695. *Substituent Interactions in* ortho-*Substituted Nitrobenzenes. Part I.*

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The adduct from hydrogen cyanide and diethyl *o*-nitrobenzylidenemalonate yields *o*-nitrophenylsuccinic acid by acidic hydrolysis, whereas in alkaline media, depending on the conditions used, it forms a derivative of 1-hydroxy-2-quinolone or of 1-hydroxyindole. Acetates derived from these *N*-hydroxy-compounds show strong infrared absorption around 1800 cm.$^{-1}$.

THE oxidising action of the nitro-group, frequently a complicating factor in reactions of nitrobenzene derivatives, takes effect in various ways. The centres which undergo oxidation may be contained wholly or partly in the nitro-compound or may be external to it: the nitro-group itself may be completely or partially reduced. A simple example is the conversion of *o*-nitrobenzaldehyde into *o*-nitrosobenzoic acid, a reaction which may be either chemically[1] or photochemically[2] induced and may proceed with the help of the environment to *o*-azoxybenzoic acid. When the nitro-group and a suitable side-chain are *ortho* to each other, heterocyclic ring-formation can occur and this may involve the nitro-group directly as is implied in the simple cyclisation of *o*-nitrophenylurea to 3-hydroxybenzotriazine *N*-oxide[3] or of *o*-nitrophenylhydrazine to 1-hydroxybenzotriazole.[4] More commonly the ring-forming step occurs after the nitro-group has been reduced, but the particular case of cyclisation following upon self-provided oxidation–reduction has been little examined and indeed is difficult to diagnose because the sequence of events leading to the ultimate product is often obscure. We propose to study interactions between the nitro-group and *ortho*-side-chains and, in Parts I—III, we now describe several examples including both known and new types of interaction.

o-Nitrophenylsuccinic acid is typical of a number of compounds for which normal preparation is hampered because the requisite intermediates are susceptible to oxidation–reduction in an alkaline medium. Originally obtained by wasteful nitration of phenylsuccinic acid,[5] it was recently prepared by Horner, Klüpfel, and Sahler[6] who succeeded in adding hydrogen cyanide to methyl α-cyano-β-*o*-nitrophenylacrylate or to dimethyl 2-nitrobenzylidenemalonate, and hydrolysed the adducts. The addition is the key-reaction and these authors did not effect it with diethyl 2-nitrobenzylidenemalonate (I). Under carefully controlled conditions, however, the adduct (II) and hence *o*-nitrophenylsuccinic acid can be prepared in good yield. On the other hand if either ester, (I) or (II), is allowed to react with potassium cyanide in ethanol there is formed a sparingly soluble potassium salt from which the cyclic hydroxamic acid (IV) is obtained.

(I) $o\text{-}NO_2{\cdot}C_6H_4{\cdot}CH{:}C(CO_2Et)_2$ (II) $o\text{-}NO_2{\cdot}C_6H_4{\cdot}CH(CN){\cdot}CH(CO_2Et)_2$

(III) $o\text{-}NO_2{\cdot}C_6H_4{\cdot}CH(CO{\cdot}NH_2){\cdot}CH(CO_2Et)_2$

The structure assigned to this hydroxamic acid is based on the following evidence. The compound and the dicarboxylic acid (V), prepared from it by hydrolysis, each gave with ferric chloride the blood-red colour characteristic of the hydroxamic grouping. The dicarboxylic acid (V), (*a*) when strongly heated with sulphuric acid, afforded the known 4-carboxy-2-quinolone (VI);[7] (*b*) when reduced by zinc and acetic acid gave the 3,4-dihydro-derivative[5] of this quinolone; (*c*) when heated with acetic anhydride gave the

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[1] Heller, *J. prakt. Chem.*, 1923, **106**, 1.

[2] Ciamician and Silber, *Ber.*, 1901, **34**, 2040.

[3] Arndt, *Ber.*, 1913, **46**, 3522; cf. Arndt and Rosenau, *Ber.*, 1917, **50**, 1248; Pfister, Tushler, Wilson, and Wolf, *J. Amer. Chem. Soc.*, 1954, **76**, 4611.

[4] Zincke and Schwarz, *Annalen*, 1900, **311**, 329.

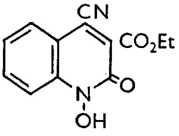
[5] Fichter and Walter, *Ber.*, 1909, **42**, 4312.

[6] Horner, Klüpfel, and Sahler, *Annalen*, 1955, **591**, 85.

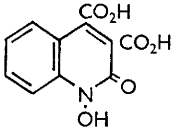
[7] Aeschlimann, *J.*, 1926, 2902.

acetylated anhydride (VII). Hydrogenolysis of the anhydride, effected over palladium–charcoal, yielded a deacetoxy-anhydride (VII; H for OAc) hydrolysable to 3,4-dicarboxy-2-quinolone, and it was ascertained that the acetate derived from the known [8] 3-carboxy-1-hydroxy-2-quinolone was similarly hydrogenolysed, affording 3-carboxy-2-quinolone.[9] A remaining slight possibility that the original compound was the 3,4-dihydro-derivative corresponding to (IV) was refuted by the ultraviolet spectral evidence.

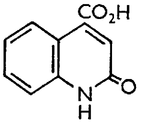
A quite different set of cyclic compounds is obtained from the adduct (II) under slightly different conditions. Thus in ethanol, potassium hydroxide (like potassium cyanide) rapidly changes the adduct into the quinolone (IV), whereas sodium carbonate in ethanol–water more slowly converts it into the indole (VIII). The amide (III), obtained from (II) in cold concentrated sulphuric acid, is likewise cyclised by aqueous sodium carbonate to the amide-ester (as VIII; $CO{\cdot}NH_2$ for CN), or by aqueous sodium hydroxide to the amide-acid (IX) which is also formed by hydrolysis of the nitrile-ester (VIII). These 1-hydroxyindoles, because of the dark green colour they impart to solutions of ferric chloride in ethanol, are easily distinguished from 1-hydroxy-2-quinolones. That they are indeed indole derivatives was proved through reduction of the amide-acid (IX), by zinc and acetic acid, to a deoxy-compound (IX; NH for N•OH), followed by alkaline hydrolysis which afforded indole-2-carboxylic acid and hence, by decarboxylation, indole itself. Like other *N*-hydroxyindoles, described in this and in the following paper, both the amide-acid (IX) and its ethyl ester furnished *O*-acetyl derivatives (*N*-acetoxy-compounds) which, by hydrogenolysis over palladium–charcoal, afforded the corresponding indoles.



(IV)



(V)



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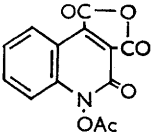
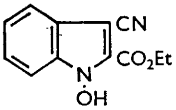


(VII)



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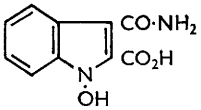
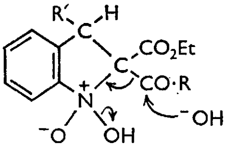


(IX)



(X)

The formation of these derivatives of 1-hydroxyindole corresponds to that of 1-hydroxyindole-2-carboxylic acid from 2-nitrobenzylmalonic acid [10] or from ethyl α-2-nitrobenzylacetoacetate [11] in aqueous alkali. The course of such reactions can be pictured as the formation and decomposition of an internal condensate of type (X). The hydroxyquinolone (IV), on the other hand, is a novel type of product from reactions of this kind. Its formation appears to require a strongly alkaline environment and reactivity in the benzylic hydrogen atom of compound (II). Thus in a weakly alkaline medium or in absence of the (activating) cyano-group (II; H for CN) the predominant product is a derivative of 1-hydroxyindole. While, however, alkali-promoted transfer of both acidic hydrogen atoms from the side-chain to the nitro-group in (II) could lead to an intermediate of the *o*-nitrosocinnamic type, the product (IV) corresponds to an intermediate of 2-hydroxyaminocinnamic type. Reduction by some external agent must therefore be involved but cannot yet be specified. It has not been overlooked that direct reduction of the adduct (II) to the corresponding hydroxylamine might lead to the quinolone (IV) through its

[8] Heller and Wunderlich, *Ber.*, 1914, **47**, 2889.

[9] Stuart, *J.*, 1888, **53**, 140.

[10] Reissert, *Ber.*, 1896, **29**, 639.

[11] Gabriel, Gerhard, and Wolter, *Ber.*, 1923, **56**, 1024.

3,4-dihydro-derivative, but Mr. J. P. Cairns has found that in practice such reduction yields the decyano-quinolone (IV; H for CN).

In the work described here and in the two succeeding papers, the *O*-acetyl derivatives of various 1-hydroxy-indoles and -quinolines have been prepared. All of them show strong carbonyl absorption in the infrared region around 1800 cm.$^{-1}$ and this feature is a valuable guide to such *N*-hydroxy-structures. The absorption frequency is higher than that observed for simple *O*-acylhydroxylamines (ν 1730—1770 cm.$^{-1}$) [12,13] but it is approached by a band (ν 1790 cm.$^{-1}$) [12] found for *ON*-diacylhydroxylamines.

EXPERIMENTAL

Ultraviolet spectra were measured for solutions in 95% ethanol: infrared spectra were taken for Nujol suspensions, and significant bands here noted were either strong or very strong unless specified (w) as weak.

Diethyl 2-Nitrobenzylidenemalonate (I).—A solution of *o*-nitrobenzaldehyde (1·5 g.) and diethyl malonate (1·6 g.) in acetic anhydride (3·6 ml.) was heated with potassium hydrogen carbonate (1·5 g.) at 100° for 2 hr. Addition of the cooled mixture to water (150 ml.) gave an oil which gradually solidified. An ethereal solution of the solid, washed with aqueous sodium carbonate, then with water, was dried (Na_2SO_4) and concentrated, affording the ester (2·2 g.), m. p. 53° (from ethanol) (Found: C, 57·4; H, 5·0; N, 4·9. Calc. for $C_{14}H_{15}O_6N$: C, 57·3; H, 4·8; N, 4·7%). Stuart [14] records m. p. 53°.

Diethyl α-Cyano-α-2-nitrobenzylmalonate (II).—To a solution of potassium cyanide (7·0 g.) in water (25 ml.) and ethanol (200 ml.) there was added, with cooling, dilute acetic acid (from 45 g. of water and 5 g. of acetic acid) and then finely powdered diethyl 2-nitrobenzylidenemalonate (25 g.). The suspension, shaken at room temperature, gradually cleared to a yellow solution from which the product crystallised. After 2 hr. this was collected, and augmented with material precipitated from the mother-liquor by water, affording *diethyl α-cyano-α-2-nitrobenzylmalonate*, m. p. 46° (21 g.; from ethanol) (Found: C, 56·2; H, 4·8; N, 8·9. $C_{15}H_{16}O_6N_2$ requires C, 56·2; H, 5·0; N, 8·7%).

Diethyl α-carbamoyl-α-2-nitrobenzylmalonate (III), m. p. 165° (from ethanol), was formed almost quantitatively when a solution of the nitrile-ester (II) in cold concentrated sulphuric acid was added to ice-water (Found: C, 53·3; H, 5·2; N, 8·5. $C_{15}H_{18}O_7N_2$ requires C, 53·3; H, 5·4; N, 8·3%).

o-*Nitrophenylsuccinic acid*, m. p. 188° [1·9 g.; from water (charcoal)], was obtained when a solution of the amide (III) (3·4 g.) in concentrated hydrochloric (150 ml.) and acetic acid (15 ml.) was heated under reflux (3 hr.) and concentrated *in vacuo* (Found: C, 50·0; H, 4·0; N, 6·2. Calc. for $C_{10}H_9O_6N$: C, 50·2; H, 3·8; N, 5·9%). Smaller yields were obtained by direct, similar hydrolysis of the nitrile-ester (II). The acid, heated with acetyl chloride, afforded *o*-nitrophenylsuccinic anhydride, m. p. 128° (from acetic anhydride) (Found: C, 54·4; H, 3·0; N, 6·4. Calc. for $C_{10}H_7O_5N$: C, 54·3; H, 3·2; N, 6·3%). Horner, Klüpfel, and Sahler [6] record m. p.s 175° for the acid and 129° for the anhydride.

Ethyl 4-Cyano-1,2-dihydro-1-hydroxy-2-oxoquinoline-3-carboxylate (IV).—A solution of potassium cyanide (2·64 g.) in water (4 ml.) was slowly added to a stirred and refluxing solution of diethyl 2-nitrobenzylidenemalonate (2·9 g.) in ethanol (30 ml.). After a further 15 minutes' stirring and heating, the mixture was cooled and the orange-red crystals which separated were collected, washed with ether, dissolved in water (100 ml.), and treated with 5N-hydrochloric acid (5 ml.). The resultant precipitate was redissolved in hot water (*ca.* 50 ml.) and strongly acidified with dilute hydrochloric acid, affording the *quinolone* (IV) as yellow needles, m. p. 158° (0·6—0·7 g.; from acetic acid), $\lambda_{max.}$ 255 and 310 mμ (ε 14,000 and 4600), infl. at 230 mμ (ε 17,400), $\nu_{max.}$ 3130 (broad), 2200w, 1745, 1640 cm.$^{-1}$ (Found: C, 60·5; H, 3·9; N, 10·9. $C_{13}H_{10}O_4N_2$ requires C, 60·4; H, 3·9; N, 10·9%).

1,2-*Dihydro*-1-*hydroxy*-2-*oxoquinoline*-3,4-*dicarboxylic acid* (V) was obtained as cream-coloured cubes of the *monohydrate*, m. p. 294° (decomp.) (from aqueous acetic acid), when a solution of the ester (IV) (1·3 g.) in a mixture of water (16 ml.), acetic acid (8 ml.), and concentrated sulphuric acid (1·2 ml.) was heated under reflux for 2 hr.; it had $\lambda_{max.}$ 235, 295, and 360

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[12] Jencks, *J. Amer. Chem. Soc.*, 1958, **80**, 4581.

[13] Exner and Horák, *Coll. Czech. Chem. Comm.*, 1959, **24**, 2992.

[14] Stuart, *J.*, 1885, **47**, 158.

mμ (ε 2700, 7000, and 4000), $\nu_{max.}$ *ca.* 3480 (broad), 1720 cm.$^{-1}$ (Found: C, 49·8; H, 3·6; N, 5·5. $C_{11}H_7O_6N,H_2O$ requires C, 49·5; H, 3·4; N, 5·2%).

This acid (1 g.) was heated with water (50 ml.) and concentrated sulphuric acid (4 ml.) in a sealed tube at 270° for 5 hr. The solid product was dissolved in dilute sodium carbonate, and the filtered solution acidified, affording 2-hydroxyquinoline-4-carboxylic acid (VI), m. p. and mixed m. p. with an authentic sample,[7] 343° (decomp.) (from acetic acid), $\lambda_{max.}$ 230, 280, and 340 mμ (ε 23,400, 4700, 4700) (Found: C, 63·3; H, 3·9; N, 7·5. Calc. for $C_{10}H_7O_3N$: C, 63·5; H, 3·7; N, 7·4%).

Zinc dust (1 g.) was added to a solution of the acid (V) (0·3 g.) in acetic acid (8 ml.) and 5N-hydrochloric acid (2 ml.), and the whole heated (1 hr.) under reflux. Concentration of the resultant solution afforded 1,2,3,4-tetrahydro-2-oxoquinoline-4-carboxylic acid, m. p. and mixed m. p. with an authentic sample[5] 221° (from water), $\lambda_{max.}$ 250 mμ (ε 10,000) (Found: C, 62·9; H, 4·6; N, 7·4. Calc. for $C_{10}H_9O_3N$: C, 62·8; H, 4·7; N, 7·3%).

1-*Acetoxy*-1,2-*dihydro*-2-*oxoquinoline*-3,4-*dicarboxylic anhydride* (VII), m. p. 232° (decomp.), $\nu_{max.}$ 1862, 1825, 1790, 1640 cm.$^{-1}$, crystallised from the solution formed by heating the 1-hydroxy-dicarboxylic acid (0·7 g.) in acetic anhydride (2 ml.) for 5 min. (Found: C, 57·5; H, 2·7; N, 5·3; *O*-Ac, 16·0. $C_{13}H_7O_6N$ requires C, 57·1; H, 2·6; N, 5·1; 1 *O*-Ac, 15·8%). The compound did not affect the colour of ferric chloride in ethanol.

2-*Hydroxyquinoline*-3,4-*dicarboxylic Acid and its Anhydride*.—A solution of the acetoxy-anhydride (VII) (0·3 g.) in acetic acid (10 ml.) was hydrogenated at ordinary temperature and pressure over 5% palladium–charcoal (0·2 g.). After the uptake of 1 mol. of hydrogen the filtered and concentrated solution afforded 2-*hydroxyquinoline*-3,4-*dicarboxylic anhydride*, m. p. 349° (decomp.) (from acetic anhydride) (Found: C, 61·5; H, 2·6; N, 6·45. $C_{11}H_5O_4N$ requires C, 61·5; H, 2·3; N, 6·5%). When warmed with dilute hydrochloric acid this anhydride gave the corresponding dicarboxylic acid, m. p. 358° (decomp.) (from water), for which various m. p.s have been recorded[15] (Found: C, 56·8; H, 3·0; N, 6·0. Calc. for $C_{11}H_7O_5N$: C, 56·7; H, 3·0; N, 6·0%). Reduction of the dicarboxylic acid by zinc in acetic acid proceeded with decarboxylation to 1,2,3,4-tetrahydro-2-oxoquinoline-4-carboxylic acid, m. p. and mixed m. p. 221°.

Experiments with 1,2-*Dihydro*-1-*hydroxy*-2-*oxoquinoline*-3-*carboxylic Acid*.—This acid[8] afforded (a) the *ethyl ester*, m. p. 168° (from ethanol), $\lambda_{max.}$ 240, 290, 360 mμ (ε 37,000, 8500, 4500), $\nu_{max.}$ (3000—2690), 1740, 1620 cm.$^{-1}$ (Found: C, 62·0; H, 4·9; N, 6·2. $C_{12}H_{11}O_4N$ requires C, 61·8; H, 4·7; N, 6·0%), and (b) 1-*acetoxy*-1,2-*dihydro*-2-*oxoquinoline*-3-*carboxylic acid*, m. p. 203° (from acetic anhydride), $\nu_{max.}$ 1805, 1750, 1640 cm.$^{-1}$ (Found: C, 58·2; H, 3·3; N, 5·8. $C_{12}H_9O_5N$ requires C, 58·4; H, 3·6; N, 5·7%). Hydrogenolysis of this acetoxy-compound, as described for its analogue (VII), gave 2-hydroxyquinoline-3-carboxylic acid,[14] m. p. 330° (from acetic acid) (Found: C, 63·5; H, 3·9; N, 7·5. Calc. for $C_{10}H_7O_3N$: C, 63·5; H, 3·7; N, 7·4%).

3-*Cyano*-1-*hydroxyindole*-2-*carboxylic Acid*.—A solution of diethyl α-cyano-α-2-nitrobenzyl-malonate (II) (3·2 g.) and sodium carbonate (3·2 g.) in water (8 ml.) and ethanol (24 ml.) was heated under reflux (2 hr.), concentrated, cooled, and added to dilute sulphuric acid, affording the *ethyl ester* (VIII), m. p. 116° (1·5 g.; from benzene–light petroleum of b. p. 40—60°), $\nu_{max.}$ 3260 (broad), 2200, 1685 cm.$^{-1}$ (Found: C, 62·3; H, 4·4; N, 11·8. $C_{12}H_{10}O_3N_2$ requires C, 62·6; H, 4·4; N, 12·1%). Hydrolysis of the ester by potassium hydroxide in aqueous ethanol gave (*a*) 3-*cyano*-1-*hydroxyindole*-2-*carboxylic acid*, m. p. 211° (from water) (Found: C, 59·5; H, 2·9; N, 13·6. $C_{10}H_6O_3N_2$ requires C, 59·4; H, 3·0; N, 13·8%) or (*b*), on prolonged reaction, the amide (IX).

3-*Carbamoyl*-1-*hydroxyindole*-2-*carboxylic Acid* (IX).—Acidification of the yellow solution obtained by warming (10 min.) the amide (III) (3·4 g.) with 5N-sodium carbonate (50 ml.) gave *ethyl* 3-*carbamoyl*-1-*hydroxyindole*-2-*carboxylate*, m. p. 207° (decomp.) (from aqueous acetic acid), $\nu_{max.}$ 3350, 3150, 1700 cm.$^{-1}$ (Found: C, 58·3; H, 4·8; N, 11·4. $C_{12}H_{12}O_4N_2$ requires C, 58·1; H, 4·9; N, 11·3%). This reacted (*a*) with acetic anhydride to form the corresponding 1-*acetoxyindole*, m. p. 168° (from ethanol), $\nu_{max.}$ 1800 cm.$^{-1}$ (Found: C, 58·1; H, 5·0; N, 9·6. $C_{14}H_{14}O_5N_2$ requires C, 58·0; H, 4·8; N, 9·6%), and (*b*) with warm dilute sodium hydroxide to give, after acidification, the *carboxylic acid* (IX), m. p. 245° (decomp.) (from acetic acid) (Found: C, 54·8; H, 3·6; N, 12·8. $C_{10}H_8O_4N_2$ requires C, 54·6; H, 3·7; N, 12·7%). This acid was also

[15] Yokoyama, *J. Chem. Soc. Japan*, 1936, **57**, 251; cf. *Chem. Abs.*, 1936, **30**, 5204; Lindwall and Zrike, *J. Amer. Chem. Soc.*, 1936, **58**, 49; King, King, and Thomson, *J.*, 1948, 552.

obtained directly from the compound (III) with warm dilute sodium hydroxide. It reacted with acetic anhydride, forming 1-*acetoxy*-3-*carbamoylindole*-2-*carboxylic acid*, m. p. 187° (from acetic anhydride), $\nu_{max.}$ 1800 cm.$^{-1}$ (Found: C, 55·2; H, 3·7; N, 10·4. $C_{12}H_{10}O_5N_2$ requires C, 55·0; H, 3·8; N, 10·7%).

Conversion of the Acid (IX) *into Indole.*—To a boiling solution of the hydroxyindole (IX) (0·5 g.) in acetic acid (30 ml.) zinc dust (1·5 g.) was added in small portions. Heating was continued for 1 hr. and then the concentrated solution gave 2-*carbamoylindole*-2-*carboxylic acid*, m. p. 284° (decomp.) (from acetic acid) (Found: C, 58·6; H, 4·0; N, 13·6. $C_{10}H_8O_3N_2$ requires C, 58·8; H, 3·9; N, 13·7%). The same compound was obtained by hydrogenolysis of the 1-acetoxyindole derived from acid (IX). It was hydrolysed with partial decarboxylation when heated for 2 hr. with aqueous sodium hydroxide affording, after acidification, indole-2-carboxylic acid, m. p. 204° (from water) (Found: C, 67·2; H, 4·6; N, 8·6. Calc. for $C_9H_7O_2N$: C, 67·1; H, 4·4; N, 8·7%), which, when briefly heated with soda-lime at 220°, yielded indole, as shown by recovery in ethanol and isolation as the picrate, m. p. and mixed m. p. 182°.

Ethyl 3-*carbamoylindole*-2-*carboxylic acid*, m. p. 200° (from ethanol), was obtained by hydrogenolysis of the corresponding 1-acetoxyindole (Found: C, 62·0; H, 5·4; N, 12·3. $C_{12}H_{12}O_3N_2$ requires C, 62·1; H, 5·2; N, 12·1%).

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