

## METHYLATION OF SUBSTITUTED 1,4-BENZOQUINONES\*

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Methylation of 1,4-benzoquinones *I* and *Ia* with diazomethane afforded methyl 15-(6-methoxy-3-methyl-1,4-benzoquinon-2-yl)pentadecanoate (*IIa*) and methyl 15-(3-methoxy-2,5-dioxobicyclo[4.1.0]hept-3-en-1-yl)pentadecanoate (*IIIa*), methylation of 1,4-benzoquinone *IVa* led to methyl 15-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-yl)pentadecanoate (*Va*) and methyl 15-(3,4-dimethoxy-6-methyl-2,5-dioxobicyclo[4.1.0]hept-3-en-1-yl)pentadecanoate (*VIa*). Structure of the products was established by spectral methods.

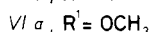
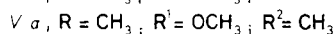
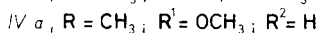
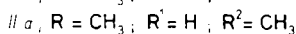
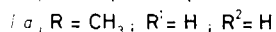
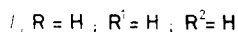
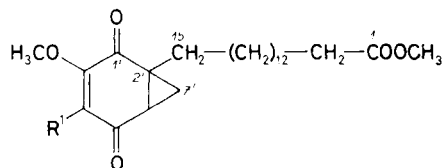
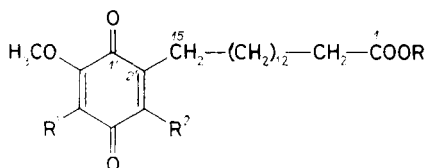
Substituted 1,4-benzoquinones can be methylated using diazomethane or diacetyl peroxide<sup>1</sup>; the latter reagent, however, gives low yields of products. In the naphthoquinone series also reactions with lead tetraacetate are employed<sup>2</sup>. Cycloaddition reactions of diazomethane can take place at the carbonyl group or at the double bond of the benzoquinone nucleus, depending on the solvent: the former type of addition occurs in methanol<sup>3-5</sup> whereas the latter in diethyl ether<sup>4,6,7</sup>.

Our present work concerns the methylation of the benzoquinone nucleus of 2-methoxy- and 2,3-dimethoxy-1,4-benzoquinones containing an aliphatic side-chain in position 6. As model compounds we used derivatives *I* and *Ia* and for the preparation of a ubiquinone analogue the derivative *IVa*. The methylations were performed with ethereal diazomethane.

The acid *I* is rapidly esterified (5 min) with an equimolecular amount of diazomethane; with an excess of diazomethane it reacts, again rapidly (5 min), to give the methylated 1,4-benzoquinone *IIa* and the bicycloheptene derivative *IIIa*. The reactivity of the benzoquinone nucleus is evident also from the fast reaction (5 min) of the methyl ester *Ia* which is converted to *IIa* and *IIIa* with only a slight excess of diazomethane (1 : 1.5). On the other hand, the reaction of the 2,3-dimethoxy-6-substituted-1,4-benzoquinone *IVa* proceeds only with a greater excess of diazomethane (molecular ratio 1 : 10) and after prolonged reaction time (60–90 min) under formation of compounds *Va* and *VIa*. No imidazole adducts were detected. The reaction products do not add further diazomethane, probably because of the presence of the bulky methoxy substituents and the aliphatic side-chain.

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Structure of the compounds *Ia*, *IIIa*, *Va*, and *VIa* was established by spectroscopic methods and elemental analysis. Similarly to compounds *I*, *Ia*, and *IVa*, the benzoquinones *IIIa* and *Va* exhibit molecular and  $M + 2$  ions and fragments characterizing substitution of the benzoquinone nucleus, *i.e.*  $m/z$  167 for *IIIa* and  $m/z$  197 for *Va*. The spectra of bicycloheptene derivatives *IIIa* and *VIa* exhibit two peaks, corresponding to two fragmentation paths. In the first fragmentation the cyclopropane ring is probably intact or only opened (peaks at  $m/z$  167 for *IIIa* and  $m/z$  197 for *VIa*), the second one is characterized by loss of methylene (peaks at  $m/z$  153 for *IIIa* and  $m/z$  183 for *VIa*). Molecular ions of *Ia*, *IIIa*, *Va*, and *VIa* lose methanol from the ester group (peaks  $M - 32$ ) and then carbonyl (peaks  $M - 32 - 28$ ). This fragmentation path was confirmed by products of decomposition of metastable ions.



Proton NMR spectral data for compounds *IIa*, *IIIa*, *Va*, and *VIa* are given in Table I. The spectrum of *IIa* exhibits only one one-proton signal. Its chemical shift ( $\delta$  5.87), together with the absence of interaction with the  $H_{(15)}$  protons, indicates that the signal belongs to the  $H_{(5')}$  proton. This assignment agrees with the published<sup>8</sup> NMR data for 2-methoxy-6-carboxyalkyl-1,4-benzoquinones (the protons  $H_{(5')}$  resonate at  $\delta$  5.56–5.88 whereas  $H_{(3')}$  at  $\delta$  6.38–6.49) and, accordingly, the methyl group (signal at  $\delta$  2.04) is bonded in the position 3'. The spectrum further contains two three-proton singlets at  $\delta$  3.67 and 3.79 due to the methyl ester and methoxy group, respectively, and two triplets at  $\delta$  2.30 and 2.49, corresponding to the two  $CH_2$  groups in positions 2 and 15.

The structure of compounds *IIIa* and *VIa* was suggested on the basis of the already described reactions of substituted 1,4-benzoquinones with diazomethane and confirmed by <sup>1</sup>H NMR spectroscopy. Signals of the  $H_{(15)}$  protons appear more upfield (1.25 ppm for *IIIa* and 1.24 ppm for *VIa*) than those for the already mentioned 1,4-benzoquinones (2.28–2.60 ppm)<sup>8</sup>. The two one-proton signals at  $\delta$  1.50 and 1.71 for *IIIa* and 1.46 and 1.65 for *VIa* were ascribed to the non-equivalent  $CH_2$  group

in position 7' on the basis of their geminal coupling constant ( ${}^2J_{7',7'} = 4.8$  Hz for *IIIa* and 4.5 Hz for *VIa*) and a decoupling experiment confirming an interaction with the  $H_{(3')}$  proton (signal at  $\delta$  2.36 for *IIIa* and 2.33 for *VIa*). The signal in the spectrum of *IIIa* at  $\delta$  5.60 is ascribed to the  $H_{(5')}$  proton. The three-proton signals at  $\delta$  3.67 for *IIIa* and  $\delta$  3.67 for *VIa* are due to the methyl ester groups and those at  $\delta$  3.73 (*IIIa*) and  $\delta$  3.92 and 3.93 (*VIa*) belong to the methoxy groups; the two-proton triplet at  $\delta$  2.30 was assigned to the methylene protons in position 2.

### EXPERIMENTAL

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

TABLE I  
Proton NMR spectral parameters for compounds *IIa*, *IIIa*, *Va*, and *VIa*

Protons	Chemical shifts			
	<i>IIa</i>	<i>IIIa</i>	<i>Va</i>	<i>VIa</i>
$H_{(2)}$	2.30 t	2.30 t	2.30 t	2.30 t
$H_{(15)}$	2.49 bt	1.25 m	2.45 bt	1.24 m
$H_{(3')}$	—	2.36 ddd	—	2.33 dd
$H_{(5')}$	5.87 s	5.60 d	—	—
$H_{(7')}$	—	1.50 dd	—	1.46 dd
		1.71 t		1.65 dd
$CH_3(3')$	2.04 bs	—	2.01 s	—
$OCH_3(5')$	—	—	3.99 s <sup>a</sup>	3.92 s <sup>a</sup>
$OCH_3(6')$	3.79 s	3.73 s	3.99 s <sup>a</sup>	3.93 s <sup>a</sup>
$COOCH_3$	3.67 s	3.67 s	3.67 s	3.67 s
Coupling constants	<i>IIa</i>	<i>IIIa</i>	<i>Va</i>	<i>VIa</i>
$J_{2,3}$	7.2	7.3	7.5	7.5
$J_{14,15}$	7.2	—	7.0	—
$J_{3',5'}$	—	2.0	—	—
$J_{3',7'}$	—	5.1	—	5.0
		8.6		8.7
$J_{7',7'}$	—	4.8	—	4.5

<sup>a</sup> May be interchanged.

1%. Other listed ions have relative intensity higher than 10%.  $^1\text{H}$  NMR spectra were measured on a Varian XL-200 instrument in deuteriochloroform with tetramethylsilane as internal standard. Chemical shifts are given in ppm, coupling constants in Hz. IR spectra were recorded on a UR-20 spectrometer in chloroform, wavenumbers are given in  $\text{cm}^{-1}$ . UV spectra were measured in methanol on a Specord UV-VIS instrument, wavelengths  $\lambda$  are given in nm, extinction coefficients  $\epsilon$  in  $1 \text{ mol}^{-1} \text{ cm}^{-1}$ . The reactions were monitored by analytical HPLC on a  $4 \times 100 \text{ mm}$  column packed with Silasorb 600  $5 \mu$  (Lachema, Brno) and the products were separated by HPLC on columns  $8 \times 250 \text{ mm}$  (Silasorb 600  $5 \mu$ , Lachema, Brno) and  $12.7 \times 500 \text{ mm}$  (Separon SI VSK  $8 \mu$ , Laboratorní přístroje, Prague).

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

An ethereal solution of diazomethane (9.9 ml; about 15 mg  $\text{CH}_2\text{N}_2/\text{ml}$ ) was added dropwise at room temperature to a solution of *I* (88.9 mg) in dichloromethane (8 ml). After standing for 5 min the solvents were evaporated *in vacuo*. The residue (96.2 mg) was separated by HPLC (column  $12.7 \times 500 \text{ mm}$ , injections about 30 mg, mobile phase 2.5% ethyl acetate in dichloromethane, flow rate 6 ml/min, pressure 4.9 MPa, detection at 293 nm).

The first fraction (15.4 mg;  $k' = 2.2$ ) after purification by HPLC under the same conditions as above afforded 10.5 mg of yellow methyl 15-(6-methoxy-3-methyl-1,4-benzoquinon-2-yl)-pentadecanoate (*IIa*), m.p. 89–90°C. For  $\text{C}_{24}\text{H}_{38}\text{O}_5$  (406.6) calculated: 70.90% C, 9.42% H; found: 70.84% C, 9.17% H. UV spectrum:  $\lambda_{\text{max}}$  275, 370 nm ( $\log \epsilon$  4.25; 2.60). IR spectrum: skeletal CO 1 650, 1 674, C=C 1 609,  $\text{COOCH}_3$  1 743  $\text{cm}^{-1}$ . Mass spectrum,  $m/z$  (rel. intensity, %): 410 (1.4), 409 (7.3), 408 (26.4), 407 (25.5), 406 ( $\text{C}_{24}\text{H}_{38}\text{O}_5$ , 100), 404 (2.7), 402 (1.8), 378 (2.7), 377 (1.1), 376 (40.0), 375 (29.1), 374 (81.8), 349 (1.8), 348 (8.2), 347 (4.5), 346 (16.4), 195 (13.6), 168 (54.5), 167 ( $\text{C}_9\text{H}_{11}\text{O}_3$ , 56.4), 166 (31.8), 122 (31.8), 105 (36.4), 81 (13.6), 77 (27.3), 69 (18.2), 67 (13.6), 57 (13.6), 55 (27.3), 43 (13.6), 41 (18.2).

The second fraction (23.2 mg;  $k' = 7.1$ ) was purified by HPLC to give 17.4 mg of colourless methyl 15-(3-methoxy-2,5-dioxobicyclo[4.1.0]hept-3-en-1-yl)pentadecanoate (*IIIa*), m.p. 74 to 75°C. For  $\text{C}_{24}\text{H}_{38}\text{O}_5$  (406.6) calculated: 70.90% C, 9.42% H; found: 70.83% C, 9.35% H. UV spectrum:  $\lambda_{\text{max}}$  235, 280 nm ( $\log \epsilon$  3.83; 3.81). IR spectrum: CO 1 672, 1 701, C=C 1 608,  $\text{COOCH}_3$  1 743  $\text{cm}^{-1}$ . Mass spectrum,  $m/z$  (rel. intensity, %): 408 (6.1), 407 (32.2), 406 ( $\text{C}_{24}\text{H}_{38}\text{O}_5$ , 100), 405 (3.5), 378 (2.2), 377 (1.7), 376 (9.6), 375 (40.0), 374 ( $\text{C}_{23}\text{H}_{34}\text{O}_4$ , 78.3), 348 (2.2), 347 (6.1), 346 ( $\text{C}_{22}\text{H}_{34}\text{O}_3$ , 20.0), 179 (33.3), 168 ( $\text{C}_9\text{H}_{12}\text{O}_3$ , 58.3), 167 ( $\text{C}_9\text{H}_{11}\text{O}_3$ , 62.5), 154 (25.0), 153 ( $\text{C}_8\text{H}_9\text{O}_3$ , 83.3), 138 (16.7), 137 (41.7), 139 (20.8), 81 (29.2), 79 (25.1), 69 (33.3), 67 (33.3), 55 (58.3), 43 (29.2), 41 (41.7).

#### Methylation of Methyl 15-(5,6-Dimethoxy-1,4-benzoquinon-2-yl)-pentadecanoate (*IVa*)

Ethereal solution of diazomethane (376  $\mu\text{l}$ ; about 15 mg  $\text{CH}_2\text{N}_2/\text{ml}$ ) was added dropwise at room temperature to a stirred solution of *IVa* (29.2 mg) in dichloromethane (4 ml). After stirring for 1 h the solvents were evaporated to give 29.4 mg of crude product. This material (27.0 mg) was subjected to HPLC (column  $8 \times 250 \text{ mm}$ , injections about 5 mg, 3% ethyl acetate in dichloromethane, 3.6 ml/min, 8.0 MPa, 285 nm), affording as the first fraction ( $k' = 3.5$ ) 6.5 mg of red methyl 15-(5,6-dimethoxy-3-methyl-1,4-benzoquinon-2-yl) pentadecanoate (*Va*), m.p. 58–60°C. For  $\text{C}_{25}\text{H}_{40}\text{O}_6$  (436.6) calculated: 68.78% C, 9.23% H; found: 68.71% C, 8.99% H. UV spectrum:  $\lambda_{\text{max}}$  270, 410 nm ( $\log \epsilon$  4.15; 2.60). IR spectrum: CO 1 653, 1 660, C=C 1 639,  $\text{COOCH}_3$  1 728  $\text{cm}^{-1}$ . Mass spectrum,  $m/z$  (rel. intensity, %): 440 (1.0), 439 (5.6), 438 (23.1), 437 (17.9), 436 ( $\text{C}_{25}\text{H}_{40}\text{O}_6$ , 62.8), 410 (2.8), 408 (3.6), 407 (5.1), 406 (17.9), 405 (15.4), 404 (35.9),

379 (2·1), 378 (4·6), 376 (10·0), 198 (143·), 197 (C<sub>10</sub>H<sub>13</sub>O<sub>4</sub> 100), 196 (37·7), 195 (20·8), 156 (13·0), 69 (15·6), 67 (11·7), 55 (28·6), 43 (15·6), 41 (23·4).

The second fraction ( $k' = 8·3$ ) was methyl 15-(3,4-dimethoxy-6-methyl-2,5-dioxobicyclo[4.1.0]-hept-3-en-1-yl)pentadecanoate (VIa) (3·0 mg), m.p. 43–45°C. For C<sub>25</sub>H<sub>40</sub>O<sub>6</sub> (436·6). UV spectrum:  $\lambda_{\max}$  214, 300 nm (log  $\epsilon$  3·93, 3·69). IR spectrum: COOCH<sub>3</sub> 1 729, CO<sub>4</sub> 1 661, 1 684, C=C 1 603 cm<sup>-1</sup>. Mass spectrum,  $m/z$  (rel. intensity, %): 439 (1·3), 438 (6·9), 437 (27·5), 436 (C<sub>25</sub>H<sub>40</sub>O<sub>6</sub> 100), 435 (8·4), 408 (3·1), 407 (3·4), 406 (8·4), 405 (20·2), 404 (18·8), 403 (5·0), 378 (1·6), 377 (5·9), 376 (15·6), 375 (3·8), 197 (37·7), 196 (30·2), 195 (11·3), 184 (15·1), 183 (50·9), 181 (30·2), 177 (13·2), 167 (35·8), 153 (15·1), 137 (15·1), 95 (13·2), 83 (13·2), 81 (18·9), 69 (22·6), 67 (13·2), 57 (13·7), 55 (30·8), 43 (15·5), 41 (20·8).

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