158. *Rearrangements in the Oxidation of 3-Phenylquinolines.*

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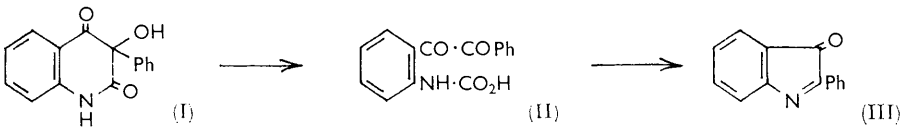
The rapid oxidation of 3-phenylquinoline by cold dilute acidic potassium permanganate to *N*-benzoylanthranilic acid, involving an apparent 1,2-migration of the phenyl group, has been confirmed and extended. 2-Methyl-3-phenylquinoline also gives benzoylanthranilic acid, together with acetylanthranilic acid, benzoic acid, and a neutral compound, 1-acetyl-2-hydroxy-2-phenyl-3-indolinone (VI). 2-Ethyl-3-phenylquinoline gives the corresponding 1-propionyl compound and benzoic acid only. A scheme for these oxidative rearrangements is suggested.

The acylindolinones, *e.g.*, (VI), exist partly as the acyclic tautomers, *o*-acylaminobenzils, *e.g.*, (VII), in solution; they rapidly hydrolyse and rearrange in dilute aqueous alkali to give 3-phenyldioxindole (IV).

From the large, rather confusing, and sometimes contradictory literature [1,2] on the oxidation of quinolines with potassium permanganate it appears that competition between the different possible reactions is often fairly evenly balanced; various reactions proceed simultaneously and predictions of which will dominate are difficult. The carbocyclic or the heterocyclic ring or both rings may be cleaved, or opening of the pyridine ring may be followed by cyclisation to give benzoxazoles or isatins. For example, 2-methyl-,[3] ethyl-,[1]

[1] von Miller, *Ber.*, 1891, **24**, 1900.
[2] Elderfield, " Heterocyclic Compounds," ed. Elderfield, J. Wiley & Sons Inc., New York, 1952, Vol. 4, p. 256.
[3] Doebner and v. Miller, *Ber.*, 1882, **15**, 3075.

and phenyl-quinoline [4] gave the corresponding acyl- or aroyl-anthranilic acid, 4-methylquinoline gave 4-methylquinolinic acid,[5] and the only products isolable from 3-methylquinoline [1] were oxalic acid, carbon dioxide, and ammonia. 3-Phenylquinoline, however, was oxidised to *N*-benzoylanthranilic acid with cold acidic potassium permanganate [6] and 7-chloro-4-hydroxy-3-phenylquinoline was oxidised to *N*-benzoyl-4-chloroanthranilic acid with hot alkaline potassium permanganate;[7] obviously a rearrangement involving the phenyl substituents in " a 1,2-shift of unknown mechanism " [2] has occurred here. By a process of elimination Ueda [6] considered that the most likely course for the former reaction was formation of *o*-aminobenzil and cyclisation of this to 2-phenyl-3*H*-indolone (III), though neither of these intermediates could be detected. Rapoport and Batcho [8] have very recently reconsidered the mechanism of this rearrangement, without presenting further experimental results, and suggested a modified route to 2-phenyl-3*H*-indolone. They suggest initial oxidation of 3-phenylquinoline to the α- and γ-quinolone, which is further oxidised at the double bond to give compound (I); oxidative cleavage of this between C-2 and C-3 leads to the carbamic acid (II) which cyclises after decarboxylation to give 2-phenyl-3*H*-indolone (III).



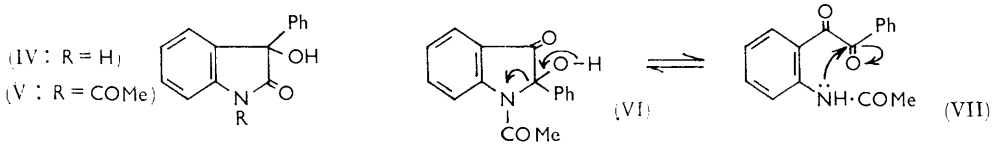
In a repetition of the oxidation of 3-phenylquinoline in cold dilute sulphuric acid the permanganate colour was rapidly discharged and benzoylanthranilic acid was isolated in small yield, in agreement with Ueda,[6] but benzoic acid was also isolated, in slightly greater yield; such rapid destruction of the pyridine ring was somewhat surprising. In the formation of benzoylanthranilic acid one carbon atom has been lost, presumably as carbon dioxide, and in the formation of benzoic acid the other product could have been *N*-formylanthranilic acid. It was considered that the fragments corresponding to these undetected products would be more readily isolated in the oxidation of 2-methyl- and 2-ethyl-3-phenylquinoline, and it would also be useful to know if any benzoylanthranilic acid is formed in these reactions. (Acetylanthranilic acid was shown to be more resistant to potassium permanganate than formylanthranilic acid but less resistant than benzoylanthranilic acid, as expected.) Oxidation of 2-methyl-3-phenylquinoline also proceeded rapidly, under the same mild conditions, to give benzoylanthranilic, acetylanthranilic, and benzoic acid and a neutral compound, m. p. 166—167°. In an exactly similar oxidation of 2-ethyl 3-phenylquinoline, however, no *N*-propionyl or benzoylanthranilic acid could be isolated. Benzoic acid was now formed in good yield together with a neutral compound m. p. 156—157° with very similar properties to that with m. p. 166—167°.

In view of the conversion of 7-chloro-4-hydroxy-3-phenylquinoline into *N*-benzoyl-4-chloroanthranilic acid,[7] though under much more vigorous conditions, it was possible that 4-hydroxy-3-phenylquinoline was an intermediate in the oxidation of 3-phenylquinoline. However, this hydroxyquinoline gave no benzoylanthranilic acid, and under the mild reaction conditions was largely recovered. The similar oxidation of 2-hydroxy-3-phenylquinoline and 2,4-dihydroxy-3-phenylquinoline, both possible intermediates, was attempted, but no benzoylanthranilic acid could be isolated. Thus the quinolones cannot be reaction intermediates under these mild conditions and the reaction scheme suggested by Rapoport and Batcho [8] must be discarded, at least in its initial stages.

The neutral products from the oxidation of 2-methyl- and 2-ethyl-3-phenylquinoline,

[4] Doebner and v. Miller, *Ber.*, 1886, **19**, 1196.
[5] Hoogewerff and v. Dorp, *Rec. Trav. chim.*, 1882, **1**, 1 (*Brit. Abs.*, 1883, 89).
[6] Ueda, *J. Pharm. Soc. Japan*, 1937, **57**, 827 (*Chem. Abs.*, 1938, **32**, 563).
[7] Elderfield and Wright, *J. Amer. Chem. Soc.*, 1946, **68**, 1276.
[8] Rapoport and Batcho, *J. Org. Chem.*, 1963, **28**, 1755.

$C_{16}H_{13}NO_3$, m. p. 166—167°, and $C_{17}H_{15}NO_3$, m. p. 156—157°, respectively, had very similar infrared (i.r.) spectra and were presumably the acetyl and propionyl derivatives of the same structure. The i.r. spectra showed an OH (or possibly NH) group and two carbonyl groups, one probably part of a tertiary amide and the other possibly that of a cyclic ketone; there appeared to be no ester carbonyl absorption. However, treatment of both compounds with warm dilute aqueous sodium hydroxide was sufficient to remove the acyl group to give the same product, 3-phenyldioxindole (IV). This suggested that the neutral compounds were *N*-acetyl (V) and propionyl derivatives of 3-phenyldioxindole or, though less likely in view of the i.r. data, the *O*-acyl derivatives. Attempts to prepare the monoacyl derivatives of 3-phenyldioxindole by direct acylation, by partial hydrolysis of the diacyl derivatives, and by reaction of phenylmagnesium bromide with the *N*-acyl derivatives of isatin, for direct comparison with these neutral products, failed. The product m. p. 166—167° was therefore further acetylated to give a diacetyl compound, $C_{18}H_{15}NO_4$, m. p. 205—206°, which was not *ON*-diacetyl-3-phenyldioxindole, m. p. 140—141°. Thus these neutral oxidation products cannot be 3-phenyldioxindole derivatives and the isomeric 2-hydroxy-3*H*-indolone structures, *e.g.*, (VI), were considered for them. Their alkaline hydrolysis would then have been accompanied by a 1,2-phenyl migration similar to that established for the base-catalysed conversion of 2-phenyl-3*H*-indolone (III) into 3-phenyldioxindole (IV).[9]



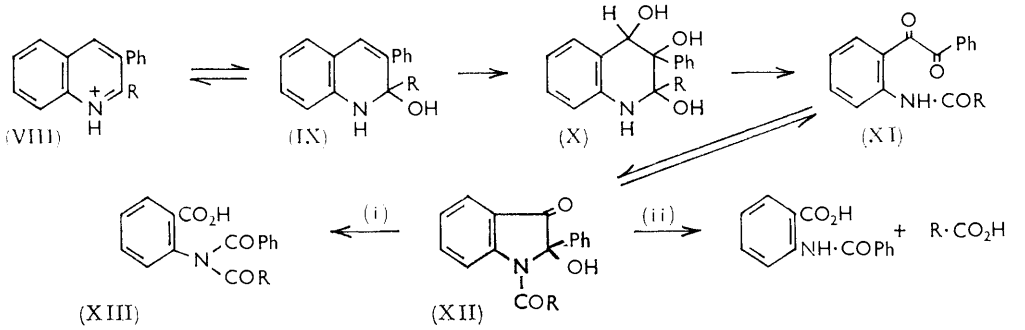
Confirmation of structure (VI) for the compound, m. p. 166—167°, was sought from the nuclear magnetic resonance (n.m.r.) spectrum in deuterochloroform. Two signals of unequal intensity, τ 7·97 and 7·74 (together 3 protons), were given for the methyl group, together with a signal, τ 4·69, for <1 proton, and a complex multiplet, τ 1·2—3·0 p.p.m. (*ca.* 9 protons) for the aromatic protons. The corresponding propionyl compound, m. p. 156—157°, similarly showed two unequal signals, centred at τ 9·05 and 8·72 (together 3 protons) for the methyl group and at τ 7·82 and 7·48 (together 2 protons) for the methylene group, at τ 5·03 for <1 proton, and a complex multiplet τ 1·1—3·0 p.p.m. (*ca.* 9 protons) for the aromatic protons. Thus these spectra indicate that, at least in deuterochloroform solution, the neutral compounds exist in two forms; the spectra are consistent with a slow tautomeric equilibrium between the cyclic structures proposed, *e.g.*, (VI) and the ring-opened forms, *o*-acylaminobenzil, *e.g.*, (VII). The resonance at τ 4·69, which integrated for <1 proton, was destroyed by shaking the *N*-acetyl compound with deuterium oxide and probably corresponds to the hydroxyl proton of tautomer (VI), the amide proton of tautomer (VII) possibly being too broad to be observable.

The i.r. spectra of these compounds in Nujol agreed well with the cyclic structures but in view of the nuclear magnetic resonance results the infrared spectrum of the *N*-acetyl compound (VI) was measured in chloroform solution. This was considerably more complex, especially in the carbonyl region, in agreement with both cyclic and acyclic forms being present to a significant extent in solution. Although this compound, which gave a positive, but slow, Brady's reaction, is a colourless crystalline solid, its solutions in various solvents are yellow, as expected for a benzil derivative. An equilibrium of the type (VI) $\rightleftharpoons$ (VII) would not, of course, have been possible if the neutral oxidation products were *O*-acyl derivatives of 2-hydroxy-2-phenyl-3-indolinone.

Oxidation Mechanism.—The annexed reaction scheme is suggested as a plausible route to the various oxidation products isolated. Attention is focused upon changes in the organic

[9] Kalb and Bayer, *Ber.*, 1912, **45**, 2150; Pfeil, Geissler, Jacquemin, and Lömker, *Chem. Ber.*, 1956, **89**, 1210.

substrates; R represents hydrogen, methyl or ethyl groups. Formation of the pseudo-base (IX) may be facilitated by diminution in the aromaticity of the pyridine ring by conjugation of the two benzene rings through the 3,4-double bond in the conjugate acid (VIII). (This may account for the apparently special behaviour of 3-phenylquinolines in



being oxidised, with rearrangement, so rapidly.) Hydroxylation of the 3,4-double bond then gives the triol (X) which would rapidly undergo oxidative ring-opening with more potassium permanganate to the *o*-acylaminobenzil (XI) described above. Cyclisation of this to the indolinone (XII) then fulfils the fundamental requirement of the rearrangement in placing the phenyl substituent on a carbon atom adjacent to the nitrogen. The indolinone (XII) in turn can suffer oxidative ring-opening with, (ii), or without, (i), concomitant loss of the *N*-acyl group. The *N*-acyl-*N*-benzoylanthranilic acid (XIII) would hydrolyse to give two pairs of products, presumably with benzoylanthranilic acid and the aliphatic acid predominating. When R = H, only benzoic and benzoylanthranilic acids were isolated since hydrolysis of the *N*-formyl compounds would be favoured and, furthermore, *N*-formylanthranilic acid is rapidly destroyed by potassium permanganate. When R = Me, three of the four possible acids were isolated (and acetic acid was detected by its smell) together with the intermediate (XII). When R = Et, only the intermediate (XII) and benzoic acid were isolated, in relatively high yield; it is possible here that the indolinone is more stable because of the greater steric hindrance to its hydrolytic oxidation by either route (i) or route (ii).

Experimental

Infrared (i.r.) spectra were determined for Nujol mulls using a Grubb–Parsons double-beam spectrophotometer and n.m.r. spectra for deuterochloroform solutions, with tetramethylsilane as internal reference, using a Perkin-Elmer 60 Mc./sec. spectrophotometer. Organic extracts were dried with anhydrous magnesium sulphate. All known reaction products were identified by mixed m. p. and by i.r. spectra comparison.

Materials.—3-Phenylquinoline, m. p. 51—52°, was prepared by the decarboxylation of 3-phenylcinchoninic acid,[10] and by the condensation of *o*-aminobenzaldehyde with phenylacetaldehyde.[11] 3-Phenylquinoline hydrochloride, recrystallised from 2N-aqueous hydrochloric acid, had m. p. 102—104° (Found: Cl, 13·3. Calc. for $C_{15}H_{12}ClN$, H_2O: Cl, 13·4%). When dried at 120° for 2 hr. it had m. p. 181° (Found: Cl, 14·4. Calc. for $C_{15}H_{12}ClN$: Cl, 14·7%), but the m. p. slowly reverted to 102—104° followed by 181°; the m. p. 93° recorded [11] for this hygroscopic salt was presumably that of the hydrate. 2-Methyl- and 2-ethyl-3-phenylquinoline were prepared by decarboxylation [12] of the corresponding cinchoninic acids.[13] The quinolines were redistilled, and gave picrates with m. p.s in agreement with the literature values.

[10] Hubner, *Ber.*, 1908, **41**, 482.
[11] Friedlander and Gohring, *Ber.*, 1883, **16**, 1833.
[12] Hausner and Murray, *J. Amer. Chem. Soc.*, 1955, **77**, 3859.
[13] Borsche and Vorbach, *Annalen*, 1939, **537**, 22.

2-Hydroxy-, 4-hydroxy-, and 2,4-dihydroxy-3-phenylquinoline were kindly supplied by Professor D. H. Hey. *N*-Acetyl- and *N*-propionyl-isatin and *N*-formyl-, *N*-acetyl-, *N*-propionyl-, and *N*-benzoyl-anthranilic acid were prepared by standard methods and had m. p.s in agreement with the literature values. 3-Phenyldioxindole,[14] m. p. 215—216°, was prepared from isatin and phenylmagnesium bromide and converted, with acetic anhydride and sodium acetate, into the *ON*-diacetyl derivative, m. p. 140—141° (Found: C, 69·4; H, 4·9. Calc. for $C_{18}H_{15}NO_4$: C, 69·9; H, 4·9%), in agreement with Inagaki;[15] a product of this reaction, with the same m. p., has been reported as a monoacetyl derivative.[16]

Oxidation of 3-Phenylquinoline.—Potassium permanganate (10 g.) in water (250 ml.) was added dropwise with stirring, to 3-phenylquinoline (3 g.) in 2N-sulphuric acid (250 ml.) at room temperature. Stirring was continued for 2 hr. and then sulphur dioxide was passed through the mixture. The precipitate (0·9 g.) was washed with water and dissolved in ether. The ether solution was thoroughly extracted with 10% aqueous sodium carbonate and then with 2N-hydrochloric acid:

(*a*) *The sodium carbonate solution.* On acidification a solid separated. Crystallisation from benzene gave benzoylanthranilic acid (0·3 g., 9%), m. p. 181°. The acid filtrate on extraction with ether gave a very small amount of benzoic acid.

(*b*) *The hydrochloric acid solution.* On basification and extraction with ether 3-phenylquinoline (0·4 g.) was recovered as a gum, picrate m. p. 204—205°.

(*c*) *The ether solution.* This was washed with water, dried, and evaporated to give 3-phenylquinoline (0·03 g.) as a gum (picrate, m. p. 204—205°). No neutral compound could be found. The original reaction solution was continuously extracted with ether; the ether was washed with water, dried, and evaporated, and the residue was sublimed at 90°/0·1 mm. Crystallisation of the sublimate from water gave benzoic acid (0·25 g., 13%), m. p. 121°.

Thus from this oxidation benzoylanthranilic acid (9%), benzoic acid (13%), and starting material (14%) were obtained.

Oxidation of 2-Methyl-3-phenylquinoline.—2-Methyl-3-phenylquinoline (3 g.) was oxidised and the reaction mixture treated exactly as described above. The sodium carbonate solution gave benzoylanthranilic acid (0·25 g., 8%), the hydrochloric acid solution gave very little starting material isolated as its picrate (0·06 g.), m. p. 167—169°, and the ether solution gave, after crystallisation from benzene, *1-acetyl-2-hydroxy-2-phenyl-3-indolinone* (0·45 g., 12%), m. p. 166—167° (Found: C, 71·7; H, 4·8; N, 5·3. $C_{16}H_{13}NO_3$ requires C, 71·9; H, 4·9; N, 5·2%); $\nu_{max.}$ 3289 (OH), 1724 (cyclic ketone C=O), and 1639 cm.$^{-1}$ (teritary amide C=O); $\nu_{max.}$ ($CHCl_3$) 3215 (OH), 1709, 1664 (broad) with a shoulder at 1637 cm.$^{-1}$.

Extraction of the original reaction solution with ether gave a mixture from which benzoic acid (0·4 g.) and *N*-acetylanthranilic acid (0·15 g.) were separated by vacuum sublimation. Basification, and extraction with ether, of the original reaction solution then gave 2-methyl-3-phenylquinoline isolated as its picrate (0·6 g.), m. p. 167—169°.

Thus from this oxidation benzoic acid (21%), acetylanthranilic acid (6%), benzoylanthranilic acid (8%), 1-acetyl-2-hydroxy-2-phenyl-3-indolinone (12%), and starting material (10%) were obtained.

Oxidation of 2-Ethyl-3-phenylquinoline.—2-Ethyl-3-phenylquinoline (3 g.) was oxidised and the reaction mixture treated exactly as described above. The sodium carbonate solution gave benzoic acid (0·03 g.) but no benzoylanthranilic acid, the hydrochloric acid solution gave very little starting material [isolated as its picrate (0·06 g.), m. p. 177°], and the ether solution gave, after crystallisation from benzene–light petroleum (b. p. 80—100°) *2-hydroxy-2-phenyl-1-propionyl-3-indolinone* (0·7 g., 19%), m. p. 156—157° (Found: C, 72·5; H, 5·5; N, 5·15. $C_{17}H_{15}NO_3$ requires C, 72·6; H, 5·4; N, 5·0%); $\nu_{max.}$ 3279 (OH), 1733 (cyclic ketone C=O), and 1642 cm.$^{-1}$ (tertiary amide C=O).

Extraction of the original reaction solution with ether, evaporation of the ether extract, and vacuum sublimation of the residue, gave benzoic acid (0·7 g.). Basification of the reaction solution gave, as before, 2-ethyl-3-phenylquinoline picrate (0·2 g.) m. p. 177°.

Thus from this oxidation benzoic acid (42%), 2-hydroxy-2-phenyl-1-propionyl-3-indolinone (19%) and starting material (4%) only were isolated.

Other Oxidations.—2-Hydroxy-, 4-hydroxy-, and 2,4-dihydroxy-3-phenylquinoline were

[14] Mills and Schofield, *J.*, 1961, 5558.
[15] Inagaki, *Chem. Abs.*, 1939, **33**, 3790.
[16] Wittig, Kleiner, and Conrad, *Annalen*, 1929, **469**, 16.

each treated with potassium permanganate as described above; these compounds were recovered in 60—84% yield and in no case could any *N*-benzoylanthranilic acid be isolated. When 1-acetyl-2-hydroxy-2-phenyl-3-indolinone was treated similarly with potassium permanganate 93% was recovered and benzoylanthranilic acid (6%) was produced.

1-*Acetyl*-2-*hydroxy*-2-*phenyl*-3-*indolinone.*—*Hydrolysis.* The indolinone (0·2 g.) was warmed for 30 min. in 2N-sodium hydroxide (5 ml.) and the cooled solution carefully acidified. A white solid separated which crystallised from benzene to give 3-phenyldioxindole (0·13 g., 76%), m. p. and mixed m. p. 215—216°. 2-Hydroxy-2-phenyl-1-propionyl-3-indolinone, treated similarly, gave 3-phenyldioxindole in similar yield.

Acetylation. The indolinone (0·26 g.) was warmed on a steam-bath in acetic anhydride (3 ml.) for 1 hr. The solution was cooled and a little water added. A colourless solid (0·2 g.) separated which crystallised from benzene–light petroleum (b. p. 60—80°) as needles of 2-*acetoxy*-1-*acetyl*-2-*phenyl*-3-*indolone*, m. p. 205—206° (Found: C, 69·9; H, 4·7; N, 4·5. $C_{18}H_{15}NO_4$ requires C, 69·9; H, 4·9; N, 4·5%); $\nu_{max.}$ 1742 (ester C=O), 1727 (cyclic ketone C=O), and 1675 cm.$^{-1}$ (tertiary amide C=O).

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