

Derivatives of Acetoacetic Acid. Part II. The Rearrangement of 3-Acyl-2:5-dihydrofuran-2-one Derivatives to Furan-3-carboxylic Acids.†*

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[Reprint Order No. 4545.]

4:5-Dialkyl or -diaryl derivatives of 3-acetyl-2:5-dihydrofuran-2-one, when heated with a mixture of acetic and hydrochloric acids, gave 2-methyl-4:5-dialkyl(or diaryl)furan-3-carboxylic acids in high yield. Similarly, 3-benzoyl-2:5-dihydro-4:5-diphenylfuran-2-one, obtained by the piperidinium acetate-catalysed condensation of benzoin and methyl benzoylacetate, rearranged to 2:4:5-triphenylfuran-3-carboxylic acid.

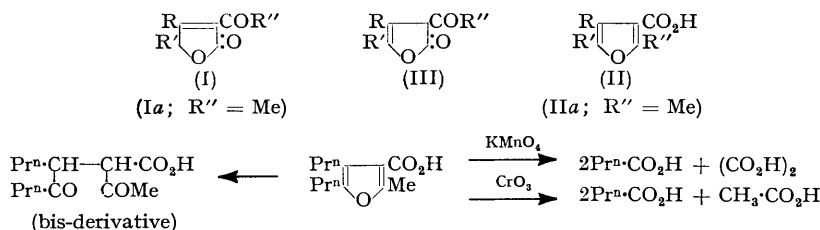
Both 3-acetyl- and 3-benzoyl-2:5-dihydro-4:5-diphenylfuran-2-one autoxidised in air, giving, among other products, the 5-hydroxy-derivatives.

IN Part I,* it was shown that aliphatic and aromatic acyloins condense with diketene and, though in somewhat poorer yields, with acetoacetic esters, to give unsaturated γ -lactones (Ia). When the lactone (Ia; $R = R' = Pr^n$) was heated with a mixture of acetic acid and hydrochloric acid, a monobasic acid was obtained, which was isomeric with the

* Part I, preceding paper.

† Patent pending: B.P. Appln. 14754/1951.

original lactone. Although it did not liberate hydrogen chloride from alcoholic hydroxylamine hydrochloride, when the acid was heated with a solution of 2:4-dinitrophenylhydrazine sulphate in aqueous ethanol, a solid bis-2:4-dinitrophenylhydrazone was obtained. Oxidation of the unknown acid with alkaline potassium permanganate gave *n*-butyric acid and oxalic acid (0.83 mol.); quantitative oxidation (Kuhn-Roth) showed a value of 2.42 terminal alkyl groups. The acid was unaffected both by boiling aqueous alkali and by hydrogen at atmospheric pressure and temperature in the presence of Raney nickel: the ultra-violet absorption spectrum had max. 2750 Å; ϵ , 7300. It was concluded that, under acid conditions, the lactone (Ia; R = R' = Prⁿ) had rearranged to a β -furoic acid (IIa; R = R' = Prⁿ); the reactions involved in the identification of the product are shown below. The acid gave a positive iodoform reaction, presumably by oxidative fission of the furan ring.



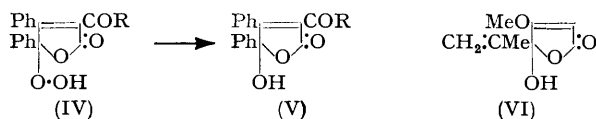
Similar rearrangements have been reported. Knorr and his co-workers (*Annalen*, 1898, **303**, 135; 1899, **306**, 355; *Ber.*, 1889, **22**, 165; 1894, **27**, 1158) and Kapf and Paal (*Ber.*, 1888, **21**, 3059; cf. Borsche and Fels, *Ber.*, 1906, **39**, 1813) have described the acid-catalysed rearrangement of $\beta\gamma$ -unsaturated lactones of type (III) to substituted β -furoic acids. Bergel, Jacob, Todd, and Work (*J.*, 1939, 1375) have reported an analogous rearrangement in the conversion of a substituted α -stearoyl*socoumarone* into an ethyl 2-heptadecylcoumarone-3-carboxylate in the presence of alcoholic hydrogen chloride.

Other lactones (Ia), described in Part I, underwent similar rearrangement in acetic acid-hydrochloric acid. The lactone (Ia; R = R' = Et) gave a 73–80% yield of the β -furoic acid (IIa; R = R' = Et), m. p. 105–106°. Hydrochloric acid could be replaced by sulphuric acid, boron trifluoride etherate, or anhydrous aluminium trichloride. The rearrangement of the lactone (Ia; R = R' = Me) to the β -furoic acid (IIa; R = R' = Me), m. p. 130–131°, provided further evidence of the nature of the reaction, since the trimethyl- β -furoic acid had been synthesised by Reichstein, Zschokke, and Syz (*Helv. Chim. Acta*, 1932, **15**, 1112) by an authentic method. The identity of the lactone (Ia; R = R' = C₁₁H₂₃) obtained by the interaction of lauroin and diketene (see Part I) had not been established by analytical evidence, since the product was a high-boiling oil. Treatment of the crude lactone with hydrochloric acid in acetic acid gave a poor yield of a solid acid, m. p. 74°, which gave analytical data in satisfactory agreement with those expected for the β -furoic acid. The lactone (Ia; R = R' = Ph) very readily rearranged to the expected β -furoic acid; the use of sulphuric acid in acetic acid gave poorer yields, while the use of alcohols as solvents gave rise to mixtures, probably as a result of partial esterification of the acid formed.

Although the lactone (Ia; R = R' = Ph) could be stored indefinitely if air were excluded, after a few days in air it became yellow and gummy; also an acetic acid solution of the lactone, on agitation at 70°, rapidly absorbed oxygen. From the product obtained on keeping the lactone in contact with air for some weeks were isolated benzil, benzoic acid, acetic acid, and a solid acid, C₁₈H₁₄O₄. The last possessed a hydroxyl and a $\cdot\text{CO}\cdot\text{CH}_2\cdot$ group, was ketonic, and gave no colour with ferric chloride. The ultra-violet absorption spectrum showed the keto-group to be $\alpha\beta$ -unsaturated, although the intensity of the absorption band was low. It was concluded that the acid has the structure (V; R = Me), possessing the maleic acid half-aldehyde ring system.

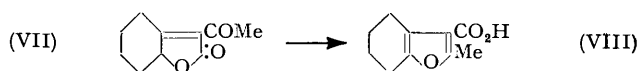
As Shaw (*J. Amer. Chem. Soc.*, 1946, **68**, 2510) and Raphael (*J.*, 1947, 805) have shown for acetylacrylic acid and penicillic acid (VI), respectively, the cyclic formula adequately

represents the acid character of such compounds. The acid (V; R = Me) was unaffected by boiling hydrochloric acid, but with alkali it formed an unidentified gum. Oxidation with alkaline potassium permanganate gave good yields of benzil and oxalic acid; the acid was unaffected by bromine in carbon tetrachloride. Clemmensen reduction gave



2-methyl-4:5-diphenylfuran-3-carboxylic acid (IIa; R = R' = Ph), the acid (V; R = Me) presumably being first reduced to the lactone (Ia; R = R' = Ph) which rearranged to the β -furoic acid. The acid (V; R = Me) probably arises, together with benzil, benzoic acid, and acetic acid, from the decomposition of the hydroperoxide (IV; R = Me), which, it is to be expected, would readily be formed by oxygen attack on the reactive tertiary carbon atom adjacent to a phenyl and a vinyl group.

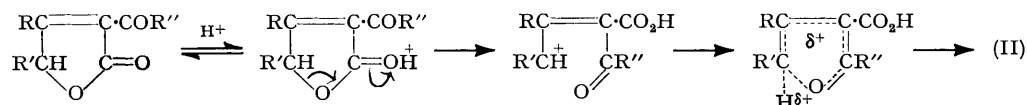
The lactone (VII), derived from diketene and 2-hydroxycyclohexanone, readily rearranged to the expected 4:5:6:7-tetrahydro-2-methylbenzofuran-3-carboxylic acid (VIII) in acetic acid-hydrochloric acid, and, even on slow distillation at 2 mm., a partial conversion was achieved.



Despite the use of prolonged reaction times and anhydrous solutions, the rearrangement of the lactone (Ia; R = Ph, R' = H) could not be accomplished.

In Part I it has been shown that lactones (Ia) can be prepared by the condensation of acylolins and acetoacetic ester. Similarly, the condensation of benzoin with methyl benzoylacetate in boiling xylene in the presence of piperidinium acetate gave the lactone (I; R = R' = R'' = Ph). The results of analysis were unsatisfactory, and the ultraviolet spectrum failed to exhibit the expected strong absorption band at 3100 Å, characteristic of the PhC:C-COPh chromophore, being in better agreement with a formulation as the $\beta\gamma$ -unsaturated lactone. Nevertheless, on treatment with acetic acid-hydrochloric acid at 100°, the lactone gave a good yield of 2:4:5-triphenylfuran-3-carboxylic acid (II; R = R' = R'' = Ph), which was decarboxylated by the method of Reichstein *et al.* (*loc. cit.*) to the known 2:3:5-triphenylfuran (Japp and Klingemann, *J.*, 1890, 674). The lactone (I; R = R' = R'' = Ph) absorbed oxygen from the air to give an acid, C₂₃H₁₆O₄ (V; R = Ph), possessing the cyclic maleic acid half-aldehyde structure.

It is thus apparent that lactones of type (I), or the corresponding $\beta\gamma$ -unsaturated isomers, will rearrange to β -furoic acids under acid conditions if (a) R'' is methyl or phenyl, (b) R is alkyl, phenyl, carboxyl, ethoxycarbonyl, or hydrogen, and (c) R' is alkyl or phenyl. When R' was hydrogen, the lactone failed to rearrange. The evident activation of the reaction by a substituent in this last position suggested a Saytzeff type of elimination of the 'onium ion formed by the addition of a hydrogen ion to the ester grouping. The formation of a cyclic transition complex would then be followed by the elimination of hydrogen ion from C₅ (or C₃ in the case of a $\beta\gamma$ -unsaturated lactone).



Clearly the nature of R can have only a minor influence on the reaction rate, since it can conjugate either with the starting material or with the product, but R' can promote the reaction either by inductive effects ($-I$) * or by conjugation (or hyperconjugation) ($-E$) with the transition complex. The very large effects obtained in the reaction rate of

* Robinson sign convention.

triad anionotropy, obtained by substituents on the carbon atom originally attached to the anion, has been well illustrated (cf. Braude, *Quart. Reviews*, 1950, 4, 404).

EXPERIMENTAL

M. p.s were determined in a Kofler block and are corrected. Light-absorption determinations were carried out in ethanol.

2-Methyl-4:5-dipropylfuran-3-carboxylic Acid (IIa; R = R' = Prⁿ).—3-Acetyl-2:5-dihydro-4:5-dipropylfuran-2-one (Ia; R = R' = Prⁿ) (5 g.) in acetic acid (30 c.c.) was added to concentrated hydrochloric acid (15 c.c.), and the mixture heated at 100° for 1 hr. Addition of water and storage, gave a white solid (4.8 g.; 96%), m. p. 61°, which crystallised from aqueous methanol as clusters of needles, m. p. 61°, of the β -furoic acid (IIa; R = R' = Prⁿ) (Found: C, 68.25; H, 8.45%; acid equiv., 212. C₁₂H₁₈O₃ requires C, 68.55; H, 8.65%; equiv., 210.3). Treatment with aqueous-alcoholic 2:4-dinitrophenylhydrazine sulphate gave the *bis*-2:4-dinitrophenylhydrazone of 2:5-dioxo-4-propyloctane-3-carboxylic acid as dark red needles (from aqueous methanol), m. p. 113—114° (Found: C, 49.25; H, 5.2; N, 18.9. C₂₄H₂₆O₁₀N₈ requires C, 49.1; H, 4.8; N, 19.05%).

The acid (5 g.) in sodium carbonate solution (25 g. of 25% solution) was treated with potassium permanganate (14.4 g.) in water (200 c.c.) during 1 hr. with agitation and cooling. After a further 0.5 hr., the excess of potassium permanganate was destroyed with sodium hydrogen sulphite, the manganese dioxide filtered off, and the filtrate evaporated almost to dryness. Acidification gave *n*-butyric acid (*p*-bromophenacyl ester); evaporation to dryness and extraction of the residue with acetone gave oxalic acid dihydrate (2.5 g.), m. p. 100—101°. The Kuhn-Roth oxidation was carried out as described by Barthel and LaForge (*Ind. Eng. Chem. Anal.*, 1944, 16, 434).

4:5-Diethyl-2-methylfuran-3-carboxylic Acid (IIa; R = R' = Et).—3-Acetyl-4:5-diethyl-2:5-dihydrofuran-2-one (Ia; R = R' = Et) (1 g.), acetic acid (10 c.c.), and concentrated hydrochloric acid (1 c.c.) were heated at 95—100° for 1 hr. Isolation as previously described gave the acid in 80% yield. Equivalent results were obtained by replacement of the acetic acid with dioxan whereas inferior results were obtained by replacement of the hydrochloric acid with aluminium trichloride (34%), boron trifluoride etherate (68%), or sulphuric acid (57%). The β -furoic acid formed prisms, m. p. 105—106°, from aqueous methanol (Found: C, 66.3; H, 7.45%; acid equiv., 179. C₁₀H₁₄O₃ requires C, 65.9; H, 7.75%; equiv., 182.2).

2:4:5-Trimethylfuran-3-carboxylic Acid (IIa; R = R' = Me).—3-Acetyl-2:5-dihydro-4:5-dimethylfuran-2-one (Ia; R = R' = Me) (3 g.), acetic acid (30 c.c.), and concentrated hydrochloric acid (15 c.c.) were heated at 100° for 0.5 hr. On pouring of the product into water, a crystalline precipitate (2.5 g., 83%), m. p. 129—130.5°, was obtained. The β -furoic acid formed prisms, m. p. 130—131°, from aqueous methanol [Reichstein *et al.*, *loc. cit.*, give m. p. 131—132° (corr.)].

2-Methyl-4:5-diundecylfuran-3-carboxylic Acid (IIa; R = R' = C₁₁H₂₃).—The crude product (50 g.) obtained from the reaction of lauroin and diketene (cf. Part I) was heated at 100° with acetic acid (100 c.c.) and concentrated hydrochloric acid (20 c.c.) with agitation (a homogeneous solution was not obtained) for 2 hr. On isolation, a semi-solid oil was obtained which was washed with dichloroethane and then crystallised from that solvent, giving the β -furoic acid as a white powder, m. p. 74° (Found: C, 77.0; H, 11.15%; acid equiv., 446. C₂₈H₅₀O₃ requires C, 77.35; H, 11.6%; equiv., 434.7).

2-Methyl-4:5-diphenylfuran-3-carboxylic Acid (IIa; R = R' = Ph).—3-Acetyl-2:5-dihydro-4:5-diphenylfuran-2-one (IIa; R = R' = Ph) (5 g.) in acetic acid (50 c.c.)—concentrated hydrochloric acid (5 c.c.) was heated at 100° for 1 hr., and the product was then cooled and filtered off; plates, m. p. 208° (3.2 g., 64%), were obtained: addition of water gave a crop (1.4 g.) of somewhat crude product. Crystallisation from ethyl acetate gave the β -furoic acid as plates, m. p. 212° (Found: C, 77.5; H, 5.0%; acid equiv., 273. C₁₈H₁₄O₃ requires C, 77.7; H, 5.05%; equiv., 275.3).

3-Acetyl-2:5-dihydro-5-hydroxy-4:5-diphenylfuran-2-one (V; R = Me).—After the lactone (IIa; R = R' = Ph) had been in contact with air for some weeks, the material was yellow and gummy, with a sharp smell of acetic acid. An ethereal solution of the product (20 g.) was extracted with aqueous sodium carbonate to give a non-acid oil (10.4 g.) and, by acidification of the sodium carbonate extract, an acid portion (8.4 g.). Vacuum distillation of the non-acid oil gave a fraction, b. p. 120—155°/1 mm. (3.1 g.), which, on crystallisation from light petroleum (b. p. 60—80°), gave benzil (1.0 g.) as pale yellow needles, m. p. and mixed m. p. 95—96°. Repeated crystallisation of the acid portion from benzene-light petroleum (b. p. 60—80°) gave

benzoic acid, m. p. 122°, and a second *acid* (V; R = Me), needles, m. p. 181° (Found: C, 73.6; H, 4.85. $C_{18}H_{14}O_4$ requires C, 73.45; H, 4.8%). Light absorption: max., 2600 Å; ϵ , 5730. A 2:4-dinitrophenylhydrazones crystallised from aqueous acetic acid as orange microcrystals, m. p. 204° (decomp.) (Found: N, 11.4. $C_{24}H_{18}O_7N_4$ requires N, 11.8%). Light absorption: max., 3720 Å; ϵ , 35,900 (cf. Braude and Jones, *J.*, 1945, 498). The acid gave no colour with ammonia solution, but afforded a *benzylthiuronium* salt as needles (from aqueous isopropanol), m. p. 103° (Found: N, 5.9. $C_{26}H_{24}O_4N_2S$ requires N, 6.1%). The acid (1 g.), acetyl chloride (1 c.c.), and pyridine (5 c.c.) were heated at 90° for 1 hr., giving the *acetate* (0.9 g.) which crystallised from ethyl acetate–light petroleum (b. p. 40–60°) as needles, m. p. 91–92° (Found: C, 71.55; H, 5.05. $C_{20}H_{16}O_5$ requires C, 71.4; H, 4.8%). Refluxing of the acid (0.25 g.) with benzaldehyde (0.1 g.) and aqueous sodium hydroxide (0.5 c.c. of 10%) in ethanol (5 c.c.) gave the *benzylidene* derivative (0.28 g. crude), needles, m. p. 185° (Found: C, 78.65; H, 4.6. $C_{25}H_{16}O_4$ requires C, 78.5; H, 4.75%). This derivative exhibited both acidic and ketonic properties. The acid (1.8 g.) in acetic acid (50 c.c.) was added to amalgamated zinc (from 4 g. of granulated zinc and 0.4 g. of mercuric chloride) and concentrated hydrochloric acid (10 c.c.), and the mixture refluxed for 5 hr., more (5 c.c.) concentrated hydrochloric acid being added after 3 and after 4 hr. Dilution and isolation with ether, and crystallisation of the product from benzene–light petroleum (b. p. 60–80°), gave needles (0.7 g.), m. p. 211° undepressed by a sample of 2-methyl-4:5-diphenylfuran-3-carboxylic acid (IIa; R = R' = Ph).

4:5:6:7-Tetrahydro-2-methylbenzofuran-3-carboxylic Acid (VIII).—3-Acetyl-2:4:5:6:7:8-hexahydrobenzofuran-2-one (VII) (3 g.) was heated at 100° for 1 hr. with acetic acid (20 c.c.)–concentrated hydrochloric acid (10 c.c.), and then poured into water. The precipitate (2.7 g., 90%) was crystallised from ethyl acetate–light petroleum (b. p. 60–80°) giving the β -furoic acid (VIII), m. p. 165–166° (Found: C, 67.0; H, 6.8%; acid equiv., 178. $C_{10}H_{12}O_3$ requires C, 66.65; H, 6.7%; equiv., 180.2). On slow distillation of (VII) at 2 mm. (bath temp. 160–170°), the later fractions, b. p. 140–145°/2 mm., partly crystallised, giving the same β -furoic acid.

3-Benzoyl-2:5(or 3)-dihydro-4:5-diphenylfuran-2-one (I; R = R' = R'' = Ph).—A mixture of benzoin (21.2 g.), methyl benzoylacetate (27 g.), piperidine (1 c.c.), and acetic acid (0.8 c.c.) in xylene (100 c.c.) was refluxed for 5 hr. with the elimination of aqueous methanol (5.1 c.c.) collected in a Dean–Stark decanter head. When the solution cooled, unchanged benzoin (9.4 g.) was precipitated, but after partial evaporation, and crystallisation of the solid residue (10.8 g.) from ethyl acetate–light petroleum (b. p. 60–80°), the *lactone* was obtained as yellowish-green needles, m. p. 137–138°. Satisfactory microanalyses were not obtained (Found: C, 79.0; H, 5.6, 5.0. $C_{23}H_{16}O_3$ requires C, 81.15; H, 4.75%). Light absorption: max. 2250 and 2700 Å; ϵ , 7800 and 8570, respectively.

3-Benzoyl-2:5-dihydro-5-hydroxy-4:5-diphenylfuran-2-one (V; R = Ph).—After several months' storage, the m. p. of the above lactone (I; R = R' = R'' = Ph) had risen to 145–155°. The product (4.0 g.) in benzene–ethyl acetate (4:1; 100 c.c.) was adsorbed on activated alumina. Elution with the same solvent mixture gave a pale yellow product, m. p. 185–187° (3.09 g.), which, on crystallisation from ethyl acetate–light petroleum (b. p. 60–80°), gave the *acid* (V; R = Ph) as needles, m. p. 196°, soluble in sodium hydrogen carbonate solution (Found: C, 77.75; H, 4.45. $C_{23}H_{16}O_4$ requires C, 77.5; H, 4.55%). Light absorption: max. 2570 Å; ϵ , 20,000: inf. 2870 Å; ϵ , 14,000.

2:4:5-Triphenylfuran-3-carboxylic Acid (II; R = R' = R'' = Ph).—The lactone (I; R = R' = R'' = Ph) (2 g.) was heated at 100° for 1.5 hr. with acetic acid (10 c.c.)–concentrated hydrochloric acid (2 c.c.). Addition of water to the cooled solution and crystallisation of the precipitate (1.7 g.) from acetic acid gave the β -furoic acid (II; R = R' = R'' = Ph), m. p. 257° (Found: C, 81.35; H, 4.95%; acid equiv., 331. Calc. for $C_{23}H_{16}O_3$: C, 81.15; H, 4.75%; Equiv., 340.4) (Adams and Melstrom, *J. Amer. Chem. Soc.*, 1946, 68, 103, give m. p. 257–258°). The acid gave a strong blue fluorescence in water.

The β -furoic acid (0.5 g.) in diethylaniline (5 c.c.) was heated under reflux for 3 hr. with copper chromite catalyst (0.1 g.; Adkins, "Organic Syntheses," Wiley, Vol. II, p. 144): carbon dioxide was evolved. After cooling, the product was taken up in ether, the solution filtered, washed with dilute sulphuric acid followed by sodium hydrogen carbonate solution, and evaporated, and the residue (0.4 g.) crystallised from isopropanol, forming needles, m. p. 92–93° undepressed with a sample of 2:3:4-triphenylfuran prepared by Japp and Klingemann's method (*J.*, 1890, 674), who give m. p. 92–93°.

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[Received, August 1st, 1953.]