The Supposed Dihydroindole Reduction Products of α-Cyano-o-nitrocinnamamide.

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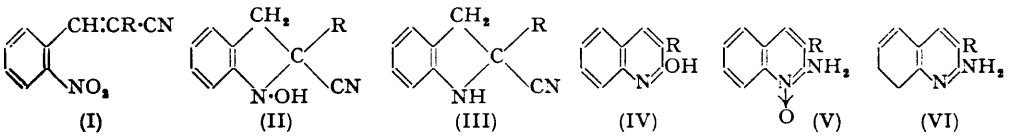
The reduction products of α-cyano-*o*-nitrocinnamamide (I*a*), previously supposed to be 2-carbamoyl-2-cyanodihydroindole (III*a*) and its *N*-hydroxy-derivative (II*a*), are shown to be 2-amino-3-carbamoylquinoline (VI*a*) and its *N*-oxide (V*a*) respectively. Treatment of the former with nitrous fumes 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 (III*a*), 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 (IV*b*) (Friedländer, *Ber.*, 1883, **16**, 1833; Mills and Watson, *J.*, 1910, **97**, 741) with liberation of ammonia, the structure 3-carbamoyl-2-hydroxyquinoline (IV*a*) was assigned to it.

The supposed carbamoyldihydroindole (III*a*) was prepared by reduction of α-cyano-*o*-nitrocinnamamide (I*a*), together with its " 1-hydroxy-derivative " (II*a*), or by the reduction of the " hydroxy-derivative " (II*a*). 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 (II*b*) and (III*b*) (though no structural evidence was advanced) of α-cyano-*o*-nitrocinnamic acid



(I) (II) (III) (IV) (V) (VI)

(*a*) R = CO·NH$_2$ (*b*) R = CO$_2$H

(I*b*). Reduction of α-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. Corpn., 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 (VI*a*) and its *N*-oxide (V*a*). 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. VI*b*). 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 (VI*a*). The cycle (VI*a*) ⟶ (VI*b*) ⟶ ester ⟶ (VI*a*) is thereby effected and shows that reduction of α-cyano-*o*-nitrocinnamamide (I*a*) gives the quinoline derivatives (V*a*) and (VI*a*). Consequently the action of nitrous fumes does not involve ring expansion.

The reduction of α-cyano-*o*-nitrocinnamic acid (I*b*) 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 (VI*a*) yielding the phenol (IV*a*), rather than with the carbamoyl group. As the sole reference to the phenolic amide (IV*a*) is that of Heller and Wunderlich (*loc. cit.*), and as its m. p. was recorded as 291° and that of the isomeric amino-acid (VI*a*) 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 (VI*a*) showed that at 60° the principal product was the phenolic amide (IV*a*) (it was converted into methyl 2-hydroxyquinoline-3-carboxylate), but that at 100° some of the phenolic acid (IV*b*) 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 (VI*b*).

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 (V*a*) was prepared by the reduction of α-cyano-*o*-nitrocinnamamide (I*a*) 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 (I*a*) (2 g.), at room temperature and pressure with platinic 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* (VI*a*) 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 0·25N-sodium hydroxide (40 ml.). The liberated ammonia was absorbed in saturated boric acid solution (40 ml.) and determined by titration with hydrochloric acid (approx. 0·04N) (Belcher and Godbert, "Semi-Micro Quantitative Organic Analysis," Longmans, Green and Co., London, 1947, p. 89) (Found: N, 7·2—7·5. Calc. for $C_{10}H_9ON_3$: 1N, 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 (*locc. 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 α-Cyano-o-nitrocinnamic Acid (I*b*).—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 $C_{10}H_6O_4N_2$: 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 α-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 (IV*a*).—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°. 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°, 290—292°) 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° after two crystallisations from methanol) of the product (200 mg.) on admixture with methyl 2-amino-3-carbamoylquinoline (m. p. 139—140°) melted at 139°.

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