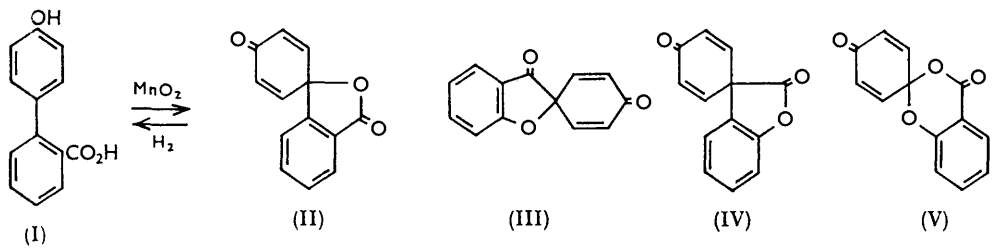
1002. *Internuclear Cyclisation. Part XIX.*[1] *Intramolecular Oxidative Coupling of 4′-Hydroxybiphenyl-2-carboxylic Acid.*

By D. H. Hey, J. A. Leonard, and C. W. Rees.

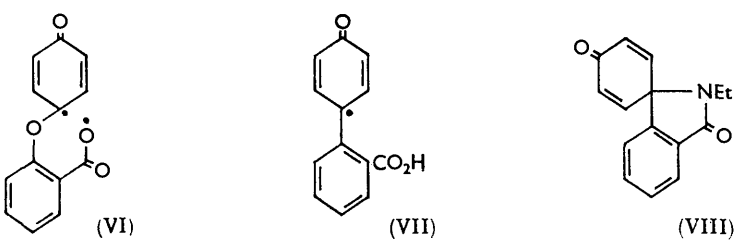
4′-Hydroxybiphenyl-2-carboxylic acid (I) is oxidised to phthalan-1-spiro-1′-cyclohexadiene-3,4′-dione (II) by manganese dioxide in ether at room temperature. 4′-Hydroxybenzanilide (IX; R = H) is oxidised to benzamide and *p*-benzoquinone by manganese dioxide in boiling chloroform or dioxan. Alkaline fusion of potassium 9-oxofluorene-2-sulphonate gives 4- and not 4′-hydroxybiphenyl-2-carboxylic acid as claimed by Courtot. With diethyl sulphate and alkali, *p*-benzamidophenyl benzoate gives benzoyl-*p*-phenetidide and not the expected *N*-ethyl derivative.

In Part XVIII of this series[1] the reduction of 4′-nitrobiphenyl-2-carboxylic acid to the hydroxylamine and its acid-catalysed rearrangement to phthalan-1-spiro-1′-cyclohexadiene-3,4′-dione (II) were described. We now report a further simple synthesis of the spiro-dienone-lactone (II) from 4′-hydroxybiphenyl-2-carboxylic acid (I) by oxidation with manganese dioxide in ether at room temperature. This reaction was suggested by the elegant radical-coupling reactions of phenols recently investigated by Barton,[2] Scott,[3] and Hassall,[4] and their collaborators, and used in the synthesis of a variety of natural products such as galanthamine,[2] pichrolichenic acid,[3] geodoxin,[4] and geodin.[5] These oxidations have been reviewed.[5,6]



(I) (II) (III) (IV) (V)

Structure (II) must now be added to the spiro-dienones (III)—(V) which can be synthesised by the intramolecular oxidative coupling of phenols, and the versatility of this process is again illustrated. The oxidation of *o*-4-hydroxyphenoxybenzoic acid to compound (V) has been represented as the formation and coupling of the carboxyl radical



(VI) (VII) (VIII)

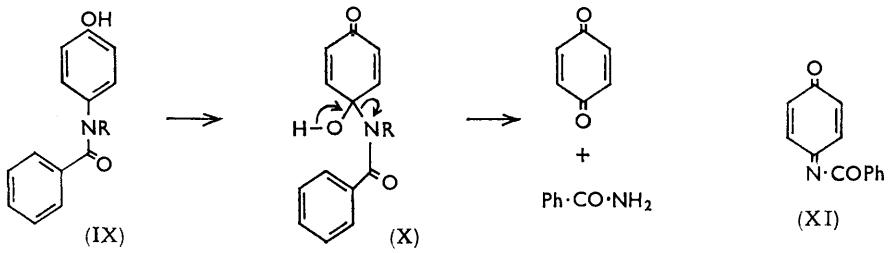
(VI).[5] The oxidation of 4′-hydroxybiphenyl-2-carboxylic acid (I) could similarly involve the corresponding diradical or, alternatively, the monoradical (VII) which undergoes intramolecular cyclisation on to the carboxylic acid group. The phenol (I) was regenerated

[1] Part XVIII, preceding paper.
[2] Barton and Kirby, *J.*, 1962, 806.
[3] Davidson and Scott, *J.*, 1961, 4075.
[4] Hassall and Lewis, *J.*, 1961, 2312.
[5] Hassall and Scott in "Chemistry of Natural Phenolic Compounds," Pergamon Press, London, 1961, p. 119.
[6] Lewis, *Chem. and Ind.*, 1962, 159.

by catalytic hydrogenation [1] of the dienone (II), in agreement with the reduction of the other spiro-dienones above.

The possible extension of this oxidation to the conversion of amides of the hydroxy-acid (I) into the corresponding lactams [7] (*e.g.*, VIII) was not investigated because of difficulties in obtaining the hydroxy-acid in quantity. This acid had previously been prepared [7] in 13% yield by heating sodium fluorene-2-sulphonate with potassium hydroxide in diphenyl ether. Fusion of potassium 2-oxofluoren-2-sulphonate with an equimolar mixture of sodium and potassium hydroxides at 305°, as described by Courtot,[8] gave an acid (55%) with the required melting point, but this was not 4'-hydroxybiphenyl-2-carboxylic acid, as claimed,[8] but the isomeric 4-hydroxybiphenyl-2-carboxylic acid. However, the oxidation of 4'-hydroxybenzanilide (IX; R = H) was briefly investigated since, if oxidation of its *N*-ethyl derivative gave the alcohol (X; R = Et) as an intermediate, it might be possible to effect cyclodehydration of this to the lactam (VIII) by the Einhorn amidomethylation procedure with hydrogen chloride: [9]

$$ArH + HO{\cdot}CH_2{\cdot}NH{\cdot}COR' \longrightarrow Ar{\cdot}CH_2{\cdot}NH{\cdot}COR' + H_2O$$



All attempts to ethylate *p*-benzamidophenyl benzoate, obtained from benzoyl chloride and *p*-aminophenol or *p*-aminophenyl acetate, with diethyl sulphate and alkali led only to hydrolysis of the ester group and *O*-ethylation to give benzoyl-*p*-phenetidide; even with a large excess of diethyl sulphate this could not be *N*-ethylated. Hydrolysis of the *ON*-dibenzoyl derivative gave 4'-hydroxybenzanilide (IX; R = H). Oxidation of this phenol with manganese dioxide in boiling chloroform or dioxan gave a mixture of *p*-benzoquinone and benzamide (71%). These products presumably arose from the intermediate (X; R = H) by the elimination indicated; the alternative route *via* quinone benzoylimine (XI) seems less likely since, by analogy with quinone benzenesulphonylimine,[10] its hydrolysis to the observed products under the reaction conditions would not be expected. Benzanilide and benzoyl-*p*-phenetidide were not oxidised under the same conditions. Milder oxidation of the phenol (IX; R = H) with silver oxide in anhydrous ethyl acetate at room temperature, and attempted intramolecular amidomethylation of the intermediate (X; R = H) by treatment of the oxidation solution with dry hydrogen chloride, were unsuccessful.

Experimental

For general directions see Part XVIII.[1] Alkaline manganese dioxide was prepared by the method of Attenburrow *et al.*; [11] silver oxide, prepared from aqueous silver nitrate and potassium hydroxide, was washed with water, acetone, and ether and dried *in vacuo*.

Alkaline Fusion of Potassium 2-Oxofluorene-2-sulphonate (cf. ref. 8).—A mixture of sodium hydroxide (41·6 g.), potassium hydroxide (58·4 g.), and water (10 ml.) was heated in a nickel crucible to 260°. Dry, finely powdered potassium 2-oxofluorene-2-sulphonate [8] (44 g.) was added with stirring to the clear melt. The temperature was gradually raised to 305°, during

[7] Hey, Leonard, Moynehan, and Rees, *J.*, 1961, 232.
[8] Courtot, *Ann. Chim.* (*France*), 1930, **14**, 5.
[9] Snyder and Brewster, *J. Amer. Chem. Soc.*, 1949, **71**, 1058.
[10] Adams and Looker, *J. Amer. Chem. Soc.*, 1951, **73**, 1145.
[11] Attenburrow, Cameron, Chapman, Evans, Hems, Jansen, and Walker, *J.*, 1952, 1104.

which time the initially red pasty mass became much darker and more mobile. Efficient stirring was essential to prevent local overheating. After being maintained at this temperature for 10 min., the mixture was allowed to cool and extracted with hot water (4 × 150 ml.). Addition of acid to pH 9 caused precipitation of dark by-products, which were separated by filtration. Acidification of the almost colourless filtrate gave a bulky white precipitate, which was collected, washed with water, and dried, to yield 4-hydroxybiphenyl-2-carboxylic acid (16·1 g.), m. p. 201°, $\nu_{max.}$ 894 and 844 (1,2,4-trisubstituted benzene) and 705 cm.$^{-1}$ (monosubstituted benzene). Admixture with authentic 4′-hydroxybiphenyl-2-carboxylic acid gave a large depression in m. p.; the two compounds had different spectra. Courtot,[8] who described this compound as 4′-hydroxybiphenyl-2-carboxylic acid, gave m. p. 205°. Huntress and Seikel [12] reported m. p. 202°. Use of sodium hydroxide (100 g.) in the above procedure gave the same product in the same yield.

Phalan-1-spiro-1′-cyclohexadiene-3,4′-dione (II).—Manganese dioxide (2 g.) was added to a solution of 4′-hydroxybiphenyl-2-carboxylic acid [7] (I) (0·2 g.) in ether (100 ml.), and the mixture was shaken for 18 hr. The mixture was filtered and the filtrate extracted with aqueous sodium hydrogen carbonate. Removal of the solvent from the dried ether solution gave phthalan-1-spiro-1′-cyclohexadiene-3,4′-dione (0·05 g., 25%), identical (mixed m. p., infrared spectra) with the product obtained from the acid-catalysed rearrangement of 4′-hydroxylaminobiphenyl-2-carboxylic acid.[1] Attempts to increase this yield were not made.

p-*Benzamidophenyl Benzoate.*—*p*-Nitrophenyl acetate (30 g.) in ethanol (450 ml.) was shaken in an atmosphere of hydrogen in the presence of Adams catalyst (3 g.). The required volume (10 l.) was absorbed in 2 hr. The mixture was filtered (Celite) and the filtrate evaporated to dryness. The impure *p*-aminophenyl acetate was suspended in 10% aqueous sodium hydroxide (300 ml.) and cooled in ice, and benzoyl chloride (40 ml.) was added with stirring. Filtration gave a residue (31 g.) which, on crystallisation from chloroform, afforded the *ON*-dibenzoyl derivative (15 g.) in white needles, m. p. 236°, identical with the product of benzoylation of *p*-aminophenol (lit.,[13] m. p. 233—234°).

Attempted Ethylation of p-*Benzamidophenyl Benzoate.*—The *ON*-dibenzoyl derivative (15 g.) in acetone (100 ml.) and 10% aqueous sodium hydroxide (150 ml.) was heated under reflux and diethyl sulphate (30 ml.) was added during 10 min. After boiling for a further 30 min., the mixture was poured into water. Filtration gave benzoyl-*p*-phenetidide (11 g.), m. p. 174° (lit.,[13] 174·5—175°). Use of sodium carbonate in place of sodium hydroxide yielded only starting material.

4′-*Hydroxybenzanilide* (IX; R = H).—*p*-Benzamidophenyl benzoate (5 g.) was suspended in ethanol (15 ml.) and 10% aqueous sodium hydroxide (100 ml.), and the mixture was boiled under reflux for 30 min. Acidification of the alkaline solution and removal of benzoic acid with aqueous sodium hydrogen carbonate afforded 4′-hydroxybenzanilide (2 g.) as an off-white powder, m. p. 216° (lit.,[14] 214—215°).

Oxidation of 4′-*Hydroxybenzanilide* (IX; R = H).—To 4′-hydroxybenzanilide (1 g.) in chloroform (350 ml.) alkaline manganese dioxide (10 g.) was added and the mixture was boiled under reflux for 20 hr. Filtration and removal of the solvent from the filtrate gave a residue (0·8 g.) consisting of colourless plates and yellow needles. On sublimation this gave *p*-benzoquinone, m. p. and mixed m. p. 113°, while the residue on crystallisation from water gave benzamide (0·4 g.) in plates, m. p. and mixed m. p. 129°. Very similar results were obtained in dioxan (125 ml.) as solvent.

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[12] Huntress and Seikel, *J. Amer. Chem. Soc.*, 1939, **61**, 816.
[13] Fawcett and Robinson, *J.*, 1927, 2419.
[14] Reverdin and Dresel, *Ber.*, 1904, **37**, 4452.