266.   *Eight- and Higher-membered Ring Compounds.   Part VIII.** *Anhydro-derivatives of 2-Carboxy-2'-hydroxybenzophenone and of* *2-Carboxy-2'-hydroxydiphenylmethane.*

By Wilson Baker, D. Clark, W. D. Ollis, and T. S. Zealley.

2-Carboxy-2'-hydroxybenzophenone and 2-carboxy-2'-hydroxy-5'-methyl-benzophenone (I; R = H and Me) yield the 7-membered lactones (II; R = H and Me) by the action of acetic anhydride, but other dehydrating agents give the 14-membered lactides (III; R =.H and Me). It is suggested that intramolecular hydrogen bonding occurs, which would cause these molecules to take up a configuration unfavourable for lactonisation, but favourable for intermolecular lactide formation. This explanation is supported by the fact that the related acids 2-carboxy-2'-hydroxydiphenylmethane and 2-carboxy-2'-hydroxy-5'-methyldiphenylmethane (VII; R = H and Me), in which similar internal hydrogen bonding cannot occur, give only the 7-membered lactones with all dehydrating agents used.

EXAMPLES have been discussed in Parts I—VII of this series (*J.*, 1951, 200, 202, 210, 1114, 1118; preceding papers) illustrating what we have termed the rigid-group principle, namely, the easy formation of large-ring compounds by union of simple units containing rigid groups of atoms. These rigid groups have been present in *o*-xylylene dibromide (Baker, Banks, Lyon, and Mann, *J.*, 1945, 27) and in various *o*-hydroxybenzoic acids (4-membered rigid groups; Parts II, III, and VI), *m*-xylylene dihalides (5-membered rigid groups), *p*-xylylene dihalides (6-membered rigid groups; Part IV), and 2 : 7-bisbromo-methylnaphthalene (7-membered rigid groups; Part V). In all these examples intra-molecular cyclisation is excluded on stereochemical grounds, and in the last the rigid group extends over two fused benzene rings. The formation of the 8-membered lactone described in Part VII is somewhat different; the hydroxy-acid, 2'-hydroxydibenzyl-2-carboxylic acid, is composed of two directly linked 4-membered rigid groups, but there was the possibility, not realised in fact, that an intermolecular reaction might occur with the formation of a 16-membered lactide.

In a further study of the rigid-group principle cases have now been investigated where both intramolecular cyclisation and the production of large-ring compounds by inter-molecular condensation could occur. At least one such case is on record; 2 : 2'-di-bromodiphenyl, when converted into the Grignard reagent and treated with anhydrous cupric chloride, gives a mixture of diphenylene (dibenzo*cyclo*butadiene) and tetra-phenylene (tetrabenzo*cyclo*octatetraene) (Rapson, Shuttleworth, and Niekerk, *J.*, 1943, 326). The same possibilities may be involved in the formation of the higher anhydro-derivatives of *o*-hydroxybenzoic acids. Thus, for example, salicyloylsalicylic acid, $HO \cdot C_6H_4 \cdot CO \cdot O \cdot C_6H_4 \cdot CO_2H$, is known to undergo intramolecular cyclisation to disalicylide, and it may be that two molecules could condense to give tetrasalicylide.

The compound first investigated was 2-carboxy-2'-hydroxybenzophenone (I; R = H) which when dehydrated might yield, as the simplest products, either the monomeric 7-membered lactone (II; R = H) or the dimeric 14-membered lactide (III; R = H). When this acid was treated in the cold with acetic anhydride it yielded the lactone (II; R = H) after several hours, but the reaction is base-catalysed and occurred very rapidly in presence of sodium acetate. Other dehydrating agents gave only the lactide (III; R = H); those used were trifluoroacetic anhydride, thionyl chloride followed by treatment with diethylaniline, phosphoric anhydride, and phosphorus oxychloride. The actual yields of the lactide (III; R = H) varied between 30 and 60%; in the case of trifluoroacetic anhydride the yield (32%) was quantitative after allowance for recovered hydroxy-acid.

Precisely analogous results were obtained by the dehydration of 2-carboxy-2'-hydroxy-5'-methylbenzophenone (I; R = Me); with cold acetic anhydride it yielded the lactone (II; R = Me), but with the other reagents mentioned it yielded the bimolecular lactide

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* Part VII, preceding paper.

(III; R = Me). In some experiments treatment of (I; R = Me) with hot acetic anhydride and sodium acetate yielded the lactone (II; R = Me), but on other occasions it gave the diacetyl derivative of the related lactol, 3-acetoxy-3-(2-acetoxy-5-methylphenyl)phthalide (IV).
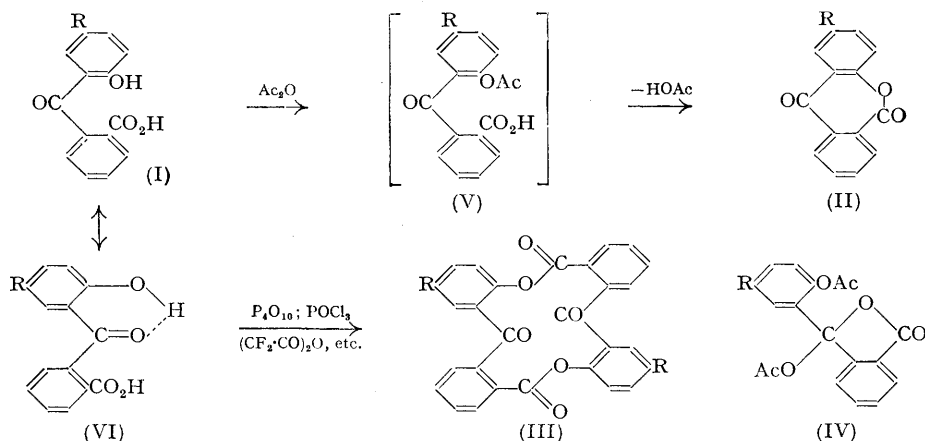
In considering the reasons why the action of acetic anhydride on the acids (I) should yield the lactones (II), whilst other methods of dehydration give the lactides (III), it is known that acetic anhydride reacts very rapidly in the cold with o-hydroxy-carbonyl compounds to give the O-acetyl derivatives. The acids (I) will hence be first converted into the acetyl derivatives (V) (these are too labile to be easily isolated) which then lose acetic acid by a base-catalysed exchange reaction to give the lactones (II). The fact that the acids (I) dissolve only slowly, presumably with chemical change, in acetic anhydride to give solutions which do not at first contain appreciable quantities of the lactone, supports this view that the acetyl derivatives (V) are intermediates. Other dehydrating agents, including doubtless trifluoroacetic anhydride, which probably first forms a mixed anhydride with the carboxyl group (see Bourne, Randles, Tatlow, and Tedder, *Nature*, 1951, **168**, 942), will leave the phenolic group free, and internal hydrogen bonding between the phenolic group and the oxygen atom of the adjacent ketone group will cause the molecule (I) to take up the configuration shown in (VI). This configuration (VI), or any modification derived by rotation of the carboxyphenyl group, is completely unfavourable for intramolecular cyclisation, but two such units [compare (VI) with the left side of formula (III) of the lactide] could clearly unite to give the lactide (III).
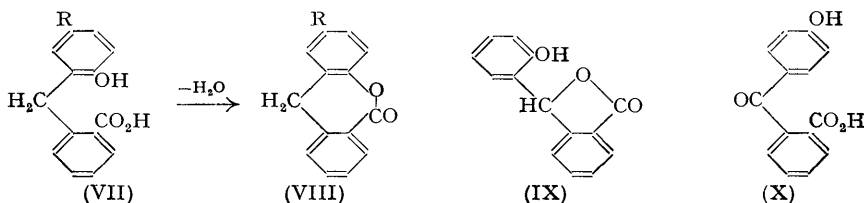
In order to test the hypothesis, we have studied the dehydration of the derived 2-carboxy-2'-hydroxydiphenylmethane (VII; R = H) and 2-carboxy-2'-hydroxy-5'-methyldiphenylmethane (VII; R = Me), in which similar hydrogen bonding cannot occur. When treated with any of the dehydrating agents previously mentioned, these acids gave only the 7-membered lactones (VIII; R = H and Me respectively) without trace of 14-membered lactides. This is probably the first case of a hydrogen bond being sterically responsible for the prevention of intramolecular cyclisation, and thereby causing intermolecular reaction with formation of a large ring (for orientation effects of hydrogen bonding see Baker, *J.*, 1934, 1684; Baker and Lothian, *J.*, 1935, 628; 1936, 274).

The four lactones (II) and (VIII) undergo rapid hydrolysis with alkali, but the two

lactides (III) are less readily hydrolysed. In all cases the original hydroxy-acids are regenerated.

The acids (VII; R = H or Me) were prepared by reduction of the related keto-acids (I; R = H or Me) with activated zinc dust and aqueous sodium hydroxide (cf. Martin, *J. Amer. Chem. Soc.*, 1936, **58**, 1438). Clemmensen reduction of the acid (I; R = H) was incomplete and yielded the γ-lactone of 2-carboxy-2'-hydroxydiphenylcarbinol (3-*o*-hydroxyphenylphthalide) (IX).

Attempted dehydration of 2-carboxy-4'-hydroxybenzophenone (X) and of the derived 2-carboxy-4'-hydroxydiphenylmethane with thionyl chloride followed by diethylaniline, or with phosphorus oxychloride gave only material of high molecular weight. The reaction of (X) with acetic anhydride was investigated by Orndorff and Murray (*J. Amer. Chem. Soc.*, 1917, **39**, 680) who obtained a diacetate, m. p. 137—140°, for which a formula was not advanced. We find that the pure compound melts at 155—156°, and it must be the diacetyl derivative of the related lactol corresponding to (IV), namely 3-acetoxy-3-*p*-acetoxyphenylphthalide. We have been unable to confirm the claim of these authors that when heated the acid gives its bimolecular anhydride, which yields a diacetyl derivative; we have isolated only the above diacetyl derivative of the lactol.

The results obtained in this and the preceding paper on the dehydration of hydroxy-acids of the type (XI) are summarised below.
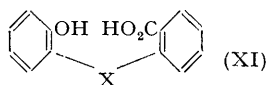
X =	Ac$_2$O	(CF$_3$·CO)$_2$O	SOCl$_2$-NPhEt$_2$	P$_4$O$_{10}$	POCl$_3$
CH$_2$	Lactone	Lactone	Lactone	Lactone	Lactone
CH$_2$·CH$_2$	*O*-Acetyl derivative	,,	,,	,,	,,
CO	Lactone	Lactide	Lactide	Lactide	Lactide

EXPERIMENTAL

M. p.s are uncorrected; in cases where they varied with the rate of heating the method described in Part II was used. Molecular weights were determined by the modified Menzies–Wright method also given in Part II. Microanalyses are by Drs. Weiler and Strauss, Oxford, and Mr. W. M. Eno, Bristol.

Lactone (II; R = H) *of 2-Carboxy-2'-hydroxybenzophenone.*—2-Carboxy-2'-hydroxybenzophenone (I; R = H) (0·50 g.; Ullmann and Schmidt, *Ber.*, 1919, **52**, 2107), when stirred with cold acetic anhydride (5 c.c.), dissolved in 7 minutes, giving a solution which did not deposit crystals when seeded with either the lactone (II; R = H) or the acid (I; R = H) (a solution of the calculated amount of lactone in this volume of acetic anhydride is supersaturated). However, after being kept either for 3 hours, or for 2 minutes after addition of anhydrous sodium acetate (2 mg.), the mixture became semi-solid with the lactone, which, after shaking with water to decompose excess of acetic anhydride, was collected, washed, and dried (yield from the two experiments, 87% and 77% respectively; m. p. 176—177°). This *lactone* (II; R = H) separates from carbon tetrachloride in needles, m. p. 179—180° [Found : C, 75·0; H, 4·0%; *M* (Rast), 223; *M* (ebullioscopic in benzene), 224. C$_{14}$H$_8$O$_3$ requires C, 75·0; H, 3·6%; *M*, 224]. The lactone (0·89 g., 96%) resulted when the acid (I) (1 g.) was boiled for 2 hours with acetic anhydride (1·95 c.c.) and benzene (100 c.c.).

The lactone (14 mg.) when shaken at room temperature with 2N-sodium hydroxide (1 c.c.) dissolved in ½ hour, and acidification regenerated the acid (I; R = H), m. p. and mixed m. p. 169—171° (95%).

Lactide (III; R = H) *of 2-Carboxy-2'-hydroxybenzophenone.*—Method (*a*) gave a lactide, m. p. 320—322°, whereas the other methods gave a product, m. p. 316°. These m. p.s are not very reliable owing to some decomposition, but the identity of all the specimens was proved by their infra-red spectra and *X*-ray powder photographs. We thank Dr. L. N. Short, Oxford, and Mr. I. S. Loupekine, Bristol, for these measurements.

(*a*) *Use of trifluoroacetic anhydride.* Trifluoroacetic anhydride (5·7 c.c.; Bourne, Stacey, Tatlow, and Tedder, *J.*, 1949, 2977) was added to 2-carboxy-2'-hydroxybenzophenone (2·0 g.) (I; R = H) in benzene (200 c.c.) at 35° (temporary red coloration). After 2 days the solution was heated on the water-bath for 2½ hours, then concentrated to 2 c.c., and light petroleum

(30 c.c.; b. p. 60—80°) was added. The solid was collected (0·58 g., 32%; m. p. 317—320°) and recrystallised from aqueous acetic acid (100 c.c.), giving the *lactide* of 2-carboxy-2'-hydroxybenzophenone (III; R = H) as hexagonal prisms, m. p. 320—322° [Found : C, 74·8; H, 3·7%; M (ebullioscopic in benzene), 468. $C_{28}H_{16}O_6$ requires C, 75·0; H, 3·6%; M, 448]. It sublimes unchanged at 240°/0·5 mm. The benzene–light petroleum filtrate yielded unchanged 2-carboxy-2'-hydroxybenzophenone (1·35 g., 68%).

(b) *Use of thionyl chloride and diethylaniline.* The acid (I; R = H) (2 g.), purified thionyl chloride (2 c.c.), and aluminium chloride (2 mg.) were heated at 45—50° for 2 hours, more thionyl chloride (1 c.c.) was added, and heating continued for 1 hour. After evaporation under diminished pressure the residue was heated on a steam-bath for 3 hours with dioxan (10 c.c.) and diethylaniline (3 c.c.) and poured into 0·5N-hydrochloric acid, and the product (1·4 g.; m. p. 305—306°) crystallised from aqueous acetic acid (25 c.c.), giving the lactide (III; R = H) (1·03 g., 56%), m. p. 316° [Found : C, 74·7; H, 3·5%; M (ebullioscopic in benzene), 458; M (ebullioscopic in chloroform), 446].

(c) *Use of phosphorus oxychloride.* The acid (I; R = H) (0·54 g.) and redistilled phosphorus oxychloride (0·3 c.c.) in benzene (10 c.c.) were heated on the steam-bath for 3 days, benzene (80 c.c.) was added, and the whole was shaken with 2N-sodium carbonate (filtered to remove sparingly soluble sodium salts), then with water, and dried. Evaporation left a residue (0·23 g.; m. p. 260—265°) which was recrystallised from slightly diluted acetic acid (30 c.c.), giving the lactide (0·16 g., 32%), m. p. and mixed m. p. 316°.

(d) *Use of phosphoric anhydride.* The acid (I; R = H) and phosphoric anhydride (3·4 g.) in benzene (110 c.c.) were heated for 5 hours, and the hot solution was decanted, washed with 5% sodium hydrogen carbonate, then with water, and dried. Evaporation left a residue (0·56 g.; m. p. 280—305°) which, after recrystallisation gave the lactide (0·3 g., 31%), m. p. and mixed m. p. 316°.

This lactide (III; R = H) (50 mg.), when boiled with 2N-sodium hydroxide (5 c.c.) for 2 hours, and then acidified, gave the acid (I; R = H) (40 mg.), m. p. and mixed m. p. 168—170°.

Action of Acetic Anhydride on 2-Carboxy-2'-hydroxy-5'-methylbenzophenone (I; R = Me).— (a) *Lactone* (II; R = Me). The acid (I; R = Me) (0·50 g.) (Ullmann and Schmidt, *Ber.*, 1919, **52**, 2102) was ground with acetic anhydride (5 c.c.) at about 30° till dissolution occurred (20 minutes). Seeding with the lactone (II; R = Me) did not cause crystallisation, but after several hours, or immediately after addition of a little anhydrous sodium acetate, the lactone separated. The mixture was shaken with water, and the solid collected, washed, dried (yield 0·44 g.; m. p. 140—143°), and recrystallised from light petroleum (b. p. 80—100°), giving the *lactone* (II; R = Me) as long needles, m. p. 145° [Found : C, 75·2; H, 4·5%; M (ebullioscopic in benzene), 240. $C_{15}H_{10}O_3$ requires C, 75·6; H, 4·2%; M, 238]. Hydrolysis by boiling the lactone with 2N-sodium hydroxide for ½ minute regenerated the acid (I; R = Me) in 96% yield.

(b) *3-Acetoxy-3-(2-acetoxy-5-methylphenyl)phthalide* (IV; R = Me). The acid (I; R = Me) (5 g.), acetic anhydride (100 c.c.), and anhydrous sodium acetate (2 g.) were heated on the steam-bath for 2 hours and poured into water, giving a solid (5·7 g.; m. p. *ca.* 150—167°) which was crystallised from carbon tetrachloride (250 c.c.). The *phthalide* (4·1 g.) separated as plates, m. p. 178—179° [Found : C, 66·4; H, 4·8; Ac, 26·9%; M (ebullioscopic in benzene), 342. $C_{15}H_{10}O_4Ac_2$ requires C, 66·2; H, 4·8; Ac, 25·3%; M, 340]. In some apparently similar experiments only the lactone (II; R = Me) was isolated.

Lactide (III; R = Me) *of 2-Carboxy-2'-hydroxy-5'-methylbenzophenone.*—(a) *Use of trifluoroacetic anhydride.* The acid (I; R = Me) (1·45 g.) and trifluoroacetic anhydride (4 c.c.) in benzene (160 c.c.) were kept for 1 hour, boiled for 2½ hours, and then evaporated under diminished pressure. The residue crystallised, giving a solid, m. p. 45°, which may be a mixed anhydride. After this had been heated with pyridine (10 c.c.) on a steam-bath for 2½ hours and poured into 2N-sodium carbonate, the product (0·683 g.; m. p. 287—292°) was triturated with 2N-hydrochloric acid and crystallised from aqueous acetic acid, giving the lactide (III; R = Me) (0·65 g., 49%) as prisms, m. p. 294—295° [Found : C, 75·5; H, 4·2%; M (ebullioscopic in benzene), 479. $C_{30}H_{20}O_6$ requires C, 75·6; H, 4·2%; M, 476].

(b) *Use of thionyl chloride and diethylaniline.* The acid (I; R = Me) gave by reaction with thionyl chloride and then diethylaniline, as described in the case of the acid (I; R = H), the recrystallised lactide (III; R = Me), m. p. and mixed m. p. 295—296°, in 59% yield.

(c) *Use of phosphorus oxychloride.* Dehydration of the acid (I; R = Me) with phosphorus oxychloride, as described for the lower homologue, gave the recrystallised lactide (III; R = Me). m. p. and mixed m. p. 295°, in 45% yield.

(d) *Use of phosphoric anhydride.* The acid (I; R = Me) and phosphoric anhydride gave, as previously described, the lactide (III; R = Me), m. p. and mixed m. p. 295—296°, in 50% yield.

The lactide was completely hydrolysed by boiling it with 2N-sodium hydroxide for 2 hours; acidification yielded the acid (I; R = Me), m. p. and mixed m. p. 194—195°, in 61% yield.

3-o-*Hydroxyphenylphthalide* (IX).—2-Carboxy-2′-hydroxybenzophenone (I; R = H) (1 g.), amalgamated zinc (2·5 g.), concentrated hydrochloric acid (15 c.c.), water (5 c.c.), and toluene (50 c.c.) were boiled under reflux for 24 hours, with the addition after 8 and 16 hours of amalgamated zinc (2 g.) and concentrated hydrochloric acid (10 c.c.). The toluene layer was united with the ethereal extract of the aqueous layer and shaken with 2N-sodium hydroxide, and the alkaline solution was acidified. The resulting oil (0·73 g.), isolated by ether, was crystallised from benzene, giving 3-o-*hydroxyphenylphthalide* (IX) as needles, m. p. 142° or 159° (dimorphic) (Found : C, 74·1; H, 4·3. $C_{14}H_{10}O_3$ requires C, 74·4; H, 4·5%). Although insoluble in cold 10% aqueous sodium carbonate, it dissolves in cold 2N-sodium hydroxide and is recovered unchanged on acidification.

2-*Carboxy*-2′-*hydroxydiphenylmethane* (VII; R = H).—Zinc dust (2·5 g.) (activated by being shaken with dilute copper sulphate) was boiled with a solution of 2-carboxy-2′-hydroxybenzophenone (1 g.) in 2N-sodium hydroxide (40 c.c.) for 5 hours, and the whole cooled, filtered, and acidified. The solid (0·84 g.; m. p. 121—123°) was crystallised from benzene and then from carbon tetrachloride, giving 2-*carboxy*-2′-*hydroxydiphenylmethane* (VII; R = H) as needles, m. p. 125° (Found : C, 73·5; H, 5·5%; equiv., 229. $C_{13}H_{11}O \cdot CO_2H$ requires C, 73·7; H, 5·3%; equiv., 228).

Lactone (VIII; R = H) *of* 2-*Carboxy*-2′-*hydroxydiphenylmethane.*—(a) *Use of acetic anhydride.* The acid (VII; R = H) (0·20 g.) was dissolved in cold acetic anhydride (0·5 c.c.) (15 minutes), and fused sodium acetate (2 mg.) was added. After a further 10 minutes, the mixture was shaken with water, and the precipitate (0·16 g.; m. p. 93—96°) crystallised from light petroleum (3 c.c.; b. p. 60—80°). The *lactone* (VIII; R = H) (120 mg.) separated as prisms, m. p. 98—99° [Found : C, 80·1; H, 4·9%; M (ebullioscopic in benzene), 209. $C_{14}H_{10}O_2$ requires C, 79·9; H, 4·8%; M, 210].

(b) *Use of thionyl chloride and diethylaniline.* The acid (VII; R = H) was converted into the chloride in benzene solution, and then treated with diethylaniline as in previous cases. The lactone (VIII; R = H), obtained in 49% yield, was purified by sublimation (150°/0·5 mm.) and then by crystallisation from light petroleum; it had m. p. and mixed m. p. 98—99°.

(c) *Use of other reagents.* Use of trifluoroacetic anhydride, phosphorus oxychloride, or phosphoric anhydride, as for the analogue, gave the lactone in 75, 51, and 59% yield, respectively, identification being by mixed m. p.s.

This lactone dissolved when heated with 2N-sodium hydroxide (4 minutes), and acidification gave the acid (VI; R = H), m. p. and mixed m. p. 123—124°.

2-*Carboxy*-2′-*hydroxy*-5′-*methyldiphenylmethane* (VII; R = Me).—This *acid* was prepared by the reduction of the keto-acid (I; R = Me) (5·3 g.) as in the case of the acid (I; R = H). The product, crystallised from aqueous acetic acid (80 c.c.) and then from carbon tetrachloride (300 c.c.), formed needles (3·75 g.), m. p. 125° (Found : C, 74·4; H, 5·4%; equiv., 262. $C_{14}H_{13}O \cdot CO_2H$ requires C, 74·4; H, 5·4%; equiv., 242).

Lactone (VIII; R = Me) *of* 2-*Carboxy*-2′-*hydroxy*-5′-*methyldiphenylmethane.*—The methods used were as described for the dehydration of the acid (VII; R = H). Identity of the lactone specimens was proved by mixed m. p. determinations in all cases.

Use of acetic anhydride. 2-Carboxy-2′-hydroxy-5′-methyldiphenylmethane (VII; R = Me) (98 mg.), acetic anhydride (10 c.c.), and sodium acetate (200 mg.) were boiled for 2½ hours, giving the *lactone* (72 mg.) as plates, m. p. 121°, from aqueous ethanol [Found : C, 80·7; H, 5·5%; M (ebullioscopic in benzene), 227. $C_{15}H_{12}O_2$ requires C, 80·4; H, 5·4%; M, 224].

Trifluoroacetic anhydride, thionyl chloride–diethylaniline, phosphorus oxychloride, and phosphoric anhydride gave yields of 99, 65, 50, and 54% respectively.

Hydrolysis of the lactone by boiling 2N-sodium hydroxide was complete in 25 minutes. Acidification gave the acid (VII; R = Me) (93% yield), m. p. and mixed m. p. 124°.

2-*Carboxy*-4′-*hydroxydiphenylmethane.*—Reduction of 2-carboxy-4′-hydroxybenzophenone (X) (10 g.; Ullmann and Schmidt, *loc. cit.*) with activated zinc dust and aqueous sodium hydroxide, as in the similar cases described above, gave 2-*carboxy*-4′-*hydroxydiphenylmethane* (8·75 g.) as needles, m. p. 151°, from slightly diluted acetic acid (Found : C, 73·6; H, 5·3%; equiv., 233. $C_{13}H_{11}O \cdot CO_2H$ requires C, 73·7; H, 5·3%; equiv., 228). The *monoacetate* formed rhombs,

m. p. 123—125°, from ethanol (Found : C, 71·2; H, 5·2. $C_{14}H_{11}O_3Ac$ requires C, 71·1; H, 5·2%).

3-*Acetoxy*-3-p-*acetoxyphenylphthalide* (see Orndorff and Murray, *loc. cit.*).—2-Carboxy-4'-hydroxybenzophenone (X) (10 g.; Ullmann and Schmidt, *loc. cit.*) and acetic anhydride (60 c.c.) were heated for 2 hours, concentrated under diminished pressure, and poured into water, and the finally solid product collected (15·3 g.; m. p. 135—145°). Repeated crystallisation from ethanol gave 3-*acetoxy*-3-p-*acetoxyphenylphthalide* as microscopic crystals, m. p. 155—156° [Found : C, 66·0; H, 4·6%; *M* (ebullioscopic in benzene), 330. $C_{18}H_{14}O_6$ requires C, 66·2; H, 4·3%; *M*, 326].

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