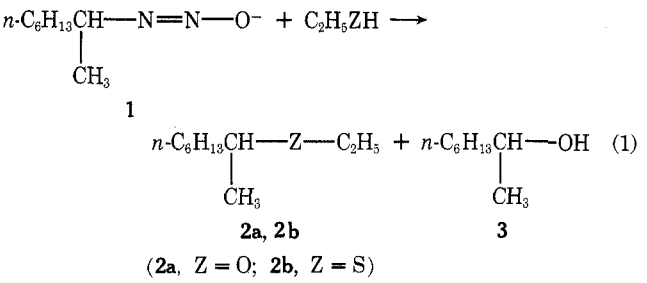


In Scheme I, Sv-H represents a protic solvent, and Sv$^-$ represents the corresponding lyate ion. The reaction of the diazotate with a protic solvent gives the key intermediate, a nitrogen-separated ion triplet. Its collapse, by *return*, or *conservation*, affords an alcohol with net stereochemical retention, although some inverted alcohol can form if R$^+$ rotates within the ion triplet prior to collapse.[7] External capture of R$^+$ occurs mainly from the rear, affording an inverted *substitution* product, Sv-R. However, a lyate ion is hydrogen bonded to the counterion of the ion triplet, making possible a front-side collapse (*exchange*) to the stereochemically retained substitution product, R-Sv. Complete inversion in the substitution process is therefore not observed.

Upon comparison of the substitution processes in the hydrolysis[4] and ammonolysis[5] of **1**, we observed a marginally *greater* overall inversion in the formation of 2-aminooctane from **1** by ammonolysis (85%) in comparison with the formation of 2-octanol-^{18}O from **1** by hydrolysis with $H_2{}^{18}O$ (76%). Was this due to the greater nucleophilicity of the solvent ammonia, or was it merely a temperature effect? (The ammonolysis was carried out at −33 °C, the hydrolysis at 0 °C.) To obtain further information on the effect of solvent or lyate ion nucleophilicity in diazotate solvolyses, we have subjected **1** to ethanolysis and thioethanolysis, and determined the stereochemical courses of the substitution and return reactions in each case. The results follow.

Results and Discussion

Octane-2-diazotate[4] (13–18 mmol) was dissolved in HMPA[4a] and added to 200 ml of dry ethanol, or ethanethiol, at 0 °C. Nitrogen evolution was nearly quantitative (93–97%) in each reaction. After an aqueous work-up, the products of interest, 2-octyl ethyl ether (**2a**), 2-octyl ethyl sulfide (**2b**), and 2-octanol (**3**), were readily isolable by GC; cf. eq 1.



(1)

The yield of **2a** was remarkably constant over three ethanolysis reactions, 25 ± 1%, as determined by GC against a 2-hexanol standard. The yield of **3**, however, was relatively more variable, 2.8–3.8%, perhaps because of selective extractive loss during work-up. A reliable value of **2a/3** could therefore not be obtained. Similar problems attended the thioethanolysis experiments, in which **2b** and **3** were formed in yields comparable to those of the analogous ethanolysis products.[8] Octenes were doubtlessly formed in these reactions,[4-6] but were not examined.

Optically active 2-aminooctane was converted to **1** via its urethane and *N*-nitrosourethane derivatives,[4,9] and solvolyzed in ethanol or ethanethiol, as above. Following work-up and GC purification, the rotations of **2a, 2b,** and **3** were polarimetrically determined. These results, and the derived *net* stereochemical courses of the reactions, are displayed