655. *Lignans. Part III.* Synthesis of* 1-*Arylnaphthalenes Related to Podophyllotoxin*

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Di-(arylmethylene)succinic anhydrides have been prepared by Stobbe condensation and cyclised to 1-arylnaphthalenes by ultraviolet irradiation.

In the absence of a satisfactory large-scale procedure for the preparation of methylenedioxy-ethers,[1] we chose piperonal as our starting material and it was converted into the 3,4-methylenedioxybenzylidenesuccinic half ester (of I)[2] by a Stobbe condensation catalysed by potassium t-butoxide. For our purpose it was essential to introduce a second, different, aryl group at a separate stage and the half ester was esterified and condensed with 3,4,5-trimethoxybenzaldehyde under similar conditions, thus affording the di-(arylmethylene)-succinic half ester (II). The alternative route to this unsymmetrical compound was also followed, using the less accessible trimethoxybenzaldehyde in the first stage of the condensation and piperonal in the second; the overall yield was slightly less and hence the original sequence was used for large-scale working.

The trimethoxybenzaldehyde for these reactions was at first prepared by Rosenmund reduction[3] of the acid chloride, but the use of lithium tri-t-butoxyaluminium hydride

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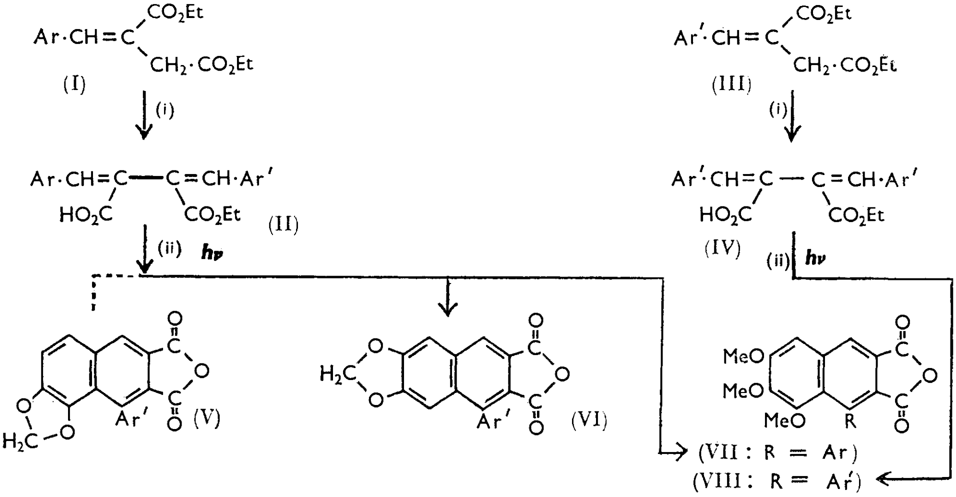
* Part II, Ayres and Pauwels, *J.*, 1962, 5025.

[1] Ayres and Denney, *J.*, 1961, 4506.

[2] El-Assal and El-Wahhab, *J.*, 1960, 849.

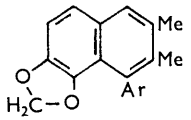
[3] Hershberg and Cason, *Org. Synth.*, 1941, **21**, 84.

proved more convenient and gave a slightly improved yield. 3,4,5-Trimethoxybenzoyl chloride reacts only slowly with nucleophiles and its hydrogenolysis by the hydride ion donor is correspondingly much slower than with acid chlorides previously reduced [4] by this procedure.



Ar = 3,4-Methylenedioxyphenyl
Ar′ = 3,4,5-Trimethoxyphenyl

(i) KOBu^t (ii) AcCl


(IX)

A two-stage condensation of trimethoxybenzaldehyde and diethyl succinate was carried out to obtain 6,7,8-trimethoxy-1-(3,4,5-trimethoxyphenyl)naphthalene-2,3-dicarboxylic anhydride (VIII) as a reference compound. In this sequence with sodium ethoxide as catalyst the condensation did not proceed beyond the half ester (of III). Potassium t-butoxide afforded the bis-condensation product (IV), but with this catalyst superior yields were obtained in the two-stage procedure even allowing for the loss on esterification and isolation of (III) at the first stage.

The di(arylmethylene)succinic half-esters were oils, probably mixtures of geometrical isomers, and were characterised as their anhydrides after treatment with acetyl chloride. In this reaction the yields obtained were inferior to those afforded [5] by arylmethylenesuccinates having a simpler alkoxylation pattern; fission of the aralkyl ether substituents may be responsible for this and for the intractable products obtained when cyclisation to 1-arylnaphthalenes was attempted with Friedel–Crafts catalysts. Dehydrogenation catalysts [6] also gave poor results in the cyclisation of the anhydrides and the best method proved to be photolysis in benzene.

The photolytic cyclisation was readily followed by the disappearance of the 425 mμ band in the diaryldiene absorption spectrum, coupled with the emergence of intense absorption at 290 mμ. The products were of low solubility and separated from solution as the reaction proceeded. Cyclisation of the unsymmetrical α-(3,4-methylenedioxybenzylidene)-β-(3,4,5-trimethoxybenzylidene)succinic anhydride afforded a mixture which

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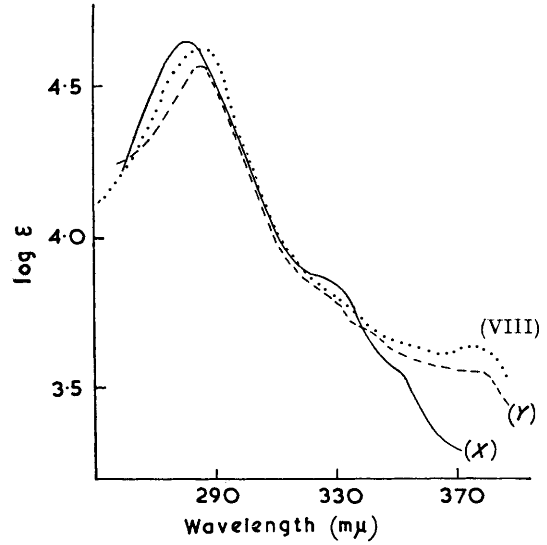
[4] Brown and McFarlin, *J. Amer. Chem. Soc.*, 1958, **80**, 5372.
[5] See Baddar, El-Assal, and Gindy, *J.*, 1948, 1270.
[6] Gilchrist, Hodges, and Porte, *J.*, 1962, 1781.

gave two compounds, (*X*) (m. p. 314°; 25%) and (*Y*) (m. p. 239°; 20%). Thin-layer chromatography of the mixture showed at least three other fluorescent products of lower R_F value, which may be dimers or higher polymers.

Because of its low solubility in ethanol, the ultraviolet absorption spectrum of compound (*X*) (Figure) was observed in ethyl acetate. Despite the difference in the solvents, the spectra of all three compounds (*X*, *Y*, and VIII) are very similar at *ca.* 285 mμ, and are typical [6-8] of 1-arylnaphthalenes over the range recorded. Besides confirming this main structural feature in the cyclisation products, comparison of the spectra in the region of 370 mμ, ascribed [7,9] to the longitudinal polarisation of the naphthalene system, gave information on the orientation of substituents. In (*X*) this band is merged in the main peak, whilst in (*Y*) and (VIII) the absorption is here more intense, consistent with enhancement by the longitudinal polarisation of 6- and 7-methoxy groups and/or the emergence of the naphthalene characteristics as a result of hindrance by an 8-methoxy group. This suggests that (*Y*) has structure (VII); (*X*) may then have structure (VI), the normal product of an electrophilic substitution of a methylenedioxy ether, although (V) cannot be excluded since a radical cyclisation has occurred.



Ultraviolet absorption of cyclisation products

Compound	Chemical shift, τ value (relative area) O–CH$_2$–O	–O–CH$_3$			
(VIII)	—	5·91(1)	6·06(2)	6·15(2)	6·58(1)
(*X*)	4·0		6·12(1)	6·17(2)	
(*Y*)	3·96	5·93(1)	6·06(1)		6·59(1)

Ca. 10% solutions of (VIII) and *Y* in deuteroacetone and of (*X*) in sulphur dioxide were used. Measurements were made at 60 Mc/s.

Conclusive assignment of the substituents has been made possible by using the hexamethoxy-compound (VIII) as a model for nuclear magnetic resonance (n.m.r.) spectroscopy. In the spectrum of (VIII) the peak at τ 6·58 is assigned to the 8-methoxy-group, shifted to high field by the ring current of the 1-substituent; one of the peaks of area 2 is due to the equivalent 3- and 5-methoxy groups of the trimethoxyphenyl (Ar′) group. The three peaks of compound (*Y*) can only arise from differently situated groups and structure (VII)

[7] Baddar and Sawires, *J.*, 1956, 395.

[8] Freudenberg and Kempermann, *Annalen*, 1957, **602**, 184.

[9] Jaffé and Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley, New York, 1962, p. 305.

must be assigned to this compound. Since the peak at τ 6·15 in (VIII) is absent from the spectrum of compound Y, it must arise from the groups at positions 3 and 5 of the Ar′ group, the peak at τ 6·06 being partly due to that at position 4. The chemical shifts and area ratio of (1 : 2) in the spectrum of compound X correspond to the substitution pattern of (V) or (VI), but the $-O-CH_2-O-$ peak at τ 4·0 can only have arisen from the 6,7-methylenedioxy-group of the latter, since it has been shown[6] that this shift corresponds to the unshielded ether (τ 3·95) of tetradehydro-otobain (IX). The peak due to the 7,8-methylenedioxy group appears at τ 4·23 in this compound.

In solutions saturated at room temperature the multiplet peaks due to benzenoid protons were too weak to be of use in structure determination.

EXPERIMENTAL

Analyses were by Messrs. D. R. Hanks and B. T. Saunderson. Infrared spectra were measured for Nujol mulls.

Preparation of 3,4,5-*Trimethoxybenzaldehyde*.—(*a*) 3,4,5-Trimethoxybenzoyl chloride, b. p. 165—170°/12 mm., m. p. 77—78°, was prepared in 80% yield by the method of Reeve and Sterling.[10] Rosenmund reduction[3] followed an established procedure, save that removal of the solvent (xylene) was more conveniently effected by steam distillation, and gave the aldehyde (74%), m. p. 76—77°, from benzene–light petroleum b. p. 60—80° (1 : 1).

(*b*) Nitrogen was passed through the acid chloride (34·6 g.) in " diglyme " (75 ml.) during the addition (1 hr.) of lithium tri-t-butoxyaluminium hydride[4] (37·8 g.) in " diglyme " (150 ml.) and for 6 hr. thereafter. The reaction mixture was kept at room temp. throughout and was worked up by addition to crushed ice (300 g.). Next morning the solid obtained was separated by centrifugation and the trimethoxybenzaldehyde (18·7 g.) was obtained on evaporation of the liquor under reduced pressure. The solid was extracted with boiling ethanol (250 ml.) for 3 hr. and the oil obtained on evaporation of the filtrate was dissolved in benzene (30 ml.) and washed with saturated sodium hydrogen carbonate (2 × 30 ml.) and water (2 × 30 ml.). Evaporation of the solvent gave a further quantity of the trimethoxy benzaldehyde (4·8 g., combined yield 79·5%), m. p. 76—77°.

Ethyl Hydrogen α-(3,4,5-*Trimethoxybenzylidene*)*succinate*.—Trimethoxybenzaldehyde (20·0 g.) and diethyl succinate (20·0 g.) in *t*-butanol (25 ml.) was added to a refluxing solution of potassium t-butoxide [from potassium (6 g.)] in t-butyl alcohol (90 ml.). Addition was complete in 30 min. and, after heating under reflux for a further 90 min., the solution was cooled and acidified with concentrated hydrochloric acid. The residue obtained on evaporation of the aqueous butyl alcohol was treated with ice–water (150 ml.) and extracted with ether (3 × 50 ml.). Acidic material was extracted with saturated sodium hydrogencarbonate (6 × 40 ml.) and recovery afforded the semi-crystalline half-ester (25·2 g., 76%).

The dicarboxylic acid obtained on boiling this product with 2N-sodium hydroxide (100 ml.) could not be crystallised, but both materials gave 3,4,5-*trimethoxybenzylidenesuccinic anhydride* on refluxing with acetyl chloride for 1·5 hr.; excess of reagent was removed *in vacuo* and the crude anhydride (0·42 g., 97% from half-ester) crystallised from benzene–light petroleum b. p. 40—60° (1 : 1), m. p. 175—176° (Found: C, 60·3; H, 5·1. $C_{14}H_{14}O_6$ requires C, 60·4; H, 5·1%), $\nu_{max.}$ 1770, 1830 cm.$^{-1}$ (anhydride C=O).

Ethyl hydrogen α-(3,4-*methylenedioxybenzylidene*)*succinate*[2] was prepared as described above from piperonal (15·0 g.) and diethyl succinate (18 g.). The crude half-ester (21·25 g., 76%) was obtained and crystallised from benzene containing ethanol (5%); it had m. p. 190—192°.

Esterification.—The product (57·8 g.) was refluxed in ethanol (50 ml.) and toluene (30 ml.) containing concentrated sulphuric acid (2 ml.) for 16 hr. and the azeotrope distilled at 75—76·5°. Toluene (10 ml.) and ethanol (30 ml.) were added and heating continued for a further 18 hr. The solution was neutralised with sodium carbonate, evaporated and the residual oil treated with ice–water (200 ml.). The neutral fraction was isolated by ether extraction (4 × 40 ml.) and washed with sodium hydrogen carbonate to give a semi-solid diester (I) (54·7 g., 85%).

Diethyl 3,4,5-*trimethoxybenzylidenesuccinate* (III) was prepared in the same way from the half-ester (22·8 g.) in 72% yield.

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[10] Reeve and Sterling, *J. Amer. Chem. Soc.*, 1949, **71**, 3657.

αβ-*Di*-(3,4,5-*trimethoxybenzylidene*)*succinic Anhydride*.—The diester (III) (15·0 g.) and trimethoxybenzaldehyde (8·5 g.) were condensed with potassium-t-butoxide as described above. The crude product (18·2 g., 85%) was converted into the *anhydride* (Found: C, 63·0; H, 5·3. $C_{24}H_{24}O_9$ requires C, 63·15, H, 5·3%) in 34% yield by treatment with acetyl chloride, and had m. p. 162° on crystallisation from benzene–light petroleum (b. p. 40—60°) (1 : 1), $\nu_{max.}$ 1765 and 1810 cm.$^{-1}$.

When the first step of this preparation was attempted from diethyl succinate (1·75 g., 0·01 mol.) and trimethoxybenzaldehyde (3·92 g., 0·02 mol.) with sodium ethoxide as catalyst, only the first stage of the condensation occurred, affording the partially crystalline half-ester (2·2 g., 68%) which was converted into 3,4,5-trimethoxybenzylidenesuccinic anhydride, m. p. 175°, by treatment with acetyl chloride.

α-(3,4-*Methylenedioxybenzylidene*)-β-(3,4,5-*trimethoxybenzylidene*)*succinic Anhydride*.—With potassium t-butoxide as catalyst, the half-ester (II) was prepared in 81% yield from diethyl 3,4-methylenedioxybenzylidenesuccinate (I; 3·06 g.), whilst crude material (3·53 g., 78%) was afforded by diethyl 3,4,5-trimethoxybenzylidenesuccinate (III) (3·52 g.) and piperonal (1·50 g.).

The anhydride was obtained from crude material (10·8 g.) from either source on heating with acetyl chloride (30 ml.) for 2 hr. and removing excess *in vacuo*. Trituration of the residue with benzene afforded a crude product (2·55 g.). Benzene-soluble material was chromatographed on silica gel when a main fraction (2·19 g.) was eluted with benzene–ethyl acetate (1 : 2) and was shown to be substantially pure product, (m. p. 192°; combined yield 4·84 g., 48%) by thin-layer chromatography. Recrystallisation from benzene–light petroleum (b. p. 60—80°) (1 : 1) gave material, m. p. 194°, $\nu_{max.}$ 1760 and 1805 cm.$^{-1}$ (Found: C, 64·3; H, 4·35. $C_{22}H_{18}O_8$ requires C, 64·4; H, 4·4%).

Cyclisation of α-(3,4-*methylenedioxy*)-β-(3,4,5-*trimethoxybenzylidene*)*succinic Anhydride*.—The diene (1·00 g.) was dissolved in benzene (300 ml.) containing iodine (30 mg.) and irradiated with light from a Hanovia Homesun 100 lamp for 74 hr.; the absorption at 325, 430 mμ of an iodine-free sample had then been replaced by a band at 287 mμ. Filtration, washing with sodium thiosulphate solution, and concentration to 20 ml., afforded a yellow solid (0·249 g.), m. p. 285—290°. Several crystallisations from acetone gave *compound* X. 6,7-*methylenedioxy*-1-(3′,4′,5′-*trimethoxyphenyl*)*naphthalene*-2,3-*dicarboxylic anhydride*, m. p. 314°, $\nu_{max.}$ 1850 and 1785 cm.$^{-1}$ (Found: C, 64·4; H, 4·15. $C_{22}H_{16}O_8$ requires C, 64·7; H, 3·95%).

A second product (0·196 g.), m. p. 230—232°, was obtained on evaporation to dryness and trituration with methanol; this was extracted with benzene and crystallised from benzene–cyclohexane (1 : 1) giving *compound* Y, 6,7,8-*trimethoxy*-1-(3′,4′-*methylenedioxyphenyl*)*naphthalene*-2,3-*dicarboxylic anhydride*, m. p. 239°, $\nu_{max.}$ 1845 and 1780 cm.$^{-1}$ (Found: C, 64·5; H, 3·95%).

6,7,8-*Trimethoxy*-1-(3,4,5-*trimethoxyphenyl*)*naphthalene*-2,3-*dicarboxylic Anhydride*.—The anhydride was obtained as described above by irradiation of di-(3,4,5-trimethoxybenzylidene)-succinic anhydride (1·00 g.) in benzene (300 ml.). On concentration of the solution two fractions were collected, the first having m. p. 234—236° (0·37 g.), and the second, m. p. 176—180° (0·23 g., combined yield 60%). Crystallisation from benzene–cyclohexane gave the pure *arylnaphthalene*, m. p. 238—239° (Found: C, 63·3; H, 4·85. $C_{24}H_{22}O_9$ requires C, 63·4; H, 4·8%), $\nu_{max.}$ 1845 and 1785 cm.$^{-1}$.

Thin-layer chromatography of products

Compound	Eluent	Colour of spot	R_F
Acyclic anhydride from (II)	Benzene	Orange	0·05
	Benzene–Me·CO_2Et (1 : 1)		0·73
(VI)	Benzene–MeOH (10 : 3)	Yellow fluorescent	0·38
	Benzene–MeOH (10 : 1)		0·10
(VII)	Benzene–MeOH (10 : 3)	,, ,,	0·49
	Benzene–MeOH (10 : 1)		0·13
(VIII)	Benzene–MeOH (10 : 3)	,, ,,	0·67

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