

**905.**  $\epsilon$ -Lactones. Part I. The Preparation of Lactones from the 2-Carboxy-2'-hydroxybenzophenones, and their Reactions.

By M. LAMCHEN.

$\epsilon$ -Lactones are formed easily from 2-carboxy-2'-hydroxybenzophenones. They react readily with dilute acids to form hydroxy-keto-acids, with ethanol to form hydroxy-keto-esters, and with primary and secondary amines to form hydroxy-keto-amides. Evidence has been found that the benzophenone-carbonyl group is hydrogen-bonded and this probably explains why  $\psi$ -esters and lactamols are not formed. On the other hand, with ammonia and hydrazine, ring closure with the loss of water occurs to form 1-isindolones and oxophthalazines.

ALTHOUGH  $\epsilon$ -lactones have been prepared they are generally not formed easily. van Natta *et al.*<sup>1</sup> had to heat 6-hydroxyhexanoic acid to 150—210° and then distil it to produce the lactone, while Stoll and Rouvé<sup>2</sup> found it necessary to apply the high-dilution technique. Very few  $\epsilon$ -lactones are known. The  $\epsilon$ -lactone structure suggested for dioscorine by Pinder<sup>3</sup> was later shown by him to be wrong<sup>4</sup> and a  $\delta$ -lactone structure was substituted. Fieser,<sup>5</sup> however, found that  $\epsilon$ -lactones from 2-(2-hydroxy-1-naphthoyl)benzoic acid were

<sup>1</sup> van Natta, Hill, and Carothers, *J. Amer. Chem. Soc.*, 1934, **56**, 455; 1936, **58**, 183.

<sup>2</sup> Stoll and Rouvé, *Helv. Chim. Acta*, 1935, **18**, 1807.

<sup>3</sup> Pinder, *J.*, 1956, 1577.

<sup>4</sup> Pinder, *Tetrahedron*, 1957, **1**, 301; Jones and Pinder, *J.*, 1959, 615.

<sup>5</sup> Fieser, *J. Amer. Chem. Soc.*, 1931, **53**, 3546.

formed readily when the acid was heated with acetic anhydride and fused sodium acetate. Orndorff and Kline<sup>6</sup> similarly converted 2-(2,4-dihydroxybenzoyl)benzoic acid into the acetoxy-lactone by boiling acetic anhydride alone.

The very easy formation of  $\epsilon$ -lactones of the latter type has now been further demonstrated. Attempts to acetylate 2-*o*-hydroxybenzoylbenzoic acid (I; OMe replaced by H, R = CO<sub>2</sub>H) and 2-(2-hydroxy-4-methoxybenzoyl)benzoic acid (I; R = CO<sub>2</sub>H) have given no *o*-acetoxy-compounds but have resulted in the formation of the  $\epsilon$ -lactones (II; OMe replaced by H) and (II) respectively in almost quantitative yields. These lactones crystallised from the acetic anhydride solutions and were formed so readily and so pure that it was often preferable to obtain the pure hydroxy-acids by heating the crude Friedel-Crafts products with acetic anhydride to form the lactones, which on recrystallisation from 5*N*-acetic acid reverted to the hydroxy-acids.

These  $\epsilon$ -lactones are stable at room temperature and, unlike the  $\epsilon$ -lactone of 6-hydroxyhexanoic acid, are not changed to linear esters even when heated for one hour at a temperature well above their melting points. On the other hand, in most reactions they behaved like the  $\gamma$ - and  $\delta$ -lactones but reacted much more readily; the benzophenone-carbonyl group may, however, greatly affect the reaction and may determine which product is formed.

Much has been published on the structure of *o*-benzoylbenzoic acid and its derivatives. A recent critical examination<sup>7</sup> indicated that, whereas the acids were in the solid entirely, and in solution mainly, in the keto-acid form, the acid chlorides always had the  $\psi$ -structure (III; R = Cl). Esters were prepared both as keto-esters and in the  $\psi$ -structure form (III; R = OMe). Amides, on the other hand, were found to have one structure only; primary and secondary amides prepared from the acid chlorides or acids always had the  $\psi$ -structure (IV; R' = OH), while tertiary amides were true keto-amides.

The reaction of  $\gamma$ -lactones with ammonia and primary amines to form hydroxy-amides or  $\gamma$ -lactams is well established.<sup>8</sup> Since the  $\psi$ -structure is not present in the above  $\epsilon$ -lactones, and since strong hydrogen bonding can be expected between the benzophenone-carbonyl group and the *o*-hydroxyl-hydrogen, keto-acids, keto-esters, and keto-amides rather than the  $\psi$ -structures can be expected to be formed from these lactones.

Unlike the  $\gamma$ -lactones which require temperatures of 200—300°, these  $\epsilon$ -lactones reacted with ammonia and amines in the cold to produce products in almost quantitative yields.

In ethylamine the lactone (II) dissolved immediately with the evolution of much heat, and after two hours, on acidification of the solution, the hydroxy-keto-amide (I; R = CO·NH<sub>2</sub>) separated quantitatively. With diethylamine, although dissolution was almost immediate, the reaction was much less vigorous and slower, but at 55° a quantitative yield of the hydroxy-keto-amide (I; R = CO·NEt<sub>2</sub>) was obtained. Both these amides absorb strongly at 1637 cm.<sup>-1</sup>, which indicates that the benzophenone-carbonyl group is strongly hydrogen-bonded. In both cases also, the infrared absorption of the amido-carbonyl group overlaps that of the benzophenone-carbonyl group. Both the secondary and tertiary amides are thus shown to be keto-amides. In contrast to the conclusions of Graf *et al.*<sup>7</sup> the secondary amide is thus not in the hydroxy-lactam form (IV) which should absorb in the region 1700—1720 cm.<sup>-1</sup> This difference could be attributed to the strong hydrogen-bonding which in these cases prevents lactam formation.

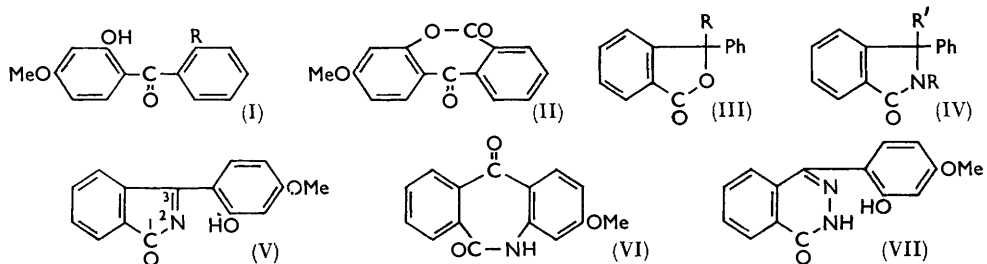
Similar results were obtained on heating the lactone with ethanol. The lactone slowly dissolved and, on addition of a little water, the ethyl keto-ester (I; R = CO<sub>2</sub>Et) was precipitated. Again hydrogen-bonding with the benzophenone-carbonyl group is indicated ( $\nu_{\max}$  1628 cm.<sup>-1</sup>), while the ester-carbonyl absorption is at its normal position ( $\nu_{\max}$  1725 cm.<sup>-1</sup>) instead of greater than 1770 cm.<sup>-1</sup> as in the  $\psi$ -esters.<sup>7</sup>

<sup>6</sup> Orndorff and Kline, *J. Amer. Chem. Soc.*, 1924, **46**, 2276.

<sup>7</sup> Graf, Girod, Schmid, and Stoll, *Helv. Chim. Acta*, 1959, **42**, 1085.

<sup>8</sup> Meyer, *Monatsh.*, 1899, **20**, 717; Späth and Lintner, *Ber.*, 1936, **69**, 2727.

Recrystallisation of the lactone (II) from 5*N*-acetic acid produced the hydroxy-keto-acid (I; R = CO<sub>2</sub>H) in which, in the solid state, both the phenolic hydrogen and the carboxylic hydrogen are bonded. The lactol form (III; R = OH) is not present. Since dissolution shifts the carboxyl carbonyl absorption from 1695 to 1722 cm.<sup>-1</sup>, but has no effect on the benzophenone-carbonyl absorption which remains at 1631 cm.<sup>-1</sup>, it is deduced



that in the solid state the phenolic hydrogen is intramolecularly bonded to the benzophenone-carbonyl, while the carboxylic hydrogen is bonded intermolecularly to the carboxyl-carbonyl of another molecule.

The lactone (II) dissolved slowly in a cold ammonia solution ( $d$  0.880); about 1 hour was required for complete dissolution in a large excess of ammonia. On acidification of the yellow solution so obtained with hydrochloric acid, a deep red solid and/or solution was obtained. The red product was easily extracted with chloroform and gave an intensely red solution, which left a red solid on evaporation. Purification of this was extremely difficult, but chromatography on specially prepared alumina with chloroform as eluant separated it into a fast-moving red band and a slow-moving yellow band [unless rigidly specified conditions (see Experimental) were followed separation was not achieved]. Evaporation of the red solution gave maroon needles which were not the expected hydroxy-amide (I; R = CO·NH<sub>2</sub>) since it (a) lacked two hydrogen atoms and one oxygen atom, (b) showed no N-H stretching vibration in the infrared spectrum, and (c) had carbonyl absorption at 1732 cm.<sup>-1</sup> which could not be due either to a benzophenone- or to an amide-carbonyl group. This value is, however, to be expected from a carbonyl group in a five-membered ring,<sup>9</sup> and the compound is thus considered to be 3-(2-hydroxy-4-methoxyphenyl)-1-isindolone (V).

The red compound was stable in cold sodium hydroxide solution but this solution decomposed when heated, ammonia being liberated, and on acidification the hydroxy-acid (I; R = CO<sub>2</sub>H) was re-formed. While these results are in agreement with the isindole structure (V) the evolution of ammonia rules out the only alternative structure (VI) which, from the method of formation, is also very unlikely.

The spontaneous ring closure of the keto-amide (I; R = CO·NH<sub>2</sub>) which could be the intermediate, is in agreement with the work of Graf *et al.*<sup>7</sup> but the spontaneous loss of water is unusual, and why ring-closure is not prevented here by hydrogen-bonding as in the case of the amide (I; R = CO·NH<sub>2</sub>) is not clear. Attempts to prepare the amide by leaving the ester (I; R = CO<sub>2</sub>Et) in cold ammonia solution resulted in the same red isindole (V) on acidification.

Similarly, ring closure and loss of water occurred when the lactone (II) was dissolved in hydrazine hydrate solution. The lactone dissolved in about five minutes and on acidification, the dihydro-oxophthalazine (VII) was obtained in quantitative yield.

<sup>9</sup> Cross, "Introduction to Practical Infrared Spectroscopy," Butterworths, Scientific Publns., London, 1960, pp. 62, 66; Bellamy, "Infra-Red Spectra of Complex Organic Molecules," 2nd edn., Methuen and Co. Ltd., London, 1958, pp. 148, 214.

## EXPERIMENTAL

2-(2-Hydroxy-4-methoxybenzoyl)benzoic Acid.—Phthalic anhydride (15 g.) was suspended in freshly distilled dry tetrachloroethane (75 ml.) and *m*-dimethoxybenzene (18 g.) was added. To this, at room temperature, anhydrous powdered aluminium chloride (25 g.) was added during 1½ hr., producing a deep purple solution. This mixture was heated under reflux on a water-bath for 3 hr., cooled, and decomposed with ice and hydrochloric acid. The product was steam-distilled to remove the tetrachloroethane and the excess of *m*-dimethoxybenzene. A thick brown oil soon settled and the solution was poured off while hot; purplish crystals separated and were recrystallised from 2*N*-acetic acid, as colourless scales (20 g.), m. p. 164—165° (Quenda<sup>10</sup> reports m. p. 164—165°) (Found: C, 66.1; H, 4.5. Calc. for C<sub>15</sub>H<sub>12</sub>O<sub>5</sub>: C, 66.2; H, 4.4%). From the brown solid left in the flask more of the compound was obtained.

A preferable method of purification was *via* the lactone as described below.

Lactone (II) of 2-(2-Hydroxy-4-methoxybenzoyl)benzoic Acid.—The acid (10 g.) was heated in boiling acetic anhydride (100 ml.) under reflux for 5 min. After filtration hot, the lactone separated as colourless needles, which were filtered off and washed with a little dry ether. On dilution of the filtrate with water a white solid was formed, which was redissolved in boiling acetic anhydride (5 ml.), and more of the lactone (1.7 g.) crystallised on cooling, bringing the total yield to 9.2 g. (98.5%). The crystals had m. p. 167° and gave a negative test with ferric chloride (Found: C, 71.1; H, 4.1. C<sub>15</sub>H<sub>10</sub>O<sub>4</sub> requires C, 71.1; H, 3.9%),  $\nu_{\max}$  (in Nujol) (no OH band) 1722, 1661, and 1620 cm.<sup>-1</sup>.

When the crude 2-(2-hydroxy-4-methoxybenzoyl)benzoic acid obtained from the Friedel-Crafts reaction was dissolved in boiling acetic anhydride, the solution filtered, and allowed to cool the pure lactone separated.

Reactions of the Lactone (II).—(a) *With dilute acetic acid.* Recrystallisation of the lactone from 5*N*-acetic acid yielded the acid (I; R = CO<sub>2</sub>H) as needles, m. p. and mixed m. p. 164—165°,  $\nu_{\max}$  (in Nujol) 2680w, 2550w (no free OH band), 1695vs, and 1632vs cm.<sup>-1</sup>; (in CHCl<sub>3</sub>) 3530w, 2530w, 1722vs, and 1632vs cm.<sup>-1</sup>.

(b) *With ethanol.* The lactone (1.0 g.) dissolved in 20 min. when heated under reflux with absolute ethanol (25 ml.). After it had been refluxed for 2 hr., the solution was diluted until it was milky and just cleared by reheating. On cooling, the benzoate (I; R = CO<sub>2</sub>Et) (1.17 g., 99%) crystallised as flakes, m. p. 70.5—71° not raised by further recrystallisations from dilute ethanol (Found: C, 67.9; H, 5.1. C<sub>17</sub>H<sub>16</sub>O<sub>5</sub> requires C, 68.0; H, 5.3%),  $\nu_{\max}$  (no OH band), 1725 and 1628 cm.<sup>-1</sup>. It gave a red-brown colour with ferric chloride.

(c) *With ethylamine.* The lactone (1 g.) dissolved immediately in ethylamine (5 g.) at 10°, with evolution of much heat. The yellow solution was cooled and after 2 hr. added to ice and concentrated hydrochloric acid; a white solid (1.2 g.), m. p. 124°, was precipitated. On recrystallisation from aqueous ethanol the amide (I; R = CO·NH<sub>2</sub>) was obtained (1.0 g., 85%) with m. p. 132—133° (from aqueous ethanol) (Found: C, 67.8; H, 5.9; N, 4.7. C<sub>17</sub>H<sub>17</sub>NO<sub>4</sub> requires C, 68.2; H, 5.7; N, 4.7%),  $\nu_{\max}$  (in Nujol) 3520sh, 3320m, 1637, and 1610 cm.<sup>-1</sup>; (in CHCl<sub>3</sub>) 3575vw, 3300br, 1696, and 1631 cm.<sup>-1</sup>. It gave a red-brown colour with ferric chloride.

(d) *With diethylamine.* The lactone (1.0 g.) was heated under reflux with diethylamine (5 ml.) for ½ hr. and the amine then distilled off at reduced pressure to leave a white solid. The diethylamide (I; R = CO·NEt<sub>2</sub>) (1.1 g., 85%) had m. p. 84—85° (from dilute ethanol) (Found: C, 69.9; H, 6.6; N, 4.6. C<sub>19</sub>H<sub>21</sub>NO<sub>4</sub> requires C, 69.6; H, 6.4; N, 4.3%),  $\nu_{\max}$  (in Nujol) 2730vw, 1638s, and 1606m cm.<sup>-1</sup>. It gave a red-brown colour with ferric chloride.

(e) *With ammonia.* The lactone (2.0 g.) was left in ammonia solution ( $d$  0.880) (50 ml.) at room temperature. Even with occasional shaking it required 3 hr. to dissolve; the yellow solution was then poured, with stirring, into ice and concentrated hydrochloric acid, and the red precipitate was filtered off (1.6 g.; m. p. 145°). The filtrate on extraction with chloroform (3 × 25 ml.) yielded more (0.4 g.) red solid. This was very soluble in alcohols, chloroform, acetone, and carbon tetrachloride, but only slightly soluble in ether or light petroleum. Purification was only achieved by the following process: acid-washed alumina was heated to 150° for 2 hr. and then allowed to cool open to the atmosphere for one day. Column-chromatography, with this alumina and chloroform (B.D.H.) as solvent and eluant, gave a fast-moving red band and a slow-moving yellow band. The red solution was evaporated to low volume and light

<sup>10</sup> Quenda, *Gazzetta*, 1890, **20**, 128.

petroleum (b. p. 60—80°) added until solid started to be formed. Reheating to clear the solution and cooling yielded the 3-(2-hydroxy-4-methoxyphenyl)-1-isoindolone as maroon-red needles (0.8 g., 40%), m. p. 205—206° (Found: C, 71.5; H, 4.5; N, 5.3.  $C_{15}H_{11}NO_3$  requires C, 71.2; H, 4.3; N, 5.5%),  $\nu_{\max}$  (in Nujol) 1732vs and 1631s  $cm^{-1}$ .

(f) *With hydrazine hydrate.* The lactone (1.0 g.) dissolved in 50% w/w hydrazine hydrate (15 ml.) in 5 min. at room temperature. Addition of the yellow solution to ice and concentrated hydrochloric acid gave the 1,2-dihydro-4-(2-hydroxy-4-methoxyphenyl)-1-oxophthalazine as white crystals (1.1 g., 100%), m. p. 286—287°. Recrystallisation from ethanol did not raise the m. p. (Found: C, 67.2; H, 4.4; N, 10.9.  $C_{15}H_{12}N_2O_3$  requires C, 67.2; H, 4.5; N, 10.5%),  $\nu_{\max}$  (in Nujol) 3280, 3210, 1661, and 1627  $cm^{-1}$ . The compound is soluble in dilute sodium hydroxide solution and is reprecipitated unchanged on acidification. An alcoholic solution gave no colour with ferric chloride.

*Lactone of 2-o-Hydroxybenzoylbenzoic Acid.*—The acid (5.0 g.) was heated with acetic anhydride (10 ml.) for 5 min. On cooling the lactone crystallised (3.75 g., 82%) and was collected and washed with dry ether (m. p. 84—85°) (Found: C, 74.9; H, 3.5.  $C_{14}H_8O_3$  requires C, 75.0; H, 3.6%). Distilling off most of the acetic anhydride gave another crop of lactone (0.5 g.).

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UNIVERSITY OF CAPE TOWN, SOUTH AFRICA.

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