810. *Syntheses in the Colchicine Series. Part I. Products from the Stobbe Condensation of Methyl γ-(2 : 3 : 4-Trimethoxybenzoyl)butyrate with Dimethyl Succinate.*

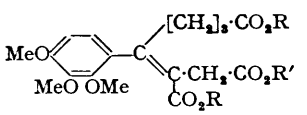
By H. J. E. Loewenthal.

The half-ester from the condensation mentioned in the title was demethylated and cyclised on being treated with strong acids, yielding a coumarin derivative. Total remethylation and subsequent Dieckmann cyclisation then led predominantly to a ketone containing a seven-membered ring fused to a coumarin ring, as well as to a derivative of 3-(2 : 3 : 4-trimethoxyphenyl)*cyclo*hex-2-enone. The former product was transformed into derivatives of 4-(2 : 3 : 4-trimethoxyphenyl)*cyclo*hept-3-enone.

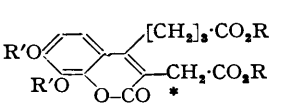
Colchicine is now believed to be represented by (I), in which ring B is seven-membered (Cook *et al.*, *J.*, 1947, 746; 1951, 1397; Rapoport *et al.*, *J. Amer. Chem. Soc.*, 1951, **73**, 1414) and ring C is that of a tropolone ether (Dewar, *Nature*, 1945, **155**, 141; Tarbell *et al.*, *J. Amer. Chem. Soc.*, 1948, **70**, 1669; 1950, **72**, 240), although final proof is lacking. The present paper describes experiments designed to yield the A–C system, and specifically to yield a 2′ : 3′ : 4′-trimethoxyphenyl*cyclo*heptane in which the seven-membered ring contains functional groups suitable both for transformation into a tropolone system and for use in construction of ring B.

Condensation of methyl γ-(2 : 3 : 4-trimethoxybenzoyl)butyrate with dimethyl succinate in the presence of potassium *tert.*-butoxide in *tert.*-butanol at room temperature gave, in excellent yield, an oily half-ester (presumably II; R = Me, R′ = H), which by hydrolysis gave a crystalline triacid in 57% overall yield. These structures are based on analogy with similar products from the same condensation with the corresponding unsubstituted and 4′-methoxy-substituted keto-esters (Johnson, Jones, and Schneider, *ibid.*, 1950, **72**, 2395; Turner, *ibid.*, 1951, **73**, 1284), but confirmation of the position of the double bond by oxidation could not be effected in the present case. When the crude half-ester was treated

(I)



(II)



(III)

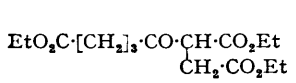
with concentrated mineral acids under conditions which, in similar compounds, lead to the removal of the tertiary alkoxycarbonyl group (cf. Johnson *et al.*, *loc. cit.*), a high-melting phenolic acid was obtained in varying yield. This was identified as a coumarin derivative (III; R = R′ = H), produced, apparently, by demethylation and hydrolysis, followed by lactonisation between the resulting 2′-hydroxyl and the tertiary carboxyl group.

Much study was devoted to improving the yield of this coumarin, and the conditions finally adopted include irradiation by ultra-violet light. This may possibly facilitate a total conversion of the half-ester, which presumably is a mixture of the *cis*- and the *trans*-isomer, into the *cis*-form (*cis* refers to the long carbon chain; cf. *J.*, 1952, 5059).

Unsuccessful attempts were made to synthesise this intermediate unambiguously, by the von Pechmann condensation of pyrogallol or of its dimethyl ether with ethyl 3-oxohexane-1 : 2 : 6-tricarboxylate (IV), which was prepared from 2-oxopentane-1 : 5-dicarboxylate (Hunter and Hagg, *ibid.*, 1949, **71**, 1922) by means of ethyl bromoacetate. However, it is known that α-substitution in β-keto-esters generally inhibits to some extent their reaction with phenols (Elderfield, "Heterocyclic Compounds," Interscience Publ., New York, 1951, Vol. II, p. 184), and pyrogallol is generally less suitable than other phenols for this reaction (Canter, Robertson, and Martin, *J.*, 1931, 1877). In fact, the unsubstituted 2-oxopentane-1 : 5-dicarboxylate condensed smoothly with pyrogallol, to give a coumarin

derivative which was converted into 7 : 8-dimethoxy-4-3′-carboxypropylcoumarin (V; R = H).

Total methylation of the intermediate (III; R = Me, R′ = H) with potassium carbonate and methyl sulphate in acetone gave, in excellent yield, the dimethyl ester (III; R = R′ = Me), whose coumarin structure was confirmed by the similarity of its



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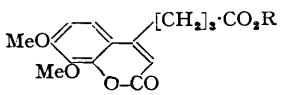

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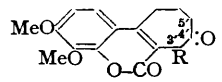
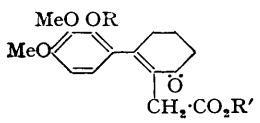
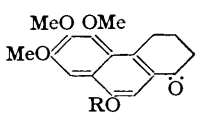


(VI)

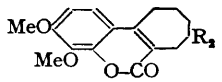
absorption spectrum to that of the monomethyl ester (V; R = Me). Dieckmann cyclisation of the diester, with sodium hydride in benzene, led to two products. One, formed in larger amount, was the *cyclo*hepteno-compound (VI; R = CO_2Me), in which the coumarin ring was intact. Its formulation as the 3′- rather than the 5′-methoxycarbonyl compound is put forward on the assumption that in (III; R = Me) the methylene group indicated by an asterisk is likely to be activated preferentially in view of its proximity to the double bond in the coumarin ring (for a similar case, see Belleau, *J. Amer. Chem. Soc.*, 1951, **73**, 5150). The second product of cyclisation was a phenolic keto-acid; apparently, the coumarin ring had been opened, and transesterification and the alternative ring-closure had led to a product which on acid hydrolysis gave, probably, (VII; R = R′ = H): methylation gave the trimethoxy-ester, whose formulation was confirmed by cyclisation to the phenol (VIII; R = H).



(VII)



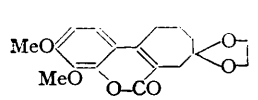
(VIII)



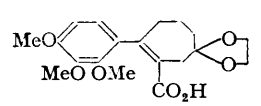
(IX)

When the Dieckmann cyclisation (of III; R = R′ = Me) was conducted with potassium *tert.*-butoxide in benzene (Johnson *et al.*, *ibid.*, 1953, **75**, 2275), the relative yield of (VII; R = R′ = H) was increased, probably owing to the appreciable solubility of the catalyst in the reaction medium.

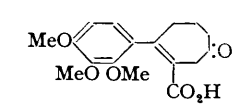
Acid hydrolysis of the keto-ester (VI; R = CO_2Me) gave a ketone, (? VI; R = H), whose exact structure is in doubt. Its 2 : 4-dinitrophenylhydrazone showed light absorption ($\lambda_{max.}$ 353 mμ, log ε 4·505) typical of that of a normal ketone (Braude and Jones, *J.*, 1945, 497), but the infra-red spectrum of the ketone itself (bands at 1602, 1650, and 1730 cm.$^{-1}$ in carbon tetrachloride, and additionally at 1713 cm.$^{-1}$ in Nujol) indicates the presence of an αβ-unsaturated ketone grouping, in addition to the coumarin ring-carbonyl group (the author is indebted to Dr. G. D. Meakins of the University of Manchester for these results), suggesting that the coumarin double bond has shifted further within the seven-membered ring (cf. Scott and Tarbell, *loc. cit.*). The presence of the *cyclo*hepteno-ring in the ketone was confirmed by hydrogenolysis of the mercaptal (IX; R = SEt) to 7 : 8-dimethoxy*cyclo*hepteno(1′ : 2′-3 : 4)coumarin (IX; R = H), whose melting point was not depressed on admixture with an authentic specimen (Boekelheide and Pennington, *J. Amer. Chem. Soc.*, 1952, **74**, 1558) kindly provided by Professor V. Boekelheide.



(X)



(XI)



(XII)

When the coumarin ring in the ketone (VI; R = H) was opened by methylation with sodium hydroxide and methyl sulphate, an oily keto-acid resulted, but the derived ketal (X), under special conditions, gave excellent yields of the crystalline ketal acid (XI), readily hydrolysed in acid to the keto-acid (XII).

2-*p*-Methoxyphenyl-6-oxo*cyclo*hexenylacetic acid, an analogue of (VII; R = Me, R′ = H), was obtained by Turner (*loc. cit.*) by Stobbe condensation with methyl γ-*p*-anisoylbutyrate under forced conditions. His formulation, with the double bond unconjugated to the carbonyl group, was reached because this acid and compounds related to it showed light absorption different from that to be expected in compounds containing the *p*-OMe·C_6H_4·C:C·CO· chromophore (as in anisylideneacetone), although it was in accord with that found for simple 3-oxo-2-phenyl*cyclo*hexenyl derivatives (Wilds, Beck, Close, Djerassi, Johnson, Johnson, and Shunk, *ibid.*, 1947, **69**, 1985). The light absorption of the methyl ester (VII; R = R′ = Me) is similar to that of Turner's compounds, but in this case the presence of an αβ-unsaturated ketone grouping is strongly indicated by the absorption of the 2 : 4-dinitrophenylhydrazone ($\lambda_{max.}$ 388 mμ, log ε 4·50) (Braude and Jones, *loc. cit.*).

In the *cyclo*hepteno-keto-acid (XII) the position is less clear. Here the tendency for the double bond to be in conjugation with either the aryl or the carbonyl group might be expected to be of roughly the same order. The experimental evidence obtained so far suggests that normally the structure is as shown, but that under acid conditions the double bond shifts towards conjugation with the carbonyl group.

Experimental

Microanalyses by Mr. J. M. L. Cameron and Miss M. W. Christie.

Methyl γ-(2 : 3 : 4-Trimethoxybenzoyl)butyrate.—To a suspension of coarsely ground aluminium chloride (158 g.) in tetrachloroethane (300 c.c.) at −30°, pyrogallol trimethyl ether (100 g.) was added, and the mixture was stirred at −10° for 0·5 hr. γ-Ethoxycarbonylbutyryl chloride (100 g.) was then added dropwise at −1° during 0·5 hr. The mixture was stirred at 4° for 3 hr., then at room temperature overnight. It was decomposed with ice and hydrochloric acid, the lower layer was separated and washed several times with water, and the solvent removed in steam. The remaining oil, which gave a positive reaction with ferric chloride, was washed with water by decantation and mixed with methyl sulphate (171 c.c.) and ethanol (150 c.c.). A solution of sodium hydroxide (74 g. in 150 c.c. of water) was then added at <30° with stirring under nitrogen during 1 hr. More sodium hydroxide was then added and the mixture was refluxed to hydrolyse the ester formed. The mixture was acidified, the oily γ-(2 : 3 : 4-trimethoxybenzoyl)butyric acid was taken up in benzene, the solution dried, and the solvent removed *in vacuo*. Recrystallised from hexane, the acid had m. p. 74—76° (Haworth, Moore, and Pauson, *J.*, 1948, 1045, report m. p. 73—75°). The *semicarbazone* formed needles (from dilute ethanol), m. p. 161—162° (Found: N, 12·3. $C_{15}H_{21}O_6N_3$ requires N, 12·4%).

The above crude acid was esterified by Clinton and Laskovsky's method (*J. Amer. Chem. Soc.*, 1948, **70**, 3136), with ethylene dichloride (160 c.c.), methanol (75 c.c.), and sulphuric acid (3 c.c.). After 6 hrs.' heating under reflux the mixture was washed with water and dilute sodium carbonate solution, the lower layer was dried ($MgSO_4$), and the solvent removed. The residue distilled at 180—185°/0·4 mm., to give the *methyl ester* (139 g.), which crystallised on cooling. Recrystallisation from light petroleum (b. p. 60—80°) gave prisms, m. p. 60—61° (Found: C, 60·9; H, 6·9. $C_{15}H_{20}O_6$ requires C, 60·8; H, 6·8%). The 2 : 4-*dinitrophenylhydrazone* formed orange needles, m. p. 122°, from methanol (Found: N, 12·3. $C_{21}H_{24}O_9N_4$ requires N, 11·8%). 5·5 G. of the acid were recovered.

Use of glutaric anhydride (Horning and Koo, *ibid.*, 1951, **73**, 5830), instead of the ester acid chloride, gave a lower yield and involved an extremely viscous reaction mixture.

Stobbe Condensation with Dimethyl Succinate.—To a solution of potassium (23·5 g.) in dry *tert.*-butanol (500 c.c.), dimethyl succinate (128 g.) was added with stirring under nitrogen, followed by the above keto-ester (128 g.), finely divided, at room temperature. The mixture was stirred until all the solid had dissolved (1 hr.), and then left at 20° overnight (cf. Johnson, Jones, and Schneider, *loc. cit.*). It was then acidified to pH 5; water (500 c.c.) was added, and most of the *tert.*-butanol removed *in vacuo*. The remaining oil was taken up in ether–benzene, the solution extracted with N-ammonia, and the extract adjusted to pH 8, washed with benzene, and acidified with hydrochloric acid. The half-ester (II; R = Me, R′ = H), which separated, was taken up in ether and dried, and the solvent removed, finally *in vacuo* at 100°. The remaining light brown oil weighed 164 g. (93%) (Found: equiv., 355—390. Calc. for $C_{20}H_{26}O_9$: equiv., 410).

Hydrolysis to 3-(2 : 3 : 4-*Trimethoxyphenyl*)*hex*-2-*ene*-1 : 2 : 6-*tricarboxylic Acid* (II; R = R′ = H).—The oily half-ester (9·7 g.) was refluxed for 2 hr. with a solution of hydrated barium hydroxide (15 g.) in ethanol (30 c.c.) and water (120 c.c.). The suspension of barium salts was acidified with hydrochloric acid and the clear solution extracted several times with chloroform. The dried extracts were evaporated and the residue again dissolved in chloroform (20 c.c.). To the hot solution benzene (50 c.c.) was added, and the solution was distilled until most of the chloroform had been displaced. On cooling and scratching, the *triacid* (5·1 g.) separated. Recrystallisation from chloroform–benzene gave needles, which after being dried *in vacuo*, first at room temperature and then at 100°, had m. p. 142—144° (decomp.). The acid was appreciably soluble in water (Found: C, 56·7; H, 5·55. $C_{18}H_{22}O_9$ requires C, 56·55; H, 5·8%). Hydrolysis with 2N-sodium hydroxide at 100° for 0·75 hr. gave similar results.

Attempts to oxidise the half-ester (by ozonisation; Johnson and Stromberg, *ibid.*, 1950, **72**, 509) or the triacid (with potassium permanganate in acetone or in alkaline solution) gave oils which showed carbonyl reactions; but neither γ-(2 : 3 : 4-trimethoxybenzoyl)butyric acid nor any of its derivatives could be isolated.

7 : 8-*Dimethoxy*-3-*methoxycarbonylmethyl*-4-3′-*methoxycarbonylpropylcoumarin* (III; R = R′ = Me).—The crude half-ester (52 g.) was added to acetic acid containing 50% hydrogen bromide (150 c.c.) in a 250-ml. quartz flask, and kept for 10—15 days in bright daylight, with occasional irradiation by a mercury-vapour lamp. During this time most of the product crystallised out. Water (150 c.c.) was then added (evolution of methyl bromide), and the product was filtered off, washed thoroughly with water, and dried at 100°. The yield was 28·5 g. (69·7%), reckoned as (III).

The above conditions were found to be the best for this reaction. When a Pyrex flask was used, the conditions otherwise being identical, the yield fell to 49%. When the half-ester (10·9 g.) was refluxed with acetic acid (80 c.c.), water (20 c.c.), and aqueous hydrogen bromide (*d* 1·42; 85 c.c.) for 18 hr., the yield was 35%, and with hydriodic acid (55%) at 100° for 8 hr. it was 39%.

The above crude reaction product (31·1 g.) was refluxed with vigorous stirring in acetone (500 c.c.) with dry potassium carbonate (115 g.) and methyl sulphate (60 c.c.) for 4 hr. Most of the acetone was then distilled off, and the residue poured into water, whereupon the *dimethyl ester* (III; R = R′ = Me) separated (32·5 g., 62·5% overall yield from the half-ester), m. p. 114—115°. It crystallised from methanol (charcoal), as needles, m. p. 115—116° (Found: C, 60·35; H, 5·4; OMe, 34. $C_{19}H_{22}O_8$ requires C, 60·3; H, 5·85; 4OMe 33%). Light absorption: $\lambda_{max.}$ 320 mμ (log ε 4·23), $\lambda_{min.}$ 269 mμ (log ε 3·75), in EtOH (see Fig. 1). This ester was hydrolysed by boiling 10% sodium hydroxide solution for 3 hr. On acidification, 7 : 8-*dimethoxy*-3-*carboxymethyl*-4-3′-*carboxypropylcoumarin* (III; R = H, R′ = Me) separated slowly; it formed needles, m. p. 240° (decomp.), from dilute acetic acid (Found: C, 58·05; H, 5·2. $C_{17}H_{18}O_8$ requires C, 58·25; H, 5·2%).

Ethyl 2-*Oxopentane*-1 : 5-*dicarboxylate*.—This was prepared by the action of γ-ethoxycarbonylbutyryl chloride on ethoxymagnesiomalonic ester (Hunter and Hagg, *loc. cit.*), in 33% yield, acetic acid containing 0·22% sulphuric acid (Bowman, *J.*, 1950, 322) being used to effect partial de-ethoxycarbonylation of the intermediate product. Bowman and Fordham's method (*J.*, 1951, 2758), employing benzyl ethyl malonate, was also used; here the yield was slightly higher, but the method was much more cumbersome. The keto-ester distilled at 99—105°/0·25 mm. and had n_D^{17} 1·4477 (Birkofer and Storch, *Chem. Ber.*, 1953, **86**, 32, report n_D^{24} 1·4511) (Found: C, 57·3; H, 8·0. Calc. for $C_{11}H_{18}O_5$: C, 57·4; H, 7·9%). The derived *phenylpyrazolone* formed pale yellow needles (from dilute methanol), m. p. 240° (decomp.) (Found: N, 10·4. $C_{15}H_{18}O_3N_2$ requires N, 10·2%).

Ethyl 3-*Oxohexane*-1 : 2 : 6-*tricarboxylate* (IV).—The above-mentioned keto-ester (8·93 g.) was added to a suspension of sodium hydride (1·03 g.) in dry ether (50 c.c.). After a clear solution of the sodium enol derivative had been obtained, ethyl bromoacetate (7·77 g.) was added with stirring, and the resultant suspension refluxed for 3 hr. The mixture was added to dilute sulphuric acid and ice; the ethereal layer was washed with water and dried, and the ether removed. The residue was fractionated *in vacuo*, to give the *keto-ester* (IV) (7·28 g.), b. p. 135—139°/0·2 mm., n_D^{17} 1·4518 (Found: C, 56·8; H, 7·2. $C_{15}H_{24}O_7$ requires C, 56·9; H, 7·6%). It gave a greenish-purple colour with ferric chloride in methanol. No phenylpyrazolone could be prepared from it.

Attempts to condense this keto-ester with pyrogallol or its 1 : 2-dimethyl ether were unsuccessful.

Acid hydrolysis gave γ-oxosuberic acid, needles (from ethyl acetate–benzene), m. p. 131—

132° (Found: C, 51·2; H, 6·5. Calc. for $C_8H_{12}O_5$: C, 51·1; H, 6·4%). Leonard and Goode (*J. Amer. Chem. Soc.*, 1950, **72**, 5404) report m. p. 130—132°.

7 : 8-*Dimethoxy-4-3'-carboxypropylcoumarin.*—Ethyl 2-oxopentane-1 : 5-dicarboxylate (4·67 g.) was mixed with finely divided pyrogallol (2·77 g.), and sulphuric acid (10 c.c.) was added with cooling. The deep red mixture was kept at 0° for 2 days and was then poured into water. The solid was filtered off, washed with water, and dried. It was then mixed with dry potassium carbonate (5·8 g.), methyl sulphate (3·6 c.c.), and acetone (40 c.c.), and the suspension was refluxed with stirring for 3 hr. The product obtained by pouring the whole into water was hydrolysed by boiling 10% sodium hydroxide solution (20 c.c.) for 2 hr. The cooled solution was adjusted to pH 8, filtered, and acidified, to give the *acid* (V; R = H) (1·75 g., 30%), needles (from water), m. p. 167° (Found: C, 61·75; H, 5·75. $C_{15}H_{16}O_6$ requires C, 61·65; H, 5·5%). The *methyl ester*, prepared in methanol–sulphuric acid, crystallised from dilute methanol in needles, m. p. 101° (Found: C, 62·7; H, 5·9. $C_{16}H_{18}O_6$ requires C, 62·8; H, 5·95%). Light absorption: $\lambda_{max.}$ 317 mμ (log ε 4·16); $\lambda_{min.}$ 265 mμ (log ε 3·75), in EtOH (see Fig. 1).

FIG. 1.

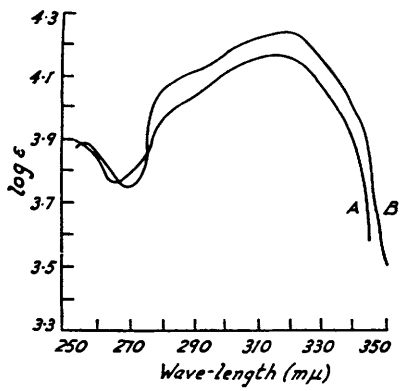


FIG. 2.

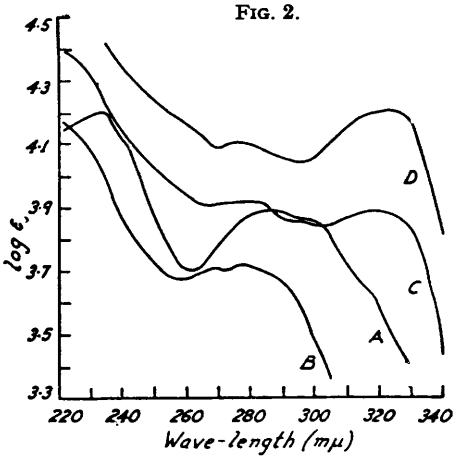


FIG. 1. *A*, 7 : 8-*Dimethoxy-4-3'-methoxycarbonylpropylcoumarin in ethanol.*
B, 7 : 8-*Dimethoxy-3-methoxycarbonylmethyl-4-3'-methoxycarbonylpropylcoumarin in ethanol.*

FIG. 2. *A*, *Methyl* 6-*oxo*-2-(2 : 3 : 4-*trimethoxyphenyl*)cyclo*hex*-1-*enylacetate in ethanol.*
B—D, *Methyl* 6 : 6-*ethylenedioxy*-2-(2 : 3 : 4-*trimethoxyphenyl*)cyclo*hept*-1-*enecarboxylic acid* (*B*) *in ethanol*, (*C*) *in ethanol containing* ca. 2% *of* HCl, *after* 1 *day, and* (*D*) *as* (*C*) *but after* 3 *weeks.*

Dieckmann Cyclisation of (III; R = R' = Me).—(a) *With sodium hydride.* The dimethyl ester (26·5 g.), sodium hydride (4·1 g.), and dry benzene (250 c.c.) were refluxed under nitrogen with stirring until hydrogen evolution had ceased (9 hr.). Excess of catalyst was destroyed by methanol, the solution cooled in ice, and ice-cold water (300 c.c.) added. The aqueous layer was washed with ether and neutralised to pH 8 by addition of solid carbon dioxide. The precipitated 7 : 8-*dimethoxy-3'-methoxycarbonyl-4'-oxo*cyclo*hepteno*(2' : 1'-3 : 4)*coumarin* (VI; R = CO_2Me) was filtered off and washed with water. Crystallisation from methanol gave fluorescent needles, m. p. 190° (decomp.), which gave a deep purple colour with ferric chloride in methanol (Found: C, 62·3; H, 5·3; OMe 27·5. $C_{18}H_{18}O_7$ requires C, 62·4; H, 5·2; 3OMe 27%). The crude keto-ester was hydrolysed by refluxing it for 2 hr. with acetic acid (100 c.c.), hydrochloric acid (50 c.c.), and water (20 c.c.). The solution was cooled, and water (200 c.c.) was added. This precipitated 7 : 8-*dimethoxy-4'-oxo*cyclo*hepteno*(2' : 1'-3 : 4)*coumarin* (VI; R = H) as yellow needles (9·3 g.), which crystallised from benzene or ethanol as needles or leaflets, m. p. 190° (Found: C, 66·8; H, 5·7. $C_{16}H_{16}O_5$ requires C, 66·7; H, 5·6%). The 2 : 4-*dinitrophenylhydrazone* formed saffron-yellow needles (from chloroform–butanol), m. p. 229—230° (decomp.) (Found: C, 56·2; H, 4·4; N, 11·3. $C_{22}H_{20}O_8N_4$ requires C, 56·4; H, 4·3; N, 11·95%). Light absorption: $\lambda_{max.}$ 353 mμ (log ε 4·505) in $CHCl_3$.

The filtrate (pH 8) from the above keto-ester was strongly acidified with hydrochloric acid, and the suspension was boiled for 1 hr. After cooling, the oil was extracted with ethyl acetate, and the extract washed several times with 5% sodium carbonate solution. Acidification of the washings gave a dark oil which slowly solidified (4·1 g.). This gave a colour with ferric chloride and a precipitate with Brady's reagent (acid A, probably VII; R = R' = H). The neutral

residue, after removal of the ethyl acetate, yielded another 0·3 g. of the ketone (VI; R = H), making the total yield of this 48%.

(b) *With potassium* tert.-*butoxide.* Potassium (1·37 g.) was dissolved in dry *tert.*-butanol (30 c.c.) and most of the excess of alcohol was removed *in vacuo*; the last traces were then distilled off as the azeotrope with dry benzene (b. p. 73—75°) through a Widmer column. The diester (III; R = R′ = Me) (10·5 g.) in dry benzene (100 c.c.) was then added under nitrogen, and the mixture was refluxed for 4 hr., during which the catalyst dissolved to give way to a fine suspension of potassio-derivatives. The mixture was then worked up as above; the yield of the ketone (VI; R = H) was 2·9 g. (36%), that of the crude acid A 2·6 g.

6-*Oxo*-2-(2 : 3 : 4-*trimethoxyphenyl*)cyclo*hex*-1-*enylacetic Acid* (VII; R = Me, R′ = H).—The above acid A (1·5 g.) was refluxed with dry potassium carbonate (2·8 g.) and methyl sulphate (1·6 c.c.) in acetone (12 c.c.) with stirring for 3 hr. The mixture was poured into water and the dark oil extracted with benzene. The washed and dried extract was passed through a column of activated alumina, which retained most of the dark impurities. The benzene eluate was concentrated; the residue crystallised from light petroleum, to give the *methyl ester* (VII; R = R′ = Me), which from light petroleum (b. p. 60—80°) formed needles, m. p. 90° (Found: C, 64·55; H, 6·7. $C_{18}H_{22}O_6$ requires C, 64·7; H, 6·65%). Light absorption: $\lambda_{max.}$ 233 (log ε 4·195) and 287 mμ (log ε 3·89); $\lambda_{min.}$ 260 mμ (log ε 3·71) in EtOH (see Fig. 2). The 2 : 4-*dinitrophenylhydrazone*, red leaflets (from ethanol), had m. p. 174—175° (Found: C, 56·25; H, 5·6; N, 10·5. $C_{24}H_{26}O_9N_4$ requires C, 56·0; H, 5·1; N, 10·9%). Light absorption: $\lambda_{max.}$ 388 mμ (log ε 4·50) in $CHCl_3$.

Alkaline hydrolysis of this ester gave the free *acid* (VII; R = Me, R′ = H) which crystallised from ligroin (b. p. 100—120°) in fine needles, m. p. 113—116° (not sharp) (Found: C, 64·0; H, 6·5. $C_{17}H_{20}O_6$ requires C, 63·75; H, 6·3%), and from carbon tetrachloride as needles, m. p. 107° (decomp.), containing half a molecule of solvent, which was not removed *in vacuo* at 80° (Found: C, 53·2; H, 5·05; Cl, 17·95. $C_{17}H_{20}O_6$,0·5CCl_4 requires C, 52·8; H, 5·05; Cl, 17·85%). The *semicarbazone*, leaflets (from dilute ethanol), had m. p. 212—214° (decomp.) (Found: N, 10·95. $C_{18}H_{23}O_6N_3$ requires N, 11·15%). The action of diazomethane on this acid in ether regenerated the methyl ester, m. p. and mixed m. p. 90°.

1 : 2 : 3 : 4-*Tetrahydro*-9-*hydroxy*-5 : 6 : 7-*trimethoxy*-1-*oxophenanthrene*.—The above acid (0·4 g.) was added to an excess of anhydrous hydrogen fluoride, which was then allowed to evaporate slowly in an open vessel overnight. Sodium acetate solution was added, and the solid collected and dissolved in warm sodium hydroxide solution. Addition of solid carbon dioxide precipitated the *phenol* (VIII; R = H) (0·3 g.), which was purified by passage of its benzene solution through activated alumina, followed by elution with chloroform–methanol. Crystallisation from benzene–ligroin gave yellow needles, m. p. 211—212° (Found: C, 67·45; H, 5·65. $C_{17}H_{18}O_5$ requires C, 67·55; H, 6·0%). Methylation with methyl sulphate and alkali gave the *methyl ether* (VIII; R = Me), which after sublimation at 180°/0·2 mm. and recrystallisation from methanol, formed needles, m. p. 131—132° (Found: C, 68·1; H, 6·15; OMe, 38. $C_{18}H_{20}O_5$ requires C, 68·3; H, 6·35; 4OMe 39%).

7 : 8-*Dimethoxy*cyclo*hepteno*(2′ : 1′-3 : 4)*coumarin* (IX; R = H).—The ketone (VI; R = H) (0·35 g.) was added to a solution of zinc chloride (0·7 g.; fused *in vacuo*) in ethanethiol (12 c.c.), and anhydrous sodium sulphate (0·7 g.) was added. The mixture was left at 0° overnight and at room temperature for 6 hr. The excess of thiol was removed *in vacuo*, sodium chloride solution and ether were added, and the ethereal layer was washed several times with sodium hydroxide solution and water, and dried. Removal of the ether and trituration of the residue with light petroleum gave 7 : 8-*dimethoxy*-4′ : 4′-*bisethylthio*cyclo*hepteno*(2′ : 1′-3 : 4)-*coumarin* (IX; R = SEt) (0·30 g.), needles (from dilute methanol), m. p. 127° (Found: C, 61·2; H, 6·95; S, 16·4. $C_{20}H_{26}O_4S_2$ requires C, 61·0; H, 6·65; S, 16·25%).

This (0·17 g.) was refluxed in absolute ethanol (20 c.c.) with Raney nickel (1·5 g.) for 5 hr. The mixture was filtered and the ethanol removed. The remaining oil crystallised when rubbed with light petroleum. The crystals (*ca.* 0·08 g.) were sublimed at 180°/0·3 mm., and the sublimate (m. p. 128—132°) was recrystallised several times from dilute ethanol and from light petroleum (b. p. 80—100°), to give lozenges, m. p. 133—135°. The mixed m. p. with an authentic sample of the coumarin (IX; R = H) of m. p. 135·5° (Boekelheide and Pennington, *loc. cit.*) was 134—135°.

7 : 8-*Dimethoxy*-4′ : 4′-*ethylenedioxy*cyclo*hepteno*(2′ : 1′-3 : 4)*coumarin*.—The ketone (VI; R = H) (8·0 g.) was refluxed in dry benzene (100 c.c.) with ethylene glycol (20 c.c.) in the presence of toluene-*p*-sulphonic acid (0·5 g.) under an azeotropic water separator for 4 hr. More benzene was added; the mixture was neutralised by addition of sodium methoxide and

poured into warm sodium chloride solution. The benzene layer was quickly dried ($MgSO_4$) and the solution concentrated. Addition of ligroin precipitated the *ketal* (X) (8·27 g.), which crystallised from ethanol or benzene in leaflets, m. p. 175—176° (Found: C, 65·5; H, 6·15. $C_{18}H_{20}O_6$ requires C, 65·1; H, 6·05%).

Opening of the Coumarin Ring.—The above ketal (8·0 g.) was suspended in boiling ethanol (18 c.c.). To this was added, at the b. p., 15% sodium hydroxide solution (35·0 c.c.), whereupon a clear light red solution resulted. After 10 min. methyl sulphate (5·6 c.c.) was added dropwise during 0·5 hr. The mixture was refluxed for a total of 8 hr., during which another 2 such additions of alkali and methyl sulphate were made. The alcohol was then distilled off and the remaining solution diluted with water to 200 c.c. and adjusted with solid carbon dioxide to pH 8. The unchanged ketal (2·17 g.) was filtered off, and the filtrate acidified to pH 5 at 0° with stirring under benzene. The benzene layer was washed thoroughly with water and dried, and the solvent removed. The remaining oil crystallised immediately with ether, to give 6 : 6-*ethylenedioxy*-2-(2 : 3 : 4-*trimethoxyphenyl*)cyclo*hept*-1-*enecarboxylic acid* (XI) (5·82 g.), which crystallised from benzene–ligroin in needles, m. p. 145—146° [Found: C, 62·7; H, 6·7; microhydrogenation (Pd in acetic acid), 0·98 H_2. $C_{19}H_{24}O_7$ requires C, 62·6; H, 6·65%]. The *methyl ester*, prepared by ethereal diazomethane, was purified by passage of its benzene solution through activated alumina, followed by crystallisation from light petroleum (b. p. 40—60°), to give needles, m. p. 80° (Found: C, 63·8; H, 7·05. $C_{20}H_{26}O_7$ requires C, 63·5; H, 6·95%). Light absorption: see Fig. 2.

Ring opening of the ketone (VI; R = H) in the above manner gave an oily keto-acid in practically quantitative yield, but this could not be crystallised or otherwise characterised. It (2·5 g.) was therefore converted into the ketal as described above, and the oily ester obtained was hydrolysed with 10% sodium hydroxide solution. Acidification as above under benzene yielded an oil which on trituration with ether gave the above ketal-acid (0·95 g.), m. p. 142—145°.

The ketal-acid (0·5 g.) in methanol (10 c.c.) and water (4 c.c.) containing hydrochloric acid (0·5 c.c.) was gently refluxed for 3 hr. The solution was concentrated *in vacuo* below 40°. The oil obtained crystallised on trituration with a little ether, to give 2-(2 : 3 : 4-*trimethoxyphenyl*)-6-*oxo*cyclo*hept*-1-*enecarboxylic acid* (XII) (0·31 g.), which separated from benzene–light petroleum (b. p. 80—100°) in needles, m. p. 115° (Found: C, 63·8; H, 6·2. $C_{17}H_{20}O_6$ requires C, 63·75; H, 6·3%). The *semicarbazone*, needles (from dilute methanol), had m. p. 189° (decomp.) (Found: N, 11·45. $C_{18}H_{23}O_6N_3$ requires N, 11·15%).

When more strongly acidic conditions were used for the cleavage of the ketal group, the product was an oil which crystallised with great difficulty, but when this was taken up in benzene, extracted with sodium carbonate solution, and re-precipitated with acetic acid, it crystallised immediately.

The action of diazomethane on this keto-acid gave an oil, which gave a gum with Brady's reagent. Chromatography of the gum in chloroform solution on alumina showed the presence of two products (red and yellow), but neither could be obtained crystalline. Esterification of the ketal-acid with methanolic hydrogen chloride at room temperature gave a similar oil.

A solution (2·0 c.c.) of the ester of (XI) in ethanol, containing $3·16 \times 10^{-4}$ mole/l., was diluted to 25·0 c.c. with ethanol containing 0·5 c.c. of hydrochloric acid. The absorption spectrum of this solution after 1 day ($\lambda_{max.}$ 315 mμ; log ε 3·89) and after 3 weeks ($\lambda_{max.}$ 325 mμ, log ε 4·205) is shown in Fig. 2.

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