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SYNTHESIS OF ACETYLATED GLYCOSIDES OF HYDROXYNAPHTHOQUINONES

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A method is proposed for the synthesis of acetylated glycosides of hydroxynaphthoquinones. The condensation of D-glucose and D-galactose (tert-butyl orthoacetate)s with lawsone and lapachol has given the tetra-O-acetyl-β-D-glucopyranosides of lawsone and of lapachol and the tetra-O-acetyl-β-galactopyranoside of lawsone. The structures of the glycosides obtained have been confirmed by IR and ^1H and ^{13}C NMR spectroscopy. The structure of the lawsone acetylgalactopyranoside described previously has been corrected.

The majority of investigation of recent years in the field of the synthesis of glycosides of hydroxynaphthoquinones have been connected with the creation of water-soluble hydroxynaphthoquinone derivatives, which are necessary for studying the influence of the carbohydrate moieties on their biological activity. The tetra-O-acetyl-β-D-glucopyranosides of lawsone (40%) and menoctone (56%) with the o-quinoid structure of the aglycone [1], and the tetra-O-acetyl-D-glucopyranosides of lawsone (30%) and of lapachol (16%) and the tetra-O-acetyl-D-galactopyranoside of lawsone (28%) with the p-quinoid structure of the aglycone [3] have been obtained by using various modifications of the Koenigs–Knorr method. The acetates of glycosides of lawsone and lapachol exhibited antitumoral activity [2, 3]. The reduction of an acetylated D-glucose residue leads to a marked increase in the immunodepressive action of lawsone [4].

The biological activity of glycosides of hydroxynaphthoquinones makes necessary a search for new and more effective methods for their synthesis.

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TABLE 1. ^{13}C Chemical Shifts of Hydroxynaphthoquinone Glycoside (ppm relative to TMS)*

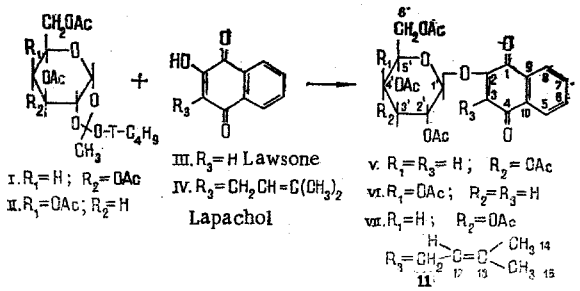
C atom	Compound				
	III†	V	VI	VIII	VII
1	180.1	178.8	178.8	179.2	180.9
2	160.2	157.4	157.4	157.1	152.6
3	109.8	114.9	114.8	115.4	137.8
4	184.8	184.8	184.4	184.8	184.8
5	126.6	126.7	126.7	126.7	126.5
6	134.3	134.2	134.3	134.3	134.1
7	133.1	133.6	133.7	133.6	133.4
8	126.1	126.1	126.1	126.2	126.0
9	131.0	131.1	131.0	131.2	131.2
10	132.0	131.7	131.6	131.8	131.9
11					25.8
12					119.4
13					134.1
14					18.1
15					23.5
1′		97.8	98.3	95.1	99.2
2′		70.6 ‡	71.9 ‡	68.4 ‡	71.7
3′		72.3 ‡	70.5 ‡	67.5 ‡	72.2 ‡
4′		68.1	67.9 ‡	67.5 ‡	68.4
5′		72.9 ‡	66.9 ‡	67.3 ‡	72.7 ‡
6′		61.9	61.6	61.4	61.7
$\underline{C}H_3COO$		20.5	20.5	20.5	20.5
$CH_3\underline{C}OO$		170	170	170	170

*The assignment of the signals from the ^{13}C spectra of the quinoid part of compounds (III, V-VII) was made on the basis of [10] and the assignment of the signals in the carbohydrate moieties of glycosides (V-VIII) on the basis of [11].

† Methyl ester.

‡ Assignment ambiguous.

Basing ourselves on a method described in the literature [5, 6], we have proposed a convenient method for the glycosylation of lawsone (III) [7], which consists in boiling equimolar amounts of the quinone with orthoesters of glucose (I) and of galactose (II) in absolute chlorobenzene. The proposed method of glycosylating hydroxy-1,4-naphthoquinones is stereospecific and gives the β-D-glycosides (V-VII) in good yields. An inert medium and the absence of any external catalysts whatever permits this method to be used for the glycosylation of labile hydroxynaphthoquinones.



The structures of glycosides (V-VII) were confirmed by the results of IR and NMR spectroscopy, and also by elementary analysis. Because of the tautomeric nature of the hydroxynaphthoquinones (III) and (IV), the formation of glycosides with either the o- or the p-quinoid structure of the aglycone is possible, in principle. The choice in favor of the p-quinoid structure of glycosides (V)-(VII) was made on the basis of a comparison of the ^{13}C spectra of 2-methoxy-1,4-naphthoquinone and of compounds (V-VII) (Table 1). The values of the SSCCs $J_{1',2'} = 7.3$ Hz in the ^1H spectrum of compound (VII) shows the β configuration of the glycosidic bond. In the case of compounds (V) and (VI), in the ^1H spectra of which no isolated signals of anomeric protons were observed, the configuration of the glycosidic bond was established from the chemical shift of the anomeric carbon atom in the ^{13}C spectra.

The conclusion of the β configuration of the glycosidic bond in (V) and (VI) was made on the basis of a comparison of the ^{13}C spectra of (V) and (VI) and those of the β- and α-tetra-O-acetyl-D-galactopyranosides (VI) and (VIII) (see Table 1), which agrees well with the results of the work of Steinerova et al. [4].

The process of glycosylation of (III) and (IV) by the orthoesters (I) and (II) apparently takes place by a mechanism of protonic catalysis [8], since 2-hydroxy-1,4-naphthoquinones are medium-strength acids (for lawsone, pK = 4) [9]. This case is obviously an example of autocatalysis when the glycosylated alcohol is simultaneously an acid catalyst. It is interesting that 5-hydroxy-1,4-naphthoquinone, the proton of the hydroxy group of which is bound by a strong intramolecular hydrogen bond and is deprived of mobility to a considerable degree as compared with the analogous proton of lawsone was practically inert under the conditions of the proposed method of glycosylation.

When the physicochemical characteristics of the glycosides (V) and (VI) which we have synthesized were compared with those of analogous substances described previously [3], considerable discrepancies in the melting points were observed. A careful analysis of the ^1H and ^{13}C spectra and a mixed melting point test of a sample of the galactopyranoside (VI) and compound (VIII) kindly supplied by Prof. M. M. de Oliveria showed that (VIII) has the α, not the β, configuration of the glycosidic bond, and the melting point of the glycoside (VI) that we had obtained did not agree with the literature figure [3]. Attempts to obtain lawsone glycosides by the method of [3] led to (V) and (VI) with the β configuration of the glycosidic bonds.

EXPERIMENTAL

Melting points were determined on a Boëtius stage. The specific rotations were measured on a Perkin-Elmer 141 polarimeter. NMR spectra were obtained on a Bruker HX-90 spectrometer with a working frequency of 90.0 MHz for ^1H and 22.6 MHz for ^{13}C at 30°C in $CDCl_3$, with TMS as internal standard. IR spectra were recorded on a Specord-IR spectrophotometer in $CHCl_3$. TLC was performed on Silufol plates (Czechoslovakia) in the hexane–benzene–acetone (2:1:1) system. The plates were previously saturated with NH_3 vapors to prevent decomposition of the orthoester during the process of chromatography. Spots were revealed by heating the plates. Column chromatography was performed on SiO_2 L (40-60 μ) (Czechoslovakia) in the hexane–acetone (10:1→2:1) system. The results of the elementary analyses of all the newly obtained compounds were in satisfactory agreement with the calculated values.

2-Hydroxy-1,4-naphthoquinone (lawsone) (III) was obtained as described by Donaldson [12], lapachol (IV) from lawsone as described by Jacobsen and Torrssel [13], 3,4,6-tri-O-acetyl-α-D-glucopyranosyl 1,2-(tert-butyl orthoacetate) (I) according to [14], and 3,4,6-tri-O-acetyl-α-D-galactopyranosyl 1,2-(tert-butyl orthoacetate) (II) according to [15].

General Procedure for the Glycosylation of Hydroxynaphthoquinones. A mixture of an orthoester (1 mmole), a hydroxynaphthoquinone (1 mmole), and 15 ml of absolute chlorobenzene was boiled until the orthoester had disappeared completely from the reaction mixture (1-6 h). The solvent was evaporated off in vacuum, the residue was dissolved in 50 ml of $CHCl_3$, and the solution was washed successively with 1 M K_2CO_3 solution (2× 20 ml) and with water (2× 20 ml) and was dried over Na_2SO_4. The solvent was eliminated and the desired glycoside was isolated from the residue by crystallization or by column chromatography. The combined wash-waters were acidified with HCl, extracted with ethyl acetate (2× 20 ml), washed with water (2× 20 ml), and dried with Na_2SO_4. The solvent was driven off, and the residue consisted of the chromatographically pure quinone.

2-(Tetra-O-acetyl-β-D-glucopyranosyloxy)-1,4-naphthoquinone (V). Yield 64%. $C_{24}H_{24}O_{12} \cdot 0.5\ CH_3OH$. mp 166.5–168.5°C (MeOH). $[\alpha]_D^{22}$ −30.6 (c 1.0; $CHCl_3$). Lit. [4], mp 168.5–170°C (ethanol). ^1H spectrum (δ, ppm): 2.05–2.12 (m, 12 H, 4 × OAc); 3.90–4.01 (m, 1 H, H_5'); 4.21–4.25 (m, 2 H $2H_6'$); 5.10–5.42 (m, 4 H, H_1', H_2', H_3', H_4'); 6.41 (s, 1 H, H_3); 7.61–7.84 (m, 2 H, H_6,H_7); 8.02–8.15 (m, 2 H, H_5, H_8). IR spectrum (ν cm^{-1}): 1758 (CH_3COO), 1689 and 1658 (C=O).

2-(Tetra-O-acetyl-β-D-galactopyranosyloxy)-1,4-naphthoquinone (VI). Yield 70%. $C_{24}H_{24}O_{12}$. mp 176–178°C (MeOH), $[\alpha]_D^{22}$ −16.6° (c 1.0; $CHCl_3$). ^1H spectra δ, ppm): 2.01–2.19 (m, 12 H, 4× OAc); 4.18 (m, 3 H, H_5', 2 H_6'); 5.12–5.22 (m, 2 H, H_2', H_3'); 5.47–5.54 (m, 2 H, H_1', H_4'); 6.46 (s, 1 H, H_3); 7.69–7.79 (m, 2 H, H_6' H_7); 8.02–8.06 (m, 2 H, H_5, H_8). IR spectra (ν, cm^{-1}): 1758 (CH_3COO), 1686 and 1656 (C=O).

2-(Tetra-O-acetyl-β-D-glucopyranosyloxy)-3-(3-methylbut-2-enyl)-1,4-naphthoquinone (VII). Yield 72%. mp 62–63°C (MeOH). Lit. [2]: mp 62–65°C (MeOH-ethyl acetate). ^1H spectrum (δ, ppm): 1.66 (s, 3 H, CH_3); 1.79 (s, 3 H, CH_3); 2.00–2.12 (m, 12 H, 4× OAc), 2.33 (d, J = 6.7 Hz, 2 H, 2 H_{11}); 3.90–4.00 (m, 1 H, H_5'); 4.08–4.20 (m, 2 H, 2 H_6'); 5.10–5.33 (m, 4 H, H_{12}, H_2', H_3', H_4'); 5.82 (d, $J_{1',2'}$ = 7.3 Hz, 1 H, 1 H_1'); 7.65–7.75 (m, 2 H, H_6, H_7); 8.00–8.09 (m, 2 H, H_5, H_8). IR spectrum (ν, cm^{-1}: 1758 (CH_3COO), 1673 and 1623 (C=O).

2-(Tetra-O-acetyl-α-D-galactopyranosyloxy)-1,4-naphthoquinone (VIII). mp 210–211°C (MeOH-ethyl acetate). $[\alpha]_D^{22}$ −170.4° (c 0.5 $CHCl_3$). ^1H spectrum (δ, ppm): 1.98–2.18 (m, 12 H, 4× OAc); 4.08–4.23 (m, 3 H,

H'_5, 2 H'_6); 5.35-5.38 (m, 1 H, H_3); 5.56-5.65 (m, 2 H, H'_2, H'_4); 5.88 (d, $J_{1',2'}$ = 3.2 Hz, 1 H, 1 H'_1); 6.54 (s, 1 H, H_3); 7.70-7.80 (m, 2 H, H_6, H_7); 8.04-8.12 (m, 2 H, H_5, H_8). IR spectrum (ν, cm^{-1}): 1748 (CH_3COO), 1681 and 1648 (C=O).

SUMMARY

A method is proposed for the synthesis of acetylated glycosides of hydroxynaphthoquinones.

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SYNTHESIS OF GLUCOSIDES OF 3-ALK[EN]YL-2-HYDROXY-1,4-NAPHTHOQUINONES

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The condensation of D-glucose (tert-butyl orthoacetate) with 3-alk[en]yl-2-hydroxy-1,4-naphthoquinones has yielded a series of acetylated glycosides of hydroxynaphthoquinones. It has been established that the time of the glycosylation reaction lengthens with an increase in the length and in the degree of branching of the side chain of the quinone. It has been shown that when the glycosides obtained are deacetylated cleavage of the glycosidic bond takes place with the formation of glucose and the corresponding quinone methyl ethers. Details of IR and ^1H and ^{13}C NMR spectra are given.

We have previously [1, 2] reported a new method of obtaining acetylated glycosides of hydroxynaphthoquinones which consists in boiling equimolar amounts of a quinone and an orthoester in absolute chlorobenzene without a catalyst. To elucidate the possibilities of the proposed method of glycosylation, a number of 3-alk[en]yl-2-hydroxy-1,4-naphthoquinones have been condensed with the glucose orthoesters (I) and (II). The results are given in Table 1.

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