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NUCLEOPHILIC RING-OPENING IN A CARBOHYDRATE NITROCYCLOPROPANE: A STEREOSPECIFIC APPROACH TO CHIRAL ISOALKYL STRUCTURES*†

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ABSTRACT

Chemical reactions to open the cyclopropane ring in (1*R*)-1,2-dideoxy-3,4:5,6-di-*O*-isopropylidene-1,2-*C*-methylene-1-nitro-D-mannitol (**1**) were investigated. Catalytic hydrogenation over Pd–C produced the corresponding 1-amino compound, isolated as its *N*-acetyl derivative, but failed to cleave the ring. However, ring opening succeeded by nucleophilic addition of sodium thiophenoxide to **1**, giving 1,2-dideoxy-3,4:5,6-di-*O*-isopropylidene-1-nitro-2-*C*-(phenylthio)methyl-D-mannitol. The latter reacted further with thiophenoxide to furnish phenyl 2-deoxy-3,4:5,6-di-*O*-isopropylidene-2-*C*-(phenylthio)methyl-D-mannothiohydroximate. Raney nickel converted both of these thio sugar derivatives into the same product, namely, 1-acetamido-1,2-dideoxy-3,4:5,6-di-*O*-isopropylidene-2-*C*-methyl-D-mannitol. The use of these transformations for the design of stereospecific syntheses of chiral isoalkyl structures is proposed.

INTRODUCTION

Recently, we described a facile synthesis[2] of (1*R*)-1,2-dideoxy-3,4:5,6-di-*O*-isopropylidene-1,2-*C*-methylene-1-nitro-D-mannitol (**1**), achieved by action of sodium hydrogencarbonate upon 1,2-dideoxy-3,4:5,6-di-*O*-isopropylidene-3-*O*-(methylsulfonyl)-1-nitro-D-*manno*-heptitol. The latter is accessible by a sequence of high-yielding steps starting from D-mannose[3]. The position 2 in **1** constitutes a configurationally defined center of chain branching, and it was therefore considered that regioselective scission of the cyclopropane ring between C-1 and C-7, followed by further functional-group transformations (which might include deprotection and oxidative degradation of the polyol chain), should provide a general route to chiral isoalkyl structures. These would be generated stereospecifically unless reactions compromising the stereochemical integrity of C-2 should be employed (see Scheme 1).

*Dedicated to Professor Hans Paulsen.
†Part XLVI of a series "Reactions of Nitro Sugars". For Part XLV, see ref. 1.

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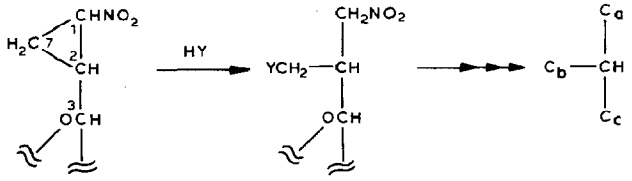


Scheme 1

One example for the application of such a strategy would be a stereospecific synthesis of (*R*)-3-amino-2-methylpropanoic acid [(−)-α-methyl-β-alanine], a metabolite that has attracted much attention in biochemistry and physiology, and appears to be associated with neoplastic processes[4]. Stereospecific syntheses of many other compounds containing a chiral isoalkyl grouping could also be designed on that principle. First endeavors to develop this concept are reported here.

RESULTS AND DISCUSSION

Although base-induced ring-opening reactions in nitrocyclopropanes bearing an electron-withdrawing substituent (*e.g.*, nitrocyclopropyl ketones) have been studied extensively[5], there appears to be a paucity of information on possible cleavage reactions for unactivated systems under any conditions–basic, neutral, or acidic. Seebach and coworkers[6], investigating the reaction of unactivated nitrocyclopropanes with various bases, observed interesting dimerizations but did not encounter fission of the ring. As there was little knowledge of chemical properties of the few, reported[2,7,8] carbohydrate derivatives incorporating that structural element, we first performed some exploratory experiments to assess the behavior of **1** toward selected reagents.

The nitrocyclopropano moiety of **1** proved to be quite acid-stable. Thus, brief treatments with hydrogen chloride in ether (15 min) or hydrogen bromide in acetic acid (1 h) at 25°, or with hydrogen chloride in refluxing ethyl acetate (2:5 h) caused no obvious changes other than partial or complete acetal cleavage; spectral analysis of the (acetylated) hydrolysis products revealed the characteristic i.r. and ^{1}H-n.m.r. features[2] associated with the nitrocyclopropano structure.

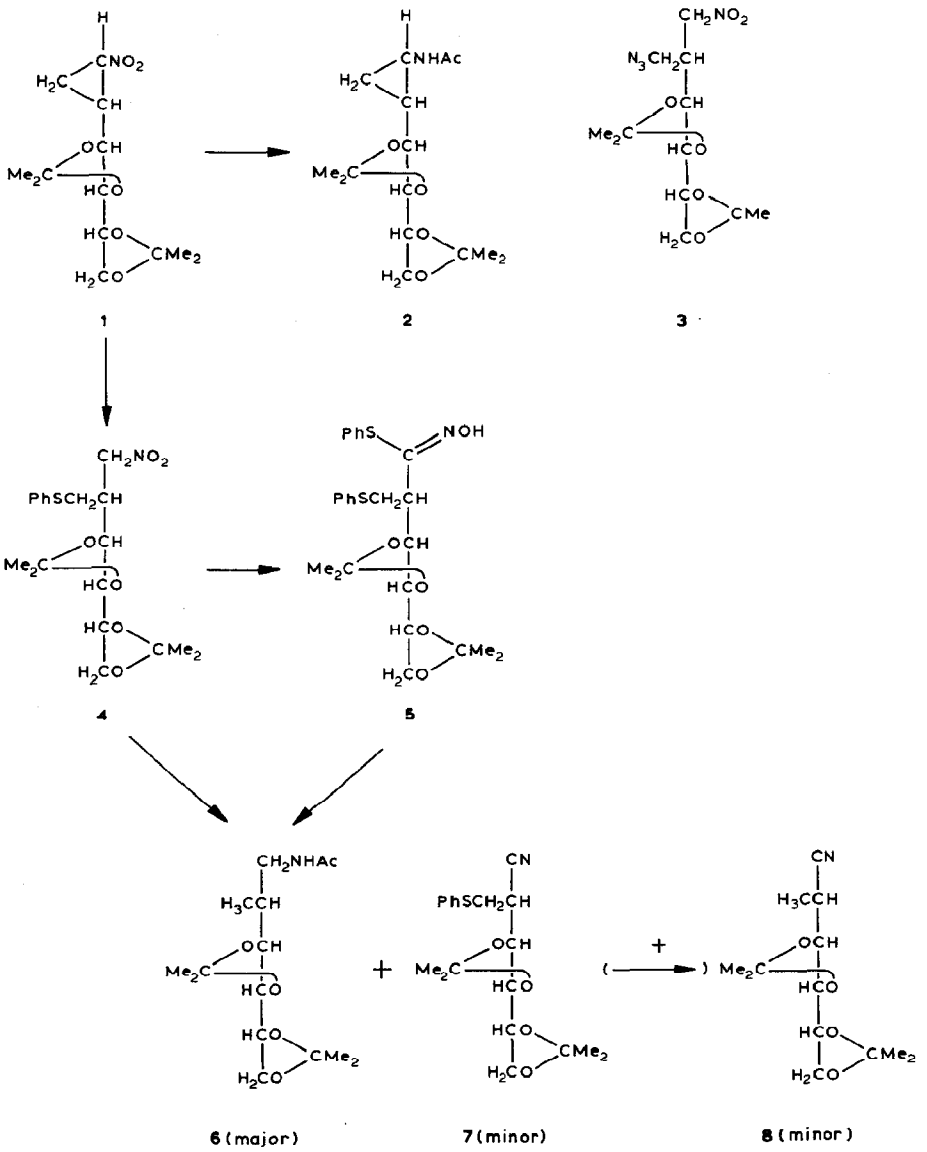
Ordinary cyclopropanes are usually cleaved by catalytic hydrogenolysis[9], although they may react less rapidly than do alkenes in catalytic hydrogenation. In the presence of palladium on charcoal, α-nitroalkenes are readily converted into nitroalkanes, and α-nitroepoxides are cleaved to nitro alcohols, normally within a few mins or an hour at ordinary temperature and pressure and with reductive attack of the nitro group occurring but slowly[10]. By contrast, **1** did not consume hydrogen rapidly under these conditions; the cyclopropane ring failed to open, and a slow reaction led to the corresponding amine, isolated as the crystalline *N*-acetyl derivative **2**. This compound was recovered unchanged after attempted ring-opening with the same catalyst but under more-forcing conditions, *e.g.*, by hydro-

genation in 2-propanol solution for 24 h at 80°. Whereas nitroalkenes and nitroepoxides react readily[11] with sodium borohydride in alcoholic solutions, **1** was completely inert toward that reagent in methanol (4 h at 25–65°). It did react rapidly with lithium triethylborohydride in oxolane even at 0°, but a complex mixture of products arose, and neither **2** nor the *C*-methyl analog **6** was found in any of the fractions chromatographically separated after acetylation.

The nitrocyclopropane **1** had first been obtained, from a side-reaction, when the methanesulfonate mentioned in the Introduction was treated with azide ion for the purpose of achieving a simple SN2 displacement. In that operation, a small proportion (3% yield) of the branched azidonitro compound **3** was isolated in addition to the byproducts **1** and its (1*S*) stereoisomer, and it was speculated that the origin of **3** had been a second side-reaction, namely, nucleophilic ring-opening in **1** or its stereoisomer. However, subsequent attempts to convert (isolated) **1** into **3** by prolonged treatment with tetrabutylammonium azide in refluxing toluene were unsuccessful. More rewarding was the treatment of **1** with sodium thiophenoxide*, which effected nucleophilic ring-opening quite readily to furnish the branched, 1,2-dideoxy-1-nitro-2-*C*-(phenylthio)methylhexitol **4**. A second, and rather surprising, product was engendered in that reaction, isolated crystalline, and shown to be the phenyl thiohydroximate **5**. When the reaction was performed in refluxing oxolane as the medium, **5** was formed more slowly than **4** during the first few h, but, in the course of the process, it increased in proportion at the expense of **4**, to become the main product by the time (24 h) all of the starting **1** had been consumed. Termination of the reaction after an optimum time of 3–4 h permitted the isolation of **4** in 30–40% yield, together with 20–40% of unreacted **1** usable for recycling, and together with 10–24% of **5** (see Table I in the Experimental section). In 1,4-dioxane at 100°, the process is faster than in oxolane, furnishing **5** in 96% yield after 4.5 h.

The structures of **4** and **5** were established on the basis of elemental analysis and spectral parameters. Thus, **4** displayed a strong nitroalkane band (1545 cm^{-1}) in the i.r. spectrum, and, in the ^{1}H-n.m.r. spectrum, all the requisite substituent resonances were present, including a doublet of doublets for each proton of the $-S-CH_2-$ group (δ 3.19 and 3.03, with J_{gem} 13.9 Hz and J_{vic} 7.2 and 7.0 Hz). Among the alditol chain protons, those at nitro-substituted C-1 expectedly resonated at lowest field, as doublets of doublets (δ 4.63 and 4.54, with J_{gem} 13.8 Hz and J_{vic} 4.8 and 7 Hz). The branch-point proton (H-2) gave a complex multiplet at δ 2.75, and the cyclopropanic methylene signals characteristic for **1** (multiplets at δ 1.83 and 1.40)[2] were no longer present. All signals exhibited by the ^{13}C-n.m.r. spectrum could also be accounted for. Further confirmation was provided by partial *O*-deisopropylidenation of **4**, readily effected by reaction with stannous chloride dihydrate in boiling methanol, which gave the corresponding 5,6-diol, whose ^{1}H-

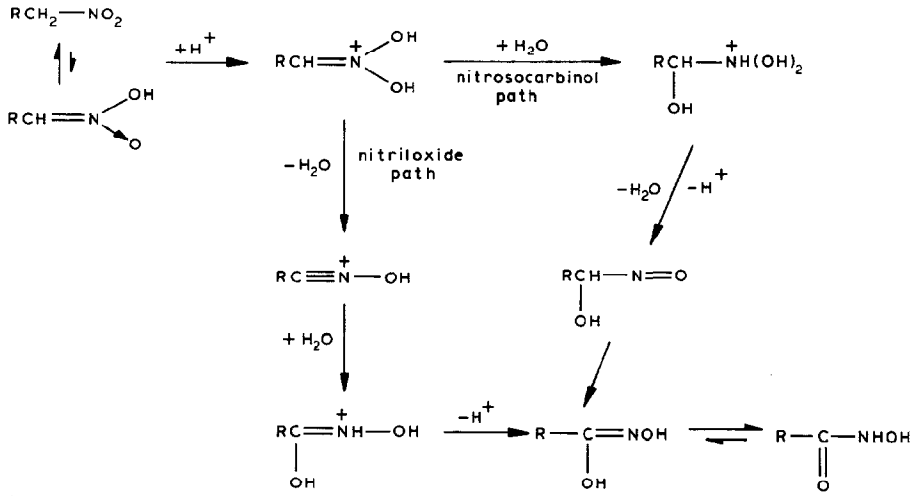
*The formation of 5-(phenylthio)-2-pentanone in 58% yield from cyclopropyl methyl ketone by action of this reagent has been reported[12].



n.m.r. spectrum was equally well interpretable. The thiohydroximic ester **5** showed broad hydroxyl absorption at 3150 cm^{-1} (OH, probably internally hydrogen-bonded), and bands at 1600 and 970 cm^{-1}, absent in **4** and compatible with C=N and N–O stretching vibrations; there was no NO_2 band in the 1550-cm^{-1} region. In the ^{1}H-n.m.r. spectra, the characteristic differences between **5** and **4** were the presence of aromatic signals integrating to 10 protons in that of **5** (as compared to 5 protons for **4**), and absence for **5** of the aforementioned, nitromethylenic signals with concomitant diminution in multiplicity of the H-2 signal at δ 2.91; all the

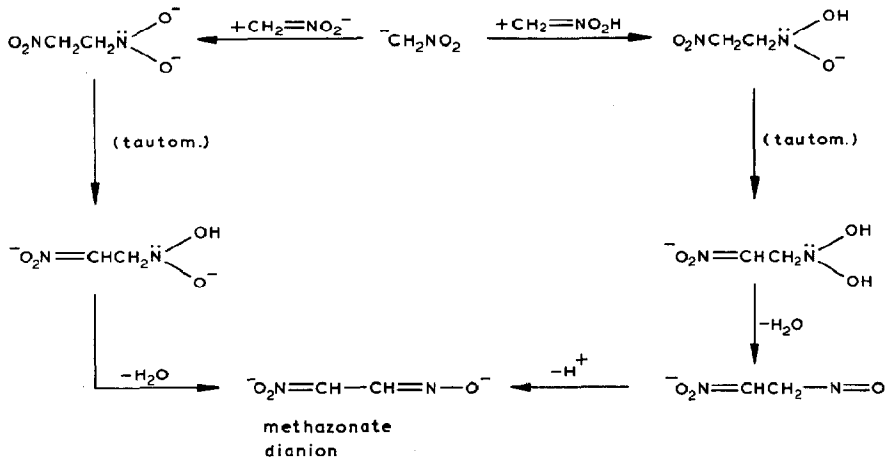
remaining signals were closely similar for **5** and **4**. All of the ^{13}C-n.m.r. signals of **5** could be assigned, including a resonance at δ 152.1 for the oximic carbon atom. Formation of an acetate from **5**, with little change in chemical shift for any of the skeletal protons, was also in accord with the structure assigned.

The mechanism of formation of **4** and **5** is now to be discussed. Compound **4** evidently arises by nucleophilic attack at the C-7 methylene group, with C-1 as nitronate anion functioning as the leaving group. We are not aware of any precedent for such a displacement, although the departure of alkanenitronate anion from a β-carbon atom is of course familiar from the base-promoted fission of *vic*-nitro alcohols (the reverse Henry addition); in the present case, relief of ring strain doubtless accounts for the reaction, in conjunction with the high nucleophilicity of thiophenoxide. More difficult to explain is the conversion of **4** into **5**, which appears to involve a nucleophilic attack on the nitroalkane carbon atom in the former. The formation of a hydroximic ester evokes the analogy of the well-known production of hydroxyamic acids from primary nitroalkanes, which does in fact involve such an attack (by water). However, this transformation (see Scheme 2) occurs in strongly acidic medium, and is assumed to proceed *via* protonated nitronic acid tautomer[13]. (Similarly, hydrogen chloride in anhydrous ether adds to nitronates, giving chloronitrosoalkanes that tautomerize to hydroximoyl chlorides[13].) In view of the

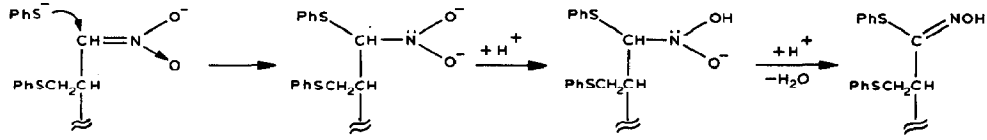


Scheme 2

reaction conditions giving rise to **5**, a more relevant analogy may be the formation of methazonic acid (nitroacetaldoxime) from two molecules of nitromethane in alkaline solution[14]. It is believed that one molecule plays the role of the attacking nucleophilic as a carbanion, adding to a molecule of un-ionized nitronic acid or, alternatively, to another anion to produce the methazonate dianion, as depicted in Scheme 3. It is suggested that formation of **5** takes place in a similar way (see Scheme 4).



Scheme 3



Scheme 4

Treatment of **4** with Raney nickel in boiling methanol effected desulfurization of the molecule and reduction of the nitro group, to give the expected aminodideoxy-*C*-methylhexitol, isolated in 23% yield as its crystalline *N*-acetyl derivative **6**. Gratifyingly, the same product was obtained, in like manner but with a higher yield (44%), from the more conveniently prepared thiohydroximate **5**. The ^{1}H-n.m.r. spectrum of **6** showed a 3-proton doublet ($J_{2,Me}$ 6 Hz) at δ 0.98 for the branching *C*-CH_3 group, and a 3-proton singlet at δ 1.93 for the $NHCOCH_3$ group, in addition to four 3-proton singlets (δ 1.38–1.31) for the isopropylidene groups; H-1 and -1′ gave multiplets at δ 3.42 and 3.30, and were coupled to H-2, which gave a complex multiplet at δ 2.05.

Involving concurrent transformations at two different functionalities both in **4** and in **5**, the reductions of these compounds were interesting to monitor by t.l.c. Spots of intermediate mobilities were seen before and during the appearance of the slow-moving amine, and some of them, being visible under u.v. light like **4** and **5** but unlike **6**, were judged to be due to transformation products still bearing a phenylthio group. However, there was also a u.v.-invisible byproduct (migrating faster than **6**) which, in the reduction of **5**, appeared to arise from one of the u.v.-active intermediates and was then changed no further. Chromatography performed after acetylation of the reaction mixtures yielded, in addition to **6**, small amounts of two of these faster-moving compounds. Both of them gave i.r. spectra lacking

amide or oxime bands but showing, instead, sharp peaks at 2240 cm^{-1}, indicative of a cyano group. (The peaks were of low intensity, as is normal for C≡N stretching vibrations in highly oxygenated nitriles.) One of the products corresponded to the u.v.-invisible t.l.c. spot just mentioned, and on the basis of elemental analysis, mass spectrum, and readily interpretable ^{1}H-n.m.r. spectrum was assigned the 2-deoxy-2-*C*-methylmannononitrile structure **8**. The other byproduct isolated was u.v.-active, and its well-resolved ^{1}H-n.m.r. spectrum accorded fully with the structure of the *C*-(phenylthio)methyl nitrile **7**. It is assumed that **7** and **8** originated from an intermediary aldoxime generated from **4** by incomplete reduction of the nitro group, and from **5**, by reductive cleavage of the thioester group. No effort was made to clarify whether dehydration followed *in situ* (as a minor event competing with amine formation), or whether surviving oximes gave the corresponding nitriles during processing of the reaction mixtures with acetic anhydride. At any rate, the survival of incompletely reduced material after several hours of exposure to Raney nickel at 65° is noteworthy.

It is expected that the chemistry reported here will lend itself to useful applications. To exemplify the point, preliminary studies were undertaken concerning the oxidative degradation of **6**. The compound was smoothly deacetonated by 90% trifluoroacetic acid, and the resultant tetraol was sequentially oxidized with lead tetraacetate and bromine according to the procedure given by Wolfrom and coworkers[15] for the degradation of 2-acetamido-1,2-dideoxy-D-glucitol to L-alanine. There was obtained levorotatory α-methyl-β-alanine, identical with the natural enantiomer that was shown by Balenović and Bregant[4] to possess the *R* configuration.

EXPERIMENTAL

General methods. — Unless otherwise stated, the following solvent combinations (v/v) were used for t.l.c. and in colomn chromatography on silica gel: *A*, 3:7 acetone–hexane; *B* and *C*, the same solvents, but 1:9 and 1:49, respectively; and *D*, 1:3 ethyl acetate–hexane. The t.l.c. plates were viewed under a u.v. lamp to visibilize spots of phenylthio derivatives, and subsequently sprayed with 10% H_2SO_4 in ethanol and heated, to make all product spots visible. The i.r. data (ν_{max}) refer to spectra of Nujol mulls for crystalline substances, and to spectra of neat substance for syrups, obtained with a Perkin–Elmer model 783 spectrometer. Optical rotations were measured at 25°. The ^{1}H-n.m.r. data were obtained at 300 MHz for solutions in chloroform-*d* ($CHCl_3$ lock signal at δ 7.24) with a Varian XL 300 spectrometer. The ^{13}C-n.m.r. spectra were recorded with the same instrument, at 75.43 MHz, also for $CDCl_3$ solutions.

*1-Acetamido-1,2-dideoxy-3,4:5,6-di-*O*-isopropylidene-1,2-*C*-methylene-*D*-mannitol* (**2**). — Compound[2] **1** (500 mg) and Pd–C (10%, 500 mg) in methanol (10 mL) were shaken overnight under H_2 at ordinary temperature and pressure. The catalyst was filtered off, and washed with methanol (40 mL), and acetic anhydride

(5 mL) was added to the filtrate which, after 20 min, was evaporated to dryness with several additions of toluene. The residue was chromatographed on a column of silica gel (12 g) by use of ethyl acetate as the eluant. Following the elution of fast-moving, unidentified products (173 mg), **2** emerged in a yield of 347 mg (67%); R_F 0.3 (ethyl acetate); m.p. 89–90° (crystallized from ether–hexane), $[\alpha]_D$ −45° (*c* 0.5, chloroform); ν_{max} 3320 (NH), 3100 (cyclopropyl), and 1650 and 1560 cm^{-1} (amide I and II); ^{1}H-n.m.r.: δ 4.10 (dd, $J_{2,3}$ 6, $J_{3,4}$ 7.7 Hz, H-3), 4.02 (m, H-5), 3.95 (dd, $J_{4,5}$ 4.6, $J_{3,4}$ 7.7 Hz, H-4), 3.88 (~t, $J_{5,6} \approx J_{6,6'} \approx$ 7.3 Hz, H-6), 3.59 (~t, $J_{5,6'} \approx J_{6,6'} \approx$ 7 Hz, H-6'), 2.75 (symm. sextet with broadened lines, spacings ~3.6 Hz, *W* 18.2 Hz, H-1), 1.91 (s, 3 H, *N*Ac), 1.39 and 1.32 (s, 6 H each, 4 Me), 1.12 (tdd, $J_{1,2}$ 3.6, $J_{2,7} = J_{2,3} = 6$, $J_{2,7'}$ 10 Hz, H-2), 1.00 (dt, $J_{1,7}$ 7.5, $J_{2,7} = J_{7,7'} = 6$ Hz, H-7), 0.75 (septet, $J_{1,7'}$ 4.2, $J_{7,7'}$ 6, $J_{2,7'}$ 10 Hz, H-7'). A set of additional, low-intensity signals indicated that the sample was not entirely pure; possibly, a small proportion of the 1*S* epimer was present.

Anal. Calc. for $C_{15}H_{25}NO_5$ (299.4): C, 60.18; H, 8.42; N, 4.68. Found: C, 60.49; H, 8.55; N, 4.68.

After attempted further hydrogenation of **2** with Pd–C in ethanol for 16 h at 25° and 4 h at 65°, or in 2-propanol for 24 h at 80°, only starting material was isolated.

Reaction of **1** *with sodium thiophenoxide. A. — Preparation of* **4** *and* **5**. A solution of thiophenol (2.05 mL, 19.9 mmol) in dry oxolane (10 mL) was added to NaH (427 mg, from 700 mg of a 61% oil dispersion; 17.8 mmol), with external cooling (0°) and under N_2. When the evolution of H_2 had ceased, compound **1** (500 mg, 1.74 mmol) in dry oxolane (10 mL) was added dropwise during 5–10 min, with continued cooling. The mixture was then boiled under reflux, in a N_2 atmosphere, for various periods of time in several similar experiments (see Table I), and the process was monitored by t.l.c. (solvent *A*). The spot for **1** (R_F 0.83, u.v.-inactive) decreased gradually in intensity but did not disappear during the first 4 h while u.v.-active spots for **4** (R_F 0.79) and an unidentified byproduct (R_F 0.17) appeared first, followed more slowly by a u.v.-active spot for **5** (R_F 0.64). After the reaction times

TABLE I

REACTION OF COMPOUND **1** WITH SODIUM THIOPHENOXIDE

Reaction time (h)	*Yield (%)*				
	Unreacted **1**[a,b]		*Compound* **4**[a,b]		*Compound* **5**[c]
2.5	37		23	3	4
3	30.5	12	30.4	8.5	9.6
4	0	20	34	15	24
24	0	tr.	10.6	tr.	60.6
1.25[d]	0	tr.	12		88
4.5[d]	0	0		tr.	96

[a]First column: material isolated. [b]Second column: estimated in mixture fractions that were not processed further. [c]Isolated crystalline. [d]In 1,4-dioxane solvent.

indicated (see Table I), the cooled mixture was partitioned between toluene and water. The organic layer was washed with water (5 ×), dried (Na_2SO_4), and evaporated. The residue was chromatographed on a column of silica gel (20 g). Elution with solvent *C* produced noncarbohydrate material in early fractions, followed by mixtures of **1** and **4**, and pure **4**. Continued elution using solvent *B* then gave **5** and finally, the unidentified byproduct. Combined mixture-fractions were partially separated by repeated chromatography (solvent *C*). Percentage yields for **4**, **5**, and recovered **1** are given in Table I.

The amount of slow-moving *byproduct* tended to be somewhat variable; in one typical 500-mg run, 56 mg of it was isolated. The syrupy material showed strong hydroxyl absorption but no NO_2 band in the infrared spectrum. Isopropylidene groups were absent (^{1}H-n.m.r.); mass spectrum (c.i., ether): *m/z* 268 (weak), 251 (strong), 233 (weak), 181 (medium), 149 (strong), 141 (base peak).

Anal. Found: C, 63.8; H, 7.6; N, 0.0; S, 11.9.

For the preparation of **5** alone, in high yield, compound **1** (345 mg) was treated with sodium thiophenoxide (from 1.42 mL of thiophenol and 485 mg of 61% NaH) exactly as described before but in 1,4-dioxane (20 mL) instead of oxolane. After reaction for 4.5 h at the reflux temperature, the mixture contained **5** together with only a trace of remnant **4**. Processing and chromatography as described yielded pure **5** (565 mg, 96%). No byproducts were seen in t.l.c.

*B. Characterization of 1,2-dideoxy-3,4:5,6-di-*O*-isopropylidene-1-nitro-2-*C*-(phenylthio)methyl-*D*-mannitol* (**4**). Compound **4** was a colorless syrup; $[\alpha]_D$ +0.3°, $[\alpha]_{578}$ +0.25°, $[\alpha]_{546}$ −0.1°, $[\alpha]_{436}$ −4.5°, $[\alpha]_{365}$ −19° (*c* 4.2, chloroform); ν_{max} 1575 (weak), 1545 (strong, NO_2), 1380–1370 (strong doublet), 1260–1210 (several bands), 1150, 1120 (weak), 1070 (strong), 905, 875, 840, 810, 790, 740, 690 cm^{-1}; ^{1}H-n.m.r.: δ 7.4–7.2 (m, 5 H, Ph), 4.63 (dd, $J_{1,2}$ 4.8, $J_{1,1'}$ 13.8 Hz, H-1), 4.54 (dd, $J_{1',2}$ 7, $J_{1,1'}$ 13.7 Hz, H-1′), 4.28 (dd, $J_{2,3}$ 4, $J_{3,4}$ 7.3 Hz, H-3), 4.11 (dd, $J_{5,6}$ 5.8, $J_{6,6'}$ 8.2 Hz, H-6), 3.98 (dt, $J_{4,5}$ 8.1, $J_{5,6}$ 5.8, $J_{5,6'}$ 4.8 Hz, H-5), 3.89 (dd, $J_{5,6'}$ 4.8, $J_{6,6'}$ 8.2 Hz, H-6′), 3.58 (dd, $J_{3,4}$ 7.3, $J_{4,5}$ 9 Hz, H-4), 3.19 (dd, $J_{2,7}$ 7.2, $J_{7,7'}$ 13.9 Hz, H-7), 3.03 (dd, $J_{2,7'}$ 7, $J_{7,7'}$ 13.9 Hz, H-7′), 2.75 (cm, *W* 30 Hz, H-2), 1.32, 1.30, 1.27, and 1.26 (s, 3 H each, 4 Me); ^{13}C-n.m.r.: δ 134.6 (C-1 of Ph), 130.4 and 129.1 (*o*- and *m*-C of Ph), 126.9 (*p*-C of Ph), 109.9 and 109.7 (2 O_2CMe_2), 79.7, 79.2 and 77.1 (C-3,4,5), 74.8 (C-1), 67.9 (C-6), 39.1 (C-2), 34.6 (*S*-CH_2), 26.8 (with double intensity), 26.4, and 25.1 (4 Me).

Anal. Calc. for $C_{19}H_{27}NO_6S$ (397.5): C, 57.41; H, 6.85; N, 3.52; S, 8.07. Found: C, 57.48; H, 6.94; N, 3.49; S, 8.34.

For partial deacetonation, a sample of **4** (42 mg) was boiled for 1 h in methanol (4 mL) containing $SnCl_2 \cdot 2\ H_2O$ (51 mg); **4** (R_F 0.6) was almost completely replaced by the corresponding *5,6-diol* (R_F 0.3, t.l.c. with solvent *D*). After evaporation of the solvent, the residue was distributed between chloroform and water containing a small amount of NH_3. The dried chloroform solution gave syrupy diol (24 mg, 63%); before spectral analysis, it was passed through a micro-column of silica gel by means of 2:3 ethyl acetate–hexane. The i.r. spectrum was

closely similar to that of **4**, except that a strong OH band was present, ν_{max} 3400 cm^{-1}; ^{1}H-n.m.r.: δ 7.4–7.2 (m, 5 H, Ph), 4.66 (dd, $J_{1,2}$ 5.3, $J_{1,1'}$ 13.8 Hz, H-1), 4.57 (dd, $J_{1',2}$ 6.5, $J_{1,1'}$ 13.8 Hz, H-1'), 4.31 (dd, $J_{2,3}$ 3.9, $J_{3,4}$ 6.9 Hz, H-3), 3.8–3.6 (m, 4 H, H-4,5,6,6'), 3.19 (dd, $J_{2,7}$ 6.9, $J_{7,7'}$ 13.8 Hz, H-7), 3.05 (dd, $J_{2,7'}$ 7.1, $J_{7,7'}$ 13.8 Hz, H-7'), 2.80 (cm, 16 lines, *W* 30 Hz, H-2), 2.33 and 1.75 (2 H each, exchangeable by D_2O, 2 OH), 1.34 and 1.31 (s, 3 H each, 2 Me).

*C. Characterization of phenyl 2-deoxy-3,4:5,6-di-*O*-isopropylidene-2-*C*-(phenylthio)methyl-*D*-mannonothiohydroximate* (**5**). Compound **5** crystallized from ether–petroleum ether and was recrystallized from 99% ethanol; m.p. 134–136°, [α] +33.6° (*c* 1.1, chloroform); ν_{max} 3150 (broad, OH), 1600, 1575 (weak), 1250, 1200, 1165, 1150, 1120, 1100–950 (several bands), 915, 890 and 870 (weak), 855 (strong), 805 (weak), 750, 740, and 685 cm^{-1}; ^{1}H-n.m.r.: δ 7.4–7.15 (m, 10 H, 2 Ph), 4.14 (~t, $J_{2,3} \approx J_{3,4} \approx$ 6.3 Hz, H-3), 4.04 (dd, $J_{5,6}$ 5.8, $J_{6,6'}$ 8.4 Hz, H-6), 3.93 (q, *W* 19.5 Hz, spacings 6.5 Hz, H-5), 3.80 (2 coinciding t, 2 H, spacings 7.5 Hz, H-4,6'), 3.34 (dd, $J_{2,7}$ 5.1, $J_{7,7'}$ 13.9 Hz, H-7), 3.23 (dd, $J_{2,7'}$ 9.1, $J_{7,7'}$ 13.9 Hz, H-7'), 2.91 (~sextet, *W* 20.5 Hz, H-2), 1.34 and 1.30 (s, 3 and 9 H, 4 Me); ^{13}C-n.m.r.: δ 152.1 (C=NOH), 136.3 and 129.4 (C-1 of 2 Ph), 134.6, 129.0, 128.9, 128.85 (*o*- and *p*-C of 2 Ph), 128.7 and 125.9 (*p*-C of 2 Ph), 109.7 (double intensity, 2 O_2CMe_2), 80.4, 79.1, and 76.6 (C-3,4,5), 66.9 (C-6), 44.6 (C-2), 34.0 (*S*-CH_2), 27.1, 27.0, 26.3, and 25.4 (4 Me).

Anal. Calc. for $C_{25}H_{31}NO_5S_2$ (489.6): C, 61.32; H, 6.38; N, 2.86; S, 13.10. Found: C, 61.47; H, 6.22; N, 2.90; S, 12.97.

A sample was *acetylated* with acetic anhydride–pyridine for 3 h at 25°; ν_{max} 1770 cm^{-1} (OAc), no OH absorption; ^{1}H-n.m.r.: δ 7.5–7.15 (m, 10 H, 2 Ph), 4.23 (dd, $J_{2,3}$ 7, $J_{3,4}$ 8.3 Hz, H-3), 4.08 (dd, $J_{5,6}$ 6.5, $J_{6,6'}$ 8.4 Hz, H-6), 3.98 (dt, $J_{4,5} = J_{5,6} = 6.4$, $J_{5,6'}$ 7.7 Hz, H-5), 3.80 (dd, $J_{5,6'} > 7$, $J_{6,6'}$ 8.4, H-6'), 3.60 (dd, $J_{4,5}$ 6.4, $J_{3,4}$ 8.3 Hz, H-4), 3.46 (dd, $J_{2,7}$ 4.5, $J_{7,7'}$ 13.8 Hz, H-7), 3.30 (dd, $J_{2,7'}$ 10.7, $J_{7,7'}$ 13.8 Hz, H-7'), 2.91 (ddd, $J_{2,7}$ 4.5, $J_{2,3}$ 7, $J_{2,7'}$ 10.7 Hz, H-2), 2.03 (s, 3 H, OAc), 1.37 and 1.29 (s, 3 and 9 H, 4 Me).

*1-Acetamido-1,2-dideoxy-3,4:5,6-di-*O*-isopropylidene-2-*C*-methyl-*D*-mannitol* (**6**). — *A. From* **4**. Raney nickel W-4 was freshly prepared[16], and a large excess[17] was added portionwise (as a methanolic slurry) in hourly intervals to a boiling solution of **4** (460 mg) in methanol (10 mL). Monitoring of the reaction by t.l.c. (solvent *D*) indicated gradual formation, from **4** (R_F 0.7, u.v.-visible), of a slow-moving (R_F 0.15) and a fast-moving (R_F 0.75) product, both invisible under u.v. light. After 4–5 h, the mixture was cooled to room temperature, stirred for several hours with added acetic anhydride (4 mL), and filtered through Celite, with extensive washing of the residue with methanol. (It is advisable to perform the *N*-acetylation directly in the reaction mixture, prior to removal of the catalyst because the latter tends to hold back free amine stubbornly even on exhaustive washing. Alternatively, the suspension may be filtered, and the filtrate and the catalyst, resuspended in methanol, may be treated separately with acetic anhydride; in this variant, pure **6** is released from the catalyst, and a mixture of **6** and by-

products is obtained from the original filtrate.) The green filtrate was evaporated together with several added portions of ethanol, and the residue was partitioned between chloroform and water in order to remove nickel salt. The crude material obtained by evaporation of the dried (Na_2SO_4) chloroform phase was chromatographed on a column of silica gel (10 g) with solvent *B*, to give crystalline byproduct **8** (R_F 0.75; 40 mg), some inhomogeneous fractions of unidentified products having intermediate mobilities (total, 44 mg), and finally, crystalline **6** (R_F 0.3; 80 mg, 23%). Recrystallized from ether–hexane, **6** had m.p. 91–93°, $[\alpha]_D$ +18.8° (*c* 0.9, chloroform); ν_{max} 3300 (NH), 1650 and 1550 (amide I and II), 1370, 1290–1200 (several bands), 1150, 1065, and 845 cm^{-1}; *m/z* (c.i., ether) 302 (base peak, M^+ + 1) and 244 (M^+ + 1 − CH_3CONH); ^{1}H-n.m.r.: δ 6.2 (broad s, NH), 4.14 (dd, *J* 6 and 8 Hz, H-3 or -4), 4.03 (dt, *J* 6 and 8 Hz, H-5), 3.93 (m, 2 H, H-6,6'), 3.78 (dd, *J* 6 and 8 Hz, H-4 or -3), 3.42 and 3.30 (m, 1 H each, J_{gem} 14 Hz, H-1,1'), 2.05 (cm, H-2), 1.93 (s, 3 H, *N*Ac), 1.38, 1.36, 1.33, 1.31 (s, 3 H each, 2 Mr_2CO_2), and 0.98 (d, 3 H, $J_{2,Me}$ 6 Hz, *CH*-Me).

Anal. Calc. for $C_{15}H_{27}NO_5$ (301.4): C, 59.78; H, 9.03; N, 4.65. Found: C, 59.93; H, 9.00; N, 4.62.

B. From **5**. Compound **5** (1.60 g) in methanol (30 mL) was treated during 19 h with Raney nickel as described for **4**, with additions of fresh catalyst after 2, 3, 4, and 8 h. Monitoring by t.l.c. (solvent *A*) showed gradual diminution in intensity of the spot for **5** (R_F 0.54, u.v.-active). After 4 h, two spots were seen, representing the desired amine (R_F 0.1) and a u.v.-active intermediate (R_F 0.60), and much of the **5** was still present; after 8 h, traces of new products (R_F 0.66 and 0.35, u.v.-inactive) were observed in addition; and, after 19 h, **5** was absent but a u.v.-inactive product migrating at the same rate was visible and the intermediate(s) having R_F 0.60 were seen as a faint spot under u.v. light but as a rather strong spot after charring. The catalyst was filtered off, and the filtrate was boiled with fresh catalyst for another 2 h, whereafter no more u.v.-active material was detected, although fast-moving byproducts persisted. The reaction mixture as well as the previously collected bulk of catalyst were processed by treatment with acetic anhydride as outlined in section *A*. Crystallization of part of the crude product, and column chromatography of the remainder, furnished pure, crystalline **6** (295 mg, 30%); m.p. 91–92° (undepressed on admixture of **6** from *A*). Early chromatographic fractions gave crystalline **8** (61 mg), which was followed by syrupy, unidentified products (85 mg) of intermediate mobility. When, after the elution of most of the **6**, the eluant was changed from solvent *B* to 1:1 acetone–hexane, the emerging material (54 mg) did not crystallize, and contained only a small proportion of **6**; the major part of it had a marginally smaller R_F value in t.l.c. and its spot was visible in u.v. light (not detected in the crude reaction-mixture). Possibly, it was the 7-phenylthio derivative of **6**.

In a similar operation, but performed on a smaller scale (294 mg of **5**), the yield of **6** (80 mg) was 44%.

*C. 2-Deoxy-3,4:5,6-di-*O*-isopropylidene-2-*C*-(phenylthio)methyl-*D*-mannono-*

nitrile (**7**) *and 2-deoxy-3,4:5,6-di-*O*-isopropylidene-2-*C*-methyl-*D*-mannononitrile* (**8**). The byproduct **8** obtained from **4** (see section *A*) melted at 75–90° and showed minor, extraneous signals in its ^{1}H-n.m.r. spectrum. Sublimed without residue (cold-finger apparatus, oil-pump vacuum, 40–50° bath temperature), it had an unchanged melting range and gave unchanged i.r. and ^{1}H-n.m.r. spectra, the main patterns of which were superposable on the spectra given by a purer sample that was obtained from **5** (see section *B*). Recrystallized from hexane, the white prisms of **8** had m.p. 98–99°; *m/z* (c.i., ether) 256 ($M^+ + 1$); ν_{max} 2230 (CN); ^{1}H-n.m.r.: δ 4.17, 4.00, and 3.82 (m, 1, 2, and 2 H, H-3,4,5,6,6'), 3.08 (dq, $J_{2,3}$ 2.1, $J_{2,Me}$ 7.4 Hz, H-2), 1.475 (d, 3 H, $J_{2,Me}$ 7.4 Hz, *CH*-Me), 1.49, 1.45, 1.40, 1.35 (singlets integrating to 12 H, 2 O_2CMe_2).

Anal. Calc. for $C_{13}H_{21}NO_4$ (255.3): C, 61.16; H, 8.29; N, 5.48. Found: C, 61.00; H, 8.32; N, 5.30.

When the treatment of **5** with Raney nickel was performed as described in section *B*, but terminated at a time when the t.l.c. spot having R_F 0.60 was still clearly visible in u.v. (*i.e.*, after 4 h), the chromatographically isolated material responsible for that spot (25 mg, from 150 mg of **5**) was a mixture of **7** and **8**, according to its ^{1}H-n.m.r. spectrum. Separation on a small column of silica gel, by elution with dichloromethane, gave a few milligrams each of pure **7** (R_F 0.2, u.v.-active) and **8** (R_F 0.1, u.v.-inactive; t.l.c. with chloroform). The former showed ν_{max} 2238 cm^{-1} (CN); ^{1}H-n.m.r.: δ 7.3–7.1 (m, 5 H, Ph), 4.15 (m, 2 H, H-3,6), 3.95 (m, 2 H, H-5,6'), 3.80 (t, $J_{3,4} \approx J_{4,5} \approx$ 8.35 Hz, H-4), 3.31 (dd, $J_{2,7}$ 7.6, $J_{7,7'}$ 13.7 Hz, H-7), 3.23 (dd, $J_{2,7'}$ 7.8, $J_{7,7'}$ 13.7 Hz, H-7'), 3.10 (td, $J_{2,7} \approx J_{2,7'} =$ 7.7 Hz, $J_{2,3}$ 1.9 Hz, H-2), 1.48, 1.38, 1.27, and 1.24 (s, 3 H each, 4 Me).

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