Unsaturated Carbohydrates. Part 28.[1,2] Observations on the Conversion of 6-Deoxyhex-5-enopyranosyl Compounds into 2-Deoxyinosose Derivatives

Regine Blattner, Robert J. Ferrier,* and Stephen R. Haines
Department of Chemistry, Victoria University of Wellington, Private Bag, Wellington, New Zealand

Mercury-containing intermediates have been isolated from the reaction of 6-deoxyhex-5-enopyranosyl compounds with mercury(II) salts in aqueous acetone. They react to give 2-deoxyinosose derivatives on further exposure to the conditions of their formation or, after isolation, by treatment with hydrogen sulphide. Mercury(II) acetate is more efficient than the previously used mercury(II) chloride for this carbohydrate-into-deoxyinosose conversion.

Our initial observation that 6-deoxyhex-5-enopyranose derivatives can be converted directly into 2-deoxyinososes by use of mercury(II) chloride in aqueous acetone[3] has been shown to have general applicability and value in the synthesis of inosamines and other compounds of interest in the areas of aminoglycoside antibiotics[4-10] and *pseudo*-oligosaccharides.[4-6]

In the initial reaction[3] the alkene triester (1) gave the 2-deoxyinosose (2) in 83% yield and similar efficiencies have been described in other cases[6,9] but, although in one of these[6] the tribenzyl ether (3) was reported to give compound (4) in 84% yield other authors[8] found that this main product was accompanied by appreciable proportions of the epimeric alcohol.

More serious restrictions in the applicability of this carbohydrate-into-carbocycle conversion reaction were found with the alkene (6) which gave none of the expected inosose (7) when treated with mercury(II) chloride,[11] although a 40% yield was obtainable by use of mercury(II) acetate followed by chloride ions,[12] and with the azido compound (8) which afforded only 55% of the cyclitol derivative (9) with mercury(II) chloride.[10] In this latter case, however, the yield was increased appreciably by use of mercury(II) trifluoroacetate.† The rearrangement reaction cannot apparently be extended to the conversion of analogous furanoid alkenes, *e.g.* (10), into cyclopentane derivatives.[13] The present investigation examines some features of the carbohydrate-into-deoxyinosose conversion—in particular, some mercury-containing reaction intermediates.

Since the tetra-*O*-benzoyl-6-deoxy-5-enopyranose (11) is readily available from penta-*O*-benzoyl-β-D-glucopyranose by way of its 5-*C*-bromo derivative[14,15] it was selected for primary study. When heated with mercury(II) chloride in refluxing aqueous acetone, *i.e.* the conditions used in the initial reaction,[3] no crystalline product was obtained on cooling [as happened with compound (2)], but chromatographic purification of the products afforded the expected ketone (16) in 55% yield. Like compound (2) this product was readily shown by [1]H n.m.r. spectroscopy to have the (*S*)-configuration at the new asymmetric centre. A reaction by-product with lower chromatographic mobility than that of the carbocycle was the 6-deoxy compound (15) which, on dehydration,[14] gave the dicarbonyl compound (14) which was readily characterised from its [1]H n.m.r. spectrum. This observation led to the supposition that the initial reaction with mercury(II) chloride first gave the hydroxymercuration product (12)[16] which then afforded the deoxyinosose (16) by attack of the carbanionic C-6 atom at C-1 of the ring-opened dicarbonyl compound (13). This concurrently underwent hydrolysis to the 6-deoxyosulose (14), hydration of

(1) R^1 = Ts, R^2= Bz
(3) R^1 = R^2 = Bn

(2) R^1 = Ts, R^2= Bz
(4) R^1 = R^2= Bn
(5) R^1 = R^2= Ac

(6)

(7)

(8)

(9)

(10)
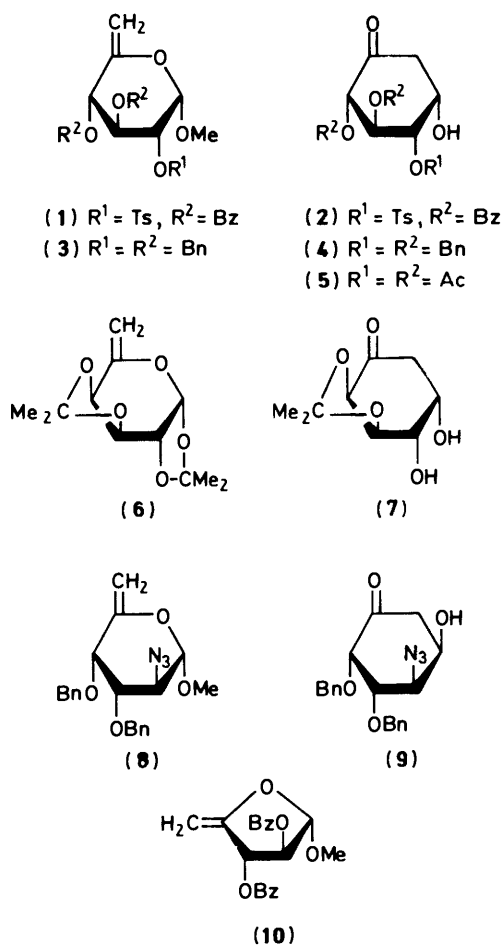
Bn = Benzyl
Bz = Benzoyl
Ts = *p*-Tolylsulphonyl

which to the cyclic hemiacetal (15) would occur in aqueous solution.

When the reaction of the alkenes (11) with mercury(II) chloride in aqueous acetone was repeated at room temperature the optical rotation of the solution increased during 6 h and a chromatographically slow moving product was formed. The rotation then slowly decreased and the slow moving material was replaced by the reaction products (15) and (16). Interruption of the reaction after 6 h, removal of the acetone, and

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† A. S. Machado, A. Olesker, and G. Lukacs (*Carbohydr. Res.*, 1985, **135**, 231) have found catalytic amounts of mercury(II) sulphate can also give enhanced yields in this reaction. See also A. S. Machado, A. Olesker, S. Castillon, and G. Lukacs, *J. Chem. Soc., Chem. Commun.*, 1985, 330.
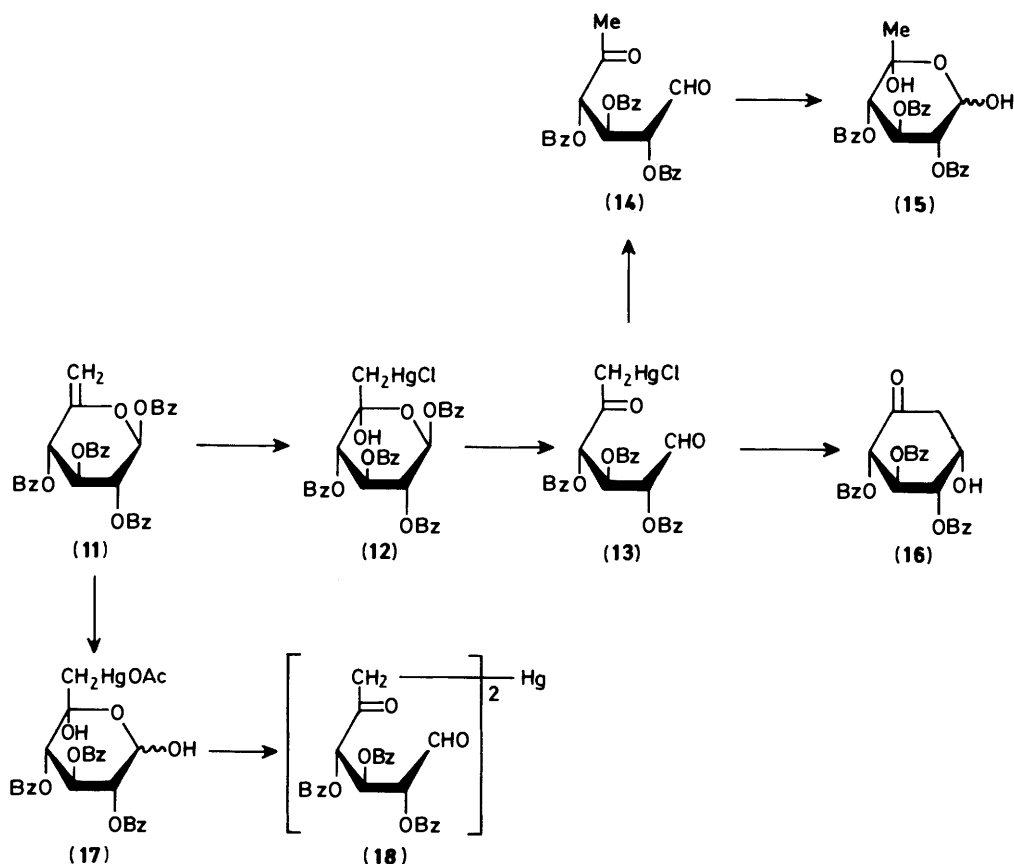
extraction into benzene gave, after exhaustive drying, a glass which had chlorine and mercury contents and a ^1H n.m.r. spectrum consistent with it being the mercurial (13). In particular, one-proton resonance at δ 9.58 revealed the presence of the formyl group, $J_{2,3}$ and $J_{3,4}$ values of 4 Hz were consistent with those expected for an acyclic compound with the xylo-configuration,[14,17] and the 6-H_2 protons resonated at δ 2.88 which is consistent with expectations for protons of a mercuriated methylene group adjacent to a ketone.[18] When the mercurial (13) was treated in dry benzene with hydrogen sulphide the cyclohexanone (16) was isolated in 75% yield after chromatography and, likewise, compound (13) gave this product, (16), when the room-temperature reaction system was kept for 8 days. Under these conditions, however, the hydrolysis product (15) comprised about 40% of the products.

In order to test the susceptibility of the alkene (11) to acid hydrolysis it was treated in aqueous acetone with hydrochloric acid of the strength which would have have been produced by complete hydrolysis of the mercury(II) chloride used in the room-temperature mercuriation reaction; it did not give the by-product (15), which strengthens the supposition that the latter was derived from the mercurial adduct (13). As hydrolysis of organomercury compounds of this type would be subject to acid catalysis,[19] and as strong acid would be produced in the overall reaction, it became appropriate to attempt the reaction under study with mercury(II) acetate, especially as this reagent might also be advantageous in reducing the possibility of the acid catalysis of the reversal of the initial hydroxymercuriation.[20] Furthermore, mercury(II) acetate, being more ionic and electrophilic than the chloride,[20] would be expected to react more readily with vinyl ethers of the kind under study.

When the acetate was used with compound (11) the deoxyinosose (16) was produced in 93% yield and, as it also now crystallised without chromatography, this modification repre-

sents an appreciable improvement in the conversion. Applied to the initial alkene (1) this modification resulted in a yield of 89% of recrystallised inosose (2) as opposed to the 83% of unpurified product obtainable with mercury(II) chloride, and a mercury-containing intermediate had, after being dried, ^1H and ^{13}C n.m.r. characteristics of the expected acetoxymercury-dicarbonyl analogue of compound (13). When tetra-O-acetyl-6-deoxy-β-D-xylo-hex-5-enopyranose (and the corresponding methyl α-glycoside) were tested no product crystallised directly, but the expected cyclohexanone (5) was isolated in 60 and 75% yield after chromatography following reactions with mercury(II) chloride and acetate, respectively. With the D-galactose-derived alkene (6) no product was obtained with the chloride, but when mercury acetate was used followed by chloride ion (see below) the expected diol (7) was isolated in 40% yield.[12]

At room temperature mercury(II) acetate added appreciably more quickly to the alkene (11) than did the chloride as would be expected of a more electrophilic salt,[20] but the overall conversion into the inosose (16) was slower, indicating that the ring closure of the mercury-containing intermediate was relatively retarded. When isolated, this intermediate was not the expected compound (17) or its dehydrated analogue; it contained no acetoxy group, and from its mercury content it is believed to be the dialkylmercury (18) formed (conceivably during its isolation) by disproportionation of the initial adduct (17) in a way which has previously afforded dialkylmercurials under similar[13,21] conditions, and in parallel work.[22]

From the observations discussed above it seemed appropriate to conduct the overall cyclisation reaction by initial addition of mercury(II) acetate followed by chloride anion (once the hydroxymercuriation had occurred) on the grounds that the nucleophilicity of C-6 would thereby be enhanced[23] and that the slow phase of the reaction would be accelerated. Applied to the tetrabenzoate (11) this procedure reduced apreciably the

time required to complete the reaction, but the yield of the deoxyinosose (16) obtained was 63% rather than the 93% afforded by use of mercury(II) acetate in refluxing acetone. Therefore the latter reaction conditions are favoured.

Experimental

N.m.r. spectra were measured with a Varian FT80A instrument for deuteriochloroform solution. Unless otherwise stated optical rotations were measured on chloroform solutions within the concentration range 0.5—2%. Organic solvents were dried over anhydrous sodium sulphate.

Reaction of 1,2,3,4-Tetra-O-benzoyl-6-deoxy-β-D-xylo-hex-5-enopyranose (11) *with Mercury(II) Salts.*—(a) *With mercury(II) chloride at reflux temperature.* The alkene (11) (1.0 g) was heated under reflux with mercury(II) chloride (2.0 g, 4.3 mol equiv.) in aqueous acetone (100 ml; 2:5) for 3 h. The acetone was removed, the aqueous suspension obtained was extracted with chloroform (3 × 50 ml), the organic solution was washed with water and dried, and the solvent was removed to leave a foam. Purification on a column of silica gel [light petroleum (b.p. 60—80 °C–ether (1:2)] gave crystalline (2S)-2,4,5/3-2,3,4-*tri-benzoyloxy-5-hydroxycyclohexanone* (16) (0.45 g, 55%) which, after recrystallisation from light petroleum–chloroform, had m.p. 186—187 °C, $[\alpha]_D$ $-4°$ (Found: C, 68.4; H, 4.7. $C_{27}H_{22}O_8$ requires C, 68.4; H, 4.7%); δ_H 2.88 (2 H, m, 6-H_2), 2.9 (1 H, br s, OH), 4.60 (1 H, m, 5-H), 5.77 (1 H, dd, $J_{3,4}$ 10.0, $J_{4,5}$ 2.5 Hz, 4-H), 5.83 (1 H, d, $J_{2,3}$ 10.0 Hz, 2-H), 6.42 (1 H, t, 3-H), and 7.1—8.1 (15 H, ArH); δ_C 43.4 (C-6), 66.9, 70.4, 74.6, and 77.2 (C-2, -3, -4, and -5), 197.1 p.p.m. (C-1), + aromatics.

The reaction by-product (14) was isolated and characterised as in method (b) below.

(b) *With mercury(II) chloride at room temperature.* A solution of the tetrabenzoate (11) (1.6 g) and mercury(II) chloride (3.2 g, 4.3 mol equiv.) in aqueous acetone (60 ml; 1:5) was left at 20 °C for 6 h after which the starting material had been replaced by a chromatographically less mobile product and the optical rotation of the solution had changed from $-0.26°$ to $+3.08°$ (constant). The acetone was removed and the reaction products were partitioned between benzene (50 ml) and water (20 ml). The benzene solution was washed with water, dried, and the solvent was removed to leave the chloromercury compound (13) as a foam (1.49 g, 75%), $[\alpha]_D$ $+53°$ (*c* 3 in benzene) (Found: Cl, 4.7; Hg, 25.4. $C_{27}H_{21}ClHgO_8$ requires Cl, 5.0; Hg, 28.2%); δ_H 2.88 (2 H, m, 6-H_2), 5.73 and 5.81 (together 2 H, 2 d, $J_{2,3}$ = $J_{3,4}$ = 4 Hz, 2- and 4-H), 6.21 (1 H, t, 3-H), 7.2—8.1 (15 H, ArH), and 9.58 (1 H, s, 1-H).

When this reaction was repeated using 0.16 g of the alkene (11) and the solution was left for 8 days at 20 °C the mercurial (13) was converted into two faster moving products. The solvent was removed, the residue was extracted with benzene, and hydrogen sulphide was passed through the extract to precipitate mercury(II) sulphide. This and the solvent were removed and the residue was resolved by preparative t.l.c. to give the deoxyinosose (16) which was characterised by ^{1}H n.m.r. spectroscopy, and the 1,5-dicarbonyl compound (14), 32 mg (25%), $[\alpha]_D$ $-8.5°$ (*c* 1 in benzene); δ_H 2.26 (3 H, s, 6-H_3), 5.77 and 5.68 (together 2 H, 2 d, $J_{2,3}$ = $J_{3,4}$ = 4.5 Hz, 2- and 4-H), 6.24 (1 H, t, 3-H), 7.1—8.1 (15 H, ArH), and 9.63 (1 H, s, 1-H).

(c) *With mercury(II) acetate at reflux temperature.* The alkene (11) (1.0 g) and mercury(II) acetate (1.0 g, 1.8 mol equiv.) were heated in refluxing aqueous acetone (100 ml; 2:5) containing 1% acetic acid for 5 h. The acetone was removed and the residue was extracted with chloroform, and the extracts were dried and reduced to small volume. The deoxyinosose (16) (0.77 g, 93%) crystallised on the addition of light petroleum. Recrystallised

from light petroleum–chloroform it had m.p. 184—187 °C, $[\alpha]_D$ $-3.5°$, and was identical with the material obtained in method (a) above by ^{1}H n.m.r. spectroscopy.

(d) *With mercury(II) acetate at room temperature.* A mixture of the alkene (11) (0.15 g) and mercury(II) acetate (0.3 g, 3.6 mol equiv.) in aqueous acetone (15 ml; 1:5) was kept at 20 °C for 15 min during which the optical rotation changed from $-0.08°$ to $+0.9°$ (constant). After a further 45 min the acetone was removed and the residue was extracted with dichloromethane (20 ml). The extract was dried, and the solvent was removed, and the residue was extracted with benzene. Removal of the benzene gave the mercurial (18) (0.15 g, 100%) (Found: Hg, 18.8. $C_{54}H_{42}HgO_{16}$ requires Hg, 17.5%); δ_H 3.03 (2 H, m, 6-H_2), 5.84 and 6.00 (together 2 H, 2 d, $J_{2,3}$ = $J_{3,4}$ = 4 Hz, 2- and 4-H), 6.35 (1 H, t, 3-H), 7.2—8.1 (15 H, ArH), and 9.69 (1 H, s, 1-H).

(e) *With mercury(II) acetate followed by sodium chloride.* The alkene (11) (1.0 g) and mercury(II) acetate (1.0 g, 1.8 mol equiv.) were heated under reflux for 5 min in aqueous acetone (100 ml, 2:5) containing acetic acid (2%), sodium chloride (1.0 g) was added, and the mixture was heated for a further 5 min by which time the reaction was complete. Isolation as in method (c) gave the deoxyinosose (16) (0.52 g, 63%), m.p. 184—186 °C; $[\alpha]_D$ $-4°$ after recrystallisation (× 2) from light petroleum–chloroform.

Reaction of Methyl 3,4-Di-O-benzoyl-6-deoxy-2-O-(p-tolyl-sulphonyl)-α-D-xylo-hex-5-enopyranoside (1) *with Mercury(II) Acetate.*—The alkene (1) (0.15 g) and mercury(II) acetate (0.18 g, 2.0 mol equiv.) were heated under reflux in aqueous acetone (10 ml; 1:4) containing acetic acid (1%) for 5.25 h. The usual processing and recrystallisation from methanol gave (2S)-2,4,5/3-2,3-dibenzoyloxy-5-hydroxy-4-(p-tolylsulphonyloxy)cyclo-hexanone (2) (0.13 g, 89%), m.p. 170—171 °C (lit.,[3] 175—176 °C), with a ^{1}H n.m.r. spectrum identical with that of an authentic sample.

When the reaction was repeated on half-scale and at 20 °C, and the product was isolated as usual, the acetoxymercury analogue of compound (13) was obtained (0.17 g, 100%); δ_H 1.96 (3 H, s, OAc), 2.23 (3 H, s, ArMe), 2.95 (2 H, s, 6-H_2), 5.2—6.1 (3 H, m, 2-, 3-, and 4-H), 7.1—8.1 (14 H, ArH), and 9.58 (1 H, s, 1-H); δ_C 21.6 and 22.4 (2 × Me), 32.4 (C-6), 69.7, 74.5, and 80.1 (C-2, -3, and -4), 177.3 (COMe), 194.2 (C-1), 201.8 p.p.m. (C-5), + aromatics.

Treatment of the Mercurial (13) *with Hydrogen Sulphide.*—Hydrogen sulphide was passed into a soluton of the mercurial (13) (1.41 g) in benzene (50 ml) for 10 min, the precipitated mercury(II) sulphide was filtered off, the filtrate was washed with water and dried, and the solvent was removed. The residual foam was purified on a column of silica gel to give the cyclo-hexanone (16) (0.91 g, 75%), m.p. 184—186 °C; $[\alpha]_D$ $-4°$; the ^{1}H n.m.r. spectrum was identical with that of the previous samples.

Likewise, the acetoxymercury intermediate (0.46 g) obtained (above) from compound (1) gave 67% of compound (2) (m.p. 172—173 °C, ^{1}H n.m.r. identification) on treatment with hydrogen sulphide.

(2S)-2,4,5/3-2,3,4-*Triacetoxy-5-hydroxycyclohexanone* (5).—1,2,3,4-Tetra-O-acetyl-6-deoxy-β-D-xylo-hex-5-enopyranose[24] (1.0 g) and mercury(II) acetate (0.36 g, 1.03 mol equiv.) were heated in refluxing aqueous acetone (100 ml; 1:2) for 3 h. The usual isolation and purification on a column of silica gel and recrystallisation from light petroleum–chloroform gave the triacetate (5) (0.75 g, 75%), m.p. 142—144 °C; $[\alpha]_D$ $-5.5°$ (Found: C, 49.6; H, 5.5. $C_{12}H_{16}O_8$ requires C, 50.0; H, 5.6%); δ_H 2.05, 2.11, and 2.15 (3 × OAc), 3.2 (OH), 2.75 (2 H, m, 6-H_2), 4.40 (1 H, br s, 5-H), 5.25 (1 H, dd, $J_{3,4}$ 10.0, $J_{4,5}$ 2.0 Hz, 4-H), 5.34 (1 H, d, $J_{2,3}$ 10.0 Hz, 2-H), and 5.73 (1 H, t, 3-H). Similar

results were obtained when methyl 2,3,4-tri-*O*-acetyl-6-deoxy-α-D-*xylo*-hex-5-enopyranoside was used.

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