DE-*O*-BENZYLATION OF BENZYL ETHERS OF CARBOHYDRATE DERIVATIVES BY THIOLS IN THE PRESENCE OF BORON TRIFLUORIDE

HEWITT G. FLETCHER, JR., AND HARRY W. DIEHL

National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service, U. S. Department of Health, Education, and Welfare, Bethesda, Maryland 20014 (U. S. A.)

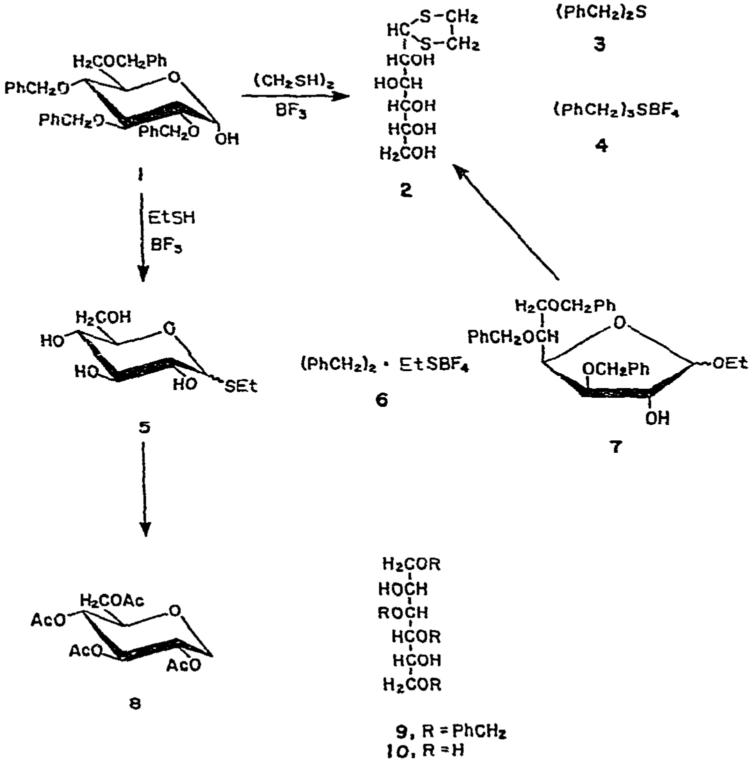
(Received October 16th, 1970)

ABSTRACT

Based on experiments with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (**1**), 1,3,4,6-tetra-*O*-benzyl-D-mannitol (**9**), and ethyl 3,5,6-tri-*O*-benzyl-D-glucofuranoside (**7**), a mixture of boron trifluoride etherate and ethanethiol or 1,2-ethanedithiol constitutes a practical reagent for the removal of *O*-benzyl groups from benzyl ethers of carbohydrates at room temperature. When 1,2-ethanedithiol was used, **1** and **7** afforded D-glucose ethylene dithioacetal [**2**; 2-(D-*gluco*-pentahydroxypentyl)-1,3-dithiolane], the benzyl groups appearing as benzyl sulfide (**3**) and tribenzylsulfonium tetrafluoroborate (**4**). With ethanethiol and boron trifluoride, **1** gave a mixture of the anomeric ethyl 1-thio-D-glucopyranosides (**5**) and dibenzylethylsulfonium tetrafluoroborate (**6**). The nonreducing compound **9** simply gave D-mannitol (**10**) under these conditions. A mechanism for this new debenzylation procedure is proposed.

INTRODUCTION AND DISCUSSION

In the course of an earlier study[1], it was found that treatment of 2,3,5-tri-*O*-benzyl-D-arabinofuranose with ethanethiol and hydrogen chloride readily affords 2,3,5-tri-*O*-benzyl-D-arabinose diethyl dithioacetal, although the isolation of this product was most conveniently accomplished through its 4-*O*-benzoyl derivative. Subsequently, 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (**1**) was subjected to similar reaction conditions, but neither the desired diethyl dithioacetal nor any other readily definable product was obtained. Recourse was then had to 1,2-ethanedithiol and boron trifluoride etherate, a combination of reagents widely used in the steroid field for masking relatively inert carbonyl groups as ethylene dithioacetals[2]. When **1** was treated with an excess of 1,2-ethanedithiol and 4.3 molar equivalents of boron trifluoride etherate at 0°, a reaction took place that could readily be followed by t.l.c. The products were easily separated by partition between water and dichloromethane; from the aqueous solution was recovered the known[3] D-glucose ethylene dithioacetal (**2**) in 62% yield. The organic solution was found to contain two compounds that were readily distinguishable by their behavior in t.l.c. One of these proved to be benzyl sulfide (**3**); the other, also a crystalline compound, burned with a transient green flame and gave a p.m.r. spectrum that showed signals only for the benzyl group. An authentic specimen of tribenzylsulfonium tetrafluoroborate (**4**) was therefore synthesized by the action of benzyl bromide and silver tetrafluoroborate on benzyl sulfide, and it was found to be identical with the third product from the debenzylation of **1**.



In another experiment with **1**, ethanethiol was used instead of 1,2-ethanedithiol, the reaction was conducted at room temperature, and the products were partitioned between water and dichloromethane. Acetylation of the material from the aqueous solution afforded a mixture of two crystalline products that had the elemental composition of an ethyl 1-thiohexoside tetraacetate but which proved difficult to separate. The mixture was, therefore, desulfurized with Raney nickel, and the well-known tetraacetate of 1,5-anhydro-D-glucitol[4] (**8**) was obtained. We conclude that the immediate product of the debenzylation step was a mixture of the anomers of ethyl 1-thio-D-glucopyranoside (**5**).

The dichloromethane solution from the reaction mixture yielded a crystalline compound that had a p.m.r. spectrum showing the presence of an ethyl group and of benzyl groups. Like **4**, it burned with a transient green flame; its elemental composition agreed with that calculated for dibenzylethylsulfonium tetrafluoroborate (**6**). With Nitron (3,5,6-triphenyl-2,3,5,6-tetraazabicyclo[2.1.1]hex-1-ene) acetate, the salt gave a highly insoluble material having a melting point close to that of the known Nitronium tetrafluoroborate[5]; the dibenzylethylsulfonium cation was characterized as its mercury triiodide salt[6].

That thioacetal formation is not in any way a necessary concomitant of the debenzylation process was shown through treatment of the recently described[7] 1,3,4,6-tetra-*O*-benzyl-D-mannitol (9) with ethanethiol and boron trifluoride etherate. Dibenzylethylsulfonium tetrafluoroborate (6) was isolated, and D-mannitol (10) was recovered in high yield.

Ethyl 3,5,6-tri-*O*-benzyl-D-glucofuranoside (7, "Glyvenol", CIBA 21 401-Ba)[8] is an anomeric mixture that has received considerable attention from the pharmacological point of view[9-11]. A sample of this substituted D-glucoside* was found to be readily debenzylated with 1,2-ethanedithiol and boron trifluoride, giving D-glucose ethylene dithioacetal (2). It is suggested that this procedure may prove a convenient means for the identification of this amorphous drug (7).

The cleavage of benzyl ethers by catalytic hydrogenation was first used in the carbohydrate field by K. Freudenberg and his associates[12] in 1928, and it remains today a synthetic tool of prime importance[13]. Other methods for removing *O*-benzyl groups from carbohydrate moieties have been devised in recent years: acetolysis[14], sodium in liquid ammonia[15], and bromination–hydrolysis[16] may be mentioned. The thiolysis described here constitutes yet another debenzylation procedure.

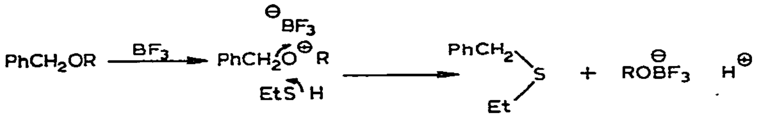
In considering the mechanism of this debenzylation, it should first be noted that the thiols, as well as the boron trifluoride, were used in substantial molar excess over the benzyl ethers taken. The nature of the noncarbohydrate products from the reactions suggests that a sulfur-bearing entity attacks the benzyl group, and it may not be unreasonable to assume that the initial function of the boron trifluoride is to facilitate the heterolysis of the benzyl–oxygen bond, as shown in Equation *1*. (The radical R in this and succeeding equations represents a carbohydrate residue.) The availability of the electrons in a sulfide should permit the benzyl ethyl sulfide that is formed to repeat the attack on another benzyl ether grouping with even greater facility (Equation *2*). The dibenzylethylsulfonium cation thus formed would be balanced by an anion that would be decomposed by water to give boron trifluoride. The latter is hydrolyzed further to tetrafluoroboric acid and orthoboric acid (Equation *3*)[17]; the sulfonium cation is then isolated in combination with the stronger acid, namely, HBF_4.

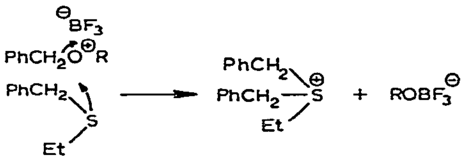
For the debenzylations involving 1,2-ethanedithiol, there must be envisaged a somewhat modified mechanism, inasmuch as the two-carbon fragment was not found among the products isolated. As a first step, we may envisage the process shown by Equation *4*, analogous to the reaction postulated for the monothiol (Equation *1*). The 2-(benzylthio)ethanethiol formed should readily undergo an intramolecular, boron trifluoride-assisted elimination to form ethylene sulfide, as shown in Equation *5*, and this compound (b.p. 54°) would have been lost when the reaction mixture was

---

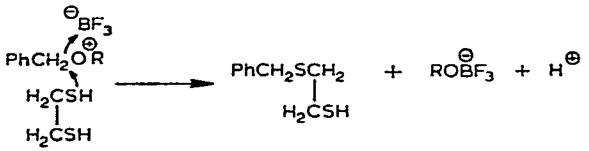
*Kindly provided by Dr. Hans Heymann.

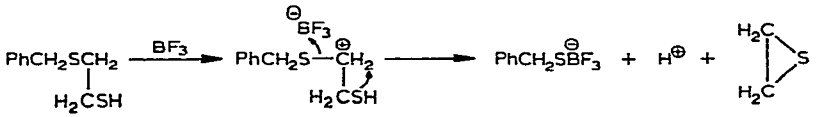
concentrated *in vacuo*. Finally, the α-toluenethiol adduct of boron trifluoride, postulated as a product in Equation *5*, would dissociate as shown in Equation *6*, providing the free thiol, which would continue the debenzylation process in a manner analogous to that postulated for ethanethiol — leading to benzyl sulfide (**3**) and, ultimately, to tribenzylsulfonium tetrafluoroborate (**4**). Such sulfonium salts as **4** may be expected to decompose in water to give benzyl sulfide and benzyl alcohol[18]; thus, the benzyl sulfide encountered in the debenzylation of **1** with 1,2-ethanedithiol may have arisen through **4**, rather than more directly as shown in Equation *5*.


(1)


(2)

$$4BF_3 + 3H_2O \longrightarrow 3HBF_4 + H_3BO_3 \qquad (3)$$


(4)


(5)

$$PhCH_2S\overset{\ominus}{B}F_3 + H^{\oplus} \longrightarrow PhCH_2SH + BF_3 \qquad (6)$$

However, neither benzyl sulfide nor benzyl ethyl sulfide was isolated from debenzylations where ethanethiol was used. In any case, it should be emphasized that the work described here is of an exploratory nature. A more thorough analysis of the non-carbohydrate products would doubtless yield data of significance to interpretation of the mechanism of these reactions. In addition, it seems likely that other allylic-type ethers would be cleaved under the conditions described here.

EXPERIMENTAL

General. — Melting points are equivalent to corrected values. T.l.c. was conducted on Silica Gel G_{254}, components being detected by viewing under a Gelman–Camag universal ultraviolet lamp, and also by heating after spraying with 10% sulfuric acid.

The debenzylation of 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose (**1**) *with 1,2-ethanedithiol and boron trifluoride etherate.* — A mixture of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose[19] (**1**, 1.0 g, 1.85 mmoles) and 1,2-ethanedithiol (1 ml, 11.88 mmoles) was cooled in an ice bath and then diluted with boron trifluoride etherate (1 ml, 7.93 mmoles), and the mixture was stirred at 0° until dissolution was complete (15 min). The progress of the reaction was followed by t.l.c. (1:4 ether–benzene); after 6 h, **1** was no longer detectable, and the mixture appeared to contain two components. The solution was concentrated *in vacuo* (water pump) at room temperature, and the residue was diluted with dichloromethane and then extracted with four 10-ml portions of water. The aqueous extracts were combined and filtered through a little decolorizing carbon (to remove turbidity). T.l.c. showed that the filtrate contained one component; it was evaporated *in vacuo* at 31° (bath) to a thick syrup which was dissolved in absolute ethanol (4 ml). On being cooled to $-5°$, the solution afforded a crystalline product (0.2 g); a second crop was obtained, increasing the yield to 0.3 g (63%). After recrystallization from absolute ethanol, the product was obtained as needles, $[\alpha]_D^{20}$ $-10.0°$ (*c* 1.2, water), m.p. 146–147°; a mixed melting point with an authentic sample of D-glucose ethylene dithioacetal[3] (**2**) was undepressed.

The dichloromethane solution which had been extracted with water was evaporated *in vacuo* to a solvent-free syrup that was examined by t.l.c. (1:4 ether–benzene); two components, of widely differing R_F value, were present. Isopropyl ether (10 ml) was added to the syrup, and the mixture was warmed briefly and then cooled to 0°, and the isopropyl ether was decanted; this extraction was repeated four times, and the extracts were combined. T.l.c. then showed that the fast-moving component was in the isopropyl ether solution, and the slow-moving component was in the residual syrup. The isopropyl ether solution was concentrated *in vacuo* to a syrup which was dissolved in isopropyl ether (0.5 ml); the resulting solution was cooled to $-5°$ and kept overnight, depositing crystalline material (20 mg) which had m.p. 48–49°, undepressed on admixture with an authentic sample of benzyl sulfide (**3**). The material remaining after concentration of the mother liquor (0.4 g) was examined by t.l.c. (1:4 ether–benzene) and found to be homogeneous and chromatographically indistinguishable from benzyl sulfide.

The residual syrup (that had been extracted with isopropyl ether) was dissolved in dichloromethane (10 ml), and the solution was filtered through a very small amount of decolorizing carbon, and evaporated *in vacuo* to a heavy syrup which was dissolved in methanol (4 ml). The solution was cooled to $-5°$, and crystalline material (80 mg) was deposited; after recrystallization from warm methanol, the material (50 mg) had m.p. 173–174°. Prepared thus, the material was chromatographically homogeneous; its i.r. absorption spectrum (Nujol mull) and chromatographic behavior were indistinguishable from those of an authentic sample of tribenzylsulfonium tetrafluoroborate (**4**), prepared as described next.

Tribenzylsulfonium tetrafluoroborate (**4**). — To a cold solution of benzyl sulfide (1.0 g) in a mixture of benzyl bromide (0.56 ml) and dichloromethane (10 ml) was added silver tetrafluoroborate (0.91 g). The mixture was stirred for 0.5 h at room temperature, and the solid was then removed by filtration on a bed of Filter-Cel and decolorizing carbon. T.l.c. (1:4 ether–benzene) revealed the presence of two components having markedly different R_F values. The filtrate was concentrated *in vacuo* to give a crystalline mass which was extracted with isopropyl ether. The crystalline residue (1.1 g) proved to be the slower-moving component noted by t.l.c.; it was recrystallized from acetone at −5° to give 0.35 g (34%, based on benzyl sulfide), m.p. 169–171°. After a further recrystallization, from methanol, the compound was obtained as plates (0.25 g), m.p. 173–174°; its p.m.r. spectrum ($CDCl_3$ solution, 100 MHz) contained but two signals, at τ 2.66 (aromatic protons) and 5.37 (benzylic protons). The ratio of the strengths of the two signals was 2.51:1. On combustion, the compound showed the transient, green flame characteristic of boron compounds.

Anal. Calc. for $C_{21}H_{21}BF_4S$: C, 64.30; H, 5.40; S, 8.17. Found: C, 64.45; H, 5.37; S, 8.23.

The debenzylation of 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose (**1**) *with ethanethiol and boron trifluoride.* — A mixture of **1** (4.0 g, 7.4 mmoles) and ethane thiol (3.56 ml, 48 mmoles) was stirred in a flask partially immersed in a water bath at room temperature while boron trifluoride etherate (4.0 ml, 31.7 mmoles) was added. The solid dissolved after ~1 min, the mixture becoming yellow, and then, after ~30 min, purplish. After the reaction mixture had been kept for 3 h at room temperature, it was examined by t.l.c. with 1:4 ether–benzene; only a single component was detected. The reaction mixture was evaporated *in vacuo* at room temperature, the residual syrup was dissolved in water (150 ml), and the solution was extracted with five 20-ml portions of dichloromethane; the extracts were combined, dried (magnesium sulfate), and filtered through a thin layer of carbon. The filtrate was evaporated *in vacuo* to a syrup (5.6 g) which was dissolved in warm ethanol (15 ml). On cooling, the solution deposited crystals; after storage overnight at −5°, these were removed by filtration and washed with cold ethanol: 3.9 g, m.p. 93–94°. On recrystallization from absolute ethanol (4 ml/g), dibenzylethylsulfonium tetrafluoroborate (**6**) was obtained in pure form, m.p. 94–95°.

The p.m.r. spectrum of **6** ($CDCl_3$, 60 MHz) included signals at τ 2.56 (multiplet, aromatic protons), 6.67 (quartet, CH_2 of ethyl group), and 8.89 (triplet, CH_3).

Anal. Calc. for $C_{16}H_{19}BF_4S$: C, 58.20; H, 5.80; F, 23.02; S, 9.71. Found: C, 58.09; H, 5.57; F, 23.71; S, 9.60.

A solution of salt **6** in dilute, aqueous acetic acid was treated with a solution of Nitron in acetic acid. The precipitate thus obtained consisted of rod-like needles, m.p. 231–232°; Nitron tetrafluoroborate is reported[5] to have m.p. 224.5° (uncorr.). Potassium nitrate was added to the filtrate, and the Nitronium nitrate precipitated was removed by filtration. Potassium iodide and mercuric iodide were added to the filtrate, which was then evaporated to dryness. Extraction of the residue with acetone afforded a product that crystallized from acetone; it had m.p. 112–114°, and its elemental composition (carbon and hydrogen) corresponded satisfactorily with that calculated for $(PhCH_2)_2EtS \cdot HgI_3$. Hilditch and Smiles[6] reported m.p. 115° for this compound.

The original aqueous solution (which had been extracted with dichloromethane as described earlier) was evaporated *in vacuo*, and the resulting syrup was dissolved in absolute ethanol (1 ml). The solution was kept overnight at −5°, and a small quantity (0.12 g) of solid was removed by filtration but not further investigated. The filtrate was evaporated *in vacuo* to a syrup (3.0 g) which was acetylated with acetic anhydride–pyridine. Conventional removal of the excess of the reactants afforded a syrup which was dissolved in isopropyl alcohol (5 ml); on storage at −5°, the solution deposited crystals (0.7 g), m.p. 65–74°. Successive recrystallization of this product from isopropyl alcohol and from isopropyl ether failed to narrow its melting-point range significantly, and yielded a heterogeneous product having $[\alpha]_D^{20}$ +98.8° (*c* 3.5, chloroform) and the elemental composition calculated for an ethyl tetra-*O*-acetylthiohexoside (**5**). A sample (200 mg) of the material was dissolved in absolute ethanol (10 ml), and the solution was treated with half a teaspoonful of fresh Raney nickel. The suspension was stirred overnight at room temperature and was then boiled for 1 h under reflux. Examination by t.l.c. (1:4 ether–benzene) showed that the desulfurization was incomplete. A second batch (0.5 teaspoonful) of catalyst was added, and the suspension was boiled under reflux for a further 1 h; t.l.c. then showed the reaction to be virtually complete. The mixture was filtered on a thin bed of decolorizing carbon and Filter-Cel, and the filtrate was evaporated *in vacuo* to a syrup which was treated overnight with a mixture of pyridine and acetic anhydride; the mixture was processed in the usual way, to give a syrup (70 mg) which crystallized from its solution in isopropyl alcohol, affording prismatic needles (60 mg) that had $[\alpha]_D^{20}$ +38.2° (*c* 1.19, chloroform) and m.p. 72–73°, undepressed on admixture with an authentic sample of 2,3,4,6-tetra-*O*-acetyl-1,5-anhydro-D-glucitol[4] (**8**).

*The debenzylation of 1,3,4,6-tetra-*O*-benzyl-D-mannitol* (**9**) *with ethanethiol and boron trifluoride.* — A mixture of 1,3,4,6-tetra-*O*-benzyl-D-mannitol[7] (**9**, 150 mg), ethanethiol (0.14 ml), and boron trifluoride etherate (0.15 ml) was stirred at room temperature until homogeneous. After 2 h, t.l.c. (1:4 ether–benzene) of the slightly yellow mixture showed the absence of starting material and the presence of what appeared to be a single product having a much lower R_F value. The mixture was evaporated *in vacuo* at room temperature to a pale-yellow syrup, water (15 ml) was added, and the mixture was extracted with five 7-ml portions of dichloromethane. The extracts were combined, dried (magnesium sulfate), and evaporated *in vacuo* to a syrup (150 mg) which crystallized on standing. Isopropyl alcohol (4 ml) was added, the mixture was kept overnight at room temperature, and the crystals were removed by filtration. The crystals (130 mg) had m.p. 89–92°; one recrystallization from absolute ethanol (6 ml/g) raised the m.p. to 93–94°, and this value was not changed on admixture of the material with dibenzylethylsulfonium tetrafluoroborate (**6**) obtained in the debenzylation of **1**.

The aqueous solution (remaining after the extraction with dichloromethane) was evaporated *in vacuo* to a syrup to which two portions of absolute ethanol were added and evaporated. The product crystallized spontaneously; it was recrystallized from absolute ethanol (1 ml): m.p. 165–166° (alone or in admixture with authentic

D-mannitol), $[\alpha]_D^{20}$ +135.5° (*c* 1.08, acidified ammonium molybdate)[20]. The yield was quantitative.

*The debenzylation of ethyl 3,5,6-tri-*O*-benzyl-*D*-glucofuranoside* (**7**) *with ethanethiol and boron trifluoride.* — A mixture of **7** (1.0 g) and 1,2-ethanedithiol (1 ml) was kept in an ice bath and stirred, while boron trifluoride etherate (1 ml) was added. After 30 min, the mixture was found to be unchanged (t.l.c., 1:4 ether–benzene), and it was therefore warmed to room temperature. The progress of the reaction was monitored by t.l.c. (1:4 ether–benzene) and, after a total reaction time of 2 h, the mixture was concentrated *in vacuo* at room temperature. Water (25 ml) was added to the residual syrup, and the mixture was washed with five 10-ml portions of dichloromethane. The aqueous solution was filtered through a very small quantity of decolorizing carbon, and the filtrate was evaporated at 32° (bath) to a syrup which was dissolved in absolute ethanol (5 ml). The slightly turbid solution was filtered through a very small quantity of decolorizing carbon, and the filtrate was kept overnight at −5°, to yield prismatic crystals of D-glucose ethylene dithioacetal (**2**): 270 mg (50%), m.p. 137–140°. After two recrystallizations from hot ethanol, the product was obtained as heavy needles: 220 mg, m.p. 145–146°. The melting point of a mixture of the product with an authentic specimen of **2** was undepressed.

ACKNOWLEDGMENTS

We thank Dr. L. A. Cohen of this laboratory for stimulating discussions of the mechanistic aspects of the reactions described. We are also indebted to Mrs. Anne H. Wright and Mr. E. A. Sokoloski for recording the p.m.r. spectra. Elemental analyses were performed by the staff of the Section on Microanalytical Services and Instrumentation of this Institute.

REFERENCES

1 H. G. FLETCHER, JR., AND H. W. DIEHL, *J. Org. Chem.*, 30 (1965) 2321.
2 *Cf.* C. DJERASSI, *Steroid Reactions*, Holden–Day, San Francisco, 1963, p. 22 *et seq.*
3 W. T. LAWRENCE, *Ber.*, 29 (1896) 548; B. GAUTHIER AND C. VANISCOTTE, *Bull. Soc. Chim. Fr.*, (1956) 30.
4 N. K. RICHTMYER AND C. S. HUDSON, *J. Amer. Chem. Soc.*, 65 (1943) 64.
5 W. LANGE, *Ber.*, 59 (1926) 2107.
6 T. P. HILDITCH AND S. SMILES, *J. Chem. Soc.*, 91 (1907) 1394.
7 R. K. NESS, H. W. DIEHL, AND H. G. FLETCHER, JR., *Carbohyd. Res.*, 13 (1970) 23.
8 G. HUBER AND A. ROSSI, *Helv. Chim. Acta*, 51 (1968) 1185.
9 R. JAQUES, G. HUBER, L. NEIPP, A. ROSSI, B. SCHÄR, AND R. MEIER, *Experientia*, 23 (1967) 149.
10 W. C. DICK, G. M. CUNNINGHAM, G. NUKI, M. K. JASANI, AND K. WHALEY, *Ann. Rheum. Dis.*, 28 (1969) 187.
11 *Rote Liste, 1969*, ed. Bundesverband der Pharmazeutischen Industrie, Editio Cantor, Aulendorf/Wurtt., p. 525.
12 K. FREUDENBERG, W. DÜRR, AND H. VON HOCHSTETTER, *Ber.*, 61 (1928) 1735.
13 *Cf.* C. M. MCCLOSKEY, *Advan. Carbohyd. Chem.*, 12 (1957) 137.
14 R. ALLERTON AND H. G. FLETCHER, JR., *J. Amer. Chem. Soc.*, 76 (1954) 1757.
15 E. J. RIST, V. J. BARTUSKA, AND L. GOODMAN, *J. Org. Chem.*, 29 (1964) 3725.
16 J. N. BEMILLER, R. E. WING, AND C. Y. MEYERS, *J. Org. Chem.*, 33 (1968) 4292.

17 H. S. Booth and D. R. Martin, *Boron Trifluoride and its Derivatives*, John Wiley & Sons, New York, 1949, p. 87.

18 *Cf.* J. Goerdler, in E. Müller (Ed.), *Methoden der organischen Chemie*, Vol. 9, Georg Thieme, Stuttgart, 1955, p. 190.

19 O. T. Schmidt, T. Auer, and H. Schmadel, *Chem. Ber.*, 93 (1960) 556.

20 N. K. Richtmyer and C. S. Hudson, *J. Amer. Chem. Soc.*, 73 (1951) 2249.