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SYNTHESES OF SOME TETRALONES RELATED TO TETRACYCLINES

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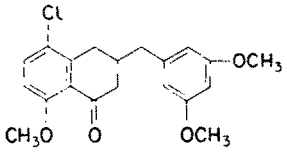
Abstract—Syntheses of 5-chloro-8-methoxy-1-tetralone (XIV), 6,8-dimethoxy-1-tetralone (XIX), 2-carbethoxy-6,8-dimethoxy-1-tetralone (VI), 3-(2′-chloro-5′-methoxybenzyl)-6,8-dimethoxy-1-tetralone (III) and 2-carbethoxy-3-(2′-chloro-5′-methoxybenzyl)-6,8-dimethoxy-1-tetralone (IV) are reported. The mode of cyclization with polyphosphoric acid of I and related compounds is described.

As a preliminary to our work[2] of building rings (B) and (C) of tetracyclines by cyclizing compounds, such as XXV (R_2 = H or C_2H_5), we investigated the cyclization of β-(2-chloro-5-methoxybenzyl), β-(3′,5′-dimethoxybenzyl)-propionic acid (I). Depending on whether the cyclization takes place on ring (A) or (D), or on both, either of the tetralones II and III or both could be formed. Actually only one tetralone was obtained on cyclization with polyphosphoric acid (PPA). A comparison (*vide* Table 1) of its UV absorption spectra with those of XIV and XIX, specially synthesized for the purpose, showed it to be III, indicating cyclization on ring (A). This preferential cyclization on ring (A) was confirmed by a study of XII, XVII, XXV (R_2 = C_2H_5) and IV. Compound XVII gave, on heating with PPA for 2 hr, the β-keto ester (VI). Under the same experimental conditions XII did not give VII. However, on prolonging the reaction time to 5 hr it yielded the tetralone (XIV). The malonic ester



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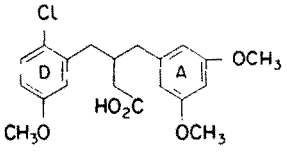

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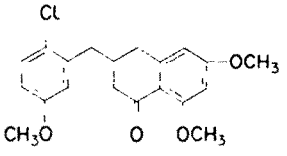

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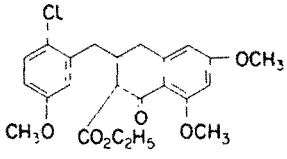

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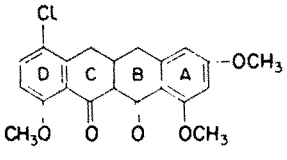

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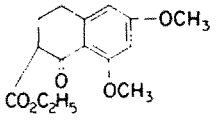

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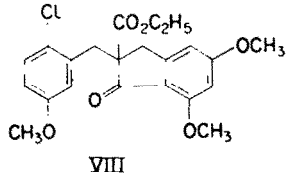

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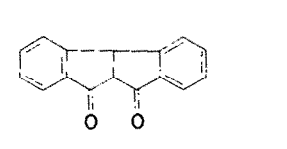
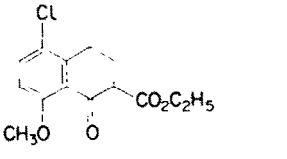


VII



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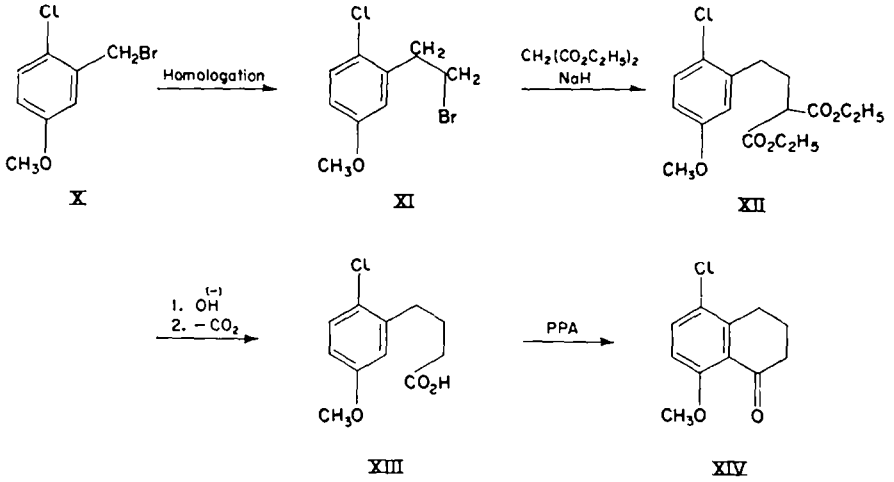
[2] A full account of the tetracycline work will be given later by Professor R. A. Raphael and coworkers.

(XXV, $R_2 = C_2H_5$) gave the β-keto ester (IV) which could not be cyclized further to the tetracycline (V). Surprisingly, XXI did not cyclize at all even after heating it with PPA for 5 hr. The failure of XXI to yield at least VIII cannot be attributed to the inability of esters of β-phenyl propionic acid to form indanones by the action of PPA, because Gilmore[3] has obtained indan-1-one in 93 % yield in this way from methyl β-phenylpropionate. The fact that monosubstituted malonic esters, like XVII and XXV ($R = C_2H_5$), undergo cyclization and the disubstituted malonic ester (XXI) does not do so probably suggests a steric effect in the case of XXI. That a monosubstituted malonic acid can lead to an indanone-system has been reported by Baker *et al.*[4] Thus IX was obtained by heating diphenylmethyl malonic acid, $(C_6H_5)_2$—CH—$CH(CO_2H)_2$.

We now describe the syntheses of the various compounds mentioned above. Their UV absorption spectra are recorded in Table 1. All the tetralones except IV and VI were characterized by their 2,4-dinitrophenylhydrazones.

5-*Chloro*-8-*methoxy*-1-*tetralone* (XIV) was obtained in an impure state by Huffman.[5] It has now been synthesized in the following manner:



2-Chloro-5-methoxybenzyl bromide (X) was homologated according to the following scheme in which R denotes a substituted phenyl group.

$$R{-}CH_2Br \xrightarrow{KCN} RCH_2CN \xrightarrow{(-)OH} RCH_2CO_2H \xrightarrow{CH_2N_2}$$

$$R{-}CH_2CO_2CH_3 \xrightarrow{LiAlH_4} RCH_2CH_2OH \xrightarrow{PBr_3} RCH_2CH_2Br$$

The resultant β-(2-chloro-5-methoxyphenyl)-ethyl bromide (XI) gave, on condensation with diethyl sodio-malonate, the ester (XII) from which γ-(2-chloro-5-methoxyphenyl)-butyric acid (XIII) was prepared by hydrolysis and subsequent decarboxylation. Compound XIII gave, on treatment with PPA, 5-chloro-8-methoxy-1-tetralone

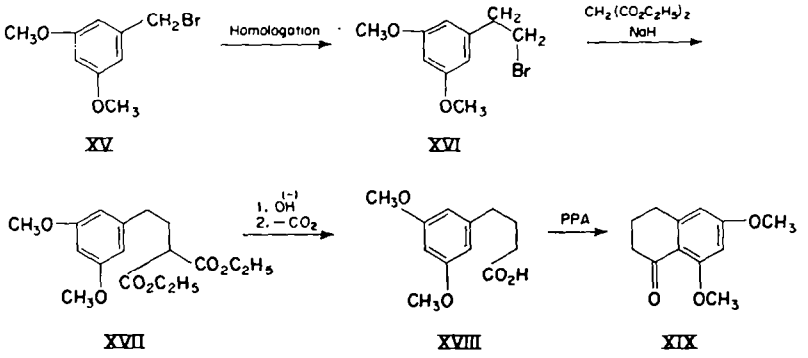
[3] R. C. Gilmore Jr., *J. Am. Chem. Soc.* **73**, 5879 (1951).

[4] W. Baker, J. F. W. McOmie, (Mrs.) S. D. Parfitt and D. A. M. Watkins, *J. Chem. Soc.* 4026 (1959).

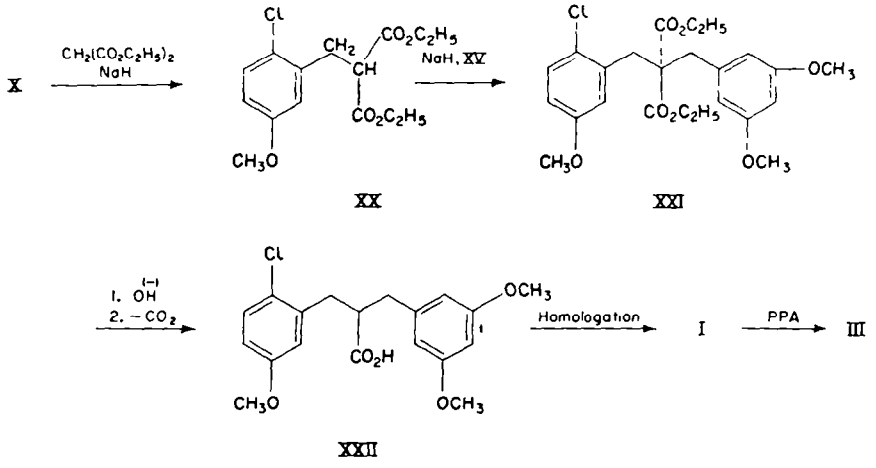
[5] J. W. Huffman, *J. Org. Chem.* **24**, 1759 (1959).

(XIV). As mentioned before, XIV was obtained directly from XII by prolonged heating with PPA.

6,8-*Dimethoxy*-1-*tetralone* (XIX) was synthesized in a similar manner from 3,5-dimethoxybenzyl bromide (XV). The scheme used is outlined below.



3-(2′-*Chloro*-5-*methoxybenzyl*)-6,8-*dimethoxy*-1-*tetralone* (III) was synthesized according to the following scheme:



2-Chloro-5-methoxybenzyl bromide (X) gave, on condensation with diethyl sodiomalonate, the known[6] malonic ester (XX) which yielded, upon further treatment with sodium hydride and 3,5-dimethoxybenzyl bromide (XV), the disubstituted malonic ester (XXI). The acid (XXII), obtained from XXI by hydrolysis and subsequent decarboxylation was homologated to I by the following general scheme in which R_1 stands for the rest of the molecule of acid (XXII):

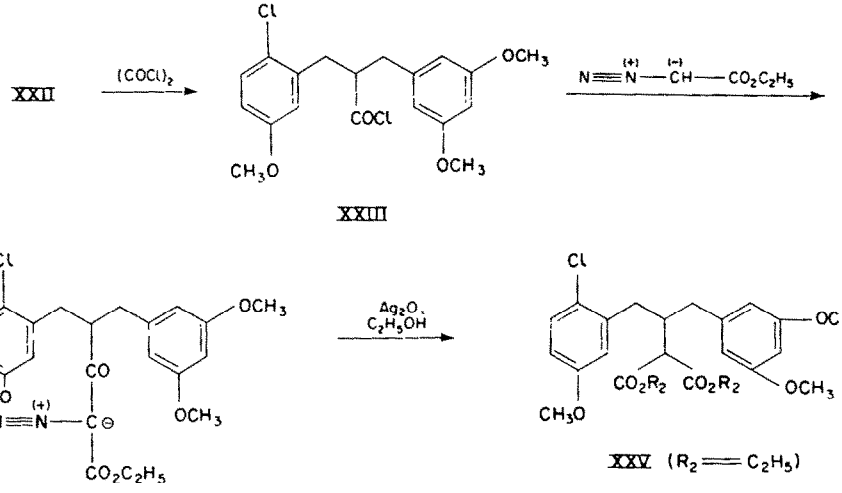
$$R_1CO_2H \xrightarrow{CH_2N_2} R_1CO_2CH_3 \xrightarrow{LiAlH_4} R_1CH_2OH \xrightarrow{PBr_3}$$

$$R_1CH_2Br \xrightarrow{KCN} R_1CH_2CN \xrightarrow{(-)OH} R_1CH_2CO_2H$$

[6] J. H. Boothe, A. S. Kende, T. L. Fields and R. G. Wilkinson, *J. Am. Chem. Soc.* **81**, 1006 (1959).

Homologation of XXII by the Arndt-Eistert method was first attempted but the product comprised a mixture of the unchanged acid and homologated material. The same difficulty was encountered during the syntheses of XIV and XIX.

2-*Carbethoxy*-3-(2′-*chloro*-5′-*methoxybenzyl*)-6,8-*dimethoxy*-1-*tetralone* (IV). As mentioned before, it was obtained by PPA-cyclization of XXV ($R_2 = C_2H_5$) which was prepared in the following way:



However, the product of cyclization consisted of a mixture of IV and III. Compound IV was, therefore, prepared in the pure state by condensing III with diethyl carbonate in presence of sodium hydride.

TABLE I

Compound	λ_{max} (mμ)	ε_{max}
XIV	224	20520
	254	6243
	324	3296
XIX	228	18350
	275	16610
	305	7180
III	226	30640
	273–75	18400
VI	229	14000
	276	13000
	310	6834
IV	227	33210
	276	22780

EXPERIMENTAL

All m.p.s are uncorrected and were determined on a Koffler block. The UV spectra refer to 95% ethanolic solution and were determined on a Unicam SP500 Spectrophotometer. The IR spectra refer to chloroform solution unless otherwise stated, and were determined on a Perkin-Elmer Infra

Cord. Pet ether refers to the fraction, b.p. 40–60°, and THF denotes anhydrous tetrahydrofuran. Anhydrous sodium sulphate was used for drying solutions. The elemental analyses are by Mr. J. M. L. Cameron and staff whom I thank.

2-Chloro-5-methoxybenzyl bromide (X) was prepared first by brominating 4-chloro-3-methyl anisole with N-bromosuccinimide.[6,7] The product, however, contained a large amount (ca. 28%) of nuclear brominated isomer.[8] In view of this difficulty X was prepared from *m*-methoxybenzoic acid.[9] Simultaneous chlorination and esterification[10] with methanol gave methyl 2-chloro-5-methoxybenzoate which was reduced with lithium aluminium hydride to 2-chloro-5-methoxybenzyl alcohol (XXVI). Treatment of XXVI with phosphorus tribromide gave X in excellent yield.

(a) *Methyl-2-chloro-5-methoxybenzoate.* Dry chlorine gas (90 g, ca. 1·2 molar equivalent) was *slowly* passed through a solution of *m*-methoxybenzoic acid (160 g) in absolute methanol (1800 ml) under cooling (ice-salt bath). The mixture was saturated with hydrogen chloride, then slowly allowed to attain the room temp at which it was finally kept for 90 hr. The residual thick oil (ca. 400 g) left after removal of volatile matter *in vacuo* on a steam-bath, was poured in ice (ca. 1000 g) and the organic matter extracted with ether (1500 ml). The neutral ether extract, obtained on washing with water (500 ml) and saturated sodium carbonate solution (200 ml), gave, on removal of the solvent, an oil (185·5 g) which yielded, upon fractional distillation, methyl-2-chloro-5methoxybenzoate (129 g). Yield, 61%, b.p. 108–110°/0·1 mm, $n_D^{24.5}$ 1·5456. On hydrolysis it gave 2-chloro-5-methoxybenzoic acid, m.p. 175°.

(b) *2-Chloro-5-methoxybenzyl alcohol* (XXVI). A solution of methyl 2-chloro-5-methoxybenzoate (115 g) in THF (75 ml) was added gradually to a mechanically stirred suspension of lithium aluminium hydride (14 g) in THF (500 ml) in 45 min and the mixture refluxed for 30 min. The excess hydride was destroyed with ethyl acetate (10 ml). After allowing it to stand overnight the mixture was cautiously poured in ice (500 g) and acidified with conc sulphuric acid (45 ml), the organic layer separated and the aqueous-acidic layer extracted with ether (2 × 700 ml). The two extracts were combined, washed successively with water, sodium carbonate solution and water, dried and solvents distilled off. The residue (94·4 g) gave on distillation a colorless oil (86·4 g), b.p. 106–108°/0·5 mm, which solidified on cooling. Its IR spectrum (film) showed it to contain traces of the unreduced ester which was removed by refluxing it with alkali. The product was redistilled, and the solidified distillate crystallized first from a mixture of ether–pet ether, and then from dil ethanol. Long shiny plates, m.p. 106–107° (Found: C, 55·25; H, 4·98. $C_8H_9ClO_2$ requires: C, 55·67; H, 5·22%).

(c) *Conversion of* XXVI *into* X. The above recrystallized product (25 g), dissolved in dry ether (600 ml), was refluxed with phosphorus tribromide (6·8 ml) for 2½ hr. The reaction-mixture was cooled and then poured in ice (200 g) and the ether layer separated and cautiously shaken with sodium carbonate solution and later with water. On drying and removal of ether an oily residue (28·36 g) was obtained. It gave on distillation a colorless liquid (27·35 g), b.p. 122–124°/1·5 mm, which solidified on cooling. Shiny plates from pet ether, m.p. 57–58°. These turn brown on standing in the air. The compound is lachrymatory and vesicant, and was indeed painful to work with (Found: C, 40·70; H, 3·41. C_8H_8ClBrO requires: C, 40·76; H, 3·39%).

2-Chloro-5-methoxybenzyl cyanide. The above bromide was converted into the corresponding nitrile by refluxing it with ethanolic potassium cyanide, employing the experimental procedure of Harley-Mason and Jackson.[11] The product was recrystallized from ether–pet ether. Shiny hard crystals, m.p. 65° (Found: N, 8·02. C_9H_8NClO requires: N, 7·89%).

2-Chloro-5-methoxyphenyl acetamide. During its crystallization from dil ethanol the above nitrile was partly converted into the corresponding amide. Shiny crystals, m.p. 142° (Found: C, 54·28; H, 4·89. $C_9H_{10}NClO_2$ requires: C, 54·06; H, 5·04%).

2-Chloro-5-methoxyphenyl acetic acid. The above nitrile (15·8 g) was refluxed with 8% methanolic

[7] R. G. Wilkinson, T. L. Fields and J. H. Boothe, *J. Org. Chem.* **26**, 637 (1961).

[8] As will be shown later in a separate communication, it is 1-methyl-2-chloro-4-bromo-5-methoxybenzene, m.p. 45°.

[9] We completed the preparation of X by this method on April 20, 1960. In March 1961 (*vide* ref. 7) Wilkinson *et al.* announced their independent preparation of X by almost the same procedure.

[10] As we have shown (A. Bhati, Ph.D. thesis, Agra University, 1952) most aromatic acids can be converted in one step into the corresponding halogenated esters.

[11] J. Harley-Mason and A. H. Jackson, *J. Chem. Soc.* 1165 (1954).

sodium hydroxide (300 ml) for 10½ hr. The soapy solid, left after removal of methanol, was dissolved in water (400 ml) and the mixture extracted with ether (250 ml). The alkaline solution gave, on acidification with conc hydrochloric acid and subsequent extraction with ether, the crude acid (16·22 g), m.p. 102–104°, which was crystallized from benzene. Shiny prisms, m.p. 104° (Found: C, 54·08; H, 4·55. $C_9H_9ClO_3$ requires: C, 53·96; H, 4·48%). On methylation with diazomethane it gave the methyl ester, b.p. 115°/0·9 mm; $n^{21°}$, 1·5315.

Diethyl β-(2-chloro-5-methoxyphenyl)ethyl malonate (XII)

(a) *β-(2-Chloro-5-methoxyphenyl)-ethanol.* Methyl 2-chloro-5-methoxyphenyl acetate (16·60 g) was reduced with lithium aluminium hydride (3·25 g) in ether medium. The reduction product (13·96 g) isolated as described before, was a colorless gum which showed a strong OH band in its IR spectrum. There was no CO band.

(b) *β-(2-Chloro-5-methoxyphenyl)ethyl bromide.* The above reduction product (12·43 g), dissolved in dry ether (75 ml), was treated with a solution of phosphorus tribromide (2·4 ml) in ether (25 ml). After refluxing the mixture for 1 hr the resultant bromide (9·28 g) was isolated as described before. It is a gummy oil.

(c) *Preparation of* XII. The above crude bromide (9·2 g), dissolved in THF (50 ml), was gradually added to a solution, prepared from freshly distilled diethyl malonate (20 ml), THF (50 ml) and sodium hydride (1·0 g), under anhydrous conditions in 30 min. After refluxing the mixture for 2 hr it was allowed to stand overnight, during which time some of the solvent escaped. The organic portion was taken up in ether (250 ml) and the extract was shaken with dil sodium carbonate solution, dried and then freed from the solvent. The residual oil was fractionally distilled. The main fraction (8·33 g) possessed, b.p. 160–162°/0·2 mm, $n^{28.5°}$, 1·5025 (Found: C, 57·75; H, 6·10. $C_{16}H_{21}ClO_5$ requires: C, 58·35; H, 6·36%).

β-(2-Chloro-5-methoxyphenyl)-ethyl malonic acid. The above malonic ester (XII) gave on hydrolysis with methanolic sodium hydroxide the corresponding malonic acid. Fine prisms from dil ethanol, m.p. 160–162° (Found: C, 53·33; H, 4·60. $C_{12}H_{13}ClO_5$ requires: C, 52·84; H, 4·77%).

γ-(2-Chloro-5-methoxyphenyl)-butyric acid (XIII). The above malonic acid (1·03 g) was heated at 180–190° for 10 min. A reddish liquid with a characteristic smell was obtained. It solidified on cooling, m.p. ca. 60°. It was sublimed at 138°/0·3 mm when a white crystalline solid, m.p. 61–63°, was obtained (Found: C, 57·57; H, 5·61. $C_{11}H_{13}ClO_3$ requires: C, 57·76; H, 5·67%).

5-Chloro-8-methoxy-1-tetralone (XIV). The above acid (0·22 g) was treated with commercial polyphosphoric acid (3·15 g). The reddish gum, so obtained, was stirred on the steam-bath for 75 min, cooled and then poured into cold water (15 ml). The organic matter was successively extracted with chloroform (25 ml) and ether (50 ml). The two extracts were combined, washed with water (20 ml) and then with sodium carbonate solution (10 ml). On drying and removal of the solvents a yellowish white oil (0·1692 g) was obtained. It solidified on cooling, and on sublimation it gave a white crystalline solid, m.p. 39–41°. Its IR spectrum (film) showed a strong CO band at 1675 cm^{-1}. (Found: C, 62·47; H, 5·18. $C_{11}H_{11}ClO_2$ requires: C, 62·70; H, 5·26%). It gave a 2,4-dinitrophenylhydrazone. Orange yellow prisms from ethyl acetate–THF, m.p. 251° (dec) (Found: C, 52·48; H, 3·70; N, 14·86. Calc. for $C_{17}H_{15}N_4ClO_5$: C, 52·21; H, 3·84; N, 14·34%).

3,5-Dimethoxybenzyl bromide (XV). Methyl-3,5-dimethoxybenzoate (139·1 g) gave, on reduction with lithium aluminium hydride, 3,5-dimethoxybenzyl alcohol (96·9 g), b.p. 124°/0·1 mm, m.p. 45–47°. The crude reduction product (8·00 g) was converted into XV (9·53 g) by treatment with phosphorus tribromide in the same way as described for X. The crude bromide, m.p. ca. 65°, was crystallized twice from pet ether. Fine prisms, m.p. 70° (Found: C, 46·77; H, 4·45. $C_9H_{11}BrO_2$ requires: C, 46·75; H, 4·76%).

3,5-Dimethoxybenzyl nitrile was prepared from XV by a procedure described before. Yield, quantitative. The crude product, m.p. 47–49°, showed in the IR (supercooled film) a CN band at 2250 cm^{-1}.

3,5-Dimethoxyphenyl acetic acid was prepared from the above nitrile by treatment with methanolic sodium hydroxide. The crude acid, m.p. 101–103°, was esterified with diazomethane. Yield, quantitative; b.p. 122°/0·1 mm; $n^{19°}$, 1·5215.

β-(3,5-Dimethoxyphenyl)-ethanol. The above methyl ester gave on reduction with lithium aluminium hydride the corresponding alcohol in quantitative yield. Colorless oil, b.p. 110°/0·1 mm, $n^{21°}$, 1·5365.

β-(3,5-Dimethoxyphenyl)-ethyl bromide was prepared from the above reduction product by reaction with phosphorus tribromide. It was obtained as a viscous oil. Yield, quantitative.

Diethyl β-(3,5-dimethoxyphenyl)-ethyl malonate (XVII). The above viscous oil (10·00 g) was condensed with diethyl malonate (40 ml) in presence of sodium hydride (0·98 g) in the same manner as described for XII. The crude product gave upon fractional distillation a colorless oil (5·04 g), b.p. 162–164°/0·15 mm (Found: C, 62·50; H, 7·88. $C_{17}H_{24}O_6$ requires: C, 62·95; H, 7·46%). It gave upon hydrolysis with methanolic sodium hydroxide the corresponding acid, m.p. ca. 86°.

γ-(3,5-Dimethoxyphenyl)-butyric acid (XVIII). The above crude malonic acid gave, upon heating at 180–190° for 10 min and subsequent sublimation of the decarboxylated product at 130°/0·2 mm, a crystalline solid, m.p. 63–64° (Found: C, 64·13; H, 6·89. $C_{12}H_{16}O_4$ requires: C, 64·27; H, 7·19%).

3,5-Dimethoxy-1-tetralone (XIX). The crude malonic acid (0·8160 g) was decarboxylated as described above, and the crude XVIII was stirred with PPA (4·85 g) in the steam-bath for 2 hr. The crude cyclization-product was isolated as described before for XIV. It was a colorless oil (0·5288 g) which solidified on cooling. On sublimation at 130°/0·1 mm a crystalline solid, m.p. 64–65°, was obtained (Found: C, 69·52; H, 6·84. $C_{12}H_{14}O_3$ requires: C, 69·88; H, 6·79%). It showed a strong CO band at 1670 cm^{-1} in the IR. It gave a 2,4-dinitrophenylhydrazone. Shiny red prisms from ethanol, m.p. 228° (dec) (Found: C, 56·18; H, 4·50; N, 14·59. $C_{18}H_{18}N_4O_6$ requires: C, 55·95; H, 4·70; N, 14·51%).

2-Carbethoxy-6,8-dimethoxy-1-tetralone (VI). Diethyl β-(3,5-dimethoxyphenyl)ethyl malonate (XVII, 0·366 g) was stirred with PPA (7 g) for 2 hr on the steam-bath. The brownish reaction-mixture was poured in ice (50 g) and the organic matter extracted with chloroform (3 × 30 ml) and the extract successively washed with water (40 ml), NaOH (40 ml) and water. On drying and removal of chloroform a thick yellowish gum (0·223 g), giving a dark green coloration with alcoholic ferric chloride, was obtained. It was distilled at ca. 160°/0·5 mm. The colorless distillate shows in the IR (film) two CO bands at 1715 cm^{-1} (ester) and 1660 cm^{-1} (tetralone)(Found: C, 64·74; H, 6·20. $C_{15}H_{18}O_5$ requires: C, 64·73; H, 6·52%).

Diethyl β-(2-chloro-5-methoxyphenyl)-ethyl, β-(3′,5′-dimethoxyphenyl)-ethyl malonate (XXI). Diethyl 2-chloro-5-methoxybenzyl malonate (XX, 31·41 g; prepared by known procedures[6,7] and possessing b.p. 162°/0·4 mm), dissolved in THF (50 ml) was gradually added to a suspension of sodium hydride (3·12 g) in THF (50 ml). To the resultant mixture was added a solution of 3,5-dimethoxybenzyl bromide (23·1 g) in THF (75 ml) at room temp in ca. 2 hr. The final mixture was refluxed for 1 hr and left overnight. On working up the mixture in the same manner as described before, a thick oil (44·0 g) was obtained. It gave on fractional distillation under high vacuum a main fraction (35·72 g; Y, 76·8%), b.p. 226–230°/2·15 × 10^{-3} mm (Found: C, 61·37; H, 5·76. $C_{24}H_{29}ClO_7$ requires: C, 62·00; H, 6·24%).

2-Chloro-5-methoxybenzyl, 3′,5′-dimethoxybenzyl acetic acid (XXII). The above ester (XXI, 35·70 g) was refluxed with 25% methanolic sodium hydroxide (400 ml). The gummy acid (30·70 g), obtained on working up the mixture in the usual way, was heated at 180–200° for 15 min. The decarboxylated acid (27·15 g; Y, 99·1%) solidified on cooling. Prisms from dil methanol, m.p. 133–134° (Found: C, 62·79; H, 5·73. $C_{19}H_{21}ClO_5$ requires: C, 62·55; H, 5·76%). It gave a silver salt, m.p. 97° (dec) (Found: C, 47·57; H, 4·00, Eq. Wt, 465·5. $C_{19}H_{20}ClO_5Ag$ requires: C, 48·38; H, 4·24% and Eq. Wt, 471·5). With diazomethane it gave the methyl ester which gave upon sublimation a white crystalline solid, m.p. 62–64° (Found: C, 63·43; H, 6·20. $C_{20}H_{23}ClO_5$ requires: C, 63·40; H, 6·08%).

β-(2-Chloro-5-methoxybenzyl),β-(3′,5′-dimethoxybenzyl)-propionic acid (I). As outlines in the discussion section it was prepared by homologation of XXII. In the conversion of the alcohol (obtained by reduction of the methyl ester of XXII by lithium aluminium hydride) into the corresponding bromide by treatment with phosphorus tribromide the product obtained contained a considerable amount of the corresponding phosphite and very little of the desired bromide. The latter was converted into the corresponding nitrile by treatment with alcoholic potassium cyanide. The nitrile gave, on alkaline hydrolysis, small amounts of I as a gummy oil.

3-(2′-Chloro-5′-methoxybenzyl)-6,8-dimethoxy-1-tetralone (III). The above acid (I, 0·1640 g) was stirred with PPA (2·5 g) on the steam-bath for 2 hr. On working up the reaction-mixture as described before, a reddish white gum (0·1430 g) was obtained. It gave on distillation a low melting solid (Found: C, 65·79; H, 5·74. $C_{20}H_{21}ClO_4$ requires: C, 66·58; H, 5·82%). It shows in the IR (supercooled film) a CO band at 1680 cm^{-1}. It gave a 2,4-dinitrophenylhydrazone. Fine red needles from

ethanol–ethyl acetate, m.p. 189–191° (dec) (Found: C, 57·82; H, 4·65; N, 10·40. $C_{26}H_{25}N_4ClO_7$ requires: C, 57·54; H, 4·63; N, 10·36%).

Diethyl (2-chloro-5-methoxybenzyl,3′,5′-dimethoxybenzyl)-methyl malonate (XXV)

(a) *2-Chloro-5-methoxybenzyl,3′,5′-methoxybenzyl acetyl chloride* (XXIII). The acid (XXII, 9·01 g) was treated with oxalyl chloride. After the evolution of gases had ceased, the mixture was kept at room temp for 20 hr. The reddish residue left after distillation of excess oxalyl chloride at 100°/0·2 mm showed in the IR (film) a strong CO band at 1800 cm^{-1} (acid chloride).

(b) *Preparation of* XXIV. A solution of the above acid chloride in THF (50 ml) was gradually added to a mechanically stirred solution of freshly distilled ethyl diazoacetate (16·1 g) in THF (50 ml), under anhydrous conditions at room temp during 1 hr. The stirring was continued for 2 hr, then the reaction-mixture was left to stand for 38 hr and finally carefully heated to ca. 65° for 5 hr. The orange-yellow viscous oil, left after removal of solvent and excess ethyl diazoacetate, showed in the IR (film) strong bands at 2100 cm^{-1} (—N=N—) and 1715 cm^{-1} (CO of ester). The CO of acid chloride was missing. It was mixed with dry toluene (50 ml), silver oxide (2·5 g) and absolute ethanol (25 ml). The mixture was gradually heated to refluxing. At about 80° there was a brisk evolution of nitrogen. As after refluxing for 3 hr the reaction mixture still showed the presence of —N≡N— in the IR, more silver oxide (1 g) was added to it and then it was refluxed for another 6 hr. As the diazo-band still persisted, more silver oxide (2 g) and ethanol (15 ml) were added and the mixture refluxed for 2 hr and finally left overnight. The reaction was now complete (absence of N≡N band in the IR). The silver oxide was filtered off, and the filtrate concentrated *in vacuo*. The dark viscous gum (13·67 g), so obtained, gave, on fractional distillation in high vacuum, a fraction (7·68 g), b.p. 190–240°/2 × 10^{-3} mm which was redistilled; b.p. ca. 200°/8·6 × 10^{-5} mm. It is a thick colorless oil (Found: C, 63·66; H, 6·48. $C_{25}H_{31}ClO_7$ requires: C, 62·69; H, 6·48%).

(c) *Cyclization of* XXV *with* PPA. A mixture of the above ester (0·3250 g) and PPA (1·8 g) was heated for 5 min on the steam-bath and then allowed to stand at room temp for 1 hr. The resultant light red gum gave on working up, as described under VI, a whitish gum (0·2906 g) which was distilled at ca. 250°/8·56 × 10^{-5} mm. The distillate showed in the IR (film) a medium band of tetralone CO at 1680 cm^{-1} and a strong band of ester CO at 1725 cm^{-1} [Found: C, 65·33; H, 6·45. λ_{max} 225–7 mμ (ε, 18240), 275 mμ (ε, 7209)]. The product gave a very faint coloration with alcoholic ferric chloride. Both the elemental analysis and its UV absorption spectra indicate it to be mostly III, containing traces of the β-keto ester IV.

2-Carbethoxy-3-(2′-chloro-5′-methoxybenzyl)-6,8-dimethoxy-1-tetralone (IV). The crude cyclized product (19·60 g), obtained similarly as described above, was stirred with a mixture of sodium hydride (12·51 g) and freshly distilled diethyl carbonate (75 ml) for 20 hr, then gradually warmed to 110° and heated at this temp for 3 hr. The reaction-mixture was cooled and the unused sodium hydride cautiously destroyed with ethanol (30 ml). The resultant mixture was poured in ice (400 g), and the mixture thoroughly shaken with ether (600 ml). The ether layer was removed and the aqueous alkaline solution extracted further with ether (2 × 100 ml), cooled in ice and acidified with 6N H_2SO_4. The liberated product (2·1 g), isolated by extraction with ether, gave on distillation at ca. 220°/8·56 × 10^{-5} mm, a colorless liquid which gives a dark green coloration with alcoholic ferric chloride (Found: C, 64·01; H, 5·04. $C_{23}H_{25}ClO_6$ requires: C, 63·72; H, 5·78%).

Attempted cyclization of IV. The above β-keto ester (0·211 g) and PPA (4·1 g) were heated at100° for 2 min and then the reddish mixture was allowed to stand at the room temp for 30 min. On working up the mixture in the manner described before, a red gum (0·171 g) was obtained. It was sublimed at ca. 220°/0·1 mm. The colorless oil so obtained possessed λ_{max} 275–6 mμ, ε 10262. In the IR (film) it showed bands at 1720 cm^{-1} (ester) and 1680 (tetralone). These data show that IV did not undergo cyclization.

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