251. *Some Extensions of the Synthesis of Hydroxyindoles from* p-*Benzoquinones.*

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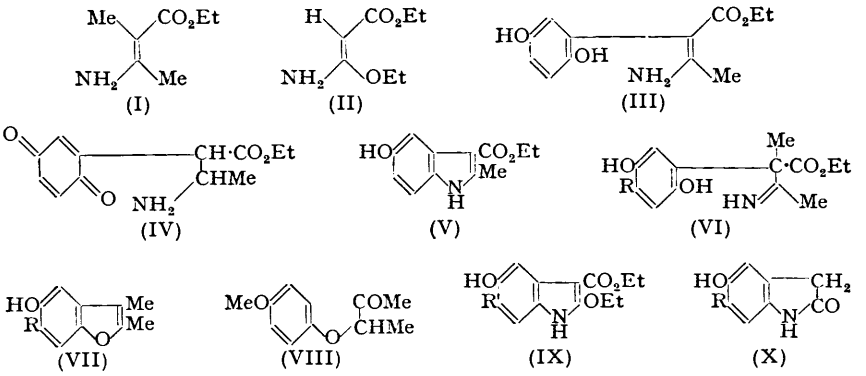
Ethyl β-amino-α-methylcrotonate reacts with *p*-benzoquinone and methoxy-*p*-benzoquinone to give the quinol derivatives (VI; R = H and OMe) which, with hot alkali, are converted into 5-hydroxy- (VII; R = H) and 5-hydroxy-6-methoxy-2 : 3-dimethylcoumarone (VII; R = OMe) respectively. With ethyl β-amino-β-ethoxyacrylate, ethyl 2-ethoxy-5-hydroxy- and ethyl 2-ethoxy-5-hydroxy-6-methoxy-indole-3-carboxylate are formed and respectively give the corresponding 5-hydroxy- and 5-hydroxy-6-methoxy-oxindole on hydrolysis.

Condensation of ethyl β-aminocrotonate with *p*-benzoquinones provided a route to certain 5-hydroxyindole derivatives (Beer, Clarke, Davenport, and Robertson, *J.*, 1951, 2029; cf. Nenitzescu, *Bull. Soc. Chim. Roumania*, 1929, **11**, 37) and the present paper describes extensions of the reaction with esters formally similar to ethyl β-aminocrotonate, *e.g.*, (I) and (II). Indole formation by this method probably proceeds by way of intermediates of type (III) which cyclise by loss of water to esters of 5-hydroxyindole-3-carboxylic acids of type (V). Harley-Mason (personal communication) has suggested that intermediates of the type (IV) are also possible. Either mechanism is consistent with the fact that the final products in the cases examined are 5-hydroxy- and not 6-hydroxy-indoles which would obtain if the initial reaction involved the attachment of the amino-group to the quinone nucleus.

The interaction of ethyl β-amino-α-methylcrotonate (I) with *p*-benzoquinone gave a somewhat unstable phenolic base, having the composition of a hydrate of the quinol (VI; R = H), which might conceivably have cyclised to form an indolenine. This did not occur, but on treatment with hot aqueous sodium hydroxide the quinol hydrate furnished 5-hydroxy-2 : 3-dimethylcoumarone (VII; R = H) with the liberation of ammonia. The structure of (VII; R = H) was substantiated by an unambiguous synthesis. 3-*p*-Methoxyphenoxybutan-2-one (VIII) was formed by the alkylation of quinol monomethyl ether with 3-chlorobutan-2-one and cyclised with sulphuric acid to give a good yield of 5-methoxy-2 : 3-dimethylcoumarone which, on demethylation, yielded 5-hydroxy-2 : 3-dimethylcoumarone (VII; R = H).



The quinol (VI; R = OMe), similarly formed from methoxy-*p*-quinone, was more stable but on treatment with hot alkali also furnished a coumarone which, by analogy, is 5-hydroxy-6-methoxy-2 : 3-dimethylcoumarone (VII; R = OMe).

The condensation of ethyl β-amino-β-ethoxyacrylate (II) with *p*-benzoquinone gave the expected ethyl 2-ethoxy-5-hydroxyindole-3-carboxylate (IX; R = H) which, however, was surprisingly resistant to mild alkaline hydrolysis and, with hot concentrated alkali under more drastic conditions, decomposed to intractable products. By means of boiling

dilute hydrochloric acid, the compound was smoothly converted into 5-hydroxyoxindole (X; R = H) which was also obtained in poor yield when *N*-chloroacetyl-*p*-anisidine was heated with aluminium chloride according to Stolle's procedure (cf. Porter, Robinson, and Wyler, *J.*, 1941, 620).

The compound obtained in this reaction by Giovanni and Portmann (*Helv. Chim. Acta*, 1948, **31**, 1381) and regarded by them as 5-methoxyoxindole is clearly 5-hydroxyoxindole, as suggested by Julian ("Heterocyclic Compounds," John Wiley and Sons, New York, Vol. III, 1952, p. 145). Methylation of the 2-ethoxy-5-hydroxyindole ester (IX; R = H) with methyl sulphate and alkali gave a product which is apparently ethyl 2-ethoxy-5-methoxy-1-methylindole-3-carboxylate, since on treatment with hot dilute hydrochloric acid it furnished 5-methoxy-1-methyloxindole.

When *p*-benzoquinone was replaced by methoxy-*p*-benzoquinone in the initial condensation the resulting ethyl 2-ethoxy-5-hydroxy-6-methoxyindole-3-carboxylate (IX; R = OMe) had properties similar to those of (IX; R = H), and on hydrolytic decomposition with warm acid gave 5-hydroxy-6-methoxyoxindole (X; R = OMe).

Although *N*-alkyl and *N*-aryl derivatives of ethyl β-aminocrotonate condense with *p*-benzoquinone to give hydroxyindoles, the *N*-acetyl derivative of the ester, as was expected, failed to react. A similar lack of reactivity was shown by ethyl aminomethylenemalonate.

Experimental

5-Hydroxy-2 : 3-dimethylbenzofuran.—(*a*) Interaction of ethyl β-amino-α-methylcrotonate (Conrad and Epstein, *Ber.*, 1887, **20**, 3055) (5·6 g.) and *p*-benzoquinone (4·0 g.) in boiling acetone (30 ml.) for 1 hour gave ethyl α-(2 : 5-dihydroxyphenyl)-β-imino-α-methylbutyrate which separated from ethyl acetate–light petroleum (b. p. 40—60°) as a *hydrate* in colourless prisms (3·0 g.), m. p. 89—90° (Found : C, 58·0; H, 7·3; N, 5·3. $C_{13}H_{17}O_4N,H_2O$ requires C, 58·0; H, 7·1; N, 5·2%). With boiling 2N-sodium hydroxide (20 ml.) in nitrogen this compound (0·5 g.) gave ammonia and *5-hydroxy-2 : 3-dimethylcoumarone*. This product was isolated with ether and purified by distillation at 90°/0·1 mm., followed by crystallisation from light petroleum (b. p. 80—100°), forming rosettes of colourless needles (0·2 g.), m. p. 79° (Found : C, 74·3; H, 6·1. $C_{10}H_{10}O_2$ requires C, 74·1; H, 6·2%).

(*b*) Alkylation of quinol monomethyl ether (5·0 g.) with 3-chlorobutan-2-one (3·0 g.) and potassium carbonate (10 g.) in boiling acetone (20 ml.) for 2 hours furnished 3-*p*-methoxyphenoxybutan-2-one as a colourless oil (4·0 g.), b. p. 164—169°/30 mm., characterised as the *semicarbazone*, needles, m. p. 114° (from methanol) (Found : N, 16·6. $C_{12}H_{17}O_3N_3$ requires N, 16·7%). Cyclisation of this ketone (4 g.) was effected with concentrated sulphuric acid (10 ml.) at 0° for 10 minutes and the resulting 5-methoxy-2 : 3-dimethylbenzofuran (2 g., b. p. 140/20 mm.) was isolated with ether after addition of ice-water and basification with aqueous sodium hydroxide. A mixture of this product (1 g.), hydriodic acid (8 ml.; *d* 1·7), and acetic acid (5 ml.) was gently heated under reflux for 30 minutes, cooled, diluted with water (100 ml.), treated with a little sulphur dioxide to remove traces of iodine, neutralised with sodium hydrogen carbonate, and extracted with ether. Distillation of the residue left on evaporation of the extracts gave 5-hydroxy-2 : 3-dimethylbenzofuran (0·3 g.), b. p. 90°/0·1 mm., m. p. 79°, after purification from light petroleum (b. p. 80—100°), identical with a specimen prepared by route (*a*).

5-Hydroxy-6-methoxy-2 : 3-dimethylbenzofuran.—Formed by condensation of ethyl β-amino-α-methylcrotonate (5·2 g.) and methoxy-*p*-benzoquinone (5 g.) in boiling acetone during 1 hour, *α-(2 : 5-dihydroxy-4-methoxyphenyl)-β-imino-α-methylbutyrate* crystallised from 95% alcohol in colourless prisms (7·4 g.), m. p. 154° (Found : C, 59·5; H, 6·7; N, 5·0. $C_{14}H_{19}O_5N$ requires C, 59·8; H, 6·8; N, 5·0%). On being heated under reflux with 2N-sodium hydroxide (30 ml.) in nitrogen for 1 hour, this product gave *5-hydroxy-6-methoxy-2 : 3-dimethylbenzofuran* which was purified by distillation at 90°/0·01 mm. and then by crystallisation from light petroleum (b. p. 80—100°), forming colourless needles (0·45 g.), m. p. 112° (Found : C, 68·6; H, 6·2. $C_{11}H_{12}O_3$ requires C, 68·7; H, 6·3%).

5-Hydroxyoxindole.—(*a*) A solution of ethyl β-amino-β-ethoxyacrylate (Glickman and Cope, *J. Amer. Chem. Soc.*, 1945, **67**, 1017) (3 g.) in alcohol (5 ml.) was added to *p*-benzoquinone (5 g.) in hot alcohol (15 ml.) and, after the initial vigorous reaction had subsided, the mixture was heated on the steam-bath for 1 hour. Kept at 0° this reaction mixture deposited *ethyl 2-ethoxy-5-hydroxyindole-3-carboxylate*, forming colourless plates (3 g.), m. p. 168° (from

alcohol), which reduced Tollens' reagent but had a negative Ehrlich reaction [Found, in a specimen dried in a vacuum at 80°: C, 62·5; H, 6·1; N, 5·9; OEt, 36·0. $C_9H_5O_2N(OEt)_2$ requires C, 62·6; H, 6·0; N, 5·6; OEt, 36·1%]. This compound was resistant to alkaline hydrolysis and after being boiled with 2N-sodium hydroxide for 2 hours was largely unchanged. When heated with 2N-hydrochloric acid (30 ml.) the ester (1 g.) slowly dissolved and distillation of the solution in a vacuum left a residue of *5-hydroxyoxindole* which was purified by sublimation at 160°/0·1 mm. and then by crystallisation from ethyl acetate–light petroleum (b. p. 40—60°), forming colourless needles (0·7 g.), m. p. about 270°, with some previous decomposition (Found: C, 64·4; H, 4·6; N, 9·1. $C_8H_7O_2N$ requires C, 64·4; H, 4·7; N, 9·4%).

(*b*) An intimate mixture of *N*-chloroacetyl-*p*-anisidine (3·1 g.) and powdered aluminium chloride (4·4 g.) was kept at 120° for 10 minutes, then heated to 240° in the course of 40 minutes, cooled, and decomposed with ice and hydrochloric acid in the usual manner. The resulting solution was heated on the steam-bath for 10 minutes, filtered to remove tarry impurities, cooled, and extracted with ethyl acetate, giving, after purification, 5-hydroxyoxindole, m. p. 265° (decomp.) undepressed on addition of a specimen obtained by method (*a*). The product described by Giovanni and Portmann (*loc. cit.*) as 5-methoxyoxindole was stated to form needles, decomp. 270°.

In an attempted cyclisation experiment at 190° the product was mainly p-*chloroacetamidophenol*, forming colourless needles, m. p. 146°, from water (Found: N, 7·8. $C_8H_8O_2NCl$ requires N, 7·5%).

5-*Methoxy*-1-*methyloxindole*.—Methylation of ethyl 2-ethoxy-5-hydroxyindole-3-carboxylate (3·0 g.) with methyl sulphate and warm alkali gave the *dimethyl* derivative (2·0 g.) which formed almost colourless needles, m. p. 95—96°, from ethanol (Found: C, 65·2; H, 6·9; N, 5·1. $C_{15}H_{19}O_4N$ requires C, 65·0; H, 6·9; N, 5·05%). This product (0·5 g.) slowly dissolved in boiling 2N-hydrochloric acid to a colourless solution, which, on evaporation, furnished 5-methoxy-1-methyloxindole, forming colourless blades (0·25 g.), m. p. 97° (depressed by admixture with the starting material) from light petroleum (b. p. 80—100°) (Found: C, 67·7; H, 6·0; N, 7·65; OMe, 17·1. Calc. for $C_9H_8ON{\cdot}OMe$: C, 67·8; H, 6·2; N, 7·9; OMe, 17·5%) (Porter, Robinson, and Wyler, *loc. cit.*, give m. p. 92°).

5-*Hydroxy*-6-*methoxyoxindole*.—Condensation of methoxy-*p*-benzoquinone (2·6 g.) and ethyl β-amino-β-ethoxyacrylate (3·0 g.) in hot alcohol gave *ethyl* 2-*ethoxy*-5-*hydroxy*-6-*methoxyindole*-3-*carboxylate* which separated from alcohol in colourless plates (2·6 g.), m. p. 160° (Found: C, 60·6; H, 6·2; N, 4·9. $C_{14}H_{17}O_5N$ requires C, 60·2; H, 6·1; N, 5·0%). Treatment of this ester (1·0 g.) with hot 2N-hydrochloric acid (30 ml.) for 30 minutes gave 5-*hydroxy*-6-*methoxyoxindole* which was purified by sublimation at 140°/0·01 mm. and then by crystallisation from alcohol, forming colourless needles (0·65 g.), m. p. 273° (decomp.) (Found: C, 59·9; H, 4·7; N, 7·9. $C_9H_9O_3N$ requires C, 60·3; H, 5·0; N, 7·8%).

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