

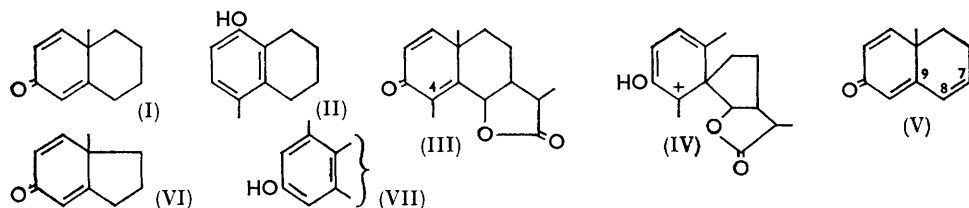
346. *The Dienone-Phenol and Related Rearrangements.*

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A new example of 1,2-methyl-migration, instead of spiran formation, in the dienone-phenol rearrangement has been observed with 7 β -benzoyloxy-2,5,6,7,8,10-hexahydro-8,8,10 β -trimethyl-2-oxonaphthalene (X). The rearrangement of the related γ -hydroxy- $\alpha\beta$ -unsaturated 6 β ,10 ξ -dihydroxy-5,5,9 β -trimethyl- Δ^3 -octal-2-one (XIII) to a phenol proceeds by a similar path. The structure of the phenol formed from the steroidal hydroxy unsaturated ketone 5 α -hydroxycholest-3-en-2-one (XVI) has been elucidated.

THE scope and mechanism of the dienone-phenol rearrangement have come to be more closely defined in recent years. Particular attention has been paid to cross-conjugated dienones of type (I), with the dienone ring fused to an alicyclic ring, and with an angular methyl blocking group. Woodward and Singh¹ showed that in acidic, anhydrous media, the simple dienone (I) rearranged to the phenol (II), possibly by two 1,2-shifts through a spiran intermediate. Confirmation of the existence of this pathway in such simple dienones was provided by both Woodward² and Bloom.³

Several examples are known, however, where 1,2-methyl-migration occurs instead of spiran formation. The classical case is that of santonin (III),⁴ where the C₍₄₎ methyl group blocks the rearrangement of the spiran (IV). When a double bond is conjugated with the dienone system, as in the ketone (V),⁵ or when the cyclohexadienone is fused to a five-membered ring (VI),⁶ methyl-migration occurs instead to give "meta"-type phenols [e.g., (VII)]. In both cases spiran formation is difficult: in compound (V) because of the partial double-bond character of the C₍₈₎-C₍₉₎ linkage in the protonated intermediate and in compound (VI) because of the difficulty of forming a four-membered ring. A more complex case was found in the steroid series, prednisone acetate giving a "meta"-type phenol.⁷



A further example of methyl-migration has now been discovered, in which steric interactions prevent the formation of a spiran intermediate.

The dienone (X) was prepared from the known benzoate (VIII).⁸ Oxidation with chromium trioxide gave the benzoyloxy-ketone (IX) which was hydrolysed to a known hydroxy-ketone.⁹ Dehydrogenation of the $\alpha\beta$ -unsaturated ketone (IX) with 2,3-dichloro-5,6-dicyanobenzoquinone¹⁰ gave the desired dienone. Treatment of this compound with acetic anhydride containing a few drops of concentrated sulphuric acid gave an oily phenol acetate which was hydrolysed directly to a crystalline hydroxy-phenol (93% yield from

¹ Woodward and Singh, *J. Amer. Chem. Soc.*, 1950, **72**, 494.

² Woodward in Todd, "Perspectives in Organic Chemistry," Interscience, New York, 1956, p. 178.

³ Bloom, *J. Amer. Chem. Soc.* 1958, **80**, 6280.

⁴ Clemo, Haworth, and Walton, *J.*, 1929, 2368; 1930, 1110.

⁵ Djerassi, Rosenkranz, Romo, Pataki, and Kaufmann, *J. Amer. Chem. Soc.*, 1950, **72**, 4540; Sandoval, Miramontes, Rosenkranz, and Djerassi, *ibid.*, 1951, **73**, 990.

⁶ Bloom, *J. Amer. Chem. Soc.*, 1959, **81**, 4728.

⁷ Bailey, Elks, Oughton, and Stephenson, *J.*, 1961, 4535.

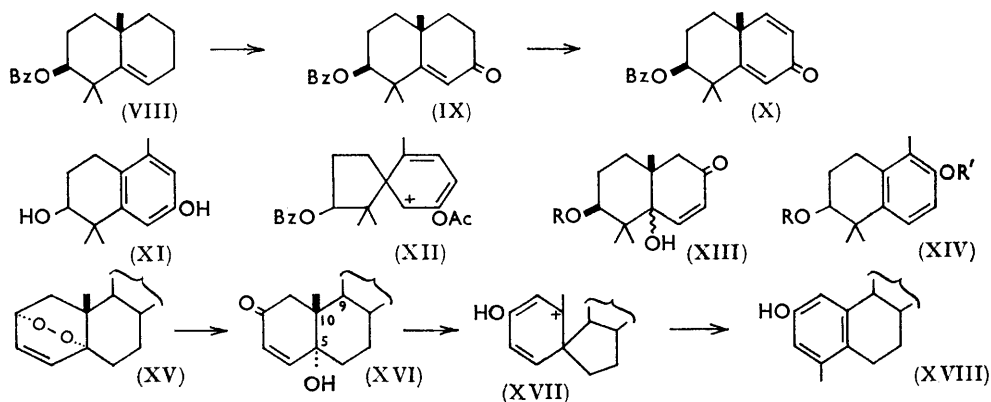
⁸ Halsall, Rodewald, and Willis, *J.*, 1959, 2798.

⁹ Cf. Mukherjee and Dutta, *J.*, 1960, 67.

¹⁰ Burn, Kirk, and Petrow, *Proc. Chem. Soc.*, 1960, 14.

the dienone). Both the infrared and the magnetic resonance spectra indicated two aromatic protons, *meta* to one another. That this phenol had structure (XI), formed by 1,2-methyl-migration, was further supported by the results of bromination experiments. Only a monobromo-compound was formed under mild conditions (bromine in aqueous dioxan) as expected since approach to the other position *ortho* to the phenolic hydroxyl group is hindered by the *gem* methyl groups. Examination of a model of a spiran intermediate (XII) shows that the carbon atoms of the "dienone" ring attached to the five-membered ring are completely eclipsed by the adjacent *gem* methyl groups, one of which is further eclipsed by the benzoyloxy-group.

A similar, but novel, rearrangement occurred when the γ -hydroxy- $\alpha\beta$ -unsaturated ketone (XIII)⁸ was heated with toluene-*p*-sulphonic acid in isopropenyl acetate. The benzoate (XIII; R = Bz) gave a crystalline acetoxy-benzoate, while the diol (XIII; R = H) gave an oily diacetate. Both compounds were hydrolysed to the same crystalline hydroxy-phenol. This phenol is assigned structure (XIV) on the basis of its infrared spectrum (1,2,3,4-substitution), the formation of a monobromo-derivative under mild conditions, and by analogy with the bicyclic dienone (X).



The acid-catalysed rearrangement of a similar hydroxy-ketone, 5-hydroxycholest-3-en-2-one (XVI), to a phenol was reported by Conca and Bergmann¹¹ in 1953 but they did not suggest a structure for their product. This hydroxy-ketone has now been obtained in high yield by alumina-catalysed isomerisation¹² of the unsaturated epidioxide (XV), and the phenolic rearrangement product obtained as described. Presumably the first step in this rearrangement is the formation of a carbonium ion at C₍₅₎. If then C₍₉₎, the mostly highly substituted carbon atom attached to C₍₁₀₎, migrates to form a spiran (XVII) and if this spiran subsequently collapses by a second migration of the more highly substituted group, the phenol will have structure (XVIII). Such migrations parallel those observed in the rearrangement of cholesta-1,4-dien-3-one.^{1,13} All evidence is in accord with this structural assignment. In the infrared spectrum the compound shows absorption typical of 1,2,3,5-substitution, while on bromination, one atom is taken up rapidly (*ca.* 10 min.) but the second reacts much more slowly (*ca.* 3 hr.). These different reactivities reflect the different degree of steric hindrance at C₍₁₎ and at C₍₃₎ in such a molecule.

During the preparation of the unsaturated epidioxide (XV) it was noted that the molecular rotation increment for the addition of oxygen to a steroidal ring A diene (-432°) is approximately equal, but opposite in sign, to that found for similar reactions in ring B dienes (see Table).

¹¹ Conca and Bergmann, *J. Org. Chem.*, 1953, **18**, 1104.

¹² Laubach, Schreiber, Agnello, and Brunings, *J. Amer. Chem. Soc.*, 1956, **78**, 4746.

¹³ Woodward, Inhoffen, Larson, and Menzel, *Chem. Ber.*, 1953, **86**, 594.

Compound	$\Delta[M_D]^a$	Compound	$\Delta[M_D]^a$
Cholesta-5,7-dien-3 β -ol	+474 ¹⁴	22,23-Dihydroergosteryl acetate	+377 ¹⁷
Ergosterol	+379 ¹⁵	Androsta-5,7-diene-3,7-diol diacetate...	+488 ¹⁷
Ergosteryl acetate	+300 ¹⁵	Cholesta-2,4-diene	-432 ¹⁷
22,23-Dihydroergosterol	+458 ¹⁶		

^a For formation of epidioxide.

EXPERIMENTAL

M. p.s were determined on a Kofler block. Ultraviolet spectra were measured on ethanol solutions. Light petroleum of b. p. 40—60° was used for chromatography and of b. p. 60—80° for crystallisation unless otherwise stated.

(\pm)-7 β -Benzoyloxy-8,8,10 β -trimethyl- $\Delta^{1(9)}$ -octal-2-one (IX).—(\pm)-2 β -Benzoyloxy-1,1,10 β -trimethyl- Δ^8 -octalin⁸ (VIII) (3.22 g.) and sodium acetate (2.8 g.) were dissolved in acetic acid (50 c.c.) and acetic anhydride (5 c.c.). The solution was kept at 55—60° during the addition of chromic acid (3.42 g.) (30 min.) and for a further 6 hr. After dilution with water, ethereal extraction afforded an oil which crystallised to give the *benzoyloxy-octalone* (IX) as needles (1.80 g.; 53%) (from ether-light petroleum), m. p. 115—118° (Found: C, 76.5; H, 7.9. C₂₀H₂₄O₃ requires C, 76.9; H, 7.7%), λ_{\max} 2340 Å (ϵ 28,600), ν_{\max} (in "Nujol") 1721 and 1675 cm⁻¹. The 2,4-dinitrophenylhydrazone crystallised from chloroform-ethanol as needles, m. p. 243—243.5° (Found: C, 63.2; H, 5.9; N, 11.2. C₂₆H₂₈N₄O₆ requires C, 63.4; H, 5.7; N, 11.4%), λ_{\max} 2290, 2500sh, and 3800 Å (ϵ 37,900, 24,400, and 35,900).

Hydrolysis of the benzoyloxy-octalone (IX) afforded the known⁹ (\pm)-7 β -hydroxy-8,8,10 β -trimethyl- $\Delta^{1(9)}$ -octal-2-one which crystallised from ether-light petroleum as prisms, m. p. 108—116° (Found: C, 75.15; H, 9.9. Calc. for C₁₃H₂₀O₂: C, 75.0; H, 9.7%), λ_{\max} 2410 and 3180 Å (ϵ 15,500 and 60), ν_{\max} (in "Nujol") 3356 and 1647 cm⁻¹. Mukherjee and Dutta⁹ give b. p. 165—170°/4 mm. The 2,4-dinitrophenylhydrazone of the hydroxy-octalone had m. p. 222.5—223.5°. Mukherjee and Dutta⁹ give m. p. 210°.

(\pm)-7 β -Benzoyloxy-2,5,6,7,8,10-hexahydro-8,8,10 β -trimethyl-2-oxonaphthalene (X).—2,3-Dichloro-5,6-dicyanobenzoquinone (610 mg.) in dry benzene was added to a solution of the benzoyloxy-octalone (IX) (740 mg.) in dry benzene and the solution was heated under reflux for 36 hr. with exclusion of moisture. After removal of some solvent and of the insoluble quinol, the solution was placed on a column of alumina (60 g.). Elution with benzene afforded the *dienone* (X) (460 mg., 63%) which crystallised from ether-light petroleum as needles, m. p. 131—133° (Found: C, 77.2; H, 7.3. C₂₀H₂₂O₃ requires C, 77.4; H, 7.1%), λ_{\max} 2340 Å (ϵ 28,300), ν_{\max} (in "Nujol") 1717 and 1669 cm⁻¹.

The 2,4-dinitrophenylhydrazone crystallised from ethyl acetate as stout needles, m. p. 227—229° (Found: C, 63.8; H, 5.25; N, 11.0. C₂₆H₂₆N₄O₆ requires C, 63.7; H, 5.3; N, 11.4%), λ_{\max} 2290, 2500sh, and 3920 Å (ϵ 34,900, 20,400, and 37,800).

5,6,7,8-Tetrahydro-2,7-dihydroxy-4,8,8-trimethylnaphthalene (XI).—The dienone (IX) (370 mg.) in acetic anhydride (20 c.c.) was treated with concentrated sulphuric acid (6 drops) in acetic anhydride (2.5 c.c.) and kept at 20° for 6 hr. The solution was then poured into water and kept for 12 hr. Extraction with dichloromethane yielded an oil which, even after chromatography, could not be crystallised but which had ν_{\max} 1718 (OBz) and 1757 cm⁻¹ (phenol acetate) and no band due to dienone. This oil in ethanol (70 c.c.) was heated under reflux with 20% aqueous potassium hydroxide (5 c.c.) for 4 hr. Some solvent was removed. The solution was then acidified and extracted with much ether to give a phenol (230 mg., 93%) which crystallised from benzene to give the *hydroxy-phenol* (XI) as needles, m. p. 148—149° (Found: C, 75.9; H, 8.7. C₁₃H₁₈O₂ requires C, 75.7; H, 8.8%), λ_{\max} 2800 Å (ϵ 2180), λ_{\min} 2480 Å (ϵ 130), ν_{\max} (in "Nujol") 887, 861, and 854 cm⁻¹, no selective absorption 840—750 cm⁻¹; (1% soln. in carbon tetrachloride, 1 cm. cell) 1720 cm⁻¹ [cf. 3,4,5-trimethylphenol with ν_{\max} (in "Nujol") 861, 855, and 845 cm⁻¹]. The nuclear magnetic resonance spectrum was measured on a ca. 10% solution in acetone, the instrument described by Leane, Richards, and Schaefer¹⁸ (29.913

¹⁴ Davis and Halsall, unpublished work.

¹⁵ Clayton, Henbest, and Jones, *J.*, 1953, 2015.

¹⁶ Windaus and Langer, *Annalen*, 1934, 508, 105.

¹⁷ Value taken from Mathieu and Petit, "Pouvoir Rotatoire Naturel," Vol. I, Steroids, Masson, Paris, 1956.

¹⁸ Leane, Richards, and Schaefer, *J. Sci. Instr.*, 1959, 36, 230.

Mc./sec.) being used. Shifts were measured by the side-band technique and are accurate to ± 0.1 c.p.s. (Found: 2 doublets centred on τ 3.43 due to two aromatic protons with J_{HH} 2.3 c.p.s.).

3-Bromo-5,6,7,8-tetrahydro-2,7-dihydroxy-4,8,8-trimethylnaphthalene.—The hydroxy-phenol (XI) (50 mg.) in dioxan (3 c.c.) and water (0.5 c.c.) was treated with 0.225M-bromine in dioxan solution, dropwise. One mol. was taken up rapidly but an additional 0.36 mol. was not decolourised after 2 hr. at 20°. The mixture was then poured into water; ether extraction afforded the *bromo-tetralin* which crystallised from benzene as rods, m. p. 170—173° (Found: C, 55.25; H, 6.1; Br, 27.5. $\text{C}_{13}\text{H}_{17}\text{BrO}_2$ requires C, 54.75; H, 6.0; Br, 28.0), λ_{max} 2890 Å (ϵ 3200), λ_{min} 2550 Å (ϵ 360), ν_{max} (in "Nujol") 854 cm^{-1} .

(\pm)-2-Acetoxy-6-benzoyloxy-5,6,7,8-tetrahydro-1,5,5-trimethylnaphthalene (XIV, R = Bz, R' = Ac).—(\pm)-6 β -Benzoyloxy-10 ξ -hydroxy-5,5,9 β -trimethyl- Δ^3 -octal-2-one⁸ (XIII; R = Bz) (500 mg.) was heated under reflux with toluene-*p*-sulphonic acid (500 mg.) in isopropenyl acetate (35 c.c.) for 18 hr. The cooled solution was poured into sodium hydrogen carbonate solution. Extraction with ether and removal of solvent afforded a brown oil which gave needles (310 mg., 58%), m. p. 144—146°, from methanol. A solution of the needles in ether was filtered through alumina and then gave the *tetralol derivative* (XIV; R = Bz, R' = Ac) as needles, m. p. 146.5—147° (Found: C, 75.1; H, 6.7. $\text{C}_{22}\text{H}_{24}\text{O}_4$ requires C, 75.0; H, 6.9%), λ_{max} 2180, 2280, 2650, 2720, and 2800 Å (ϵ 22,000, 20,400, 1100, 1200, and 830), ν_{max} (in chloroform) 1754 and 1709 cm^{-1} .

The acetoxy-benzoate (XIV; R = Bz, R' = Ac) was hydrolysed with boiling 2.5% aqueous methanolic potassium hydroxide for 1½ hr. to give 5,6,7,8-tetrahydro-2,6-dihydroxy-1,5,5-trimethylnaphthalene (XIV; R = R' = H) which crystallised from benzene as prisms, m. p. 174—175° (Found: C, 75.8; H, 8.8. $\text{C}_{13}\text{H}_{18}\text{O}_2$ requires C, 75.7; H, 8.8%), λ_{max} 2790 Å (ϵ 1800), λ_{min} 2490 Å (ϵ 350), ν_{max} (in "Nujol") 811 cm^{-1} ; 1848 cm^{-1} (1% soln. in chloroform, 1 cm. cell).

This compound was also prepared from (\pm)-6 β ,10 ξ -dihydroxy-5,5,9 β -trimethyl- Δ^3 -2-octalone (405 mg.) which was heated under reflux for 16 hr. in isopropenyl acetate (20 c.c.) with toluene-*p*-sulphonic acid (300 mg.). When the mixture was worked up as before the diacetate of compound (XIV; R = R' = H) was obtained as a brown oil. Hydrolysis gave compound (XIV; R = R' = H) (320 mg., 86%) which crystallised from benzene to give prisms, m. p. 175—175.5°.

3-Bromo-5,6,7,8-tetrahydro-2,6-dihydroxy-1,5,5-trimethylnaphthalene.—5,6,7,8-Tetrahydro-2,6-dihydroxy-1,5,5-trimethylnaphthalene (50 mg.) in dioxan (3 c.c.) and water (0.5 c.c.) was treated with a solution of bromine in dioxan (0.236M), dropwise. Decolorisation was rapid until 1.04 c.c. had been added; a further 0.02 c.c. did not react during 30 min. (Calc. for 1 mol.: uptake, 1.03 c.c.). Ether extraction yielded the *bromo-tetralin* as prisms, m. p. 135—136° (from ether-light petroleum) (Found: C, 55.0; H, 6.2; Br, 27.85. $\text{C}_{13}\text{H}_{17}\text{BrO}_2$ requires C, 54.75; H, 6.0; Br, 28.0%), λ_{max} 2860 Å (ϵ 2250), λ_{min} 2540 Å (ϵ 410), ν_{max} (in "Nujol") 864 cm^{-1} .

5 α -Hydroxycholest-3-en-2-one (XVI).—2 α ,5 α -Epidioxycholest-3-ene¹⁰ (640 mg.) in benzene-light petroleum (1:1) was adsorbed on alumina (activity I—II; 70 g.). After 4½ hr. the column was eluted. Benzene-ether mixtures gave a little oil. Ether-methanol (99:1) gave 5-hydroxycholest-3-en-2-one (545 mg., 85%) which, after crystallisation from methanol, had m. p. 165—167°, λ_{max} 2220 Å (ϵ 8200). Conca and Bergmann¹¹ give m. p. 172—173°, λ_{max} 2230 Å (ϵ 7900).

4-Methyl-19-norcholesta-1,3,5(10)-trien-2-ol (XVIII).—5-Hydroxycholest-3-en-2-one (640 mg.) and toluene-*p*-sulphonic acid (160 mg.) were heated under reflux in dry benzene (50 c.c.) for 40 min. Extraction with ether yielded an oil which was adsorbed on alumina (50 g.). Elution with benzene-light petroleum (1:3) gave cholesta-3,5-dien-2-one (280 mg., 46%), m. p. 125—126° (from acetone) (lit.,¹¹ m. p. 123—124°), λ_{max} 2900 Å (ϵ 15,300), ν_{max} 1670, 1632, and 1580 cm^{-1} . Elution with benzene-ether (1:1) gave an oil (290 mg.) which, on crystallisation from light petroleum (b. p. 40—60°), gave the phenol (XVIII) as needles (190 mg., 31%), m. p. 120—120.5° (lit., m. p. 119—120.5°), λ_{max} 2810 Å (ϵ 2170), λ_{min} 2490 Å (ϵ 160), ν_{max} (in "Nujol") 3175 (OH) and 857 cm^{-1} (1,2,3,5-tetrasubstituted benzene), 1721 > 1848 cm^{-1} (1% soln. in carbon tetrachloride, 1 cm. cell).

1,3-Dibromo-4-methyl-19-norcholesta-1,3,5(10)-trien-2-ol.—The phenol (XVIII) (87 mg.) in dioxan (3.5 c.c.) and water (0.5 c.c.) containing calcium carbonate (200 mg.) was treated with a solution of bromine in dioxan (0.186M). After 1 mol. had been taken up (1.22 c.c.; ca. 10 min.) uptake of bromine became slower, and the solution was kept with a further 1.35 c.c. of

¹⁰ Brown and Halsall, unpublished work.

bromine solution for 3 hr. in the dark. After this, the solution was almost colourless and it was poured into water. Extraction with ether afforded an oil which solidified on trituration with methanol. Three recrystallisations from methanol gave the *dibromo-trienol* as needles, m. p. 94—96°, $[\alpha]_D +140^\circ$ (Found: C, 60.0; H, 7.6; Br, 29.7. $C_{27}H_{40}Br_2O$ requires C, 60.0; H, 7.5; Br, 29.6%), λ_{max} . 2960 Å (ϵ 2900), λ_{min} . 2710 Å (ϵ 850), ν_{max} . (in carbon disulphide) 3450 cm^{-1} (OH), no selective absorption 790—910 cm^{-1} .

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