

METHOXYLATION OF SUBSTITUTED 1,4-BENZOQUINONES*

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Methoxylation of 1,4-benzoquinones *I* and *Ia* with boron trifluoride–methanol complex afforded methyl 15-(5,6-dimethoxy-1,4-benzoquinon-2-yl)pentadecanoate (*Ila*) and methyl 15-(2-hydroxy-3,5-dimethoxyphenyl)pentadecanoate (*IIIa*). Structure of the products was established by spectroscopic methods.

Some time ago we isolated some new 2-methoxy-6-carboxyalkyl-1,4-benzoquinones from the wood-rotting fungus *Sarcondontia setosa* (PERS.) DONK¹. The present communication deals with methoxylation of the benzoquinone nucleus in these compounds. Our aim was to introduce another methoxy group *ortho* to the methoxyl in the starting benzoquinone, a reaction important for preparation of ubiquinone analogues from 2-methoxy-6-alkyl-1,4-benzoquinones. Substituted 1,4-benzoquinones can be alkoxyated by the Thiele acetylation^{2,3} or by reaction with alcohols^{4,5}. However, no *ortho* substitution to the methoxy group in the starting 1,4-benzoquinone has been hitherto described.

In our study, we used the 1,4-benzoquinones *I* and *Ia* as model compounds and boron trifluoride–methanol complex as the methoxylation reagent.

The acid *I* undergoes first esterification and then, on prolonged treatment, the benzoquinone nucleus is methoxylated to give 2,3-dimethoxy-6-substituted 1,4-benzoquinone (*Ila*), together with the side-products *IIIa* and *IVa*. The methyl ester *Ia* reacts directly on the benzoquinone nucleus. The quality of solvent plays an important role in the reaction: if the water content is higher than 0.1 mg/1 ml methanol, the reaction does not proceed in the desired way and gives predominantly compound *IVa*.

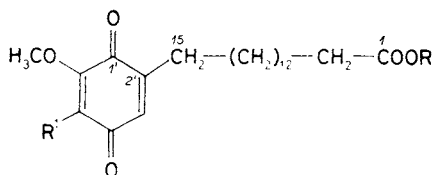
The structure of compounds *Ila* and *IIIa* was determined by spectroscopic methods, the structure of compound *IVa* is only tentative.

Mass spectrum of the benzoquinone *Ila* exhibits, similarly to those of *I* and *Ia*, characteristic molecular and $M + 2$ ions together with the ion at m/z 183, characterizing substitution of the benzoquinone ring. Molecular ions of *Ila*, *IIIa*, and *IVa* lose methanol from the ester group (peaks $M - 32$) and then carbonyl (peaks

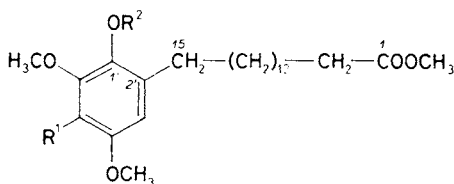
* Part I.I in the series Plant Substances; Part L: Biochem. Syst. Ecol., in press.

M – 32 – 28). This fragmentation path has been confirmed by products of decomposition of metastable ions.

The ^1H NMR spectrum of compound *Ila* exhibited only one one-proton signal at δ 6.38 (Table I). The published data for analogous compounds¹, together with a decoupling experiment, show that this signal can be ascribed to the $\text{H}_{(3')}$ proton, interacting with the $\text{H}_{(15)}$ protons ($^3J_{3',15} = 1.5$). The methoxy group is thus attached in the position 5'.



- I, R = H ; R' = H
 Ia, R = CH₃ ; R' = H
 II a, R = CH₃ ; R' = OCH₃



- III a, R¹ = H ; R² = H
 III b, R¹ = H ; R² = CONHCOCCI₃
 IV a, R¹ = OCH₃ ; R² = H
 IV b, R¹ = OCH₃ ; R² = CONHCOCCI₃

Oxidation of compound *IIIa* with ferric chloride afforded *Ia*. Compound *IIIa* contains a hydroxy group which can occupy position 1' or 4'. The found acylation shifts of $\text{H}_{(3')}$ ($\Delta\delta +0.04$) and $\text{H}_{(5')}$ ($\Delta\delta +0.05$), after reaction with trichloroacetyl isocyanate show that the hydroxyl is bonded in the position 1'. The second possibility (position 4') would have required about one order of magnitude higher acylation shifts⁶.

Proton NMR spectrum of compound *IVa* exhibits three signals due to methoxy groups. Compound *IVa* contains also a hydroxyl and there are thus several structures possible: methoxy groups in positions 4', 5', and 6' and hydroxyl in position 1', methoxy groups in positions 1', 5', and 6' and hydroxyl in position 4', or finally methoxy groups in positions 1', 3', and 6' and hydroxyl in position 4'. Spectral

analysis of *IVa* after reaction with trichloroacetyl isocyanate shows that the first alternative (methoxy groups in positions 4', 5', and 6' and hydroxyl in position 1') is the most probable. The reasoning is based on the assumption that the hydroxy group in position 4' is methylated only after methoxylation of the benzoquinone nucleus in position 5' (partial methylation of the hydroxyquinone corresponding to *IIa*) and that the acylation shift of the $H_{(15)}$ proton is negative ($\Delta\delta -0.07$). This is typical for cases where the acetylated hydroxyl and the proton in question are separated by several bonds but are close in space; the Van der Waals effect is described as the result of delocalization of lone electron pairs on the oxygen atom of the esterified hydroxyl group.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Analytical samples were dried at 13–1.3 Pa over phosphorus pentoxide for 12–15 h. Mass spectra were measured on an A.E.I. MS 902 spectrometer (70 eV, ion source temperature 120–150°C). The abridged data

TABLE I

Proton NMR spectral parameters of compounds *IIa*, *IIIa* and *IVa*

Protons	Chemical shifts				
	<i>IIa</i>	<i>IIIa</i>	<i>IIIb</i> ^a	<i>IVa</i>	<i>IVb</i> ^b
$H_{(2)}$	2.30 t	2.30 t	2.30 t	2.30 t	2.30 t
$H_{(15)}$	2.40 t	2.60 t	2.51 dd	2.56 t	2.49 t
$H_{(3')}$	6.38 t	6.29 d	6.33 d	6.43 bs	6.49 s
$H_{(5')}$	—	6.35 d	6.40 d	—	—
$OH_{(1')}$	—	5.34 s	—	5.42 s	—
$OCH_3(4')$	—	3.76 s ^c	3.81 s ^c	3.81 s ^c	3.86 s ^c
$OCH_3(5')$	4.02 s ^c	—	—	3.95 s ^c	3.92 s ^c
$OCH_3(6')$	4.00 s ^c	3.85 s ^c	3.80 s ^c	3.87 s ^c	3.86 s ^c
$COCH_3$	3.67 s	3.66 s	3.66 s	3.67 s	3.66 s
Coupling constants	<i>IIa</i>	<i>IIIa</i>	<i>IVa</i>		
$J_{2,3}$	7.8	7.5	7.5		
$J_{14,15}$	7.8	7.5	7.6		
$J_{15,3'}$	1.5	—	—		
$J_{3',5'}$	—	2.8	—		

^a $\delta_{NH} = 8.76$; ^b $\delta_{NH} = 8.74$; ^c may be interchanged.

give structurally important ions of relative intensity higher than 1%, other ions of relative intensity higher than 10%. Proton NMR spectra were taken on a Varian XL-200 instrument in deuteriochloroform, internal standard tetramethylsilane, chemical shifts in ppm, coupling constants in Hz. The reaction with trichloroacetyl isocyanate was performed according to the described standard procedure⁶. Infrared spectra were recorded on a UR-20 spectrometer in chloroform (wavenumbers in cm^{-1}), UV spectra on a Specord UV-VIS instrument in methanol (wavelengths λ in nm, extinction coefficients ϵ in $1 \text{ mol}^{-1} \text{ cm}^{-1}$). Analytical high performance liquid chromatography (HPLC) was carried out on a 4×100 mm column packed with silica gel Silasorb 600, 5μ (Lachema, Brno), semimicro preparative HPLC on a 12.7×500 mm column (silica gel Separon SI VSK 8 μ ; Laboratorní přístroje, Prague) and on a 25.3×500 mm column (Separon SI VSK 20 μ).

Methoxylation of 15-(6-Methoxy-1,4-benzoquinon-2-yl)pentadecanoic Acid (*I*)

Boron trifluoride-methanol complex (10 ml) was added to a solution of compound *I* (440.4 mg) in dry methanol (200 ml; 0.1 mg $\text{H}_2\text{O}/\text{ml}$ methanol) in the course of about 28 h. After addition of each portion the mixture was heated to the boil and left to cool slowly without stirring. The reaction was monitored by HPLC (4×100 mm column, mobile phase 5% ethyl acetate in dichloromethane, flow rate 1 ml/min, pressure 6.7 MPa, detection at 285 nm). After 140 h the mixture was mixed with toluene (100 ml) and water (100 ml) and the layers were separated. The aqueous layer was extracted with toluene (3×30 ml) and the combined organic layers were dried over magnesium sulfate and filtered. The solvent was evaporated in vacuo leaving 448.8 mg of crude residue. This material (437.1 mg) was subjected to HPLC (column 25.3×500 mm, injections 100 mg, mobile phase 2% ethyl acetate in dichloromethane, flow rate 21 ml/min, pressure 2 MPa, detection at 290 nm) to give 104.1 mg of a crude fraction, $t_{\text{R}} = 26$ min. This was further purified by HPLC (12.7×500 mm column, injections about 25 mg, 5% ethyl acetate in dichloromethane, 6 ml/min, 7.3 MPa, 292 nm) affording 64.6 mg of methyl 15-(5,6-dimethoxy-1,4-benzoquinon-2-yl)pentadecanoate (*IIa*) as orange crystals, m.p. 59–61°C. For $\text{C}_{24}\text{H}_{38}\text{O}_6$ (422.6) calculated: 68.21% C, 9.01% H; found: 68.12% C, 9.05% H. UV spectrum: λ_{max} 270, 405 nm ($\log \epsilon$ 4.09; 2.85). IR spectrum: CO 1 652, 1 672, C=C 1 608, COOCH_3 1 738 cm^{-1} . Mass spectrum, m/z (rel. intensity, %): 425 (3.5), 424 (14.2), 423 (15.4), 422 ($\text{C}_{24}\text{H}_{38}\text{O}_6$, 45.8), 394 (1.7), 393 (3.1), 392 (9.8), 391 (11.5), 390 ($\text{C}_{23}\text{H}_{34}\text{O}_5$, 22.9), 364 (1.7), 363 (1.7), 362 ($\text{C}_{22}\text{H}_{34}\text{O}_4$, 5.6), 209 (12.5), 184 (18.8), 183 ($\text{C}_9\text{H}_{11}\text{O}_4$, 100), 182 (25.0), 181 (39.6), 177 (12.5), 169 (16.7), 167 (12.5), 153 (12.5), 81 (12.5), 69 (19.8), 67 (14.6), 55 (45.8), 43 (27.1), 41 (40.6).

Another fraction ($t_{\text{R}} = 14$ min; 88.3 mg) from the first chromatography of the crude methoxylation mixture was purified by HPLC to give 83.9 mg of colourless methyl 15-(2-hydroxy-3,5-dimethoxyphenyl)pentadecanoate (*IIIa*), m.p. 47–48°C. For $\text{C}_{24}\text{H}_{40}\text{O}_5$ (408.6) calculated: 70.55% C, 9.87% H; found: 70.82% C, 9.86% H. UV spectrum: λ_{max} 223, 290 nm ($\log \epsilon$ 3.81; 3.56). IR spectrum: COOCH_3 1 734, OH 3 380, Ar 1 597, 1 609, $=\text{CH}$ 2 298 cm^{-1} . Mass spectrum, m/z (rel. intensity, %): 410 (3.9), 409 (23.0), 408 ($\text{C}_{24}\text{H}_{40}\text{O}_5$, 100), 407 (1.6), 406 (2.7), 378 (3.1), 377 (15.4), 376 (35.4), 375 (1.5), 349 (1.5), 348 (5.6), 168 ($\text{C}_9\text{H}_{12}\text{O}_5$, 28.7), 167 ($\text{C}_9\text{H}_{11}\text{O}_5$, 28.7), 55 (10.5).

Third fraction ($t_{\text{R}} = 32$ min; 21.1 mg) from the first chromatography of the crude methoxylation mixture was purified by HPLC to afford 5.9 mg of colourless methyl 15-(2-hydroxy-3,4,5-trimethoxyphenyl)pentadecanoate (*IVa*), m.p. 55°C. $\text{C}_{25}\text{H}_{42}\text{O}_6$ (438.6). IR spectrum: COOCH_3 1 725, OH 3 438 (in CCl_4 3 541), Ar 1 501, 1 602 cm^{-1} . Mass spectrum, m/z (rel. intensity, %): 440 (7.7), 439 (35.3), 438 ($\text{C}_{25}\text{H}_{42}\text{O}_6$, 100), 408 (5.5), 407 (22.6), 406 (34.0), 380 (1.3), 379 (3.4), 378 (12.8), 198 (17.0), 197 ($\text{C}_{10}\text{H}_{13}\text{O}_4$, 100), 183 (17.0), 121 (29.8), 69 (25.5), 55 (19.1), 41 (27.7).

Oxidation of Compound *IIIa*

A solution of *IIIa* (35.5 mg) in a mixture of toluene (5 ml) and acetic acid (2 ml) was stirred with 10% solution of ferric chloride at 30–40°C for 3 days. After separation, the aqueous layer was extracted with toluene (3 × 1 ml), the combined organic portions were dried over magnesium sulfate, filtered and the solvent was evaporated, leaving 33.8 mg of residue. This material (31.9 mg) was subjected to HPLC (12.7 × 500 mm column, 2% ethyl acetate in dichloromethane, 6 ml/min, 7.1 MPa, detection at 285 nm), affording 6.2 mg of *Ia*, m.p. 107–109°C, $t_R = 37$ min; M^+ m/z 392. $(M + 2)^+$ m/z 394, and 16.2 mg of starting *IIIa*, m.p. 45–47°C, $t_R = 16$ min; M^+ m/z 408.

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