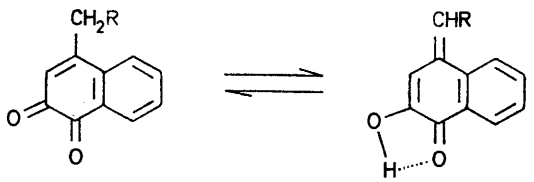
Steroidal 1-Methyl-3,4-naphthoquinones

By S. Mahmood Ali and Alan B. Turner,* Department of Chemistry, University of Aberdeen, Aberdeen AB9 2UE

Dienone–phenol rearrangement of steroidal 1,4,6-triene-3,11-diones gives 1-methyl-AB-aromatic steroids, which are oxidised by potassium nitrosodisulphonate to the title compounds. The instability of these quinones is ascribed to their quinone methide character.

TAUTOMERISATION to the quinone methide form [(A) ⇌ (B)] accounts for the instability of 4-alkyl-1,2-naphthoquinones.[1,2] Naphthoquinones of this type decompose



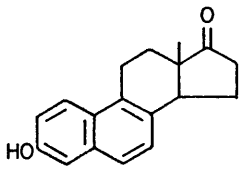
(A) (B)

readily upon exposure to oxygen, and on heating, and reactions occur *via* the quinone methide form. Since attempts to prepare steroidal quinone methides in this laboratory, for investigation of their antitumour activity,[3] have resulted only in tautomeric products,[4] we have turned our attention to the synthesis of steroidal quinones which are capable of tautomerisation to quinone methides. Steroidal naphthoquinones have been prepared previously by oxidation of naphthols with Fremy's salt [5] [(1) ⟶ (2)] and with periodic acid [6] [(3) ⟶ (4)], and 1-methyl derivatives of naphthols similar to (1) and (3) are readily available by trienone–phenol rearrangement of 1,4,6-trien-3-ones followed by dehydrogenation of the resulting styrenes.[4,7]

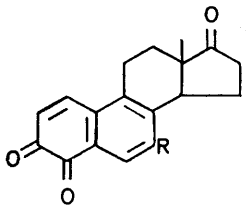
Oxidation of the naphthol (5) with potassium nitrosodisulphonate in aqueous acetone gave the 1-methyl-3,4-quinone (6).[7] Spectral data furnished by the crude material were adequate for preliminary characterisation, but attempts to purify it were not successful. It decomposed upon heating in a variety of solvents, and during column chromatography on silica gel. It

[1] L. F. Fieser and C. K. Bradsher, *J. Amer. Chem. Soc.*, 1939, **61**, 417; L. F. Fieser and M. Fieser, *ibid.*, p. 596.
[2] H. Cassebaum, *Z. Elektrochem.*, 1958, **62**, 426.
[3] R. L. Hanson, H. A. Lardy, and S. M. Kupchan, *Science*, 7110, **168**, 378.
[4] W. Brown, J. W. A. Findlay, and A. B. Turner, *Chem. Comm.*, 1968, 10.
[5] H. J. Teuber, *Chem. Ber.*, 1953, **86**, 1495.
[6] M. Heller, R. H. Lenhard, and S. Bernstein, *J. Amer. Chem. Soc.*, 1967, **89**, 1911.
[7] W. Brown, Ph.D. Thesis, Aberdeen, 1969.

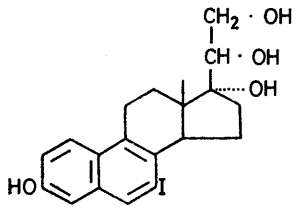
was finally characterised as its quinoxaline derivative (7). Attention was then directed towards the synthesis of 11-oxo-derivatives of these 1-methyl-3,4-naphthoquinones, in the hope that the electron-withdrawing



(1)



(2) R = H
(4) R = I

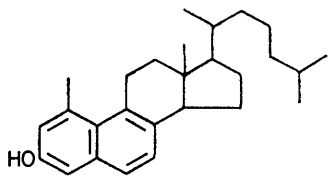


(3)

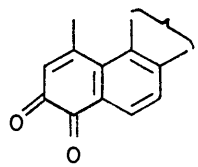
conjugating group in ring C would stabilise the chromophore.

Dienone–phenol rearrangement of the pregnatriene-trione (8) with perchloric acid [8] or toluene-*p*-sulphonic acid in acetic anhydride [9] gave two main products, neither of which contained a 9α-proton signal in its n.m.r. spectrum. One of these was identified as the AB-aromatic acetate (9) from its spectral data,* in particular its mass spectrum. Apart from loss of keten from the parent ion, this also showed an intense peak at *m/e* 198, corresponding to two possible modes of cleavage across ring C. Hydrolysis of the acetate (9) with methanolic potassium hydroxide gave the phenol (10). The second main product appeared to be the 9(11)-enol acetate (11) of the expected product, 3-acetoxy-1-methylpregna-1,3,5(10),6-tetraene-11,20-dione. On hydrolysis with base it gave a phenol whose spectral characteristics were best interpreted in terms of the 9(11)-enol acetate structure (12).[8]

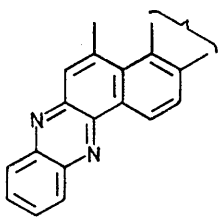
Rearrangement of androsta-1,4,6-trien-3,11,17-trione (13) under similar conditions also gave two major products, one of which was the AB-aromatic acetate (14). On hydrolysis with base, it gave the naphthol (15). The second major product also appeared to be an AB-aromatic steroid. Its n.m.r. spectrum contained a broad singlet at δ 4·53, which was not resolved when the spectrum was run at −22°, and a signal for an exchangeable proton at δ 3·24. Structure (16) is considered to be the most likely one for this product, with the low degree of coupling of the 11-proton indicating distortion of ring C from the normal half-chair conformation. Other spectral data were in accord with this structure, and on acetylation of the 11-hydroxy-group to give the diacetate (17), the C-11 methine proton signal appeared downfield at δ 5·82, in good agreement with the expected degree of deshielding upon acetylation. In addition, the chemical shift of the 13-methyl group in this diacetate suggested that the oxygen function at C-11 has the α-configuration in compounds (16) and (17). Furthermore, attempts to oxidise the alcohol (16) to the 11-ketone (14), with chromic acid and with dichlorodicyanobenzoquinone (DDQ), were unsuccessful, again indicating the 11α-configuration for the hydroxy-group. Prominent peaks in the mass spectrum of the diacetate (17) were formed by fragmentation across rings C and D (*e.g.* $M - C_5H_8O$). Formation of the 11-alcohol (16) can be explained by



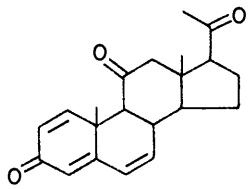
(5)



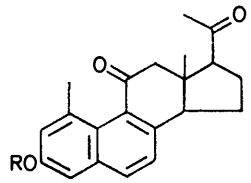
(6)



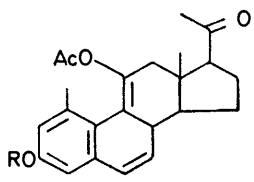
(7)



(8)



(9) R = Ac
(10) R = H



(11) R = Ac
(12) R = H

enolisation of the 11-oxo-group, followed by migration of the 9(11)-double bond to the 8,9-position with con-

* The n.m.r. spectra (see Table) of compounds (9), (10), and (14)—(16) show *meta*-coupled ring A protons (*J* 2—3 Hz) rather than an *ortho*-coupled system (*J* 6—10 Hz), thereby eliminating from consideration possible alternative 1-acetoxy-4-methyl structures (*cf.* ref. 6).

[8] E. J. Bailey, J. Elks, J. F. Oughton, and L. Stephenson, *J. Chem. Soc.*, 1961, 4535.

[9] *Cf.* D. N. Kirk, D. K. Patel, and V. Petrow, *J. Chem. Soc.* 1957, 1046.

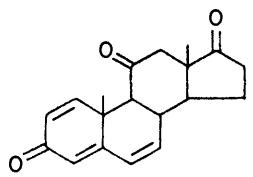
comitant aromatisation of ring B. No evidence as to the nature of the hydrogen acceptors involved in the formation of the naphthol derivatives (9) and (14) was obtained. It is possible that they arise by oxidation of the 11-alcohols, but attempts to oxidise the alcohol (16) to the ketone (14) with chromic acid and DDQ failed.

Oxidation of the naphthols (10) and (15) with potassium nitrosodisulphonate was carried out under the conditions recently developed by Gelbke *et al.*[10] for the preparation of oestrogen *ortho*-benzoquinones. The naphthoquinones (18) and (19) were obtained in 28—30% yield after purification by t.l.c. Their n.m.r. spectra showed the C-2 proton signal as a multiplet at δ 6·46, and the C-6 proton, being adjacent to the carbonyl group at C-4, is strongly deshielded (doublet at δ 8·18—8·24). As expected, their mass spectra contained strong $M + 2$ peaks, and showed considerable resemblance in the region below *m/e* 250, particularly with respect to doubly charged ions appearing at non-integral mass numbers (region *m/e* 140—160). Again, these naphthoquinones proved to be unstable, decomposing during attempts to purify them by crystallisation, but the crude products are sufficiently stable for evaluation of their antitumour properties.

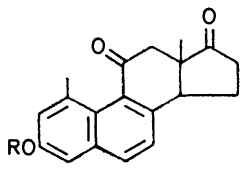
N.m.r. data * for steroidal naphthols and naphthoquinones

Compd.	1-CH_3 (s)	2-H	3-OAc (s)	4-H (d)	6- and 7-H (q)	12-H_2 (ABq)	13-CH_3 (s)	20-CH_3
(6)	2·59	6·34 (s)			8·00, 7·20		0·50	0·98 (d, *J* 5 Hz)
(7)	2·99	7·71 (s)			9·36, 7·43		0·55	0·99 (d, *J* 5 Hz)
(9)	2·33	7·20 (m)	2·38	7·45 (*J* 2 Hz)	7·90, 7·30	3·06	0·77	2·20 (s)
(10)	2·34	6·94 (d, *J* 2 Hz)		7·03 (*J* 2 Hz)	7·72, 7·14	3·04	0·78	2·20 (s)
(12)	2·43	7·28br (s)		7·28 (s)	6·70	2·76	0·76	2·08
(14)	2·34	7·20 (d, *J* 3 Hz)	2·38	7·45 (*J* 3 Hz)	7·94, 7·30	2·86	1·00	
(15)	2·34	6·98 (d, *J* 2 Hz)		7·05 (*J* 2 Hz)	7·84, 7·30	2·84	1·00	
(16)	2·34	7·22 (d, *J* 3 Hz)	2·38	7·48 (*J* 3 Hz)	7·95, 7·34		0·97	
(17)	2·33	7·24 (m)	2·38	7·44 (m)	7·98, 7·24		1·03	
(18)	2·16	6·45 (m)			8·18, 7·25	3·03	0·80	2·18
(19)	2·16	6·46 (m)			8·24, 7·36	2·84	1·01	

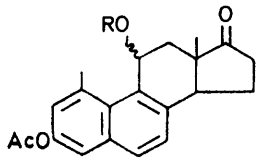
* δ Values; solvent $CDCl_3$.



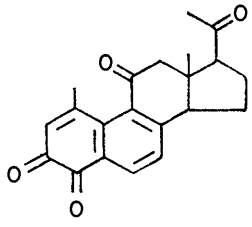
(13)



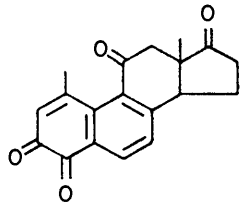
(14) R = Ac
(15) R = H



(16) R = H
(17) R = Ac



(18)



(19)

The 1-methyl group appears to be the cause of the instability of this group of quinones; however we have been unable to characterise the decomposition products. The 11-oxo-compounds are slightly more stable than 11-unsubstituted ones, perhaps owing to greater steric interaction with the 1-methyl group. (No evidence of intramolecular addition to the methyl group was obtained.) Quinones of type (2) and (4) are stable under normal conditions, and do not undergo appreciable decomposition upon exposure to the atmosphere.

EXPERIMENTAL

M.p.s were determined with a Kofler hot-stage apparatus. I.r. spectra were obtained for KBr discs and u.v. spectra for ethanolic solutions. N.m.r. spectra (see Table) were obtained with a Varian HA-100 spectrometer for solutions in deuteriochloroform with tetramethylsilane as internal standard. Mass spectra were determined with an A.E.I. MS30 spectrometer.

Starting Materials.—*Pregna-1,4,6-triene-3,11,20-trione.* Dehydrogenation of pregn-4-ene-3,11,20-trione with chloranil,[11] followed by oxidation of the resulting pregna-4,6-diene-3,11,20-trione with DDQ,[12] gave the trienetrione (8), m.p. 177° (lit.,[13] 177—179°) in 58% overall yield.

Androsta-1,4,6-triene-3,11,17-trione. The trienetrione (13), m.p. 213° (lit.,[14] 215°), was obtained in a similar way from androst-4-ene-3,11,17-trione in 60% overall yield.

[10] H. P. Gelbke, O. Haupt, and R. Knuppen, *Steroids*, 1973, **21**, 205.

[11] E. J. Agnello and G. D. Laubach, *J. Amer. Chem. Soc.*, 1960, **82**, 4293.

[12] D. Burn, D. N. Kirk, and V. Petrow, *Proc. Chem. Soc.*, 1960, 14; D. Burn, V. Petrow, and G. Weston, *J. Chem. Soc.*, 1962, 29.

[13] D. N. Kirk, B.P. 854,343.

[14] D. Gould, E. L. Shapiro, H. L. Herzog, M. L. Gentles, E. B. Hershberg, W. Charney, M. Gilmore, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Amer. Chem. Soc.*, 1957, **79**, 502.

Rearrangement of Pregna-1,4,6-triene-3,11,20-trione.—The trienetrione (8) (324 mg) was dissolved in acetic anhydride (10 ml) containing perchloric acid (0·1 ml) at 0°. The solution was left for 45 min, then added to iced water. After 15 h the solid was collected and resolved by multiple-development t.l.c. into 3-*acetoxy*-1-*methyl*-19-*norpregna*-1,3,5(10),6,8-*pentaene*-11,20-*dione* (9) (77 mg, 21%), m.p. 158° [from petroleum (b.p. 40—60°)–ethyl acetate] (Found: M^+, 364·1673. $C_{23}H_{24}O_4$ requires M, 364·1674), $\lambda_{max.}$ 220, 248, and 312 nm (ε 31,300 24,800, and 5900), $\nu_{max.}$ 1760, 1725, 1665, 1610, 1595, 900, 815, and 730 cm^{-1}, and a more polar component which could not be crystallised. This was dissolved in methanol (50 ml) and methanolic 2% potassium hydroxide (5 ml) was added. The mixture was stirred under nitrogen for 1 h, acidified with acetic acid, and diluted with water. The solid which separated after refrigeration was crystallised from hexane–ethyl acetate (1 : 1) to give 11-*acetoxy*-3-*hydroxy*-1-*methyl*-19-*norpregna*-1,3,5(10),6,9(11)-*pentaen*-20-*one* (12) (73 mg, 20%), m.p. 182°, $\lambda_{max.}$ 226, 248, and 308 nm (ε 28,200, 38,900, and 30,400), $\nu_{max.}$ 3420, 1760, 1700, 1610, 860, and 760 cm^{-1}, *m/e* 366 (M^+, 2·5%), 324 (15), 323 (56), 279 (12), 201 (18), 200 (33), and 185 (34).

3-*Hydroxy*-1-*methyl*-19-*norpregna*-1,3,5(10),6,8-*pentaene*-11,20-*dione* (10).—Hydrolysis of the acetate (9) by the above method gave the *naphthol* (10), m.p. 189° (from ethyl acetate–hexane, 1 : 1) (Found: M^+, 322·1569. $C_{21}H_{22}O_3$ requires M, 322·1568), $\lambda_{max.}$ 225, 257, and 320 nm (ε 24,900, 21,100, and 4400), $\nu_{max.}$ 3350, 1700, 1665, 1620, 860, and 770 cm^{-1}, *m/e* 323 (16%), 322 (M^+, 75%), 279 (10), 261 (12), 252 (12), 251 (16), 237 (22), 211 (35), and 198 (30).

Rearrangement of Androsta-1,4,6-triene-3,11,17-trione.—The trienetrione (13) (296 mg) was rearranged with perchloric acid in acetic anhydride as described above giving 3-*acetoxy*-1-*methyloestra*-1,3,5(10),6,8-*pentaene*-11,17-*dione* (14) (84 mg, 25%), m.p. 226° (from ethyl acetate–light petroleum) (Found: M^+, 336·1360. $C_{21}H_{20}O_4$ requires M, 336·1361), $\lambda_{max.}$ 220, 250, and 313 nm (ε 25,600, 23,900, and 5600), $\nu_{max.}$ 1760, 1720, 1665, 1605, 1595, 900, 815, and 735 cm^{-1}, *m/e* 336 (M^+, 50%), 295 (19), 294 (100), 280 (27), 261 (17), 225 (20), 220 (20), 211 (41), 210 (75), and 165 (20), and 3-*acetoxy*-11-*hydroxy*-1-*methyloestra*-1,3,5(10),6,8-*pentaen*-17-*one* (16) (54 mg, 16%), m.p. 186° (from ethyl acetate–hexane) (Found: M^+, 338·1515. $C_{21}H_{22}O_4$ requires M, 338·1517), $\nu_{max.}$ 3470, 1740, 1610, 1600, 1510, 865, and 760 cm^{-1}, *m/e* 338 (M^+, 40%), 337 (72), 309 (28), 296 (12), and 295 (22). Acetylation of this alcohol (50 mg) with acetic anhydride–pyridine gave 3,11-*diacetoxy*-1-*methyloestra*-1,3,5(10),6,8-*pentaen*-17-*one* (17) (42 mg, 74%), m.p. 168° (from ethyl acetate–light petroleum) (Found: M^+, 380·1619. $C_{23}H_{24}O_5$ requires M, 380·1623), $\lambda_{max.}$ 223, 253, and 318 nm (ε 19,900, 18,400, and 4900), $\nu_{max.}$ 1750, 1600, 900, and 805 cm^{-1}, *m/e* 380 (M^+, 18%), 297 (22), and 296 (28).

3-*Hydroxy*-1-*methyloestra*-1,3,5(10),6,8-*pentaene*-11,17-*dione* (15).—Hydrolysis of the acetate (14) as before gave the naphthol (15), m.p. 214° (from ethyl acetate–hexane, 1 : 1) (Found: M^+, 294·1255. $C_{19}H_{18}O_3$ requires M, 294·1255), $\lambda_{max.}$ 224, 258, 316, and 364 nm (ε 34,700, 26,800, 4200, and 3100), $\nu_{max.}$ 3380, 1735, 1680, 1610, and 870 cm^{-1}.

1-*Methyl*-19-*norpregna*-1,5(10),6,8-*tetraene*-3,4,11,20-*tetrone* (18).—To a solution of the naphthol (10) (322 mg) in acetone (50 ml) was added a mixture of acetic acid (8 ml) and water (72 ml), followed by potassium nitrosodisulphonate (500 mg), and the mixture was shaken vigorously for 15 min. More potassium nitrosodisulphonate (500 mg) was added, and shaking was continued for a further 15 min before the orange solution was extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated. The red solid residue was purified by t.l.c. to give the *naphthoquinone* (18) (94 mg, 28%) as an orange solid, m.p. 121—125° (Found: M^+, 336·1360. $C_{21}H_{20}O_4$ requires M, 336·1361), $\lambda_{max.}$ 220, 260, 285, and 375 nm, $\nu_{max.}$ 1710, 1665, and 1580 cm^{-1}, *m/e* 338 (M + 2, 89%), 336 (5), 322 (25), 267 (18), 265 (16), 263 (32), 254 (20), 253 (18), 251 (14), 249 (15), 227 (18), 211 (18), 165 (20), 152 (20), and 43 (100).

1-*Methyloestra*-1,5(10),6,8-*tetraene*-3,4,11,17-*tetrone* (19).—The naphthol (15) (294 mg) was oxidised with potassium nitrosodisulphonate as above to give the naphthoquinone (19) (93 mg, 30%) as an orange powder, m.p. 132—134° (Found: M + 2, 310·1203. $C_{19}H_{16}O_8$ requires M + 2, 310·1205), $\lambda_{max.}$ 220, 250, 288, and 375 nm, $\nu_{max.}$ 1740, 1665, and 1575 cm^{-1}, *m/e* 310 (M + 2, 24%), 308 (1·5), 306 (7), 294 (7), 252 (11), 251 (14), 250 (45), 226 (19), 222 (14), 165 (13), 44 (70), 43 (50), and 41 (100).

1-*Methyl*-19-*norcholesta*-1,5(10),6,8-*tetraene*-3,4-*dione* (6) (with W. Brown).—Solutions of potassium nitrosodisulphonate (1·5 g) in water (118 ml) and 3-hydroxy-1-methyl-19-norcholesta-1,3,5(10),6,8-pentaene [15] (500 mg) in acetone (60 ml) were mixed, and the mixture was purged with nitrogen and stored at 15° under nitrogen for 12 h. The orange-red precipitate (370 mg) was collected and purified by t.l.c. on silica gel [developed with chloroform–ether (9 : 1) under nitrogen]. Decomposition occurred on heating the product in solution during work-up.

A solution of the crude quinone (6) (250 mg) and *o*-phenylenediamine (172 mg) in glacial acetic acid (20 ml) was heated on a steam-bath for 15 min. Water was added to the cooled solution and the precipitate (210 mg) was collected and purified by t.l.c. on silica gel (developed with chloroform–ether, 9 : 1). Extraction of the main band with chloroform gave, on evaporation, an orange solid (168 mg) which was crystallised from aqueous acetic acid to give the *quinoxaline derivative* (7), m.p. 147—148° (Found: C, 85·4; H, 8·8; N, 6·2. $C_{33}H_{40}N_2$ requires C, 85·3; H, 8·6; N, 6·0%), $\lambda_{max.}$ 240, 257, 288, 298, 410, and 426 nm (ε 48,900, 37,600, 47,800, 52,600, 12,900, and 14,500).

We thank the Cancer Research Campaign for financial support, and Dr. W. Brown for preliminary work on the project.

[4/887 *Received*, 3rd *May*, 1974]

[15] J. Romo, C. Djerassi, and G. Rosenkranz, *J. Org. Chem.*, 1950, **15**, 896.