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AUTOCATALYTIC CONDENSATION OF 1,2-ORTHOESTERS OF SUGARS WITH 2,3-DIHYDROXY-1,4-NAPHTHOQUINONE (ISONAPHTHAZARIN)

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The autocatalytic glycosylation of isonaphthazarine and its derivatives with 1,2-orthoesters of D-glucose and maltose in chlorobenzene has been studied. It has been established that the ratio of mono- and bisglycoside forms depends on the acidity of the glycosylated hydroxy group and its steric accessibility. Free monoglycosides of 2,3-dihydroxy-1,4-naphthoquinone have been synthesized by deacetylation with sodium methoxide in methanol.

In a number of cases, the conversion of 1,4-naphthoquinones into acetylated glycoside derivatives leads to an enhancement of antitumoral [1], immunotropic [2], and antifungal [3] activity of the basic aglycons. There is information on the presence of O-glycosides of naphthoquinone in natural materials. Thus, among the products of the microbial transformation of a natural antitumoral naphthoquinone – lapachol– its 2-O-β-D-glycoside has been found [4]. The isolation from the roots of the African plant Sesamum angolese Welw. (Pedaliacae) of two new naphthoxirane derivatives and their glycosides, which possess antifungal and cytotoxic action, has been reported [5].

The glycosylation of hydroxynaphthoquinones is usually performed by the Koenigs–Knorr method [1, 2, 6]. We have proposed to use for this purpose the autocatalytic condensation of hydroxynaphthoquinone with sugar 1,2-orthoesters [7]. We later [8] reported the reaction of orthoesters of D-glucose and of maltose with isonaphthazarin.

The aim of the present work was a detailed study of the autocatalytic reaction of 1,2-orthoesters of D-glucose (I) and of maltose (II) with isonaphthazarin (III) and its derivatives (IV, V), and also of the possibility of the deacetylation of the acetylglycosides obtained. When the orthoesters (I) and (II) were condensed with the quinones (III-V) in boiling chlorobenzene, the acetylated glycosides (VI-XII) were obtained. The structures of these compounds were established by IR and ^1H and ^{13}C NMR spectroscopies. The presence in each case of an intense band of the valence vibrations of a carbonyl group in the 1650-1640 cm^{-1} region showed the p-quinoid structure of the aglycon. The ^{13}C spectra (Table 1) also agreed well with the suggested structures and with literature information [7]. For each of bisglycosides (VII) and (IX) five signals belonging to the carbon atoms of the aglycon were observed, which showed the existence of a plane of symmetry in their structures. For the same reason, coincidence of the signals of the carbon atoms of the carbohydrate radicals was observed. The β-configuration of the glycosidic bond in (VI-IX) was confirmed by the value of the chemical shift of the anomeric C-1' carbon atom (99-100 ppm) and the SSCC of

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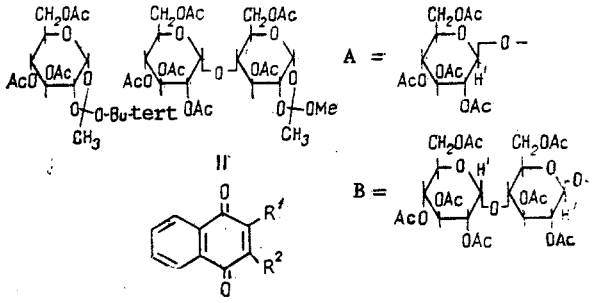
TABLE 1. ^{13}C Chemical Shifts of Isonaphthazarin Glycosides (δ, ppm)

C atom	Compound			
	VI	VII	VIII	IX
1	179,9	180,5	179,9	180,7
2	146,8	145,2	146,3	145,6
3	136,8	145,2	136,6	145,6
4	181,4	180,5	181,5	180,7
5	126,4[a]	126,4	126,3[a]	126,5
6	134,8[b]	134,1	134,8[b]	134,1
7	133,7[b]	134,1	133,5[b]	134,1
8	126,8[a]	126,4	126,7[a]	126,5
9	129,5[c]	130,5	128,3[c]	130,6
10	131,1[c]	130,5	131,2[c]	130,6
1	100,1	99,4	99,4	99,2
2	71,5*	71,5*	72,2*	72,5*
3	72,3*	72,4*	72,7*	72,7*
4	68,4*	68,1*	68,1*	68,1*
5	72,6*	72,6*	72,7*	72,7*
6	61,9	61,7	61,6	61,5
1	—	—	95,6	95,7
2	—	—	70,1*	70,1*
3	—	—	69,3*	69,4*
4	—	—	75,1*	75,1*
5	—	—	68,6*	68,5*
6	—	—	62,8	62,7

Note. The assignment of the signals was made as in [7]. The signals denoted by a, b, and c may be mutually interchanged. The signals marked with asterisks were not assigned. The signals of the acetate groups appeared at ∿20.5 and ∿170.5 ppm.

the anomeric proton (7.5 Hz) (X-XII). The absence from the reaction products of even traces of the α-anomers showed the stereospecificity of this method of glycosylation.



III. $R^1 = R^2 = OH$
IV. $R^1 = OH$; $R^2 = OMe$
V. $R^1 = OH$; $R^2 = OAc$
VI. $R^1 = A$; $R^2 = OH$
VII. $R^1 = R^2 = A$
VIII. $R^1 = B$; $R^2 = OH$
IX. $R^1 = R^2 = B$
X. $R^1 = A$; $R^2 = OMe$
XI. $R^1 = A$; $R^2 = OAc$
XII. $R^1 = B$, $R^2 = OAc$
XIII. $R^1 = \beta$-D-Glc; $R^2 = OH$
XIV. $R^1 = \beta$-Malt; $R^2 = OH$

In order to elucidate the reactivity of the hydroxy groups of isonaphthazarin, the reaction was performed at various ratios of quinone to orthoester. The results of these experiments are shown in Table 2. We have reported previously [7] that the glycosylation of 2-hydroxy-3-alkyl(alkenyl)-1,4-naphthoquinone with the D-glucose orthoester (I) becomes more difficult with an increase in the volume of the hydrocarbon radical. However, on the condensation of equimolar amounts of isonaphthazarin and the orthoester (I) (experiment 1)

TABLE 2. Conditions and Results of the Condensation of Isonaphthazarin (III) with Orthoesters of D-glucose (I) and of Maltose (II)

Experiment No.	Initial substances, mmole		Reaction time, h	Reaction products,* %		Recovery of the initial quinone, %
	quinone	orthoester		monoglycoside	bisglycoside	
1	1	(I), 1	1	(VI), 20	(VII), 22	43
2	1	(I), 2	1	(VI), 4	(VII), 72	14
3	1	(II), 1	5	(VIII), 46	(IX), 8	27
4	1	(II), 2	11	(VIII), 52	(IX), 41	3

*The yields are given on the isonaphthazarin taken in the reaction.

the predominant formation of the bisglucoside (VII) was observed. This result is apparently due to the increased acidity of the hydroxy group in the monoglycoside (VI) as compared with the acidity of the initial quinone (III). In actual fact, according to the results of potentiometric titration in 80% aqueous ethanol [9] the pK_a values (first dissociation constants) for these compounds were 5.35 for (VI), 5.95 for (VIII), and 7.30 for (III). On the condensation of (III) with the orthoester of maltose (II), the steric effect of the disaccharide radical directed the course of the reaction mainly towards the formation of the monomaltoside (VIII) (experiments 3 and 4).

In the following stage of the work the saponification of the acetylglycosides was carried out. It has been reported previously [6, 7] that on the deacetylation of acetylglycosides of 1,2- and 1,4-naphthoquinones the glycosidic bond undergoes cleavage taking place through the nucleophilic substitution of the glycosidic residue by a methoxide ion. On the deacetylation of the bisglycosides (VII) and (IX) we again observed the conversion of the initial substances into 2,3-dimethoxy-1,4-naphthoquinone. However, the deacetylation of the monoglycosides (VI) and (VIII) led to the formation of the free glycosides (XIII) and (XIV). We assume that in these compounds the stability of the glycoside bond is due to the presence of a hydroxy group in the vicinal position. The ionization of a quinoid hydroxy group considerably intensifies its electron-donating effect, which leads to a decrease in the positive charge on the carbon atom bearing the carbohydrate substituent and prevents the occurrence of the nucleophilic substitution reaction. For comparison, the saponification of the 3-methoxy derivative (X) having a weaker electron-donating substitutent than the phenoxy group in the monoglycoside (VI) led to the formation of 2,3-dimethoxy-1,4-naphthoquinone with a yield of 85%. It is more convenient to obtain the free monoglycosides from the acetyl derivatives (XI) and (XII), since the latter are formed in high yield. The isonaphthazarin glycosides (XIII) and (XIV) are readily soluble in ethanol, methanol, and water and are stable on storage. Their structure has been confirmed by IR spectroscopy and elementary analysis.

EXPERIMENTAL

Melting points were determined on a Boëtius stage. Optical rotation were measured on a Perkin-Elmer 141 polarimeter. NMR spectra were recorded on a Bruker XH-90 E instrument (90 MHz for ^1H and 22.63 MHz for ^{13}C) in $CDCl_3$; TMS – 0; δ, ppm. IR spectra were recorded on a Specord IR-75 spectrophotometer in $CHCl_3$ for (VI-XII) and in KBr tablets for (XIII) and (XIV).

Column chromatography was performed on silica gel L 40/100 μm prepared as described in [7]. The column was eluted with mixtures of the solvents hexane and acetone in ratios of 10:1-10:3.

For TLC we used Silufol plates impregnated with a 0.5 M alcoholic solution of oxalic acid and dried in the air. TLC was conducted in the following systems: 1) hexane–benzene–acetone (2:1:1); and 2) benzene–ethyl acetate–methanol (2:1:1). Uncolored substances were detected by heating the plates until the chromatographic spots had darkened.

The initial naphthoquinones were obtained as described in [10].

For all the new compounds obtained the results of elementary analysis agreed with the calculated figures.

General Method for Performing the Condensation of Isonaphthazarin (III) with the Orthoesters (I) and (II). A mixture of 1 mmole of the quinone, 1-2 mmole of the orthoester, and 10-15 ml of absolute chlorobenzene was boiled until all the orthoester had disappeared. This was checked by TLC, as in [7]. The chlorobenzene was evaporated off in vacuum and the residue was chromatographed on a column, giving glycosides (VI-XI).

2-Hydroxy-3-(tetra-O-acetyl-β-D-glucopyranosyloxy)-1,4-naphthoquinone (VI). Amorphous light-yellow powder, $[\alpha]_D^{25}$ −75.7° (c 1.0; $CHCl_3$). IR spectrum (ν, cm^{-1}): 1664, 1754, 3410. PMR spectrum (ppm): 2.04-2.10 (12H, 4 × OAc), 3.85 (1H, m H-5'), 4.20 (2H, m, 2 × H-6'), 5.16-5.44 (4H, m, H-1', H-2', H-3', H-4'), 7.67-7.84 (2H, m, H-6, H-7), 8.04-8.14 (2H, m, H-5, H-8).

2,3-Bis(tetra-O-acetyl-β-D-glucopyranosyloxy)-1,4-naphthoquinone (VII). Amorphous light-yellow powder, $[\alpha]_D^{25}$ +90.7° (c 1.0; $CHCl_3$). IR spectrum (ν, cm^{-1}): 1667, 1756. PMR spectrum (ppm): 2.01-2.10 (24H, 8 × OAc), 3.85 (2H, m, 2 × H-5'), 4.27 (4H, m, 4 × H-6'), 5.21-5.31 (6H, m, 2 × H-2', 2 × H-3', 2 × H-4'), 5.84 (2H, m, 2 × H-1'), 7.69-7.79 (2H, m, H-6, H-7), 8.02-8.12 (2H, m, H-5, H-8).

2-Hydroxy-3-[tri-O-acetyl-4-O-(tetra-O-acetyl-α-D-glucopyranosyl)-β-D-glucopyranosyloxy]-1,4-naphthoquinone (VIII). mp 173-174°C (ethanol–water, 80%), $[\alpha]_D^{25}$ +80.0° (c 1.0; $CHCl_3$). IR spectrum (ν, cm^{-1}), 1664, 1754, 3406. PMR spectrum (ppm): 2.01-2.13 (21H, 7 × OAc), 3.88-4.93 (7H, m, carbohydrate protons), 5.16-5.58 (7H, m, carbohydrate protons), 7.70-7.79 (2H, m, H-6, H-7), 8.04-8.14 (2H, m, H-5, H-8).

2,3-Bis-[tri-O-acetyl-4-O-(tetra-O-acetyl-α-D-glucopyranosyl)-β-D-glucopyranosyloxy]-1,4-naphthoquinone (IX). Amorphous light-yellow powder, $[\alpha]_D^{25}$ +24.0° (c 1.0; $CHCl_3$). IR spectrum (ν, cm^{-1}): 1670 and 1751. PMR spectrum (ppm): ...* (42H, 14 × OAc), 3.87-4.94 (14H, carbohydrate protons), 5.13-5.46 (12H, m, carbohydrate protons), 5.75 (2H, d, J = 6.5 Hz, 2 × H-1'), 7.69-7.79 (2H, m, H-6, H-7), 8.02-8.16 (2H, m, H-5, H-8).

2-Methoxy-3-(tetra-O-acetyl-β-D-glucopyranosyloxy)-1,4-naphthoquinone (X). A mixture of 1 mmole of the quinone (IV), 1 mmole of the orthoester (I), and 15 ml of absolute chlorobenzene was boiled for 2 h. The chlorobenzene was evaporated off in vacuum, the residue was dissolved in 30 ml of chloroform, the solution was washed with 15 ml of a 1 M solution of K_2CO_3 and with 2 × 20 ml of water, and the organic layer was dried over Na_2SO_4. The chloroform was evaporated off and the residue was crystallized from MeOH to give 0.42 g (78%) of (X). Yellow needles, mp 168-169°C, $[\alpha]_D^{25}$ −93.9°(c 1.0; $CHCl_3$). IR spectrum (ν, cm^{-1}): 1652, 1678, 1756. PMR spectrum (ppm): 2.00-2.15 (12H, 4 × OAc), 3.75 (1H, m, H-5), 4.20 (3H, s, CH_3O), 4.24 (2H, m, 2 × H-6'), 5.12-5.38 (3H, m, H-2', H-3', H-4'), 5.55 (1H, d, J = 7.5 Hz, H-1'), 7.70-7.80 (2H, m, H-6, H-7), 8.03-8.17 (2H, m, H-5, H-8).

2-Acetoxy-3-(tetra-O-acetyl-β-D-glucopyranososyloxy)-1,4-naphthoquinone (XI). A mixture of 1 mmole of the quinone (V), 1 mmole of the orthoester (I), and 15 ml of absolute chlorobenzene was boiled for 5 min. The reaction mixture was worked up as in the synthesis of (X). From the residue, 0.45 (80%) of (XI) was isolated by column chromatography. Amorphous light-yellow powder, $[\alpha]_D^{25}$ −67.5° (c 1.0; $CHCl_3$). IR spectrum (ν, cm^{-1}): 1671, 1752. PMR spectrum (ppm): 2.03-2.11 (12H, 4 × OAc), 2.38 (3H, s, ArOAc), 3.75 (1H, m, H-5'), 4.19 (2H, m, 2 × H-6'), 5.16-5.28 (3H, m, H-2', H-3', H-4'), 5.73 (1H, d, J = 7.5 Hz, H-1'), 7.70-7.84 (2H, m, H-6, H-7), 8.05-8.15 (2H, m, H-5, H-8).

2-Acetoxy-3-[tri-O-acetyl-4-O-(tetra-O-acetyl-α-D-glucopyranosyl)-β-D-glucopyranosyloxy]-1,4-naphthoquinone (XII). A mixture of 1 mmole of the quinone (V), 1 mmole of the orthoester (II), and 15 ml of absolute chlorobenzene was boiled until the (II) had disappeared (1.5 h). The reaction mixture was worked up as in the synthesis of (X). The residue was dissolved in acetone, and 0.64 g (76%) of the glycoside (XII) was precipitated by the slow addition of hexane. Light-yellow needles. mp 114-116°C, $[\alpha]_D^{25}$ +9.6° (c 1.0; $CHCl_3$). IR spectrum (ν, cm^{-1}): 1673, 1749. PMR spectrum (ppm): 2.00-2.12 (21H, 7 × OAc), 2.38 (3H, c, ArOAc), 3.82-4.90 (8H, m, carbohydrate protons), 5.10-5.45 (5H, m, carbohydrate protons), 5.84 (1H, d, J = 7.5 Hz, H-1'), 7.74-7.80 (2H, m, H-6, H-7), 8.06-8.14 (2H, m, H-5, H-8).

2-(β-D-Glucopyranosyloxy)-3-hydroxy-1,4-naphthoquinone (XIII). A solution of 0.2 mmole of the acetylglycoside (VI) or (XI) in 5 ml of 0.1 N methanolic sodium methanolate solution was left at 5°C for 1.5 h. The reaction mixture was neutralized with KU-2 (H^+) resin, the

*Values omitted in the Russian original – Translator.

resin was separated off and washed with methanol, and the filtrate was evaporated in vacuum. The resulting viscous residue was triturated with acetone until a yellow-brown powder had been formed. The powder was filtered off, washed with chloroform, and dried in vacuum to give 0.05-0.06 g (71-85%) of (XIII). $[\alpha]_D^{25}$ −53.8° (c 0.5; MeOH). IR spectrum (ν, cm^{-1}): 1657, 3200-3600.

2-[4-O-(α-D-Glucopyranosyl)-β-D-glucopyranosyloxy]-3-hydroxy-1,4-naphthoquinone (XIV). This was obtained by the deacetylation of (VIII) in a similar manner to (XII) for 3 h. Weight 0.07-0.08 g (66-80%). Light-brown powder, $[\alpha]_D^{25}$ +26.9° (c 1.0; MeOH). IR spectrum (ν, cm^{-1}): 1655, 3200-3600.

Interaction of the Acetylglycosides (VII), (IX), and (X) with Sodium Methanolate. A solution of 0.2 mmole of one of the acetylglycosides in 10 ml of methanol was treated with 0.2 ml of a 0.2 N solution of sodium methanolate. After 10 min, according to TLC (systems 1 and 2), the initial substance had disappeared from the reaction mixture and a product of low polarity with Rf 0.82 (system 1) had appeared. The reaction mixture was worked up as in the synthesis of (XIII), giving yellow needles with mp 112-114°C of a substance showing no depression of the melting point with an authentic sample of 2,3-dimethoxy-1,4-naphthoquinone. Weight 30-38 mg (68-85%).

SUMMARY

1. The autocatalycic glycosylation of isonaphthazarin (2,3-dihydroxy-1,4-naphthoquinone) and its derivatives by sugar 1,2-orthoesters has been studied.

2. The ratio of the mono- and bisglycosides formed depends on the acidity of the hydroxy group undergoing glycosylation and its steric accessibility.

3. Free monoglycosides of 2,3-dihydroxy-1,4-naphthoquinone have been synthesized for the first time.

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