Carbohydrate Research, 61 (1978) 511–518

SELECTIVE REPLACEMENT OF PRIMARY HYDROXYL GROUPS IN CARBOHYDRATES: PREPARATION OF SOME CARBOHYDRATE DERIVATIVES CONTAINING HALOMETHYL GROUPS*†

ABUL KASHEM M. ANISUZZAMAN AND ROY L. WHISTLER
Department of Biochemistry, Purdue University, West Lafayette, Indiana 47907 (U.S.A.)
(Received August 4th, 1977; accepted for publication, September 28th, 1977)

ABSTRACT

Selective halogenation of hydroxymethyl groups in sugars and nucleosides has been achieved by use of triphenylphosphine and carbon tetrahalides (chloride, bromide, or iodide) in pyridine. Methyl α-D-glucopyranoside, 1,2-*O*-isopropylidene-α-D-glucofuranose, inosine, and uridine give almost quantitative yields of their primary halomethyl analogs. Similarly, 6,6′-dichloro-6,6′-dideoxysucrose is prepared from sucrose. Chlorination and bromination of 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose by these reagents give 6-chloro-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose and 6-bromo-6-deoxy-1,2-*O*-iso-propylidene-α-D-glucofuranose, respectively.

INTRODUCTION

Deoxyhalogeno sugars constitute an important and versatile class of compounds for potential application in synthesis of other carbohydrate derivatives[1,2]. The carbon–halogen bond is susceptible to attack by a nucleophile, and products arising from substitution, elimination, or anhydro-ring formation may be processed further, giving rise to useful compounds[3–8]. The ease of displacement by a nucleophile is in the order I > Br > Cl > F, making iodo and bromo derivatives more reactive than the chloro analogs, but as the chloro compounds are easier to obtain, all three types find equal synthetic utility. A variety of reagents[9–16] is available for the direct replacement of a hydroxyl group by a halogeno substituent. Methanesulfonyl chloride in *N*,*N*-dimethylformamide[17] or triphenylphosphine and *N*-halosuccinimide in *N*,*N*-dimethylformamide[18–20] are reported to effect halogenation only at the primary hydroxyl group. Edwards and coworkers[21], however, found that with methanesulfonyl chloride–*N*,*N*-dimethylformamide, halogenation of the secondary hydroxyl groups also takes place. The use of triphenylphosphine–*N*-halosuccinimide–*N*,*N*-dimethylformamide as the reagent gives low yields in many instances[19,20] and for a

---

*Dedicated to Professor Dexter French on the occasion of his 60th birthday.

†Journal Paper No. 6827 of the Purdue University Agricultural Experiment Station.

number of nucleosides the method is not selective[19]. Moreover, acetal migration can occur[19] with this reagent and purification steps may involve further chemical modifications[19,20]. To circumvent these difficulties, we have developed an alternative but efficient method for selective halogenation of primary hydroxyl groups.

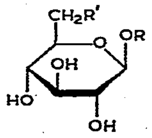
DISCUSSION

Mixtures of triarylphosphines with carbon tetrahalides are found useful for replacing both primary and secondary hydroxyl groups by halogens[22–25] and, in the absence of neighboring-group participation, inversion occurs at the carbon atoms bearing a hydroxyl group[26]. Although verification is still lacking, it has been assumed that halogenation with these reagents proceeds via the mechanism shown[22].

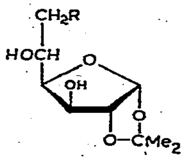
$$Ar_3P\colon XCX_3 \rightarrow [Ar_3P^+\text{-}CX_3X^-] \xrightarrow{ROH} CHX_3 + Ar_3P^+\text{-}O\text{-}R\ X^- \rightarrow Ar_3PO + RX$$

As the reaction is generally performed at room or higher temperatures, the reaction was examined to determine whether some measure of selectivity might occur if the reactions were conducted at lower temperatures.

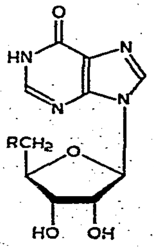
Initially, experiments were tried with the readily available methyl α-D-glucopyranoside (**1**) in pyridine at 5° by the use of one molar equivalent of both triphenylphosphine and carbon tetrachloride, as indicated in the projected mechanism. Pyridine was selected as the medium because of its excellent solvent properties and



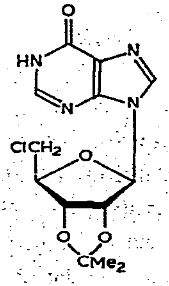
1 R = OMe, R′ = OH
2 R = OMe, R′ = Cl
3 R = OMe, R′ = Br
4 R = OMe, R′ = I
8 R = OH, R′ = Cl (α anomer)

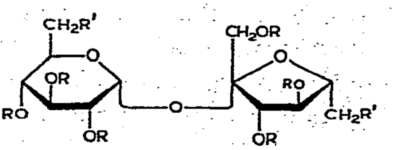


5 R = OH
6 R = Cl
7 R = Br

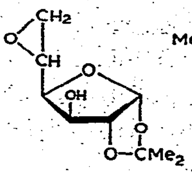


9 R = OH
10 R = Cl

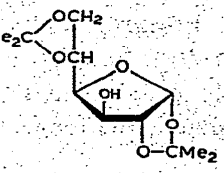




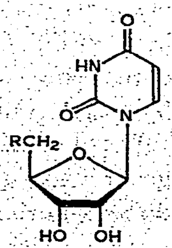
12 R = H, R′ = OH
13 R = H, R′ = Cl
14 R = Bz, R′ = Cl



15



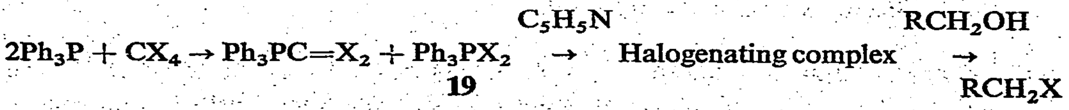
16



17 R = OH
18 R = Cl

its volatility. T.l.c. of the mixture with solvent *A* showed two spots, one corresponding to methyl 6-chloro-6-deoxy-α-D-glucopyranoside (**2**) and the other to the starting glycoside **1**. Column-chromatographic separations gave **2** in 49% yield and no enhancement of yield or formation of any other compound was observed by prolonging the reaction time. However, if the proportion of triphenylphosphine was changed to two molar equivalents, an almost quantitative yield of **2** was obtained. Similar results were also obtained at higher temperatures; at 65° the halogenation was selective and complete within a few min.

Subsequent experiments with carbon tetrabromide or carbon tetraiodide in place of carbon tetrachloride gave methyl 6-bromo-6-deoxy-α-D-glucopyranoside (**3**), and methyl 6-iodo-6-deoxy-α-D-glucopyranoside (**4**), respectively. In these halogenation reactions, the aforementioned selectivity and dependence of yield on the proportion of triphenylphosphine in relation to carbon tetrahalide was observed (see Table I). These results clearly demonstrate that combinations of two molar equivalents of triphenylphosphine with one molar equivalent of carbon tetrahalide in pyridine are excellent reagents for the selective halogenation of primary hydroxyl groups. It is further evident that, in pyridine at least, halogenation with these reagents proceeds by a mechanism different from that written earlier. A more-probable course for halogenation might be via the initial formation of a triphenylphosphine dihalide **19** (X = Cl, Br, or I) to produce a bulky halogenating complex involving the solvent:



$$2Ph_3P + CX_4 \rightarrow Ph_3PC{=}X_2 + \underset{\mathbf{19}}{Ph_3PX_2} \xrightarrow{C_5H_5N} \text{Halogenating complex} \xrightarrow[RCH_2X]{RCH_2OH}$$

The formation of **19** (X = Br) from the reaction of 2 mol of triphenylphosphine and one mol of carbon tetrabromide is known[27], and the usefulness of triphenylphosphine dibromide as a reagent for bromination through complexation with *N*,*N*-dimethylformamide has been reported[28].

To determine the general usefulness of the halogenation procedure, it was extended to a variety of polyhydroxy compounds. Each compound examined could be converted into the primary halide in excellent yield, provided optimum proportions of the reactants were used. The n.m.r. spectrum of 6-chloro-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**6**), obtained as a crystalline solid from the chlorination of 1,2-*O*-isopropylidene-α-D-glucofuranose (**5**) showed the H-1, H-2, and H-6 (Ha and Hb) signals as doublets ($J_{1,2}$ 3.5 Hz, $J_{5,6}$ 3 Hz) at τ 4.12, 5.52, and 6.22, respectively, and the two sets of methyl protons gave peaks at τ 8.57 and 8.65. The foregoing n.m.r.-spectral parameters were consistent with structure **6**, and these data resembled the recorded values for similarly constituted molecules[23,29]. The two hydroxyl resonances appeared at τ 6.82 and 6.85 and disappeared on exchange with deuterium oxide. Further proof for structure **6** was provided by hydrolysis with aqueous sulfuric acid to the known 6-chloro-6-deoxy-D-glucose[30] (**8**). The n.m.r. spectrum of 6-bromo-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**7**), also obtained as a crystalline solid from **5**, showed features similar to those for **6** and its other properties

TABLE I

REACTION CONDITIONS FOR HALOGENATION

Starting compound, (5 mmol)	*Triphenylphosphine (mmol)*	*Carbon tetrahalide (5 mmol)*	*Temperature (°)*	*Time (h)*	*Solvent for chromatography*[a]	*Product*	*Yield (percent)*
1	5	CCl_4	5	18	*E*	**2**	49
1	5	CCl_4	5	36	*E*	**2**	49
1	10	CCl_4	5	18	*E*	**2**	98
1	10	CCl_4	25	18	*E*	**2**	98
1	10.5	CCl_4[b]	65	0.2	*E*	**2**	98
1	5	CBr_4	5	18	*E*	**3**	48
1	10	CBr_4	60	0.2	*E*	**3**	98
1	5	CI_4	25	18	*E*	**4**	48
1	10	CI_4	25	18	*E*	**4**	97
5	10	CCl_4	5	20	*F*	**6**	96
5	10	CBr_4	60	0.15	*F*	**7**	95
9	10	CCl_4	65	0.2	*C*	**10**	94
12	30	CCl_4[c]	70	2	*C*	**13**	92
15	10	CCl_4	60	1	*F*	**6**	75
15	10	CBr_4	60	1	*F*	**7**	80
16	10	CCl_4	60	1		No reaction	
16	10	CCl_4	25	18		No reaction	
17	10	CCl_4	25	18	*E*	**18**	92

[a]See Experimental section. [b]5.2 mmol. [c]15 mmol.

are identical to those recorded for a sample of **7** prepared by a different route[31]. The ready preparation of **6** and **7** in high yield is of considerable synthetic importance because **7** (and possibly **6**) is the precursor[32] for 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose (**13**), which itself is a valuable intermediate in synthesis[33].

5′-Haloribonucleosides are useful precursor for the synthesis of nucleotides[34], anhydronucleosides[35], sulfur analogs[36], deoxynucleosides[37], and cobalamin analogs[38]; introduction of a halogen atom at the 5′-position is therefore of particular importance. Previous attempts[39] to prepare 5′-chloroinosine (**10**) by the hydrolysis of 5′-chloro-5′-deoxy-2′,3′-*O*-isopropylideneinosine (**11**) resulted in the formation of a syrup for which no analytical data or physical constants were given. However, by using the present method, crystalline **10** was obtained in high yield by direct chlorination of inosine (**9**). Similarly, uridine was converted into the known 5′-chloro-5′-deoxyuridine[24]. The n.m.r. spectrum of **10** showed the anomeric-proton signal as a doublet at τ 4.12 ($J_{1,2}$ 5.5 Hz), the H-2′ signal as a triplet at τ 5.4 ($J_{2,3}$ 6.5 Hz), and the H-2 and H-8 resonances at τ 1.8 and 2.0, respectively. Conclusive proof for the location of the chlorine atom was obtained by preparing 5′-chloro-5′-deoxy-2′,3′-*O*-isopropylideneinosine (**11**) by the reaction of **10** with acetone containing *p*-toluenesulfonic acid and 2,2-dimethoxypropane. Under these conditions, the yield of **17** was high, but no reaction took place if 2,2-dimethoxypropane was excluded from the mixture.

There has been considerable recent interest in the synthesis of sucrose derivatives modified at the primary positions[40]. Preparation of halogeno derivatives has been achieved by multistep reactions[41]. Work indicates[40a,42] that, of the three primary sites, reactions take place more readily at the 6,6′-positions than at the 1′-position. It was anticipated that, by the present method, the reaction of sucrose (**12**) with triphenylphosphine–carbon tetrachloride in pyridine might effect chlorination at the 6 and 6′ positions. This expectation was borne out when 6,6′-dichloro-6,6′-dideoxysucrose (**13**) was obtained in high yield. The easy, one-step preparation of **13** offers a simple route for preparation of other sucrose derivatives modified at the 6 and 6′ positions. These results further indicate that the halogenating species might be quite bulky, thus preventing halogenation not only of the secondary hydroxyl groups but also of the primary 1′-position. The physical constants of **13** and its hexabenzoate **14** are in agreement with those recorded[40b].

Isaacs and Kirkpatrick reported[43] the formation of *cis*-1,2-dichloro compounds from the reaction of epoxides with triphenylphosphine in carbon tetrachloride. It is assumed that the epoxide ring is opened by the chloride anion of $Ph_3P^+CCl_3Cl^-$ (initially formed from triphenylphosphine and carbon tetrachloride) with simultaneous bond-formation between the epoxide oxygen atom and phosphorus.

To examine whether the course of halogenation of oxiranes by triphenylphosphine–carbon tetrahalide reagents is influenced by solvents, 5,6-anhydro-1,2-*O*-isopropylidene-α-D-glucofuranose (**15**) was treated separately in pyridine with triphenylphosphine–carbon tetrachloride and triphenylphosphine–carbon tetrabromide. From these reactions, 6-chloro-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**6**) and 6-bromo-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (**7**) were isolated in high yield.

The results indicate that halogenation of the epoxide with triphenylphosphine–carbon tetrahalide in pyridine does not follow the mechanism suggested[43]. Had it done so, elimination of the epoxide oxygen atom would be expected, in view of the strong affinity of phosphorus for oxygen. The products **6** and **7** are possibly formed from **15** through nucleophilic attack by a halide anion at the sterically available C-6 without bond formation between the epoxide oxygen atom and phosphorus.

Previous efforts to halogenate the 3-hydroxyl group of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**16**) by the use of triphenylphosphine-based reagents have led to acetal migration, culminating in the formation of 6-deoxy-6-halo-1,2:3,5-di-*O*-isopropylidene α-D-glucofuranoses[19,23,29]. To examine if acetal migration would take place under the present halogenating conditions, **18** was treated with triphenylphosphine with carbon tetrachloride. Thin-layer chromatograms of reaction mixtures with 20:1 chloroform–acetone showed no change in **16**, and thus not migration of acetal groups occurred under the conditions chosen.

EXPERIMENTAL

General methods. — Purity of products was determined by t.l.c. on glass plates coated with silica gel GF-254 (E. Merck, Darmstadt, Germany) and irrigated with *A*, 6:1 chloroform–methanol, *B*, 9:2 chloroform–acetone, *C*, 45:5:3 ethyl acetate–ethanol–water, and *D*, 20:1 chloroform–acetone. Components were located by spraying the plates with 5% sulfuric acid in ethanol and heating or by viewing under a short-wavelength u.v. lamp. Column chromatography was performed on silica gel powder (J. T. Baker Chemical Co.). Columns were eluted with *E*, 20:1 chloroform–methanol, *F*, 6:1 chloroform–acetone, *G*, 3:1 hexane–ethyl acetate, and *C*. Optical rotations were measured with a Perkin–Elmer model 141 polarimeter and n.m.r. spectra were recorded with a Varian T60A spectrometer with tetramethylsilane as the internal standard. Evaporations were conducted under diminished pressure with a bath temperature below 40°.

General procedure. — The polyhydroxy compound was dissolved in pyridine (0.1 g/5–10 ml) by stirring at 25° or at boiling temperature. The solution was cooled to 0° and triphenylphosphine was added, followed by the addition at 0° of carbon tetrahalide in several portions. The resulting mixture was protected from moisture and stirred where precipitation occurred. After keeping the mixture at the desired temperatures for the required length of time, methanol (10 ml/1 g of hydroxyl compound) was added to decompose any excess of reagent. Solvent was removed by evaporation and the residue was chromatographed on silica gel. Non-carbohydrate material was removed by elution with chloroform, and further elution with *C*, *E*, or *F* gave the pure halogeno derivatives. Data related to the proportions of the reactants, yields of products, and reaction conditions are given in Table I.

Methyl 6-chloro-6-deoxy-α-D-glucopyranoside (**2**). — The glycoside **2** was a white crystalline solid; m.p. 111–112° after crystallization from chloroform–hexane; $[\alpha]_D^{25}$ +153° (*c* 1, methanol) (lit.[44] m.p. 110–112°, $[\alpha]_D$ +139° in water).

Methyl 6-bromo-6-deoxy-α-D-glucopyranoside (**3**). — The glucoside **3** was a white solid, m.p. 130° after crystallization from chloroform–hexane; $[\alpha]_D^{25}$ +125.2° (*c* 1, methanol) (lit.[44] m.p. 129–130°, $[\alpha]_D$ +107.4° in water).

Methyl 6-deoxy-6-iodo-α-D-glucopyranoside (**4**). — The glucoside **4** was a white solid, m.p. 148° after crystallization from chloroform–hexane, $[\alpha]_D^{25}$ +107.8° (*c* 1, methanol) (lit.[45] m.p. 148° $[\alpha]_D$ +99° in water).

6-Chloro-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (**6**). — Compound **6** was obtained from **5** or **15** as a crystalline solid, m.p. 80° after crystallization from ether–hexane; $[\alpha]_D^{25}$ −11° (*c*, 2, chloroform); n.m.r. in $CDCl_3$ see Discussion.

Anal. Calc. for $C_9H_{15}ClO_5$: C, 45.29; H, 6.33; Cl, 14.85. Found: C, 45.17; H, 6.51; Cl, 14.69.

6-Chloro-6-deoxy-D-glucose (**8**). — A mixture of **6** (240 mg) and 15 ml of 0.5M sulfuric acid was stirred for 5 h at 70°. T.l.c. with solvent *A* indicated complete conversion of **6** into **8**. The acid was neutralized with IR-45 (OH^-) resin and the mixture was filtered. Evaporation of the filtrate gave **8** (180 mg) as a syrup that crystallized on keeping. After crystallization from ethanol, **8** had m.p. 137°, $[\alpha]_D^{25}$ + 96 → +51° (20 h, *c* 1, water) (lit.[30] m.p. 135–136°, $[\alpha]_D$ 95.8 → 51.1° in water).

6-Bromo-6-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (**7**). — Compound **7** was obtained from **4** or **15** as a white crystalline solid, m.p. 87° after crystallization from ether–hexane; $[\alpha]_D^{25}$ $-13.2°$ (*c* 1, water), n.m.r. in $CDCl_3$: τ 4.1 (d, H-1, $J_{1,2}$ 3.75 Hz), 5.52 (d, H-2), 6.37 (d, 2H-6, $J_{5,6}$ 3 Hz), 6.82 (broad, 3-OH and 5-OH), 8.5, 8.7 (CMe_2). (Lit.[32] m.p. 87°, $[\alpha]_D^{20}$ $-13.1°$ in water).

5'-Chloro-5'-deoxyinosine (**10**). — Compound **10** was obtained from **9** as a white crystalline solid, m.p. 191° after crystallization from methanol; $[\alpha]_D^{25}$ $-47.5°$ (*c* 1, dimethyl sulfoxide); n.m.r. in dimethyl sulfoxide-d_6, see Discussion.

Anal. Calc. for $C_{10}H_{11}ClN_4O_4$: C, 41.89; H, 3.87; Cl, 12.37, N, 19.54. Found: C, 42.10, H, 4.11; Cl, 12.60; N, 19.30.

5'-Chloro-5'-deoxy-2,3-O-isopropylideneinosine (**11**). — A mixture of **10** (140 mg) in 30 ml of acetone containing *p*-toluenesulfonic acid (100 mg) and 2,2-dimethoxypropane (15 ml) was stirred for 2 h at 25°. T.l.c. with solvent *C* indicated complete conversion of **10** into **11**. *p*-Toluenesulfonic acid was neutralized with an excess of sodium hydrogencarbonate and the mixture was filtered. Evaporation of the filtrate gave **11** (140 mg, 87.5%) as a crystalline solid, m.p. 201° after crystallization from methanol (lit.[24] m.p. 201–201.5°).

In the absence of 2,2-dimethoxypropane, the foregoing reaction did not occur.

5'-Chloro-5'-deoxyuridine (**18**). — The chloro compound **18** obtained from **17** had m.p. 172–174° (lit.[12] m.p. 170–172°).

6,6'-Dichloro-6,6'-dideoxysucrose (**13**). — The dichloro derivative **13** obtained from sucrose (**12**) had m.p. 82–85° after crystallization from butanone; $[\alpha]_D^{25}$ $+60°$ (*c* 1, water) (lit.[40b] m.p. 85–88°, $[\alpha]_D^{25}$ $+60°$ in water).

2,3,4,1',3',4'-Hexa-O-benzoyl-6,6'-dichloro-6,6'-dideoxysucrose (**14**). — Benzoyl chloride (5 ml) was added to a solution of **13** (190 mg) in 20 ml of pyridine. After keeping the mixture for 40 h at 25°, solvent was removed by evaporation. The syrupy residue was treated with saturated sodium hydrogencarbonate solution and extracted with chloroform. Evaporation of the dried extract gave a syrup that was purified by chromatography on silica gel. Elution with 20:1 hexane–ethyl acetate separated the non-carbohydrate material. Further elution with solvent *G* gave pure **14** (400 mg, 80%), m.p. 88–89° after crystallization from ethanol; $[\alpha]_D^{25}$ $+5.7°$ (*c* 1, chloroform) (lit.[42] m.p. 85–87°, $[\alpha]_D^{25}$ $+5.8°$ in chloroform).

Anal. Calc. for $C_{54}H_{44}Cl_2O_{15}$: C, 64.83; H, 4.43; Cl, 6.89. Found: C, 64.71; H, 4.71; Cl, 6.99.

REFERENCES

1 J. E. G. BARNETT, *Adv. Carbohydr. Chem.*, 22 (1967) 177–227.
2 A. H. HAINES, *Adv. Carbohydr. Chem. Biochem.*, 33 (1976) 11–109.
3 C.-W. CHIU AND R. L. WHISTLER, *J. Org. Chem.*, 28 (1973) 832–834.
4 B. T. LAWTON, W. A. SZAREK, AND J. K. N. JONES, *Chem. Commun.*, (1969) 787–788.
5 B. T. LAWTON, W. A. SZAREK, AND J. K. N. JONES, *Carbohydr. Res.*, 14 (1970) 255–258.
6 R. G. ALMQUIST AND E. J. REIST, *Carbohydr. Res.*, 46 (1976) 33–41.
7 M. J. ROBINS, Y. FOURON, AND R. MENGEL, *J. Org. Chem.*, 39 (1974) 1564–1570.
8 B. J. MAGERLEIN, *Tetrahedron Lett.*, (1970) 33–36.
9 B. HELFERICH, *Ber.*, 54 (1921), 1082–1084.
10 A. KLEMER AND G. MERSMANN, *Carbohydr. Res.*, 22 (1972) 425–431.

11 G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Am. Chem. Soc.*, 86 (1964) 964–965.

12 R. F. Dods and J. S. Roth, *J. Org. Chem.*, 34 (1969) 1627–1630.

13 H. B. Sinclair, *J. Org. Chem.*, 30 (1965) 1283–1284.

14 J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, 35 (1970) 2319–2326, 2868–2877.

15 B. Castro, Y. Chapleur, B. Gross, and C. Selve, *Tetrahedron Lett.*, (1972) 5001–5004.

16 N. K. Kochetkov and A. I. Usov, *Tetrahedron*, 19 (1963) 973–983.

17 M. E. Evans, L. Long, Jr., and F. W. Parrish, *J. Org. Chem.*, 33 (1968) 1074–1076.

18 M. M. Ponpipom and S. Hanessian, *Carbohydr. Res.*, 18 (1971) 342–344.

19 S. Hanessian, M. M. Ponpipom, and P. Lavallée, *Carbohydr. Res.*, 24 (1972) 45–56.

20 S. Hanessian and P. Lavallée, *Carbohydr. Res.*, 28 (1973) 303–311.

21 R. G. Edwards, L. Hough, A. C. Richardson, and E. Tarelli, *Carbohydr. Res.*, 35 (1974) 111–129.

22 J. B. Lee and I. M. Downie, *Tetrahedron*, 23 (1967) 359–363.

23 C. R. Haylock, L. D. Melton, K. N. Slessor, and A. S. Tracey, *Carbohydr. Res.*, 16 (1971) 375–382.

24 J. P. H. Verheyden and J. G. Moffatt, *J. Org. Chem.*, 37 (1972) 2289–2299.

25 K. Haga, M. Yoshikawa, and T. Kato, *Bull. Chem. Soc. Jpn.*, 43 (1970) 3922–3924.

26 R. G. Weiss and E. I. Snyder, *J. Org. Chem.*, 35 (1970) 1627–1632; D. Brett, I. M. Downier, J. B. Lee, and M. F. S. Matough, *Chem. Ind. (London)*, (1969) 1017–1718.

27 F. Ramirez, N. B. Desai, and N. McKelvie, *J. Am. Chem. Soc.*, 84 (1962) 1745–1747.

28 R. K. Boeckman and B. Ganem, *Tetrahedron Lett.*, (1974) 913–916; M. E. Herr and R. A. Johnson, *J. Org. Chem.*, 37 (1972) 310–312.

29 S. Hanessian and N. R. Plessas, *J. Org. Chem.*, 34 (1969) 2163–2170.

30 D. C. C. Smith, *J. Chem. Soc.*, (1956) 1244–1247.

31 K. Freudenberg and G. Uthemann, *Ber.*, 52 (1919) 1509–1513.

32 K. Freudenberg, H. Toepfer, and C. C. Anderson, *Ber.*, 61 (1928) 1750–1760.

33 R. D. Guthrie, in W. Pigman and D. Horton (Eds.), *The Carbohydrates*, 2nd edn., Vol. IA, Academic Press, New York, 1972, pp. 423–471.

34 A. Anand, V. M. Clark, R. H. Hall, and A. R. Todd, *J. Chem. Soc.*, (1952) 3665–3669.

35 D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, (1957) 868–872.

36 B. Bannister and F. Kagan, *J. Am. Chem. Soc.*, 82 (1960) 3363–3368.

37 I. Wempen, I. L. Doerr, and J. J. Fox, *J. Am. Chem. Soc.*, 82 (1960) 1624–1629.

38 H. P. Hogenkamp, *Biochemistry*, 13 (1974) 2736–2740.

39 K. Kusashio and M. Yoshikawa, *Bull. Chem. Soc. Jpn.*, 41 (1968) 142–149.

40 (*a*) R. U. Lemieux and J. P. Barrette, *Can. J. Chem.*, 38 (1960) 656–662; (*b*) L. Hough and K. Mufti, *Carbohydr. Res.*, 25 (1972) 497–503; (*c*) R. G. Almquist and E. J. Reist, *J. Carbohydr. Nucleos. Nucleot.*, 1 (1974) 461–467; (*d*) L. Hough, S. Phadnis, and E. Tarelli, *Carbohydr. Res.*, 44 (1974) C12–C13; (*e*) R. G. Almquist, and E. J. Reist, *Carbohydr. Res.*, 46 (1976) 33–41; (*f*) D. H. Ball, F. H. Bissett, and R. C. Chalk, *Carbohydr. Res.*, 55 (1977) 149–163.

41 R. Khan, *Carbohydr. Res.*, 25 (1972) 504–510; ref. 40b; ref. 40d.

42 C. H. Bolton, L. Hough, and R. Khan, *Carbohydr. Res.*, 21 (1972) 133–143.

43 N. Isaacs and D. Kirkpatrick, *Tetrahedron Lett.*, (1972) 3869–3870.

44 B. Helferich, W. Klein, and W. Schafer, *Ber.*, 59 (1926) 79–89.

45 A. L. Raymond and E. F. Schroeder, *J. Am. Chem. Soc.*, 70 (1948) 2785–2791.