Acta Chemica Scandinavica B 29 (1975) 948—952

Periodate Oxidation of Phenols. XVIII.* Oxidation of 2-Methoxyphenols with Periodic Acid in Methanol

GUNVOR ANDERSSON and PEDER BERNTSSON

Department of Organic Chemistry, Chalmers University of Technology and University of Göteborg, Fack, S-402 20 Göteborg 5, Sweden

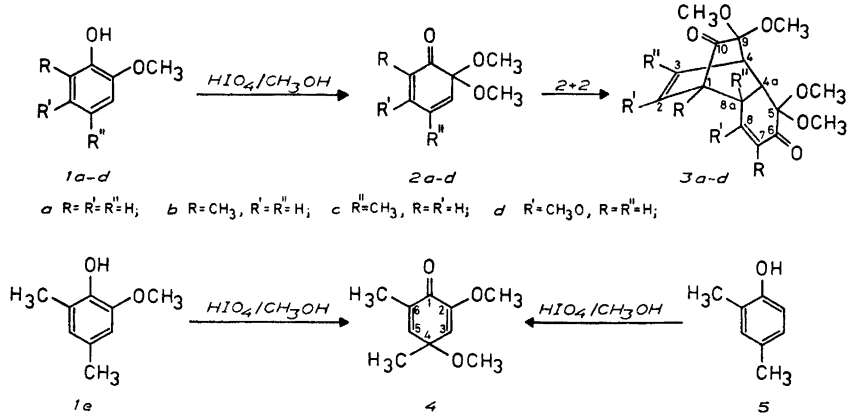
Treatment of the 2-methoxyphenols *1a—d* with methanolic periodic acid gives the corresponding 6,6-dimethoxy-2,4-cyclohexadienones (*o*-quinone dimethyl ketals) *2a—d*, which more or less rapidly undergo Diels-Alder dimerization to the bis(ketals) *3a—d*. The competitive formation of 4-methoxy-4-methyl-2,5-cyclohexadienones (*4*, *11*) from the 4-methyl substituted phenols *1c* and *1e*, as well as the formation of iodinated by-products (*10*, *13*), is also described.

In Part XVII[1] of this series the oxidation of various 2-methylphenols with periodic acid (HIO_4) in methanolic solution to give 6-methoxy-6-methyl-2,4-cyclohexadienones ("*o*-quinol methyl ethers") has been reported. The present paper describes the analogous formation of the 6,6-dimethoxy-2,4-cyclohexadienones *2a—d* ("*o*-quinone dimethyl ketals"; the term "*o*-quinals" has also been proposed[2]) on similar treatment of the 2-methoxyphenols *1a—d*.

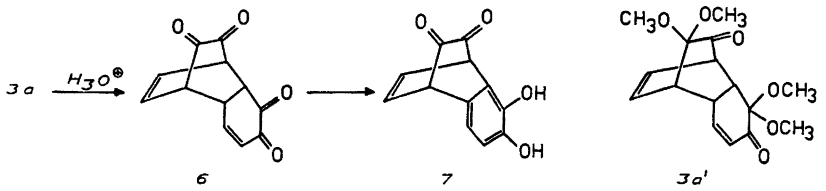
The ketals *2a*, *2b*, and *2c* could not be isolated as monomers, since they underwent Diels-Alder dimerization during the reaction or during the work-up to give *3a*, *3b*, and *3c*, respectively (Scheme 1). From the mixture obtained on oxidation of *1d*, however, the monomeric ketal *2d* was isolated as a yellow oil which showed the spectroscopic characteristics of a 2,4-cyclohexadienone. During a period of two days it changed into the crystalline dimer *3d*.

Although a few cyclic diaryl ketals (spiroketals) of *o*-quinones,[3] as well as ketals of *p*-quinones,[3b,4] have been described, only one *o*-quinone dialkyl ketal of type *2* seems to have been reported earlier.[3b] The tetramethyl ketals of *o*- and *p*-benzoquinone have been obtained by electrochemical oxidation of veratrol and hydroquinone dimethyl ether, respectively.[5]

* Part XVII, see Ref. 1.



Scheme 1.

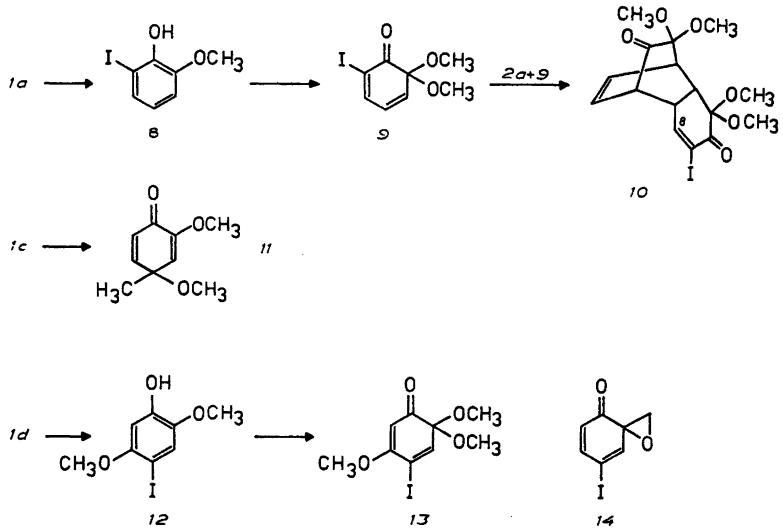


Scheme 2.

The UV, IR, and NMR data of dimers *3a–d* were in accord with those of previously investigated dimeric 2,4-cyclohexadienones (see Part XVII[1] and preceding papers in this series). Furthermore, chemical support for structure *3a* was provided by acid hydrolysis of the ketal groups of *3a*, which yielded the expected catechol *7*[7] *via* the dimeric *o*-benzoquinone *6*.[6,7] (Scheme 2). Admittedly, neither the spectroscopic data available nor the result of the hydrolysis experiment permit a decision to be made between *3a* and its regioisomer *3a'*. Structure *3a* and, correspondingly, structures *3b–d* are preferred, however, because dipole measurements[8] and X-ray crystallography,[9] as well as chemical evidence,[10,11,1] have shown that the dimerization of various types of 2,4-cyclohexadienones exclusively gives the regioisomers of type *3a*.

The occurrence of *para* oxidation has been demonstrated in two of the cases investigated. Thus, 2-methoxy-4-methylphenol (*1c*) gave the *p*-quinol ether *11* (Scheme 3) in addition to the dimeric *o*-quinone ketal *3c*, and the homologous compound *4* was the only product isolated from the reaction mixture obtained on oxidation of phenol *1e* with the methanolic periodic acid (Scheme 1). As reported recently,[1] *p*-quinol ether *4* is also a by-product in the oxidation of 2,4-dimethylphenol (*5*) with methanolic periodic acid, a twofold oxidative methoxylation taking place in this case.

Furthermore, the liberation of iodine in the course of the oxidation (*cf.* Ref. 1) gave rise to iodophenols which were converted to the corresponding iodinated *o*-quinone ketals. The oxidation of guaiacol (*1a*) gave a small amount of compound *10*, which is the Diels-Alder adduct between the noniodinated ketal *2a* acting as a diene and its 2-iodinated analogue *9*, which originates from iodophenol *8*, acting as dienophile (Scheme 3).



Scheme 3. By-products (*10*, *11*, *13*) obtained from phenols *1a*, *1c*, and *1d*.

The location of the iodine in *10* was derived from a comparison of spectral data for *3a* and *10*. Whereas the $\pi \rightarrow \pi^*$ band of the α,β-conjugated carbonyl system of *3a* has λ_{max} at 232 nm (calc.[12] 227 nm), that of *10* is found at 264 nm. The bathochromic shift of 32 nm is in accord with the presence of a halogen atom in the α- or β-position of the system (an α- or β-bromine substituent causes a bathochromic shift of 25 or 30 nm, respectively[12]). The IR strectching frequency of the conjugated carbonyl group of *10* (1705 cm^{-1}) is 15 cm^{-1} higher than that of *3a* (1690 cm^{-1}) which indicates that the iodine is located in the α-position (C-7) (*cf.* Ref. 13). Finally, the NMR spectrum of *10* shows a doublet (1 H) at δ 7.10 which must be ascribed to the hydrogen atom at C-8 ($J_{8,8a} = 4.5$ Hz).

From the oxidation of 2,5-dimethoxyphenol (*1d*), the iodinated *o*-quinone ketal *13*, obviously formed *via* the iodophenol *12*, was obtained in addition to the noniodinated ketal *2d*. Contrary to *2d*, its 4-iodo derivative *13* does not dimerize; this can be ascribed to steric hindrance exerted by the iodo substituent. The similar 4-iodo-2,4-cyclohexadienone *14* has earlier been found to be stable as monomer.[14]

The total yields of products isolated from the reaction mixtures obtained on oxidation of phenols *1a—d* were in the range of 20—34 %. During the oxidation, the solutions acquired an intense red colour indicating the formation of considerable amounts of *o*-quinones. The latter reaction can be ascribed to the presence of water arising by the interaction between periodic acid and methanol (*cf.* Ref. 1). No efforts were made to isolate the red products; they were removed, together with the inorganic acids present, by filtering the solution through a column of an anion-exchange resin in the acetate form,[15] or by chromatography on a column of aluminium oxide which firmly adsorbs *o*-quinones.

On the basis of experiments performed in $H_2{}^{18}O$, the degradation of monoethers of catechols and hydroquinones by aqueous periodate to give *o*- and *p*-quinones, in addition to the corresponding alcohol or phenol, has been interpreted to be due to the intermediate formation of the quinone hemiketals.[16] The analogous formation of *o*-quinone dimethyl ketals on treatment of 2-methoxyphenols with methanolic periodic acid lends further support to this interpretation. It may be noted that both periodic acid and iodic acid in aqueous media also were found to effect the oxidative demethoxylation of 2-methoxyphenols.[17]

EXPERIMENTAL

UV, IR, and NMR spectra were recorded on a Cary Model 14, a Beckman 9A, and a Varian A-60 instrument, respectively. Chemical shifts are given in δ units, TMS being used as internal standard.

Oxidation. A solution of the phenol (10—25 mmol) in absolute methanol (50 ml) was mixed with the solution of an equimolar amount of anhydrous periodic acid[18] in the same solvent (450 ml). After 2 h at room temperature, the deep red reaction mixtures were worked up by one of the following three procedures.

Procedure 1. The reaction mixture was passed through a column of Amberlite IRA-400 (600 g) in the acetate form.[15] After the addition of water, the yellow filtrate was extracted with five 50 ml-portions of dichloromethane. The combined extracts were dried over anhydrous $CaSO_4$ and evaporated under vacuum, leaving "residue A". The latter was chromatographed on a column (3 × 110 cm) of silica gel (Mallinckrodt, 100 mesh), benzene-ethyl acetate (4:1) being used as eluent.

Procedure 2. Residue A obtained as above was dissolved in ethyl acetate and the brown solution passed through a column (4 × 15 cm) of aluminium oxide ("neutral", Woelm). Dark brown material remained firmly adsorbed in the upper part of the column. The filtrate, on evaporation, gave "residue B" which was chromatographed on silica gel as in procedure 1.

Procedure 3. The red reaction mixture, after dilution with water, was extracted with dichloromethane (5 × 50 ml), the combined red extracts were washed with saturated aqueous $NaHCO_3$ and with water and dried over $CaSO_4$. Evaporation gave "residue C", which was purified with Al_2O_3 (see procedure 2) to give "residue D" which, in turn, was chromatographed on silica gel according to procedure 1.

Thin layer chromatography was performed on silica gel with benzene-ethyl acetate (4:1) as mobile phase.

Oxidation of guaiacol (1a). The reaction mixture obtained from 2.90 g of the phenol was worked up according to procedure 3 to give "residue C" (2.90 g) as a brown oil and "residue D" as a slightly yellow crystalline solid (1.03 g), which was separated on silica gel into the following two compounds:

(a) *1,4a,5,8a-Tetrahydro-7-iodo-5,5,9,9-tetramethoxy-1,4-ethanonaphthalene-6,10(4H)-dione* (10). $R_F = 0.4$. Colourless rods, m.p. 210 °C (dec.) after recrystallization from chloroform-hexane. Yield, 3 %. (Found: I 29.04. Calc. for $C_{16}H_{19}O_6I$: I 29.23). UV (ethanol): λ_{max}, nm (logε) 205 (4.05), 264 (3.56), sh 300 (3.29). IR (KBr): ν_{max}, cm^{-1} 1595 (w), 1705 (s), 1740

(s). NMR ($CDCl_3$): δ 3.10, 3.26, 3.45 and 3.50 (12 H, 4 CH_3O) overlapping a multiplet (4 H, H-1, H-4, H-4a, H-8a), 5.88–6.43 (m, 2 H, H-2, H-3), 7.10 (d, 1 H, H-8). $J_{8,8a}=4.5$ Hz.

(b) *1,4a,5,8a-Tetrahydro-5,5,9,9-tetramethoxy-1,4-ethanonaphthalene-6,10(4H)-dione* (3a). $R_F=0.2$, m.p. 187–190 °C (yield, 23 %). After recrystallization from ethyl acetate colourless needles, m.p. 191–192 °C. (Found: C 62.41; H 6.46; OCH_3 40.32. Calc. for $C_{16}H_{20}O_6$: C 62.33; H 6.54; OCH_3 40.26). UV (ethanol): λ_{max}, nm (log ε) 205 (3.88), 232 (3.89), 324 (2.25). IR (KBr): ν_{max}, cm^{-1} 1625 (w), 1690 (s), 1735 (s). NMR ($CDCl_3$): δ 3.08, 3.27, 3.42 and 3.48 (4 CH_3O) overlapping a multiplet (4 H, H-1, H-4, H-4a, H-8a), 5.75–6.64 (m, 4 H, H-2, H-3, H-7, H-8).

1,4-Dihydro-5,6-dihydroxy-1,4-ethanonaphthalene-9,10-dione (7). Dimer *3a* (100 mg) was dissolved in methanol (10 ml), and after the addition of water (30 ml) and conc. hydrochloric acid (1 ml), the mixture was refluxed for 15 min. The yellow solution was extracted with 5 × 15 ml of ethyl acetate. The extract was thoroughly washed with water, dried over $CaSO_4$ and evaporated to dryness. The semi-solid yellow residue on recrystallization from ethyl acetate-hexane gave 35 % of *7*, m.p. 194–195 °C, identical by mixed m.p. with authentic material (m.p. 195–196 °C, Ref. 7).

1,4a,5,8a-Tetrahydro-5,5,9,9-tetramethoxy-1,7-dimethyl-1,4-ethanonaphthalene-6,10(4H)-dione (*3b*). Oxidation of 2-methoxy-6-methylphenol (*1b*) and work-up according to procedure 1 gave a light-brown, partly crystalline "residue A". On silica gel chromatography, the first eluate fractions gave small amounts of an amorphous, brown material. According to TLC, subsequent fractions contained only *3b* ($R_F=0.34$), colourless crystals of m.p. 152–155 °C (yield, 34 %); recrystallization from isopropyl ether raised the m.p. to 156–157 °C. (Found: C 64.49; H 7.45; OCH_3 36.84. Calc. for $C_{18}H_{24}O_6$: C 64.27; H 7.19; OCH_3 36.90). UV (ethanol): λ_{max}, nm (log ε) 205 (3.79), 245 (3.89), 324 (2.27). IR (KBr): ν_{max}, cm^{-1} 1648 (w), 1701, 1730. NMR ($CDCl_3$): δ 1.31 (s, 3H, CH_3-1), 1.82 (t, 3 H, CH_3-7), 3.04, 3.22, 3.40, 3.47 (12 H, 4 CH_3O) overlapping a multiplet (3 H, H-4, H-4a, H-8a), 5.52 (dd, 1 H, H-2), 6.06–6.22 (m, 2 H, H-3, H-8). $J_{CH_3\text{-}7,\ H\text{-}8} = J_{CH_3\text{-}7,\ H\text{-}8a}$ *ca.* 1 Hz, $J_{2,3}=8$ Hz, $J_{2,4}$ *ca.* 1.5 Hz.

Oxidation of 2-methoxy-4-methylphenol (1c). Procedure 1 gave a light-brown, partly crystalline "residue A". Silica gel chromatography provided two crystalline products:

(a) *1,4a,5,8a-Tetrahydro-5,5,9,9-tetramethoxy-3,8a-dimethyl-1,4-ethanonaphthalene-6,10(4H)-dione* (3c). $R_F=0.3$, m.p. 131–135 °C (yield, 11.5 %), after recrystallization from isopropyl ether colourless prisms of m.p. 133–135 °C. (Found: C 63.96; H 6.92; OCH_3 36.58. Calc. for $C_{18}H_{24}O_6$: C 64.27; H 7.19; OCH_3 36.90). UV (ethanol): λ_{max}, nm (log ε) 206 (3.92), 229 (3.91), 324 (2.36). IR (KBr): ν_{max}, cm^{-1} 1625 (w), 1698, 1736. NMR ($CDCl_3$): δ 1.39 (s, 3 H, CH_3-8a), 1.76 (d, 3 H, CH_3-3), 2.80 (d, 1 H, H-1), 2.87 (broadened s, 2 H, H-4, H-4a), 3.08, 3.32, 3.40, 3.42 (s, 3 H each, 4 CH_3O), 5.53 (dq, 1 H, H-2), 5.95 and 6.20 (pair of doublets, 1 H each, H-7, H-8). $J_{1,2}=6.5$ Hz, $J_{H\text{-}1,CH_3\text{-}3}$ *ca.* 1 Hz, $J_{7,8}=10$ Hz.

(b) *2,4-Dimethoxy-4-methyl-2,5-cyclohexadienone* (11). $R_F=0.2$, m.p. 108–110 °C (yield, 10.5 %), after recrystallization from isopropyl ether and sublimation at 40 °C/0.01 mmHg colourless plates of m.p. 110–111 °C. (Found: C 64.00; H 7.02; OCH_3 36.98. Calc. for $C_9H_{12}O_3$: C 64.27; H 7.19; OCH_3 36.90). UV (ethanol): λ_{max}, nm (log ε) 231 (3.99); 295 (3.22). IR (KBr): ν_{max}, cm^{-1} 1615 (s, enol ether), 1648, 1672 (both s).[19] NMR ($CDCl_3$): δ 1.48 (s, 3 H, CH_3-4), 3.18 (s, 3 H, CH_3O-4), 3.70 (s, 3 H, CH_3O-2), 5.63 (d, 1 H, H-3), 6.33 (d, 1 H, H-6), 6.78 (dd, 1 H, H-5). $J_{3,5}=3$ Hz, $J_{5,6}=10$ Hz.

Oxidation of 2,5-dimethoxyphenol (1d).[20] Procedure 2 gave a brown, oily "residue A" (R_F values 0.0, 0.2, and 0.4). The subsequent purification on Al_2O_3 gave a yellow oil ("residue B") which on silica gel chromatography afforded the following compounds:

(a) *4-Iodo-3,6,6-trimethoxy-2,4-cyclohexadienone* (13). $R_F=0.4$, yellow oil (yield, 10 %). UV (ethanol): λ_{max}, nm (log ε) 333 (3.37). IR (KBr): ν_{max}, cm^{-1} 1580 (s, enol ether), 1625 (w), 1670 (s). NMR ($CDCl_3$): δ 3.41 (s, 6 H, $(CH_3O)_2$-6), 3.85 (s, 3 H, CH_3O-3), 5.42 (s, 1 H, H-2), 7.20 (s, 1 H, H-5).

(b) *3,6,6-Trimethoxy-2,4-cyclohexadienone* (2d). $R_F=0.2$, light-yellow oil (10 %) containing traces of dimer *3d* ($R_F=0.1$). The spectra of the freshly prepared oil were as follows: UV (ethanol): λ_{max} 315 nm. IR (KBr): ν_{max}, cm^{-1} 1590 (s, enol ether), 1668 (s). NMR ($CDCl_3$): δ 3.38 (s, 6 H, $(CH_3O)_2$-6), 3.79 (s, 3 H, CH_3O-3), 5.40 (d, 1 H, H-2), 6.20 (dd, 1 H, H-4), 6.41 (d, 1 H, H-5). $J_{2,4}=2.5$ Hz, $J_{4,5}=10$ Hz.

1,4a,5,8a-Tetrahydro-2,5,5,8,9,9-hexamethoxy-1,4-ethanonaphthalene-6,10(4H)-dione (3d). The yellow oil *2d* had solidified after two days at room temperature. Recrystallization from ethyl acetate gave *3d*, m.p. 199–200 °C. (Found: C 58.58; H 6.42; OCH_3 50.48. Calc. for $C_{12}H_{24}O_8$: C 58.69; H 6.57; OCH_3 50.54). UV (ethanol): λ_{max}, nm (log ε) 250 (4.07), sh 302 (2.63). IR (KBr): ν_{max}, cm^{-1} 1623 and 1649 (enol ethers), 1690 (conj. CO) 1740 (CO), all strong. NMR ($CDCl_3$): δ 3.05, 3.22, 3.38 (9 H, 3 CH_3O) overlapping multiplet (4 H, H-1, H-4, H-4a, H-8a), 3.42 (s, 6 H, 2 CH_3O), 3.61 (s, 3 H, CH_3O), 4.78 (dd, 1 H, H-3), 5.32 (s, 1 H, H-7). $J_{1,3}$ *ca.* 1.5 Hz, $J_{3,4}=7.5$ Hz.

2,4-Dimethoxy-4,6-dimethyl-2,5-cyclohexadienone (4). Oxidation of 6-methoxy-2,4-dimethylphenol (*1e*, preparation see below) and work-up according to procedure 1 yielded "residue A" as a brownish, partly crystalline product which showed only one distinct spot on TLC ($R_F=$ 0.25). Silica gel chromatography gave *4*, colour-

less crystals of m.p. 77 – 79 °C (11 % yield); the m.p. was raised to 80 – 81 °C on sublimation at 40 °C/5 mmHg. The substance was identical by m.p., mixed m.p. and IR spectrum with a by-product obtained on oxidation of 2,4-dimethylphenol with methanolic periodic acid.[1]

6-Methoxy-2,4-dimethylphenol (1e).* A solution of 2-hydroxymethyl-6-methoxy-4-methylphenol[21] (10.8 g) in ethanol (100 ml) was shaken in a hydrogen atmosphere over a 10 % Pd/C catalyst (1 g). The required amount of hydrogen was consumed after 30 min. Filtration over Celite and evaporation of the filtrate gave an oil (9.3 g) which crystallized on cooling. M.p. 35 °C, $b.p._{13}$ 111 °C, after recrystallization from acetic acid-water (Lit.[22] m.p. 36 °C, $b.p._{12}$ 110 °C).

Acknowledgements. We are greatly indebted to Professor E. Adler for his kind interest and valuable advice. This work has been financially supported by the Swedish Natural Science Research Council.

REFERENCES

1. Adler, E., Andersson, G. and Edman, E. *Acta Chem. Scand. B 29* (1975) 909.
2. Obst, J. R. and Harkin, J. M. *J. Org. Chem. 38* (1973)3227.
3. a. Ried, W. and Radt, W. *Justus Liebigs Ann. Chem. 676* (1964) 110; Hewgill, F. R. and Hewitt, D. G. *J. Chem. Soc.* (1965) 3660; Bowman, D. F., Hewgill, F. R. and Kennedy, B. R. *J. Chem. Soc. C* (1966) 2274. b. Hewitt, D. G. *Ibid.* (1971) 2967.
4. Martius, C. and Eilingsfeld, H. *Justus Liebigs Ann. Chem. 607* (1957) 159; Müller, E., Kaufmann, H. and Rieker, A. *Ibid. 671* (1964) 61; Becker, H.-D. *J. Org. Chem. 29* (1964) 3068; Dürckheimer, W. and Cohen, L. A. *Biochemistry 3* (1964) 1948.
5. Belleau, B. and Weinberg, N. L. *J. Amer. Chem. Soc. 85* (1963) 2525.
6. Willstätter, R. and Müller, F. *Ber. Deut. Chem. Ges. 44* (1911) 2171; Goldschmidt, S. and Graef, F. *Ibid. 61* (1928) 1868.
7. Patchett, A. A. and Witkop, B. *J. Org. Chem. 22* (1957) 1477; Harley-Mason, J. and Laird, A. H. *J. Chem. Soc.* (1958) 1718; Horner, L. and Dürckheimer, W. *Chem. Ber. 91* (1958) 2532.
8. Brown, T. L., Curtin, D. Y. and Fraser, R. R. *J. Amer. Chem. Soc. 80* (1958) 4339.
9. Karlsson, B., Pilotti, A.-M. and Wiehager, A.-C. *Acta Chem. Scand. 27* (1973) 2945, 2955.
10. Becker, H.-D. *Justus Liebigs Ann. Chem.* (1973) 1675.
11. Adler, E. and Holmberg, K. *Acta Chem. Scand. B 28* (1974) 465, 549; Holmberg, K. *Ibid. 857.*
12. Scott, A. I. *Interpretation of the Ultraviolet Spectra of Natural Products*, Pergamon, Oxford 1964, p. 58.
13. Campbell, R. D. and Cromwell, N. H. *J. Amer. Chem. Soc. 79* (1957) 3456.
14. Becker, H.-D., Bremholt, T. and Adler, E. *Tetrahedron Lett.* (1972) 4206.
15. Smith, M. A., Webb, R. A. and Cline, L. J. *J. Org. Chem. 30* (1965) 995.
16. Adler, E. and Magnusson, R. *Acta Chem. Scand. 13* (1959) 505; Adler, E., Falkehag, I. and Smith, B. *Ibid. 16* (1962) 529.
17. Andersson, G. *Unpublished results.*
18. Partington, J. R. and Bahl, R. K. *J. Chem. Soc.* (1944) 1088.
19. Derkosch, J. and Kaltenegger, W. *Monatsh. Chem. 90* (1959) 872, 877; Rieker, A., Rundel, W. and Kessler, H. *Z. Naturforsch. 24b* (1969) 547.
20. Bertram, C. A., Battye, D. A. and Worthing, C. R. *J. Chem. Soc.* (1963) 4691.
21. Gierer, J., Söderberg, S. and Thorén, S. *Sv. Papperstidn. 66* (1963) 990.
22. Lock, G. *Monatsh. Chem. 85* (1954) 802.

Received March 8, 1975.

* Experiment carried out by J. Törnquist and B. Looström.