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## Curvularin. Part VI.<sup>1</sup> The Preparation of Some Acylated Dimethoxyphenylacetic Acids and Related Compounds

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The substituted octanoic acids  $HO_2C\cdot[CH_2]_3\cdot CHY\cdot Me$  (Y = Br, OH, OAc, and OMe) are prepared from 7-oxo-octanoic acid. The acylation of methyl 3,4-dimethoxyphenylacetate with hexanoic acid (using polyphosphoric acid) or with octanoyl chloride (using aluminium chloride or silver perchlorate) gives the expected methyl 2-acyl-4,5dimethoxyphenylacetates. Similar acylation reactions employing the substituted octanoic acids (or the corresponding acid chlorides) are successful and give similar 2-acyl derivatives only when the acyl group is 7-oxo-, 7-hydroxy-, or 7-acetoxy-octanoyl. Hydrogenation of methyl 4,5-dimethoxy-2-(7-oxo-octanoyl)phenylacetate gives 1-(6-hydroxyheptyl)-6,7-dimethoxyisochroman-3-one while treatment with ethanolic alkali in the presence of air gives 2-hydroxy-6,7-dimethoxy-3-(5-oxohexyl)-1,4-naphthaquinone. Methyl 3,5-dimethoxyphenylacetate reacts with octanoyl chloride and aluminium chloride to give 3,5-dimethoxy-2-octanoylphenylacetic acid but the reactions with the substituted octanoic acids (or their acid chlorides) using the above conditions fail to give acylated products. Acylation does occur however with 7-hydroxyoctanoic acid in trifluoracetic anhydride with the formation of methyl 2-(7-hydroxyoctanoyl)-3,5-dimethoxyphenylacetate. Hydrolysis of this ester gives the corresponding acid while hydrogenation gives 2-(7-hydroxyoctyl)-3,5-dimethoxyphenylacetic acid. Neither of these hydroxy-acids can be dehydrated to give the corresponding lactone and the synthesis of derivatives of curvularin by this route is therefore not possible.

SEVERAL schemes may be devised for the synthesis of the fungal metabolite curvularin<sup>2</sup> (IV; R = H) and its derivatives. One of the more attractive involves the acylation of the dimethoxyphenylacetic ester (I) with either a suitably substituted octanoic acid (II) or the corresponding acid chloride to give, ultimately, the hydroxy-acid (III; R = H, Y = OH). This would be expected to undergo lactone formation to yield racemic di-O-methylcurvularin (IV; R = Me). We describe below an examination of these and related reactions.



RŎ

ö

(IV)

MeŎ

(III)

The group Y of the octanoic acid (II) is the precursor of the hydroxy-group of the hydroxy-keto-acid (III; R = H, Y = OH) and must not be affected adversely by the conditions of the acylation reaction. With this in mind we prepared several such octanoic acids carrying different substituents at C-7 from the readily accessible 7-oxo-octanoic acid. Reduction of the latter with sodium borohydride gave the hydroxy-acid (II; Y = OH) which on acetylation provided the acetoxy-acid (II; Y = OAc; both these products were readily converted into the bromo-acid (II; Y = Br). Diazomethane converted 7-hydroxyoctanoic acid into the corresponding methyl ester which on further methylation using di-

<sup>1</sup> Part V, H. D. Munro, O. C. Musgrave, and R. Templeton, J. Chem. Soc. (C), 1967, 947. <sup>2</sup> A. J. Birch, O. C. Musgrave, R. W. Rickards, and H. Smith,

J. Chem. Soc., 1959, 3146.

<sup>3</sup> Cf. P. J. Corish and W. H. T. Davison, J. Chem. Soc., 1955, 2431.

azomethane and boron trifluoride followed by alkaline hydrolysis gave 7-methoxyoctanoic acid (II; Y = OMe). The i.r. spectrum of the pure methoxy-acid shows, in addition to the normal dimeric-acid carbonyl band at 1715 cm.<sup>-1</sup>, a second band of similar intensity at 1745 cm.<sup>-1</sup>. The latter band no longer appears when a dilute solution of the acid in carbon tetrachloride is examined and we attribute it to carboxy-groups which are involved in intermolecular hydrogen-bonding with methoxy-groups.<sup>3</sup> Treatment of the sodium salts of 7-oxooctanoic acid and of the octanoic acids (II; Y = H, OAc. OMe, and Br) with oxalyl chloride 4 gave the corresponding acid chlorides which showed the expected i.r. absorption bands at ca. 1800 cm.<sup>-1</sup> and were used in acylation reactions without further purification.

The dimethoxyphenylacetic ester (I) had previously been acylated without difficulty using ethoxalyl chloride,<sup>5</sup> acetyl chloride,<sup>6</sup> and ethyl 6-chloroformylhexanoate<sup>6</sup> in the presence of aluminium chloride, and using acetic anhydride with perchloric acid.<sup>7</sup> In each case the 2-acyl derivative resulted, the yield (25%) obtained with the long-chain ( $C_7$ ) acylating agent being considerably lower than the yields (67-83%) obtained with the shorter  $(C_2)$  reagents. We encountered similar behaviour in the reaction between the dimethoxyphenylacetic ester (I), octanoyl chloride, and aluminium chloride, which gave an 18% yield of the keto-acid (III; R = Y = H). The orientation of the octanoyl group was shown by the close resemblance of the u.v. absorption of the compound to that of methyl 2-acetyl-3,5-dimethoxyphenylacetate.<sup>6</sup> Similar reactions using the acid chlorides derived from the substituted octanoic acids (II; Y = OAc and Br) and from 7-oxo-octanoic acid were unsuccessful, the i.r. and u.v. absorption of the reaction mixtures showing

599; A. L. Wilds and C. H. Shunk, *ibid*, 1950, 72, 2388.
<sup>5</sup> O. C. Musgrave, J. Chem. Soc., 1957, 1104.
<sup>6</sup> A. J. Birch, B. Moore, and R. W. Rickards, J. Chem. Soc., 1962, 220.

<sup>7</sup> B. W. Bycroft and J. C. Roberts, J. Chem. Soc., 1962, 2063.

<sup>4</sup> R. Adams and L. H. Ulich, J. Amer. Chem. Soc., 1920, 42,

the complete absence of the desired aryl alkyl ketones. Attempted acylations of the dimethoxyphenylacetic ester (I) with the octanoic acids (II; Y = OAc and Br) and with 7-oxo-octanoic acid in the presence of either boron trifluoride etherate or polyphosphoric acid also failed.

To learn something of the factors governing these reactions we examined various methods for the acylation of the isomeric ester methyl 3,4-dimethoxyphenylacetate (V) which is more readily available and had previously been shown to undergo normal Friedel-Crafts reactions with acetyl chloride and related compounds,<sup>8</sup> benzoyl chloride,<sup>8</sup> and ethoxalyl chloride.<sup>5</sup> In the presence of aluminium chloride octanovl chloride reacted with this ester to give the keto-ester (VI; R =Me, Y = H (22%) while the acid chlorides prepared from



7-oxo-octanoic acid and from the acetoxyoctanoic acid (II; Y = OAc) gave the related compounds (VI; R = Me, -CO- in place of -CHY-) (19%) and (VI; R = H, Y = OAc) (0.3%). Silver perchlorate <sup>9</sup> was more effective than was aluminium chloride in bringing about such acylations, and by its use the simple octanoyl derivative (VI; R = Me, Y = H) was obtained in 44% yield. The acid chloride from the acetoxyoctanoic acid (II; Y = OAc) now afforded the hydroxy-keto-ester (VI; R = Me, Y = OH) (16%), hydrolysis of the acetate group having occurred during the isolation procedure. The products from the above reactions showed u.v. absorption similar to that of methyl 2-acetyl-4.5-dimethoxyphenylacetate so establishing their structures. Both aluminium chloride and silver perchlorate failed to effect acylation when the acid chloride from the methoxy-acid (II; Y = OMe) was used.

Polyphosphoric acid also brought about the acylation of the dimethoxyphenylacetic ester (V). Hexanoic acid gave methyl 2-hexanoyl-4,5-dimethoxyphenylacetate (61%), and 7-oxo-octanoic acid gave the diketo-ester (VI; R = Me, -CO- in place of -CHY-) (36%). However, both the methoxy- (II; Y = OMe) and the acetoxy-(II; Y = OAc) octanoic acid failed to give the expected products. No ketonic material was obtained from the first of these reactions and the second gave a low (10%)yield of methyl 2-acetyl-4,5-dimethoxyphenylacetate. The formation of the latter compound is clearly a result of attack by the initial acylium ion on the singlebonded oxygen of the acetate group which releases the acetylium ion. The complete failure of some of the substituted octanoic acids (II) and their acid chlorides to acylate the dimethoxyphenylacetic esters (I) and (V) is presumably a consequence of related reactions involving 251

the substituent groups. The marked difference in reactivity found between the two dimethoxyphenylacetic esters (I) and (V) must be due to the greater steric effects present in the former which prevent the approach of the more bulky acylating agents.

The most accessible of the substituted octanoyldimethoxyphenylacetic esters at this stage was the diketoester (VI; R = Me, -CO- in place of -CHY-) and we briefly examined reactions by which it might be converted into the hydroxy-keto-acid (VI; R = H, Y =OH). Hydrogenation of the diketo-ester over platinum did not result in selective reduction of the aliphatic ketonic group. The only compound isolated (after prolonged hydrogenation) was the isochromanone (VII:  $R^1 = OMe, R^2 = H$ ) (13%) resulting from the reduction of both the original ketonic groups and subsequent lactonisation. Its u.v. absorption resembled closely that of other 4,5-dialkylveratrole derivatives.<sup>10</sup> When



hydrolysis of the diketo-ester was attempted using cold dilute aqueous alkali at pH 11 the solution rapidly became deep purple. The product, which was more easily obtained by treatment of the diketo-ester with ethanolic sodium ethoxide in air, was the hydroxynaphthaquinone (VIII;  $R = [CH_2]_4 Ac$ ) (70%) formed by cyclisation with subsequent aerial oxidation of the resulting dihydric naphthol. Its structure follows from the resemblance of its light absorption to that of the known hydroxy-naphthaquinone (VIII; R = H) and from its conversion into the corresponding leuco-acetate which shows the characteristic u.v. absorption of a naphthalene derivative.

At this point we learnt of the successful use of trifluoroacetic anhydride by Roberts and his co-workers <sup>11</sup> in bringing about the acylation of the dimethoxyphenylacetic ester (I) with 7-oxo-octanoic acid to give the diketo-ester (III; R = Me, -CO- in place of -CHY-). By using the hydroxy-acid (II; Y = OH) in a similar reaction we obtained the hydroxy-keto-ester (III; R = Me, Y = OH (65%) without difficulty and converted it by alkaline hydrolysis under nitrogen into the hydroxy-keto-acid (III; R = H, Y = OH). The dehydration of the latter hydroxy-acid was attempted using thionyl chloride, phosphoryl chloride, phosphorus pentoxide, toluene-p-sulphonic acid (under 'high dilution' conditions), dicyclohexylcarbodi-imide, and trifluoroacetic anhydride, and by careful heating under reduced pressure. The products were examined by thin-layer chromatography but in no case was there evidence of

<sup>8</sup> H. R. Bentley, W. Dawson, and F. S. Spring, J. Chem. Soc., 1952, 1763.

H. Burton and P. F. G. Praill, J. Chem. Soc., 1950, 2034.

<sup>&</sup>lt;sup>10</sup> I. M. Davidson and O. C. Musgrave, J. Chem. Soc., 1963,

<sup>3154.</sup> <sup>11</sup> B. W. Bycroft, J. C. Roberts, and P. M. Baker, J. Chem. Soc., 1964, 2289.

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the formation of the lactone (IV; R = Me). This reluctance to undergo lactone formation is presumably a result of the unfavourable conformation of the hydroxyoctanoyl group. With the object of modifying the stereochemistry of this group we subjected the hydroxyketo-ester (III; R = Me, Y = OH) to hydrogenation over platinum and obtained the hydroxy-acid (III; R = H, Y = OH,  $-CH_2$ - in place of -CO-) (68%), together with some of the isochromanone (VII;  $R^1 = H$ ,  $R^2 = OMe$ ) (20%). The structures of these products were indicated by their u.v. absorption spectra which are very similar to those of related 1,3-dimethoxybenzene derivatives.<sup>6</sup> Dehydration of the hydroxyacid using a selection of the methods described above failed, however, to result in lactone formation. Roberts and his co-workers have also found that the dehydration of the hydroxy-keto-acid (III; R = H, Y = OH) fails to give  $(\pm)$ -di-O-methylcurvularin (IV; R = Me) and have been obliged to use a different route in their recent synthesis of this compound.12

## EXPERIMENTAL

Ultraviolet absorption spectra were measured for ethanolic solutions using Unicam SP 500 and Hilger 'Ultrascan' spectrophotometers. Infrared spectra were measured, unless stated otherwise, for Nujol mulls or liquid films using Perkin-Elmer 'Infracord' models 137 and 237 spectrophotometers.

7-Hydroxyoctanoic Acid (II; Y = OH).—A solution of sodium borohydride (1.5 g.) in methanol (60 ml.) was adjusted to pH 10-11 by the addition of aqueous sodium hydroxide and added portionwise, with swirling, during 20 min. to a solution of 7-oxo-octanoic acid <sup>13</sup> (20 g.) in cold aqueous 5N-sodium hydroxide (28 ml.). After being kept at pH 10—11 for 3 hr. at  $18^{\circ}$  the mixture was cooled to  $0^{\circ}$ , adjusted to pH 5 by the addition, with stirring, of conc. hydrochloric acid, and saturated with sodium chloride. It was shaken with ether  $(3 \times 30 \text{ ml. portions})$  and the extract was dried  $(MgSO_4)$  and evaporated under reduced pressure. Distillation of part of the resulting crude 7-hydroxyoctanoic acid (19 g.) was accompanied by dehydration and afforded only a small quantity of the hydroxy-acid as an oil b. p.  $133^{\circ}/2 \times 10^{-4}$  mm. (Found: C, 59.7; H, 10.0.  $C_8H_{16}O_3$  requires C, 60.0; H, 10.05%),  $v_{max}$  3400 (hydroxy), ca. 2900 (broad; carboxy OH), and 1715 cm.<sup>-1</sup> (carboxy C=O). The involatile residue appeared to be polymeric.

7-Acetoxyoctanoic Acid (II; Y = OAc).—A mixture of crude 7-hydroxyoctanoic acid (15 g.), glacial acetic acid (31 g.), acetic anhydride (5 g.), and conc. hydrochloric acid (3·1 g.) was heated under reflux for 2 hr. Distillation gave 7-acetoxyoctanoic acid (9·3 g.) as an oil, b. p. 126—128°/10<sup>-3</sup> mm. (Found: C, 59·2; H, 9·0; Ac, 20·7%; Equiv. (by titration), 199.  $C_{10}H_{18}O_4$  requires C, 59·4; H, 8·95; Ac, 21·25%; Equiv., 202·3),  $v_{max}$ . ca. 3000 (broad; carboxy OH), 1745 (ester C=O), 1710 (carboxy C=O), and 1245 cm.<sup>-1</sup> (acetate C-O).

7-Bromoctanoic Acid (II; Y = Br).—(a) A mixture of crude 7-hydroxyoctanoic acid (20 g.) and a 45% (w/v) <sup>12</sup> P. M. Baker, B. W. Bycroft, and J. C. Roberts, J. Chem. Soc. (C), 1967, 1913.

solution of hydrogen bromide in glacial acetic acid (48 g.) was kept at 18° for 30 hr. and then heated at 100° for 3 hr. Distillation gave 7-bromoctanoic acid (22 g.) as an oil, b. p. 108°/0·15 mm.,  $n_{\rm p}^{25}$  1·469 (Found: C, 43·3; H, 6·7; Br, 34·8%; Equiv. (by titration), 221. C<sub>8</sub>H<sub>15</sub>BrO<sub>2</sub> requires C, 43·05; H, 6·8; Br, 35·8%; Equiv., 223·1),  $v_{\rm max.}$  ca. 3000 (broad; carboxy OH), and 1720 cm.<sup>-1</sup> (carboxy C=O).

(b) A mixture of 7-acetoxyoctanoic acid (10 g.) and 47%(w/w) aqueous hydrobromic acid (12 ml.) was heated under reflux for 2 hr. The excess of hydrobromic acid was distilled off and the residue was shaken with ether and aqueous sodium hydrogen carbonate. Acidification of the aqueous layer and extraction with ether afforded 7-bromoctanoic acid (5 g.) as an oil, b. p.  $108-109^{\circ}/0.05$  mm., the i.r. absorption of which was identical with that of the specimen prepared by method (a).

7-Methoxyoctanoic Acid (II; Y = OMe).—A mixture of 7-hydroxyoctanoic acid (20 g.) and an ethereal solution of distilled diazomethane [from N-nitrosomethylurea (38 g.), 50% aqueous potassium hydroxide (105 ml.), and ether (500 ml.)] was kept for 3 hr. and then distilled giving methyl 7-hydroxyoctanoate (18 g.) as an oil, b. p. 80°/0·1 mm.,  $v_{\text{max}}$  3450 (hydroxy) and 1750 cm.<sup>-1</sup> (ester C=O). A dry ethereal solution of distilled diazomethane [from N-nitrosomethylurea (18 g.), 50% aqueous potassium hydroxide (50 ml.), and ether (250 ml.)] was added slowly with stirring to a mixture of methyl 7-hydroxyoctanoate (5 g.), boron trifluoride etherate (redistilled; 0.5 g.), and dry ether (50 ml.).14 Next day the filtered solution was washed with aqueous sodium hydrogen carbonate, dried (MgSO<sub>4</sub>), and filtered through a column of basic alumina (pH 7.6) to remove unmethylated material. Evaporation of the filtrate gave the crude methoxy-ester which was heated under reflux with 2M-sodium hydroxide (30 ml.) for 1 hr. Acidification of the mixture and extraction with ether gave 7-methoxyoctanoic acid (3.8 g.) as an oil, b. p.  $108-109^{\circ}/$ 0.2 mm. (lit.,15 b. p. 121-122°/1 mm.) [Found: MeO, 18.2%; Equiv. (by titration), 174.1. Calc. for C<sub>9</sub>H<sub>18</sub>O<sub>3</sub>: MeO, 17.8%; Equiv., 174.2],  $\nu_{max}$  ca. 3000 (broad; carboxy OH), 1715 and 1745 (shoulder) (carboxy C=O), and  $1089 \text{ cm}^{-1}$  (ether C-O).

3,5-Dimethoxy-2-octanoylphenylacetic Acid (III; R = Y =H).—Finely ground anhydrous aluminium chloride (2.5 g)was added in portions to a swirled mixture of methyl 3,5-dimethoxyphenylacetate  $^{6}$  (2.6 g.), freshly distilled octanoyl chloride (b. p. 73°/10 mm.) (2.0 g.), and dry nitrobenzene (40 ml.) at  $0^{\circ}$ . Next day the mixture was poured into ice and conc. hydrochloric acid, shaken with ether, and the ethereal solution was steam-distilled until free from nitrobenzene. Extraction of the residue with ether gave an oil which partly solidified on keeping. Trituration with ether and crystallisation of the residue from benzene-light petroleum (b. p. 60-80°) or from aqueous ethanol gave 3,5-dimethoxy-2-octanoylphenylacetic acid (0.7 g.) as needles, m. p. 79-79.5° (Found: C, 67.2; H, 7.9. C<sub>18</sub>H<sub>26</sub>O<sub>5</sub> requires C, 67.05; H, 8.15%),  $\nu_{max}$  ca. 3000 (broad; carboxy OH), 1710 (carboxy C=O), and 1655 cm.<sup>-1</sup> (hydrogenbonded aryl ketone C=O);  $\lambda_{max}$  2220 (log  $\varepsilon$  4·129), 2660  $(\log \varepsilon 3.773)$ , and 2900 Å  $(\log \varepsilon 3.627)$ . When the reaction was effected by stannic chloride (in benzene) only a trace of

Soc. (C), 1967, 1913.
 <sup>13</sup> R. M. Manyick, F. C. Frostick, J. J. Sanderson, and C. R. Hauser, J. Amer. Chem. Soc., 1953, 75, 5030; C. R. Hauser, F. W. Swamer, and B. I. Ringler, *ibid.*, 1948, 70, 4023.

<sup>&</sup>lt;sup>14</sup> Cf. E. Muller and W. Rundel, Angew. Chem., 1958, **70**, 105; E. Müller, M. Bauer, and W. Rundel, Z. Naturforsch., 1959, **14**b, 209.

<sup>&</sup>lt;sup>15</sup> C. Michel and S. Tchelitcheff, Bull. Soc. chim. France, 1964, 2230.

this acid (0.2%) resulted. None was obtained when silver perchlorate (in nitromethane) was employed.

Methyl 2-Hexanoyl-4,5-dimethoxyphenylacetate.—A mixture of hexanoic acid (1·2 g.), methyl 3,4-dimethoxyphenylacetate <sup>5</sup> (2 g.), and polyphosphoric acid (18 g.) was heated at 85° for 1 hr. with occasional stirring and added to crushed ice. The mixture was shaken with ether and the extract was washed with aqueous sodium hydrogen carbonate and evaporated. The residue crystallised from methanol to give methyl 2-hexanoyl-4,5-dimethoxyphenylacetate (1·8 g.), m. p. 72·5—73° (Found: C, 66·3; H, 7·8; MeO, 30·8. C<sub>17</sub>H<sub>24</sub>O<sub>5</sub> requires C, 66·2; H, 7·85; 3MeO, 30·2%),  $\nu_{max.}$ 1740 (ester C=O) and 1670 cm.<sup>-1</sup> (aryl ketone C=O);  $\lambda_{max.}$ 2290 (log  $\varepsilon$  4·321), 2750 (log  $\varepsilon$  3·979), and 3030 Å (log  $\varepsilon$ 3·779).

A solution of potassium hydroxide (0.87 g.) in water (10 ml.) was added with ice-cooling to a solution of the above ester (0.48 g.) in methanol (10 ml.) and the mixture was kept under nitrogen at room temperature overnight. Acidification and extraction with ether gave 2-hexanoyl-4,5-dimethoxyphenylacetic acid (0.28 g.) which crystallised from water as needles, m. p. 126.5—127.5° (Found: C, 65.3; H, 7.5; MeO, 23.0. C<sub>16</sub>H<sub>22</sub>O<sub>5</sub> requires C, 65.3; H, 7.55; 2MeO, 21.1%),  $\nu_{max}$  ca. 3000 (broad; carboxy OH), 1715 (carboxy C=O), and 1670 cm.<sup>-1</sup> (aryl ketone C=O);  $\lambda_{max}$ . 2280 (log  $\varepsilon$  4.319), 2730 (log  $\varepsilon$  3.943), and 3010 Å (log  $\varepsilon$  3.734).

Methyl 4,5-Dimethoxy-2-octanoylphenylacetate (VI; R =Me, Y = H).—(a) A mixture of sodium octanoate (1 g.), freshly distilled oxalyl chloride (2 ml.), dry benzene (20 ml.), and pyridine (1 drop) was kept at  $0^{\circ}$  for 0.5 hr., then at room temperature for 3 hr. The solvent was evaporated under reduced pressure, and benzene  $(3 \times 15 \text{ ml. portions})$ was added and removed in the same way. A solution of the resulting crude octanoyl chloride in dry nitromethane (20 ml.) was added in portions, with stirring, to a mixture of methyl 3,4-dimethoxyphenylacetate (1.2 g.) and silver perchlorate (2.5 g.) in dry nitromethane (20 ml.) at  $0^{\circ}$ . The mixture was kept at room temperature for 3 hr. with occasional shaking and then poured on to ice. Extraction with ether gave a solid (1.5 g.) which on crystallisation first from ether-light petroleum (b. p. 40-60°), and then from benzene-light petroleum (b. p. 60-80°) gave methyl 4,5-dimethoxy-2-octanoylphenylacetate (0.84 g.) as needles, m. p. 72·5-73° (Found: C, 67·6; H, 8·2. C<sub>19</sub>H<sub>28</sub>O<sub>5</sub> requires C, 67.85; H, 8.4%),  $v_{max.}$  (KBr disc) 1745 (ester C=O) and 1685 cm.<sup>-1</sup> (aryl carbonyl C=O);  $\lambda_{max}$ , 2305 (log  $\epsilon$  4.328), 2745 (log  $\epsilon$  3.976), and 3030 Å (log  $\epsilon$  3.772).

(b) Finely powdered anhydrous aluminium chloride (1.5 g.) was added slowly with stirring to a mixture of crude octanoyl chloride [prepared as described above from sodium octanoate (1 g.)], methyl 3,4-dimethoxyphenylacetate (1.4 g.), and dry nitrobenzene (20 ml.) at 0°. Next day the mixture was stirred with ice and conc. hydrochloric acid, and extracted with ether. The extract was steam-distilled and the residue was again extracted with ether. The ethereal solution was washed with aqueous sodium hydrogen carbonate, dried (MgSO<sub>4</sub>), and evaporated. Crystallisation of the residue from light petroleum (b. p. 60-80°) gave methyl 4,5-dimethoxy-2-octanoylphenylacetate as needles (0.48 g.), m. p. 72°, identical (mixed m. p. and i.r. absorption) with the specimen prepared by method (a).

Methyl 4,5-Dimethoxy-2-(7-oxo-octanoyl)phenylacetate (VI;  $R = Me, -CO^{-}$  in place of  $-CHY^{-}$ ).—(a) A mixture of methyl 3,4-dimethoxyphenylacetate (1 g.), 7-oxo-octanoic acid (0.75 g.), and polyphosphoric acid (12 g.) was kept at 60° for 1.5 hr. with frequent stirring, poured on to ice, and shaken with ether. The ethereal layer was washed with aqueous sodium hydrogen carbonate, evaporated, and the residue was crystallised (charcoal) from benzene-light petroleum (b. p. 60—80°) to give methyl 4,5-dimethoxy-2-(7-oxo-octanoyl)phenylacetate as needles (0.6 g.), m. p. 79.5° (Found: C, 64.9; H, 7.6. C<sub>19</sub>H<sub>26</sub>O<sub>6</sub> requires C, 65.15; H, 7.5%),  $v_{max.}$  (KBr disc) 1750 (ester C=O), 1720 (alkyl ketone C=O), and 1680 cm.<sup>-1</sup> (aryl ketone C=O);  $\lambda_{max.}$  2305 (log  $\varepsilon$  4.353), 2740 (log  $\varepsilon$  3.971), and 3035 Å (log  $\varepsilon$  3.771). The mono-2,4-dinitrophenylhydrazone separated from ethanol as orange needles, m. p. 131.5—132.5° (Found: C, 56.3; H, 5.6; N, 10.4. C<sub>25</sub>H<sub>30</sub>N<sub>4</sub>O<sub>9</sub> requires C, 56.6; H, 5.7; N, 10.55%).

(b) A mixture of sodium 7-oxo-octanoate (2.3 g.), dry benzene (30 ml.), pyridine (3 drops), and freshly distilled oxalyl chloride (3.6 g.) was kept at  $0^{\circ}$  for 0.5 hr., and then at room temperature for 3 hr.; the solution was then evaporated under reduced pressure. A mixture of the resulting 7-oxo-octanovl chloride,<sup>16</sup> methyl 3,4-dimethoxyphenylacetate (2.8 g.) and redistilled nitrobenzene (40 ml.) was treated at 0° with finely-ground anhydrous aluminium chloride (2.6 g.). Next day the mixture was added to ice and conc. hydrochloric acid, shaken with ether, and the extract was steam-distilled. An ethereal solution of the residue was washed with aqueous sodium hydrogen carbonate, and evaporated. The resulting oil (3 g.) partly solidified on keeping, and trituration with ether gave methyl which 4,5-dimethoxy-2-(7-oxo-octanoyl)phenylacetate crystallised from benzene-light petroleum (b. p. 60-80°) as needles (0.87 g.), m. p. 78-79°, identical (mixed m. p. and i.r. absorption) with the specimen prepared by method (a).

1-(6-Hydroxyheptyl)-6,7-dimethoxyisochroman-3-one (VII;  $R^1 = OMe, R^2 = H$ ).—A mixture of methyl 4,5-dimethoxy-2-(7-oxo-octanoyl)phenylacetate (0.5 g.), glacial acetic acid (20 ml.), and Adams catalyst (pre-reduced; 0.1 g.) was shaken with hydrogen for 3.5 hr., filtered, and the filtrate was evaporated. A solution of the resulting oil in ether was washed with aqueous sodium hydroxide and evaporated. The neutral residue (0.13 g.) crystallised from a mixture of benzene, ethanol, and light petroleum (b. p. 60—80°) to give the *isochromanone* as plates (0.06 g.), m. p. 104—105° (Found: C, 67.1; H, 8.2.  $C_{18}H_{28}O_5$  requires C, 67.05; H, 8.15%),  $v_{max}$ . 3330 (hydroxy) and 1727 cm.<sup>-1</sup> ( $\delta$ -lactone C=O);  $\lambda_{max}$ . 2320 (log  $\varepsilon$  3.822) and 2840 Å (log  $\varepsilon$  3.538).

2-Hydroxy-6,7-dimethoxy-3-(5-oxohexyl)-1,4-naphthaquinone (VIII; R =  $[CH_2]_4COMe$ ).—A solution of sodium ethoxide [from sodium (0·18 g.) and ethanol (5 ml.)], and methyl 4,5-dimethoxy-2-(7-oxo-octanoyl)phenylacetate (1 g.) in ethanol (25 ml.) was heated under reflux for 20 min. and kept overnight with free access of air. The mixture was diluted with water, and acidified with dilute sulphuric acid. The resulting solid (0·66 g.) crystallised from benzene-light petroleum (b. p. 60—80°) (charcoal) to give the hydroxynaphthaquinone as orange needles, m. p. 149—150° (Found: C, 64·8; H, 6·2.  $C_{18}H_{20}O_6$  requires C, 65·05; H, 6·05%),  $v_{max}$ . 3250 (hydroxy), 1710 (ketone C=O), 1645 and 1635 cm.<sup>-1</sup> (quinone C=O);  $\lambda_{max}$ . 2760 (log  $\varepsilon$ 4·494) and 3165 Å (log  $\varepsilon$  4·204),  $\lambda_{infl}$ . 2235 (log  $\varepsilon$  4·101), 2705 (log  $\varepsilon$  4·457), and 3460 Å (log  $\varepsilon$  3·613).

2-Hydroxy-6,7-dimethoxy-1,4-naphthaquinone (VIII;  $R = {}^{16}$  Cf. R. H. Jaeger and R. Robinson, Tetrahedron, 1961, 14, 320.

H).—This compound, prepared from methyl 2-acetyl-4,5-dimethoxyphenylacetate by a similar method,<sup>8</sup> had  $\nu_{max}$  3250 (hydroxy), 1650 and 1635 cm.<sup>-1</sup> (quinone C=O);  $\lambda_{max}$  2725 (log  $\varepsilon$  4·431) and 3090 Å (log  $\varepsilon$  4·157),  $\lambda_{infl.}$  2210 (log  $\varepsilon$  4·069) and 3360 Å (log  $\varepsilon$  3·722).

1,2,4,-Triacetoxy-6,7-dimethoxy-3-(5-oxohexyl)naphthalene. —Triethylamine (2 drops) was added to a mixture of 2-hydroxy-6,7-dimethoxy-3-(5-oxohexyl)-1,4-naphtha-

quinone (0.21 g.), zinc dust (0.31 g.), and acetic anhydride (5 ml.). The mixture was heated under reflux for 15 min., filtered, and the residue was washed with hot acetic acid. The combined filtrates were boiled and diluted with water until the solution became cloudy. The solid (0.13 g.) which separated on cooling was crystallised from acetic acid and then from benzene-light petroleum (b. p. 80-90°) to give the *triacetoxynaphthalene* as needles, m. p. 125-127.5° (Found: C, 62.5; H, 6.2.  $C_{24}H_{28}O_9$  requires C, 62.6; H, 6.15%),  $\nu_{max}$  (KBr disc) 1760 (aryl acetate C=O) and 1710 cm.<sup>-1</sup> (ketone C=O);  $\lambda_{max}$  2390 (log  $\varepsilon$  4.940), 2450 (log  $\varepsilon$  4.904), 2770 (log  $\varepsilon$  3.773), 3140 (log  $\varepsilon$  3.375), and 3280 A (log  $\varepsilon$  3.551),  $\lambda_{infl}$  2690 (log  $\varepsilon$  3.734), 2840 (log  $\varepsilon$ 3.747), and 2965 Å (log  $\varepsilon$  3.551).

Acylations of Methyl 3,4-Dimethoxyphenylacetate (V) by 7-Acetoxvoctanoic Acid and by 7-Acetoxvoctanovl Chloride.---(a) A mixture of 7-acetoxyoctanoic acid (2.53 g.), methyl 3,4-dimethoxyphenylacetate (2.63 g.), and polyphosphoric acid (30 g.) was kept at 60° for 1 hr. with occasional stirring, added to ice, and shaken with ether. The ethereal layer was washed with aqueous sodium hydrogen carbonate, dried (MgSO<sub>4</sub>), and filtered through a column of alumina. Elution with ether afforded, in addition to yellow oils, a solid (0.32 g.) which sublimed at 80-100° (bath)/0.05 mm. and then crystallised from benzene-light petroleum (b. p. 60-80°) to give methyl 2-acetyl-4,5-dimethoxyphenylacetate as needles, m. p. 112-113° (Found: C, 62.0; H, 6.5. Calc. for  $C_{13}H_{16}O_5$ : C, 61.9; H, 6.4%),  $\nu_{max}$  (KBr disc) 1745 (ester C=O) and 1670 cm.<sup>-1</sup> (aryl ketone C=O);  $\lambda_{\rm max}$  2300 (log  $\epsilon$  4.369), 2750 (log  $\epsilon$  3.979), and 3050 Å (log  $\epsilon$ 3.773). There was no depression of m. p. on admixture with an authentic<sup>8</sup> specimen, m. p. 113-114°, and the i.r. and u.v. spectra of the two specimens were identical.

(b) A mixture of sodium 7-acetoxyoctanoate (2 g.), freshly distilled oxalyl chloride (2.37 g.), pyridine (1 drop), and dry benzene (20 ml.) was kept at 0° for 0.5 hr. and then at 18° for 3 hr. The solvent was evaporated under reduced pressure and benzene  $(3 \times 15 \text{ ml. portions})$  was added and removed in the same manner. Finely ground anhydrous aluminium chloride (3 g.) was added in portions to a stirred solution of the resulting crude 7-acetoxyoctanoyl chloride and methyl 3,4-dimethoxyphenylacetate (2 g.) in dry nitrobenzene (30 ml.) at 0°. Next day the mixture was poured into ice and conc. hydrochloric acid, shaken with ether, and the ethereal solution was steam-distilled. The residue was extracted with ether which was then washed with aqueous sodium hydrogen carbonate. Acidification of the latter and ether extraction afforded an oil (0.7 g)which was heated at 120°/0·1 mm. to remove unchanged 7-acetoxyoctanoic acid (0.2 g.). A solution of the residue in ether was filtered through a column of 'Florisil' (magnesia-silica gel) to give a solid which on crystallisation from carbon tetrachloride-light petroleum (b. p. 60-80°) afforded 2-(7-acetoxyoctanoyl)-4,5-dimethoxyphenylacetic acid (VI; R = H, Y = OAc) as needles (0.01 g.), m. p. 98-98.5° (Found: C, 62.9; H, 7.5. C<sub>20</sub>H<sub>28</sub>O<sub>7</sub> requires C, 63.15; H, 7.4%),  $\nu_{max}$  (KBr disc) ca. 3000 (broad; carboxy OH),

1710 and 1725 (shoulder) (unresolved carboxy and ester C=O), 1675 (aryl ketone C=O), and 1245 cm.<sup>-1</sup> (acetate C=O);  $\lambda_{max}$ , 2295 (log  $\varepsilon$  4·338), 2735 (log  $\varepsilon$  3·952), and 3025 Å (log  $\varepsilon$  3·738).

(c) A solution of 7-acetoxyoctanoyl chloride [from sodium 7-acetoxyoctanoate (7.6 g.), oxalyl chloride (5.8 ml.), benzene (50 ml.), and pyridine (1 drop)] in redistilled nitromethane (35 ml.) was added with stirring during 10 min. to a mixture of methyl 3,4-dimethoxyphenylacetate (7.15 g.) and silver perchlorate (14.1 g.) in nitromethane (35 ml.) at 0°. The mixture was kept for 3 hr. at 18° with occasional stirring, and then added to ice. Extraction with ether gave an oil which was boiled under reflux with methanol (100 ml.) containing conc. hydrochloric acid (10 ml.) for 2 hr. and then diluted with water (100 ml.). The dark oil (12.3 g.) obtained by ether-extraction, in carbon tetrachloride, was filtered through a column of silicic acid. Elution with mixtures of carbon tetrachloride and ether gave a solid which crystallised from benzene-light petroleum (b. p. 60-80°) to give methyl 2-(7-hydroxyoctanoyl)-4,5-dimethoxyphenylacetate (VI; R = Me, Y = OH) as needles (1.9 g.), m. p. 86-87° (Found: C, 65.0; H, 7.9. C19H28O6 requires C, 64.75; H, 8.0%), v<sub>max.</sub> 3530 (hydroxy), 1740 (ester C=O), and 1665 cm.<sup>-1</sup> (aryl ketone C=O);  $\lambda_{max}$  2300 (log  $\varepsilon$  4.337), 2730 (log  $\varepsilon$  3.955), and 3020 Å (log  $\varepsilon$  3.762).

2-(7-Hydroxyoctanoyl)-3,5-dimethoxyphenylacetic Acid (III; R = H, Y = OH).—A solution of methyl 3,5-dimethoxyphenylacetate (1·3 g.) and 7-hydroxyoctanoic acid (1·0 g.) in trifluoroacetic anhydride (8 ml.) was kept at room temperature with occasional swirling for 24 hr., and was then poured into aqueous sodium hydrogen carbonate and shaken with ether. Chromatography of the conc. ethereal solution as previously described <sup>11</sup> gave methyl 2-(7-hydroxyoctanoyl)-3,5-dimethoxyphenylacetate (1·4 g.) as an oil,  $v_{max}$ . 3480 (hydroxy), 1740 (ester C=O), and 1680 cm.<sup>-1</sup> (aryl ketone C=O);  $\lambda_{max}$ . 2340 (log  $\varepsilon$  3·635). It was identical (i.r. and u.v.) with a specimen obtained by the reduction of the corresponding diketo-ester with sodium borohydride.<sup>11</sup>

A solution of potassium hydroxide (1.2 g.) in water (15 ml.) was added to a solution of methyl 2-(7-hydroxyoctanoyl)-3,5-dimethoxyphenylacetate (0.75 g.) in methanol (15 ml.). Nitrogen was passed through the mixture for 6 hr. after which it was acidified to pH 6, shaken with ether, and the ethereal layer was washed with aqueous sodium hydrogen carbonate. Acidification of the latter solution and extraction with ether gave 2-(7-hydroxyoctanoyl)-3,5-dimethoxyphenylacetic acid (0.25 g.) which crystallised from benzene as nearly colourless prisms, m. p. 92-93° and sublimed at 140°/10-3 mm. (lit., 12 m. p. 90-93°) (Found: C, 63.8; H, 7.9. Calc. for C<sub>18</sub>H<sub>26</sub>O<sub>6</sub>: C, 63.9; H, 7.75%), v<sub>max</sub> (KBr disc) 3420 (hydroxy), ca. 2900 (broad; carboxy OH), 1700 and 1735 (carboxy C=O), and 1655 cm.<sup>-1</sup> (aryl ketone C=O);  $\lambda_{max}$  2330 (log  $\epsilon$  3.953) and 2660 (log  $\varepsilon$  3.738),  $\lambda_{infl.}$  2870 Å (log  $\varepsilon$  3.573).

Hydrogenation of Methyl 2-(7-Hydroxyoctanoyl)-3,5-dimethoxyphenylacetate (III; R = Me, Y = OH).—A mixture of the hydroxy-keto-ester (32 mg.), 60% aqueous perchloric acid in glacial acetic acid (1:150 v/v; 3 ml.), and pre-reduced Adams platinum oxide catalyst (2 mg.) was shaken under hydrogen at atmospheric pressure in a microhydrogenation apparatus until *ca.* 1.9 moles of hydrogen had been absorbed (3 min.). The filtered solution was evaporated under reduced pressure, and the residue was shaken with ether and aqueous sodium hydrogen carbonate. Acidification of the aqueous solution and extraction with ether gave 2-(7-hydroxyoctyl)-3,5-dimethoxyphenylacetic acid (III; R = H, Y = OH,  $-CH_2^-$  in place of  $-CO^-$ ) as plates (20 mg.), m. p. 90–91° (Found: C, 66-7; H, 8-7. C<sub>18</sub>H<sub>28</sub>O<sub>5</sub> requires C, 66-65; H, 8-7%), v<sub>max</sub>. (KBr disc) 3400 (hydroxy), ca. 2900 (broad; carboxy OH), and 1710 cm.<sup>-1</sup> (carboxy C=O);  $\lambda_{max}$ . 2800 (log  $\varepsilon$  3-554),  $\lambda_{infl}$ . 2250 (log  $\varepsilon$  3-933) and 2840 Å (log  $\varepsilon$  3-546).

Hydrogenation of a larger quantity of the keto-ester (100 mg.) gave, in addition to the above acid, a neutral product which crystallised from benzene containing a little ethanol giving 1-(6-hydroxyheptyl)-6,8-dimethoxyiso-chroman-3-one (VII; R<sup>1</sup> = H, R<sup>2</sup> = OMe) as plates (18 mg.), m. p. 97–98° (Found: C, 67·2; H, 8·2. C<sub>18</sub>H<sub>26</sub>O<sub>5</sub> requires C, 67·05; H, 8·15%),  $\nu_{max}$  (KBr disc) 3350 (hydroxy) and 1730 cm.<sup>-1</sup> ( $\delta$ -lactone C=O);  $\lambda_{infl}$  2230 (log  $\epsilon$  3·887) and  $\lambda_{max}$  2830 Å (log  $\epsilon$  3·351).

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