170. *The Stobbe Condensation. Part II.*[1] *The Cyclisation of Methyl Hydrogen* cis-γ-*3,4-Methylenedioxyphenyl- and Methyl Hydrogen* cis-γ-*3,4-Dimethoxyphenyl-itaconate to the Corresponding Polysubstituted Naphthalene Derivatives.*

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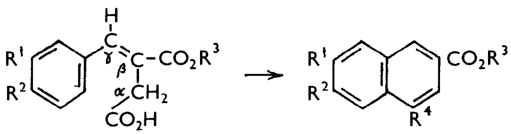
β-Methyl α-hydrogen *cis*-γ-3,4-methylenedioxyphenyl- and -γ-3,4-dimethoxyphenyl-itaconate are cyclised by acetic anhydride and sodium acetate to methyl 4-acetoxy-6,7-methylenedioxy- and -6,7-dimethoxy-2-naphthoate which are converted into 1-methoxy-6,7-methylenedioxy- and 1,6,7-trimethoxy-naphthalene, respectively.

Alcoholysis of *cis*-γ-3,4-methylenedioxyphenyl- and *cis*-γ-3,4-dimethoxyphenyl-itaconic anhydride yields α-methyl β-hydrogen *cis*-γ-3,4-methylenedioxyphenyl- and -γ-3,4-dimethoxyphenyl-itaconate, respectively.

THE aim of this investigation was to study the Stobbe condensation as an easy new method for the synthesis of polysubstituted naphthalenes [1] and at the same time, to confirm the *cis*-configuration assigned [1] to the intermediate of the products.

Heating piperonaldehyde or veratraldehyde with methyl succinate in presence of potassium t-butoxide in t-butyl alcohol [2] gave β-methyl α-hydrogen *cis*-γ-3,4-methylenedioxyphenyl- (Ia; R^3 = Me) and 3,4-dimethoxyphenyl-itaconate (Ib; R^3 = Me), respectively, in about 80% yield. In the former reaction, αβ-dipiperonylidenesuccinic acid [3,4] was

	R^1	R^2
Ia	$-O\cdot CH_2\cdot O-$	
Ib	OMe	OMe



	R^1	R^2	R^4
IIa	$-O\cdot CH_2\cdot O-$		OAc
IIb	OMe	OMe	OAc

also isolated, in about 6% yield. The unexpected formation of this disubstituted acid at high temperature [5,6] could be attributed to (*a*) the completely anhydrous conditions which hindered hydrolysis of methyl succinate (especially in the t-butyl alcohol), and thus facilitated attack at the second activated methylene group, or (*b*) the comparative reactivity of piperonaldehyde.

The structure and the *cis*-configuration of the β-half esters (Ia and b) were, as in Part I, confirmed by their almost quantitative cyclisation by sodium acetate in acetic anhydride to the naphthoates (IIa and b; R^3 = Me); the absence of isomers indicates steric hindrance at position 2. This cyclisation provides a route to polysubstituted naphthalenes which are difficult to prepare otherwise.

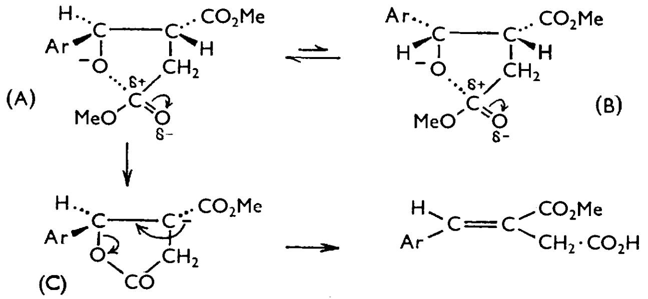
Alkaline hydrolysis of the acetoxy-esters (IIa and b; R^3 = Me) gave 4-hydroxy-6,7-methylenedioxy- and -6,7-dimethoxy-2-naphthoic acid (as II), respectively. These acids were converted by methyl sulphate and potassium carbonate in acetone into methyl 4-methoxy-6,7-methylenedioxy- and 4,6,7-trimethoxy-2-naphthoate which on hydrolysis gave the naphthoic acids. Thence decarboxylation with copper bronze in quinoline gave 1-methoxy-6,7-methylenedioxy- and 1,6,7-trimethoxy-naphthalene.

Hydrolysis of either the crystalline *cis*-β-half esters (Ia and b; R^3 = Me) or the oil from their mother-liquor (see Experimental) with boiling aqueous barium hydroxide gave the *cis*-γ-arylitaconic acids [7-9] (Ia and b; R^3 = H). The anhydrides with boiling methanol

[1] Part I, El-Abbady and El-Assal, *J.*, 1959, 1024.
[2] Cf. Johson and Daub, " Organic Reactions," J. Wiley and Sons, Inc., 1951, Vol. VI, p. 1.
[3] Stobbe, Viewig, Eckert, and Reddelien, *Annalen*, 1911, **380**, 78.
[4] Haworth and Woodcock, *J.*, 1938, 1985.
[5] Stobbe and Naoum, *Ber.*, 1904, **37**, 2240.
[6] Stobbe, *Ber.*, 1908, **41**, 4350.
[7] Baddar, El-Assal, Doss, and Shehab, *J.*, 1959, 1016.
[8] Cornforth, Hughes, and Lions, *J. Proc. Roy. Soc.*, *N.S. Wales*, 1939, **72**, 238.
[9] Stobbe and Leuner, *Annalen*, 1911, **380**, 75.

gave the *cis*-α-methyl half-esters which were different from the *cis*-β-half esters (I; R^3 = Me) obtained by the Stobbe condensation.[1] These *cis*-α-half esters could not be the *trans*-isomers since methylation of both the *cis*-β- (Ia) and the *cis*-α-half ester gave authentic dimethyl *cis*-γ-3,4-methylenedioxyphenylitaconate.[7] The formation of the *cis*-α-methyl half-esters by alcoholysis of the *cis*-anhydrides further supports the mechanism of their formation put forward by El-Abbady and El-Assal.[1] We have noted that the polar nature and position of substituents in the anhydrides noticeably affect the rate of alcoholysis.

The *cis*-acids and their half-esters were unaffected by direct sunlight for 20 days (June/Cairo), or by ultraviolet irradiation (mercury-vapour quartz lamp) for 12—15 hr.



(I)

We tried unsuccessfully to isolate or identify the *trans*-β-half esters or their corresponding *trans*-acids or anhydrides: we attribute this failure to their formation in very low proportions[6] or to the instability of the *trans*-isomers towards heat or reagents used (which might convert them into the more stable *cis*-isomers[6]). This finds theoretical support if we accept the mechanism of the Stobbe condensation postulated by Johnson and Daub.[2] Formation of only the *cis*-β-half-esters (I) may be attributed to the fact that the "*trans*"-conformation (*A*) is more stable than the "*cis*"-conformation (*B*) owing to steric factors. The former (*A*) will lead to the intermediate lactone (*C*) which rearranges to the *cis*-β-half esters (I).

Experimental

Microanalyses were by Dr. A. Bernhardt, Max-Plank Institut für Kohlenforschung, Mülheim (Ruhr), Germany.

β-*Methyl* α-*Hydrogen* cis-γ-3,4-*Methylenedioxyphenylitaconate* (Ia; R^3 = Me).—Piperonaldehyde (15 g., 1 mol.), methyl succinate (17·5 g., 1·2 mol.) in t-butyl alcohol (25 ml.), and potassium t-butoxide [from metallic potassium (5·8 g.)] were treated as described previously.[1] The product (*ca.* 25 g.) was extracted with boiling benzene, and the insoluble residue (2·5 g.) was filtered off. The benzene-soluble product was repeatedly crystallised from benzene to give β-*methyl* α-*hydrogen* cis-γ-3,4-*methylenedioxyphenylitaconate* (*ca.* 16 g.), m. p. 135—136° (Found: C, 59·5; H, 4·6; OMe, 10·8. $C_{13}H_{12}O_6$ requires C, 59·1; H, 4·55; OMe, 11·7%).

The combined benzene mother-liquors gave, on concentration, another crop (*ca.* 3 g.) of the same product. Evaporation of its benzene filtrate left only a viscous oil which on hydrolysis by boiling aqueous barium hydroxide gave an acid (Ia; R^3 = H) (*ca.* 2·8 g.), identical with that obtained by the hydrolysis of the pure preceding *cis*-β-half ester (Ia; R^3 = Me) (see below).

The benzene-insoluble product (*ca.* 2·5 g.) crystallised from acetic acid, to give yellowish-green αβ-dipiperonylidenesuccinic acid, m. p. 211—212°. Stobbe *et al.*[3] and Haworth and Woodcock[4] give m. p. 210° and 207—208°, respectively. On repeated crystallisation of the acid from glacial acetic acid, it was gradually transformed into its anhydride, as indicated by the lowering of its m. p. (155—165°) and by a change of colour. The anhydride was obtained from the acid (2·5 g.) and acetyl chloride (20 ml.) (4 hours' refluxing) as red rosettes, m. p. 229—231° (from benzene). Stobbe *et al.*[3] and Haworth and Woodcock[4] give m. p. 210° and 212—213°, respectively. The *dimethyl ester*, prepared by use of dimethyl sulphate and potassium carbonate in acetone, had m. p. 184—185° (from benzene), depressed on admixture with dimethyl γ-3,4-methylenedioxyphenylitaconate [7] (Found: C, 64·4; H, 4·4; OMe, 14·9. $C_{22}H_{18}O_8$ requires C, 64·4; H, 4·4; 2OMe, 15·1%).

Methyl 4-Acetoxy-6,7-methylenedioxy-2-naphthoate (IIa; R^3 = Me).—The above *cis*-β-half ester (8 g.) was cyclised with sodium acetate (2·7 g.) in acetic anhydride (45 ml.) as usual.[1] The product (*ca.* 8 g.) was crystallised from benzene to give *methyl 4-acetoxy-6,7-methylenedioxy-2-naphthoate* in light brown needles, m. p. 151—152° (Found: C, 62·0; H, 4·1; OMe, 10·7. $C_{15}H_{12}O_6$ requires C, 62·5; H, 4·2; OMe, 10·8%). The combined benzene mother-liquors, on concentration and storage, gave another crop, m. p. and mixed m. p. 149—151°, which indicated the absence of an isomeric product.

This ester (4 g.) was hydrolysed with 16% aqueous-alcoholic potassium hydroxide solution (50 ml.) (3 hours' refluxing) to 4-hydroxy-6,7-methylenedioxy-2-naphthoic acid (*ca.* 3·5 g.), m. p. 288—290°. This acid, being insoluble in many organic solvents and partly soluble in glacial acetic acid with darkening in colour (decomposition), was directly methylated.

Methyl 4-Methoxy-6,7-methylenedioxy-2-naphthoate.—The preceding crude acid (3·5 g.) with dimethyl sulphate (9 g.) and potassium carbonate (12 g.) in acetone (100 ml.) gave the *ester* (*ca.* 3·5 g.), m. p. 108·5—110° (from benzene) (Found: C, 64·8; H, 4·6; OMe, 23·2. $C_{14}H_{12}O_5$ requires C, 64·6; H, 4·6; 2OMe, 23·8%), hydrolysed as above to *4-methoxy-6,7-methylenedioxy-2-naphthoic acid* (0·7 g.), m. p. 247—248° (from acetic acid) (Found: C, 63·1; H, 3·95; OMe, 12·35. $C_{13}H_{10}O_5$ requires C, 63·4; H, 4·1; OMe, 12·6%).

1-Methoxy-6,7-methylenedioxynaphthalene.—A solution of the above methoxy-acid (0·4 g.) in quinoline (6 ml.) was heated to the b. p. with copper bronze (0·2 g.) during 15 min., then an equal amount of copper-bronze was added in portions to the boiling solution during 45 min.; the whole was then refluxed for a further 30 min. and worked up as usual. The product (*ca.* 0·3 g.) crystallised from light petroleum (b. p. 60—70°) to give *1-methoxy-6,7-methylenedioxynaphthalene*, m. p. 82—83° (Found: C, 71·5; H, 4·9; OMe, 14·9. $C_{12}H_{10}O_3$ requires C, 71·3; H, 4·95; OMe, 15·3%).

β-Methyl α-Hydrogen cis-*γ-3,4-Dimethoxyphenylitaconate* (Ib; R^3 = Me).—Veratraldehyde (16·6 g., 1 mol.) and methyl succinate (17·6 g., 1·2 mol.) in t-butyl alcohol (20 ml.) were added to a boiling solution of potassium t-butoxide [from potassium (5·8 g.) and the alcohol (85 ml.)] during 15 min. and the whole was refluxed for a further hour, then worked up as usual.[1] The solid product (*ca.* 25 g.) was digested with boiling benzene; the benzene solution, on concentration, afforded *β-methyl α-hydrogen* cis-*γ-3,4-dimethoxyphenylitaconate* which on repeated crystallisation from benzene had m. p. 149—150° (*ca.* 17 g.) (Found: C, 60·45; H, 5·7; OMe, 32·2. $C_{14}H_{16}O_6$ requires C, 60·0; H, 5·7; 3OMe, 33·2%).

The combined benzene mother-liquors afforded another crop (*ca.* 3 g.) and on evaporation gave a light brown semisolid product (*ca.* 3·5 g.). This, on hydrolysis by concentrated aqueous barium hydroxide gave the *cis*-acid (Ib; R^3 = H), identical with that from the pure *cis*-β-half ester (I*b*, R^3 = Me) (see below).

Methyl 4-Acetoxy-6,7-dimethoxy-2-naphthoate (IIb; R^3 = Me).—The preceding *cis*-β-half ester (4·2 g.) was cyclised with sodium acetate (1·6 g.) in boiling acetic anhydride (50 ml.) (5 hours' refluxing) in the usual manner. Crystallisation of the product from benzene gave pale brown *methyl 4-acetoxy-6,7-dimethoxy-2-naphthoate* (*ca.* 4 g.), m. p. 141—142° (Found; C, 63·2; H, 5·15; OMe, 30·0. $C_{16}H_{16}O_6$ requires C, 63·2; H, 5·3; 3OMe, 30·6%).

Hydrolysis of this acetoxy-ester (3 g.) with 15% aqueous-alcoholic potassium hydroxide solution (40 ml.) (2 hours' refluxing) gave 4-hydroxy-6,7-dimethoxy-2-naphthoic acid (2·5 g.), m. p. 245—246°.

Methyl 4,6,7-Trimethoxy-2-naphthoate.—The crude phenolic acid (1·3 g.) with methyl sulphate (3·5 g.) and potassium carbonate (6 g.) in acetone (40 ml.) (12 hours' refluxing) gave *methyl 4,6,7-trimethoxy-2-naphthoate* (1·2 g.) in needles (from benzene), m. p. 126—127° (Found: C, 65·5; H, 6·05; OMe, 43·45. $C_{15}H_{16}O_5$ requires C, 65·2; H, 5·8; 4OMe, 44·9%).

Hydrolysis as above gave the *trimethoxynaphthoic acid* (2·5 g.) (tablets, from benzene), m. p. 227—228° (Found: C, 64·6; H, 5·5; OMe, 34·9. $C_{14}H_{14}O_5$ requires C, 64·1; H, 5·35; 3OMe, 35·5%). Crystallisation of this acid from acetic acid gave diamond-shaped solvated crystals (Found: C, 61·5; H, 5·6; OMe, 31·1. $C_{14}H_{14}O_5,\frac{1}{2}C_2H_4O_2$ requires C, 61·6; H, 5·5; 3OMe, 31·5%).

1,6,7-Trimethoxynaphthalene.—The preceding acid (1·3 g.) was decarboxylated with copper bronze (0·4 + 0·4 g.) in quinoline (12 ml.) as described for the above methylenedioxy-derivative, affording *1,6,7-trimethoxynaphthalene* in plates [from light petroleum (b. p. 60—70°)], m. p.

132—133° (Found: C, 71·8; H, 6·5; OMe, 42·0. $C_{13}H_{14}O_3$ requires C, 71·6; H, 6·4; OMe, 42·7%).

cis-γ-3,4-*Methylenedioxyphenylitaconic Acid* (Ia; R^3 = H).—The *cis*-β-half-ester (Ia; R^3 = Me) (5 g.) was hydrolysed with concentrated aqueous barium hydroxide (150 ml.) (6 hours' refluxing), and the precipitated barium salt was treated as usual.[1] The liberated *cis*-γ-3,4-methylenedioxyphenylitaconic acid (*ca.* 4 g.) crystallised from acetone in diamond-shaped crystals, m. p. and mixed m. p. 201—202° (Found: C, 57·8; H, 4·05. Calc. for $C_{12}H_{10}O_6$: C, 57·6; H, 4·0%). Baddar *et al.*[7] and Cornforth *et al.*[8] give m. p. 200—201° and 114—115°, respectively, for this acid (of unidentified configuration). Another crop of the same *cis*-acid (0·5 g.) was obtained on acidification of the aqueous-alkaline filtrate, indicating the partial solubility of its barium salt.

cis-γ-3,4-*Methylenedioxyphenylitaconic Anhydride*.—The above *cis*-acid (2 g.) was boiled with acetyl chloride (8 ml.) for 3 hr. After evaporation, *anhydride* formed pale orange crystals (1·8 g.), m. p. 158—159°, from benzene (Found: C, 62·35; H, 3·3. $C_{12}H_8O_5$ requires C, 62·1; H, 3·4%).

α-Methyl β-Hydrogen cis-γ-3,4-*methylenedioxyphenylitaconate*.—The *cis*-anhydride (1 g.) was refluxed in absolute methanol (15 ml.) for 4 hr. Evaporation and crystallisation of the residue (*ca.* 1 g.) from benzene gave *α-methyl β-hydrogen* cis-γ-3,4-*methylenedioxyphenylitaconate* in needles, m. p. 143—144°, depressed on admixture with the isomeric β-half ester (Ia; R^3 = Me) (Found: C, 58·95; H, 4·6; OMe, 11·2. $C_{13}H_{12}O_6$ requires C, 59·1; H, 4·55; OMe, 11·7%).

Dimethyl cis-γ-3,4-*Methylenedioxyphenylitaconate*.—(*a*) The *cis*-β-half ester (Ia) (2 g.) with dimethyl sulphate (3 ml.) and potassium carbonate (6 g.) in acetone (30 ml.) (10 hours' refluxing) gave dimethyl *cis*-γ-3,4-methylenedioxyphenylitaconate, m. p. and mixed m. p. 82—83° [from benzene–light petroleum (b. p. 60—80°)] (Found: C, 60·6; H, 5·1. Calc. for $C_{14}H_{14}O_6$: C, 60·4; H, 5·0%). (*b*) The *cis*-α-half ester similarly gave the same diester, m. p. and mixed m. p. 82—83°.

cis-γ-3,4-*Dimethoxyphenylitaconic Acid* (Ib; R^3 = H).—The *cis*-β-half ester (Ib; R^3 = Me) (*ca.* 2 g.) was refluxed with concentrated aqueous barium hydroxide (50 ml.) for 5 hr., then worked up as described for its isomer. The *cis*-acid (1·5 g.) was obtained in diamond-shaped crystals, m. p. 168—169° (from acetone or chloroform) (Found: C, 58·2; H, 5·45; OMe, 23·0. Calc. for $C_{13}H_{14}O_6$: C, 58·6; H, 5·3; 2OMe, 23·3%). Stobbe and Leuner[9] give m. p. 175° for this acid (from water or chloroform) (with unidentified configuration).

cis-γ-3,4-*Dimethoxyphenylitaconic Anhydride*.—The *cis*-acid (Ib; R^3 = H) (2·6 g.) with acetyl chloride (25 ml.) (4 hours' refluxing) gave the anhydride (*ca.* 2·4 g.) in pale brown needles (from benzene), m. p. 169—170°, depressed on admixture with the *cis*-acid. Stobbe and Leuner[9] give m. p. 167° (Found: C, 62·8; H, 4·7; OMe, 24·45. Calc. for $C_{13}H_{12}O_5$: C, 62·9; H, 4·8; 2OMe, 25·0%).

α-Methyl β-Hydrogen cis-γ-3,4-*Dimethoxyphenylitaconate*.—The *cis*-anhydride (*ca.* 2·5 g.) in absolute methanol (100 ml.) gave, as in the preceding case, *α-methyl β-hydrogen* cis-γ-3,4-*dimethoxyphenylitaconate* (*ca.* 2·3 g.) in needles (from benzene), m. p. 151—152°, depressed on admixture with the *cis*-β-half ester (Found: C, 60·2; H, 5·9; OMe, 32·9. $C_{14}H_{16}O_6$ requires C, 60·0; H, 5·7; 3OMe, 33·2%).

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