190. *The Methoxymercuration of* D-*Glucal and Tri*-O-*acetyl*-D-*glucal: a New Route to 2-Deoxyglycopyranosides.*

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Methoxymercuration of D-glucal gives mainly methyl 2-acetoxymercuri-2-deoxy-α-D-manno(?)pyranoside. Tri-*O*-acetyl-D-glucal yields methyl 3,4,6-tri-*O*-acetyl-2-chloromercuri-2-deoxy-β-D-glucopyranoside and a syrup, probably the α-D-manno-isomer. Reduction of the mercurials gives the corresponding 2-deoxyglucopyranosides in good yield.

The work described here was undertaken in search of better methods for the preparation of the methyl 2-deoxy-α- and -β-D-glucopyranosides, which were required in another investigation. Both compounds have previously been prepared from D-glucal, through 2-deoxy-D-glucose, by two-stage [1,2] and five-stage [3] syntheses, respectively, the overall yields being *ca.* 20% and *ca.* 15%. A four-stage synthesis of the β-anomer from tri-*O*-acetyl-D-glucal with an overall yield of *ca.* 10% has also been described.[4] A major factor limiting the yields in syntheses by way of 2-deoxy-D-glucose is that the hydration of D-glucal to this compound is complicated by the formation of an unsaturated by-product.[5] Despite a report [2] that methyl 2-deoxy-α-D-glucopyranoside can be obtained in 59% yield by the acid-catalysed addition of methanol to D-glucal, this reaction gave unpromising results in our hands; chromatographic evidence showed the presence of the desired compound but by-products prevented its crystallisation. It has already been noted [6] that large amounts of a furan derivative are produced when this reaction is carried out under milder conditions.

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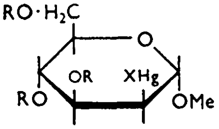
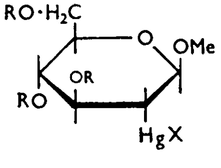
[1] Bergmann, Schotte, and Lechinsky, *Ber.*, 1922, **55**, 158.
[2] Hughes, Overend, and Stacey, *J.*, 1949, 2846.
[3] Bergmann, Schotte, and Leschinsky, *Ber.*, 1923, **56**, 1052.
[4] Fischer, Bergmann, and Schotte, *Ber.*, 1920, **53**, 509.
[5] Matthews, Overend, Shafizadeh, and Stacey, *J.*, 1955, 2511.
[6] Shafizadeh and Stacey, *J.*, 1952, 3608.

In view of the complications which seem to beset acid-catalysed additions to D-glucal, it appeared profitable to investigate indirect methods of adding the elements of methanol to the double bond, *e.g.*, methoxymercuration[7,8] followed by reduction $[\cdot CH{:}CH\cdot \longrightarrow \cdot CH(Hg\cdot OAc)\cdot CH(OMe)\cdot \longrightarrow \cdot CH_2\cdot CH(OMe)\cdot]$. Since the methoxymercuration of D-glucal can be regarded[7,8,9] as a typical electrophilic addition to a vinyl ether, it was expected that the mercury atom and the methoxyl group would become attached to $C_{(2)}$ and $C_{(1)}$, respectively, and that *trans*-addition would occur.* Hence the most likely products are methyl 2-acetoxymercuri-2-deoxy-α-D-mannopyranoside (I; R = H, X = OAc) and the β-D-gluco-isomer (II; R = H, X = OAc). The former compound might be expected to predominate, since it would be formed by diaxial addition[12] to the most stable half-chair conformation[13] of D-glucal ($C_{(6)}$ and $O_{(4)}$ equatorial, $O_{(3)}$ quasi-equatorial).

(I)





(II)

In fact, optical-rotation measurements showed that D-glucal reacted rapidly with mercuric acetate in methanol, and a crystalline methoxymercuriacetate was isolated in 60—70% yield. On reduction with potassium borohydride in the presence of alkali, this gave methyl 2-deoxy-α-D-glucopyranoside which was freed from borate by acetylation.[14] The configuration at $C_{(1)}$ in the mercuriacetate is therefore established and, if *trans*-addition is assumed, the compound must be methyl 2-acetoxymercuri-2-deoxy-α-D-mannopyranoside (I; R = H, X = OAc), the isomer expected on conformational grounds. To confirm this, Dr. H. W. W. Ehrlich kindly undertook an *X*-ray examination of the compound. Unfortunately, this proved unpromising (see Experimental section). Attempts were made to prepare the corresponding mercurichloride and mercuribenzoate in the hope that these compounds might be more suitable for *X*-ray structure determination; however, only syrups were obtained when a solution of the mercuriacetate in methanol was percolated through a column of Amberlite IRA-400 resin in the chloride or benzoate form.

The procedure described above provides a convenient route to methyl 2-deoxy-α-D-glucopyranoside, the overall yield from D-glucal being 45—50%. When the reduction was carried out without prior isolation of the mercuriacetate, the overall yield was 32%. Paper chromatography and optical rotations indicated that only a small proportion of methyl 2-deoxy-β-D-glucopyranoside was formed in the latter reduction, showing that the methoxymercuration is highly stereospecific.

The reaction of tri-*O*-acetyl-D-glucal with mercuric acetate in methanol was also studied. The syrupy product was clearly a mixture and, although a solid mercuriacetate could be obtained from it, it was more convenient to replace the ionic acetate by chloride. This yielded a crystalline mercurichloride (38% yield) and a syrupy residue which failed

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* A contrary view of methoxymercuration has been expressed by Wright and his co-workers,[10] who have pointed out that earlier *X*-ray evidence[11] for the occurrence of *trans*-addition in the methoxymercuration of cyclohexene is inconclusive.

[7] Chatt, *Chem. Rev.*, 1951, **48**, 7.

[8] Henbest and Nicholls, *J.*, 1959, 227; Henbest and McElhinney, *J.*, 1959, 1834; Henbest, Nicholls, Jackson, Wilson, Crossley, Meyers, and McElhinney, *Bull. Soc. chim. France*, 1960, 1365.

[9] Kreevoy and Kowitt, *J. Amer. Chem. Soc.*, 1960, **82**, 739.

[10] Berg, Lay, Rodgman, and Wright, *Canad. J. Chem.*, 1958, **36**, 358; Abercrombie, Rodgman, Bharucha, and Wright, *ibid.*, 1959, **37**, 1328.

[11] Brook and Wright, *Acta Cryst.*, 1951, **4**, 50.

[12] Barton and Cookson, *Quart. Rev.*, 1956, **10**, 44.

[13] Ferrier and Overend, *Quart. Rev.*, 1959, **13**, 265.

[14] Abdel-Akher, Hamilton, and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 4691.

to crystallise.* An *X*-ray structure analysis, kindly undertaken by Dr. H. W. W. Ehrlich,[15] showed that the crystalline compound was methyl 3,4,6-tri-*O*-acetyl-2-chloromercuri-2-deoxy-β-D-glucopyranoside (II; R = Ac, X = Cl). This agrees with the assumption made earlier that methoxymercuration is a *trans*-addition. Reductive demercuration of the crystalline mercurichloride with potassium borohydride in the presence of alkali was accompanied by deacetylation and yielded methyl 2-deoxy-β-D-glucopyranoside, which was isolated as the triacetate. This confirms the stereochemistry at $C_{(1)}$ and constitutes a convenient preparation of methyl 2-deoxy-β-D-glucopyranoside, the overall yield of the triacetate from tri-*O*-acetyl-D-glucal being 28%.

Reduction of the syrupy residue from the crystalline mercurichloride was again accompanied by deacetylation, and optical-rotation measurements and paper chromatography suggested that the product was mainly methyl 2-deoxy-α-D-glucopyranoside together with a little of the β-anomer. The former was isolated as the 4,6-*O*-benzylidene compound;[2] we have confirmed that the triacetate is a syrup.[16] The above evidence suggests that the syrupy mercurichloride is mainly methyl 3,4,6-tri-*O*-acetyl-2-chloromercuri-2-deoxy-α-D-mannopyranoside (I; R = Ac, X = Cl), although the α-D-*gluco*-configuration cannot be excluded except on theoretical grounds.

It is interesting that, whereas D-glucal gives mainly the expected α-D-*manno*-isomer, tri-*O*-acetyl-D-glucal gives a high proportion of the β-D-*gluco*-isomer. Detailed discussion of this difference is postponed until further work, particularly in the galactose series, is complete. The formation of the β-D-*gluco*-isomer may proceed through a boat form[17] since the chair intermediate which fulfils the stereochemical requirements of electrophilic addition has all the substituents axial (the latter conformation may, however, be stabilised by complex-formation between the mercury atom and the 4-acetoxy-group, as postulated by Henbest and his co-workers[8]).

While the present work was in progress, an abstract[18] appeared in which it is stated that methoxymercuration of D-glucal and its triacetate gives methyl 2-acetoxymercuri-2-deoxy-β-D-mannopyranoside and the methyl 2-acetoxymercuri-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside, respectively. The former conclusion appears to be incompatible with our results.

Methyl tri-*O*-acetyl-2-deoxy-β-D-glucopyranoside has also been obtained by addition of hydrogen bromide to tri-*O*-acetyl-D-glucal[19] followed by reaction of the crude product with methanol and silver carbonate; this procedure gave a lower yield (*ca.* 20%) than the mercuration route and is also less convenient.

EXPERIMENTAL

Paper chromatography (descending) was done on Whatman No. 1 paper with the following solvent systems: (i) butanol–ethanol–water (4 : 1 : 5, upper layer); (ii) dimethyl sulphoxide as stationary phase and di-isopropyl ether as mobile phase;[20] (iii) dimethyl sulphoxide as stationary phase and di-isopropyl ether–benzene (1 : 1) as mobile phase. Sprays were: (*a*) sodium periodate–potassium permanganate;[21] (*b*) 2% sodium periodate solution followed by

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* [*Added in Proof, January 23rd,* 1962.—In a later experiment, the second isomer crystallised spontaneously (47% yield, m. p. 111—113°) on addition of ether to the mother liquor from the β-D-gluco-compound. After crystallisation from ethyl acetate–light petroleum, it had m. p. 112—114°, $[\alpha]_D$ −37° (*c* 1 in $CHCl_3$) (Found: C, 29·0; H, 4·0; Cl, 7·2. $C_{13}H_{19}ClHgO_8$ requires C, 28·9; H, 3·5; Cl, 6·6%). Reduction in the manner described for the syrup gave crystalline methyl 2-deoxy-α-D-glucopyranoside.]

[15] Ehrlich, *J.*, 1962, 509.

[16] Rudloff and Tulloch, *Canad. J. Chem.*, 1957, **35**, 1504.

[17] Valls and Toromanoff, *Bull. Soc. chim. France*, 1961, 758.

[18] Manolopoulos, Litchin, and Mednick, Abs. Papers, 138th Meeting, Amer. Chem. Soc., September 1960, p. 36P.

[19] Davoll and Lythgoe, *J.*, 1949, 2526; Bonner, *J. Org. Chem.*, 1961, **26**, 908.

[20] Wickberg, *Acta Chem. Scand.*, 1958, **12**, 615.

[21] Lemieux and Bauer, *Analyt. Chem.*, 1954, **26**, 920.

p-nitroaniline;[22] (*c*) 0·1N-sodium hydroxide in 50% ethanol, followed after 10 min. by treatment (*b*); (*d*) 0·04% of Rhodamine 6G[23] in ethanol, preceded by one or two immersions of the paper in a saturated solution of iodine in light petroleum (this treatment revealed the mercurichlorides as yellow spots on a pink background; the spots fluoresced strongly in ultraviolet light). When dimethyl sulphoxide was used as stationary phase, the papers were heated at 125° for 10 min. before spraying. The α- and the β-anomer of methyl 2-deoxy-D-glucopyranoside could not be readily distinguished in solvent (i), but the corresponding triacetates were clearly resolved in solvent (ii) (R_F *ca.* 0·50 and 0·42, respectively). Although D-glucal and methyl 2-deoxy-α-D-glucopyranoside travelled at the same rate (R_F *ca.* 0·5) in solvent (i), the former could be detected in presence of the latter, since it gave an instantaneous spot with spray (*a*).

Evaporations were carried out under reduced pressure at 40° or below, usually on a rotatory evaporator. Optical rotations were measured in a 1-dm. tube, and infrared spectra were obtained with a Perkin-Elmer model 137 Infracord spectrophotometer. Methanol used in methoxymercurations and deacetylations was dried according to Vogel's directions.[24] The light petroleum used had b. p. 60—80°.

Methoxymercurations.—Mercuric acetate was obtained from Hopkin and Williams Ltd.; some other commercial samples smelt strongly of acetic acid.

Methoxymercuration of D-*Glucal*.—D-Glucal (6·12 g., 41·9 mmoles) in methanol (30 ml.) was added to mercuric acetate (13·71 g., 43·0 mmoles) in methanol (150 ml.) with cooling under the tap. The optical rotation rapidly became positive and rose to a constant value within 25 min. After 1 hr., a little flocculent material was filtered off and the solution was evaporated to 60 ml. *Methyl 2-acetoxymercuri-2-deoxy-α-*D-*manno*(?)*pyranoside* (I; R = H, X = OAc) gradually separated as prisms (9·07 g., 50%), m. p. 152·5—153° (decomp.), unchanged by crystallisation from methanol, $[\alpha]_D^{20}$ +18° (*c* 1 in MeOH) $\nu_{max.}$ 1570 and 1590 cm.$^{-1}$ (in Nujol) [Found: C, 25·2; H, 3·7%; *M* (*X*-ray), 433. $C_9H_{16}HgO_7$ requires C, 24·7; H, 3·7%; *M*, 437]. The mother-liquor yielded identical material (1·88 g., 10%). A similar preparation in which ethanol was added during the working-up gave 70% yield.

X-*Ray data on methyl 2-acetoxymercuri-2-deoxy-α-*D-*manno*(?)*pyranoside* (kindly determined by Dr. H. W. W. Ehrlich). Orthorhombic, *a* = 14·3, *b* = 20·4, *c* = 8·1 Å, D_m = 2·43 (by flotation), *Z* = 8. Weissenberg photographs about the *c*-axis suggested that the compound had a very high temperature factor, which is unusual in substances that permit hydrogen-bonding. It appeared probable that the substance had a disordered structure; detailed analysis would have been very time-consuming and was not attempted.

Methoxymercuration of Tri-O-*acetyl*-D-*glucal*.—The glycal (2·50 g., 9·2 mmoles) in methanol (10 ml.) was added to mercuric acetate (3·07 g., 9·6 mmoles) in methanol (35 ml.). After 2 hr., sodium chloride (0·565 g., 9·65 mmoles) in water (10 ml.) was added, followed by water (20 ml.). *Methyl 3,4,6-tri*-O-*acetyl-2-chloromercuri-2-deoxy-β-*D-*glucopyranoside* (II; R = Ac, X = Cl) crystallised and was collected after storage in the refrigerator overnight. The prisms (1·90 g., 38·5%) had m. p. 172—174°, $[\alpha]_D^{18}$ +11° (*c* 1 in $CHCl_3$), unchanged by crystallisation from ethanol–acetone (Found: C, 29·0; H, 4·1; Cl, 6·4. $C_{13}H_{19}ClHgO_8$ requires C, 28·9; H, 3·5; Cl, 6·6%). The mother-liquor was concentrated, dioxan (20 ml.) being added to reduce frothing, and extracted three times with chloroform after addition of water. The extract, which had a negative optical rotation, was evaporated to a syrup [A; probably methyl 3,4,6-tri-*O*-acetyl-2-chloromercuri-2-deoxy-α-D-manno(?)pyranoside] (3·5 g.) which still contained some solvent.

The two mercurichlorides were clearly resolved on chromatography in solvent (iii) (spray *d*); heavy spotting revealed that the syrup A contained little, if any, of the faster-moving crystalline mercurichloride (relative R_F *ca.* 1·3).

Reductions of the Mercurials by Potassium Borohydride.—In these, the deposition of finely divided mercury was instantaneous, but the solutions were left for several hours to clear and a further quantity of borohydride was then added to check that the reduction was complete. Before acetylation, the products were evaporated repeatedly with methanol, dioxan, or acetone to remove water. Acetylations were done with a large excess of acetic anhydride in " AnalaR " pyridine, and the products were worked up by addition of water and extraction with chloroform.

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[22] Edward and Waldron, *J.*, 1952, 3631.

[23] Lemieux and Barrette, *Canad. J. Chem.*, 1960, **38**, 656.

[24] Vogel, " Practical Organic Chemistry," 3rd edn., Longmans, Green and Co., London, 1956, p. 169.

Deacetylations were carried out with a catalytic quantity of sodium methoxide in methanol; after being kept overnight, the solutions were neutralised with Amberlite IRC-50.

*Methyl 2-deoxy-α-*D-*glucopyranoside from methyl 2-acetoxymercuri-2-deoxy-α-*D-*manno*(?)-*pyranoside.* Potassium borohydride (0·13 g., 2·4 mmoles) in N-sodium hydroxide (3·1 ml.) was added dropwise to the mercurial (4·0 g., 9·15 mmoles) in a mixture of methanol (60 ml.) and N-sodium hydroxide (11·2 ml.). Additional potassium borohydride (0·09 g.) was added as a solid in three portions at intervals. 98% of the theoretical quantity of mercury was recovered and the optical rotation of the resulting solution corresponded approximately to quantitative formation of methyl 2-deoxy-α-D-glucopyranoside. Evaporation, followed by acetylation and deacetylation, yielded a syrup which began to crystallise spontaneously. Crystallisation from dry ethyl acetate–acetone–light petroleum gave methyl 2-deoxy-α-D-glucopyranoside (1·2 g., 73%), m. p. 89—91·5°, $[\alpha]_D^{20}$ +135° (*c* 1 in H_2O). The mixed m. p. with a specimen prepared from 2-deoxy-D-glucose [1,2] was undepressed; this specimen had $[\alpha]_D^{20}$ +157° (*c* 1 in MeOH) and $[\alpha]_D^{22}$ +144° (*c* 1 in 50% aqueous MeOH). Recorded values [2,6] are $[\alpha]_D$ +135° and +145° in water and methanol, respectively.

Chromatography [solvent (i), spray (*a*)] of the product before acetylation suggested the absence of D-glucal, although in another experiment in which less alkali was used chromatographic evidence showed that some D-glucal was formed, presumably by elimination; [7,8] the acetylated product, as a film, then had $\nu_{max.}$ *ca.* 1650 cm.$^{-1}$ (C=C), and the deacetylated product did not crystallise. Methyl 2-deoxy-α-D-glucopyranoside is sometimes difficult to crystallise; anhydrous conditions and slow cooling are advisable.

*Methyl 2-deoxy-β-*D-*glucopyranoside triacetate from methyl* 3,4,6-*tri*-O-*acetyl-2-chloromercuri-2-deoxy-β-*D-*glucopyranoside.* Potassium borohydride (0·10 g., 1·85 mmoles) in N-sodium hydroxide (7·0 ml.) was added dropwise at intervals to the mercurial (1·90 g., 3·52 mmoles) in dioxan (30 ml.) and N-sodium hydroxide (10·5 ml.). Additional borohydride (0·05 g.) was added as a solid after 2 hr., no further darkening being observed. Evaporation followed by acetylation and crystallisation of the product from ethanol–light petroleum gave methyl 2-deoxy-β-D-glucopyranoside triacetate (0·79 g., 74%), m. p. 96—98°, $[\alpha]_D^{22}$ −24° (*c* 1 in $CHCl_3$), identical (mixed m. p. and infrared spectrum) with a specimen prepared as described below. Fischer, Bergmann, and Schotte [4] give m. p. 96—97°, $[\alpha]_D^{19}$ −30° in tetrachloroethane. Chromatography [solvent (ii), spray (*c*)] of the mother-liquor showed that at least three by-products were formed.

Reduction of the syrup A. Potassium borohydride (0·15 g., 2·78 mmoles) in N-sodium hydroxide (6·9 ml.) was added dropwise at intervals to the syrup (2·5 g., <4·6 mmoles) in methanol (30 ml.) and N-sodium hydroxide (14 ml.). The optical rotation of the solution became strongly positive (1·50°; volume 55 ml.). Evaporation and acetylation yielded a syrup. Chromatography [solvent (ii), spray (*c*)] gave a large spot travelling at the same rate as authentic methyl 2-deoxy-α-D-glucopyranoside triacetate and a trace corresponding to the β-anomer. Deacetylation gave a syrup and, although D-glucal appeared to be absent [as indicated by the infrared spectrum of the acetate and by chromatography of the deacetylated product in solvent (i)], this did not crystallise. Reaction with benzaldehyde (2 ml.) and zinc chloride (0·5 g.) yielded methyl 4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (0·36 g.), m. p. 148—150°, undepressed by a specimen prepared from authentic methyl 2-deoxy-α-D-glucopyranoside. The authentic benzylidene compound had m. p. 149—150° (Found: C, 63·1; H, 6·4. Calc. for $C_{14}H_{18}O_5$: C, 63·1; H, 6·8%). Hughes, Overend, and Stacey [2] give m. p. 137—139°.

Reduction of the reaction mixture obtained by methoxymercuration of D-*glucal.* D-Glucal (2·0 g., 13·7 mmoles) in methanol (15 ml.) was added to mercuric acetate (4·80 g., 15 mmoles) in methanol (30 ml.) with cooling under the tap. After 1 hr., solid mercuric acetate (0·43 g.) was added. Thirty minutes later, N-sodium hydroxide (49 ml.) was added with cooling. Potassium borohydride (0·36 g., 6·7 mmoles) in N-sodium hydroxide (7 ml.) was then added dropwise. After 5 hr., solid potassium borohydride (0·18 g.) was added. The optical rotation of the resulting solution was *ca.* 80% of the theoretical value expected for the quantitative formation of methyl 2-deoxy-α-D-glucopyranoside. Evaporation, followed by acetylation, yielded a syrup which was shown by chromatography [solvent (ii), spray (*c*)] to contain mainly methyl 2-deoxy-α-D-glucopyranoside triacetate with a very small proportion of the β-anomer. Deacetylation gave a syrup which crystallised from dry ethyl acetate–acetone (m. p. 75—85°; 1·13 g.). Recrystallisation yielded methyl 2-deoxy-α-D-glucopyranoside (0·78 g., 32%), m. p. and mixed m. p. 89—92°.

*Methyl 2-Deoxy-*β-D-*glucopyranoside Triacetate from Tri-*O-*acetyl-*D-*glucal through the Acetobromo-compound.*—Hydrogen bromide[25] (6 g., 74 mmoles; freed from bromine by bubbling through phenol in carbon tetrachloride) in dried benzene (65 ml.) was added to tri-*O*-acetyl-D-glucal (10 g., 37 mmoles) in benzene (35 ml.) containing benzoyl peroxide (0·09 g.), the mixture being cooled under the tap. After 50 min. the solution had a high positive optical rotation (25·4°, *i.e.*, $[\alpha]_D$ *ca.* +200°). It was then concentrated at 30° to a pale yellow, mobile syrup which was evaporated with benzene. The product was immediately dissolved in methanol (75 ml.), and silver carbonate (15 g.) was added in portions. After being kept overnight, the mixture was filtered and concentrated. Crystallisation from acetone–light petroleum, ether–light petroleum, and ethanol–light petroleum gave (with some difficulty) methyl 2-deoxy-β-D-glucopyranoside triacetate (2·23 g., 20%), m. p. 93—96°, which after further crystallisation had m. p. 96—98°, $[\alpha]_D^{18}$ $-24°$ (*c* 1·5 in $CHCl_3$). Deacetylation gave methyl 2-deoxy-β-D-glucopyranoside, m. p. 121—122°, $[\alpha]_D^{17}$ $-48°$ (*c* 1 in H_2O). Fischer, Bergmann, and Schotte[4] give m. p. 121—122°, $[\alpha]_D^{17}$ $-48°$ (in water).

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[25] Ref. 24, p. 182 (method 2).