Reaction of halogenated carbohydrates with sodium cobalt tetracarbonyl and carbon monoxide. A new novel synthesis of unsaturated sugars

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Received December 18, 1967

Methyl tri-*O*-acetyl-2-deoxy-2-iodo-β-D-glucopyranoside reacted at room temperature with sodium cobalt tetracarbonyl and carbon monoxide in ether to give in high yield methyl 4,6-di-*O*-acetyl-2,3-dideoxy-β-D-*erythro*-hex-2-enoside (**5**). Under the same reaction conditions the corresponding 2-iodo-α-D-mannopyranoside failed to react, but at 100° it was smoothly converted into the anomeric α-D-*erythro*-hex-2-enoside (**7**). When methanol was used in place of ether no appreciable ester formation took place but elimination of iodine and an acetoxy group occurred, accompanied by complete deacetylation of the remaining ester groups.

Canadian Journal of Chemistry, **46**, 2245 (1968)

This investigation was undertaken to find a new route for preparing branched-chain sugars. Renewed interest in the chemistry of these unusual sugars has arisen partly because of their presence in some recently discovered antibiotics (1–3).

The great difficulty in introducing branched-chains into carbohydrates by classical chemical reactions led us to explore the possibility of using transition metal catalysts for inserting carbon monoxide into the carbon chain. One attractive route is based on the finding (4) that cobalt tetracarbonyl anion can displace active halogen from an alkyl halide to yield an unstable alkylcobalt tetracarbonyl (**1**). Under an atmosphere of carbon monoxide, the latter undergoes carbonyl insertion (5, 6) to afford an acylcobalt tetracarbonyl (**2**) as shown in eq. [2]. The addi-

[1] $$RX + NaCo(CO)_4 \longrightarrow \underset{\mathbf{1}}{RCo(CO)_4} + NaX$$

[2] $$RCo(CO)_4 \longrightarrow RCOCo(CO)_3 \xrightarrow{CO} \underset{\mathbf{2}}{RCOCo(CO)_4}$$

tion of triphenylphosphine (7) to (**2**) results in the displacement of a carbonyl ligand by triphenylphosphine to yield a stable acylcobalt tricarbonyl triphenylphosphine complex (**3**). Cleavage of the

[3] $$RCOCo(CO)_4 + PPh_3 \longrightarrow \underset{\mathbf{3}}{RCOCo(CO)_3PPh_3} + CO$$

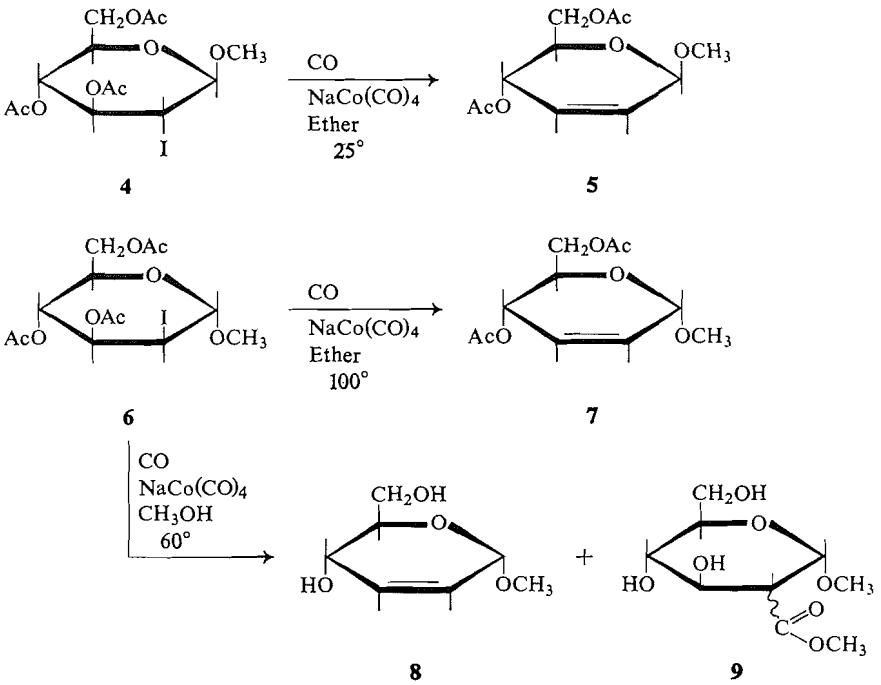
latter is readily effected by treatment with sodium methoxide to yield an ester. Alternatively, the alkyl halide has been allowed to react with carbon monoxide and sodium cobalt tetracarbonyl in methanol (addition of a tertiary amine facilitates the reaction) under elevated temperature and pressure to yield the ester directly (8), as shown in eq. [5].

[4] $$RCOCo(CO)_3PPh_3 + NaOCH_3 \longrightarrow RCO_2CH_3$$

[5] $$RX + NaCo(CO)_4 + CO + CH_3OH \xrightarrow[60°]{} RCO_2CH_3$$

In the carbohydrate field it has been shown that tetra-*O*-acetyl-α-D-glucopyranosyl bromide readily reacted with sodium cobalt tetracarbonyl and carbon monoxide in ether at room temperature to afford alkyl and acylcobalt derivatives of carbohydrates which could be readily isolated as their triphenylphosphine complexes (9). It therefore seemed feasible to allow the readily available 2-halogenated carbohydrates to react under similar conditions to afford sugars containing a branched-chain on C-2 as shown in structure **9**.

When methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-β-D-glucopyranoside (**4**) was allowed to react with sodium cobalt tetracarbonyl and carbon monoxide in ether at room temperature, both halogen and the acetoxy group on the adjoining carbon were readily removed to afford in almost quantitative yield an unsaturated sugar, namely, methyl 4,6-di-*O*-acetyl-2,3-dideoxy-β-D-*erythro*-hex-2-enoside (**5**). Although the latter has not been previously isolated in the pure state, a mixture of it and its α anomer (**7**) has been synthesized by treatment of 3,4,6-tri-*O*-acetyl-D-glucal with methanol at elevated temperature (10). Repeated attempts in our laboratory to separate the α and β anomeric mixture by vapor-phase chromatography (v.p.c.) or thin-layer chromatography (t.l.c.) have failed. Direct



comparison by nuclear magnetic resonance (n.m.r.) of **5** with the α and β mixture conclusively showed that **5** was identical to the β anomer obtained from 3,4,6-tri-*O*-acetyl-D-glucal. Similar treatment of methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-α-D-mannopyranoside (**6**) with sodium cobalt tetracarbonyl and carbon monoxide in ether at room temperature (even for 8 days) gave only unreacted starting material. However, when **6** was allowed to react at 100° for 8 h, then it was converted in high yield into the pure unsaturated sugar (**7**). Again, direct comparison (by n.m.r.) of **7** with the α and β anomeric mixture showed conclusively its identity. Both of the unsaturated sugars (**5** and **7**) had the same v.p.c. retention time. Mass spectrometry of **5** and **7** showed that both the allylic hydrogen and methoxyl group on C-1 were removed to afford ions of *m/e* 243 and 213. In the n.m.r. spectrum of **5** the vinyl protons occurred as a multiplet at τ 4.04, whereas those of **7** resonated at τ 4.10. The methoxyl protons also differed in their resonances by 1.5 Hz.

When the unsaturated carbohydrates (**5** and **7**) were de-*O*-acetylated with sodium methoxide in methanol the resulting unsaturated sugars were unstable at room temperature. However, deacetylation of **5** with barium methoxide in the cold, followed by immediate benzoylation with *p*-nitrobenzoyl chloride and pyridine at 0°, gave a stable crystalline bis-*p*-nitrobenzoate derivative. Attempts to prepare a similar derivative of **7** were unsuccessful.

Attempts to isolate the expected cobalt derivative of **4** as the triphenylphosphine complex were unsuccessful. Injection of methanol and iodine during the course of the reaction failed to lead to the production of the anticipated branched-chain ester.

Direct treatment of methyl tri-*O*-acetyl-2-deoxy-2-iodo-α-D-mannopyranoside with sodium cobalt tetracarbonyl and carbon monoxide in methanol at 60° gave predominately the deacetylated elimination product (**8**) and what was presumed to be (on the basis of n.m.r. evidence only), in less than 3% yield, the branched-chain ester (**9**) (both isolated as the acetates). It is possible that, in the presence of methanol, the sodium cobalt tetracarbonyl dissociates to yield sodium methoxide and the latter leads to deacetylation of the substrate.

When methyl tri-*O*-acetyl-2-bromo-2-deoxy-β-D-*gluco*- (and 2-bromo-α-D-*manno*-) pyranoside were allowed to react with sodium cobalt tetra-

carbonyl and carbon monoxide in ether at 100° for 8 h, no reaction occurred.

Although methyl tri-*O*-acetyl-2-deoxy-2-iodo-β-D-glucopyranoside failed to undergo a carbonyl insertion reaction, it is interesting to consider the possible mechanism of formation of the unsaturated compound because such a consideration might help give a better insight into carbonyl insertion reactions. In this connection, it is interesting to consider the carbonyl insertion products obtained by the treatment of ethyl α-bromopropionate with potassium cobalt tetracarbonyl and carbon monoxide at 0°, followed by cleavage of the products with iodine and ethanol (11). Orchin (12), in his discussion of the probable mechanism to account for the formation of a mixture of esters, has suggested two possibilities. In the first suggestion, one can consider the displacement of bromine by cobalt tetracarbonyl anion to give an alkylcobalt tetracarbonyl (see eq. [6]), followed by an elimination (see eq. [7]), and readdition of $HCo(CO)_4$ (see eq. [8]) to give a mixture of alkylcobalt tetracarbonyls. Cleavage of these with ethanol and iodine might be expected to afford the isolable mixture of esters (see eq. [9]). An alternative

[6] $CH_3\underset{\underset{Br}{|}}{C}HCO_2Et + KCo(CO)_4 \rightarrow CH_3\underset{\underset{Co(CO)_4}{|}}{C}HCO_2Et$

[7] $CH_3\underset{\underset{Co(CO)_4}{|}}{C}HCO_2Et \rightleftarrows CH_2{=}CHCO_2Et + HCo(CO)_4$

[8]

$$CH_2\underset{\underset{Co(CO)_4}{|}}{C}H_2CO_2Et$$

[9]

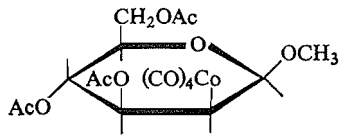
$$\downarrow I_2$$
$$\downarrow EtOH$$

Mixture of Esters

mechanism also considered (12) was the possibility of an initial dehydrohalogenation of the ester to acrylate, followed by subsequent addition of $HCo(CO)_4$ (see eq. [10]). The second

[10] $CH_3\underset{\underset{Br}{|}}{C}HCO_2Et + [Co(CO)_4]^- \rightarrow CH_2{=}CHCO_2Et + HCo(CO)_4 + Br^-$

mechanism (prior elimination) in all probability could not apply to the 2-iodo compound (**4**) because there exists no secondary hydrogen in a *trans* position to the iodine. If the first suggestion applies, then the resulting sugar cobalt tetracarbonyl might be expected to have the D-*manno*-configuration (**10**). A *trans* elimination of $HCo(CO)_4$ from **10**, as envisaged by Orchin (12) would not give the 2,3-ene (**5**). Although the



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evidence thus far adduced rules out the mechanisms suggested by Orchin, it merely shows that no single mechanism applies for the elimination of iodine and acetate which are either *cis* or *trans* oriented. To the best knowledge of the authors this is the first recorded instance of such an elimination, although elimination of iodine and a tosyl group from adjacent carbons to form a 2,3-ene is well known (13).

Experimental

General Considerations

The reactions were performed in an Aminco autoclave fitted with an injector septum. Ether solutions of sodium cobalt tetracarbonyl (14, 15) were prepared by treating an ether solution of dicobalt octacarbonyl (Alfa Inorganics, Inc., Beverley, Massachusetts) with sodium amalgam. Nuclear magnetic resonance spectra were performed on a 100-MHz HA spectrometer, using tetramethylsilane as the internal standard set at $\tau = 10$. Mass spectra were measured with an A.E.I. M.S.9 spectrometer. Vapor-phase chromatography (v.p.c.) was performed on a Varian Aerograph model 1525 instrument operated at 215° using 5% butanediol succinate or 10% SE 52 on Chromosorb W.

Reaction of Methyl 3,4,6-Tri-O-acetyl-2-deoxy-2-iodo-β-D-glucopyranoside with Sodium Cobalt Tetracarbonyl to Yield Methyl 4,6-Di-O-acetyl-2,3-dideoxy-β-D-erythro-hex-2-enoside (5)

Procedure A

A solution of methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-β-D-glucopyranoside (16) (1 g) dissolved in 30 ml of anhydrous ether was placed in a glass liner contained in a shaking autoclave of 200 ml internal capacity. The autoclave was then sealed with the pressure head which was fitted with an injector septum (from an Aerograph v.p.c. instrument) and a gauge. After the autoclave was flushed three times with 100 p.s.i. of anhydrous carbon monoxide it was pressurized with 1 atm of carbon monoxide. An ether solution of sodium cobalt tetracarbonyl (100 ml of 0.25 *M*) was then injected through the septum with a syringe. After the autoclave was again flushed with carbon monoxide, it was filled with 150 p.s.i. of carbon monoxide and then rocked at 60° for about 2 h. The contents of the liner were placed in a beaker and allowed to stand in a hood until the ether had evaporated. The resultant residue was extracted with 100 ml of ether and on evaporation this extract gave 490 mg of syrup which was distilled, b.p.

78–85°/0.04 mm. The product was homogeneous by thin-layer chromatography (t.l.c.) and by v.p.c., and absorbed 1.05 moles hydrogen per mole sugar: $[\alpha]_D^{20}$ +142° (*c*, 3.0 in benzene); n_D^{23} 1.4617.

Anal. Calcd. for $C_{11}H_{16}O_6$ (mol. wt., 244): C, 54.1; H, 6.56. Found *m/e* 243 (loss of H) and 213 (loss of OCH_3): C, 53.8; H, 6.80.

Nuclear magnetic resonance (deuteriochloroform): multiplet at τ 4.04 equal to 2 vinyl protons; singlet at τ 6.54 equal to 3 methoxyl protons; singlet at τ 7.90 equal to 6 acetyl H; in deuteriobenzene the acetyl protons appeared at τ 8.30 and 8.36.

Preparation of methyl 2,3-dideoxy-4,6-di-O-p-nitrobenzoyl-β-D-erythro-hex-2-enoside—Methyl 4,6-di-*O*-acetyl-2,3-dideoxy-β-D-erythro-hex-2-enoside was first de-*O*-acetylated with barium methoxide in methanol at 0° (17). The residual syrup, which was unstable at room temperature, was immediately converted into a *p*-nitrobenzoate derivative by treatment with *p*-nitrobenzoyl chloride and pyridine at 0° for 1 day. The product was worked up in the usual way and recrystallized from methanol, m.p. 130–132°. A trace of a contaminant was present (t.l.c.) which could not be removed.

Anal. Calcd. for $C_{21}H_{18}O_{10}N_2$: mol. wt. 458. Found: *m/e* 457 (loss of H) and *m/e* 427 (loss of OCH_3).

Procedure B

To the autoclave, filled with 1.5 sugar and 20 ml carbon monoxide-saturated ether, were injected 100 ml of approximately 0.25 *M* sodium cobalt tetracarbonyl in ether. The vessel was pressurized with 10 atm of carbon monoxide and heated, with rocking, at 60° for 2 h. After the vessel was cooled, 3 g of triphenylphosphine in 15 ml ether were injected into the vessel. The contents of the autoclave were filtered in an atmosphere of nitrogen. The residue was extracted with water, the extracts filtered, and on evaporation a red, velvety material remained which was quite deliquescent. This residue gave positive tests for cobalt, sodium, iodine, and acetate ions. To the filtrate 20 ml of methyl iodide were added and the mixture allowed to stand at 0° for 10 h. The mixture was filtered under nitrogen, the filtrate evaporated to a syrup which was extracted with boiling petroleum ether (30–60° b.p.), and, on cooling the extracts, a crystalline solid, m.p. 156°, was obtained which was shown by n.m.r. and mass spectroscopy to be triphenylphosphine oxide. The crystals were removed by filtration and the resultant solution evaporated to afford 700 mg of a syrup which was identical to methyl 4,6-di-*O*-acetyl-2,3-dideoxy-β-D-*erythro*-hex-2-enoside obtained from the previous reaction.

Procedure C

The halogenated sugar (1 g) was allowed to react with sodium cobalt tetracarbonyl in ether and 10 atm of carbon monoxide for 3 days at 24°. After the autoclave was cooled to −3°, 20 ml of 0.5 *N* iodine in anhydrous methanol solution was added, and the reactants were shaken for a further 12 h at room temperature. The contents of the autoclave were removed and allowed to stand in an open beaker until all ether and methanol had evaporated. The resultant residue was extracted with ether and on evaporation of the ether gave 490 mg of syrup (homogeneous by t.l.c.) which was identical to that obtained in the previous two procedures.

Reaction of Methyl 3,4,6-Tri-O-acetyl-2-deoxy-2-iodo-α-D-mannopyranoside (6) with Sodium Cobalt Tetracarbonyl and Carbon Monoxide to Yield Methyl 4,6-Di-O-acetyl-2,3-dideoxy-α-D-erythro-hex-2-enoside (7)

Procedure A

Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-iodo-α-D-mannopyranoside (16) (0.5 g) was allowed to react with 50 ml of an ether solution of 0.25 *M* sodium cobalt tetracarbonyl and 10 atm of C.P. carbon monoxide at 100° for 6 h. Work-up of the product, as described previously in Experimental Procedure A, afforded 200 mg of a syrup, $[\alpha]_D^{21}$ +126° (*c*, 1.2 in benzene), n_D^{23} 1.4580.

Anal. Calcd. for $C_{11}H_{16}O_6$: C, 54.1; H, 6.56. Found: C, 53.9, H, 6.50.

Nuclear magnetic resonance: singlet with shoulders at τ 4.10 equal to 2 vinyl protons; singlet at τ 6.55 equal to 3 methoxyl protons; singlet at τ 7.88 equal to 6 acetyl H.

Procedure B

When the same sugar (**6**) was allowed to react with sodium cobalt tetracarbonyl in ether and carbon monoxide at 25° for 8 days no reaction occurred.

Procedure C

Treatment of sugar (**6**) with sodium cobalt tetracarbonyl in methanol and carbon monoxide at 60° for 2 h yielded methyl 2,3-dideoxy-α-D-*erythro*-hex-2-enoside which was too unstable to be characterized. It was immediately acetylated using acetic anhydride and pyridine to yield methyl 4,6-di-*O*-acetyl-2,3-dideoxy-α-D-*erythro*-hex-2-enoside. Nuclear magnetic resonance of the latter compound revealed the presence of an additional singlet at τ 6.25 which might be due to the presence of a trace (less than 3%) of a compound containing a carbomethoxy group.

Treatment of methyl 3,4,6-tri-O-acetyl-2-bromo-2-deoxy-β-D-gluco- (and α-D-manno-) pyranoside with sodium cobalt tetracarbonyl and carbon monoxide—Under similar conditions to those described in I-A (except at a temperature of 100° for 8 h), both methyl 3,4,6-tri-*O*-acetyl-2-bromo-2-deoxy-β-D-gluco- (and α-D-manno-) pyranoside (16) underwent no appreciable reaction.

Preparation of Methyl 4,6-Di-O-acetyl-2,3-dideoxy-α,β-D-erythro-hex-2-enoside

3,4,6-Tri-*O*-acetyl-D-glucal (2 g) (18) was allowed to react with methanol in a rocking autoclave (previously flushed with nitrogen) at 180° for 4 h. After the methanol and acetic acid were removed from the unsaturated sugars by evaporation under reduced pressure, the residual syrup was distilled; yield 1.4 g, b.p. 80–83° (0.04 mm), $[\alpha]_D^{21}$ +136° (*c*, 1.2 in benzene), n_D^{23} 1.4565. Attempts to separate the mixture of unsaturated sugars by v.p.c. were unsuccessful. Nuclear magnetic resonance: vinyl protons at τ 4.04 and τ 4.10 (ratio of β:α anomer 5:9).

Acknowledgments

The authors gratefully acknowledge financial assistance from the U.S. Public Service Research Grant No. CA-08382, National Cancer Institute, and from the National Research Council of Canada.

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