Reaction of acetylated 1,4-naphthoquinone thioglucosides with nucleophilic reagents

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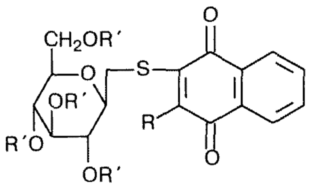
Acetylated thioglucosides of the 1,4-naphthoquinone series readily undergo heterocyclization into linear tetracyclic 2,3-(2′-oxy-β-D-glucopyranosyl-1′-thio)-1,4-naphthoquinone under the action of MeONa/MeOH. The treatment of these thioglucosides with NH_3/MeOH affords 2-amino-3-(glucopyranosyl-1′-thio)-1,4-naphthoquinone.

Key words: 1,4-naphthoquinones, thioglucosides, heterocyclization, amination.

Natural quinones and their nitrogen- and sulfur-containing heterocyclic derivatives are of great interest due to their high biological activity.[1,2]

To study the influence of carbohydrate radicals on the fungicidal and cytostatic activity of naphthoquinones, we have synthesized several acetylated thioglucosides of the 1,4-naphthoquinone series (**1a—e**).[3] Saponification of glycosides **1a,b** by MeONa/MeOH afforded the expected water-soluble glucoside (**2**) (yield 85 %).

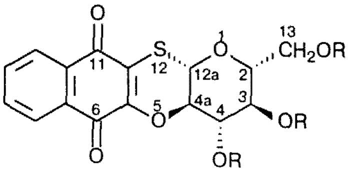
Under the same conditions of deacetylation of the related glycosides **1c—e**, the formation of a poorly soluble, orange precipitate was observed.



1a: R = OH, R′ = Ac
1b: R = AcO, R′ = Ac
1c: R = H, R′ = Ac
1d: R = OMe, R′ = Ac

1e: R = SGlc(Ac)$_4$, R′ = A
2: R = OH, R′ = H
4a: R = NH$_2$, R′ = Ac
4b: R = NH$_2$, R′ = H

The formation of the identical product from different starting compounds points to possible heterocyclization of the carbohydrate moiety of thioglucosides with the quinone nucleus into a structure of type **3a**.[4]



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R = H (**a**), Ac (**b**)

The ^{1}H NMR spectrum of a solution of compound **3a** in DMSO-d$_6$ exhibits characteristic multiplets of the H(8), H(9) and H(7), H(10) protons at 7.82 and 7.96 ppm, three one-proton signals of hydroxyl groups of the carbohydrate ring, which disappear after addition of CD_3OD, and the doublet of the anomeric proton of thioglucose H(12a) at 4.99 ppm ($J_{4a',12a}$ = 7.5 Hz).

Acetate **3b** was obtained by acetylation of **3a** with Ac_2O/Py. The signals of protons of three acetate groups, six protons of the carbohydrate ring, and four aromatic protons of naphthoquinone are observed in the ^{1}H NMR spectrum of acetate **3b**. Disappearance of the singlet of the quinone proton H(3) in the ^{1}H NMR spectrum of starting glucoside **1c** at 6.88 ppm and the upfield shift of the H(2′) signal of the carbohydrate ring to 3.91 ppm indicate participation of the hydroxyl group C(2′)—OH in bonding C(2′)—O—C(3) with 1,4-naphthoquinone. The presence of the base peak of the molecular ion (*m/z* 476) in mass spectrum of triacetate **3b** confirms our assumption on the formation of the cyclic product. Practically the same shape of signals of the aromatic protons H(7)—H(10) in the ^{1}H NMR spectra of com-

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pounds **3a** and **3b** compared to the starting glucosides, as well as the position of absorption bands of the quinone carbonyls in the IR spectrum characteristic of 1,4-naphthoquinones,[5] make it possible to rule out the alternative structure of chrysene type.

One can assume that the cyclization of substituted glycosides **1d—e** proceeds as the intramolecular Michael addition of C(2′)—OH-thioglucose to quinone ring and elimination of the substituent at C(3). In the case of glycoside **1c** devoid of a good leaving group, this process apparently proceeds through aromatization followed by oxidation of the hydroquinone intermediate. The observed easiness of the cyclization of thioglucosides of the 1,4-naphthoquinone series apparently results from the proximity of the C(2′)—OH hydroxyl group and the quinone nucleus and negligible solubility of the tetracyclic product in methanol.

Glycosides **1a** and **1b**, whose quinone hydroxyl groups are rapidly ionized in a basic medium, do not enter the heterocyclization.

When methanolic ammonia was used, tetracyclic compound **3a** was not formed. In this case, acetyl glucosides **1a** and **1b** are smoothly saponified to thioglucoside **2**, and acetyl derivatives **1c—e** rapidly transform to 2-aminoacetylglucoside (**4a**), which is slowly deacetylated to **4b**. The easiness of replacement of different radicals by amino group observed for these compounds is apparently related to the effect of the sulfur atom of the thioglucoside radical and more soft nucleophilicity of NH_3/MeOH *vs.* MeONa/MeOH. Under similar conditions (MeONa/MeOH; NH_3/MeOH), for acetylated O-glucosides of 1,4-naphthoquinone homologous to **1c—e**, the replacement of carbohydrate radicals by the methoxy group and the formation of 2-methoxy- and 2,3-dimethoxy-1,4-naphthoquinones were observed.[6—8]

Experimental

Melting points were measured with a Boetius heating stage. The IR spectra were recorded with a Specord IR-75 instrument, the ^{1}H NMR spectra were recorded with a Bruker WM-250 spectrometer using tetramethylsilane as the standard, and the mass spectra were measured with an LKB-9000S instrument. Optical rotations were measured with a Perkin-Elmer 141 polarimeter. Analytical and preparative TLC was carried out on Silufol UV-254 plates and silica gel L 5—40 μ using the following solvent systems: hexane—benzene—acetone (2 : 1 : 1) (A); benzene—ethyl acetate—methanol (2 : 1 : 1) (B). Slightly colored spots on chromatograms were displayed by treatment with vapors of aqueous ammonia and careful heating of the plates.

2-(β-D-Glucopyranosyl-1′-thio)-3-hydroxy-1,4-naphthoquinone (2). A 0.1 *N* solution of MeONa in MeOH (5 mL) was added to a suspension of **1a** or **1b** (2.0 mmol) in anhydrous MeOH (80 mL) and allowed to stay at 25 °C for 18 h. The reaction mixture was neutralized with a cation exchange resin KU-2(H+), the resin was filtered off, and washed with MeOH, and the filtrate was evaporated. Preparative TLC (system B) of the residue (0.72 g) gave amorphous, chromatographically pure thioglucoside **2** (0.63 g, yield 85 %), which was crystallized from MeOH—PrOH, m.p. 196—198 °C. $[\alpha]_D^{20}$ 0.0° (*c* 0.5, 50 % MeOH). IR (KBr), ν/cm^{-1}: 3378 (OH), 2895, 1664 (CO), 1623 (C=C), 1576, and 1546. ^{1}H NMR (DMSO-d$_6$) δ: 2.98—3.24 (m, 4 H, H(2′), H(3′), H(4′), H(5′)); 3.33 (dd, 1 H, H(6a′), $J_{5',6b'}$ = 5.0 Hz; $J_{6a',6b'}$ = 11.9 Hz); 3.47 (dd, 1 H, H(6b′), $J_{5',6b'}$ = 1.9 Hz); 5.25 (d, 1 H, H(1′), $J_{1',2'}$ = 9.3 Hz); 7.73—7.85 (m, 2 H, H(6) and H(7)); 7.93—7.99 (m, 2 H, H(5) and H(8)). Found (%): C, 52.40; H, 4.17; S, 8.92. $C_{16}H_{16}O_8S$. Calculated (%): C, 52.17; H, 4.38; S, 8.70.

(2*R*,3*R*,4*R*,4a*S*,12a*S*)-2-Hydroxymethyl-3,4-dihydroxy-12-thia-1,5-dioxa-2*H*,3*H*,4*H*,4a*H*,12a*H*-naphthacene-6,11-dione (3a). A solution of MeONa/MeOH (8 mL 0.1 *N*) was added to **1d** (0.22 g, 0.20 mmol), and the mixture was stirred for 1 h. The orange precipitate was filtered off, and washed with $CHCl_3$ and MeOH, and quinone **3a** was obtained. Yield 0.128 g (91 %), m.p. 337—340 °C (decomp.). IR (KBr) ν/cm^{-1}: 3464, 3350 (OH), 1644 (CO), 1590, and 1568 (C=C). ^{1}H NMR (DMSO-d$_6$) δ: 3.25—3.65 (m, 5 H, H(2), H(3), H(4), H(4a), H(13a)); 3.74 (ddd, 1 H, H(13b), $J_{13a,13b}$ = 10.0 Hz, $J_{2,13b}$ = 1.2 Hz; $J_{13b,C(13)-OH}$ = 5.7 Hz); 4.77 (t, 1 H, C(13)—OH); 4.99 (d, 1 H, H(12a), $J_{4a',12a}$ = 7.5 Hz); 5.43 (d, 1 H, C—OH, *J* = 5.3 Hz); 5.71 (d, 1 H, C—OH, *J* = 5.3 Hz); 7.78—7.86 (m, 2 H, H(8) and H(9)); and 7.91—8.01 (m, 2 H, H(7) and H(10)). Under the similar conditions, acetyl glucosides **1c** and **1e** afforded tetracyclic compound **3a** in yields 48 and 79 %, respectively.

(2*R*,3*R*,4*R*,4a*S*,12a*S*)-2-Acetoxymethyl-3,4-diacetoxy-12-thia-1,5-dioxa-2*H*,3*H*,4*H*,4a*H*,12a*H*-naphthacene-6,11-dione (3b). Ac_2O (1 mL) was added to a suspension of quinone **3a** (0.150 g) in Py (2 mL), and the resulting mixture was stirred for 16 h. The reaction mixture was poured into ice, the precipitated crystals of **3a** were filtered off, washed with diluted a HCl solution and water, dried and recrystallized from MeOH. Yield 0.130 g (65 %). M.p. 205—207 °C. $[\alpha]_D^{20}$ +118.1° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$), δ: 2.08, 2.14, 2.18 (3 Ac); 3.91 (dd, 1 H, H(4a), $J_{4a,12a}$ = 8.0 Hz; $J_{4,4a}$ = 9.5 Hz); 3.95 (ddd, 1 H, H(2), $J_{2,13a}$ = 2.3 Hz; $J_{2,13b}$ = 4.7 Hz; $J_{2,3}$ = 9.5 Hz); 4.20 (dd, 1 H, H(13a), $J_{13a,13b}$ = 12.0 Hz), 4.31 (dd, 1 H, H(13b); 4.89 (d, 1 H, H(12a); 5.24 (d, 1 H, H(4), $J_{3,4}$ = 9.0 Hz); 5.48 (dd, 1 H, H(3)), 7.74 (m, 2 H, H(8) and H(9)); and 8.08 (m, 2 H, H(7) and H(10)). Mass spectrum (10 eV), *m/z* (I_{rel} (%)): 476 $[M]^+$ (100), 415 (18), 373 (76), 313 (75), 296 (28), and 168 (15). IR ($CHCl_3$) ν/cm^{-1}: 1750 (COOR), 1670, 1660 (CO), 1596, and 1572 (C=C). Found (%): C, 55.16; H, 4.01; S, 6.95. $C_{22}H_{20}O_{10}S$. Calculated (%): C, 55.46; H, 4.23; S, 6.73.

2-Amino-3-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl-1′-thio)-1,4-naphthoquinone (4a). A 9 *N* methanolic NH_3 solution (2.5 mL) was added to quinone **1d** (0.275 g) in MeOH (15 mL) with stirring. After 5 min, **1d** transformed to a more polar, yellow compound. The reaction mixture was evaporated and preparative TLC of the residue (system A) afforded **4a** (0.275 g, 88 %). M.p. 191—193 °C (acetone—hexane). $[\alpha]_D^{20}$ +64.0° (*c* 0.1, MeOH). ^{1}H NMR ($CDCl_3$), δ: 1.96, 2.02, 2.06, and 2.16 (4 Ac); 3.67 (ddd, 1 H, H(5′), $J_{5',6a'}$ = 2.5 Hz; $J_{5',6b'}$ = 5.0 Hz; $J_{4',5'}$ = 10.0 Hz); 4.12 (dd, 1 H, H(6a′), $J_{6a',6b'}$ = 12.5 Hz); 4.25 (dd, 1 H, H(6b′)); 4.77 (d, 1 H, H(1′), $J_{1',2'}$ = 9.5 Hz); 4.98 (t, 1 H, H(4′), $J_{3',4'}$ = 9.0 Hz); 5.05 (t, 1 H, H(2′), $J_{2',3'}$ = 9.5 Hz); 5.20 (t, 1 H, H(3′)); 6.42 (br.s, 2 H, NH_2); 7.65 (dt, 1 H, H(6) or H(7)), J_m = 1.5 Hz, J_o = 7.0); 7.76 (dt, 1 H, H(6) or H(7)); 8.09 (dd, 1 H, H(5) or H(8), J_m = 1.5 Hz, J_o = 7.0 Hz); and 8.15 (dd, 1 H, H(5) or H(8)). IR ($CHCl_3$), ν/cm^{-1}: 3472, 3366 (NH_2), 1756 (COOR), 1680 (CO), 1602, and 1576 (C=C). Found (%): C, 53.53; H, 4.60; N, 2.43; S, 6.08. $C_{24}H_{25}NO_{11}S$. Calculated (%): C, 53.83; H, 4.71; N, 2.62; S, 5.99. Under the similar conditions, acetylglucosides **1c** and **1e** afforded acetylaminoquinone **4a** in yields 64 and 76 %, respectively, and **1a** and **1b** gave thioglucoside **2** (yields 78—81 %).

2-Amino-3-(β-D-glucopyranosyl-1′-thio)-1,4-naphthoquinone (4b). A 9 *N* solution NH_3 in MeOH (2.5 mL) was added to quinone **1e** (0.275 g) in MeOH (15 mL). The reaction mixture allowed to stay overnight. The orange precipitate was filtered off and recrystallized from a mixture of anhydrous MeOH and acetone (2 : 1), giving **4b** (0.130 g, 71 %). M.p. 271—274 °C. $[\alpha]_D^{20}$ +19.2° (*c* 0.063, 50 % MeOH). ^1H NMR (DMSO-d_6), δ: 2.99 m (2 H, carbohydrate. protons); 3.17 m (2 H, carbohydrate. protons); 3.34 m (1 H, H(6a′), $J_{6a',6b'}$ = 12.0 Hz); 3.63 (m, 1 H, H(6b′), J = 1.5 Hz); 4.41 (d, 1 H, H(1′), $J_{1',2'}$ = 9.5 Hz; 4.53 (t, 1 H, C(6′)—OH, J = 6.0 Hz); 5.01 (d, 1 H, C′—OH, J = 5.5 Hz); 5.10 (d, 1 H, C′—OH, J = 4.5 Hz); 5.26 (d, 1 H, C′—OH, J = 4.5 Hz); 7.77 (ddd, 1 H, H(6) or H(7), J_m = 1.5 Hz, J_o = 7.0 Hz), 7.86 (ddd, 1 H, H(6) or H(7)); 8.01 (ddd, 1 H, H(5) or H(8), J_m = 1.5 Hz, J_o = 7.0 Hz); 8.03 (ddd, 1 H, H(5) or H(8)). IR (KBr), ν/cm^{-1}: 3492 (OH), 3396 (NH_2), 3250, 1686 (CO), 1600, and 1574 (C=C). Found (%): C, 52.07; H, 4.42; N, 3.64; S, 8.92. $C_{16}H_{17}NO_7S$. Calculated (%): C, 52.31; H, 4.66; N, 3.81; S, 8.73.

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