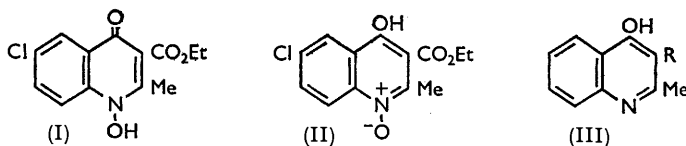


697. *Substituent Interactions in ortho-Substituted Nitrobenzenes.*
*Part III.*¹

By J. D. LOUDON and I. WELLINGS.

In presence of hydrogen chloride *o*-nitrobenzaldehyde reacts with ethyl acetoacetate, acetylacetone, or diethyl acetonedicarboxylate, forming in each case a derivative of 6-chloro-1-hydroxy-4-quinolone, *e.g.*, (I).

o-NITROBENZALDEHYDE reacts with ethyl acetoacetate in presence of hydrogen chloride, affording a condensate, $C_{13}H_{12}O_4NCl$, from which the infrared absorption characteristics of a nitro-compound are lacking. The aldehyde likewise condenses with acetylacetone and with diethyl acetonedicarboxylate, in each case yielding a product formed, with loss of two molecules of water, from equimolar proportions of the organic reagents and hydrogen chloride. 2-Nitrobenzylidene derivatives of the respective ketones are potential intermediates in these reactions: indeed 2-nitrobenzylideneacetylacetone may be isolated and yields the ultimate product on renewed treatment with hydrogen chloride. In contrast, the 2-nitrobenzylidene derivative which was isolated from ethyl benzoylacetate appears to resist further reaction, and from acetone under similar conditions only the di-*o*-nitrobenzylidene derivative was identified. The scope of the more deep-seated reaction requires further inquiry and attention here is focused on the nature of its products.



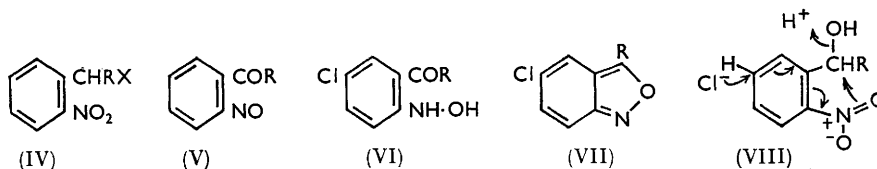
The properties and transformations of the compound, $C_{13}H_{12}O_4NCl$, showed it to be the 1-hydroxy-4-quinolone (I) or the tautomeric 4-hydroxyquinoline *N*-oxide (II). The compound was feebly both acidic and basic: it contained non-ionic chlorine, an acetyl-atable hydroxyl group, and an ethoxycarbonyl group. The ester group could be removed by acidic or alkaline hydrolysis and thermal decarboxylation of the resultant acid, affording a product (I; H for CO_2Et) which resembled the original ester in giving a red-brown colour with ferric chloride in ethanol and in forming an *O*-acetyl derivative.

¹ Part II, preceding paper.

Reduction, which could be made selective, revealed the essential structure of the molecule. When the acetates derived from the compounds (I) and (I; H for CO₂Et) were hydrogenated over palladium-charcoal, the acetate group and chlorine atom in each were replaced by hydrogen, and the products were identified as ethyl 4-hydroxyquinaldine-3-carboxylate (III; R = CO₂Et) (m. p. 232° and not 104–107° as stated in the literature²) and 4-hydroxyquinaldine³ (III; R = H) respectively. By similar treatment of the parent compound (I) the chlorine atom only was replaced and the product (I \rightleftharpoons II; H for Cl) was identical with that obtained by reductive cyclisation from ethyl α -*o*-nitrobenzoyl-acetoacetate.⁴ A third course of reduction, representing simple deoxidation, occurred when the carboxylic acid corresponding to the ester (I) was reduced with zinc and acetic acid: thereby the (6-)chloro-derivative of compound (III; R = CO₂H) was formed.

The location of the chloro-substituent in these compounds was decided by oxidising the ester (I) with chromic acid, whereby a chloroazoxybenzoic acid was formed and was identified after reduction to 5-chloroanthranilic acid. The 6-chloroquinoline structure thus indicated was confirmed by an independent synthesis of the 6-chloro-derivative of the acid (III; R = CO₂H), this compound being identical with the product obtained as described by hydrolysis and reduction of the original ester.

An analogous structure, *viz.*, (I; COMe for CO₂Et), was likewise proved for the condensate from acetylacetone. This condensate was oxidised to the same 4,4'-dichloroazoxybenzene-2,2'-dicarboxylic acid and was hydrogenolysed to 3-acetyl-4-hydroxyquinaldine *N*-oxide which was independently synthesised. The condensate from diethyl acetonedicarboxylate is regarded by analogy as ethyl (6-chloro-3-ethoxycarbonyl-1,4-dihydro-1-hydroxy-4-oxoquinolyl)acetate (I; CH₂·CO₂Et for Me).



The mechanism by which these condensates are formed presents an interesting problem. A reaction which appears to be analogous is the formation of 5-chloro-3-*p*-hydroxyphenyl-anthranil (VII; R = *p*-C₆H₄·OH) from *o*-nitrobenzaldehyde, phenol, and hydrogen chloride in acetic acid.⁵ Both reactions are explicable through stepwise formation of intermediates (IV; X = OH or Cl) \rightarrow (VI), and appropriate cyclodehydration of the hydroxylamine (VI) according as R is the phenol or (substituted) acetone residue. Since the anthranil reaction can occur in an excess of phenol⁵ it seems unlikely that introduction of the chloro-substituent involves the chlorinium ion, and the known formation of *p*-chlorophenylhydroxylamine from hydrogen chloride and nitrosobenzene⁶ provides analogy for the step (V) \rightarrow (VI). The oxygen transfer, (IV) \rightarrow (V), is also conceivable as an individual step but a more concerted mechanism is possible and is exemplified for the early stages by the process (VIII). These considerations sufficiently indicate at present some aspects of the mechanistic problem and we are examining their implications.

EXPERIMENTAL

Light petroleum refers to the fraction of b. p. 60–80°.

6-Chloro-1,4-dihydro-1-hydroxy-2-methyl-4-oxoquinoline-3-carboxylic Acid and its Ethyl Ester (cf. I \rightleftharpoons II).—A solution of *o*-nitrobenzaldehyde (3.02 g.) and ethyl acetoacetate (2.6 ml.) in dry ether (50 ml.) was saturated with hydrogen chloride at 18°. After 12 hr. the crystalline

² Gould and Jacobs, *J. Amer. Chem. Soc.*, 1939, **61**, 2890.

³ Conrad and Limpach, *Ber.*, 1887, **20**, 944.

⁴ McClusky, *J. Amer. Chem. Soc.*, 1922, **44**, 1574.

⁵ Zincke and Siebert, *Ber.*, 1906, **39**, 1930.

⁶ Bamberger, Busdorf, and Szolayski, *Ber.*, 1899, **32**, 210.

product was collected, and the mother-liquor re-saturated with hydrogen chloride (total yield, 3.7 g.). The ester (I) had m. p. 226° (decomp.) (from ethanol), λ_{max} 220, 265, 330 m μ (ϵ 31,000, 11,000, 10,000), ν_{max} 2400 (broad), 1720 cm.⁻¹ (Found: C, 55.5; H, 4.2; N, 4.9. C₁₅H₁₂O₄NCl requires C, 55.45; H, 4.25; N, 4.95%). When warmed with acetic anhydride it formed the 1-acetoxy-derivative, m. p. 155° (from ethanol), ν_{max} 1800, 1715 cm.⁻¹ (Found: C, 55.7; H, 4.4; N, 4.5. C₁₅H₁₄O₅NCl requires C, 55.7; H, 4.3; N, 4.35%).

Hydrolysis of the ester (I) (1.4 g.) by heating it for 3 hr. with acetic acid (8 ml.), water (16 ml.), and concentrated sulphuric acid (2 ml.) gave 6-chloro-1,4-dihydro-1-hydroxy-2-methyl-4-oxoquinoline-3-carboxylic acid which crystallised from the concentrated solution; this acid had m. p. 236° (from dimethylformamide) with decarboxylation (cf. below), resolidification, and re-melting at 285° (Found: C, 51.9; H, 3.2; N, 5.5. C₁₁H₈O₄NCl requires C, 52.1; H, 3.2; N, 5.5%). The 1-acetoxy-derivative had m. p. 190° (from acetic anhydride) (Found: C, 52.6; H, 3.6; N, 5.0. C₁₃H₁₀O₅NCl requires C, 52.8; H, 3.4; N, 4.75%).

6-Chloro-1,4-dihydro-1-hydroxy-2-methyl-4-oxoquinoline, m. p. 285° (decomp.) (from dimethylformamide), was obtained by heating the 3-carboxylic acid at 220° for 10 min. (Found: C, 57.0; H, 3.8; N, 6.8. C₁₀H₈O₂NCl requires C, 57.2; H, 3.8; N, 6.7%). It reacted (a) with warm acetic anhydride to give the 1-acetoxy-derivative, m. p. 164° (from benzene-light petroleum), ν_{max} 1795 cm.⁻¹ (Found: C, 57.3; H, 4.0; N, 6.0. C₁₂H₁₀O₃NCl requires C, 57.4; H, 4.0; N, 5.7%), and (b) with picric acid in ethanol to form the picrate, m. p. 185° (from ethanol) (Found: C, 44.1; H, 2.8; N, 12.6. C₁₆H₁₁O₉N₄Cl requires C, 43.9; H, 2.5; N, 12.8%).

4-Hydroxyquinaldine. — 1-Acetoxy-6-chloro-1,4-dihydro-2-methyl-4-oxoquinoline was hydrogenated in ethanol over 5% palladium-charcoal. After absorption of 2 mols. of hydrogen, the filtered and concentrated solution was mixed with one of picric acid in ethanol, whereupon 4-hydroxyquinaldine was precipitated as the picrate, m. p. and mixed m. p. with an authentic sample,³ 201—202° (from ethanol) (Found: C, 49.8; H, 3.2; N, 14.4. Calc. for C₁₆H₁₄O₈N₄: C, 49.6; H, 3.1; N, 14.4%).

Ethyl 4-Hydroxyquinaldine-3-carboxylate (III; R = CO₂Et).—(a) Ethyl 1-acetoxy-6-chloro-2-methyl-4-oxoquinoline-3-carboxylate was hydrogenated as in the foregoing experiment, the filtered and concentrated solution affording the product (III; R = CO₂Et). (b) The same product, m. p. and mixed m. p. 232° (from ethanol), was obtained by condensing diethyl acetylmalonate⁷ with aniline in presence of a crystal of iodine and, after 8 hr. at room temperature, cyclising² the resultant anil in boiling diphenyl ether (Found: C, 67.5; H, 5.5; N, 6.2. C₁₃H₁₃O₃N requires C, 67.5; H, 5.6; N, 6.1%). With picric acid in ethanol it formed the picrate, m. p. 156° (from ethanol) (Found: C, 49.8; H, 3.3; N, 12.2. C₁₉H₁₆O₁₀N₄ requires C, 49.6; H, 3.5; N, 12.2%).

Ethyl 1,4-Dihydro-1-hydroxy-2-methyl-4-oxoquinoline-3-carboxylate (I; H for Cl), m. p. and mixed m. p. with an authentic sample,⁴ 175—176°, was obtained by hydrogenating the 6-chloro-derivative (I) in ethanol over palladium-charcoal (Found: C, 63.2; H, 5.1; N, 5.8. Calc. for C₁₃H₁₃O₄N: C, 63.2; H, 5.3; N, 5.7%). Identical infrared spectra were obtained from both samples which also gave the same picrate, m. p. 132° (from ethanol) (Found: C, 48.0; H, 3.6; N, 11.6. C₁₅H₁₆O₁₁N₄ requires C, 47.95; H, 3.4; N, 11.7%).

6-Chloro-4-hydroxy-2-methylquinoline-3-carboxylic Acid.—(a) A solution of 6-chloro-1,4-dihydro-1-hydroxy-2-methyl-4-oxoquinoline-3-carboxylic acid (0.6 g.) in acetic acid (20 ml.) was heated for 1 hr. with zinc dust (1.5 g.) and the resultant solution concentrated *in vacuo*. (b) The anil, m. p. 63° (from light petroleum), obtained after 8 hr. at 18° from a mixture of diethyl acetylmalonate (10.1 g.), *p*-chloroaniline (6.4 g.), and a crystal of iodine (Found: C, 58.1; H, 5.9; N, 4.7. C₁₅H₁₃O₄NCl requires C, 58.0; H, 5.8; N, 4.5%), was cyclised in boiling diphenyl ether (30 min.), affording ethyl 6-chloro-4-hydroxy-2-methylquinoline-3-carboxylate, m. p. 275° (decomp.) (from dimethylformamide) (Found: C, 58.6; H, 4.4; N, 5.4. C₁₃H₁₂O₃NCl requires C, 58.7; H, 4.5; N, 5.3%). Alkaline hydrolysis of this ester gave the acid, identical in m. p. [315° (decomp.) (from dimethylformamide)] and infrared spectrum with the product from (a) (Found: C, 55.8; H, 3.5; N, 6.2. C₁₁H₈O₃NCl requires C, 55.6; H, 3.4; N, 5.9%).

4,4'-Dichloroazoxybenzene-2,2'-dicarboxylic Acid.—A solution of sodium dichromate (12 g.) in water (30 ml.) was added gradually to a boiling solution of the ester (I) (2 g.) in acetic acid (40 ml.), water (25 ml.), and concentrated sulphuric acid (10 ml.), and the whole was then heated under reflux for 1 hr. The azoxy-compound, m. p. 264° (decomp.) (from acetic acid),

⁷ Bowman, J., 1950, 322.

crystallised from the cooled solution (Found: C, 47.3; H, 2.25; N, 7.7; Cl, 20.4. $C_{14}H_9O_5N_2Cl_2$ requires C, 47.3; H, 2.25; N, 7.9; Cl, 20.0%). To a refluxing solution of the compound in acetic acid and hydrochloric acid zinc dust was added and, after 1 hour's heating, the resultant solution was cooled and concentrated, affording 5-chloroanthranilic acid, m. p. 206° (from ethanol), identified by mixed m. p. and comparison of infrared spectrum with an authentic specimen.

3-Acetyl-6-chloro-1,4-dihydro-1-hydroxy-2-methyl-4-oxoquinoline, m. p. 286° (decomp.) (from dimethylformamide), λ_{max} 220, 270, 330 $m\mu$ (ϵ 40,000, 16,000, 12,000), ν_{max} 2500 (broad), 1670 cm^{-1} , was obtained when a solution of *o*-nitrobenzaldehyde (3.02 g.) and acetylacetone (2.06 g.) in dry ether (50 ml.) was saturated with hydrogen chloride at 18° and set aside for 8 hr. (Found: C, 57.0; H, 3.9; N, 5.8. $C_{12}H_{10}O_3NCl$ requires C, 57.2; H, 4.0; N, 5.6%). It reacted (a) with ferric chloride in ethanol giving a red-brown solution, (b) with acetic anhydride forming the 1-acetoxy-derivative, m. p. 166° (from acetic anhydride), ν_{max} 1795, 1680 cm^{-1} (Found: C, 57.3; H, 4.1; N, 5.1. $C_{14}H_{12}O_4NCl$ requires C, 57.25; H, 4.1; N, 4.8%), (c) with dimethyl sulphate and alkali giving the 1-methoxy-derivative, m. p. 172° (from methanol) (Found: C, 58.7; H, 4.5; N, 5.4. $C_{13}H_{12}O_3NCl$ requires C, 58.8; H, 4.5; N, 5.3%), and (d) with sodium dichromate in aqueous acetic acid forming the same azoxy-compound as was obtained from the ester (I).

In another experiment the ethereal solution, 10 min. after being saturated with hydrogen chloride, was concentrated *in vacuo* and the resultant oil crystallised from ethanol at 0°, affording 2-nitrobenzylideneacetylacetone, m. p. 76° (from ethanol) (Found: C, 61.8; H, 4.9; N, 6.2. $C_{12}H_{11}O_3N$ requires C, 61.8; H, 4.7; N, 6.0%). This, on renewed treatment with hydrogen chloride in ether, gave the same ultimate product, m. p. and mixed m. p. 286° (decomp.).

2-Nitrobenzoylacetylacetone.—To one half (25 ml.) of an ethanolic solution of sodium ethoxide from 3.1 g. of sodium, there were added acetylacetone (5.6 g.) and then, slowly with stirring at 0°, *o*-nitrobenzoyl chloride (5.6 g.). After 30 min. 12.5 ml. of the ethoxide solution and, again slowly, more of the chloride (2.8 g.) were added: this was repeated 30 min. later. Stirring was continued for 4 hr., then the yellow solid was collected and, after being washed with ethanol and ether, was added to iced dilute hydrochloric acid, liberating *o*-nitrobenzoylacetylacetone, m. p. 72° (10.2 g.; from ethanol) (Found: C, 57.8; H, 4.2; N, 5.5. $C_{12}H_{11}O_3N$ requires C, 57.8; H, 4.4; N, 5.6%).

3-Acetyl-1,4-dihydro-1-hydroxy-2-methyl-4-oxoquinoline was obtained (a) by hydrogenating the 6-chloro-derivative in acetic acid over palladium-charcoal; (b) by adding *o*-nitrobenzoylacetylacetone (12 g.) to a stirred solution of stannous chloride (71 g.) in acetic acid (225 ml.) previously saturated with hydrogen chloride: after passage of this gas for 30 min. the product crystallised. It formed colourless crystals, m. p. 259° (decomp.) (from dimethylformamide) (Found: C, 66.6; H, 5.0; N, 6.4. $C_{12}H_{11}O_3N$ requires C, 66.5; H, 5.1; N, 6.4%).

3-Acetyl-6-chloro-4-hydroxy-2-methylquinoline, m. p. 310° (decomp.) (from acetic acid), was obtained when the 1-hydroxy-ketone (I) (COME for CO_2Et) was reduced by zinc dust in boiling acetic acid (Found: C, 61.7; H, 4.3; N, 6.1. $C_{12}H_{10}O_2NCl$ requires C, 61.5; H, 4.25; N, 5.9%).

Ethyl (6-Chloro-3-ethoxycarbonyl-1,4-dihydro-1-hydroxy-4-oxoquinolyl)acetate, m. p. 202° (decomp.) (from ethanol), was formed when a solution of *o*-nitrobenzaldehyde (3.02 g.) and diethyl acetonedicarboxylate (4 g.) in dry ether was saturated with hydrogen chloride at 18° and left for 24 hr.: it was recovered from the ethereal solution as an oil which solidified when washed with aqueous acetic acid (Found: C, 54.4; H, 4.4; N, 4.2. $C_{16}H_{16}O_6NCl$ requires C, 54.2; H, 4.5; N, 4.0%).

Ethyl α -2-nitrobenzylidenebenzoylacetate, m. p. 107° (from ethanol), was obtained by saturating with hydrogen chloride a solution of *o*-nitrobenzaldehyde and ethyl benzoylacetate in anhydrous ether, removing the solvent after 24 hr., and rubbing the oily residue with ethanol (Found: C, 66.4; H, 4.8; N, 4.4. $C_{18}H_{15}O_5N$ requires C, 66.5; H, 4.6; N, 4.3%).

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