

*The Supposed Dihydroindole Reduction Products of  $\alpha$ -Cyano-*o*-nitrocinnamamide.*

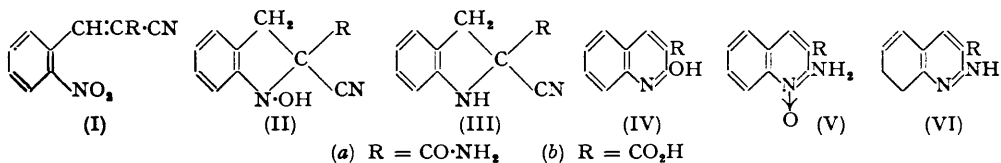
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The reduction products of  $\alpha$ -cyano-*o*-nitrocinnamamide (Ia), previously supposed to be 2-carbamoyl-2-cyanodihydroindole (IIIa) and its *N*-hydroxy-derivative (IIa), are shown to be 2-amino-3-carbamoylquinoline (VIa) and its *N*-oxide (Va) respectively. Treatment of the former with nitrous fumes does not cause the ring expansion (to a quinoline derivative), claimed by Heller and Wunderlich (*Ber.*, 1914, **47**, 1621), but merely replacement of the 2-amino-group by a hydroxyl group.

HELLER and WUNDERLICH (*Ber.*, 1914, **47**, 1621) claimed ring expansion when the substance  $C_{10}H_9ON_3$ , believed to be 2-carbamoyl-2-cyanodihydroindole (IIIa), was treated with nitrous fumes at 60°, yielding nitrogen, and a new compound  $C_{10}H_8O_2N_2$  in quantitative yield. Because this compound was readily converted by dilute alkali into the known 2-hydroxyquinoline-3-carboxylic acid (IVb) (Friedländer, *Ber.*, 1883, **16**, 1833; Mills and Watson, *J.*, 1910, **97**, 741) with liberation of ammonia, the structure 3-carbamoyl-2-hydroxyquinoline (IVa) was assigned to it.

The supposed carbamoyldihydroindole (IIIa) was prepared by reduction of  $\alpha$ -cyano-*o*-nitrocinnamamide (Ia), together with its "1-hydroxy-derivative" (IIa), or by the reduction of the "hydroxy-derivative" (IIa). These structures were based essentially on two suggested mechanisms for the production of the latter compound and on presumption of a *N*-hydroxy-group from a ferric chloride reaction; alkaline hydrolysis of the amides gave acids, which were identical with the reduction products, thought to be (IIb) and (IIIb) (though no structural evidence was advanced) of  $\alpha$ -cyano-*o*-nitrocinnamic acid



(Ib). Reduction of  $\alpha$ -substituted *o*-nitrocinnamonitriles, however, produces 3-substituted 2-aminoquinolines and the corresponding *N*-oxides (Pschorr and Wolfes, *Ber.*, 1899, **32**, 3399; Rupe and Heckendorn, *Helv. Chim. Acta*, 1926, **9**, 981; Bauer, *Ber.*, 1938, **71**, 2226). This may be expected from a consideration of the configuration of an intermediate hydroxylamine derivative, particularly since the interaction of nitriles with hydroxylamine is well known (Migrdichian, "Chemistry of Organic Cyanogen Compounds," Reinhold Publ. Corp., New York, 1947, p. 70 for collected references). Thus the "dihydroindole" compounds  $C_{10}H_9ON_3$  and  $C_{10}H_9O_2N_3$  are more probably 2-amino-3-carbamoylquinoline (VIa) and its *N*-oxide (Va). It has now been found that the compound  $C_{10}H_9ON_3$  and dilute alkali yield one equivalent of ammonia under mild conditions which indicate the reaction of an amide rather than of a 2-aminoquinoline. The product of hydrolysis of  $C_{10}H_9ON_3$  gave methyl and ethyl esters whose melting points and analyses agree with those for the 2-aminoquinoline-3-carboxylic esters (cf. VIb). The structure of (a) this acid and its methyl ester (Koller and Strang, *Monatsh.*, 1928, **50**, 144), and (b) the ethyl ester (Rupe and Heckendorn, *loc. cit.*) have been proved independently.

The methyl ester provided the original amide,  $C_{10}H_9ON_3$ , on ammonolysis and this therefore has the quinoline structure (VIa). The cycle (VIa)  $\rightarrow$  (VIb)  $\rightarrow$  ester  $\rightarrow$  (VIa) is thereby effected and shows that reduction of  $\alpha$ -cyano-*o*-nitrocinnamamide (Ia) gives the quinoline derivatives (Va) and (VIa). Consequently the action of nitrous fumes does not involve ring expansion.

The reduction of  $\alpha$ -cyano-*o*-nitrocinnamic acid (Ib) at low temperature (cf. Heller and Wunderlich, *loc. cit.*) was repeated: the product and its methyl and ethyl ester gave analyses correct for the 3-substituted 2-aminoquinoline *N*-oxides. The melting point of the ethyl ester agreed with that recorded by Bauer (*loc. cit.*) who established the structure.

There seemed to be no reason why nitrous fumes at 60° should react specifically with the amino-group of 2-amino-3-carbamoylquinoline (VIa) yielding the phenol (IVa), rather than with the carbamoyl group. As the sole reference to the phenolic amide (IVa) is that of Heller and Wunderlich (*loc. cit.*), and as its m. p. was recorded as 291° and that of the isomeric amino-acid (VIa) is 290—292° (decomp.) (Rupe and Heckendorn, *loc. cit.*; Koller and Strang, *loc. cit.*), or >290° (Heller and Wunderlich, *loc. cit.*), an authentic specimen was prepared by ammonolysis of methyl 2-hydroxyquinoline-3-carboxylate. Re-investigation of the action of nitrous fumes on the amino-amide (VIa) showed that at 60° the principal product was the phenolic amide (IVa) (it was converted into methyl 2-hydroxyquinoline-3-carboxylate), but that at 100° some of the phenolic acid (IVb) was also produced. However, after reaction at 20—30° (Sudborough, *J.*, 1895, **67**, 602; cf. Bouveault, *Bull. Soc. chim.*, 1892, **9**, 368) the product, when esterified, yielded methyl 2-aminoquinoline-3-carboxylate and was therefore the amino-acid (VIb).

#### EXPERIMENTAL

Microanalyses were, in part, by the Micro-Analytical Laboratory of the Imperial College of Science and Technology, London.

2-Amino-3-carbamoylquinoline *N*-oxide (Va) was prepared by the reduction of  $\alpha$ -cyano-*o*-nitrocinnamamide (Ia) with zinc and dilute acetic acid (Heller and Wunderlich, *loc. cit.*). It was precipitated on dilution of the acid medium (accompanying 2-amino-3-carbamoylquinoline remained in solution), and formed yellow needles on crystallisation from ethanol (50%) to a constant m. p. [303° (decomp.); rapid heating; Heller and Wunderlich, *loc. cit.*, record m. p. >290°] (Found: C, 59.2; H, 4.6; N, 20.6.  $C_{10}H_9ON_3$  requires C, 59.1; H, 4.5; N, 20.7%).

Catalytic hydrogenation of the cinnamamide (Ia) (2 g.), at room temperature and pressure with platonic oxide (0.02 g.; *Org. Synth.*, 2nd Edn., Coll. Vol. I, p. 463) in 1:4 ethyl acetate-ethanol (100 ml.), also afforded the *N*-oxide, which was precipitated during the reduction (absorption: 99%). After dissolution of the product in ethyl acetate-ethanol-pyridine-water (300 ml.; 1:1:1:1) the catalyst was removed by centrifugation, and the solution was evaporated to dryness. The residue (1.75 g.) gave needles [1.10 g.; m. p. 303° (decomp.)] after two crystallisations from 1:1 aqueous ethanol (Found: C, 58.7; H, 4.4%).

2-Amino-3-carbamoylquinoline (VIa) was obtained most conveniently by reduction with zinc and aqueous ammonia at 80°, of the oxide (Heller and Wunderlich, *loc. cit.*). Crystallisation from water or 1:1 aqueous ethanol provided pale yellow needles, m. p. 237° (Heller and Wunderlich, *loc. cit.*, record 237—238°), which are not deliquescent though so described (Found: C, 63.9; H, 4.9; N, 22.5.  $C_{10}H_9ON_3$  requires C, 64.3; H, 4.9; N, 22.5%).

*Alkaline Hydrolysis of 2-Amino-3-carbamoylquinoline.*—The amide (500 mg.) was heated for 45—55 min. with 0.25*N*-sodium hydroxide (40 ml.). The liberated ammonia was absorbed in saturated boric acid solution (40 ml.) and determined by titration with hydrochloric acid (approx. 0.04*N*) (Belcher and Godbert, "Semi-Micro Quantitative Organic Analysis," Longmans, Green and Co., London, 1947, p. 89) (Found: N, 7.2—7.5. Calc. for  $C_{10}H_9ON_3$ : 1*N*, 7.5%). The acid (480—490 mg.) separated on acidification of the solution with acetic acid. Decomposition occurred at the m. p. which was always sharp but variable, occasionally about 290°, but generally 326—328°; Heller and Wunderlich (*loc. cit.*) record >290°; Rupe and Heckendorn and Koller and Strang (*loc. cit.*) record 290—292° (decomp.). The high m. p. (326—328°) remained constant on crystallisation of the acid from water or 1% acetic acid (Found: C, 64.1; H, 4.6; N, 14.8. Calc. for  $C_{10}H_8O_2N_2$ : C, 63.8; H, 4.3; N, 14.9%).

The methyl ester, prepared (60—70%) by methanol-hydrogen chloride, formed yellow blades, m. p. 140—141° (Koller and Strang record 140—141°), from methanol (Found: C, 65.3; H, 5.2; N, 14.2. Calc. for  $C_{11}H_{10}O_2N_2$ : C, 65.3; H, 5.0; N, 13.9%). Methanol and sulphuric acid gave a 52% yield.

*Ethyl 2-Aminoquinoline-3-carboxylate* (XVII).—The ethyl ester, prepared (70—80%) by the hydrogen chloride method, formed yellow blades, m. p. 135° (Rupe and Heckendorn, *loc.*

*cit.*, record 135°), from ethanol (Found: C, 67.1; H, 5.7; N, 12.9. Calc. for  $C_{12}H_{12}O_2N_2$ : C, 66.6; H, 5.6; N, 13.0%).

*Ammonolysis of Methyl 2-Aminoquinoline-3-carboxylate.*—To the ester (200 mg.) dissolved in ethanol, an equal volume of aqueous ammonia ( $d$  0.880) was added, and the solution kept in a sealed tube for 18 days. The solvents were removed. Impurities were extracted from the residue (174 mg.; cloudy melt at 235–237°) by suspending it in benzene (2 ml.) and then in 0.5% sodium hydroxide (1 ml.). The amide crystallised from 1:1 aqueous ethanol as yellow needles (79 mg.), m. p. and mixed m. p. 236–237°.

*Reduction of  $\alpha$ -Cyano-o-nitrocinnamic Acid (Ib).*—Addition of water (2.5 ml.) to a hot solution of the acid [2.5 g.; prepared by Fiquet's method (*Ann. Chim. Phys.*, 1893, 29, 490); (Found: C, 55.0; H, 3.1; N, 12.9. Calc. for  $C_{10}H_8O_4N_2$ : C, 55.0; H, 2.8; N, 12.8%)] in acetic acid (12.5 g.) afforded a fine precipitate of the acid, which was reduced by the addition of zinc dust (2.5 g.) at 30–40°. The mixture was stirred for a further 0.5 hr. (cf. Heller and Wunderlich, *loc. cit.*). Water (5 ml.) was added and the suspension filtered, washed and treated with 5% sodium hydroxide solution (30 ml.). Unchanged zinc was removed. 2-Aminoquinoline-3-carboxylic acid N-oxide was precipitated by excess of 50% acetic acid (4 ml.), and after collection was washed and dried [1.99 g.; m. p. 305–307° (decomp.), rapid heating]. Crystallisation from 10% sodium acetate solution gave a yellow product, m. p. 318–320° (decomp.; rapid heating) (Heller and Wunderlich, *loc. cit.*, give m. p. >295°) (Found: C, 58.1; H, 4.1; N, 13.8.  $C_{10}H_8O_3N_2$  requires C, 58.8; H, 4.0; N, 13.7%).

The foregoing acid was not esterified by methanol–hydrogen chloride but when refluxed for 18 hr. with sulphuric acid (2 ml.) in anhydrous methanol (25 ml.), gave the *methyl ester* (0.45 g. from 0.80 g.), yellow blades, m. p. 168.5–169° (from methanol) (Found: C, 60.5; H, 4.8; N, 12.8.  $C_{11}H_{10}O_3N_2$  requires C, 60.5; H, 4.6; N, 12.8%).

The ethyl ester was prepared similarly but was extracted with ether. It had m. p. 137–138° (from ethanol) (Bauer, *loc. cit.*, records 141–142°) (Found: C, 62.4; H, 5.5; N, 12.2. Calc. for  $C_{12}H_{12}O_3N_2$ : C, 62.1; H, 5.2; N, 12.1%).

*Methyl 2-Hydroxyquinoline-3-carboxylate.*—This was prepared by refluxing 2-hydroxyquinoline-3-carboxylic acid [100 mg.; prepared by the reduction of  $\alpha$ -carboxy-o-nitrocinnamic acid (Meyer, *loc. cit.*) (Found: C, 63.1; H, 3.8; N, 7.1. Calc. for  $C_{10}H_7O_3N$ : C, 63.5; H, 3.7; N, 7.4%)] with anhydrous methanol (5 ml.) and sulphuric acid (0.5 ml.) for 7 hr. (yield 75 mg.). It formed white blades, m. p. 186–186.5°, from methanol (Meyer, *loc. cit.*, gives 186°) (Found: C, 65.1; H, 4.9; N, 6.7. Calc. for  $C_{11}H_9O_3N$ : C, 65.0; H, 4.5; N, 6.9%).

*3-Carbamoyl-2-hydroxyquinoline (IVa).*—A solution of the methyl ester (120 mg.) in anhydrous methanol (10 ml.) and aqueous ammonia ( $d$  0.880; 5 ml.) was kept in a sealed tube. The product began to separate during the first day. After 2 days, the solvents were removed, and the residue (m. p. 290°) gave cream-coloured needles (91 mg.), m. p. 290°, on crystallisation from water (25 ml.) (Heller and Wunderlich, *loc. cit.*, record 290–291°) (Found: N, 14.8. Calc. for  $C_{10}H_8O_2N_2$ : N, 14.9%).

*Action of Nitrous Fumes on 2-Amino-3-carbamoylquinoline.*—(a) At 60°. Two samples (each 300 mg.) of the amino-amide, suspended in water (30 ml.) and heated at 60°, were treated with a stream of nitrous fumes (cf. Heller and Wunderlich, *loc. cit.*) for 2 and 10 min. respectively. The products were collected after 3 hr. [254, 215 mg.; m. p. 236° (decomp.)] and were suspended in 5% sodium hydroxide solution (2 ml.). Unchanged amino-amide (106, 35 mg.) was filtered off. Acidification of the filtrate with 10% acetic acid gave precipitates (95, 148 mg.; m. p. 286–287°, 284–285°), which, after crystallisation from water, both melted at 290° (79, 127 mg.), and were identical (mixed m. p.) with authentic 3-carbamoyl-2-hydroxyquinoline. More unchanged amino-amide (65 mg. after crystallisation) was recovered when the original acid solution of the second experiment was acidified. The yields of the hydroxy-amide are 49 and 74% respectively.

A sample (150 mg.) of the hydroxy-amide was esterified by methanol–sulphuric acid, and after crystallisation from methanol the crude product (117 mg.) gave methyl 2-hydroxyquinoline-3-carboxylate, m. p. 185–186°.

(b) At 100°. The experiment with nitrous fumes (10 min.) was also conducted on a boiling-water bath. The product (277 mg.; m. p. 265–267°) did not contain unchanged amino-amide. It was extracted with 2% potassium carbonate solution (10 ml.); the residue gave cream-coloured needles of 3-carbamoyl-2-hydroxyquinoline (128 mg.), m. p. 289–290°, from water. Addition of 10% acetic acid to the alkaline filtrate gave 2-hydroxyquinoline-3-carboxylic acid, m. p. and mixed m. p. 330–331° (89 mg.) (from water).

*Action of Nitrous Acid on 2-Amino-3-carbamoylquinoline.*—0.5N-Sodium nitrite (3.2 ml.)

was gradually introduced below the surface of a solution of the amide (300 mg.) in 90% (w/v) sulphuric acid (3 ml.) at  $<30^{\circ}$ . Nitrogen was evolved, and a cream-coloured precipitate separated. After dilution to 10 ml., the suspension was left for 1 hr. Unchanged amino-amide (42 mg.) was removed from the precipitate (367 mg.) by treatment with 5% sodium hydroxide solution (2 ml.), and the acidic material was reprecipitated (207 mg.; variable m. p.  $306-308^{\circ}$ ,  $290-292^{\circ}$ ) by 50% acetic acid (Found: N, 15.3. Calc. for  $C_{10}H_8O_2N_2$ : N, 14.9%). The methyl ester (m. p.  $139^{\circ}$  after two crystallisations from methanol) of the product (200 mg.) on admixture with methyl 2-amino-3-carbamoylquinoline (m. p.  $139-140^{\circ}$ ) melted at  $139^{\circ}$ .

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