[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

THE STRUCTURES OF SOME ALLEGED DIHYDROINDOLES

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The reduction of *o*-nitrobenzalcyanoacetamide (I) with zinc dust and aqueous acetic acid has been reported to yield two products, to which the structures α-cyano-α-carboxamido-N-hydroxydihydroindole (IIA) and α-cyano-α-carboxamidodihydroindole (IIIA) were assigned (1). Numerous transformation products of IIA and IIIA have been described (Figure 1). It has already been suggested that the structures of IIA and IIIA are incorrect, and IIA has been formulated as 2-aminoquinoline-3-carboxamide-1-oxide (IIB) and IIIA as 2-aminoquinoline-3-carboxamide (IIIB) (2). It seemed desirable, however, to attempt to support these formulations with chemical and physical evidence, since the original structures have been recently reaffirmed (3), the purported ring expansion of a dihydroindole to a quinoline (IIIA → V, Figure 1) has been cited as a precedent for other work (4), and several derivatives of the dihydroindoles of Heller and Wunderlich (1) have been included in *The Ring Index* (5). As a consequence of the present work, we have been able to confirm the structures IIB and IIIB as suggested by Pachter and Kloetzel (2) and have reassigned structures to most of the transformation products of the alleged dihydroindoles IIA and IIIA (see Figure 1).

Confirmation of the structures IIB and IIIB for IIA and IIIA respectively as suggested by Pachter and Kloetzel was obtained as follows. Examination of the infrared spectra of the two reduction products showed the absence of a $-C{\equiv}N$ group (Figure 2), thus excluding the originally assigned structures. Compound IIIA was shown to be 2-aminoquinoline-3-carboxamide (IIIB) by direct comparison (mixture melting points, comparison of infrared spectra) with an authentic sample prepared independently by (a) the condensation of *o*-aminobenzaldehyde with malononitrile to give 2-amino-3-cyanoquinoline, followed by conversion to the amide with alkaline hydrogen peroxide, and (b) the condensation of *o*-aminobenzaldehyde and cyanoacetamide in the presence of sodium ethoxide. An attempt to prepare IIIB by ammonolysis of 2,4-dihydroxypyrimido[4,5-*b*]quinoline (XII), prepared by the condensation of *o*-aminobenzaldehyde and barbituric acid (6), gave 2-aminoquinoline-3-carboxylic acid (IVB) as the only product isolated. IVB was also formed by heating IIIB under similar conditions with concentrated ammonium hydroxide in a sealed tube; attempts to repeat the alkaline hydrolysis of IIIB to IVB (reported by Heller and Wunderlich as the conversion of IIIA to IVA, Figure 1) were not successful.

It follows that IIA is 2-aminoquinoline-3-carboxamide-1-oxide (IIB), a conclusion substantiated by the infrared spectrum (Figure 2), and by the observed reduction of IIB to IIIB with ammonia and zinc dust (1) or acetic

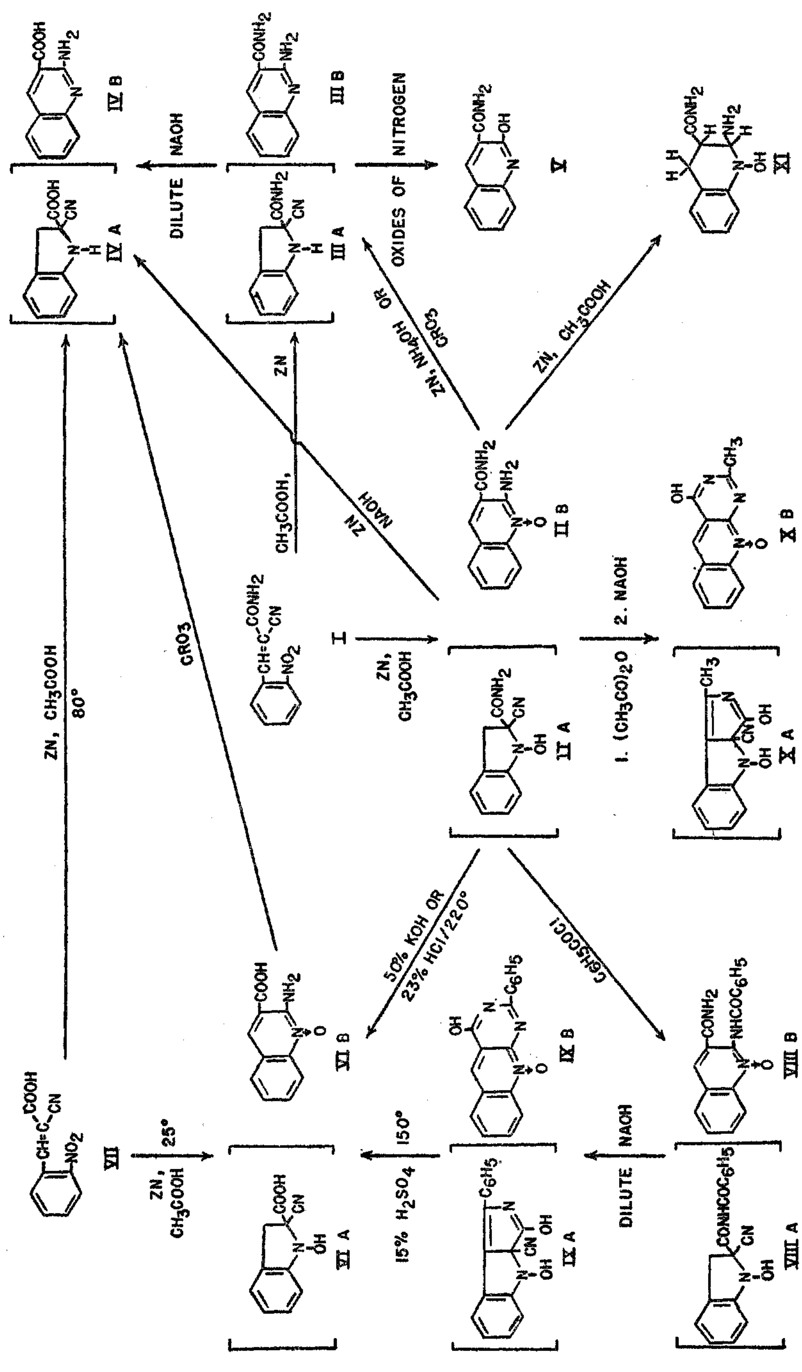


FIGURE I. REACTIONS OF ALLEGED DIHYDROINDOLES AND REINTERPRETATION IN TERMS OF REVISED STRUCTURES

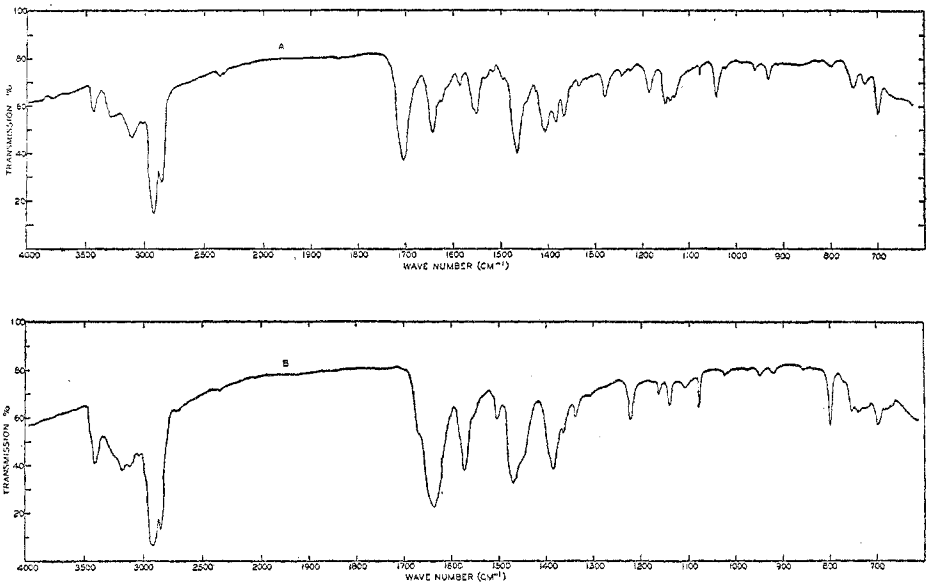
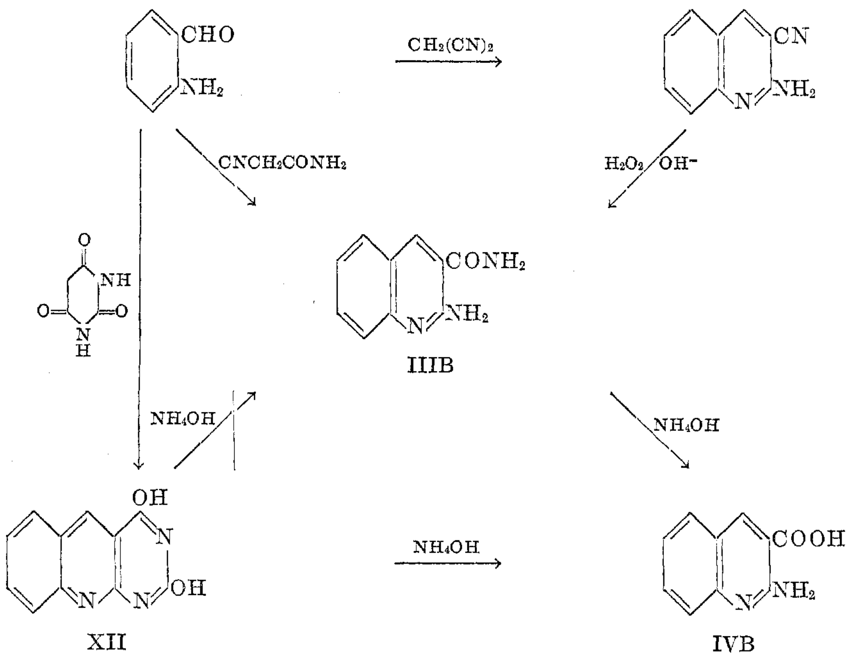


FIG. 2. CURVE A, 2-Aminoquinoline-3-carboxamide-1-oxide (IIB); CURVE B, 2-Aminoquinoline-3-carboxamide (IIIB).

acid and zinc dust (see Experimental). The conversion of IIB to IIIB by the action of chromic acid has been discussed previously (2).



The reduction of IIA with zinc and sodium hydroxide was reported by Heller and Wunderlich (1) to give α-cyano-α-carboxydihydroindole (IVA), alternatively formed (a) by reduction of *o*-nitrobenzalcyanoacetic acid with acetic acid and zinc dust at 80°, (b) by hydrolysis of α-cyano-α-carboxamidodihydroindole (which has been shown, *vide infra,* to be IIIB) with sodium hydroxide, and (c) by "oxidative reduction" of VIA with chromic acid. Direct comparison of IVA with an authentic sample of 2-aminoquinoline-3-carboxylic acid (IVB) prepared as described above and also from quinoline-2,3-dicarboxylic acid by the method of Koller and Strang (7) showed them to be identical. It follows that VIA, prepared by the reduction of *o*-nitrobenzalcyanoacetic acid with acetic acid and zinc dust at 25°, is 2-aminoquinoline-3-carboxylic acid-1-oxide (VIB).

It also follows that the products formed by the treatment of 2-aminoquinoline-3-carboxamide-1-oxide (IIB) with benzoyl chloride or acetic anhydride, followed by cyclization with alkali, are 2-phenyl-4-hydroxypyrimido[4,5-*b*]quinoline-10-oxide (IXB) and 2-methyl-4-hydroxypyrimido[4,5-*b*]quinoline-10-oxide (XB) respectively. A search of the literature has revealed that no authenticated preparation of a derivative of the pyrrolo[3,4-*b*]indole ring system (IXA, XA) has been reported.

Since IIIA has been shown to be 2-aminoquinoline-3-carboxamide (IIIB), its conversion to 2-hydroxyquinoline-3-carboxamide (V) with oxides of nitrogen is straightforward, and arguments which have cited this alleged ring expansion (IIIA → V) for support (4) should be re-examined.

Heller and Wunderlich (1) reported the formation of a compound $C_{10}H_{13}N_3O_2$ from a reduction of IIA with zinc dust and aqueous acetic acid. No structure was assigned to this product. It seems probable from the present work that this reduction product is 1-hydroxy-2-amino-3-carboxamido-1,2,3,4-tetrahydroquinoline (XI).

The revised structures for the compounds reported by Heller and Wunderlich (1) are summarized in Table I.

The formation of IIB from *o*-nitrobenzalcyanoacetamide (I) and of VIB from *o*-nitrobenzalcyanoacetic acid (VII) undoubtedly involves preliminary reduction of the nitro group to a hydroxylamino group [also proposed by Heller and Wunderlich (1)], followed by addition to the carbon-nitrogen triple bond of the nitrile rather than addition to the carbon-carbon double bond as previously postulated. IIIB and IVB probably arise by subsequent reduction of the oxide groupings of IIB and VIB respectively, although they could also be formed directly by preliminary reduction of the nitro group of I and VII to an amino group, followed by ring closure by addition to the nitrile group. The formation of 2-amino-3-cyanoquinoline from *o*-aminobenzaldehyde and malononitrile, and of 2-aminoquinoline-3-carboxamide from *o*-aminobenzaldehyde and cyanoacetamide (see Experimental) are examples of the latter reaction. Similar ring closures resulting from the addition of $—NH_2$ or —NHOH to $—C{\equiv}N$ are well known (8–17) and the formation of IIB and VIB thus parallels the analogous reductive cyclizations with hydrogen and palladium of *o*-nitrobenzalphenylacetonitrile and ethyl *o*-nitrobenzalcyanoacetate to 2-amino-3-phenylquinoline-N-oxide and ethyl 2-aminoquinoline-3-carboxylate-N-oxide respectively (18).

TABLE I

FORMER STRUCTURE	REVISED STRUCTURE
α-Cyano-α-carboxamido-N-hydroxydihydroindole (IIA)	2-Aminoquinoline-3-carboxamide-1-oxide (IIB)
α-Cyano-α-carboxamidodihydroindole (IIIA)	2-Aminoquinoline-3-carboxamide (IIIB)
α-Cyano-α-carboxydihydroindole (IVA)	2-Aminoquinoline-3-carboxylic acid (IVB)
α-Cyano-α-carboxy-N-hydroxydihydroindole (VIA)	2-Aminoquinoline-3-carboxylic acid-1-oxide (VIB)
α-Cyano-α-carboxybenzamido-N-hydroxydihydroindole (VIIIA)	2-Benzoylaminoquinoline-3-carboxamide-1-oxide (VIIIB)
α-Cyano-N-hydroxydihydroindole-2,3-(8-hydroxy-10-phenyl-9-azole) (3,4-Dihydroxy-1-phenyl-11-cyano-4,11-dihydropyrrolo[3,4-*b*]indole) (IXA)	2-Phenyl-4-hydroxypyrimido[4,5-*b*] quinoline-10-oxide (IXB)
α-Cyano-N-hydroxydihydroindole-2,3-(8-hydroxy-10-methyl-9-azole) (3,4-Dihydroxy-1-methyl-11-cyano-4,11-dihydropyrrolo[3,4-*b*]indole) (XA)	2-Methyl-4-hydroxypyrimido[4,5-*b*]quinoline-10-oxide (XB)
Compound $C_{10}H_{13}N_3O_2$	1-Hydroxy-2-amino-3-carboxamido-1,2,3,4-tetrahydroquinoline (XI)

EXPERIMENTAL[1]

2-Amino-3-cyanoquinoline. A mixture of 5.64 g. (0.047 mole) of *o*-aminobenzaldehyde and 3.1 g. (0.047 mole) of freshly-distilled malononitrile in 50 ml. of 95% ethanol was treated with a few drops of pyridine and the reaction mixture was heated under reflux for eight hours. Evaporation of the reaction mixture to half of its original volume and cooling caused the separation of a yellow solid (5.45 g., 76%). The product was purified either by sublimation or by recrystallization from ethanol, m.p. 228.5–230°.

Anal. Calc'd for $C_{10}H_7N_3$: C, 71.0; H, 4.2; N, 24.8.

Found: C, 71.3; H, 4.1; N, 24.9.

2-Aminoquinoline-3-carboxamide (IIIB). (*a*). A mixture of 1.0 g. of 2-amino-3-cyanoquinoline, 20 ml. of absolute ethanol, 0.42 g. of potassium hydroxide, and 20 ml. of 30% hydrogen peroxide was placed in a 500-ml. 3-necked flask equipped with a mechanical stirrer and was heated at 60–70° for one-half hour with continual stirring. At the end of this time, the initial fuming had subsided and an additional 5 ml. of 30% hydrogen peroxide was added. After one-half hour of additional heating and stirring, the reaction mixture was cooled to 0° and the yellow solid which separated was collected (0.79 g., 72%) and recrystallized from water, m.p. 240–242°.

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[1] All melting points are corrected. The microanalyses were performed by Mrs. Katherine Pih, Mrs. Esther Fett, and Mr. Joseph Nemeth. The infrared absorption spectra were determined by Miss Helen Miklas.

Anal. Calc'd for $C_{10}H_9N_3O$: C, 64.2; H, 4.8; N, 22.5.
Found: C, 64.3; H, 5.1; N, 22.7.

(*b*). To a solution of sodium ethoxide prepared by dissolving 0.72 g. of sodium in 50 ml. of absolute ethanol was added 2.1 g. (0.025 mole) of cyanoacetamide followed by 3.03 g. (0.025 mole) of *o*-aminobenzaldehyde, and the reaction mixture was heated under reflux on a water bath for 20 minutes. Cooling caused the separation of 3.19 g. of 2-aminoquinoline-3-carboxamide, m.p. 240–241°, while dilution of the filtrate precipitated an additional 0.28 g. of amide, m.p. 234–236° (total yield 3.47 g., 74%). The product was recrystallized from water, m.p. 240.5–242°.

(*c*). A mixture of 1.5 g. of 2-aminoquinoline-3-carboxamide-1-oxide (1) (IIA), 30 ml. of glacial acetic acid, 3 ml. of water, and 1 g. of zinc (20 mesh) was heated under reflux for three hours. After cooling, the reaction mixture was filtered and the filtrate was diluted with an equal volume of water. After allowing the solution to stand for several hours, a small amount of unreacted 2-aminoquinoline-3-carboxamide-1-oxide was filtered off and the filtrate was brought to *p*H 6 with concentrated ammonium hydroxide. Cooling the neutralized filtrate at 0° overnight caused the separation of a yellow solid which was first purified by digesting with glacial acetic acid to form the insoluble acetate salt, followed by neutralization of a hot, aqueous solution of the salt by the cautious addition of dilute sodium carbonate solution, and finally by recrystallization from water, m.p. 238.5–240.5°.

The products obtained by methods (*a*), (*b*), and (*c*) above were identical as shown by a comparison of their infrared spectra and by a determination of mixture melting points, and were also identical with a sample of "α-cyano-α-carboxamidodihydroindole" (IIIA) prepared by the method of Heller and Wunderlich (1).

2-Aminoquinoline-3-carboxylic acid (IVB). (*a*) A mixture of 1.4 g. of 2,4-dihydroxypyrimido[4,5-*b*]quinoline (2,4-dihydroxy-1,3-diazaacridine), prepared by the condensation of *o*-aminobenzaldehyde with barbituric acid (6), and 50 ml. of concentrated ammonium hydroxide was heated in a sealed steel bomb at 180° for 12½ hours. Evaporation of the cooled reaction mixture under reduced pressure gave a tan residue (1.0 g., m.p. 290–291°, 82% yield) which was recrystallized from water, m.p. 320–320.5°.

Anal. Calc'd for $C_{10}H_8N_2O_2$: C, 63.8; H, 4.3; N, 14.9.
Found: C, 63.9; H, 4.5; N, 15.2.

(*b*). A mixture of 1.32 g. of 2-aminoquinoline-3-carboxamide (IIIB) and 50 ml. of concentrated ammonium hydroxide was heated in a sealed steel bomb at 180° for four hours. Filtration of the cooled reaction mixture removed 0.12 g. of unreacted IIIB. Partial evaporation of the filtrate under reduced pressure caused the separation of a small amount of product; acidification of the filtrate precipitated the remainder of the product to give a total yield of 1.02 g. (76.8%). Repeated recrystallization from water gave a crystalline pale yellow solid melting at 324–325°.

(*c*). 2-Aminoquinoline-3-carboxylic acid was also prepared by the method of Koller and Strang (7) from quinoline-2,3-dicarboxylic acid.

The products obtained by methods (*a*), (*b*), and (*c*) above were identical, as shown by a comparison of their infrared spectra and by a determination of mixture melting points, and were also identical with a sample of "α-cyano-α-carboxydihydroindole" (IVA) prepared by the method of Heller and Wunderlich (1).

SUMMARY

Compounds previously reported to be derivatives of α-cyano-α-carboxydihydroindole have been shown instead to be derivatives of 2-aminoquinoline-3-carboxylic acid.

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