Notes

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Synthetic Studies on Anthracyclinones. XI.[1] Abnormal Products from Phenolic Compounds on Methylation with Dimethyl Sulfate in Tetrahydrofuran

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In the course of our synthetic works[1] on anthracyclinones,[3] 6,11-dihydroxynaphthacenequinone (I)[4] was found to be methylated with dimethyl sulfate in tetrahydrofuran to give four products, whose structures were established as II, III, IV and V.

The naphthacenequinone (I) was synthesized from 2-(4-bromo-1-hydroxy-2-naphthoyl)-benzoic acid (VI)[5] by cyclization with boric acid and concentrated sulfuric acid, followed by treatment with potassium hydroxide in glycerol in 54% yield.

Due to the poor solubility of I in other solvents, naphthacenequinone (I) was refluxed with dimethyl sulfate in tetrahydrofuran in the presence of anhydrous potassium carbonate for 18 hours to afford II, III, IV and V in 7%, 21%, 23% and 6% yields, respectively.

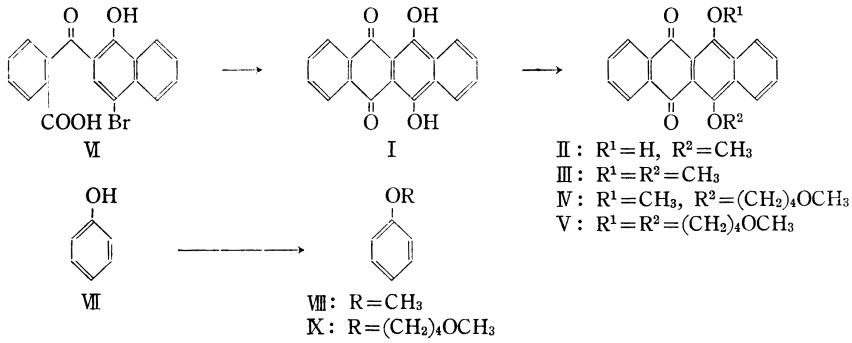


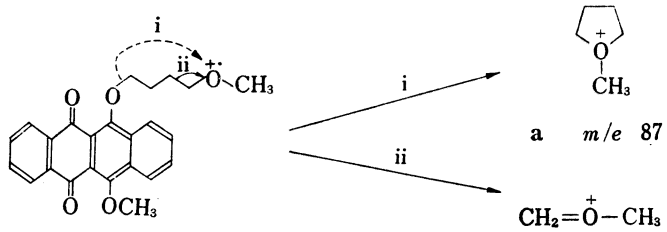
Chart 1

Compounds (II) and (III) were normal mono- and di-methyl ether, and identified with authentic samples obtained from I with dimethyl sulfate in acetone.

The third product (IV) was analyzed for $C_{24}H_{22}O_5$, which was supported by the appearance of the molecular ion peak at *m/e* 390 in the mass spectrum. Its infrared (IR) spectrum shows nonchelated quinone carbonyl absorption at 1679 cm^{-1}, and its ultraviolet (UV) spectrum is almost the same as that of III. The nuclear magnetic resonance (NMR) spectrum exhibits one aromatic methoxyl at 4.13 ppm, one aliphatic methoxyl at 3.37 ppm, one methylene adjacent to aryloxyl at 4.20 ppm as triplet with coupling constant of $J=6.5$ cps, one methylene adjacent to methoxyl at 3.54 ppm as triplet with coupling constant of $J=6.0$ cps, and two methylenes at

1) Part X: Z. Horii, H. Hakusui, T. Shigeuchi, M. Hanaoka, and T. Momose, *Yakugaku Zasshi*, **92**, 503 (1972).
2) Location: *6-1-1, Toneyama, Toyonaka, Osaka.*
3) H. Brockmann, *Fortshr. Chem. Org. Naturstoffe*, **21**, 121 (1963).
4) I. Ya. Postovskii and L.N. Goldyrev, *J. Gen. Chem.*, **11**, 429 (1941) [*Chem. Abstr.*, **35**, 6589[1] (1941)].
5) W. Logemann, F. Lauria, and E. Fachinelli, *Il Farmaco (Pavia), Ed. sci.*, **11**, 274 (1956) [*Chem. Abstr.*, **50**, 13940c (1956)].

2.50—1.70 ppm as multiplet besides eight aromatic protons. These data deduced the structure of IV as depicted, which was confirmed by the mass spectrum. The fragment peaks appear at *m/e* 375 (M^+-CH_3), *m/e* 303 (M^+-**a**), *m/e* 275 (M^+-**a**-CO), *m/e* 87 (**a**, base peak) and *m/e* 45 (**b**).



IV

Chart 2

The fourth product (V) has a molecular formula of $C_{28}H_{30}O_6$ (M^+ 462) and gave an IR or UV spectrum similar to that of IV. The fragment peaks also appear at *m/e* 87 (base peak) and *m/e* 45 in the mass spectrum, which led the structure of V to 6,11-bis(4-methoxybutoxy)-naphthacenequinone.

Similarly, phenol (VII) was methylated under the same reaction condition as above to yield anisole (VIII) and 4-methoxybutyl phenyl ether (IX) in 40% and 3.3% yields, respectively. The structure of IX was established by IR, UV, NMR and mass spectra.

Thus, when the phenolic compounds were treated with dimethyl sulfate in tetrahydrofuran as solvent, it was found that they reacted with tetrahydrofuran to afford new 4-methoxybutyl ethers besides normal methyl ether products.

Experimental[6]

6,11-Dihydroxynaphthacenequinone (I)——To the solution of conc. H_2SO_4 (78 ml) and H_3BO_3 (7.8 g) was added 2-(4-bromo-1-hydroxy-2-naphthoyl)benzoic acid (VI, 600 mg) in portions with stirring. The mixture was stirred at 110—120° for 10 min and at 140—150° for 20 min, and poured into ice water. The precipitates were collected, washed with sat. aq. $NaHCO_3$ solution and water, and dried to give dark red crystals (430 mg), which were suspended in glycerol (18 ml) with heating and stirring. To this suspension was added KOH (6 g) at 100°, and the mixture was stirred at 170—175° for 30 min. The reaction mixture was cooled, poured into ice water and acidified to Congo red with conc. HCl. The red precipitates were dried and recrystallized from nitrobenzene to yield 260 mg (54%) of I as dark red needles, mp 343—344° (lit.[4] 344—346°). *Anal.* Calcd. for $C_{18}H_{10}O_4$: C, 74.48; H, 3.47. Found: C, 74.79; H, 3.43. IR ν_{max}^{Nujol} cm^{-1}: 1630 (chelated quinone), ν_{max}^{KBr} cm^{-1}: 1635. Mass Spectrum *m/e* (%): 290 (M^+, 100).

Methylation of 6,11-Dihydroxynaphthacenequinone (I) in Tetrahydrofuran——Compound I (200 mg) was refluxed with dimethyl sulfate (400 mg) in THF (20 ml) in the presence of anhyd. K_2CO_3 (10 g) for 18 hr. After the solvent was removed, H_2O (50 ml) was added to the residue, and excess dimethyl sulfate was decomposed with conc. NH_4OH. The mixture was extracted with $CHCl_3$, and the extract was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give an orange solid (161 mg), which gave five spots on TLC with $CHCl_3$ as solvent. The crude product was chromatographed on silica gel with C_6H_6–$CHCl_3$ as eluent.

The first fraction gave 9 mg (4.5%) of starting material.

The second fraction gave crystals which were recrystallized from acetone to give 14 mg (7%) of 6-hydroxy-11-methoxynaphthacenequinone (II) as yellow needles, mp 197—199°. *Anal.* Calcd. for $C_{19}H_{12}O_4$: C, 74.99; H, 3.97. Found: C, 75.25; H, 4.25. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1677 (quinone), 1633 (chelated quinone), ν_{max}^{KBr} cm^{-1}: 1662, 1621. UV λ_{max}^{EtOH} mμ (log ε): 258 (4.84), 283sh (4.34), 299sh (4.14), 443 (4.14). Mass Spectrum *m/e* (%): 304 (M^+, 78), 275 (100).

The third fraction gave crystals which were recrystallized from EtOH to give 37 mg (21%) of 6,11-dimethoxynaphthacenequinone (III) as yellow needles, mp 196—197°. *Anal.* Calcd. for $C_{20}H_{14}O_4$: C, 75.46:

6) All melting points are uncorrected. NMR spectra were taken on Hitachi H-6013 spectrometer at 60 Mc in $CDCl_3$ with $(CH_3)_4Si$ as the internal standard. Mass spectra were taken on Hitachi RMU-6E spectrometer at 70 eV. Silica gel, Mallinckrodt or Kieselgel HF_{254}, was used for column chromatography or thin-layer chromatography (TLC).

H, 4.43. Found: C, 75.32; H, 4.40. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1679 (quinone), ν_{max}^{KBr} cm^{-1}: 1676. UV λ_{max}^{EtOH} mμ (log ε): 251 (4.85), 278—282infl. (4.53), 296 (4.51), 405 (4.08). Mass Spectrum *m/e* (%): 318 (M^+, 100), 289 (68).

The fourth fraction gave crystals which were recrystallized from EtOH–H_2O to give 62 mg (23%) of 6-methoxy-11-(4-methoxybutoxy)naphthacenequinone (IV) as yellow needles, mp 81—83°. *Anal.* Calcd. for $C_{24}H_{22}O_5$: C, 73.83; H, 5.68. Found: C, 73.83; H, 5.57. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1679 (quinone), ν_{max}^{KBr} cm^{-1}: 1682. UV λ_{max}^{EtOH} mμ (log ε): 251 (4.84), 279—283infl. (4.49), 294 (4.48), 405 (4.06). NMR δ: 8.60—8.10 (4H, m, arom.), 7.90—7.50 (4H, m, arom.), 4.20 (2H, t, J=6.5 cps, Ar–OC$\underline{H}_2$), 4.13 (3H, s, Ar–OC$\underline{H}_3$), 3.54 (2H, t, J=6.0 cps, –C$\underline{H}_2$OCH$_3$), 3.37 (3H, s, –CH$_2$OC$\underline{H}_3$), 2.50—1.70 (4H, m, C–C$\underline{H}_2$C$\underline{H}_2$–C). Mass Spectrum *m/e* (%): 390 (M^+, 5), 375 (1), 303 (5), 290 (5), 275 (16), 87 (100), 55 (11), 45 (45).

The fifth fraction gave crystals which were recrystallized from EtOH–H_2O to give 20 mg (6.3%) of 6,11-bis(4-methoxybutoxy)naphthacenequinone (V) as yellow needles, mp 84—86°. *Anal.* Calcd. for $C_{28}H_{30}O_6$: C, 72.71; H, 6.54. Found: C, 72.90; H, 6.47. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1679 (quinone), ν_{max}^{KBr} cm^{-1}: 1683. UV λ_{max}^{EtOH} mμ (log ε): 252 (4.57), 279—284infl. (4.20), 296 (4.17), 405 (3.73). Mass Spectrum *m/e* (%): 462 (M^+, 5), 375 (2), 290 (11), 87 (100), 55 (17), 45 (53).

Methylation of 6,11-Dihydroxynaphthacenequinone (I) in Acetone——Compound I (200 mg) was refluxed with dimethyl sulfate (600 mg) in acetone (30 ml) in the presence of anhyd. K_2CO_3 (10 g) for 18 hr. The reaction mixture was treated as above to give the crude product (193 mg), which was chromatographed on silica gel with C_6H_6–$CHCl_3$ as eluent.

The first fraction gave 44 mg (22%) of the starting material.

The second fraction gave 14 mg (7%) of II and was identified with that obtained above by mp, mixed mp, TLC and IR spectrum comparison.

The third fraction gave 133 mg (60%) of III and was identified with that obtained above by mp, mixed mp, TLC and IR spectrum comparison.

Methylation of Phenol (VII) in Tetrahydrofuran——Phenol (VII, 1.0 g) was refluxed with dimethyl sulfate (2.8 g) in THF (50 ml) in the presence of anhyd. K_2CO_3 (20 g) for 18 hr. The reaction mixture was treated in the same manner as in the case of the naphthacenequinone (I). The crude product was distilled to give 470 mg (40%) of anisole (VIII) as a colorless oil, bp 55° (20 mmHg), which was identical with authentic sample in bp, TLC and IR spectrum.

Chromatography of the residue resulted from distillation on silica gel with $CHCl_3$ as eluent, followed by distillation gave 64 mg (3.3%) of 4-methoxybutyl phenyl ether (IX) as a pale yellow oil, bp 135° (7 mmHg) (bath temp.). *Anal.* Calcd. for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.93; H, 8.90. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1600 (arom.). UV λ_{max}^{EtOH} mμ (log ε): 220.5 (4.00). NMR δ: 7.45—6.70 (5H, m, arom.), 3.98 (2H, t, J=6.0 cps, ArOC$\underline{H}_2$–), 3.44 (2H, t, J=6.0 cps, –C$\underline{H}_2$OCH$_3$), 3.34 (3H, s, –CH$_2$OC$\underline{H}_3$), 1.95—1.60 (4H, m, C–C$\underline{H}_2$C$\underline{H}_2$–C). Mass Spectrum *m/e* (%): 180 (M^+, 7), 94 (27), 87 (78), 55 (28), 45 (100).

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Studies on the Physical Properties of Aromatic Sulfinamides. II.[1] Infrared Absorption Spectrum[2]

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Although the physical properties of sulfonamide derivatives have been investigated in detail,[4] those of sulfinamide derivatives have been left almost in ambiguity. This paper deals with the results obtained from the infrared spectra of 25 aromatic sulfinamide derivatives[5] measured in both $CHCl_3$ solution and KBr disks.

1) Part I: K. Mori and Y. Ueda, *Yakugaku Zasshi*, **91**, 940 (1971).
2) A part of this paper was read at the 90th Annual Meeting of the Pharmaceutical Society of Japan (Sapporo) on July 29, 1970.
3) Location: *Katakasu, Fukuoka.*
4) A review by J.K. Seydel, *J. Pharm. Sci.*, **57**, 1455 (1968).
5) We are expecting these spectra will be published by I.R.D.C. cards.