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Note

Glucopyranosides derived from 2-hydroxy-1,4-naphthoquinones†

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As an approach to improving the ease of formulation of the antimalarial drug 3-(1-cyclohexyloctyl)-2-hydroxy-1,4-naphthoquinone[1] (menoctone, **2**), attempts were made to convert it into the D-glucopyranosyl derivative. As a model for this work, similar studies were carried out with 2-hydroxy-1,4-napthoquinone (lawsone, **1**). We have not found any reports of glycosides of such hydroxybenzoquinones.

The Koenigs–Knorr condensation of **1** and **2** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide gave in moderate yields, in both cases, products difficult to purify. On the basis of spectral data[2] and after assuming the normal production of anomers in the glycoside formation from 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide[3], the major reaction products have been assigned the structures 4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1,2-naphthoquinone (**3**) and 4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-3-(1-cyclohexyloctyl)-1,2-naphthoquinone (**4**), respectively. Both compounds showed similar u.v. spectra with strong bands in the 400-nm region; such bands are not observed for 1,4-naphthoquinones[2] (Table I).

TABLE I

ULTRAVIOLET ABSORPTION BANDS FOR 1,2- AND 1,4-NAPHTHOQUINONES

Compound	λ_{max} (*log ε*)			*Ref.*
1,4-Naphthoquinone	246(4.28),	256(4.13),	334(3.44)	4
1,2-Napthoquinone	~250(4.4),	~345(3.4),	~395(3.5)	5
2-Methoxy-1,4-naphthoquinone[a]	~275(4.6),	~330(3.9)		6
4-Methoxy-1,2-naphthoquinone	250(4.07),	339(3.26),	403(3.29)	2
α-Lapachone[b]	248(4.41),	281(4.18),	333(3.43)	2
β-Lapachone[c]	257(4.45),	333(3.24),	430(3.28)	2
3	250(4.18),	335(3.14),	396(3.12)	
4	252(4.09),	331(3.11),	408(2.89)	

[a]Absorption bands below 260 nm were not determined. [b]A 1,4-naphthoquinone. [c]A 1,2-naphthoquinone.

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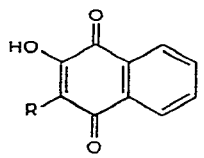
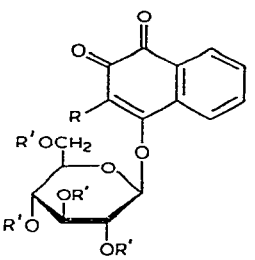
A minor product, isolated from the reaction with **1**, is thought to be 2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1,4-naphthoquinone, based on spectral data. Fieser[7] noted that alkylation of the silver salt of **1** gave predominantly the 4-alkoxy-1,2-naphthoquinone but pointed out that alkylations of 3-substituted 2-hydroxy-1,4-naphthoquinones should result in increased amounts of the 1,4-naphthoquinone product relative to its 1,2-naphthoquinone isomer. Thus, our results with **2** are somewhat surprising.

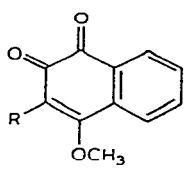
All attempts to deacetylate **3** and **4** to give the parent glycosides (**5** and **6**, respectively) were unsuccessful. Both compounds were very alkali-sensitive in accordance with Fieser's[7] observations on the alkali-sensitivity of ethers of hydroxynaphthoquinones. Attempted deacetylation of **4** with sodium methoxide, diisopropylamine[8], diethylamine, a weak base ion-exchange resin, or anhydrous zinc acetate[9] led to cleavage of the glycosidic linkage. In the reactions of **4** with sodium methoxide or amines in methanol the initial product was a material characterized by u.v.[2] and n.m.r. studies as the methoxy derivative **8**; on extended reaction this was slowly



1 R = H
2 R = $C_6H_{11}(CH_2)_8$



3 R = H, R' = Ac
4 R = $C_6H_{11}(CH_2)_8$, R' = Ac
5 R = R' = H
6 R = $C_6H_{11}(CH_2)_8$, R' = H



7 R = H
8 R = $C_6H_{11}(CH_2)_8$

converted into the starting material **2**. Similarly, attempted deacetylation of **3** with diisopropylamine in methanol led to the isolation of the known[7] compound, 4-methoxy-1,2-naphthoquinone (**7**). A careful search for methyl α-D-glucopyranoside was made but none was detected. This indicates that cleavage occurs by attack of the methoxide ion at the aglycon–oxygen bond and is analogous to the type of cleavage that has been noted for other alkali-sensitive glycosides[10].

EXPERIMENTAL

General. — Melting points are uncorrected. N.m.r. spectra were recorded at 60 MHz with a Jeolco C-60HL spectrometer and at 100 MHz with a Varian HA-100 spectrometer using tetramethylsilane as an internal reference. U.v. spectra were recorded with a Cary 15 spectrophotometer. Qualitative t.l.c. was performed on Eastman Chromagram Sheets 6060 (silica gel). Preparative t.l.c. was performed on gradient (1000–125 μm) plates coated with Silica Gel H (E. Merck, Darmstadt,

Germany). The microanalyses were performed by Micro-Analysis, Inc., Wilmington, Delaware. All evaporations were carried out *in vacuo* using either a water aspirator or a vacuum pump.

4-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-1,2-naphthoquinone (**3**). — A mixture of **1** (0.87 g, 5.0 mmoles), 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (1.64 g, 4.0 mmoles), silver oxide (0.55 g, 2.4 mmoles), powdered, anhyd. calcium sulfate (1.09 g), and dichloromethane (50 ml) was stirred for 26 h at room temp. The insoluble salts were removed by filtration and the solvent evaporated to give 2.60 g of a dark-red gum. T.l.c. (chloroform) indicated the presence of unreacted **1** and two additional products (one in a minor amount). Most of the unreacted **1** was removed by repeated extraction with 5% aqueous sodium acetate solution. Purification of the residue by crystallization failed and pure samples of the products were obtained by preparative t.l.c. (chloroform). The major product (R_F 0.46, chloroform) was successfully crystallized from hexane–carbon tetrachloride, m.p. 162.5–163.0°, and characterized as **3** (yield ~40%); u.v. data λ_{max}^{EtOH} 205 (log ε 4.09), 250 (log ε 4.18), 335 (log ε 3.14), 396 nm (log ε 3.12); n.m.r. data (chloroform-*d*): δ 8.01 (multiplet, 1 H, aromatic proton), 7.63 (multiplet, 2 H, aromatic protons), 7.20 (singlet, 1 H, aromatic proton), 5.97 (singlet, 1 H, olefinic proton), 5.30 (multiplet, 4 H, sugar protons), 4.16 (multiplet, 3 H, sugar protons), 2.03 (multiplet, 12 H, acetyl protons); the anomeric sugar proton was not resolved.

Anal. Calc. for $C_{24}H_{24}O_{12}$: C, 57.14; H, 4.80. Found: C, 57.03; H, 4.83.

The minor product (R_F 0.70, chloroform) is thought to be the isomeric 2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-1,4-naphthoquinone (yield ~16%) based on the u.v. data: λ_{max}^{EtOH} 250 (log ε 4.29), 273 nm (log ε 4.17).

4-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyloxy)-3-(1-cyclohexyloctyl)-1,2-naphthoquinone (**4**). — A mixture of **2** (1.84 g, 5.0 mmoles), 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide (4.11 g, 10.0 mmoles), silver oxide (2.32 g, 10.0 mmoles), powdered, anhyd. calcium sulfate (2.72 g), and dichloromethane (50 ml) was stirred for 18 h at room temp. The insoluble salts were removed by filtration and the solvent evaporated to give 5.10 g of a dark-red gum. T.l.c. (chloroform) indicated the presence of unreacted **2** and two yellow-colored products which were obtained in pure form by chromatographic separation of the reaction mixture on a column containing Silica Gel 0.05–0.2 mm (E. Merck, Darmstadt, Germany). The major product (R_F 0.65, chloroform) is a gum which failed to crystallize; this material has been characterized as the monohydrate of 4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxy)-3-(1-cyclohexyloctyl)-1,2-naphthoquinone (**4**; yield ~56%); u.v. data: λ_{max}^{EtOH} 242 (log ε 4.08), 252 (log ε 4.09), 331 (log ε 3.11), 408 nm (log ε 2.89); n.m.r. data (chloroform-*d*): δ 8.06 (doublet, 1 H, aromatic proton), 7.80–7.40 (multiplet, 3 H, aromatic protons), 5.50–5.00 (multiplet, 4 H, sugar protons), 4.36–3.86 (multiplet, 3 H, sugar protons), 2.70–0.40 (multiplets, 39 H, acetyl and cyclohexyloctyl protons); the anomeric sugar proton was not resolved. A sample was dried under high vacuum for 18 h at 80° before analysis.

Anal. Calc. for $C_{38}H_{50}O_{12}\cdot H_2O$: C, 63.67; H, 7.31. Found: C, 63.71; H, 7.10.

The minor reaction product has not been characterized, but it does not appear to be the 1,4-naphthoquinone isomer of **4**.

Attempted deacetylation of **4** *with sodium methoxide.* — A sample of **4** (0.070 g, 0.1 mmole) was dissolved in anhyd. methanol (1 ml), 0.1M methanolic sodium methoxide (5 μl) added, and the solution heated over a steam-bath for 2 min; t.l.c. indicated that no change had taken place. The addition of more sodium methoxide failed to cause a reaction until a total of 75 μl had been added. At this point the appearance of a new compound (R_F 0.83, chloroform), later shown to be 3-(1-cyclohexyloctyl)-4-methoxy-1,2-naphthoquinone (**8**) was observed. When a total of 160 μl of sodium methoxide had been added, **4** had reacted and only **2** and **8** remained. Finally, the addition of more sodium methoxide was found to decrease the amount of **8** and increase the amount of **2**. Similar results were obtained with diisopropylamine, diethylamine, or Amberlite IR-45 (OH^-) in methanol.

Attempted deacetylation of **4** *with anhydrous zinc acetate.* — A solution of **4** (0.050 g, 0.072 mmole) and anhyd. zinc acetate (0.013 g, 0.072 mmole) in abs. ethanol (8 ml) was heated for 20 h under reflux. T.l.c. indicated that **4** had been completely converted to **2**.

3-(1-Cyclohexyloctyl)-4-methoxy-1,2-naphthoquinone (**8**). — A solution of **4** (0.20 g, 0.29 mmole) and diisopropylamine (0.19 g, 1.9 mmole) in anhyd. methanol (20 ml) was heated for 75 min under reflux and then evaporated to give a dark oil. T.l.c. indicated the presence of one major product and small amounts of **2** and **4**; D-glucose was identified as the only sugar cleavage product. The major product was isolated as an orange gum by preparative t.l.c. and characterized as 3-(1-cyclohexyloctyl)-4-methoxy-1,2-naphthoquinone (**8**; yield ~20%) by spectral data; u.v. data: λ_{max}^{EtOH} 254 (log ε 4.44), 332 (log ε 3.29), 421 nm (log ε 3.22); n.m.r. data (chloroform-*d*): δ 7.84–6.84 (multiplets, 4 H, aromatic protons), 3.80 (singlet, 3 H, methoxyl protons), 2.37 and 1.77–0.40 (multiplets, 27 H, cyclohexyloctyl protons).

4-Methoxy-1,2-naphthoquinone (**7**). — A solution of **3** (0.097 g, 0.19 mmole) and diisopropylamine (0.14 g, 1.33 mmole) in anhyd. methanol (10 ml) was heated for 30 min under reflux and then evaporated to give a dark oil. T.l.c. indicated the presence of **1** and a major product that was isolated by preparative t.l.c. and characterized as 4-methoxy-1,2-naphthoquinone (**7**, yield ~43%); yellow–orange needles from methanol, m.p. 189–190.5° (lit.[7]: m.p. 190°); u.v. data: λ_{max}^{EtOH} 208 (log ε 4.12), 250 (log ε 4.24), 275 (log ε 3.85), 329 (log ε 3.22), 404 nm (log ε 3.15); n.m.r. data (chloroform-*d*): δ 7.94–6.97 (multiplet, 4 H, aromatic protons), 5.74 (singlet, 1 H, olefinic proton), 3.87 (singlet, 3 H, methoxyl protons).

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