A Novel Rearrangement Reaction: Single-step Conversion of 2-(6-Carboxy-3-oxoheptyl)-3,4-dihydro-6-methoxynaphthalen-1(2*H*)-one into 1-(3-Carboxybutyl)-2-(2-carboxyethyl)-3,4-dihydro-6-methoxynaphthalene

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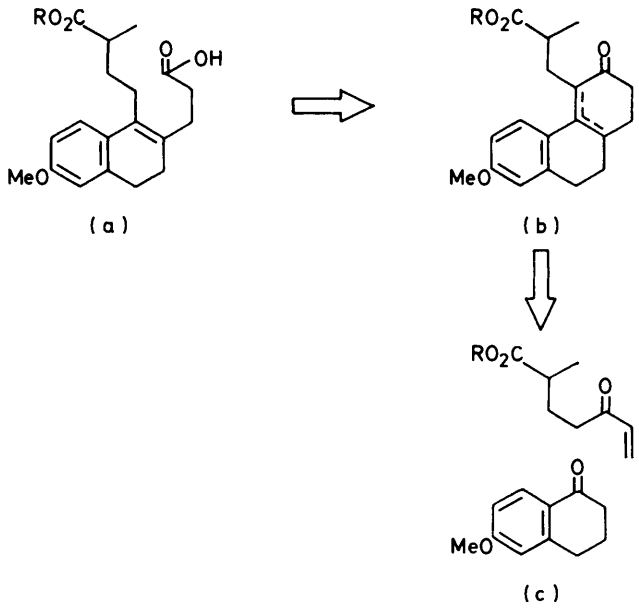
The synthesis of 2-(2-carboxyethyl)-1-(3-carboxypropyl)-3,4-dihydro-6-methoxynaphthalene (28) and the homologous diacid (30) has been achieved in a single step from the 2-(6-carboxy-3-oxoalkyl)-3,4-dihydro-6-methoxynaphthalen-1(2*H*)-ones (22) and (24), respectively, *via* a novel acid-catalysed cyclisation–rearrangement reaction. The structure of the diacids (28) and (30) is supported by the high resolution mass spectrometric data of their respective dimethyl esters (29) and (31). The aromatic methoxy-group and the carboxy-function at C-6 in the side chain are critical for the rearrangement, but not for the cyclisation, part of the reaction. Based on this and other observations a mechanism for this novel rearrangement reaction has been proposed.

The dihydronaphthalene derivatives (29) and (31) were required for possible elaboration into 13,14-*seco*-estradiol analogues. The synthesis of these molecules was envisaged *via* a Robinson annelation reaction between 3,4-dihydro-6-methoxynaphthalen-1(2*H*)-one and suitable chain elements (c), followed by an appropriate fragmentation of the resulting tricyclic system (b), as outlined in Scheme 1.

During the course of exploratory work on this route, we came across a novel rearrangement reaction, which led to a facile synthesis of the required diesters (29) and (31). Thus, the 1-tetralone derivatives (22) and (24) carrying suitable chain elements at C-2, when refluxed briefly with acetic acid–dilute hydrochloric acid, furnished the required diacids (28) and (30) respectively, in *ca.* 30% yield. The present paper describes this unprecedented rearrangement reaction and deals with the elaboration of its mechanism.

The tetralone derivatives (22) and (24) were synthesised by two different routes. Michael addition of 2-formyl-3,4-dihydro-6-methoxynaphthalen-1(2*H*)-one (1) on the enone ester (4), furnished the adduct (16), which on treatment with aqueous sodium hydroxide followed by ethereal diazomethane, furnished the ester (23) *via* the crystalline diketo-acid (22). Alternatively, condensation of the quarternary ammonium iodide (3) with diethyl β-oxopimelate (10) according to the procedure of Brown *et al.*,[1,2] furnished the diketo-ester (19) in high yield. Hydrolysis of (19) with barium hydroxide in aqueous ethanol, followed by decarboxylation, gave the diketo-acid (22) in moderate yield, along with 2-(2-carboxyethyl)-3,4-dihydro-6-methoxynaphthalen-1(2*H*)-one as the ketonic hydrolysis product.

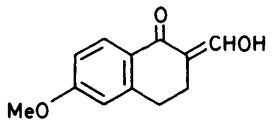
For the synthesis of the appropriate α-methyl-substituted diketo-acid (24), the enone ester (8) and β-keto-ester (11), were required as the starting materials. For their synthesis, the Michael adduct (13) of diethyl methylmalonate and ethyl acrylate, prepared according to Floyd and Miller,[3] was subjected to controlled saponification followed by decarboxylation to obtain the half ester (5), carrying the methyl group adjacent to its ester function. Reaction of (5) with thionyl chloride brought about a rearrangement to furnish ethyl 5-chloro-2-methyl-5-oxopentanoate (6) and ethyl 5-chloro-4-methyl-5-oxopentanoate (7), as a mixture of products. It is known that half esters of unsymmetrically substituted succinic and glutaric acids react with thionyl chloride in a similar manner,[4–6] furnishing ester acid chlorides as a mixture of two isomers. The mixture of acid chlorides (6) and (7) was converted into the 1,3-enones (8) and (9), and the β-keto-esters



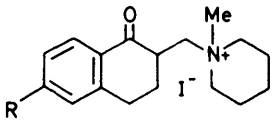
Scheme 1

(11) and (12), according to the procedure reported for the enone (4)[7] and diethyl β-oxopimelate,[8] respectively, from methyl glutaryl chloride. The enones and the β-keto-esters were found to be 3 : 2 mixtures on the basis of their n.m.r. data and g.l.c. analysis. Attempted resolution of these mixtures by fractional distillation proved abortive. The subsequent reactions were, therefore, carried out with the mixtures as such.

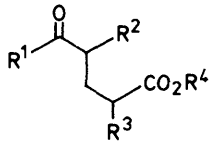
Michael condensation of 3,4-dihydro-2-formylnaphthalen-1(2*H*)-one (1) with enones (8) and (9) furnished the adducts (17) and (18), which upon treatment with aqueous sodium hydroxide afforded the diketo-acids (24) and (26), as a mixture. Along the alternative route, condensation of the diesters (11) and (12) with the quarternary ammonium iodide (3) gave a mixture of the adducts (20) and (21). Hydrolysis and decarboxylation of these adducts furnished the diketo-acids (24) and (26), which on esterification furnished compounds (25) and (27) as a mixture. In the n.m.r. spectrum of these esters, the isomeric methyl groups appear as two separate



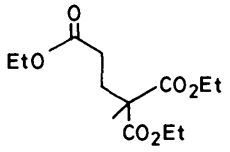
(1)



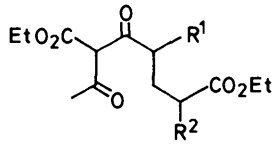
(2) R = H
(3) R = OMe



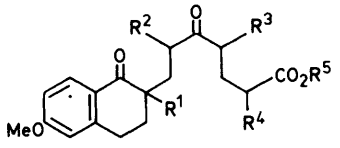
(4) R^1 = vinyl, R^2 = R^3 = H, R^4 = Me
(5) R^1 = OH, R^2 = H, R^3 = Me, R^4 = Et
(6) R^1 = Cl, R^2 = H, R^3 = Me, R^4 = Et
(7) R^1 = Cl, R^2 = Me, R^3 = H, R^4 = Et
(8) R^1 = vinyl, R^2 = H, R^3 = Me, R^4 = Et
(9) R^1 = vinyl, R^2 = Me, R^3 = H, R^4 = Et
(10) R^1 = EtO_2CCH_2, R^2 = R^3 = H, R^4 = Et
(11) R^1 = EtO_2CCH_2, R^2 = H, R^3 = Me, R^4 = Et
(12) R^1 = EtO_2CCH_2, R^2 = Me, R^3 = H, R^4 = Et



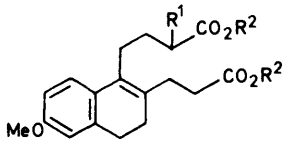
(13)



(14) R^1 = H, R^2 = Me
(15) R^1 = Me, R^2 = H

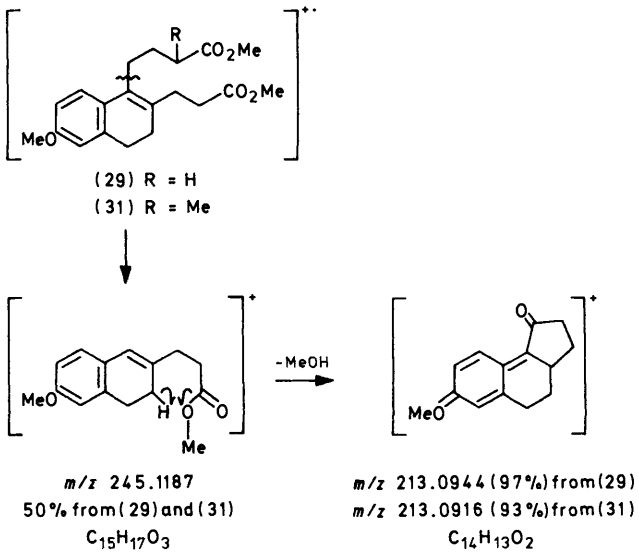


(16) R^1 = CHO, R^2 = R^3 = R^4 = H, R^5 = Me
(17) R^1 = CHO, R^2 = R^3 = H, R^4 = Me, R^5 = Et
(18) R^1 = CHO, R^2 = R^4 = H, R^3 = Me, R^5 = Et
(19) R^1 = R^3 = R^4 = H, R^2 = CO_2Me, R^5 = Et
(20) R^1 = R^3 = H, R^2 = CO_2Et, R^4 = Me, R^5 = Et
(21) R^1 = R^4 = H, R^2 = CO_2Et, R^3 = Me, R^5 = Et
(22) R^1 = R^2 = R^3 = R^4 = R^5 = H
(23) R^1 = R^2 = R^3 = R^4 = H, R^5 = Me
(24) R^1 = R^2 = R^3 = R^5 = H, R^4 = Me
(25) R^1 = R^2 = R^3 = H, R^4 = R^5 = Me
(26) R^1 = R^2 = R^4 = R^5 = H, R^3 = Me
(27) R^1 = R^2 = R^4 = H, R^3 = R^5 = Me



(28) R^1 = R^2 = H
(29) R^1 = H, R^2 = Me
(30) R^1 = Me, R^2 = H
(31) R^1 = R^2 = Me

doublets, centred at τ 8.94 and 8.89. The latter signal was subsequently found to correspond to the undesired isomer (27), which constituted 60% of the mixture.



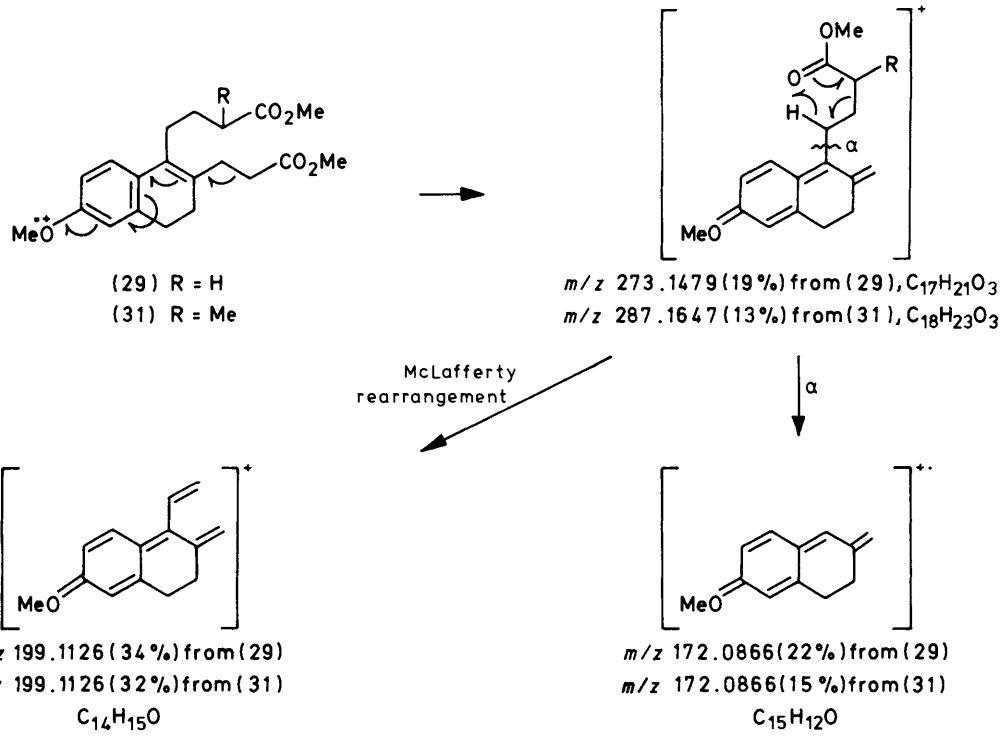
Scheme 2

As the next step of the original scheme, cyclisation of the diketo-carboxy-derivatives, such as (22), was attempted. In one such attempt, the acid (22) or its ester (23) was refluxed for 2 h in acetic acid–dilute hydrochloric acid. Work-up of the reaction mixture led to the isolation of a crystalline compound in 33% yield, which was characterised as the diacid (28). Treatment of this compound (28) with ethereal diazomethane gave the diester (29). The disappearance of the i.r. bands at 1 672, 1 710, and 1 735 cm^{-1}, characteristic for the diketo-ester (23), and the appearance of the band at 1 700 cm^{-1} for the acid (28) and at 1 735 cm^{-1} for the ester (29) indicated that the transformation had utilized the keto-groups of the starting material. The appearance of a six-proton singlet at τ 6.28 in the n.m.r. spectrum of compound (29) indicated it to be a dimethyl diester, and consequently compound (28) to be a diacid. More conclusive support for the structure of the diester (29) was forthcoming from its mass fragmentation pattern (see later).

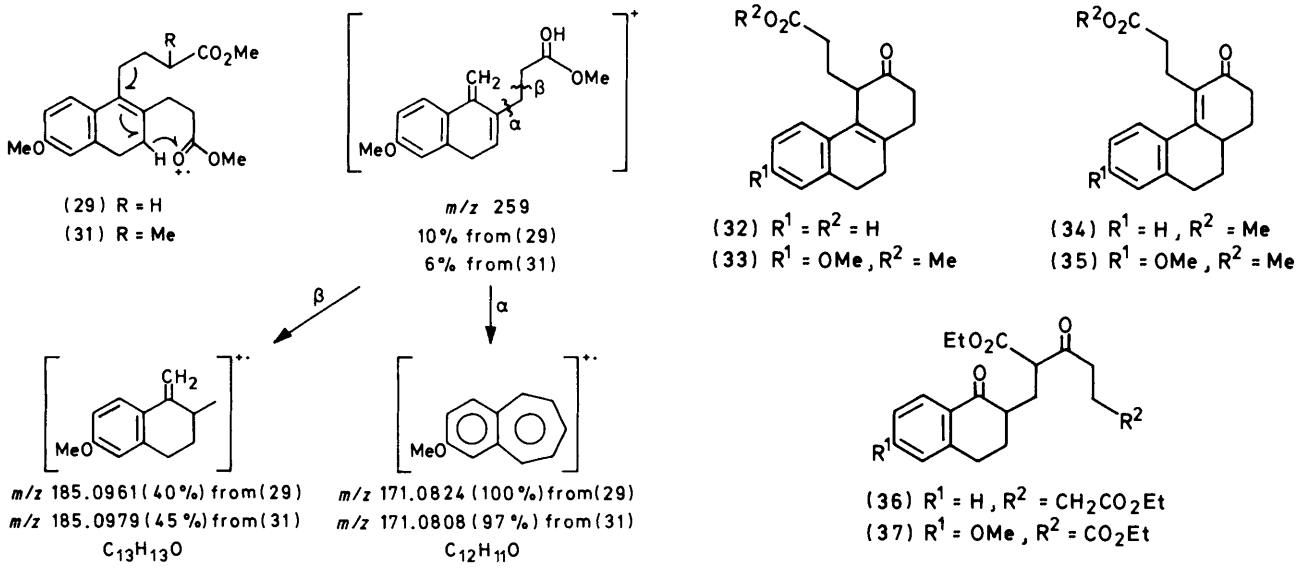
The mixture of isomeric diketo-acids (24) and (26) was next subjected to the rearrangement reaction. This resulted in the transformation of the monoacid (24) into the required diacid (30), while the isomer (26) was recovered unchanged. Treatment of the reaction product with ethereal diazomethane, followed by chromatography over a column of silica gel, led to the isolation of the diester (31) and the diketo-ester (27) as pure products. The n.m.r. spectrum of the diester (31) was in accordance with its homology with the diester (29), with its methyl ester functions appearing as two separate singlets at τ 6.33 and 6.37 and its α-methyl residue appearing as a doublet at τ 8.82. The diketo-ester (27) was found to be identical with the previously obtained mixture of (25) and (27) on the basis of t.l.c. as well as n.m.r., except for the doublet at τ 8.94 in case of the mixture, which was thus assigned to the isomer (25).

Mass Fragmentation Pattern of the Diesters (29) *and* (31).—In the high resolution mass spectrum, the diesters (29) and (31) showed prominent M^+ ions at *m/z* 346.1781 ($C_{20}H_{26}O_5$, 94%) and *m/z* 360.1950 ($C_{21}H_{28}O_5$, 100%), respectively. A prominent peak at *m/z* 171, common to both the compounds and corresponding to elemental composition $C_{12}H_{11}O$, was rationalised as indicated in Scheme 2.

The origins of the peaks at *m/z* 273 and 287 for compounds



Scheme 3

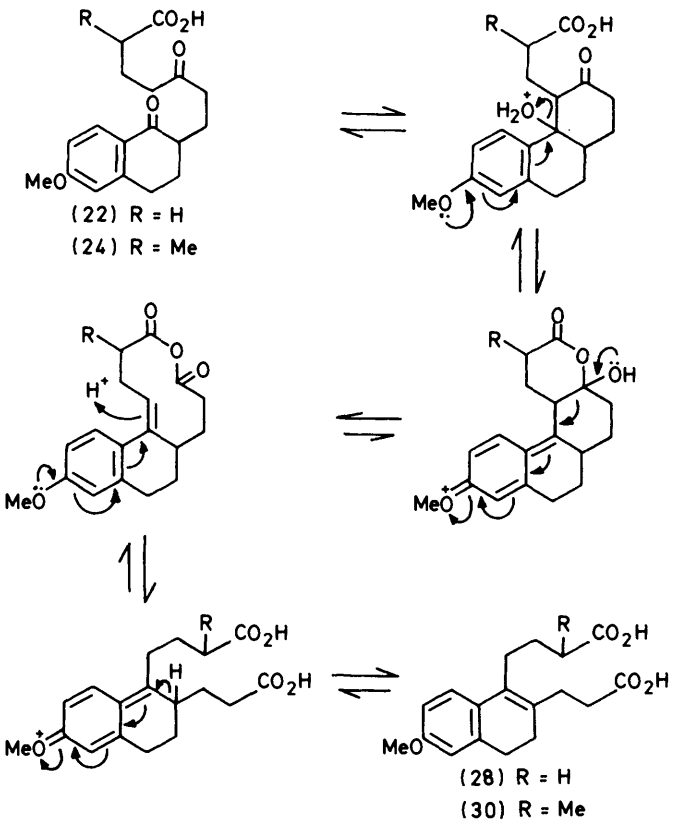


Scheme 4

(29) and (31), respectively, and their common ion peaks at *m/z* 172 and 199, have been rationalised as shown in Scheme 3.

An α-cleavage of the side chain at C-1 and formation of the ion peaks at *m/z* 245 and 213, as shown in Scheme 4, appears to be the major mode of fragmentation for (29) as well as (31).

Mechanism of the Rearrangement Reaction.—Treatment of the diketo-ester (23) with 30% methanolic hydrochloric acid for 2 h at room temperature furnished the isomeric cyclised keto-esters (33) and (35), in 80% overall yield. Compounds (33) and (35) when subjected to the conditions for the rearrangement reaction, individually or as a mixture, furnished the diacid (28), in *ca.* 30% yield. The diketo-ester (37), with its side chain shortened by one carbon atom, was next synthesised by condensation of diethyl β-oxoadipate with the quaternary ammonium iodide (3), and was subjected



Scheme 5

to the rearrangement reaction. This resulted in formation of the isomeric tricyclic keto-acids (38) and (40), as the sole identifiable products, in *ca.* 70% overall yield. The desmethoxy-diketo-ester (36), synthesised in the usual manner starting from the tetralone derivative (2) and diethyl β-oxopimelate, when subjected to the conditions for the rearrangement reaction, furnished the crystalline diketo-acid (32), while the mother-liquor, on esterification and chromatography, furnished the isomeric tricyclic keto-ester (34) and an additional amount of (32) as its methyl ester. The cyclised materials, together accounting for *ca.* 80% of the reaction product, were the only identifiable products formed in this reaction as well.

From these experimental observations it is apparent that the rearrangement reaction proceeds in two steps, *viz.*, cyclisation followed by a rearrangement. The aromatic methoxy-group and the carboxy-function at C-6 in the side chain are, understandably, not important for the first step, but are crucial for the rearrangement. Based on these observations, the mechanism outlined in Scheme 5 has been proposed for the rearrangement reaction.

Experimental

The n.m.r. spectra were recorded on a Varian A-60D instrument in $CDCl_3$ solution, unless otherwise stated, using tetramethylsilane as internal reference. The mass spectra were recorded on a Hitachi RMU-6E mass spectrometer fitted with a direct inlet system, and high resolution mass spectra on a Jeol JMS-O1SG-2 instrument. The i.r. spectra were recorded on Perkin-Elmer 337 or 177 grating instruments, either as KBr films or as neat samples, and the u.v. spectra on a Perkin-Elmer 202 automatic recording spectrophotometer. Homogeneity of the compounds was checked by t.l.c. either on silica gel or alumina plates and by g.l.c. on a Varian Aerograph 1800 instrument. Ether refers to diethyl ether throughout.

Diethyl 2-Ethoxycarbonyl-2-methylglutarate (13).—To a suspension of diethyl methylmalonate (24 ml) and sodium ethoxide [prepared from sodium metal (0.55 g) and absolute ethanol (12 ml)] in dry ether (200 ml), ethyl acrylate (16.5 ml) was added cautiously and the reaction mixture refluxed for 4 h. It was then cooled and acidified with aqueous AcOH (2%; 100 ml) and extracted with ether (3 × 100 ml). The combined organic layer was washed with water (2 × 100 ml), dried (Na_2SO_4) and concentrated. The residue was distilled under reduced pressure to furnish the triester [3] (13) (32 g), b.p. 145 °C at 3 mmHg; $\nu_{max.}$ 1 735 cm^{-1} (CO_2Et); τ 5.60—6.15 (6 H, m, $CO_2CH_2CH_3$), 7.65—7.95 (4 H, m, CH_2CH_2), 8.66 (3 H, m, CH_3), and 8.78 (9 H, t, *J* 7.0 Hz, $CO_2CH_2CH_3$).

Ethyl Hydrogen 2-Methylglutarate (5).—A solution of the triester (13) (55 g) in absolute ethanol (750 ml) was refluxed with KOH pellets (30 g) for 2.5 h. Most of the ethanol was removed under reduced pressure and the residue dissolved in water (700 ml), acidified with 2M-HCl and extracted with ether (3 × 200 ml). The combined ethereal layer was washed with water (3 × 200 ml), dried (Na_2SO_4) and concentrated. The crude product was decarboxylated by heating at 150 °C at 20 mmHg for 2 h and finally distilled to give the half-ester (5) (28 g), b.p. 144—145 °C at 8 mmHg; $\nu_{max.}$ 1 735 (CO_2Et) and 1 710 cm^{-1} (CO_2H); τ 5.84 (4 H, q, *J* 7.0 Hz, $CO_2CH_2CH_3$), 7.40—8.10 (4 H, m, CH_2CH_2), 8.62 (3 H, s, CH_3), and 8.77 (6 H, t, *J* 7.0 Hz, $CO_2CH_2CH_3$).

Ethyl 5-Chloro-2-methyl-5-oxopentanoate (6) *and Ethyl 5-chloro-4-methyl-5-oxopentanoate* (7).—A mixture of the foregoing ester (16 g) was treated with thionyl chloride (48 g) according the described procedure,[9] to afford a mixture of the acid chlorides (6) and (7) (15.2 g), b.p. 87—89 °C; $\nu_{max.}$ 1 795 (COCl) and 1 735 cm^{-1} (CO_2Et).

Ethyl 2-Methyl-5-oxohept-6-enoate (8) *and Ethyl 4-Methyl-5-oxohept-6-enoate* (9).—The preceding mixture of isomeric acid chlorides (6) and (7) (15 g) was converted into a mixture of the isomeric vinyl ketones (8) and (9) (9 g) according to the procedure described in ref. 7 for the methyl ester (4), b.p. 80—82 °C at 1 mmHg; $\nu_{max.}$ 1 735 (CO_2Et) and 1 675 cm^{-1} (vinyl ketone); τ 3.40—4.18 (3 H, m, $COCHCH_2$), 5.95 (2 H, m, $COCH_2CH_3$), 7.30—8.55 (5 H, m, 2-, 3-, 4-H), 8.82 (3 H, *m*, $CO_2CH_2CH_3$), 8.84 and 8.92 [3 H, 2 d, *J* 7.0 Hz, $CH(CO_2Et)CH_3$ and $COCHCH_3$].

Diethyl 6-Methyl-3-oxopimelate (11) *and Diethyl 4-Methyl-3-oxopimelate* (12).—The mixture of acid chlorides (6) and (7) (110 g) were first treated with ethyl acetoacetate in the presence of sodium ethoxide and then with ammonia according to the described procedure [8] to give the β-ketoesters (11) and (12) (16 g), *via* the diketo-diesters (14) and (15), $b.p._{\cdot 1.5}$ 122—125 °C at 1.5 mmHg; $\nu_{max.}$ 1 725 cm^{-1} (CO_2Et and CO); τ 5.84 and 5.91 (4 H, 2q, *J* 7.0 Hz, 2 $CO_2CH_2CH_3$), 6.51 and 6.61 (2 H, 2 s, $COCH_2CO_2Et$), 7.10—8.50 (5 H, m, 4-, 5-, and 6-H), and 8.60—9.10 (9 H, m, 2 $CO_2CH_2CH_3$ and isomeric CH_3); g.l.c. column [3% SE-30 on chromosorb W(HP); carrier gas, nitrogen; temp. 180 °C] retention time 7.0 min (40%) and 7.5 min (60%).

2-Formyl-3,4-dihydro-6-methoxy-2-(6-methoxycarbonyl-3-oxohexyl)naphthalen-1(2H)-one (16).—To a cooled mixture of 3,4-dihydro-2-hydroxymethylene-6-methoxynaphthalen-

1(2*H*)-one [10] (3 g) and vinyl ketone [7] (4) (2.3 g), triethylamine (0.25 ml) was added and the reaction mixture stirred at room temperature for 16 h. It was diluted with ether (100 ml), washed with aqueous $NaHCO_3$ (5%; 2 × 25 ml), 2M-HCl (25 ml), and finally with water (2 × 50 ml), dried (Na_2SO_4) and concentrated. The residue was passed through a short column of silica gel, eluting with benzene, to give the substituted tetralone (16) (4.2 g), as a yellow oil; $\nu_{max.}$ 1 740 (CO_2Me), 1 727 (CHO), 1 712 (CO), and 1 670 cm^{-1} (ArCO); τ 0.26 (1 H, s, CHO), 1.98 (1 H, d, *J* 9.0 Hz, ArH, m to OCH_3), 2.95—3.30 (2 H, m, Ar*H*, *o* to OCH_3), 6.11 (3 H, s, OCH_3), 6.30 (3 H, s, CO_2CH_3), and 6.85—8.45 (14 H, m, 1′-, 2′-, 4′-, 5′-, 6′-, 3-, and 4-H).

2-(6-*Carboxy*-3-*oxohexyl*)-3,4-*dihydro*-6-*methoxynaphthalen*-1(2H)-*one* (22).—A mixture of the ester (16) (1.1 g) and aqueous NaOH (2M; 25 ml) was stirred at room temperature for 24 h. It was then diluted with water (125 ml) and extracted with ether (2 × 50 ml). The aqueous layer was cooled to 0 °C and acidified with 2M-HCl to give a precipitate, which was filtered off, dried (P_2O_5) *in vacuo* and crystallised from benzene to afford the *diketo-acid* (22) (0.9 g), m.p. 140—141 °C; $\nu_{max.}$ 1 712 (CO), 1 690 (CO_2H), and 1 660 cm^{-1} (ArCO); τ 0.50 (1 H, bh, CO_2H), 1.97 (1 H, d, *J* 9.0 Hz, ArH, *m* to OCH_3), 2.93—3.35 (2 H, m, ArH, *o* to OCH_3), 6.12 (3 H, s, OCH_3), and 6.85—8.35 (15 H, m, 1′-, 2′-, 4′-, 6′-, 2-, 3-, and 4-H) (Found: C, 67.85; H, 7.15. $C_{18}H_{22}O_5$ requires C, 67.91; H, 6.97%).

3,4-*Dihydro*-6-*methoxy*-2-(6-*methoxycarbonyl*-3-*oxohexyl*)-*naphthalen*-1(2H)-*one* (23).—A solution of the acid (22) (150 mg) in methanol–ether (1 : 4; 10 ml) was treated with ethereal diazomethane [prepared from 1 g of nitrosomethylurea] at 5 °C. After being kept at room temperature for 1 h, the excess of diazomethane and ether was evaporated off and the residual oil was purified by passing it through a column of silica gel in benzene to furnish the *diketo-ester* (23) as an oil (148 mg); $\nu_{max.}$ 1 735 (CO_2Me), 1 710 (CO), and 1 672 cm^{-1} (ArCO); *m*/*z* 332 (M^+); τ 1.99 (1 H, d, *J* 9.0 Hz, ArH, *m*, to OCH_3), 2.95—3.30 (2 H, m, ArH, *o* to OCH_3), 6.12 (3 H, s, OCH_3), 6.30 (3 H, s, CO_2CH_3), and 6.85—8.35 (15 H, m, 1′-, 2′-, 4′-, 6′-, 2-, 3-, and 4-H) (Found: C, 68.95; H, 7.45. $C_{19}H_{24}O_5$ requires C, 68.66; H, 7.28%).

2-*Formyl*-2-(6-*ethoxycarbonyl*-6-*methyl*-3-*oxohexyl*)-3,4-*dihydro*-6-*methoxynaphthalen*-1(2H)-*one* (17) *and* 2-*Formyl*-2-(6-*ethoxycarbonyl*-4-*methyl*-3-*oxohexyl*)-3,4-*dihydro*-6-*methylnaphthalen*-1(2H)-*one* (18).—A mixture of 3,4-dihydro-2-hydroxymethylene-6-methoxynaphthalen-1(2*H*)-one (1) (5 g), the vinyl ketones (8) and (9) (4.5 g) and triethylamine (0.5 ml) was allowed to react for 16 h at room temperature and then worked up as described earlier for the ester (16) to give the mixture of substituted 1-tetralones (17) and (18) (7.6 g) as an oil; $\nu_{max.}$ 1 735 (CO_2Et), 1 727 (CHO), 1 712 (CO), and 1 670 cm^{-1} (ArCO); τ 0.6 (1 H, s, CHO), 2.10 (1 H, d, *J* 9.0 Hz, ArH, *m* to OCH_3), 3.10—3.45 (2 H, m, ArH, *o* to OCH_3), 5.95 (2 H, q, *J* 7.0 Hz, $CO_2CH_2CH_3$), 6.20 (3 H, s, OCH_3), 6.90—8.50 (13 H, m, 1′-, 2′-, 4′-, 6′-, 3-, and 4-H), 8.80 (3 H, t, $CO_2CH_2CH_3$), 8.91 and 8.96 [3 H, 2 d, $COCHCH_3$ and $CH(CO_2Et)CH_3$].

2-(6-*Carboxy*-6-*methyl*-3-*oxohexyl*)-3,4-*dihydro*-6-*methoxynaphthalen*-1(2H)-*one* (24) *and* 2-(6-*Carboxy*-4-*methyl*-3-*oxohexyl*)-3,4-*dihydro*-6-*methoxynaphthalen*-1(2H)-*one* (26).—The foregoing mixture (3 g) was deformylated and saponified as described earlier for the ester (16) to give the isomeric diketo-acids (24) and (26) as a mixture (2.4 g); $\nu_{max.}$ 1 712 (CO, CO_2H), and 1 660 cm^{-1} (ArCO); τ 0.53 (1 H, bh, CO_2H), 2.03 (1 H, d, *J* 9.0 Hz, ArH, *m* to OCH_3), 6.90—8.50 (14 H, m, 1′-, 2′-, 4′-, 6′-, 2-, 3-, and 4-H), 8.80 and 8.89 [3 H, 2d, *J* 7.0 Hz, $CH(CO_2H)CH_3$ and $COCHCH_3$].

3,4-*Dihydro*-6-*methoxy*-2-(6-*methoxycarbonyl*-6-*methyl*-3-*oxohexyl*)*naphthalen*-1(2H)-*one* (25) *and* 3,4-*Dihydro*-6-*methoxy*-2-(6-*methoxycarbonyl*-4-*methyl*-3-*oxohexyl*)*naphthalen*-1(2H)-*one* (27).—The preceding mixture (1.5 g) was esterified by treatment with a solution of ethereal diazomethane [prepared from 3 g of nitrosomethylurea] as described earlier for the acid (22) to give the esters (25) and (27) as an oil (1.6 g); $\nu_{max.}$ 1 735 (CO_2Me), 1 710 (CO), and 1 672 cm^{-1} (ArCO); τ 2.03 (1 H, d, *J* 9.0 Hz, ArH, *m* to OCH_3), 3.06—3.40 (2 H, m, *o* to OCH_3), 6.17 (3 H, s, OCH_3), 6.34 (3 H, s, CO_2CH_3), ArH, 6.85—8.45 (14 H, m, 1′-, 2′-, 4′-, 6′-, 2-, 3-, and 4-H), 8.85 and 8.89 [3 H, 2d, *J* 7.0 Hz, $CH(CO_2Me)CH_3$ and $COCHCH_3$].

2-(2,6-*Dimethoxycarbonyl*-3-*oxohexyl*)-3,4-*dihydro*-6-*methoxynaphthalen*-1(2H)-*one* (19).—A solution of the β-keto-ester [7] (10) (10 g) in absolute methanol (20 ml) was added into a stirred solution of sodium methoxide [prepared from Na metal (1.2 g)] in absolute methanol (20 ml) at room temperature. Most of the solvent was removed under reduced pressure and the residue, suspended in dry dioxan (300 ml), was treated with the methiodide [1] (3) (20 g) and the reaction mixture stirred at 80 °C for 8 h. After most of the solvent had been removed under reduced pressure, cold 2M-HCl (500 ml) was added to the residue which was then extracted with ether (3 × 150 ml). The combined organic layer was washed with water (2 × 200 ml), dried (Na_2SO_4) and concentrated. The residual oil was filtered through a short column of silica gel in benzene to furnish the diketo-diester (19) (16 g) as an oil; $\nu_{max.}$ 1 735 (CO_2Me), 1 712 (CO), and 1 670 cm^{-1} (ArCO); *m*/*z* 390 M^+; τ 2.05 (1 H, d, *J* 9.0 Hz, Ar*H*, *m* to OCH_3), 3.08—3.40 (2 H, m, ArH, *o* to OCH_3), 6.12 (3 H, s, OCH_3). 6.25 and 6.30 (6 H, 2 s, CO_2CH_3), and 6.85—8.35 (14 H, m. 1′-, 2′-, 4′-, 6′-, 2-, 3-, and 4-H).

Hydrolysis and Decarboxylation of the Ester (19).—A suspension of compound (19) (950 mg) and $Ba(OH)_2$ (6 g) in methanol–water (1 : 2; 20 ml) was refluxed for 45 min. It was then cooled in ice, acidified with 2M-HCl and extracted with ether (3 × 50 ml). The combined ethereal layer was washed with water (2 × 50 ml), dried (Na_2SO_4) and concentrated. The residual oil (760 mg) was pyrolysed by heating at 150 °C and finally crystallised from benzene to give the acid (22) (250 mg), m.p. 140—141 °C. The mother-liquor was taken up in methanol–ether (1 : 4; 10 ml) and treated with a solution of ethereal diazomethane (prepared from 1 g of nitrosomethylurea) at 5 °C for 1 h. Evaporation of the solvent and chromatography of the crude concentrate over a column of silica gel eluting with benzene, afforded the diketo-ester (23) (120 mg) and 3,4-*dihydro*-6-*methoxy*-2-(2-*methoxycarbonylethyl*)*naphthalen*-1(2H)-*one* (140 mg), m.p. 88—89 °C; $\nu_{max.}$ 1 720 (CO_2Me) and 1 665 cm^{-1} (CO); τ 2.03 (1 H, d, *J* 8.0 Hz, ArH, *m* to OCH_3), 3.07—3.38 (2 H, m, ArH, *o* to OCH_3), 6.15 (3 H, s, OCH_3), 6.32 (3 H, s, CO_2CH_3), and 6.80—8.50 (9 H, m, 1′-, 2′-, 2-, 3-, and 4-H) (Found: C, 68.3; H, 6.9. $C_{15}H_{18}O_4$ requires C, 68.70; H, 6.87%).

2-(2,6-*Diethoxycarbonyl*-6-*methylhexyl*)-3,4-*dihydro*-6-*methoxynaphthalen*-1(2H)-*one* (20) *and* 2-(2,6-*Diethoxycarbonyl*-4-*methylhexyl*)-3,4-*dihydro*-6-*methoxynaphthalen*-1(2H)-*one* (21).—Finely cut sodium metal (0.75 g) was taken up in dry dioxan (200 ml) and absolute ethanol 15 ml) was added and the reaction mixture stirred at room temperature until the formation of sodium ethoxide was complete. A solution of the

β-keto-esters (11) and (12) (9 g) in dry dioxan (50 ml) was then added into it in one portion, followed by the methiodide (3) (12 g), and the reaction mixture was refluxed for 8 h. Most of the solvent was then removed under reduced pressure and the residue treated with cold aqueous AcOH (10%; 150 ml). It was then extracted with ether (2 × 200 ml), the combined ethereal layer washed with water (3 × 100 ml), dried (Na_2SO_4) and concentrated. The residual oil was purified by passing it through a column of silica gel, eluting with benzene, to give the diketo-diesters (20) and (21) as a mixture (13 g); $\nu_{max.}$ 1 732 (CO_2Et), 1 712 (CO), and 1 670 cm^{-1} (ArCO); τ 2.05 (1 H, d, *J* 9.0 Hz, ArH, *m* to OCH_3), 3.10—3.45 (2 H, m, ArH, *o* to OCH_3), 5.60—6.25 (4 H, m, 2 $CO_2CH_2CH_3$), 6.18 (3 H, s, OCH_3), 6.90—8.50 (12 H, m, 1'-, 2'-, 4'-, 6'-, 2-, 3-, and 4-H), and 8.60—9.30 (9 H, m, 2 $CO_2CH_2CH_3$ and side chain CH_3).

Hydrolysis and Decarboxylation of the Diesters (20) *and* (21).—The hydrolysis and pyrolytic decarboxylation of compounds (20) and (21) (1 g) was carried out as described earlier for the diester (19). Chromatography of the crude reaction product over a column of silica gel, eluting with ethyl acetate–benzene (1 : 5), furnished the isomeric diacids (24) and (26) (0.3 g) as a mixture.

2-(2-*Carboxyethyl*)-1-(3-*carboxypropyl*)-6-*methoxy*-3,4-*dihydronaphthalene* (28).—A solution of the acid (22) (500 mg) or the ester (23) (540 mg) in AcOH, HCl, and H_2O (4 : 2 : 1, v/v; 16 ml) was heated at 120 °C for 2 h, poured over crushed ice (100 g) and extracted with ethyl acetate (3 × 50 ml). The combined organic layer was washed with water (3 × 30 ml), dried (Na_2SO_4) and concentrated. The residue was crystallised from ethyl acetate–benzene to furnish the *diacid* (28) (164 mg), m.p. 159—162 °C; $\nu_{max.}$ 1 700 cm^{-1} (CO_2H); $\lambda_{max.}$ (MeOH) 277 and 224 nm; τ −0.20 (2, bh, 2 CO_2H), 2.72 (1 H, d, *J* 9.0 Hz, ArH, *m* to OCH_3), 3.10—3.0 (2 H, m, ArH, *o* to OCH_3), 6.19 (s, 3 H, $ArOCH_3$), and 7.10—8.50 (14 H, m, 1'', 3'-, 1''-, 2''-, 3-, and 4-H) (Found: C, 67.7; H, 7.1. $C_{18}H_{22}O_5$ requires C, 67.91; H, 6.97%).

3,4-*Dihydro*-6-*methoxy*-2-(2-*methoxycarbonylethyl*)-1-(3-*methoxycarbonylpropyl*)*naphthalene* (29).—A solution of the diacid (28) (80 mg) in methanol–ether (1 : 4; 10 ml) was treated with a solution of ethereal diazomethane [prepared from 750 mg of nitrosomethylurea] at 5 °C for 1 h. After the solvent had been evaporated off, the residual oil was subjected to chromatography over a column of silica gel, eluting with benzene, to give the diester (29) (80 mg) as an oil; $\nu_{max.}$ 1 727 cm^{-1} (CO_2Me); $\lambda_{max.}$ (MeOH) 277 and 224 nm; *m/z* 346 (94%, M^+), 344 (32), 315 (11), 273 (19), 259 (10), 245 (50), 227 (10), 214 (17), 213 (97), 199 (34), 197 (16), 185 (40), 173 (10), 172 (22), 171 (100), 153 (11), 141 (11), 128 (13), and 115 (11); τ 2.72 (1 H, d, *J* 9.0 Hz, ArH, *m* to OCH_3), 3.10—3.30 (2 H, m, ArH, *o* to OCH_3), 6.18 (3 H, s, $ArOCH_3$), 6.30 (6 H, s, 2 CO_2CH_3), and 7.10—8.50 (14 H, m, 1'-, 2'-, 3'-, 1'', 2''-, 3-, and 4-H).

3,4-*Dihydro*-6-*methoxy*-1-(3-*methoxycarbonylbutyl*)-2-(2-*methoxycarbonylethyl*)*naphthalene* (31).—A mixture of the isomeric acids (24) and (26) (500 mg) or the esters (25) and (27) (530 mg) was subjected to the reaction conditions described earlier for compound (22) to obtain an oil, which was esterified by similar treatment with diazomethane. The crude product, on chromatography over a column of silica gel eluting with benzene with an increasing proportion of ethyl acetate, furnished the diester (31) (90 mg), as an oil; $\nu_{max.}$ 1 735 cm^{-1} (CO_2Me); *m/z* 360 (100%, M^+), 358 (30), 330 (24), 329 (11), 287 (13), 259 (6), 245 (50), 227 (14), 214 (16), 213 (93), 199 (32), 197 (10), 186 (10), 185 (45), 172 (15), 171 (97), 153 (8), 141 (8), 128 (9) and 115 (12); τ 2.83 (1 H, d, *J* 9.0 Hz, ArH, *m* to OCH_3), 3.20—3.40 (2 H, m, ArH, *o* to OCH_3), 6.25 (3 H, s, $ArOCH_3$), 6.33 (3 H, s, CO_2CH_3), 6.37 (3 H, s, CO_2CH_3), 7.20—8.50 (13 H, m, 1'-, 3'-, 1''-, 2''-, 3-, and 4-H), and 8.82 (3 H, d, *J* 7.0 Hz, CH_3), and the diketo-ester (27) (210 mg); $\nu_{max.}$ 1 735 (CO_2Me), 1 710 (CO), and 1 673 cm^{-1} (ArCO); *m/z* 346 (M^+); τ 2.03 (1 H, d, *J* 9.0 Hz, ArH, *m* to OCH_3), 3.06—3.40 (2 H, m, ArH, *o* to OCH_3), 6.17 (3 H, s, $ArOCH_3$), 6.34 (3 H, s, CO_2CH_3), 6.85—8.45 (14 H, m, 1'-, 2'-, 4'-, 6'-, 2-, 3-, and 4-H), and 8.89 (3 H, d, *J* 7.0 Hz, $COCHCH_3$).

Reaction of the Ester (23) *with Methanolic Hydrochloric Acid.*—A solution of the diketo-ester (23) (475 mg) in methanolic HCl (15%, 20 ml) was kept at room temperature for 4 h, after which time t.l.c. indicated complete disappearance of the starting material. It was then concentrated under reduced pressure and the residue was taken up in ether (100 ml); the ethereal layer was washed with water (3 × 50 ml), dried (Na_2SO_4), and concentrated. The crude concentrate, when subjected to chromatography on a column of silica gel, eluting with benzene in increasing proportions of ethyl acetate, furnished the enone (35) (150 mg) as an oil; $\nu_{max.}$ 1 725 (CO_2Me) and 1 665 cm^{-1} (conjugated ketone); $\lambda_{max.}$ (MeOH) 314, 242, and 218sh nm; *m/z* 314 (M^+); τ(CCl_4) 2.63 (1 H, d, *J* 9.0 Hz, ArH, *m* to OCH_3), 3.25—3.55 (2 H, m, ArH, *o* to OCH_3), 6.30 (3 H, s, OCH_3), 6.34 (3 H, s, CO_2CH_3), and 7.10—8.40 (13 H, m, 1'-, 2'-, 1-, 2-, 9-, 10-, and 10a-H), and its isomer (33) (170 mg) as an oil; $\nu_{max.}$ 1 725 (CO_2Me) and 1 705 cm^{-1} (CO); $\lambda_{max.}$ (MeOH) 276 and 222 nm; *m/z* 314 (M^+); τ(CCl_4) 2.99 (1 H, d, *J* 9.0 Hz, ArH, *m* to OCH_3), 3.30—3.60 (2 H, m, ArH, *o* to OCH_3), 6.32 (3 H, s, OCH_3), 6.38 (3 H, s, CO_2CH_3), and 6.60—8.33 (13 H, m, 1'-, 2'-, 1-, 2-, 4-, 9-, and 10-H).

Rearrangement Reaction of the Isomeric Esters (33) *and* (35).—A solution of the esters (33) and (35) (230 mg) in AcOH, H_2O, and HCl (4 : 2 : 1, v/v; 10 ml) was refluxed for 2 h. It was then poured over crushed ice (50 g) and extracted with ethyl acetate (2 × 50 ml). The ethyl acetate extract was washed with water (3 × 25 ml), dried (Na_2SO_4) and concentrated. The crude oil, on crystallisation from ethyl acetate–benzene afforded the diacid (28) (70 mg), m.p. 159—162 °C.

2-(2,5-*Diethoxycarbonyl*-3-*oxopentyl*)-3,4-*dihydro*-6-*methoxynaphthalen*-1(2H)-*one* (37).—Condensation of the methiodide (3) (4.5 g) with diethyl β-oxoadipate [11] (3 g) in the presence of sodium ethoxide (prepared from 340 mg of sodium metal) according to the procedure described for the diester (19), furnished the diketo-diester (37) (2.5 g) as an oil; $\nu_{max.}$ 1 735 (CO_2Et), 1 710 (CO), and 1 675 cm^{-1} (ArCO); *m/z* 404 (M^+); τ 2.05 (1 H, d, *J* 9.0 Hz, ArH, *m* to OCH_3), 3.10—3.45 (2 H, m, ArH, *o* to OCH_3), 5.84 and 5.90 (4 H, 2 q, *J* 7.0 Hz, 2 $CO_2CH_2CH_3$), 6.35 (3 H, s, OCH_3), 6.90—8.22 (12 H, m, 1'-, 2'-, 4'-, 5'-, 2-, 3-, and 4-H), and 8.73 (6 H, t, *J* 7.0 Hz, 2 $CO_2CH_2CH_3$).

Attempted Rearrangement Reaction of the Diester (37).—A solution of compound (37) (450 mg) in AcOH, HCl, and H_2O (4 : 2 : 1, v/v; 20 ml) was refluxed for 3 h. It was then poured over crushed ice (100 g) and extracted with ethyl acetate (2 × 100 ml). The organic layer was washed with water (3 × 50 ml), dried (Na_2SO_4) and concentrated to give a viscous brown oil (360 mg) which was taken up in methanol–ether (1 : 1; 20 ml), and then treated with ethereal diazomethane (5%; 10 ml) at 0 °C for 3 h. The solvent was evaporated off and the residue subjected to chromatography over a column of silica gel, eluting with benzene, to give the

enone (39) (104 mg); $\nu_{max.}$ 1 728 (CO_2Me) and 1 655 cm^{-1} (conjugated ketone); $\lambda_{max.}$ (MeOH) 314, 242 and 218sh nm; τ 2.67 (1 H, d, *J* 9.0 Hz, ArH, *m* to OCH_3), 3.15—3.45 (2 H, m, ArH, *o* to OCH_3), 6.53 (2 H, br s, 1′-H), and 7.05—8.75 (9 H, m, 1-, 2-, 9-, 10-, and 10a-H), and its isomer (41) (84 mg); $\nu_{max.}$ 1 732 (CO_2Me) and 1 712 cm^{-1} (CO); $\lambda_{max.}$ (MeOH) 276 and 222 nm; τ 2.65—3.45 (3 H, m, ArH), 6.22 (3 H, s, OCH_3), 6.38 (3 H, s, CO_2CH_3), and 6.85—7.95 (11 H, m, 1′-, 1-, 2-, 4-, 9-, and 10-H).

Alkaline Hydrolysis of the Methyl Esters (39) *and* (41).—Compounds (39) and (41) were hydrolysed individually by refluxing them with ethanolic KOH (20%). Most of the solvent was removed under reduced pressure and the residue was taken up in water, acidified with cold 2M-HCl, and then extracted with ethyl acetate. The organic layer was washed with water, dried (Na_2SO_4) and concentrated. The residue, on crystallization from benzene, afforded the *acid* (38), m.p. 149—150 °C; $\nu_{max.}$ 1 700 (CO_2H) and 1 655 cm^{-1} (conjugated ketone); $\lambda_{max.}$ (MeOH) 315, 242, and 218sh nm; τ 0.33 (1 H, bh, D_2O exchangeable, CO_2H), 2.57 (1 H, d, *J* 9.0 Hz, ArH, *m* to OCH_3), 3.05—3.40 (2 H, m, ArH, *o* to OCH_3), 6.20 (3 H, s, OCH_3), 6.50 (2 H, br d, 1′-H), and 7.05—8.50 (9 H, m, 1-, 2-, 9-, 10-, and 10a-H) (Found: C, 71.2; H, 6.35. $C_{17}H_{18}O_4$ requires C, 71.31; H, 6.34%), and its *isomer* (40), m.p. 128—130 °C; $\nu_{max.}$ 1 710 cm^{-1} (CO, C*O*OH); $\lambda_{max.}$ (MeOH) 272 and 222 nm; τ 2.65—3.45 (3 H, m, ArH), 5.10 (1 H, bh, D_2O exchangeable, CO_2H), 6.22 (3 H, s, OCH_3), and 6.50—8.10 (11 H, m, 1′-, 1-, 2-, 4-, 9-, and 10-H) (Found: C, 71.65; H, 6.2. $C_{17}H_{18}O_4$ requires C, 71.31; H, 6.34%).

2-(2,6-*Diethoxycarbonyl*-3-*oxohexyl*)-3,4-*dihydronaphthalen*-1(2H)-*one* (36).—Condensation of the methiodide [1] (2) (10 g) with dimethyl β-oxopimelate [8] (9 g) in the presence of sodium methoxide (prepared from 690 mg of sodium metal) according to the procedure described earlier for compound (19) gave the diketo-diester (36) (11 g) as an oil; $\nu_{max.}$ 1 732 (CO_2Me), 1 710 (CO), and 1 678 cm^{-1} (ArCO); *m*/*z* 360 (M^+); τ 1.95—2.22 (1 H, m, 8-H), 2.50—3.10 (3 H, m, 5-, 6-, and 7-H), 6.00—6.50 (1 H, m, 2′-H), 6.32 (3 H, s, CO_2), 6.42 and 6.44 (3 H, 2 s, CO_2CH_3), and 6.80—8.50 (13 H, m, 1′-, 4′-, 6′-, 2-, 3-, and 4-H).

Attempted Rearrangement of the Diester (36).—A solution of compound (36) (3 g) in AcOH, HCl, and H_2O (4 : 2 : 1, v/v; 50 ml) was refluxed for 3 h. Work-up gave a viscous acidic material (2.6 g) which, upon crystallisation from benzene–hexane, furnished the *enone-acid* (32) (1.05 g), m.p. 119.5—121 °C; $\nu_{max.}$ 1 700 cm^{-1} (CO, *C*OOH); $\lambda_{max.}$ (MeOH) 265, 226, and 222 nm; τ 0.33 (1 H, bh, D_2O exchangeable, CO_2H), 2.00—3.00 (4 H, m, ArH), and 7.00—8.30 (13 H, m, 1′-, 2′-, 1-, 2-, 4-, 9-, and 10-H) (Found: C, 75.9; H, 6.7. $C_{17}H_{18}O_3$ requires C, 75.53; H, 6.71%).

A solution of the mother-liquor (800 mg) in methanol–ether (1 : 1; 10 ml) was treated with ethereal diazomethane (5%; 5 ml) at 0 °C for 2 h. Evaporation of the solvent and chromatography of the crude oil over a column of silica gel eluting with benzene furnished the enone-ester (34) (150 mg); $\nu_{max.}$ 1 735 (CO_2Me) and 1 660 cm^{-1} (conjugated ketone); τ 2.50—3.00 (4 H, m, ArH), 6.46 (3 H, s, CO_2CH_3), 6.90—8.50 (13 H, m, 1′-, 2′-, 1-, 2-, 9-, 10-, and 10a-H) and the methyl ester of the acid (32) (270 mg).

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