Synthesis of a Benzo[*a*]fluorenone Lactone Related to Etiojervine

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The synthesis of ring-A aromatic precursors of the etiojervine system has been achieved by Robinson annulation of a benz[*e*]indenone.

INTEREST in the physiological activity of modified steroids has led to syntheses [1,2] of a number of etiojervine [3] derivatives with a C-nor-D-homo-steroid nucleus, a structural feature characteristic of the veratrum alkaloids.[4,5] All these syntheses are based on the ring formation sequences DC-B-A or DCB-A, from suitable indane or fluorene derivatives. We now report work based on an alternative A-B-C-D approach. The synthesis of a C-nor-D-homo-steroid derivative along these lines has been described,[6] and a similar route has been used in these laboratories for the synthesis of an etiojervine analogue.[7]

We used the benz[*e*]indenone (1) [8] as starting material. Attempted hydroxymethylenation at position 3 gave only the bishydroxymethylene derivative (2); the dihydro-analogue (3) was obtained by the French workers.[6]

It appeared that for successful monohydroxymethylenation a 3a-substituent was required which could be removed easily at a later stage. In fact the 3a-methoxycarbonyl derivative (4) [8] † was used and was converted into the hydroxymethylene derivative (5) by a modified procedure [9] in good yield. Reaction of the product (5) with methyl vinyl ketone afforded, after chromatographic separation, three products. Two of these were the *O*-methyl-lactols (6a) and (7a), epimeric at C-3. The third, minor product, was the desired ester (8a). The structures of the lactol ethers (6a) and (7a) are supported by i.r. bands at 1770 (γ-lactone), 1695—1698 (cyclopentenone), and 1710—1715 cm^{-1} (saturated ketone) and n.m.r. signals at δ 2·17 (MeCO), 3·57—3·58 (3-OMe), 5·34—5·4 (MeO·C*H*),[10] and 6·27 (vinylic). The production of the ethers (6a) and (7a) was envisaged as involving the initial formation of the enol lactone (A) (*cf.* ref. 11), which could then undergo base-catalysed addition of methanol [12] to yield the anion (B). A Michael-type reaction with the alkyl vinyl ketone would then give the lactol ethers (see Scheme).

The validity of this mechanism is borne out by the isolation, albeit in low yield, of the *O*-methyl-lactol (10) when the hydroxymethylene compound (5) was treated with methanol and triethylamine. Structure (10) is supported by i.r. (1780 cm^{-1}; γ-lactone) and n.m.r. spectra [δ 3·57 (OMe), 5·48 (MeO·C*H*), and 6·3 (vinylic)]. The fusion of the rings c and c′ is assumed to be *cis* on the basis of the following considerations. Exclusive formation of a *cis*-bicyclo[3.3.0]octane system of which a γ-lactone is a part has been established.[13] Moreover, there is precedence for production of a lactone by protonation [of the anion (B) in this case] at a bridgehead carbon atom to produce a *cis* ring junction.[14] The configuration of the methoxy-group and, consequently, of H_A in (10) was deduced from n.m.r. data. The signals for H_A and H_B appear as singlets, indicating the torsion angle [15] between C–H bonds to be close to 90°. Such a requirement would be satisfied if the H_A and H_B are *trans* to each other and the methoxy-group is *cis* to the H_B as depicted. The configuration of the lactol methoxy-group in the products (6a) and (7a) was then derived

† The original method of preparation did not work well in our hands. A modified method of preparation of (4) is described in the Experimental section.

[1] S. M. Kupchan and M. J. Abu El-Haj, *J. Org. Chem.*, 1968, **33**, 647 and references cited therein; W. F. Johns, *ibid.*, 1972, **36**, 711 and references therein; F. C. Chang and R. C. Ebersole, *Tetrahedron Letters*, 1968, 3521; T. Masamune and T. Orito, *Bull. Chem. Soc., Japan*, 1972, **45**, 1888.

[2] R. F. Barnes and M. Sedlak, *J. Org. Chem.*, 1962, **27**, 4562 and references therein; P. W. Schiess, D. M. Bailey, and W. S. Johnson, *Tetrahedron Letters*, 1963, 459; W. S. Johnson, H. A. P. deJohngh, C. E. Coverdale, J. W. Scott, and U. Bruckhardt, *J. Amer. Chem. Soc.*, 1967, **89**, 4523; W. S. Johnson, J. M. Cox, D. W. Graham, and H. W. Whitlock, *ibid.*, p. 4524; T. Masamune, M. Takasugi, A. Murai, and K. Kobayashi, *ibid.*, p. 4521; W. S. Johnson, N. Cohen, E. R. Habicht, D. P. G. Hamon, G. P. Rizzi, and D. J. Faulkner, *Tetrahedron letters*, 1969, 2829; M. J. Green, N. A. Abraham, E. B. Fleisher, J. Case, and J. Fried, *Chem. Comm.*, 1970, 234: D. Mukherjee, *Indian J. Chem.*, 1971, **9**, 635.

[3] For the nomenclature of etiojervanes (12,14-cyclo-13,14-secoandrostanes), see S. M. Kupchan, T. Masamune, and G. W. Milne, *J. Org. Chem.*, 1964, **29**, 755; S. M. Kupchan and S. D. Levine, *J. Amer. Chem. Soc.*, 1964, **86**, 701; F. C. Chang and R. C. Ebersole, *Tetrahedron Letters*, 1968, 3521.

[4] S. M. Kupchan and A. W. By in ' The Alkaloids,' ed. R. H. F. Manske, Academic Press, New York, 1968, ch. 2.

[5] L. F. Fieser and M. Fieser, ' Steroids,' Reinhold, New York, 1959, p. 867.

[6] E. Brown, M. Ragault, and J. Touet, *Tetrahedron Letters*, 1971, 1043; E. Brown, J. Touet and M. Ragault, *Bull. Soc. chim., France*, 1972, 212.

[7] W. F. Johns, personal communication.

[8] R. E. Juday, B. Bukwa, K. Keiser, and G. Webb, *J. Medicin Chem.*, 1970, **13**, 313.

[9] T. A. Spencer, T. D. Weaver, R. M. Villarica, R. J. Friary, J. Posler, and M. A. Schwartz, *J. Org. Chem.*, 1968, **33**, 712.

[10] E. Wenkert, R. A. Mueller, E. J. Reardon, S. S. Sathe, D. J. Scharf, and G. Tosi, *J. Amer. Chem. Soc.*, 1970, **92**, 7428.

[11] C. N. R. Rao, ' Chemical Applications of Infrared Spectroscopy,' Academic Press, New York, 1963, p. 212.

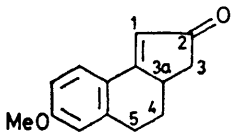
[12] W. S. Johnson and W. F. Johns, *J. Amer. Chem. Soc.*, 1957. **79**, 2005; P. Chamberlain and G. H. Whitham, *J. Chem. Soc.* (*B*), 1969, 1131; R. Luft, S. Delattre, and J. Arnaudo, *Bull. Soc. chim., France*, 1971, 1317.

[13] P. Crabbé, L. M. Guerrero, J. Romo, and F. Sánchez-Viesca, *Tetrahedron*, 1963, **19**, 25.

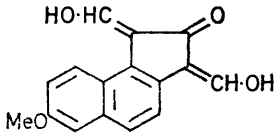
[14] W. H. Tallent, *Tetrahedron*, 1964, **20**, 1781.

[15] N. S. Bhacca and D. H. Williams, ' Applications of NMR Spectroscopy in Organic Chemistry,' Holden-Day, San Francisco, 1964, p. 159.

by correlating the solvent-induced change [16] in chemical shifts of H_A in these compounds with the change in that



(1)



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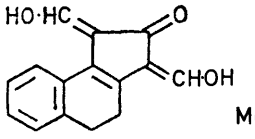

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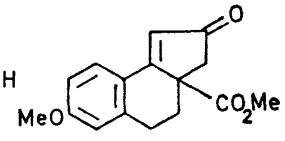

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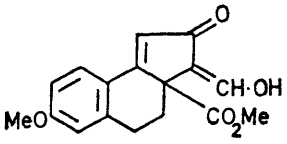

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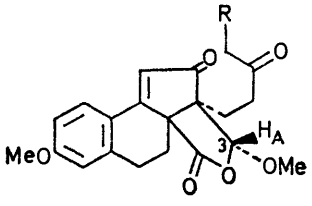
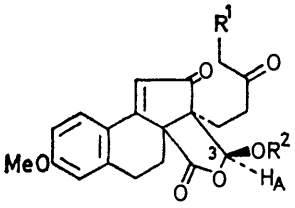
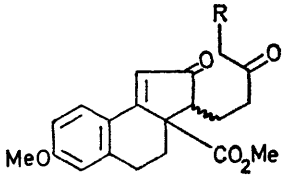


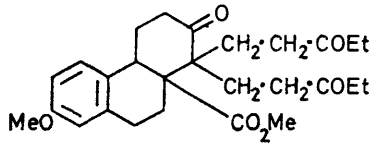
(6) a; R = H
b; R = Me



(7) a; R^1 = H, R^2 = Me
b; R^1 = R^2 = Me
c; R^1 = R^2 = H



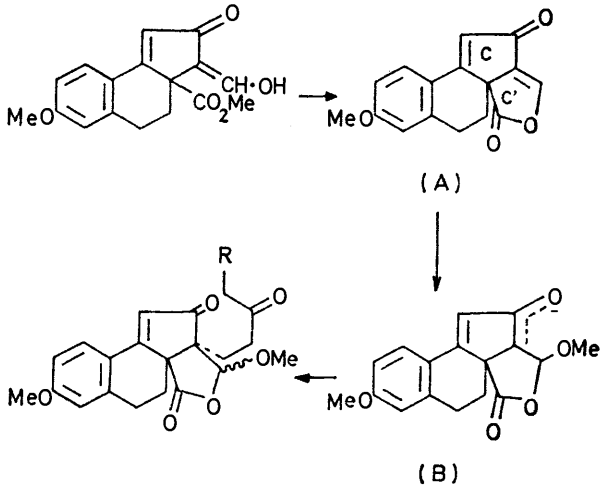
(8) a; R = H
b; R = Me



(9)

of H_A in compound (10) (Table). This indicated that the configuration of the H_A in compounds (6a) and (10) is the same.

Reaction of the hydroxymethylene derivative (5) with ethyl vinyl ketone afforded the *O*-methyl-lactols (6b) and (7b). The configuration of the lactol methoxy-groups in these compounds was assigned by correlating the chemical shifts of H_A with those of the products (6a) and (7a). Two other products, isolated in small quantities, were the ester (8b) and the bis-adduct (9). The



(A)

(B)

SCHEME

product (9) (M^+ 440) shows i.r. bands for the hydroxy-group and the saturated ketone and cyclopentenone

Chemical shifts (Hz)

Compound	(I) in $CDCl_3$	(II) in C_6D_6	Δ[(I) − (II)]
(6a)	324	324	0
(7a)	317	298	19
(10)	328	326	2

systems. The n.m.r. spectrum shows two singlets for the vinylic protons and two singlets for the ester methyl groups. This suggests that compound (9) exists, at least partly, as a side-chain aldol condensation product.

The products with *exo*-methoxy-groups (6a and b) were formed in much greater yields than the *endo*-methoxy-products (7a and b). Conjugate addition of methanol to a conformationally rigid cyclohexenone has been shown to yield the energetically unfavoured 3-methoxycyclohexanone with the methoxy-group axial as the major product. This has been explained in terms of maximum orbital overlap and minimum torsional interaction in the product-like transition state and the absence of unfavourable interaction of the polar bonds in the major product.[17] The high *exo* : *endo* ratio of the product pairs (6a) and (7a) and (6b) and (7b) can be rationalised in terms of steric hindrance [18] of approach of the nucleophile (MeOH) from the *endo*-side of the U-shaped bicyclo[3.3.0]octane intermediate [rings c and c' in (A)] and the synperiplanar interaction between the polar bonds (C–OMe and C–CO) [17] in the compounds

[16] L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' 2nd Edn., Pergamon, New York, 1969, p. 104.

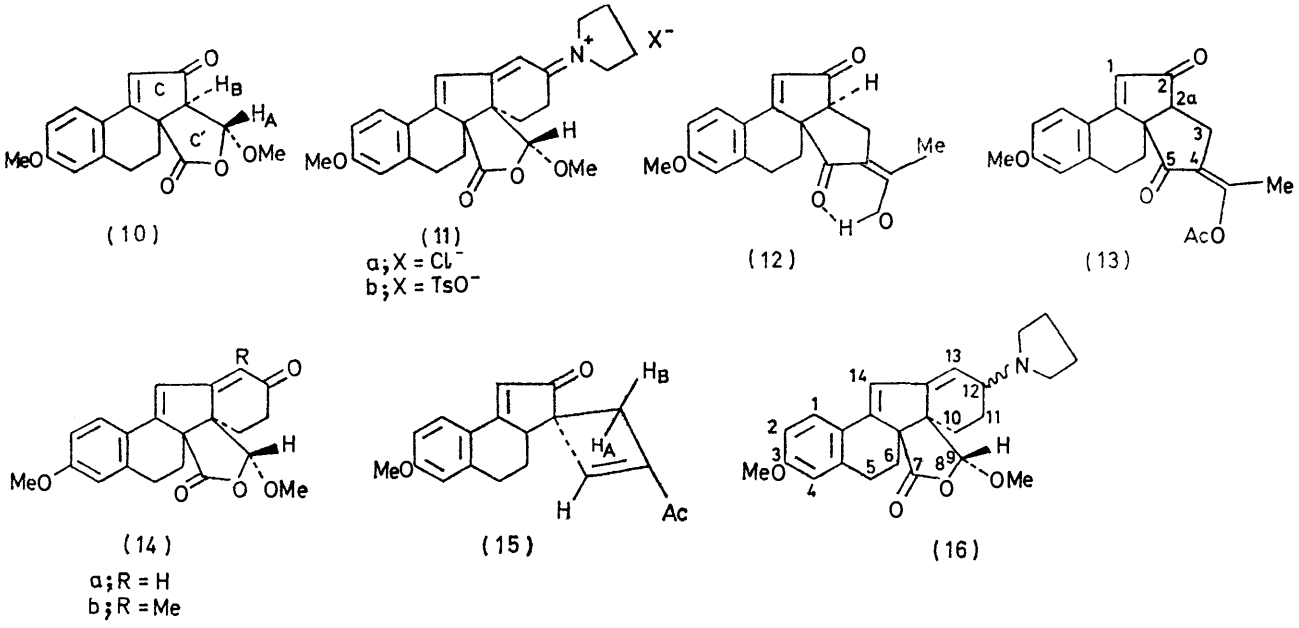
[17] P. Chamberlain and G. H. Whitham, *J.C.S. Perkin II*, 1972, 130.

[18] H. C. Brown, 'Boranes in Organic Chemistry,' Cornell University Press, London, 1972, p. 198.

with *endo*-methoxy-groups (7a and b). Such interaction is absent in the compounds with *exo*-methoxy-groups (6a and b).

Attempts were then made to hydrolyse the lactone group and simultaneously to close ring D under basic [19] and under acidic conditions.[6,20] Treatment of compound (6a) with methanolic potassium hydroxide at room temperature yielded the β-diketone (12), which gave a violet colouration with alcoholic ferric chloride. The n.m.r. spectrum shows a broadened singlet ($W_{1/2}$ 2 Hz) at δ 2·01 for the methyl group, a sharp singlet

Heating compound (6a) with hydrochloric acid gave the acetylcyclobutene derivative (15). The i.r. spectrum of this shows a band at 1671 cm^{-1} due to the αβ-unsaturated keto-group [23] of the acetylcyclobutene system. The n.m.r. spectrum (60 MHz; deuteriochloroform) shows signals at δ 2·23 (3H, s, Ac) and 6·67 (dd, vinyl proton of cyclobutene ring). The signals for the cyclobutene methylene protons (H_A and H_B) in a 100 MHz spectrum (in [$^2H_5$]pyridine) appear as the AB part of an ABX system (J_{AB} 14, J_{BC} 2, J_{AC} 2·4 Hz, from first-order analysis) and the signal for the cyclobutene



($W_{1/2}$ 1·5 Hz) for the methoxy-group and a broad signal at low field (δ 13·4) for the enolic hydroxy-group. This suggests that the compound exists predominantly as the enol; the existence of the keto tautomer would have shown another signal for the MeCO group, provided that the interconversion of keto and enol tautomers was not too rapid.[21] The i.r. spectrum of (12) also shows that it exists as the enol, showing no band above 1700 cm^{-1} attributable to a saturated ketone and containing a band at 1650 cm^{-1} corresponding to the hydrogen-bonded unsaturated keto-group of an enolised β-diketone.[22] Treatment of compound (12) with acetic anhydride–pyridine at room temperature gave the enol acetate (13) the n.m.r. spectrum of which shows signals at δ 2·2 (3H, s, OAc) and 2·25 (3H, t, *J* 2 Hz, MeC=C). Irradiation of the C(3)H_2 signal caused the triplet at δ 2·25 to collapse to a singlet (homoallylic coupling).

vinyl proton at δ 6·91 is hidden under the signals of the aromatic protons. The signals at δ 2·97 and 3·31 collapse to form an AB quartet upon irradiation at δ 6·91. The mass spectrum shows peaks at *m/e* 294 (M^+) and 251 (M^+ — Ac) (*cf.* ref. 23).

Since the cleavage of the lactone group and simultaneous closure of ring D could not be achieved, the formation of ring D without affecting the lactone group was then attempted by utilising procedures successfully employed in the synthesis of perhydroindenones. Treatment of either of the *O*-methyl-lactols (6a) and (7a) with phosphoric acid at room temperature or at elevated temperature gave the same lactol (7c). Treatment of compound (6a) with either toluene-*p*-sulphonic acid [24] or pyrrolidine [25] under reflux failed to close ring D; only starting material was recovered.

The process of ring closure by use of pyrrolidine has been postulated to involve an intermediate enamine.[26]

[19] D. Caine, A. M. Alejande, K. Ming, and W. J. Powers, *J. Org. Chem.*, 1972, **35**, 706.
[20] V. Prelog and M. Zimmermann, *Helv. Chim. Acta*, 1949, **32**, 2361.
[21] L. M. Jackman, ' Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon, New York, 1959, p. 71.
[22] R. S. Rasmussen, D. D. Tunnicliff, and R. R. Brattain, *J. Amer. Chem. Soc.*, 1949, **71**, 1069.
[23] J. F. Bagli and T. Bogri, *Tetrahedron Letters*, 1969, 1639.
[24] S. Ramchandran and M. S. Newman, *Org. Synth.*, 1961, **41**, 38.
[25] C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.*, 1959, 2022.
[26] T. A. Spencer, H. S. Neel, T. W. Flechtner, and R. A. Zayle, *Tetrahedron Letters*, 1965, 3889 and references therein.

Therefore, ring closure of (6a) by treatment with pyrrolidine and toluene-*p*-sulphonic acid (the usual method of preparation of enamines [27]) was attempted. This gave the iminium salt (11). Treatment of the crude product with hydrochloric acid afforded the iminium chloride (11a), whereas direct work-up gave the toluene-*p*-sulphonate (11b). Both salts had the same u.v. absorption at long wavelength. Attempted hydrolysis of the iminium function in (11a) to produce the ketone (14a) with acid gave no identifiable product. Reduction of the salt (11b) with sodium borohydride gave the C-nor-D-homo-steroid derivative (16). Its n.m.r. spectrum shows the vinylic 14-proton signal as a singlet and that of the 13-proton as a doublet (J 5 Hz).

Unlike the methyl vinyl ketone adduct (6a), the ethyl vinyl ketone adduct (6b) underwent smooth ring closure with toluene-*p*-sulphonic acid to yield the etiojervine analogue (14b) in high yield. Its n.m.r. spectrum shows the 14-proton signal as a singlet and that of 13-methyl group as a singlet. The u.v. spectrum ($\lambda_{max.}$ 370 nm) is in accord with an extensively conjugated ketone system.[28] Attempted ring closure of (6b) with pyrrolidine, however, was unsuccessful. Treatment of compound (6b) with pyrrolidine and toluene-*p*-sulphonic acid also produced the tetracyclic ketone (14b) and not the iminium salt analogous to compound (11b).

EXPERIMENTAL

M.p.s. were determined with a Mel-Temp apparatus. U.v. and visible spectra were determined for solutions in methanol. I.r. spectra were determined for solutions in chloroform except where otherwise stated. N.m.r. spectra were measured at 60 MHz for solutions in deuteriochloroform (except where otherwise stated) with tetramethylsilane as internal standard. Mass spectra were obtained by direct insertion of the sample into the ion source of an A.E.I. MS30 instrument. Silica for chromatography refers to Mallinckrodt silicic acid CC-7. All solutions were dried with anhydrous sodium sulphate. All the compounds described here are racemic.

Methyl 3,3a,4,5-*Tetrahydro*-7-*methoxy*-2-*oxobenz*[e]*inden*-3a-*carboxylate*.—A slurry of sodium hydride (2 g; 52% mineral oil suspension, washed with dry toluene before use) in dry toluene (200 ml) under nitrogen was treated with dimethylacetamide (6 ml) and methyl 2-acetonyl-1,2,3,4-tetrahydro-6-methoxy-1-oxonaphthalene-2-carboxylate [7] (20 g). The mixture was heated (in a preheated oil-bath) to 60—65°, and dry methanol (0·25 ml) was then added. The mixture was then heated to reflux for 3 min, cooled rapidly to 5° in solid carbon dioxide–acetone, and then acidified with cold dilute acetic acid. The solid which separated was filtered off and triturated with hot methanol; a yellow solid (4), m.p. 176—179° (7·6 g), was obtained. The toluene layer was separated from the aqueous layer and evaporated. The residual oil crystallised from methanol to furnish another crop, m.p. 177—180° (700 mg).

Methyl 3,3a,4,5-*Tetrahydro*-3-*hydroxymethylene*-7-*methoxy*-2-*oxobenz*[e]*inden*-3a-*carboxylate* (5).—A solution of compound (4) (15 g) in dry benzene (400 ml) and ethyl formate (200 ml) was cooled in ice–ethanol. The flask was flushed with nitrogen and the solution was treated with sodium hydride (4·2 g; 52% suspension in mineral oil) followed by dry methanol (3 drops), stirred at room temperature for 94 h, cooled in ice, and carefully decomposed with water (800 ml). The aqueous layer was separated, cooled, acidified with 50% hydrochloric acid, and extracted with chloroform (800 ml). The extract was washed with water, dried, and evaporated. Crystallisation of the residue from dichloromethane–ether gave yellow needles (10·1 g), m.p. 165—168°, used for the next step. Recrystallisation gave material of m.p. 175·5—177·5° (Found: C, 67·85; H, 5·45. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·35%); $\nu_{max.}$ 1735, 1670, and 1612 cm^{-1}; $\lambda_{max.}$ 238, 300sh, and 399 nm (ε 6900, 18,600, and 29,350); δ 3·6 (3H, s, OCH_3), 3·83 (3H, s, arom. OCH_3), 6·38 (1H, s, vinylic), 6·6—7·0 (2H, m, arom.), and 7·5—7·7 (1H, d, arom.).

Reaction of the Hydroxymethylene Derivative (5) *with Methyl Vinyl Ketone*.—A solution of the hydroxymethylene derivative (5) (10 g) in dry methanol (300 ml) containing methyl vinyl ketone (6 g) and triethylamine (5 ml) was stirred in nitrogen for 14 days. The methanol was removed under reduced pressure and the residue was dissolved in benzene (400 ml). The solution was washed with 2% potassium hydroxide solution (300 ml) and water, then dried and evaporated. The oily residue (12·8 g) was chromatographed on silica (1000 g) and eluted with benzene–ethyl acetate (5—50%) (with t.l.c. monitoring). The least polar fractions crystallised from dichloromethane–ether to give 2a,3,6,7-*tetrahydro*-3α,9-*dimethoxy*-2aα-(3-*oxobutyl*)*benz*[4,5]-*indeno*[1,7a-c]*furan*-2,5-*dione* (6a) as needles (6·3 g, 49%), m.p. 173·5–174° (Found: C, 68·0; H, 6·05. $C_{21}H_{22}O_6$ requires C, 68·1; H, 6·0%); $\nu_{max.}$ 1770, 1710, 1695, and 1610 cm^{-1}; $\lambda_{max.}$ 244 and 336 nm (ε 9620 and 27,380); δ 2·17 (3H, s, CH_3), 3·57 (3H, s, OCH_3), 3·87 (3H, s, arom. OCH_3), 5·4 (1H, s, MeO·C*H*), 6·27 (1H, s, vinylic), 6·65—7·0 (2H, m, arom.), and 7·5—7·7 (1H, d, arom.); δ (C_6D_6) 1·82 (3H, s, CH_3), 3·12 (3H, s, OCH_3), 3·32 (3H, s, arom. OCH_3), 5·4 (1H, s, MeO·C*H*), 6·08 (1H, s, vinylic), and 6·5—7·25 (3H, m, arom.). The fractions of intermediate polarity crystallised from methanol (charcoal) to give *methyl* 3,3a,4,5-*tetrahydro*-7-*methoxy*-2-*oxo*-3-(3-*oxobutyl*)*benz*[e]*indene*-3a-*carboxylate* (8a) as a solid (520 mg, 4%), m.p. 155—156° (Found: C, 70·2; H, 6·65. $C_{20}H_{23}O_5$ requires C, 70·15; H, 6·5%); $\nu_{max.}$ 1735, 1720, 1700, and 1600 cm^{-1}; $\lambda_{max.}$ 239, 300sh, and 319 nm (ε 9576, 18,639, and 25,479); δ 2·14 (3H, s, CH_3), 3·57 (3H, s, OCH_3), 3·83 (3H, s, arom. OCH_3), 6·4 (1H, s, vinylic), 6·65—7·0 (2H, m, arom.), and 7·5—7·7 (1H, d, arom.). The most polar fractions crystallised from dichloromethane–ether to yield 2a,3,6,7-*tetrahydro*-3β,9-*dimethoxy*-2aα-(3-*oxobutyl*)*benz*[4,5]*indeno*[1,7a-c]*furan*-2,5-*dione* (7a) (950 mg, 7%), m.p. 162—164° (Found: C, 68·15; H, 6·15%); $\nu_{max.}$ 1770, 1715, 1698, and 1590 cm^{-1}; $\lambda_{max.}$ 243 and 332 nm (ε 8602 and 27,302); δ 2·17 (3H, s, CH_3), 3·58 (3H, s, OCH_3), 3·87 (3H, s, arom. OCH_3), 5·28 (1H, s, MeO·C*H*), 6·27 (1H, s, vinylic), 6·65—7·0 (2H, m, arom.), and 7·5—7·7 (1H, d, arom.); δ (C_6D_6) 1·8 (3H, s, CH_3), 3·25 (3H, s, OCH_3), 3·33 (3H, s, arom, OCH_3), 4·97 (1H, s, MeO·C*H*), 6·08 (1H, s, vinylic), and 6·4—7·3 (3H, m, arom.).

Reaction of the Hydroxymethylene Compound (5) *with Ethyl Vinyl Ketone*.—A mixture of the hydroxymethylene derivative (5) (12 g) in dry methanol (300 ml), ethyl vinyl ketone (10 g), and triethylamine (5 ml) was stirred in

[27] H. O. House, 'Modern Synthetic Reactions,' Benjamin, California, 1965, p. 198.

[28] A. I. Scott, 'Interpretation of the Ultraviolet Spectra of Natural Products,' Pergamon, New York, 1964, p. 107.

nitrogen for 21 days. The solution was evaporated and the residue was dissolved in benzene (200 ml). The solution was washed with 5% potassium hydroxide solution (300 ml) and water, then dried and evaporated. The residue (14·5 g) was crystallised several times from dichloromethane–ether to give needles of the 2a,3,6,7-*tetrahydro*-3α,9-*dimethoxy*-2aα-(3-*oxopentyl*)*benz*[4,5]*indeno*[1,7a-c]*furan*-2,5-*dione* (6b) (2·1 g), m.p. 149—150°. The residue from the mother liquor was separated by chromatography on silica (1400 g) [benzene–ethyl acetate (5—30%) as eluant]. The least polar fractions, crystallised from dichloromethane–ether, gave compound (6b) as needles (3·5 g), m.p. 149—150° (total yield 5·6 g, 39%) (Found: C, 68·75; H, 6·55. $C_{22}H_{24}O_6$ requires C, 68·75; H, 6·3%); $\nu_{max.}$ 1780, 1710sh, 1700, and 1610 cm^{-1}; $\lambda_{max.}$ 244 and 336 nm (ε 8640 and 28,992); δ 1·07 (3H, t, CH_3), 3·6 (3H, s, OCH_3), 3·87 (3H, s, arom. OCH_3), 5·4 (1H, s, MeO·C*H*), 6·3 (1H,s, vinylic), 6·7—7·0 (2H, m, arom.), and 7·5—7·8 (1H, d, arom.). More polar fractions upon treatment with methanol gave a solid (700 mg), m.p. 149—157°, further crystallisation of which yielded *methyl* 3,3a,4,5-*tetrahydro*-7-*methoxy*-2-*oxo*-3-(3-*oxopentyl*)-*benz*[e]*indene*-3a-*carboxylate* (8b) as needles (320 mg, 2%), m.p. 156—162° (Found: C, 70·9; H, 6·9. $C_{21}H_{24}O_5$ requires C, 70·75; H, 6·8%); $\nu_{max.}$ 1735, 1715sh, 1700, and 1605 cm^{-1}; $\lambda_{max.}$ 239, 300sh, and 318 nm (ε 9612, 18,868, and 25,632); δ 1·07 (3H, t, CH_3), 2·4 (2H,q, CH_2), 3·6 (3H, s, OCH_3), 3·87 (3H, s, arom. OCH_3), 6·3 (1H, s, vinylic), 6·6—7·0 (2H, m, arom.), and 7·5—7·8 (1H, d, arom.). Fractions of higher polarity, on crystallisation from dichloromethane–ether, yielded 2a,3,6,7-*tetrahydro*-3β,9-*dimethoxy*-2aα-(3-*oxopentyl*)*benz*[4,5]*indeno*[1,7a-c]*furan*-2,5-*dione* (7b) as needles (1·5 g, 10%), m.p. 139·5—140·5° (Found: C, 68·85; H, 6·35%); $\nu_{max.}$ 1770, 1710sh, 1700, and 1605 cm^{-1}; $\lambda_{max.}$ 244 and 332 nm (ε 8640 and 27,456); δ 1·1 (3H, t, CH_3), 3·56 (3H, s, OCH_3), 3·83 (3H, s, arom. OCH_3), 5·27 (1H, s, MeO·C*H*), 6·25 (1H, s, vinylic), 6·7—7·0 (2H, m, arom.), and 7·5—7·75 (1H, d, arom.). The most polar fractions upon trituration with acetone–ether gave a dark solid which was extracted with hot ether (20 ml). The insoluble residue on crystallisation from acetone–ether (charcoal) gave *methyl* 2,3,4,5-*tetrahydro*-7-*methoxy*-2-*oxo*-3,3-*bis*-3-*oxopentylbenz*[e]*indene*-3a-*carboxylate* (9) as needles (60 mg), m.p. 180—186° (Found: C, 70·85; H, 7·45. $C_{26}H_{32}O_6$ requires C, 70·9; H, 7·3%); $\nu_{max.}$ 3600, 1735, 1710, and 1695sh cm^{-1}; $\lambda_{max.}$ 239, 300sh, and 318 nm (ε 9900, 18,920, and 27,280); δ 0·9 (t, CH_3), 3·6 and 3·65 (singlets, CO_2Me), 3·8 (s, arom. OCH_3), 6·3 and 6·43 (singlets, vinylic), 6·65—7·0 (m, arom.), and 7·55—7·75 (d, arom,); *m/e* 440 (M^+) and 422 ($M^+ - H_2O$).

4-*Acetyl*-3,4,6,7-*tetrahydro*-9-*methoxypentaleno*[1,6a–a]-*naphthalene*-2(2aH),5-*dione* (12).—A solution of the product (6a) (1·1 g) in methanol (100 ml) containing potassium hydroxide (5 g) was stirred in nitrogen for 118 h. The solvent was removed under reduced pressure and the residue was treated with water (150 ml). The aqueous solution was extracted with dichloromethane (150 ml). The dichloromethane solution was washed with water, dried, and evaporated to leave an intractable gummy residue (300 mg). The aqueous alkaline solution was acidified with concentrated hydrochloric acid, saturated with sodium chloride, and extracted with chloroform (150 ml). The chloroform solution was washed with water, dried, and evaporated. The gummy residue (730 mg) was chromatographed on silica (16 g), and eluted with benzene (200 ml) followed by ether (400 ml). Material eluted with ether (500 mg), upon crystallisation from dichloromethane–ether (charcoal), afforded compound (12) as needles (230 mg, 20%), m.p. 170–172° (Found: C, 73·35; H, 5·95. $C_{19}H_{18}O_4$ requires C, 73·55; H, 5·85%); $\nu_{max.}$ 1690, 1650, and 1600 cm^{-1}; $\lambda_{max.}$ 243, 301, and 328 nm (ε 9920, 23,405, and 24,955); δ 2·01 (3H, s, CH_3), 3·87 (3H, s, arom. OCH_3), 6·33 (1H, s, vinylic), 6·7—7·0 (2H, m, arom.), and 7·5—7·7 (1H, d, arom.).

4-(1-*Acetoxyethylidene*)-3,4,6,7-*tetrahydro*-9-*methoxypentaleno*[1,6a-a]*naphthalene*-2,5-*dione* (13).—A solution of compound (12) (80 mg) in acetic anhydride (1 ml) and dry pyridine (1 ml) was left at room temperature for 16 h. The reagents were removed under reduced pressure and the semisolid residue was crystallised from dichloromethane–ether (charcoal) to give the *acetate* (13) as needles (41 mg), m.p. 181·5—183·5° (Found: C, 71·7; H, 5·85. $C_{21}H_{20}O_5$ requires C, 71·6; H, 5·7%); $\nu_{max.}$ 1760, 1710, 1685, 1640, and 1600 cm^{-1}; $\lambda_{max.}$ 245, 267sh, and 330 nm (ε 19,712, 12,320, and 26,400); δ 2·2 (3H, s, CH_3), 2·25 (3H, t, CH_3), 3·76 (3H, s, arom. OCH_3), 6·3 (1H, s, vinylic), 6·7—7·0 (2H, m, arom.), and 7·5—7·75 (1H, d, arom.).

2a,3,6,7-*Tetrahydro*-3-*hydroxy*-9-*methoxy*-2a-(3-*oxobutyl*)-*benz*[4,5]*indeno*[1,7a-c]*furan*-2,5-*dione* (7c).—(*a*) The product (7a) (100 mg) was treated with phosphoric acid (2 ml; 85%) and left at room temperature for 26 h. The mixture was decomposed with crushed ice and then extracted with chloroform (60 ml). The extract was washed with water, dried, and concentrated. The product was separated from starting material by p.l.c. on silica [ethyl acetate–chloroform (1 : 1)] and crystallised from dichloromethane–ether to give the *lactol* (7c) as needles (35 mg), m.p. 162—164° (decomp.) (Found: C, 67·3; H, 5·85. $C_{20}H_{20}O_6$ requires C, 67·4; H, 5·65%); $\nu_{max.}$ (KBr) 3600—3100, 1775, 1715, 1695, and 1615 cm^{-1}; $\lambda_{max.}$ 244 and 334 nm (ε 8544 and 27,412); δ 2·13 (3H, s, CH_3), 387 (3H, s, arom. OCH_3), 5·2br (1H), 5·9 (1H, d), 6·3 (1H, s, vinylic), 6·7—7·0 (2H, m, arom.), and 7·55—7·8 (1H, d, arom.); δ (C_5D_5N) 2·07 (3H, s, CH_3), 3·77 (3H, s, arom. OCH_3), 6·47 (1H, s, MeO·C*H*), 6·67 (1H, s, vinylic), 6·8—7·0 (2H, m, arom.), and 7·8—8·0 (1H, d, arom.).

(*b*) The *O*-methyl-lactol (7a) (100 mg) was treated with phosphoric acid (2 ml; 85%) and then heated at 54° for 18 h. The solution was decomposed with crushed ice and extraced with dichloromethane (40 ml). The extract was washed with water, dried, and evaporated. The residue, homogeneous on t.l.c., crystallised from dichloromethane–ether to give needles of the lactol (7c) (41 mg), m.p. 159—161° (decomp.), identical with the material prepared in (*a*) (i.r. and n.m.r. spectra).

(*c*) The product (6a) (100 mg) was treated with phosphoric acid under the same conditions as in (*b*). The product (37 mg), m.p. 162—164° (decomp.) was identified as the lactol (7c) by mixed m.p. and comparison of i.r. and n.m.r. spectra.

3′-*Acetyl*-3,3a,4,5-*tetrahydro*-7-*methoxyspiro*(*benz*[e]*indene*-3,1′-*cyclobut*-2-*en*)-2-*one* (15).—A solution of compound (6a) (200 mg) in glacial acetic acid (10 ml) was treated with concentrated hydrochloric acid (4 ml) and water (1 ml), and the mixture was heated to reflux for 105 min. The solution was evaporated under reduced pressure and the residue was dissolved in chloroform (70 ml). The solution was washed with water, dried, and evaporated. The residue (200 mg) was chromatographed on silica (20 g) and eluted with chloroform (125 ml), followed by ethyl acetate (125 ml). Material from the latter eluate was dissolved in chloroform

and treated with charcoal, and the solution was concentrated. The yellow solid obtained (160 mg), m.p. 210—212° gave colourless *needles*, m.p. 216—217° (from methanol) (Found: C, 77·35; H, 6·3. $C_{19}H_{18}O_3$ requires C, 77·55; H, 6·15%); $\nu_{max.}$ (KBr) 1685, 1671, and 1615 cm^{-1}; $\lambda_{max.}$ 230, 300sh, and 324 nm (ε 18,228, 14,206, and 24,702); δ 2·23 (3H, s, CH_3), 3·87 (3H, s, arom. OCH_3), 6·2 (1H, s, vinylic), 6·67 (1H, t, cyclobutene olefinic), 6·8—7·0 (2H, m, arom.), and 7·5—7·7 (1H, d, arom.); *m/e* 294 (M^+), 251 ($M^+ - COCH_3$).

N-(5,6,11,12-*Tetrahydro*-3,9-*dimethoxy*-7-*oxo*-7H,9H,10H-*benzo*[1,2]*fluoreno*[4a,4b-c]*furan*-12-*ylidene*)*pyrrolidinium Salts* (11a and b).—(*a*) A solution of the diketone (6a) (200 mg) in dry benzene (70 ml) containing pyrrolidine (4 drops) was heated to reflux under a Dean–Stark head for 18 h. T.l.c. then showed the presence of starting material only. The solution was treated with a few crystals of toluene-*p*-sulphonic acid and pyrrolidine (2 drops), and heating under reflux with separation of water was continued for 20 h. The mixture was cooled, treated with dilute hydrochloric acid (20%; 5 ml), and stirred; a yellow solid (140 mg) then separated. Crystallisation from methanol–ether (charcoal) gave the *chloride* (11a) as yellow needles, m.p. 253—254° (decomp.) (Found: C, 66·75; H, 6·25; N, 2·95. $C_{25}H_{28}ClNO_4,0{\cdot}5H_2O$ requires C, 66·6; H, 6·45; N, 3·1%); $\nu_{max.}$ (KBr) 3600—3200, 1815, 1655, and 1620 cm^{-1}; $\lambda_{max.}$ 273, 298, 319, and 430 nm (ε 6757, 3000, 2811, and 44,149); δ (CD_3OD) 3·6 (s, OCH_3), 3·87 (s, OCH_3), 5·45 (1H, s), 6·6 (1H, s), 6·8—7·0 (3H, m), and 7·7—8·0 (1H, d).

(*b*) A solution of compound (6a) (2 g) in dry benzene (125 ml) containing pyrrolidine (1·6 g) and toluene-*p*-sulphonic acid (1 g) was heated to reflux with the separation of water (Dean–Stark head) for 70 h. The solution was filtered and evaporated. The residue was washed with hot ether. The insoluble solid, m.p. 270—273° (decomp.) (2·8 g) crystallised from methanol–ether as orange needles of the *tosylate* (11b), m.p. 283—284° (decomp.) (Found: C, 66·7; H, 6·2; N, 2·3. $C_{32}H_{35}NO_7S$ requires C, 66·55; H, 6·1; N, 2·4%); $\nu_{max.}$ (KBr) 1770, 1620, and 1605 cm^{-1}; $\lambda_{max.}$ 221·5, 227, 255sh, 272, 296, 312, and 430 nm (ε 20,772, 14,714, 5441, 6232, 2319, 2422, and 44,430); δ 2·2 (s, arom, CH_3), 3·5 (s, OCH_3), 3·85 (s, arom. OCH_3), 5·68 (1H, s, MeO·C*H*), 6·6 (1H, s, vinylic), and 6·7—7·7 (7H, m, vinylic and arom.).

5,6,11,12-*Tetrahydro*-3,9-*dimethoxy*-12-(*pyrrolidin*-1-*yl*)-9H,10H-*benzo*[1,2]*fluoreno*[4a,4b-c]*furan*-7-*one* (16).—The toluene-*p*-sulphonate (11b) (1·4 g) was dissolved in methanol (100 ml) and treated with sodium borohydride (2·8 g). The methanol was removed under reduced pressure and the residue was treated with water (100 ml) and extracted with dichloromethane (100 ml). The extract was washed with water, dried, and evaporated. The oily residue crystallised from methanol as *needles* (920 mg), m.p. 170—171° (decomp.) (Found: C, 73·65; H, 7·35; N, 3·25. $C_{25}H_{29}NO_4$ requires C, 73·7; H, 7·15; N, 3·45%); $\nu_{max.}$ 1770 and 1610 cm^{-1}; $\lambda_{max.}$ 238, 295sh, 308, and 318 nm (ε 10,989, 23,199, 28,897, and 28,083); δ 3·1 (1H, m, N·CH), 3·53 (3H, s, OCH_3), 3·8 (3H, s, arom. OCH_3), 5·43 (1H, s, MeO·C*H*), 5·75 (1H, d, vinylic), 6·3 (1H, s, vinylic), 6·6—6·8 (2H, m, arom.), and 7·25—7·35 (1H, d, arom.).

5,6,10,11-*Tetrahydro*-3α,9-*dimethoxy*-13-*methyl*-9H-*benzo*-[1,2]*fluoreno*[4a,4b-c]*furan*-7,12-*dione* (14b).—(a) *With toluene*-p-*sulphonic acid*. A solution of the diketone (6b) (4·5 g) in dry benzene (100 ml) containing toluene-*p*-sulphonic acid (1 g) was heated under reflux (Dean–Stark head) for 72 h. The solution was washed with sodium hydrogen carbonate solution (5%) and water, then dried, concentrated to 25 ml, and treated with methanol (30 ml); a solid (3·5 g), m.p. 261—266° (decomp.), separated out. Crystallisation from chloroform–methanol gave yellow *needles* (2·8 g), m.p. 270—271° (decomp.) (Found: C, 72·0; H, 6·1. $C_{22}H_{22}O_5$ requires C, 72·1; H, 6·05%); $\nu_{max.}$ 1780, 1650, and 1610 cm^{-1}; $\lambda_{max.}$ 253 and 370 nm (ε 5124 and 23,607); δ 1·95 (3H, s, CH_3), 3·53 (3H, s, OCH_3), 3·82 (3H, s, arom. OCH_3), 5·25 (1H, s, MeO·C*H*), 6·7—6·9 (3H, m, vinylic and arom.), and 7·5—7·75 (1H, d, arom.).

(b) *With pyrrolidine and toluene*-p-*sulphonic acid*. A solution of the diketone (6b) (400 mg) in dry benzene containing pyrrolidine (350 mg) and toluene-*p*-sulphonic acid (300 mg) was heated to reflux (Dean–Stark head) for 24 h. The solution was concentrated and the residue was washed with water and then dissolved in chloroform (100 ml). The chloroform solution was dried and evaporated. The residue crystallised from methanol–ether as a yellow solid (360 mg), m.p. 264—266° (decomp.), identical with the material prepared in (a) (i.r. and n.m.r. data).

2a,3,6,7-*Tetrahydro*-3α,9-*dimethoxybenz*[4,5]*indeno*[1,7a-c]-*furan*-2,5-*dione* (10).—The hydroxymethylene compound (5) in methanol (100 ml) containing triethylamine (2 ml) was stirred under nitrogen for 17 days. The methanol was removed under reduced pressure and the residue was dissolved in benzene (100 ml). The solution was washed with potassium hydroxide solution (5%; 200 ml) and the alkaline solution was back-washed with chloroform (60 ml), which was then mixed with the benzene solution. The organic solution was washed with water, dried, and evaporated. The oily residue (810 mg) was separated on a dry column of silica [benzene–ethyl acetate (20%) as eluant] to give two homogeneous fractions. The less polar oily fractions (350 mg) consisted of compound (4) (i.r. and n.m.r. spectra). The more polar fractions (300 mg) crystallised from dichloromethane–ether (charcoal) to give a *solid* (60 mg), m.p. 206—208° (Found: C, 67·6; H, 5·55. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·35%); $\nu_{max.}$ (KBr) 1780, 1710, and 1610 cm^{-1}; $\lambda_{max.}$ 243 and 332 nm (ε 7950 and 24,300); δ 3·0 (1H, s, quaternary CH), 3·57 (3H, s, OCH_3), 3·87 (3H, s, arom. OCH_3), 5·47 (1H, s, MeO·C*H*), 6·3 (1H, s, vinylic), 6·75—7·0 (2H, m, arom.), and 7·5—7·7 (1H, m, arom.); δ (C_6D_6) 2·73 (1H, s, quaternary, CH), 3·07 (1H, s, OCH_3), 3·25 (3H, s, arom. OCH_3), 5·44 (1H, s, MeO·C*H*), 6·0 (1H, s, vinylic), and 6·4—6·7 (3H, m, arom.)

1,3-*Dihydro*-1,3-*bis*(*hydroxymethylene*)-7-*methoxybenz*[e]-*inden*-2-*one* (2).—A solution of the benzindenone (1) (3 g) in freshly distilled ethyl formate (50 ml) was cooled in ice–ethanol and treated with sodium hydride (3 g; 52% suspension in mineral oil). The mixture was stirred in nitrogen at room temperature for 1 h, treated with dry benzene (50 ml), left at room temperature for 18 h, and then cooled in ice and decomposed with cold water (100 ml). The aqueous solution was separated from the benzene phase, acidified with glacial acetic acid, and extracted with chloroform (100 ml). The chloroform solution was washed with water, dried, and evaporated to leave a red gum (2·8 g). This was dissolved in a small amount of dichloromethane and the solution was diluted with ether; an unstable solid (800 mg) separated out. The filtrate was evaporated and the residue was chromatographed on silica (25 g). Elution with chloroform (200 ml) and chloroform–ethyl acetate (2%) (200 ml) gave a solid (300 mg) which crystallised from dichloromethane–ether as yellow needles, m.p. 186—189° (Found: C, 71·65; H, 4·55. $C_{16}H_{12}O_4$ requires C, 71·65; H, 4·5%); $\nu_{max.}$ 3720, 3400—3200, 1685, 1640, and 1630 cm^{-1};

$\lambda_{max.}$ 258, 271, 296·5, and 330 nm (ε 39,664, 32,160, 20,904, and 18,760); δ 3·9 (3H, s, OCH_3) and 6·7—8·3 (7H, m).

I thank Dr. R. Bible and Miss L. Swenton for assistance in n.m.r. interpretations, Dr. J. Hribar for mass spectral data and interpretations, Dr. J. Ahlberg and his staff for analytical and spectral data and for chromatographic separations, and Mrs. J. Strauss for preparation of the manuscript.

[3/244 *Received, 5th February,* 1973]