621. *Periodate Oxidation. Part VII.* Reactions of Periodate-oxidised Methyl 4,6-O-Benzylidene-α-D-glucoside with Methanol and with Some Amino-compounds.*

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Structures are suggested for the products of methanolysis of periodate-oxidised methyl 4,6-*O*-benzylidene-α-D-glucoside and for derivatives formed with *o*-, *m*-, and *p*-nitroaniline, ethanolamine, and thiosemicarbazide.

Acid-catalysed removal of the benzylidene group from the hemialdal (I; R = R′ = OH) in the presence of methanol gave a compound $C_8H_{14}O_6$; a product of the same composition has been reported previously,[1] but without details. The reaction proceeds through an unidentified intermediate, detected chromatographically and by changes in optical rotation. On the available evidence, the compound, which contains two methoxyl groups, is assigned structure (II; R = OH). It gave no infrared absorption in the C=O stretching region but reduced Fehling's solution, indicative of a hemiacetal group. Reduction with potassium borohydride, followed by acid hydrolysis, gave glycollaldehyde and D-erythrose, showing that the second methoxyl group is present at position 5 and not at position 3. The presence of one hydroxyl group was proved by Purdie methylation, which introduced a third methoxyl group, and by formation of a mono-*p*-nitrobenzoate; neither of the derivatives absorbed in the OH stretching region of the infrared. Condensation compound (II; R = OH) with *o*- or *p*-nitroaniline yielded the derivatives (II; R = $NH{\cdot}C_6H_4{\cdot}NO_2$-*o* or -*p*). A prominent band near 815 cm.$^{-1}$ in the infrared spectra of compound (II; R = OH) and its derivatives may be characteristic of the bicyclic ring system.

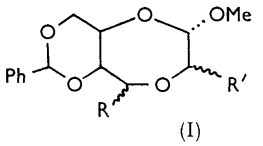
The hemialdal (I; R = R′ = OH) did not condense with *o*-, *m*-, or *p*-nitroaniline in boiling methanol, but in hot dimethylformamide containing acid the expected [2] derivatives

* Part VI, Guthrie, *J.*, 1961, 2525.

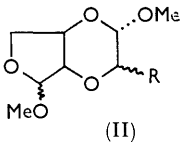
[1] Goldstein and Smith, *Chem. and Ind.*, 1958, 40; Goldstein, Lewis and Smith, American Chemical Society, Abstracts of Meeting, September 1957, 17D.

[2] Guthrie, Honeyman, and Parsons, *J.*, 1959, 2449.

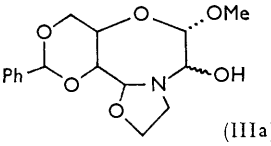
(I; R = R′ = NH·C_6H_4·NO_2) were formed. Reaction in methanol under acid conditions, however, rapidly produced the methylated nitroanilino-compounds (I; R or R′ = NH·C_6H_4·NO_2, R′ or R = OMe). With *o*-nitroaniline, loss of benzaldehyde and rearrangement occurred on prolonged heating, yielding the derivative (II; R = NH·C_6H_4·NO_2-*o*).



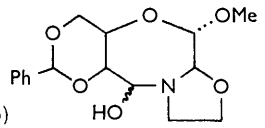
(I)



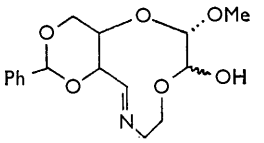
(II)



(IIIa)



(IIIb)



(IV)

On re-investigation, the reaction [3] of ethanolamine with compound (I; R = R′ = OH) was found to give a product, $C_{16}H_{21}NO_6$, which in carbon tetrachloride showed only a free OH stretching band (3580 cm.$^{-1}$) in the 3100—3600 cm.$^{-1}$ region, and is believed to be a perhydro-oxazepine (IIIa or b). A nuclear magnetic resonance spectrum measured in deuterochloroform is consistent with the presence of both isomers (a : b = 2 : 1) in solution and excludes the alternative structure (IV), since there is no signal due to a proton on carbon doubly bonded to nitrogen. The oxazepine is rapidly converted into a methyl ether by warm methanol.

From elementary analysis and the absence of infrared absorption at 1630—1700 cm.$^{-1}$ due to water of hydration or C=N groups, the derivative from the hemialdal and thiosemicarbazide is formulated as (I; R = R′ = NH·NH·CS·NH_2). Since the compound in ethanol shows $\lambda_{max.}$ at 237 and 275 mμ (0·5 ε = 12,700 and 22,800, respectively), characteristic of thiosemicarbazones,[4] dehydration must occur readily.

Experimental

The resin catalyst used was Amberlite IR-120 (H^+ form). Descending-flow paper chromatography was used with Whatman No. 1 paper and butan-1-ol–ethanol–water (40 : 11 : 19, v/v) as solvent. Rates of movement of compounds on chromatograms are quoted relative to that of L-rhamnose (R_{Rh} value). Infrared spectra were recorded on a Perkin-Elmer Infracord spectrophotometer and have been assigned D.M.S. Nos. between 10,412 and 10,429.

Reactions of trans-*Perhydro*-7,9-*dihydroxy*-6α-*methoxy*-2-*phenyl*-m-*dioxino*[5,4-e][1,4]-*dioxepin* (I; R = R′ = OH).*—(*a*) *With methanol and acid.* The hemialdal hydrate [5] (10 g.) in dry methanol (150 ml.) was boiled under reflux with resin (5 g.) for 2·5 hr. {$[\alpha]_D^{22}$ (5 cm. tube), + 0·04° (0 min.) ⟶ +0·87° (max., 60 min.) ⟶ +0·60° (150 min.)}. Paper chromatograms of the mixture, developed with an alkaline silver nitrate spray,[6] showed that the ether (I; R or R′ = OMe, R′ or R = OH) (R_{Rh} 2·0) and an unidentified intermediate compound (R_{Rh} 1·5) were present after 90 min. After 150 min., however, only one product (R_{Rh} 1·8) was detected and concentration of the solution then gave a solid, which crystallised from benzene as needles (3·8 g., 58%). This was recrystallised twice from carbon tetrachloride, to give cis-*perhydro*-3-*hydroxy*-2,5-*dimethoxyfuro*[3,4-b][1,4]*dioxin* (II; R = OH), m. p. 130—131°, $[\alpha]_D^{24}$ +25° (*c* 1·04 in $CHCl_3$), $[\alpha]_D^{22}$ +20° (*c* 1·00 in MeOH) [Found: C, 46·8; H, 6·8; OMe, 29·5%; *M* (Rast), 213. $C_8H_{14}O_6$ requires C, 46·6; H, 6·8; OMe, 30·1%; *M*, 206].

(*b*) *With* p-*nitroaniline.* A solution of the hemialdal hydrate (1 g.) in dry methanol (50 ml.) was boiled under reflux for 2 hr. with *p*-nitroaniline (0·9 g.) and resin (0·5 g.), filtered, and

* In structures I and II *trans* and *cis* define the respective manners of ring fusion.

[3] Colbran, Guthrie, and Parsons, *J.*, 1960, 3532.
[4] Evans and Gillam, *J.*, 1943, 565.
[5] Guthrie and Honeyman, *J.*, 1959, 2441.
[6] Trevelyan, Proctor, and Harrison, *Nature*, 1950, **166**, 444.

concentrated to 25 ml. The pale yellow product, after three recrystallisations from methanol, yielded trans-*perhydro*-6α,9(or 7)-*dimethoxy*-7(or 9)-p-*nitroanilino*-2-*phenyl*-m-*dioxino*[5,4-e]-[1,4]*dioxepin* (I; R or R′ = OMe, R′ or R = ·NH·C_6H_4·NO_2) [Found: C, 59·6; H, 5·7; N, 6·5. OMe, 13·9%; *M* (Rast), 413. $C_{22}H_{24}N_2O_8$ requires C, 59·5; H, 5·4; N, 6·3; OMe, 14·0%; *M*, 444].

The hemialdal hydrate (1 g.), *p*-nitroaniline (0·9 g.), and resin (*ca.* 0·5 g.) were boiled together in dimethylformamide for 30 min. The filtered mixture was then evaporated to dryness *in vacuo*. Extraction of the residue with acetone left trans-*perhydro*-6α-*methoxy*-7,9-*di*-p-*nitroanilino*-2-*phenyl*-m-*dioxino*[5,4-e][1,4]*dioxepin* (I; R = R′ = NH·C_6H_4·NO_2) as a pale yellow solid (0·7 g., 41%) which, after three recrystallisations from dimethylformamide, had m. p. 206·5—207° (Found: C, 58·1; H, 5·0; N, 10·3; OMe, 5·8. $C_{26}H_{26}N_4O_9$ requires C, 58·0; H, 4·9; N, 10·4; OMe, 5·8%).

(*c*) *With* o-*nitroaniline*. The hemialdal hydrate (2·0 g.) in dry methanol (50 ml.), was boiled for 10 min. with *o*-nitroaniline (1·8 g.) and resin (1 g.). trans-*Perhydro*-6α,9(or 7)-*dimethoxy*-7(or 9)-o-*nitroanilino*-2-*phenyl*-m-*dioxino*[5,4-e][1,4]-*dioxepin* (0·24 g., 9%) separated from the hot solution as yellow needles which, recrystallised from aqueous pyridine, had m. p. 244—245° (decomp.) (Found: C, 59·0; H, 5·8; N, 6·5; OMe, 14·3%). When a similar reaction mixture was heated for 2 hr., the first product slowly redissolved. On cooling, yellow crystals of cis-*perhydro*-2,5-*dimethoxy*-3-o-*nitroanilinofuro*[3,4-b][1,4]*dioxin* (I; R = ·NH·C_6H_4·NO_2) were formed, which, after recrystallisation from nitromethane, had m. p. 213·5—215·5° (decomp.), $[\alpha]_D^{21}$ +29° (*c* 0·91 in $CHCl_3$) [Found: C 51·6; H, 5·6; N, 8·8; OMe, 18·6%, *M* (Rast), 332. $C_{14}H_{18}N_2O_7$ requires C, 51·5; H, 5·6; N, 8·6; OMe, 19·0%; *M*, 326]. The same product was obtained when sulphuric acid was used as catalyst.

A mixture of the hemialdal hydrate (2 g.), *o*-nitroaniline (1·8 g.), and resin (1 g.) was boiled in dimethylformamide for 15 min., then filtered, and evaporated. The residue, on extraction with acetone followed by crystallisation from dimethylformamide, gave yellow trans-*perhydro*-6α-*methoxy*-7,9-*di*-o-*nitroanilino*-2-*phenyl*-m-*dioxino*[5,4-e][1,4]-*dioxepin* (I; R = R′ = ·NH·C_6H_4·NO_2) (0·22 g., 7%), m. p. 210·5—211° (Found: C, 57·7; H, 5·3; N, 9·8; OMe, 6·0. $C_{26}H_{26}N_4O_9$ requires C, 58·0; H, 4·9; N, 10·4; OMe, 5·8%).

(*d*) *With* m-*nitroaniline*. The hemialdal hydrate (2 g.), *m*-nitroaniline (2 g.), and resin (1 g.) were boiled for 30 min. in dry methanol. The solution was filtered, concentrated, and allowed to cool. Yellow trans-*perhydro*-6α,9(or 7)-*dimethoxy*-7(or 9)-m-*nitroanilino*-2-*phenyl*-m-*dioxino*[5,4-e][1,4]*dioxepin* separated and, recrystallised from methanol, had m. p. 200·5—201·5° (Found: C, 59·2; H, 5·9; N, 6·8; OMe, 14·2%).

The hemialdal hydrate (1 g.), *m*-nitroaniline (1 g.), and resin were boiled in dimethylformamide (50 ml.) for 30 min. Evaporation of the filtered solution *in vacuo* to dryness and crystallisation of the residue from acetone yielded yellow trans-*perhydro*-6α-*methoxy*-7,9-*di*-m-*nitroanilino*-2-*phenyl*-m-*dioxino*[5,4-e][1,4]*dioxepin*, m. p. 192—193° (Found: C, 58·4; H, 5·3; N, 10·9; OMe, 5·8%).

(*e*) *With ethanolamine*. A solution of the hemialdal hydrate (5 g.) in ethanolamine (20 ml.) was kept at 100° for 15 min., cooled, and poured on acetic acid (20 ml.) and ice. The precipitated solid (3·2 g.) was isolated, washed with water, dried at 20°, and crystallised from acetonitrile to give *perhydro*-7-*hydroxy*-6α-*methoxy*-2-*phenyl*-m-*dioxino*[5,4-f]*oxazolo*[3,2-d][1,4]-*oxazepine* (IIIa) or *perhydro*-10-*hydroxy*-6α-*methoxy*-2-*phenyl*-m-*dioxino*[5,4-f]*oxazolo*[2,3-c]-[1,4]*oxazepine* (IIIb), m. p. 160—161° (Found: C, 59·5; H, 6·8; N, 4·3. $C_{16}H_{21}NO_6$ requires C, 59·4; H, 6·6; N, 4·3%).

The hydro-oxazepine (1 g.) in methanol (2 ml.) was boiled for 30 min. and the solution then cooled to 0°. The solid product was collected and crystallised from light petroleum (b. p. 60—80°), to give colourless needles of the *dimethyl ether*, m. p. 123—127° (Found: C, 60·3; H, 6·8; N, 4·2; OMe, 17·0. $C_{17}H_{23}NO_6$ requires C, 60·5; H, 6·9; N, 4·2; OMe, 18·4%).

(*f*) *With thiosemicarbazide*. The hemialdal hydrate (10 g.) in ethanol (500 ml.) and thiosemicarbazide (10 g.) in 50% aqueous ethanol (200 ml.) were mixed at the b. p. The solution was then cooled and concentrated *in vacuo* to 100 ml.; a gum was deposited, which, on trituration with cold water (500 ml.), afforded a white powder (12·5 g.). The crude product (6 g.) dissolved readily in cold acetonitrile (30 ml.), but after a short time crystallisation occurred, to give trans-*perhydro*-6α-*methoxy*-2-*phenyl*-7,9-*bisthiosemicarbazido*-m-*dioxino*[5,4-e][1,4]*dioxepin* (I; R = R′ = NH·NH·CS·NH_2), m. p. 142—144° (Found: C, 43·6; H, 5·2; N, 19·2; S, 14·3. $C_{16}H_{24}N_6O_5S_2$ requires C, 43·3; H, 5·4; N, 18·9; S, 14·4%).

Reactions of cis-*Perhydro*-3-*hydroxy*-2,5-*dimethoxyfuro*[3,4-b][1,4]*dioxin.*—(*a*) *With* p-*nitrobenzoyl chloride.* The compound (0·5 g.) in pyridine (10 ml.), was treated with *p*-nitrobenzoyl chloride (0·5 g.) at 100° for 5 min., and then at 20° for a further 30 min. The product, isolated in the usual way, on recrystallisation from light petroleum (b. p. 80—100°), gave white needles of cis-*perhydro*-2,5-*dimethoxy*-3-p-*nitrobenzoyloxyfuro*[3,4-b][1,4]*dioxin* (II; R = ·O·CO·C_6H_4·NO_2) (0·32 g., 37%), m. p. 142—143°, $[\alpha]_D^{21}$ +2° (*c* 1·04 in $CHCl_3$) (Found: C, 50·7; H, 4·7; N, 4·3; OMe, 17·3. $C_{15}H_{17}NO_9$ requires C, 50·7; H, 4·8; N, 3·9; OMe, 17·5%).

(*b*) *With potassium borohydride.* A solution of potassium borohydride (0·06 g.) and the compound (0·5 g.) in 50% aqueous methanol (25 ml.) was kept at room temperature until its optical rotation was constant (90 min.), then brought to pH 3—4 with dilute hydrochloric acid and evaporated to dryness, and the residue extracted with ethyl acetate. The extract was concentrated to a syrup, water (10 ml.) and resin (0·5 g.) were added, and the solution was boiled for an hour, then filtered. The filtrate gave a red colour with acidified ethanolic phloroglucinol, a reaction given by D-erythrose [7] but not by erythritol, glyoxal, or glycollaldehyde, and it rapidly reduced Fehling's solution in the cold, a property of D-erythrose and glycollaldehyde, but not of glyoxal and erythritol. Paper chromatograms, sprayed with alkaline silver nitrate, revealed hydrolysis products with the R_{Rh} values of glycollaldehyde (1·6—2·1) and D-erythrose (0·8—1·3). A benzamidine–sodium hydrogen carbonate spray [8] did not give the intense pink streak characteristic of glyoxal, and no precipitate was obtained when the mixture was treated with aqueous thiosemicarbazide.

(*c*) *Methylation.* A solution of the hemiacetal (1 g.) in methyl iodide (25 ml.) and methanol, containing one drop of dimethylformamide, was heated under reflux. Fresh silver oxide (2 g.) was added in three portions during 1 hr., and after 5 hr. the mixture was filtered and evaporated to dryness. The residue crystallised from light petroleum (b. p. 60—80°), giving cis-*perhydro*-2,3,5-*trimethoxyfuro*[3,4-b][1,4]*dioxin* (II; R = OMe) (0·76 g., 71%) as white needles, which, after two further crystallisations, followed by sublimation *in vacuo*, had m. p. 110—112·5°, $[\alpha]_D^{21}$ +61° (*c* 0·327 in MeOH) (Found: C, 49·5; H, 7·5; OMe, 41·1. $C_9H_{16}O_6$ requires C, 49·1; H, 7·3; OMe, 42·3%).

(*d*) *With* o- *and* p-*nitroaniline.* The compound (0·5 g.) was dissolved in methanol (20 ml.), and *o*-nitroaniline (0·4 g.) was added. After addition of resin (0·5 g.) the solution was boiled under reflux for 2 hr., filtered, and concentrated until a yellow product separated. Crystallisation of this from nitromethane gave *cis*-perhydro-2,5-dimethoxy-3-*o*-nitroanilinofuro-[3,4-b][1,4]dioxin (II; R = ·NH·C_6H_4·NO_2), m. p. 214—215°, not depressed on admixture with an authentic sample. Under similar conditions, *p*-nitroaniline gave needles of cis-*perhydro*-2,5-*dimethoxy*-3-p-*nitroanilinofuro*[3,4-b][1,4]*dioxin*, m. p. 213—214° (from methanol) (Found: C, 51·4; H, 5·6; N, 8·7; OMe, 19·3. $C_{14}H_{18}N_2O_7$ requires C, 51·5; H, 5·6; N, 8·6; OMe, 19·0%).

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[8] Ekeley and Ronzio, *J. Amer. Chem. Soc.*, 1935, **57**, 1353.