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3-(2-Carboxybenzyl) isocoumarin, a Byproduct in the Preparation of Homophthalimide*

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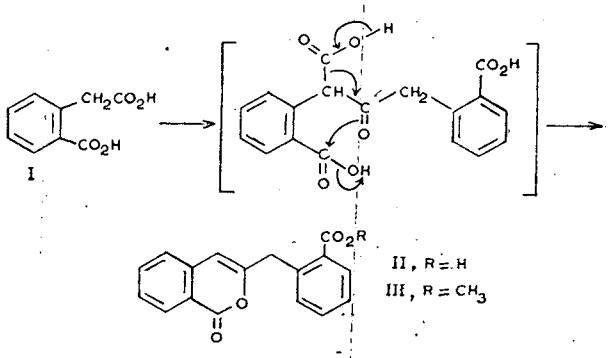
3-(2-Carboxybenzyl) isocoumarin is formed as a byproduct in the conversion of homophthalic acid to its imide. The structure has been established by alkaline hydrolysis to α,α′-bis(2-carboxyphenyl) acetone. Further transformations of the diacid are described.

IN the course of a large scale conversion of homophthalic acid (I) into its imide by the pyrolysis of the ammonium salt in *o*-dichlorobenzene, a nitrogen-free acid (II), m.p. 208-9°, was isolated as a byproduct in about 5 per cent yield. The substance (II, $C_{17}H_{12}O_4$) obviously arose by self condensation of homophthalic acid. Its UV spectrum showed absorption maxima at 230, 256, 266, 276 and 328 mμ. The IR spectrum had bands at 1605, 1610, 1662, 1685 and 1725 cm.$^{-1}$. These data were indicative of (II) being an isocoumarin derivative. Treatment of (II) with ethereal diazomethane gave the methyl ester (III), $C_{12}H_{18}O_4$, m.p. 107-9°. Its UV and IR spectra were again characteristic of an isocoumarin. Its NMR spectrum (Fig. 1) showed signals at 234 (singlet, 3H), 260 (singlet, 2H), 368 (singlet, 1H), 430-473 (multiplet, 6H), 483 (broad doublet, 1H) and 497 *cps* (broad doublet, 1H). Structure (II) could be thus deduced for the byproduct, which could arise from homophthalic acid by the obvious route indicated. The structure assignment was supported by further transformations.



Alkaline hydrolysis of the isocoumarin (II) gave a dibasic acid (IV), $C_{17}H_{14}O_5$, m.p. 204-5° (decomp.) (*p*Ka 5·94, 7·95 in 80 per cent MCS). Its UV ($\lambda_{max.}$ 228 and 280 mμ) and IR spectra (bands at 1670 and 1710 cm.$^{-1}$) were indicative of its being an aromatic dicarboxylic acid.

Esterification with ethereal diazomethane gave the dimethyl ester (V), $C_{19}H_{18}O_5$, m.p. 90-92°, from

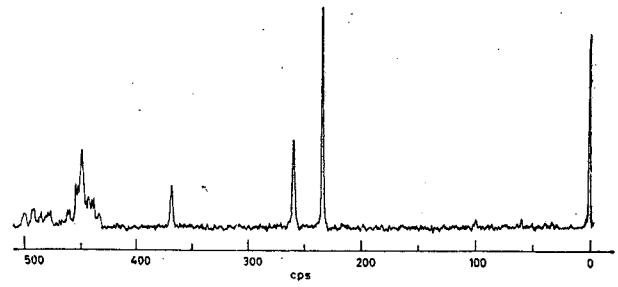
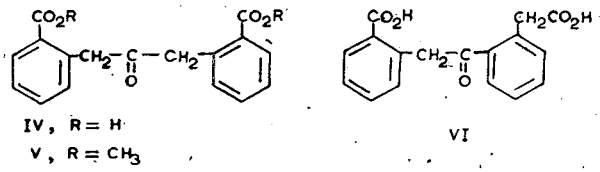


Fig. 1 — NMR spectrum of 3-(*o*-carboxybenzyl) isocoumarin methyl ester (III)

which (IV) could be recovered by saponification. The IR and UV spectra of (V) were again characteristic of benzoates. The NMR spectrum of (V) showed signals at 229 (singlet, 6H), 253 (singlet, 4H), 423-455 (multiplet, 6H) and 475 *cps* (broad doublet, 2H). The diester (V) was not reducible catalytically. It formed a yellow 2,4-dinitrophenylhydrazone, m.p. 125-6°, showing IR bands at 1600, 1615, 1715 and 1722 cm.$^{-1}$. The UV spectrum ($\lambda_{max.}$ 365 mμ) indicated that (V) was a saturated ketone. Permanganate oxidation of the diacid (IV) yielded only phthalic acid. The structure of the diacid can thus be deduced as α,α′-bis(2-carboxyphenyl) acetone (IV).



A literature search revealed that a dibasic acid, $C_{17}H_{14}O_5$, m.p. 205°, had been obtained by the halolysis of the self-condensation product of homophthalic acid half ester chloride[1]. Since its published IR spectrum was identical with that of diacid (IV) (both in KBr), a sample was obtained and their identity established by m.m.p. The structure of the literature product was originally proposed as (VI), but has been now revised to (IV) (Prof. J. Knabe, private communication). In view of the

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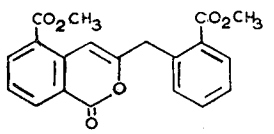
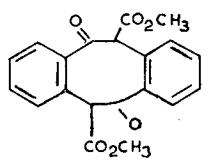
strong resemblance of the UV and NMR spectra of their primary condensation product to those of the isocoumarin ester (III), a reasonable formulation of the former would be (VII) and not (VIII) which was adopted earlier[1] as a 'working formula'.

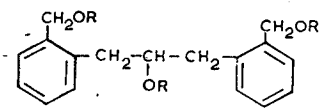


VII

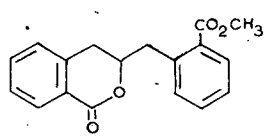


VIII

Lithium aluminium hydride reduction of the ester (V) afforded the triol (IX), showing only benzenoid absorption in the UV spectrum. The tris-*p*-nitrobenzoate (X), prepared in poor yield from the triol, showed besides the aromatic protons, the benzylic protons (4) as a doublet at 195 *cps* (J = 7 *cps*), the methylene protons (4) of the esterified primary alocholic group as a singlet at 325 *cps* and the methine proton as a multiplet (quintet ?) at 343 *cps* (J = 7 *cps*).



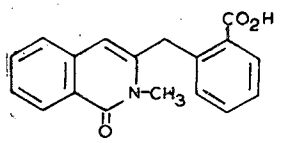
IX, R = H
X, R = p-nitrobenzoyl



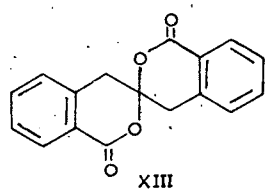
XI

Treatment of the diester (V) with sodium borohydride yielded the dihydroisocoumarin (XI), m.p. 126-7°, by reduction of the keto group, followed by lactonization. Its UV spectrum showed maxima at 230 and 280 mμ and the IR spectrum had bands at 1712 and 1722 cm.$^{-1}$, in agreement with the structure. The NMR spectrum showed a doublet (2H) at 180 *cps* (J = 7·5 *cps*) (—CH_2 group at position 3 of the isocoumarin ?), a multiplet (2H) between 202 and 217 *cps* (protons at position 4 of the isocoumarin), a singlet (3H) at 233 *cps* for the methyl ester, an approximate quintet (J = 7·5 *cps*) at 291 *cps* for the methine proton at position 3, a multiplet between 425 and 467 *cps* (6 aromatic H) and a multiplet (2 aromatic H *ortho* to carbonyl groups) at 482 *cps*.

Two reactions of the diacid (IV) were of interest and deserve mention. Pyrolysis of the methyl amine salt afforded an acidic compound, $C_{18}H_{15}NO_3$, m.p. 252-4°; $\lambda_{max.}$ 226, 250, 284 and 332 mμ; IR bands at 1610, 1630, 1690 and 1703 cm.$^{-1}$. These characteristics were reminiscent of the isocoumarin (II) and the product may be accordingly formulated as (XII). Pyrolysis of the acid (IV) or refluxing it with conc. hydrochloric acid for 2 hr gave a neutral product, $C_{17}H_{12}O_4$, m.p. 288-90°, which on treatment with hot alkali regenerated the acid (IV). The product was unaffected by diazomethane and gave no ferric colour. Its IR spectrum showed bands at 1726 and 1738 cm.$^{-1}$ and had no absorption in the hydroxyl region. Its UV spectrum having maxima at 237 and 282 mμ was distinctly similar to those of (IV), (V) and (XI). The dilactone structure (XIII) is thus strongly indicated for the product. Treatment of (IV) with hot 65 per cent sulphuric acid did not result in the formation of compound (XIII); the products seemed to be water-soluble and were not characterized. Hot acid treatment of the isocoumarin (II) likewise afforded very little, if at all, of the dilactone (XIII). It is however, interesting to note that prolonged acid catalysed reaction of (II), (IV) and (XIII) with hot methanol affords varying proportions of the isocoumarin ester (III) and the diester (V), indicative of expected interconversions. It should be also mentioned that in the esterification of isocoumarin (II) with diazomethane in methanol solution, the diester (V) is formed as a minor product, probably by opening of the isocoumarin ring by the solvent to a small extent.

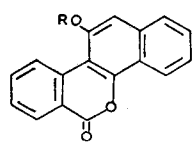


XII



XIII

Knabe and Grund[1] have noted that treatment of VII with hot concentrated hydrochloric acid or 65 per cent sulphuric acid affords a product, $C_{17}H_{10}O_3$, m.p. 285-290°. They also reported that the same product was obtained by an analogous reaction of (IV) with 65 per cent sulphuric acid. The product was formulated by them as 5-hydroxy-3,4,7,8-dibenzocoumarin (XIV) and the structure established[2] by synthesis of its methyl ether (XV). The properties of the dilactone (XIII) are quite different from those reported for (XIV), but for the fortuitous coincidence in melting points.*



XIV, R = H
XV, R = CH_3

Two other points that emerged in the course of this work still merit attention. The mass spectrum of the diester (V) did not show a molecular ion peak at all, even by the direct inlet technique. The peak with the highest mass number was at m/e 294, arising by the loss of methanol from the parent compound. A type E_2 elimination[3], characteristic of methyl esters of *o*-methylbenzoic acids is thus strongly operative. The fragment of mass 294 again loses the elements of methanol to produce a peak at m/e 262. The last fragment could lose carbon monoxide[4] thrice in three consecutive steps to yield peaks at m/e 234, 206 and 178. In addition, a peak at m/e 89 characteristic of isocoumarins[5] is also seen. The fragmentation pathway (Chart 1)

*After the submission of this paper, we have received, through the kind courtesy of Prof. Knabe, a copy of the manuscript he has submitted for publication in *Archive der Pharmacy*, wherein the authors report that our dilactone (XII) has been isolated by them by treatment of the diacid (IV) with hot 2*N* hydrochloric acid.

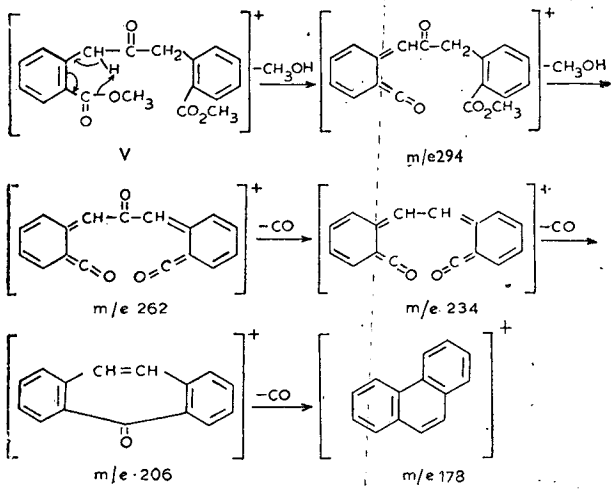


Chart 1 — Fragmentation pattern of the diester (V)

is supported by appearance of appropriate metastable peaks. It should however, be noted that valence isomers of the fragments depicted are possible.

The NMR spectrum (Fig. 2) of the triol (IX) revealed a surprising feature. In $CDCl_3$ solution alone, the spectrum showed a doublet (J = 6 *cps*) at 172 *cps* for the two $-CH_2$ groups flanking the secondary carbinol, a quintet for the methine proton at 235 *cps* (J = 6 *cps*) and a singlet at 433 *cps* for the eight aromatic protons. The signals due to the two methylene groups of the primary alcohol functions and the three hydroxylic protons were seen as a broad hump between 245 and 285 *cps*. Addition of D_2O altered only this region of the spectrum (Fig. 2 inset), revealing the alcoholic methylene groups as an AB quartet (at 259 and 277 *cps* respectively) (J = 12 *cps*). It would thus appear that the methylene protons adjacent to the secondary carbinol are not showing the expected nonequivalence[6]. On the other hand, surprisingly, the more remote methylene protons on the benzyl alcohol groups display magnetic nonequivalence. The phenomenon is not caused by some rigidity due to hydrogen bonding, as the AB quartet persists even after addition of trifluoracetic acid (Fig. 2 inset). The appearance of only a singlet at 325 *cps* for the protons concerned in the NMR spectrum of the *tris-p*-nitrobenzoate (X) must, therefore, be due to an accidental equivalence. This phenomenon needs further investigation.

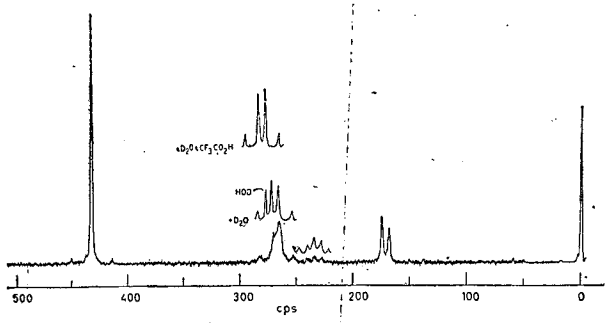


Fig. 2 — NMR spectrum of 1,3-bis(*o*-hydroxymethylphenyl) propanol-2

After completing the above work, we came across a publication by Aknin and Molho[5] on the pyridine catalysed self-condensation product of homophthalic anhydride. These authors have established the structure as (II) mainly using spectral data. Our present work confirms these findings and provides additional evidence for the structure.

Experimental Procedure

All melting points are uncorrected. IR spectra were taken as nujol mulls, unless otherwise stated. UV spectra were taken in 95 per cent ethanol. NMR spectra were run in $CDCl_3$ solutions, using a Varian A-60 spectrometer. Chemical shifts are reported in *cps* from TMS as internal standard.

Pyrolysis of ammonium homophthalate — Homophthalic acid (I, 135 g.) was mixed with conc. aq. ammonia (400 ml.) with cooling and the resulting clear solution evaporated to dryness under reduced pressure. The residue was heated with *o*-dichlorobenzene (300 ml.) at 200-10° (outside bath temperature) for 6 hr (air condenser). Most of the solvent was then distilled off and methanol added to the concentrate till crystals of homophthalimide separated which were filtered (91·5 g.). Approximately 1 kg. of homophthalic acid was thus processed to give 689 g. of homophthalimide. The methanolic mother liquors were combined and concentrated to a small volume to yield about 51 g. of crude 3-(*o*-carboxybenzyl) isocoumarin (II). The product was further purified by two recrystallizations from tetrahydrofuran-methanol-ether mixture; m.p. 208-9°; $\lambda_{max.}$ 230, 256, 266, 276, 328 mμ (log ε 4·57, 4·01, 4·06, 4·00, 3·66) (Found: C, 72·54; H, 4·50. $C_{17}H_{12}O_4$ requires C, 72·85; H, 4·32%).

3-(*o-Carboxybenzyl*) *isocoumarin methyl ester* (III) — A suspension of the acid (II, 0·2 g.) in methanol (5 ml.) was treated with a solution of diazomethane (from 5 g. nitrosomethylurea) in ether (40 ml.). The substance dissolved rapidly with evolution of nitrogen. After 10 hr at room temperature, the ether was evaporated and water added to the residual solution. The crystalline product was recrystallized from methanol; yield 0·14 g.; m.p. 80-103°. On fractional crystallization from ether, a sparingly soluble portion, m.p. 104-7°, was obtained which was recrystallized from methylene chloride-ether mixture to afford (III) (65 mg.), m.p. 107-9°; $\lambda_{max.}$ 228, 258, 266, 276, 326 mu (log ε 4·55, 4·01, 4·06, 3·99, 3·63); $\nu_{max.}$ 1600, 1652, 1720 cm.$^{-1}$ (Found: C, 73·74; H, 4·82. $C_{18}H_{14}O_4$ requires C, 73·46; H, 4·80%).

The ether soluble part from the reaction was recrystallized from methanol to give the diester (V) (31 mg.) m.p. 90-91°.

Esterification of (III, 0·2 g.) in refluxing methanol (20 ml.) containing sulphuric acid (5 drops) for 36 hr afforded a mixture of crystalline products (0·13 g.) m.p. 80-103°, consisting of (III) and (V), with the former predominating (IR analysis).

αα'-bis(o-Carboxyphenyl) acetone (IV) — The isocoumarin (II, 0·2 g.) was dissolved in aq. sodium hydroxide (20 per cent, 5 ml.) and the solution heated on the steam-bath for 2 hr. Water was

added to dissolve the salt and the clear solution acidified. The precipitated acid was filtered and washed with water; yield, 0·18 g., m.p. 197-9°. Recrystallization from methanol afforded white crystals of (IV); m.p. 204-5° (decomp.). $\lambda_{max.}$ 228, 280 mμ (log ε 4·24, 3·46) (Found: C, 68·21, 68·28; H, 4·86, 5·00; mol. wt by titration, 310. $C_{17}H_{14}O_5$ requires C, 68·45; H, 4·73%; mol. wt 298·3).

αα'-bis(o-Carboxyphenyl) acetone dimethyl ester (V) — The acid (IV, 2·0 g.) suspended in methanol (20 ml.) was treated with 40 ml. of an ethereal solution of diazomethane (from 6 g. of nitrosomethylurea) to give 1·9 g. crude ester; m.p. 86-88°. Recrystallization from aqueous methanol afforded pure (V); m.p. 90-92°; $\lambda_{max.}$ 228, 279 mμ (log ε 4·33, 3·54) (Found: C, 69·88; H, 5·90; OCH_3, 18·52. $C_{19}H_{18}O_5$ requires C, 69·92; H, 5·56; 2-OCH_3, 19·0%). The compound formed a 2,4-dinitrophenylhydrazone which was crystallized from methanol; m.p. 125-6°; $\lambda_{max.}$ 226, 365 mμ (log ε 4·51, 4·37) (Found: C, 59·66; H, 4·61; N, 11·26. $C_{25}H_{22}N_4O_8$ requires C, 59·28; H, 4·38; N, 11·06%).

Esterification of the acid (IV, 4·0 g.) in boiling methanol (120 ml.) containing sulphuric acid (20 drops) for 36 hr afforded on fractional crystallization (V), yield 1·7 g., m.p. 90-91°; III, yield 0·25 g., m.p. 106-8°; and a fraction consisting of a mixture of (III) and (V).

Saponification of the diester (V, 0·5 g.) with methanolic potassium hydroxide (10 per cent, 25 ml.) on a steam-bath for 4 hr afforded 0·3 g. starting acid IV.

Permanganate oxidation of the diacid (IV) — A solution of the diacid (1 g.) in aq. sodium carbonate (10 per cent, 5 ml.) was treated with a solution of potassium permanganate (5 g.) in water (50 ml.). The mixture was boiled, treated with sodium bisulphite and acidified with conc. HCl. Extraction with ether afforded a solid (0·2 g.) which was recrystallized from water to give phthalic acid, m.p. 206-8° (decomp.), undepressed by admixture with an authentic sample (Found: C, 57·88; H, 3·78. $C_8H_6O_4$ requires C, 57·83; H, 3·64%).

1,3-bis(o-Hydroxymethylphenyl)-propanol-2 (IX) — A solution of the diester (V, 3·1 g.) in tetrahydrofuran (15 ml.) was added during 1 hr to a stirred suspension of $LiAlH_4$ (2 g.) in tetrahydrofuran (15 ml.). After stirring for 3 days at room temperature, the mixture was decomposed with moist ether and the product obtained as a gum (2·6 g.), which crystallized on trituration with ether; yield 1·5 g. Recrystallization from aq. methanol afforded pure (IX); m.p. 100-1° (Found: C, 75·31; H, 7·93. $C_{17}H_{20}O_3$ requires C, 74·97; H, 7·40%).

The triol (0·2 g.) was heated with *p*-nitrobenzoyl chloride (0·5 g.) in benzene (5 ml.) containing pyridine (1 ml.) for 2 hr. On working up as usual, it afforded the tris-*p*-nitrobenzoate (X); m.p. 168-70° (transition at 135°) (Found: C, 63·66, 63·65; H, 4·29, 4·42; N, 5·26. $C_{38}H_{29}N_3O_{12}$ requires C, 63·51; H, 4·07; N, 5·84%).

3-(2-Carbomethoxybenzyl)-3,4-dihydroisocoumarin (XI) — A solution of the diester (V, 0·2 g.) in 6 ml. methanol was treated with $NaBH_4$ (0·1 g.) and then left at room temperature. Addition of water gave the crystalline product (XI) which recrystallized from methanol (97 mg.); m.p. 127°; $\lambda_{max.}$ 230, 280 mμ (log ε 4·22, 3·38) (Found: C, 72·75, 73·02; H, 5·71, 5·75. $C_{18}H_{16}O_4$ requires: C, 72·96; H, 5·44%).

3-(2-Carboxybenzyl)-1-oxo-2-methyl-1,2-dihydroisoquinoline (XII) — A solution of the diacid (IV, 0·5 g.) in alcoholic methyl amine (30 per cent, 10 ml.) was evaporated to dryness and the residue heated at 160° for several hours. The tarry product became crystalline on trituration with methanol. Recrystallization from aq. acetic acid gave (XII); m.p. 252-4°; $\lambda_{max.}$ 226, 250, 284 and 332 mμ (log ε 4·44, 3·99, 4·05, 3·74) (Found: C, 73·36, 73·91; H, 5·09, 5·49; N, 5·21, 4·80. $C_{18}H_{15}NO_3$ requires C, 73·70; H, 5·15; N, 4·78%).

3,3'-spirobis(3,4-Dihydroisocoumarin) (XIII) — A suspension of the diacid (IV, 2 g.) in conc. HCl (20 ml.) was heated under reflux for 3 hr and left overnight. The product was filtered, washed with water, acetone and methanol to give (XIII) (1·5 g.); m.p. 287-90°; recrystallized from dimethylformamide-ether (1·4 g.), m.p. 288-90° (Found: C, 72·44, 72·54; H, 4·37, 4·67. $C_{17}H_{12}O_4$ requires C, 72·85; H, 4·32%).

The same product was obtained in 50 per cent yield by heating the acid above its m.p. until evolution of gas stopped, washing off unchanged material with aq. sodium bicarbonate and recrystallizing from excess acetone; m.p. 288-90°, undepressed by admixture with the sample obtained by the previous procedure. The IR spectra were superimposable.

Treatment of a suspension of the dilactone (XIII, 0·2 g.) with excess diazomethane in ether for 24 hr led to 70 per cent recovery of starting material. But refluxing a solution of the lactone (0·2 g.) in methanol (20 ml.) and H_2SO_4 (5 drops) for 36 hr led to esterification. The crystalline product (0·12 g.), m.p. 78-84°, consisted mostly of the diester (V) and some of the isocoumarin ester (III) (IR analysis).

Saponification of the dilactone (0·1 g.) with sodium hydroxide (0·5 g.) in water (3 ml.) and methanol (1 ml.) for 2 hr on the steam-bath led to a clear solution. Acidification gave an acid (82 mg.), m.p. 193-5°, identical with the diacid (IV).

Acknowledgement

The authors express their thanks to Prof. T. R. Govindachari for his interest in this work, to Prof. Knabe for a sample of the acid (IV), to Dr H. Hürzeler for the mass spectrum, to Dr R. Zürcher for some NMR spectra and to Dr Selvavinayakam and his associates for analytical and spectral data.

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