695. *Lactones. Part III.* A Further Example of Alkyl–Oxygen Bond Fission in Phthalide Ring Opening.*

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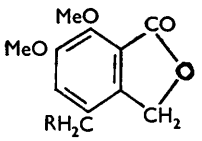
Dimethyl α-(1 : 3-dihydro-6 : 7-dimethoxy-1-oxo-4-benzo[*c*]furylmethyl)-malonate, obtained by interaction of 4-chloromethylmeconin and methyl malonate, though normally hydrolysed by aqueous alkali to the corresponding lactone dicarboxylic acid, is isomerised by methanolic sodium methoxide to 5 : 6-dimethoxy-2 : 2-di(methoxycarbonyl)indane-4-carboxylic acid. The mechanism of the rearrangement is discussed.

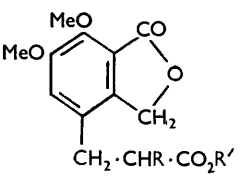
THE conversion of a 4-hydroxymethylphthalide (*e.g.*, I; R = OH) into the isomeric phthalan-4-carboxylic acid [1] (*e.g.*, II) has been examined by Blair and Newbold [2] who reported that methanolic sodium methoxide was a very effective isomerising agent. A mechanism for the rearrangement using this base was proposed [2] envisaging the participation of a carbonium ion formed by fission of the phthalide ring with rupture of the methylene–oxygen bond, *i.e.*, B_{AL} fission.[3]

This hypothesis of the formation of a carbonium ion being used it seemed of interest to endeavour to effect its union with a suitable carbanion, such as that derived from a malonic ester. No evidence of any competing reaction was forthcoming when 4-hydroxymethylmeconin (I; R = OH) was heated with an excess of methyl sodiomalonate;



(I)

(II)



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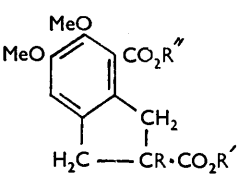


(IV)

only the normal rearrangement product 5 : 6-dimethoxyphthalan-4-carboxylic acid (II) was isolated. Attention was then turned to a possible intramolecular reaction between a carbonium ion from B_{AL} phthalide fission and a carbanion from a suitably placed α-substituted malonic ester in the same molecule; such a molecule was dimethyl α-(1 : 3-dihydro-6 : 7-dimethoxy-1-oxo-4-benzo[*c*]furylmethyl)malonate (III; R = CO_2Me, R′ = Me).

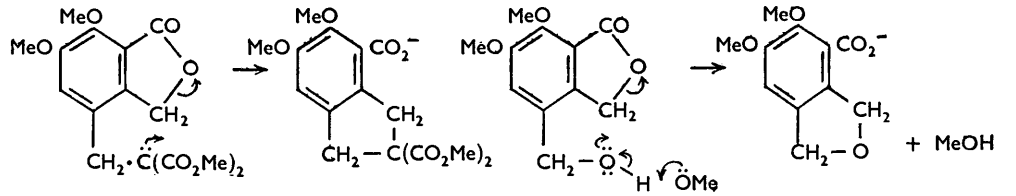
Reaction of equimolecular proportions of 4-chloromethylmeconin (I; R = Cl) and methyl sodiomalonate gave as major product this ester (III; R = CO_2Me, R′ = Me), the other constituent of the neutral fraction being the corresponding αα-di-(1 : 3-dihydro-6 : 7-dimethoxy-1-oxo-4-benzo[*c*]furylmethyl)malonate. The latter ester was characterised by hydrolysis to the malonic acid which gave back the original ester on treatment with diazomethane. The ester (III; R = CO_2Me, R′ = Me) was insoluble in aqueous sodium hydrogen carbonate and when heated with aqueous sodium hydroxide was hydrolysed to α-(1 : 3-dihydro-6 : 7-dimethoxy-1-oxo-4-benzo[*c*]furylmethyl)malonic acid (III; R = CO_2H, R′ = H) which with diazomethane gave back the ester (III; R = CO_2Me, R′ = Me); hence no change in the carbon skeleton had taken place on the aqueous alkaline treatment. The acid (III; R = CO_2H, R′ = H) was smoothly decarboxylated to β-(1 : 3-dihydro-6 : 7-dimethoxy-1-oxo-4-benzo[*c*]furyl)propionic acid (III; R = R′ = H) which showed infrared bands at 1754 (phthalide-carbonyl stretching frequency), 1698 (carboxylic acid), and 1613 cm.$^{-1}$ (aromatic ring); its methyl ester (III; R = H, R′ = Me) showed bands at 1750 (phthalide-carbonyl stretching frequency) and 1718 cm.$^{-1}$ (methoxycarbonyl group), both determinations being effected in Nujol mull.

* Part II, *J.*, 1955, 2871.

[1] Brown and Newbold, *J.*, 1952, 4878.
[2] Blair and Newbold, *J.*, 1954, 3935.
[3] Ingold, " Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 752 *et seq.*

Dimethyl α-(1 : 3-dihydro-6 : 7-dimethoxy-1-oxo-4-benzo[*c*]furylmethyl)malonate (III; R = CO_2Me, R′ = Me), when heated in methanol with 1 mol. of sodium methoxide, was isomerised to 5 : 6-dimethoxy-2 : 2-di(methoxycarbonyl)indane-4-carboxylic acid (IV; R = CO_2Me, R′ = Me, R″ = H). The latter compound was also obtained from the acid fraction of the reaction product from 4-chloromethylmeconin and methyl sodiomalonate. Alkaline hydrolysis of the acid gave 5 : 6-dimethoxyindane-2 : 2 : 4-tricarboxylic acid (IV; R = CO_2H, R′ = R″ = H), esterified by diazomethane to the trimethyl ester (IV; R = CO_2Me, R′ = R″ = Me) which was also obtained by the same treatment of the acid ester (IV; R = CO_2Me, R′ = Me, R″ = H). When dimethyl α-(1 : 3-dihydro-6 : 7-dimethoxy-1-oxo-4-benzo[*c*]furylmethyl)malonate (III; R = CO_2Me, R′ = Me) was heated with an excess of methanolic sodium methoxide a dicarboxylic acid, $C_{15}H_{16}O_8$, was formed; we formulate this compound as 5 : 6-dimethoxy-2-methoxycarbonylindane-2 : 4-dicarboxylic acid (IV; R = CO_2Me, R′ = R″ = H) since on hydrolysis it gave the tricarboxylic acid (IV; R = CO_2H, R′ = R″ = H) and on esterification with diazomethane the triester (IV; R = CO_2Me, R′ = R″ = Me). The formation of the dicarboxylic acid presumably proceeds *via* the monoacid (IV; R = CO_2Me, R′ = Me, R″ = H) by hydrolysis effected by the traces of water in the redistilled commercial methanol used as solvent.

5 : 6-Dimethoxyindane-2 : 2 : 4-tricarboxylic acid was smoothly decarboxylated by heat, to give 5 : 6-dimethoxyindane-2 : 4-dicarboxylic acid (IV; R = R′ = R″ = H) which shows infrared bands in Nujol mull at 1695 (carboxylic acid) and 1592 cm.$^{-1}$ (aromatic ring).



(V) (VI) (VII) (VIII)

Reaction of 4-chloromethylmeconin with ethyl sodiomalonate gave two solid products, (III; R = CO_2Et, R′ = Et) and the corresponding αα-disubstituted malonate. The former product on aqueous-alkaline hydrolysis gave the diacid (III; R = CO_2H, R′ = H) and on treatment with sodium ethoxide followed by hydrolysis of the acidic fraction of the reaction product gave the indane triacid (IV; R = CO_2H, R′ = R″ = H).

Electrometric titrations have been carried out on all the acids described above and, except that for (III; R = CO_2H, R′ = H), which was 6% high, the results agree closely with the calculated values of the equivalents, thus supporting the structures assigned. In their ultraviolet spectra the compounds in the phthalide series (III; R = CO_2Me, R′ = Me; R = CO_2H, R′ = H; R = R′ = H; and R = H, R′ = Me) exhibit a band at 3110—3130 Å (cf. in meconin [1] at 3080 Å) whereas the compounds in the indane series (IV; R = CO_2Me, R′ = Me, R″ = H; R = CO_2Me, R′ = R″ = H; R = CO_2H, R′ = R″ = H; and R = R′ = R″ = H) show a band at 2960—2990 Å [cf. *o*-veratric acid which shows light absorption in ethanol with maxima at 2100 (ε 20,200) and 2950 Å (ε 2100)]; this difference in spectra supports the respective structures.

Though we have used the carbonium–carbanion union as a working hypothesis we consider that the mechnism of the conversion of the phthalide-malonic ester to the indane derivative is best represented by (V) ⟶ (VI), *i.e.*, as a concerted electron-transfer. It is difficult to visualise B_{AL} phthalide fission which, while initiated by the methoxide ion, is not followed by reaction of the carbonium ion to form a methyl ether, as in the $B_{AL}2$ (S_N2) reaction of methyl benzoate with methoxide ion to give dimethyl ether and benzoate ion.[4] It follows that the hydroxymethylphthalide–phthalancarboxylic acid rearrangement is represented by (VII) ⟶ (VIII).

These mechanisms still involve B_{AL} fission of the phthalide ring but avoid the difficulties

[4] Bunnett, Robison, and Pennington, *J. Amer. Chem. Soc.*, 1950, **72**, 2378.

associated with initial carbonium-ion formation. The hydroxymethylphthalide–phthalan-carboxylic acid rearrangement is also brought about by aqueous sodium carbonate, a reagent less effective than sodium methoxide but much more effective than sodium hydroxide.[2] The carbonate-induced reaction may involve carbonium-ion formation ($B_{AL}1$ fission) as an initial step, support being given for this by the experiences of Kenyon *et al.*[5] in the hydrolysis of methylphenylallyl alcohols by sodium carbonate and hydroxide. The remaining stage of the reaction could then follow Blair and Newbold's scheme.[2]

Experimental

Ultraviolet absorption spectra were determined for EtOH solutions; equivalents were determined in water under nitrogen according to the method of Catch, Cook, and Kitchener.[6] Redistilled commercial methanol was used in all experiments.

Dimethyl α-(1 : 3-*Dihydro*-6 : 7-*dimethoxy*-1-*oxo*-4-*benzo*[c]*furylmethyl*)*malonate.*—A solution of 4-chloromethylmeconin (4·85 g.) in warm methanol (55 c.c.) was added in one portion to methanolic methyl sodiomalonate prepared from the ester (2·64 g.), methanol (25 c.c.), and sodium (0·46 g.). The solution was refluxed for 3 hr., rapid separation of sodium chloride being observed. The mixture was concentrated under reduced pressure, and the residue diluted with water (25 c.c.) and extracted with chloroform (3 × 30 c.c.). The combined extracts were washed with 10% aqueous sodium hydrogen carbonate (2 × 30 c.c.) (combined extract A), then water, and dried (Na_2SO_4). Evaporation of the chloroform gave a clear yellow gum (5·72 g.) which partially solidified. The crystals (solid B) were separated by addition of benzene (25 c.c.) and filtration. The filtrate was percolated through a column of Grade II alumina (2 × 6 cm.) which was further washed with benzene (50 c.c.). Evaporation of the combined eluates gave a clear gum which was dissolved in methanol (36 c.c.), concentrated to 12 c.c., and kept at 0°. The crystalline crop was extracted with warm methanol (35 c.c.) and filtered (solid C). Concentration and cooling of the filtrate gave crystals, m. p. 122—124° (1·42 g.), which separated from methanol to give *dimethyl* α-(1 : 3-*dihydro*-6 : 7-*dimethoxy*-1-*oxo*-4-*benzo*-[c]*furylmethyl*)*malonate* as prismatic needles, m. p. 123—125°, or blades from benzene–light petroleum (b. p. 60—80°) (Found : C, 57·0; H, 5·4. $C_{16}H_{18}O_8$ requires C, 56·8; H, 5·4%). The compound sublimes at 130°/10^{-4} mm. (bath-temp.). Light absorption : max. at 2100 (ε 48,000) and 3110 Å (ε 5600).

Dimethyl αα-Di-(1 : 3-*Dihydro*-6 : 7-*dimethoxy*-1-*oxo*-4-*benzo*[c]*furylmethyl*)*malonate.*—Solids B (195 mg.; m. p. 186—191°) and C (182 mg.; m. p. 192—193°) from the preceding experiment were combined and crystallised from benzene, to give the *ester* (340 mg.) as needles, m. p. 197—198° (Found : C, 59·5, 59·8; H, 5·5, 5·2; OMe, 34·3. $C_{27}H_{28}O_{12}$ requires C, 59·55; H, 5·2; 6OMe, 34·2%).

Reaction of 4-*Chloromethylmeconin with Ethyl Malonate.*—The same molar proportions being used as in the methyl malonate reaction, 4-chloromethylmeconin (6·0 g.) was refluxed for 2 hr. with ethanolic ethyl sodiomalonate. Isolation by use of chloroform gave a neutral fraction (5·9 g.), m. p. 80—100°. Crystallisation from benzene gave as the component of smaller solubility *diethyl αα-di-*(1 : 3-*dihydro*-6 : 7-*dimethoxy*-1-*oxo*-4-*benzo*[c]*furylmethyl*)*malonate* (1·5 g.) which separated as needles, m. p. 168—169·5° (Found : C, 61·1; H, 5·6. $C_{29}H_{32}O_{12}$ requires C, 60·8; H, 5·6%). Fractional crystallisation of the material in the benzene mother-liquors gave the more soluble component, *diethyl* α-(1 : 3-*dihydro*-6 : 7-*dimethoxy*-1-*oxo*-4-*benzo*[c]*furyl-methyl*)*malonate* (1·1 g.) which separated from benzene–light petroleum (b. p. 60—80°) as needles, m. p. 114—115° (Found : C, 58·9; H, 6·1. $C_{18}H_{22}O_8$ requires C, 59·0; H, 6·05%). Light absorption : Max. at 2080 (ε 44,000) and 3100 Å (ε 4300). No crystalline material was obtained from the bicarbonate-soluble fraction (0·5 g.).

αα-Di-(1 : 3-*dihydro*-6 : 7-*dimethoxy*-1-*oxo*-4-*benzo*[c]*furylmethyl*)*malonic Acid.*—Dimethyl αα-di-(1 : 3-dihydro-6 : 7-dimethoxy-1-oxo-4-benzo[*c*]furylmethyl)malonate (50 mg.) was refluxed in a mixture of ethanol (2·5 c.c.) and 2N-aqueous sodium hydroxide (2·5 c.c.) for 2 hr. Removal of ethanol and acidification (Congo-red) with hydrochloric acid gave the *acid* (35 mg.) which separated from aqueous acetone as needles, m. p. 228° (Found : C, 58·2; H, 4·8%; equiv., 245. $C_{25}H_{24}O_{12}$ requires C, 58·1; H, 4·7%; equiv., 258). Esterification with diazomethane gave the dimethyl ester as needles, m. p. and mixed m. p. 197—198°, from benzene. The same acid was obtained by hydrolysis of the diethyl ester and separated from aqueous acetone as needles, m. p. and mixed m. p. 228°.

[5] Kenyon, Partridge, and Phillips, *J.*, 1936, 85; 1937, 207.
[6] Catch, Cook, and Kitchener, *J.*, 1945, 319.

α-(1 : 3-*Dihydro*-6 : 7-*dimethoxy*-1-*oxo*-4-*benzo*[c]*furylmethyl*)*malonic Acid.*—(*a*) Dimethyl α-(1 : 3-dihydro-6 : 7-dimethoxy-1-oxo-4-benzo[*c*]furylmethyl)malonate (100 mg.) was heated under reflux with 2N-aqueous sodium hydroxide (4 c.c.) for 1 hr. The cooled solution was acidified (Congo-red) with concentrated hydrochloric acid. The crystalline precipitate was separated and crystallised from water, to give the *acid* (80 mg.) as plates, m. p. 153—155° (decomp.) (Found : C, 54·1; H, 4·9%; equiv., 165. $C_{14}H_{14}O_8$ requires C, 54·2; H, 4·55%; equiv., 155). Light absorption : Max. at 2100 (ε 30,000) and 3130 Å (ε 4450).

(*b*) By the same method the corresponding diethyl ester gave the acid, as plates (from water), m. p. 153—155° (decomp.) alone or mixed with preparation (*a*).

Treatment of the acid with excess of ethereal diazomethane followed by evaporation and crystallisation of the residue from methanol gave dimethyl α-(1 : 3-dihydro-6 : 7-dimethoxy-1-oxo-4-benzo[*c*]furylmethyl)malonate as prismatic needles, m. p. and mixed m. p. 123—125°.

β-(1 : 3-*Dihydro*-6 : 7-*dimethoxy*-1-*oxo*-4-*benzo*[c]*furyl*)*propionic Acid.*—α-(1 : 3-Dihydro-6 : 7-dimethoxy-1-oxo-4-benzo[*c*]furylmethyl)malonic acid (100 mg.) was heated at 190—200° (bath-temp.) at atmospheric pressure until decarboxylation was complete and the residue sublimed at 170—180°/10^{-3} mm. (bath-temp.), to give the *acid* (70 mg.) which separated from methanol as flat prisms, m. p. 166—168° (Found : C, 58·5; H, 5·5%; equiv., 264. $C_{13}H_{14}O_6$ requires C, 58·6; H, 5·3%; equiv., 266). Light absorption : Max. at 2100 (ε 33,500) and 3120 Å (ε 4750). The *methyl ester*, prepared by using ethereal diazomethane, separated from aqueous methanol as flat prisms, m. p. 93—94° (Found : C, 60·15; H, 6·1. $C_{14}H_{16}O_6$ requires C, 60·0; H, 5·75%). Light absorption : Max. at 2130 (ε 30,000) and 3120 Å (ε 4600).

5 : 6-*Dimethoxy*-2 : 2-*di*(*methoxycarbonyl*)*indane*-4-*carboxylic Acid.*—(*a*) The sodium hydrogen carbonate extract A (above) was acidified (Congo-red) with concentrated hydrochloric acid and extracted with chloroform (3 × 50 c.c.). After being washed with water the combined extract was dried ($NaSO_4$) and evaporated to a light yellow gum (750 mg.) which was triturated with cold methanol (5 c.c.), and the resulting solid separated. Crystallisation from aqueous methanol gave the *acid* (300 mg.) as blades, m. p. 131—132° (Found : C, 57·2; H, 5·5%; equiv., 337·5. $C_{16}H_{18}O_8$ requires C, 56·8; H, 5·4%; equiv., 338). Light absorption : Max. at 2110 (ε 25,700 and 2980 Å (ε 4200).

(*b*) A solution of dimethyl α-(1 : 3-dihydro-6 : 7-dimethoxy-1-oxo-4-benzo[*c*]furylmethyl)-malonate (338 mg.) in methanol (10 c.c.) containing sodium methoxide from sodium (23 mg.; 1 equiv.) was refluxed for 8 hr. The solution was evaporated under reduced pressure, the residue treated with water (15 c.c.) (partial solution), and the mixture extracted with chloroform (3 × 25 c.c.). The acid fraction was isolated by means of sodium hydrogen carbonate as in (*a*), to give 5 : 6-dimethoxy-2 : 2-di(methoxycarbonyl)indane-4-carboxylic acid (190 mg.) which separated from aqueous methanol as blades, m. p. 130—131·5° alone or mixed with preparation (*a*). Unchanged material (100 mg.), prismatic needles (from methanol), m. p. and mixed m. p. 121—123°, was obtained from the neutral fraction.

5 : 6-*Dimethoxy*-2-*methoxycarbonylindane*-2 : 4-*dicarboxylic Acid.*—A solution of dimethyl α-(1 : 3-dihydro-6 : 7-dimethoxy-1-oxo-4-benzo[*c*]furylmethyl)malonate (1·0 g.) in methanol (25 c.c.) containing sodium methoxide [from sodium (0·55 g.)] was refluxed for 9 hr., concentrated under reduced pressure, and diluted with water. Isolation of the acid fraction through chloroform and sodium hydrogen carbonate gave an amber gum (900 mg.), which solidified. Trituration with dry ether, filtration from a trace of insoluble material, concentration of the filtrate, and treatment with light petroleum (b. p. 40—60°) gave a solid, two crystallisations of which from ether–light petroleum (b. p. 40—60°) gave the *acid* (500 mg.) as prismatic needles, m. p. 163—165° (Found : C, 55·85; H, 5·2%; equiv., 168. $C_{15}H_{16}O_8$ requires C, 55·55; H, 5·0%; equiv., 162). Light absorption : Max. at 2090 (ε 19,000) and 2990 Å (ε 3600).

5 : 6-*Dimethoxyindane*-2 : 2 : 4-*tricarboxylic Acid.*—(*a*) 5 : 6-Dimethoxy-2 : 2-di(methoxycarbonyl)indane-4-carboxylic acid (250 mg.) was heated on the steam-bath for 1 hr. with 2N-aqueous sodium hydroxide (5 c.c.). The cooled solution was made acid (Congo-red) with hydrochloric acid (*d* 1·15), and the precipitate collected. Crystallisation from water gave 5 : 6-*dimethoxyindane*-2 : 2 : 4-*tricarboxylic acid* (190 mg.) as prismatic needles, m. p. 185—187° (decomp.) (Found : C, 54·5; H, 4·8%; equiv., 103. $C_{14}H_{14}O_8$ requires C, 54·2; H, 4·55%; equiv., 103). Light absorption : Max. at 2080 (ε 25,800) and 2975 Å (ε 3900). The same acid, m. p. and mixed m. p. 185—187°, was obtained by hydrolysis of 5 : 6-dimethoxy-2-methoxycarbonylindane-2 : 4-dicarboxylic acid.

(*b*) Diethyl α-(1 : 3-dihydro-6 : 7-dimethoxy-1-oxo-4-benzo[*c*]furylmethyl)malonate (1·25 g.) was added to a warm solution of sodium ethoxide in dry ethanol (25 c.c.) [from sodium (0·7 g.)]. The yellow solution was refluxed for 8 hr., concentrated to small bulk under reduced pressure,

diluted with water, and acidified (Congo-red) with hydrochloric acid (*d* 1·15). The acid fraction, a clear light brown gum (1·0 g.), was isolated by using chloroform and aqueous sodium hydrogen carbonate. Hydrolysis of the gum, which did not solidify, as in (*a*) gave the acid (0·55 g.), crystallising from water as prismatic needles, m. p. 185—187° alone or mixed with preparation (*a*) (Found: C, 54·4; H, 4·7%).

Methyl 5 : 6-*Dimethoxyindane*-2 : 2 : 4-*tricarboxylate*.—5 : 6-Dimethoxy-2 : 2-di(methoxycarbonyl)indane-4-carboxylic acid (100 mg.) in methanol (5 c.c.) was treated with excess of ethereal diazomethane and kept overnight. Removal of solvent and crystallisation from benzene–light petroleum (b. p. 40—60°) gave the *ester* as prisms, m. p. 78·5—80·5° (Found: C, 58·3; H, 6·0. $C_{17}H_{20}O_8$ requires C, 57·95; H, 5·7%). Light absorption: Max. at 2080 (ε 21,500) and 2990 Å (ε 4200). The same ester, m. p. and mixed m. p. 78·5—80·5°, was obtained by the action of diazomethane on 5 : 6-dimethoxyindane-2 : 2 : 4-tricarboxylic or 5 : 6-dimethoxy-2-methoxycarbonylindane-2 : 4-dicarboxylic acid.

5 : 6-*Dimethoxyindane*-2 : 4-*dicarboxylic Acid*.—5 : 6-Dimethoxyindane-2 : 2 : 4-tricarboxylic acid (100 mg.) was heated at 200—210° (bath-temp.) under atmospheric pressure until no further evolution of carbon dioxide took place. Sublimation at 160°/10^{-4} mm. followed by crystallisation from ethyl acetate–light petroleum (b. p. 40—60°) gave 5 : 6-*dimethoxyindane*-2 : 4-*dicarboxylic acid* (60 mg.) as prisms, m. p. 153·5—155° (Found: C, 59·1; H, 5·5%; equiv., 131. $C_{13}H_{14}O_6$ requires C, 58·6; H, 5·3%; equiv., 133). Light absorption: Max. at 2100 (ε 23,000) and 2960 Å (ε 3900).

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