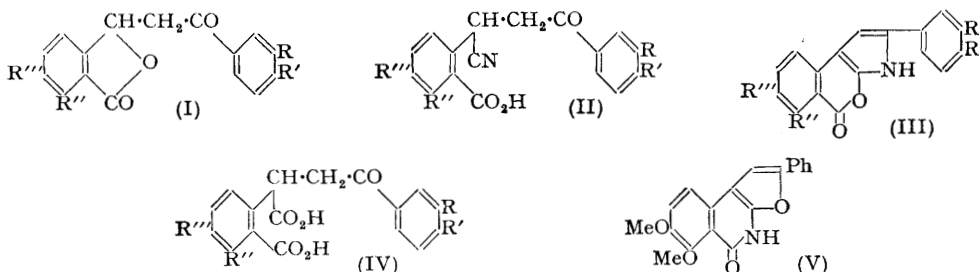


### 399. The Preparation of Some Substituted Homophthalic Acids.

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Addition of hydrogen cyanide to 3-phenacylphthalides in 2-methoxyethanol, followed by a two-stage hydrolysis, is a general method for the preparation of substituted homophthalic acids.

ADDITION of hydrogen cyanide to 6 : 7-dimethoxy-3-(3 : 4-dimethoxyphenacyl)phthalide (I;  $R = R' = R'' = R''' = \text{OMe}$ ) gave  $\alpha$ -(2-carboxy-3 : 4-dimethoxyphenyl)- $\beta$ -(3 : 4-dimethoxybenzoyl)propionitrile (II;  $R = R' = R'' = R''' = \text{OMe}$ ), which was converted by heat or mineral acids into the lactone of 3-(2-carboxy-3 : 4-dimethoxyphenyl)-5-(3 : 4-dimethoxyphenyl)-2-hydroxypyrrole (III;  $R = R' = R'' = R''' = \text{OMe}$ ). This was then hydrolysed by alkali to  $\alpha$ -(2-carboxy-3 : 4-dimethoxyphenyl)- $\beta$ -(3 : 4-dimethoxybenzoyl)propionic acid (IV;  $R = R' = R'' = R''' = \text{OMe}$ ) (Bailey and Robinson, *J.*, 1950, 1375).



This series of reactions has now been shown to be general for phenacylphthalides, the following phthalides having been taken through the sequence (I  $\rightarrow$  IV) : 6 : 7-dimethoxy-3-4'-methoxyphenacylphthalide (I;  $R = \text{H}$ ,  $R' = R'' = R''' = \text{OMe}$ ), 6 : 7-dimethoxy-3-*p*-tolylphthalide (I;  $R = \text{H}$ ,  $R' = \text{Me}$ ,  $R'' = R''' = \text{OMe}$ ), and phenacylphthalide (I;  $R = R' = R'' = R''' = \text{H}$ ).

The nitrile (II;  $R = R' = R'' = R''' = \text{H}$ ) is more sensitive to mineral acids than are the corresponding nitriles having methoxyl or methyl groups at  $R'$ , and may be partly converted into the pyrrole lactone during isolation; this is presumably due to the deactivation of the carbonyl group of (II) by methoxyl or methyl at  $R'$ .

The only other example of this sequence of reactions appears to be due to Haworth (*J.*, 1937, 1312) who treated 6 : 7-dimethoxy-3-phenacylphthalide (I;  $R = R' = \text{H}$ ,  $R'' = R''' = \text{OMe}$ ) with hydrogen cyanide at room temperature and obtained a gum which, on being boiled with hydrochloric acid, gave a solid to which Haworth ascribed structure (V). Alkaline hydrolysis of this solid gave an unidentified substance (m. p. 185°).

Addition of hydrogen cyanide to (I;  $R = R' = \text{H}$ ,  $R'' = R''' = \text{OMe}$ ) under the conditions described by Bailey and Robinson (*loc. cit.*) gave  $\beta$ -benzoyl- $\alpha$ -(2-carboxy-3 : 4-dimethoxyphenyl)propionitrile (II;  $R = R' = \text{H}$ ,  $R'' = R''' = \text{OMe}$ ) as a solid. The latter was converted by heat or acid into (III;  $R = R' = \text{H}$ ,  $R'' = R''' = \text{OMe}$ ) identical with the substance obtained by Haworth. We prefer structure (III) to (V) for reasons set out previously (Bailey and Robinson, *loc. cit.*). The ultra-violet spectra of (III;  $R = R' = R'' = R''' = \text{OMe}$ ), (III;  $R = \text{H}$ ,  $R' = \text{Me}$ ,  $R'' = R''' = \text{OMe}$ ), and (III;  $R = R' = \text{H}$ ,  $R'' = R''' = \text{OMe}$ ) were very similar, showing that the compound prepared by Haworth belongs to this class of substance. Hydrolysis of (III;  $R = R' = \text{H}$ ,  $R'' = R''' = \text{OMe}$ ) gave  $\beta$ -benzoyl- $\alpha$ -(2-carboxy-3 : 4-dimethoxyphenyl)propionic acid (IV;  $R = R' = \text{H}$ ,  $R'' = R''' = \text{OMe}$ ), m. p. 172–174°. This had the expected properties and the melting point could not be raised, even after conversion of the acid into its anhydride and hydrolysis of the purified anhydride. The nature of the product obtained by Haworth is obscure.

Acids of type (II) have been esterified with diazomethane. The esters so obtained were stable to mineral acids or heat under conditions which rapidly transformed the free acids into the pyrrole lactones (III), indicating that the free carboxyl group is essential for the conversion (II)  $\rightarrow$  (III).

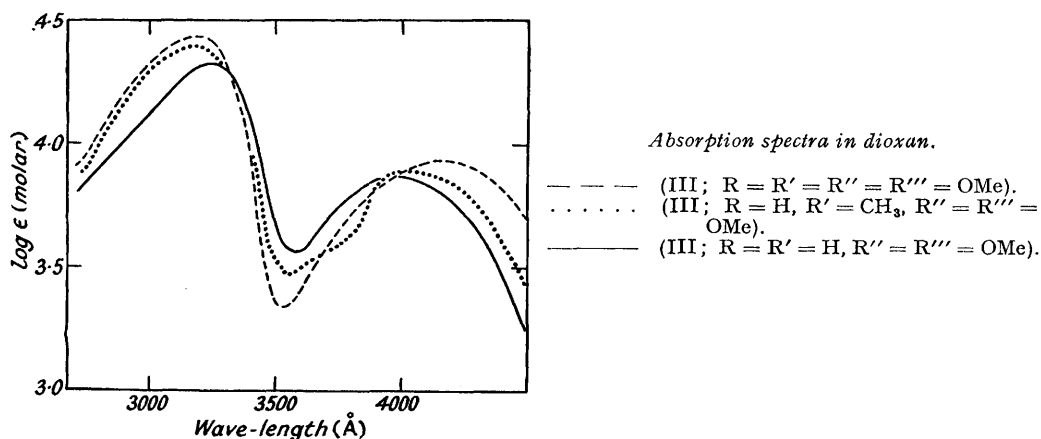
## EXPERIMENTAL

*Phthalides*.—6 : 7-Dimethoxy-3-4'-methoxyphenacylphthalide. Methanol (ca. 40 c.c.) was added to a suspension of *p*-methoxyacetophenone (16 g.) and opianic acid (21 g.) in 10% sodium hydroxide solution (70 c.c.) until a homogeneous solution was obtained. The reaction mixture was kept at room temperature for 24 hours and then acidified with dilute hydrochloric acid. The gum which separated soon solidified. It was collected, washed with water, and crystallised from 70% acetic acid (29.5 g.; m. p. 144—146°). The *phthalide* formed colourless needles (from dilute acetic acid), m. p. 146—147° (Found: C, 66.9; H, 5.3.  $C_{19}H_{18}O_6$  requires C, 66.7; H, 5.2%).

6 : 7-Dimethoxy-3-4'-methylphenacylphthalide, prepared from *p*-methylacetophenone and opianic acid, formed colourless needles (from 80% acetic acid), m. p. 142—143° (Found: C, 69.7; H, 5.3.  $C_{19}H_{18}O_6$  requires C, 70.0; H, 5.5%).

6 : 7-Dimethoxy-3-phenacylphthalide and phenacylphthalide were prepared in aqueous-methanolic solution as described above rather than in aqueous solution as used by Goldschmidt (*Monatsh.*, 1891, 12, 476). When the substances were crystallised from ethanol as suggested by Goldschmidt they decomposed on storage; crystallisation from dilute acetic acid gave stable products.

*Nitriles*.— $\alpha$ -(2-Carboxy-3 : 4-dimethoxyphenyl)- $\beta$ -*p*-methoxybenzoylpropionitrile. Sodium acetate (4 g., 1.1 mols.) was added to a solution of 6 : 7-dimethoxy-3-4'-methoxyphenacylphthalide



(10 g., 1 mol.) in boiling 2-methoxyethanol (30 c.c.). Potassium cyanide (4 g., 2.3 mols.) in water (10 c.c.) was added during 2 mins. below the surface of the yellow solution which was heated in a boiling-water bath. The heating was continued for 10 minutes, the liquid being gently stirred every minute, then the solution was cooled and acidified with 2N-hydrochloric acid, and the gum which separated washed by decantation. Digestion with warm 50% acetic acid gave a crystalline solid (ca. 70%) which was crystallised from light petroleum (b. p. 40—60°)—ethyl acetate (1 : 3). The *nitrile* formed colourless needles (Found: C, 64.8; H, 5.3; N, 3.4.  $C_{20}H_{19}O_6N$  requires C, 65.1; H, 5.2; N, 3.7%) which melted at 120—122°, evolving gas and forming a bright yellow solid which then melted at 244—246°. The substance was soluble in dilute sodium carbonate solution; when heated on the water-bath for 5 minutes, its colourless solution in aqueous ammonia (*d* 0.88) became deep green.

$\alpha$ -(2-Carboxy-3 : 4-dimethoxyphenyl)- $\beta$ -*p*-methylbenzoylpropionitrile was similarly prepared from 6 : 7-dimethoxy-3-4'-methylphenacylphthalide. From benzene it formed colourless rhombs (Found: C, 68.3; H, 5.6; N, 4.0.  $C_{20}H_{19}O_6N$  requires C, 68.0; H, 5.4; N, 4.0%) which became pale yellow at 114° and melted at 132—133° with decomposition setting to an orange solid, m. p. 256—257°. The colourless solution of the nitrile in aqueous ammonia (*d* 0.88) became deep green when heated.

$\beta$ -Benzoyl- $\alpha$ -*o*-carboxyphenylpropionitrile was similarly prepared from phenacylphthalide. Its solution in 2-methoxyethanol must be thoroughly cooled before the addition of mineral acid. The nitrile crystallised directly without digestion with 50% acetic acid. Crystallisation from methanol or ethyl acetate gave colourless rods, m. p. 270—280° (decomp.) (yellow at 110° without melting) (Found: C, 73.3; H, 5.0; N, 5.2%; equiv., 292.  $C_{16}H_{12}ON \cdot CO_2H$  requires

C, 73.2; H, 4.7; N, 5.0%; equiv., 279). A blue solution was formed when the nitrile was heated in aqueous ammonia ( $d$  0.88).

$\beta$ -Benzoyl- $\alpha$ -(2-carboxy-3:4-dimethoxyphenyl)propionitrile is also rather sensitive to mineral acids. It crystallised from benzene in colourless rhombs, double m. p. 122—125° and (yellow solid) 282—284° (Found: C, 67.5; H, 5.0; N, 3.6, 4.4.  $C_{19}H_{17}O_5N$  requires C, 67.3; H, 5.0; N, 4.0%). Its ammoniacal solution became blue on being heated.

**Lactones (III).**—Lactone of 3-(2-carboxy-3:4-dimethoxyphenyl)-2-hydroxy-5-*p*-methoxyphenylpyrrole [7:8-dimethoxy-5'-*p*-methoxyphenylpyrrolo(2':3'-3:4)isocoumarin]. The crude material (II; R = H, R' = R'' = R''' = OMe) from the cyanide addition was dissolved in boiling glacial acetic acid (15 c.c.), the source of heat removed, and concentrated hydrochloric acid (1 c.c.) added. A thick yellow precipitate appeared immediately. The mixture was heated on the water-bath for 10 minutes, then cooled, water (10 c.c.) was added, and the solid was collected, washed well with water and 50% methanol, and dried (3.4 g. from 5 g. of phthalide). Two crystallisations from nitrobenzene gave the lactone as long orange needles, m. p. 247—248° (Found: C, 68.4; H, 4.9; N, 4.1.  $C_{20}H_{17}O_5N$  requires C, 68.4; H, 4.8; N, 4.0%).

The lactone of 3-(2-carboxy-3:4-dimethoxyphenyl)-2-hydroxy-5-*p*-tolylpyrrole, obtained in 90% yield from the phthalide, formed orange needles, m. p. 256—257° from dioxan (Found: C, 71.5; H, 5.0; N, 4.2.  $C_{20}H_{17}O_4N$  requires C, 71.6; H, 5.1; N, 4.2%).

The lactone of 3-(2-carboxyphenyl)-2-hydroxy-5-phenylpyrrole started to separate immediately  $\beta$ -benzoyl- $\alpha$ -o-carboxyphenylpropionitrile was dissolved in boiling acetic acid, before the hydrochloric acid was added. Crystallisation from 2-ethoxyethanol gave clusters of yellow needles, m. p. 278—280° (decomp.) (Found: C, 78.0; H, 4.3; N, 5.0.  $C_{17}H_{11}O_2N$  requires C, 78.2; H, 4.2; N, 5.4%).

The lactone of 3-(2-carboxy-3:4-dimethoxyphenyl)-2-hydroxy-5-phenylpyrrole was prepared in three ways: (a) by the action of concentrated hydrochloric acid on a solution of the corresponding nitrile in acetic acid (it had m. p. 286—287°); (b) by heating the nitrile at 140—150°, crystallisation of the resulting glass from nitrobenzene giving yellow needles, m. p. 287—288° (Found: C, 71.2; H, 4.6; N, 4.2.  $C_{19}H_{16}O_4N$  requires C, 71.0; H, 4.7; N, 4.4%); (c) as described by Haworth (*loc. cit.*). The three preparations were identical (mixed m. p.).

**Acids (IV).**— $\alpha$ -(2-Carboxy-3:4-dimethoxyphenyl)- $\beta$ -*p*-methoxybenzoylpropionic acid. The lactone of 3-(2-carboxy-3:4-dimethoxyphenyl)-2-hydroxy-5-*p*-methoxyphenylpyrrole (5 g.) was heated with 10% sodium hydroxide solution (50 c.c.) on the water-bath for 1.5 hours and then refluxed until evolution of ammonia ceased (*ca.* 30 minutes). Acidification of the filtered solution with hydrochloric acid gave a white solid which, collected, washed with water, and crystallised from 50% acetic acid, had m. p. 176—178° (4.9 g.). Two further crystallisations gave  $\alpha$ -(2-carboxy-3:4-dimethoxyphenyl)- $\beta$ -*p*-methoxybenzoylpropionic acid as colourless rhombs, m. p. 179—180° (decomp.) [Found: C, 61.6; H, 5.2%; equiv., 201.  $C_{18}H_{18}O_4(CO_2H)_2$  requires C, 61.8; H, 5.3%; equiv., 194]. Refluxing the acid with acetic anhydride gave the anhydride, colourless rhombs (from benzene), m. p. 170—171° (Found: C, 64.9; H, 4.9.  $C_{20}H_{18}O_7$  requires C, 64.8; H, 4.9%). The anhydride is soluble in 2*N*-sodium hydroxide, forming a yellow solution.

$\alpha$ -(2-Carboxy-3:4-dimethoxyphenyl)- $\beta$ -*p*-tolylpropionic acid, obtained by hydrolysis of the appropriate lactone, formed rods, m. p. 210—211° (decomp.), from 70% acetic acid [Found: C, 64.3; H, 5.7%; equiv., 188.  $C_{18}H_{18}O_3(CO_2H)_2$  requires C, 64.5; H, 5.4%; equiv., 186]; the anhydride formed plates, m. p. 161—162°, from benzene (Found: C, 67.3; H, 4.8.  $C_{20}H_{18}O_6$  requires C, 67.8; H, 5.1%).

$\beta$ -Benzoyl- $\alpha$ -o-carboxyphenylpropionic acid formed clusters of diamond-shaped plates, m. p. 181—183° (decomp.), from 70% acetic acid [Found: C, 68.8; H, 4.9%; equiv., 148.  $C_{15}H_{12}O(CO_2H)_2$  requires C, 68.5; H, 4.7%; equiv., 149]. The anhydride formed a felted mass of needles, m. p. 156—157°, from ethyl acetate (Found: C, 73.1; H, 4.6.  $C_{17}H_{12}O_4$  requires C, 72.9; H, 4.3%).

$\beta$ -Benzoyl- $\alpha$ -(2-carboxy-3:4-dimethoxyphenyl)propionic acid was prepared by the hydrolysis of the lactone of 3-(2-carboxy-3:4-dimethoxyphenyl)-2-hydroxy-5-phenylpyrrole. It crystallised from 60% acetic acid in rods, m. p. 172—174° (decomp.) unchanged by crystallisation from benzene-ethanol (9:1) [Found: C, 63.8; H, 4.9.  $C_{17}H_{16}O_3(CO_2H)_2$  requires C, 63.7; H, 5.0%]. The anhydride formed rhombs, m. p. 150—151° from benzene (Found: C, 67.2; H, 4.9.  $C_{19}H_{16}O_6$  requires C, 67.1; H, 4.7%). The yellow solution of this anhydride in 2*N*-sodium hydroxide was heated on the water-bath until the colour disappeared (15 minutes); acidification and crystallisation from dilute acetic acid then gave the acid, m. p. 170—171° (decomp.) (Found: C, 63.7; H, 5.2%; equiv., 178. Required: equiv., 179).

**Esters of (II).**— $\alpha$ -(2-Carbomethoxy-3:4-dimethoxyphenyl)- $\beta$ -(3:4-dimethoxybenzoyl)propio-

*nitrile*. A solution of  $\alpha$ -(2-carboxy-3 : 4-dimethoxyphenyl)- $\beta$ -(3 : 4-dimethoxybenzoyl)propionitrile (1 g.) was dissolved in methanol (5 c.c.) and esterified with excess of diazomethane. The solvents were removed and the *ester* crystallised from ethyl acetate as colourless rods, m. p. 149—150° (Found : C, 64.2; H, 5.8; N, 3.3.  $C_{22}H_{23}O_7N$  requires C, 64.0; H, 5.6; N, 3.4%).

$\beta$ -Benzoyl- $\alpha$ -(2-carbomethoxy-3 : 4-dimethoxyphenyl)propionitrile formed prisms (from ethanol), m. p. 115—116° (Found : C, 68.0; H, 5.5; N, 4.1.  $C_{20}H_{19}O_5N$  requires C, 68.1; H, 5.4; N, 4.0%).

$\alpha$ -(2-Carbomethoxy-3 : 4-dimethoxyphenyl)- $\beta$ -p-methoxybenzoylpropionitrile formed clusters of rods (from ethanol), m. p. 90—91° (Found : C, 66.4; H, 5.6; N, 4.1.  $C_{21}H_{21}O_6N$  requires C, 65.9; H, 5.5; N, 3.7%).

These esters were stable to heat and mineral acids under conditions which caused dehydration of the free acids to the corresponding pyrrole lactones.

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