A NEW SYNTHETIC APPROACH TO THE BENZO[*c*]PHENANTHRIDINE SYSTEM: INTERNUCLEAR CYCLIZATION ONTO A PYRIDINE RING

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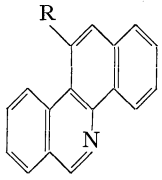
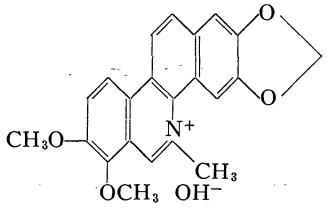
ABSTRACT

Benzo[*c*]phenanthridine has been synthesized in low overall yield by the Pschorr cyclization of *trans*-α-(4-isoquinolyl)-*o*-aminocinnamic acid. The condensation of 4-isoquinolylacetonitrile with *o*-nitrobenzaldehyde gave the *cis*-cinnamonitrile. The preparation of a number of intermediates is described.

The benzo[*c*]phenanthridine ring system (I) is found in a number of alkaloids such as chelidonine, chelerythrine, and sanguinarine (1). A number of these and their derivatives have been synthesized (2–4) starting from an alicyclic system, the nitrogen-containing ring being built up in the course of the synthesis. Current interest in chelerythrine (III) stems from its synergistic effect in enhancing the cancer chemotherapeutic action of colchicinamide (5). It was decided to develop a more flexible synthesis of the ring system which would permit the introduction of various substituents into the nucleus, and to use the Pschorr cyclization to achieve this end.

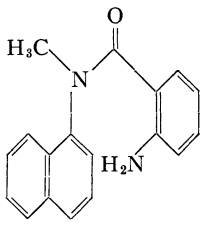


I, R = H
II, R = CO_2H

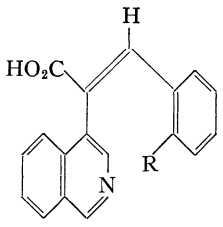


III

There have been a number of attempts made to apply a Pschorr type of ring closure to the synthesis of this ring system (6–8) but these failed in each case. The diazotization and subsequent decomposition of 2-amino-*N*-methylbenzo-1′-naphthalide (IV) was studied in detail by Hey and Turpin (9). No benzophenanthridone was formed, the only identifiable product being benzo-1-naphthalide, which results from the demethylation and deamination of IV. In the present work the cyclization of *trans*-α-(4-isoquinolyl)-*o*-aminocinnamic acid (V) to II, which would involve an internuclear attack onto a pyridine ring, has been studied.



IV



V, R = NH_2
VI, R = NO_2

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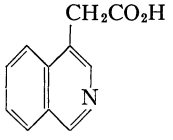
It had been suggested (10) that the pyridine ring is more difficult to attack than a benzene ring in such reactions, a conclusion based on the fact that poor yields had been obtained in two examples studied (11, 12). It was shown, however, that under suitable conditions excellent yields of cyclized products resulting from attack onto a pyridine ring may be obtained (13). Another example of such a cyclization has been reported more recently (14). There seemed, therefore, to be no reason to suppose that the cyclization of V would not take place, provided the necessary amine having the right geometry could be prepared.

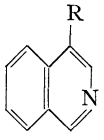
The route chosen initially for the preparation of V was the straightforward one involving the Perkin condensation of *o*-nitrobenzaldehyde with 4-isoquinolylacetic acid (VII) (15). Various attempts were made to prepare VII or its ethyl ester or anilide via an Arndt-Eistert homologation of isoquinoline-4-carboxylic acid. Though an acid chloride hydrochloride could be readily obtained from the latter and treatment of this with an excess of diazomethane gave a yellow crude diazoketone in no case could any of the required rearrangement products be obtained. This may be due to the fact that the acid chloride hydrochloride is insoluble in ether and is used in the form of a suspension. It could have been, then, that a coating of diazoketone was formed which prevented further reaction with the diazomethane. On the other hand, the infrared spectrum of the solid yellow product exhibited bands characteristic of a diazo group (2115 cm^{-1}) but not of the starting acid chloride hydrochloride. In any event, this route to the acetic acid had to be abandoned. An attempt was made to condense 4-bromoisoquinoline or its *N*-oxide with diethyl sodiomalonate under a variety of conditions: in no case did any reaction take place.

4-Isoquinolyl methyl ketone (VIII) could be prepared (in 20% yield) in one step from 4-aminoisoquinoline using the Beech reaction (16). This is a more convenient procedure than that which requires the preparation of the β-ketoester from ethyl isoquinoline 4-carboxylate followed by ketonic hydrolysis (17): the overall yields are of the same order of magnitude but many more steps are required in the latter procedure. When the methyl ketone (VIII) was subjected to a Willgerodt reaction only a low yield (9%) of ethyl 4-isoquinolylacetate was obtained. Other approaches were therefore investigated. Ethyl isoquinoline 4-carboxylate was reduced to the alcohol (IX) with lithium aluminum hydride and the latter oxidized to the corresponding aldehyde (X) with manganese dioxide in benzene. Various attempts were made to condense X with *o*-nitrophenylacetic acid but without success. Though condensation with oxindole took place no pure product could be obtained. A very low yield of 5-(4′-isoquinolylidene)-2-phenyloxazolone was obtained from the reaction of X with hippuric acid, so that this route was also not pursued further.

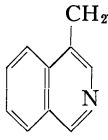
4-Isoquinolylmethanol (IX) was converted into its hydrochloride, which, with thionyl chloride, gave 4-chloromethylisoquinoline hydrochloride. The latter gave moderate yields of 4-isoquinolylacetonitrile (XI) when treated with sodium cyanide in either aqueous ethanol (18) or dimethyl sulphoxide (19). The moderate to low yields are probably due to a certain amount of polymerization of the free 4-chloromethylisoquinoline formed



VII

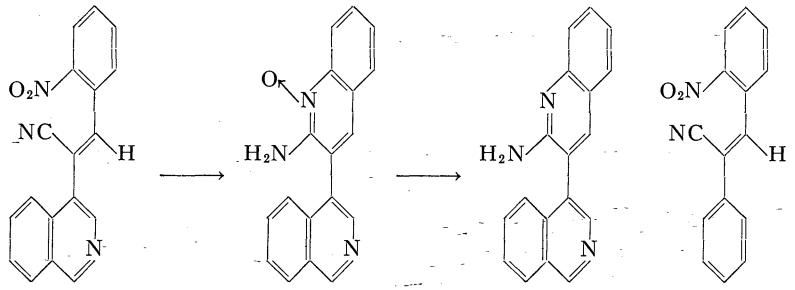


VIII, R = CO—CH_3
IX, R = CH_2OH
X, R = CHO



XI

when its hydrochloride reacted with the basic sodium cyanide. The yields reported for the analogous synthesis of 3-pyridylacetonitrile are also not high (18, 20). The condensation of 4-isoquinolylacetonitrile with *o*-nitrobenzaldehyde in acetic anhydride in the presence of triethylamine gave the α-(4-isoquinolyl)-*o*-nitrocinnamonitrile, of unknown geometry, in good yield. Catalytic reduction of this led to absorption of two molar equivalents of hydrogen and the formation of a product, $C_{18}H_{13}N_3O$, m.p. 261°, in quantitative yield. The same substance was obtained when the cinnamonitrile was reduced with hydrazine and Raney nickel. This product was soluble in acid but not in base; it effervesced on attempted diazotization and the resulting solution did not give a coupling product with alkaline β-naphthol. It was unaffected by prolonged boiling with acid or with base. The absence of a cyano group was confirmed by the fact that no band was present in the infrared at about 2200 cm^{-1}; the bands observed at 3350 and 1625 cm^{-1} were attributed to N—H and C=N groups respectively. The reduction product gave a positive test for *N*-oxides (21), and on further reduction with stannous chloride in acetic acid saturated with hydrogen chloride, or on heating with ferrous oxalate (22), gave a primary amine, $C_{18}H_{13}N_3$, m.p. 253° (positive carbylamine test). The cinnamonitrile has, therefore, the undesired cis configuration (XII) and, on reduction, gives the amine oxide (XIII). Deoxygenation of this gives 2-amino-3-(4′-isoquinolyl)quinoline (XIV). That diazotization of the 2-amino group does not take place normally is now understandable. This sequence of reactions is not exceptional since Pschorr and Wolfe (23) found that reduction of the product (XV) of condensation of phenylacetonitrile and *o*-nitrobenzaldehyde gave



XII XIII XIV XV

2-amino-3-phenylquinoline; XV must thus also have the cis configuration. An attempt was made to isomerize XII to the trans form by irradiating its benzene solution in a quartz vessel with ultraviolet light. No isomerization appeared to take place.

The most convenient method for the conversion of the nitrile (XI) to the required acid (VII) was to hydrolyze XI to the amide, which, on treatment with nitrous acid, gave VII in good yield. Lower yields were obtained by ethanolysis or complete hydrolysis of XI. Condensation of VII with *o*-nitrobenzaldehyde gave the expected *trans*-cinnamic acid (VI), which was reduced to the amine (V) with ferrous sulphate and ammonia. Diazotization and cyclization in the presence of copper powder gave the expected benzo[*c*]phenanthridine-11-carboxylic acid (II) in 50% yield. The crude acid was readily decarboxylated to benzo[*c*]phenanthridine. The overall yield of I from 4-bromoisoquinoline was of the order of 1%, though the individual steps gave yields of at least 50%. Had the Arndt-Eistert reaction given the required acid this synthetic sequence would have been rendered much more attractive. The method should still be useful for the synthesis of substituted benzo[*c*]phenanthridines which may not be readily available using the Bailey–Robinson approach.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Model 21 spectrophotometer using sodium chloride optics. The main peaks only are reported. Unless otherwise specified, light petroleum refers to the fraction boiling between 36° and 48°, which was purified by stirring with concentrated sulphuric acid followed by distillation.

Attempted Arndt-Eistert Reactions

Isoquinoline 4-carboxylic acid (24) (3 g) was dissolved in warm ethanol (50 ml) and hydrogen chloride bubbled through the solution for 1 hour. The hydrochloride (3.6 g), m.p. 310°, was filtered, washed with absolute ethanol, dried, and boiled under reflux with thionyl chloride (12 ml) for 1½ hours. Benzene (30 ml) was added to the reaction mixture to precipitate isoquinoline 4-carboxylic acid chloride hydrochloride (3.8 g), m.p. > 310°. The solid was washed with dry benzene and dried. Infrared spectrum (KBr disk): 1745 (s), 1710 (s), 1580 (m), 1360 (m), 1225 (m), 1055 (m), 790 (w), 777 (w), and 745 cm^{-1} (m).

The acid chloride hydrochloride (1 g) was suspended in anhydrous ether (50 ml) and the suspension gradually added, with vigorous stirring, to a solution of diazomethane (from 4 g of *N*-nitroso-*N*-methylurea) in ether (50 ml) cooled to 5°. Nitrogen was evolved and initially some of the acid chloride dissolved, but most of the added solid turned yellow. The mixture was stirred for a further hour, the ether evaporated, and the yellow diazoketone used directly in the next step. Infrared spectrum (KBr disk): 2990 (m), 2115 (m), 1730 (m), 1685 (s), 1618 (s), 1465 (s), 1125 (m), 877 (m), and 760 cm^{-1} (m). The above diazoketone in ethanol (60 ml) was stirred and treated with a slurry of silver oxide (from 600 mg of silver nitrate) in ethanol (30 ml). The mixture was stirred at 60–70° for 4 hours, and then boiled under reflux for 1 hour. A silver mirror formed on the walls of the flask and the solution turned brown. The solvent was filtered and evaporated and the brown amorphous residue (0.50 g) extracted with benzene (0.15 g was insoluble). The solution was chromatographed on a column of alumina (30 g) but no pure product could be isolated. Similar intractable amorphous solids were obtained when, for instance, aqueous dioxane containing aniline was used to decompose the diazoketone.

4-Bromoisoquinoline 2-Oxide

A solution of 4-bromoisoquinoline (5 g) in acetic acid (10 ml) containing hydrogen peroxide (30%, 3 ml) was heated at 60–70° for 4 hours, a further amount of hydrogen peroxide (3 ml) was added, and heating continued for another 15 hours. The solution was evaporated under vacuum and the residue dissolved in chloroform (10 ml) and boiled under reflux with an excess of solid sodium carbonate for 30 minutes. The suspension was filtered, the solid washed with chloroform, and the combined filtrates evaporated to dryness. Ethyl acetate (0.5 ml) was added; when the sides of the flask were scratched with a glass rod nearly white crystals of *4-bromoisoquinoline 2-oxide* (0.5 g) separated which, after recrystallization from ethanol, had m.p. 182–183°. (Calc. for C_9H_6NOBr: C, 48.22; H, 2.68. Found: C, 48.47; H, 2.63.) Infrared spectrum (Nujol mull): 1597 (m), 1470 (m), 1355 (s), 1177 (s), 1130 (s), 765 (m), and 755 cm^{-1} (m). Evaporation of the ethyl acetate mother liquor gave 4-bromoisoquinoline (4.5 g) as a pale yellow oil which crystallized on standing and had m.p. 38–39°.

4-Isoquinolyl Methyl Ketone

Ice (6 g) was added with stirring to a solution of 4-aminoisoquinoline (2 g) in concentrated hydrochloric acid (4.5 ml) and water (4 ml) at 0–5°. To this was slowly added a solution of sodium nitrite (1 g) in water (2 ml) and the resulting deep red suspension neutralized to Congo red by the addition of sodium acetate (2 g) in water (3 ml). The diazonium salt solution was slowly introduced under the surface of a cold (10–15°) solution of acetaldoxime (1.3 g), copper sulphate (0.7 g), and sodium sulphite (0.055 g) in water (10 ml), with stirring. A solution of sodium acetate (9 g) in water (10 ml) was added and stirring was continued at room temperature for 1 hour, during which time nitrogen was evolved. The resulting suspension was acidified with enough hydrochloric acid to dissolve all the solid material. The red solution was boiled under reflux for 3 hours, cooled, basified with aqueous ammonia, and extracted with ether. The dried (Na_2SO_4) ether extract was evaporated and the brown tarry residue (0.88 g) dissolved in benzene and chromatographed on a column of alumina (60 g). Elution with benzene gave 4-isoquinolyl methyl ketone (0.40 g), m.p. 70–72°. Padbury and Lindwall (17) give m.p. 70–71° for this ketone.

Ethyl 4-Isoquinolylacetate (by the Willgerodt Reaction)

4-Isoquinolyl methyl ketone (0.189 g), sulphur (0.035 g), and morpholine (0.415 g) were boiled under reflux for 15 hours. Ethanolic sodium hydroxide (5%) (2 ml) was added to the black solution, which was boiled under reflux for a further 73 hours. The reaction mixture was poured into water (5 ml), the solution evaporated to about one third of its original volume under reduced pressure, water (5 ml) added, the solution saturated with salt and extracted with ether. The aqueous layer was taken almost to dryness, the dark oil remaining was treated with hydrochloric acid, and the mixture evaporated to dryness. The resulting light brown solid was warmed with absolute ethanol, filtered from any sodium chloride, and the filtrate poured into ether. A light brown flocculent precipitate which separated was filtered and dissolved in absolute ethanol

saturated with dry hydrogen chloride, and the solution boiled under reflux overnight. It was poured into a saturated aqueous solution of sodium chloride, the solution basified with ammonia and extracted with ether. The dried (Na_2SO_4) ether extract was evaporated to give a brown gum which was sublimed at 100° at 15 mm. Colorless needles (0.020 g), m.p. 60–62°, of *ethyl 4-isoquinolylacetate* were obtained which, on recrystallization from light petroleum, had m.p. 62.5°. (Calc. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09. Found: C, 72.33; H, 6.34.) Infrared spectrum (film): 1725 (s), 1627 (m), 1512 (m), 1299 (m), 1205 (s), 1115 (m), 800 (w), and 765 cm^{-1} (m).

4-Isoquinolylmethanol

Ethyl 4-isoquinoline carboxylate (7.9 g) in anhydrous ether (125 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (1.9 g) in dry ether (250 ml) at 0°. The mixture was stirred for 1 hour and water (40 ml) added carefully. Carbon dioxide was bubbled through the mixture for 10 minutes, the ether layer removed, and the pasty aqueous phase washed with ether (5×100 ml). The combined ether layers were dried (Na_2SO_4) and evaporated to give an oil (5.6 g) which, on trituration with a small amount of ether, gave *4-isoquinolylmethanol* (4.3 g). Recrystallization from ether gave colorless crystals, m.p. 93–94°. (Calc. for $C_{10}H_9NO$: C, 75.45; H, 5.70. Found: C, 75.38; H, 5.84.) Infrared spectrum (Nujol mull): 3170 (s) (br), 1640 (m), 1475 (m), 1100 (s), 785 (w), and 755 cm^{-1} (m).

4-Formylisoquinoline

A solution of 4-isoquinolylmethanol (0.46 g) in benzene (100 ml) was shaken with activated manganese dioxide (1 g) (25) for 16 hours at room temperature, the mixture filtered and evaporated to dryness to give the aldehyde (0.40 g) as a white solid, m.p. 103.5–104.5°. (Calc. for $C_{10}H_7NO$: C, 76.42; H, 4.49. Found: C, 76.59; H, 4.69.) Angyal, Penman, and Warwick report m.p. 103° for 4-formylisoquinoline (26).

5-(4'-Isoquinolylidene)-2-phenyloxazolone

4-Formylisoquinoline (0.052 g), hippuric acid (0.060 g), fused sodium acetate (0.025 g), and acetic anhydride (0.153 g) were heated together at 140–145° for 15 minutes. Water (10 ml) was added to the hot melt, the brown solid was filtered and recrystallized from benzene to give the *azlactone* (0.009 g) as green hair-like crystals, m.p. 251–252°. (Calc. for $C_{19}H_{12}N_2O_2$: C, 75.99; H, 4.03. Found: C, 76.33; H, 4.60.)

4-Chloromethylisoquinoline Hydrochloride

4-Isoquinolylmethanol (4.3 g) in benzene (70 ml) was treated with dry hydrogen chloride gas and the solid hydrochloride which precipitated (4.63 g) was filtered, washed with benzene, and dried. It was then boiled under reflux with thionyl chloride (13 ml) for 1 hour. Benzene (35 ml) was added to the cold mixture and the white solid which precipitated was filtered, washed with benzene, and dried to give *4-chloromethylisoquinoline hydrochloride* (4.76 g), m.p. 225° (decomp.). (Calc. for $C_{10}H_8NCl,HCl$: C, 56.10; H, 4.25. Found: C, 56.18; H, 3.89.) Infrared spectrum (KBr disk): 2310 (s) (br), 2070 (s), 1645 (m), 1615 (m), 1375 (m), 1240 (m), 865 (m), 785 (s), and 755 cm^{-1} (m).

4-Isoquinolylacetonitrile

(i) Using aqueous ethanol as solvent.—4-Chloromethylisoquinoline hydrochloride (4.3 g) in 50% aqueous ethanol (30 ml) was added dropwise to a stirred, boiling solution of sodium cyanide (7 g) in water (12 ml) and ethanol (80 ml) over a period of 30 minutes. The resulting brown mixture was stirred and boiled under reflux for a further 40 minutes, evaporated to dryness under reduced pressure, and the black oily residue extracted with ether (6×70 ml). The dried (Na_2SO_4) ether extract was evaporated and the residual brown oil (3 g), which partially crystallized on cooling, was dissolved in benzene and chromatographed on a column of alumina (200 g). A mixture of benzene – light petroleum (2:1 v/v) eluted *4-isoquinolylacetonitrile* (1.45 g), m.p. 108–110°, which, on recrystallization from benzene – light petroleum (b.p. 60–80°), had m.p. 109–110°. (Calc. for $C_{11}H_8N_2$: C, 78.55; H, 4.79. Found: C, 78.54; H, 4.87.) Infrared spectrum (KBr disk): 2250 (w), 1625 (m), 1592 (m), 1391 (s), 870 (m), 780 (m), and 741 cm^{-1} (s).

(ii) Using dimethyl sulphoxide as solvent.—A suspension of 4-chloromethylisoquinoline hydrochloride (12 g) in dimethyl sulphoxide (110 ml) was added over 30 minutes to a stirred solution of sodium cyanide (6.2 g) in dimethyl sulphoxide (50 ml) at room temperature. The solution was stirred for 2½ hours, poured into water (1 l.), and the suspension extracted with ether (5×100 ml). The combined ether extracts were washed with water (3×100 ml), dried (Na_2SO_4), and evaporated to give a brown oil (8.9 g) which crystallized partly on standing. A small amount of ether was added, and the crystals of the nitrile (4.7 g), m.p. 107–109°, thus obtained were filtered and washed with a little ether.

cis-α-(4-Isoquinolyl)-o-nitrocinnamonitrile

4-Isoquinolylacetonitrile (1 g) and *o*-nitrobenzaldehyde (0.92 g) in acetic anhydride (12 ml) containing triethylamine (1.5 ml) were heated on a steam bath overnight and the reaction mixture cooled, when the *cis-cinnamonitrile* separated. Ether (1 ml) was added to the mixture and the solid (1.6 g) filtered, washed with a small amount of ether, and recrystallized from ethanol to give the pure product, m.p. 177–178°. (Calc. for $C_{18}H_{11}N_3O_2$: C, 71.75; H, 3.68. Found: C, 71.50; H, 3.78.) Infrared spectrum (KBr disk): 2220 (w), 1623 (w), 1570 (w), 1515 (s), 1355 (s), 907 (w), 850 (w), 780 (m), 755 (m), and 720 cm^{-1} (m).

2-Amino-3-(4'-isoquinolyl)quinoline 1-Oxide

cis-α-(4-Isoquinolyl)-*o*-nitrocinnamonitrile (0.20 g) in ethyl acetate (70 ml) was hydrogenated at room temperature and pressure over 10% palladium–charcoal (0.05 g) for 24 hours. Two equivalents of hydrogen were absorbed. The deep yellow solution was filtered and evaporated to give *2-amino-3-(4'-isoquinolyl)-quinoline 1-oxide* (0.185 g), m.p. 248–250° (decomp.), which, after recrystallization from acetone, had m.p. 260–261°. (Calc. for $C_{18}H_{13}N_3O$: C, 75.24; H, 4.56; N, 14.63. Found: C, 75.25, 75.20; H, 4.68, 4.56; N, 14.37.) Infrared spectrum (KBr disk): 3300 (s) (br), 1625 (s), 1590 (m), 1395 (m), 1360 (m), 753 (m), and 743 cm^{-1} (m).

2-Amino-3-(4'-isoquinolyl)quinoline

(i) 2-Amino-3-(4'-isoquinolyl)quinoline 1-oxide (0.10 g) was treated with a solution of stannous chloride in acetic acid saturated with dry hydrogen chloride (27) (2 ml) and the resulting solution boiled under reflux for 18 hours. Water (10 ml) was then added, the solution made alkaline with 40% aqueous potassium hydroxide and extracted with chloroform (3×15 ml), and the extracts dried (Na_2SO_4) and evaporated to give a waxy solid (0.085 g). Recrystallization from ethanol afforded the *amine* (0.055 g), m.p. 252–253.5°, as pale yellow crystals. (Calc. for $C_{18}H_{13}N_3$: C, 79.68; H, 4.83. Found: C, 79.28; H, 5.12.) Infrared spectrum (KBr disk): 3350 (s) (br), 1647 (s), 1613 (m), 1435 (s), 757 (s), and 745 cm^{-1} (s).

(ii) The *N*-oxide (0.10 g), ferrous oxalate dihydrate (0.11 g), and granulated lead (2 g) were mixed and heated at 330° for 20 minutes under air condenser to give 2-amino-3-(4'-isoquinolyl)quinoline (0.009 g), m.p. 250–253°, undepressed on admixture with a sample obtained as above.

Ethyl 4-Isoquinolylacetate (from the Nitrile)

4-Isoquinolylacetonitrile (0.10 g) was dissolved in a mixture of anhydrous ethanol (0.7 ml) and concentrated sulphuric acid (0.7 ml) and the solution boiled under reflux for 3 hours. The resulting dark brown solution was poured into ice and water, made alkaline by the careful addition of ammonia, and the precipitated ester (0.070 g), m.p. 62–64°, filtered. The melting point was undepressed on admixture with a sample prepared by the Willgerodt reaction, and the infrared spectra of the compounds were identical.

4-Isoquinolylacetamide

4-Isoquinolylacetonitrile (0.50 g) was dissolved in concentrated sulphuric acid (3 ml) and the solution kept at room temperature for 17 hours, poured into water, and made just basic with 20% aqueous sodium hydroxide solution. The solid (0.475 g), m.p. 219–220°, which precipitated was recrystallized from water to give *4-isoquinolylacetamide* as fine white needles, m.p. 232–232.5°. (Calc. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41. Found: C, 70.75; H, 5.42.) Infrared spectrum (KBr disk): 3470 (s), 1628 (m), 1400 (m), 1256 (m), 790 (m), and 758 cm^{-1} (m).

4-Isoquinolylacetic Acid Hydrochloride

The amide (0.31 g) in 6 *N* hydrochloric acid (10 ml) was treated with a large excess of sodium nitrite in water and the solution kept at room temperature overnight, when *4-isoquinolylacetic acid hydrochloride* (0.32 g) separated as colorless rods. These were recrystallized from absolute ethanol and had m.p. 241–243° (decomp.). (Calc. for $C_{11}H_9NO_2,HCl$: C, 59.06; H, 4.47. Found: C, 59.09; H, 4.71.) Infrared spectrum (KBr disk): 3000 (s) (br), 2680 (s) (br), 2020 (w), 1723 (s), 1650 (m), 1378 (s), 1175 (s), and 788 cm^{-1} (s).

trans-α-*(4-Isoquinolyl)-o-nitrocinnamic Acid*

4-Isoquinolylacetic acid hydrochloride (1.41 g) and *o*-nitrobenzaldehyde (0.97 g) were boiled under reflux with acetic anhydride (16 ml) containing triethylamine (14 ml) and anhydrous sodium acetate (0.4 g) for 35 minutes. The mixture was poured into water (80 ml), heated, and filtered to remove some tarry material and the filtrate kept in the refrigerator overnight, when *trans*-α-*(4-isoquinolyl)-o-nitrocinnamic acid* (1.14 g) separated as orange-yellow crystals. Recrystallization from methanol gave the pure acid, m.p. 246–247°. (Calc. for $C_{18}H_{12}N_2O_4$: C, 67.50; H, 3.78. Found: C, 67.78; H, 3.98.) Infrared spectrum (KBr disk): 3400 (m) (br), 2400 (w) (br), 1700 (m), 1526 (s), 1316 (s), 1295 (m), 785 (m), and 752 cm^{-1} (m).

trans-α-*(4-Isoquinolyl)-o-aminocinnamic Acid*

trans-α-(4-Isoquinolyl)-*o*-nitrocinnamic acid (1 g) was dissolved in hot aqueous ammonia and the solution added to a rapidly stirred and boiling solution of ferrous sulphate (6 g) in water (17 ml). The reaction mixture was stirred for a further 10 minutes while ammonia was added to it to maintain it basic. It was then filtered, neutralized with acetic acid, and kept in the refrigerator for 3 hours, when the *amino acid* (0.40 g) separated as a yellow solid. This was recrystallized from ethanol and had m.p. 279–281° (decomp.). (Calc. for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86. Found: C, 74.02; H, 5.03.) Infrared spectrum (Nujol mull): 2400 (w) (br), 1685 (m), 1620 (m), 1460 (s), 1378 (m), 1256 (s), and 751 cm^{-1} (m).

Benzo[c]phenanthridine

trans-α-(4-Isoquinolyl)-*o*-aminocinnamic acid (0.250 g) in 5% hydrochloric acid (10 ml) was diazotized with a solution of sodium nitrite (0.070 g) in water (5 ml), the temperature being kept below 1°. The excess nitrous acid was decomposed by the addition of urea, and Gattermann copper powder (0.25 g) added to the mixture, which was stirred at room temperature for 5 hours. The mixture was made just acid with acetic

acid, filtered, and the solid extracted with methanol in a Soxhlet extractor for 15 hours. The methanol solution was evaporated to dryness and the brown solid residue washed with a little cold methanol to give what is presumed to be benzo[c]phenanthridine-11-carboxylic acid (0.120 g), m.p. 270–272° (decomp.), as a nearly white solid. Several attempts to recrystallize this solid to obtain an analysis specimen were unsuccessful. Infrared spectrum (KBr disk): 3400 (s) (br), 1700 (s), 1620 (s), 1450 (m), 1285 (s), 1230 (s), 760 (s), and 730 cm^{-1} (m).

The acid (0.050 g) was dissolved in purified quinoline (5 drops), copper powder (0.010 g) was added, and the suspension was heated under reflux (metal bath). After the initial vigorous evolution of gas had subsided heating was continued for a further 10 minutes, water (1.5 ml) was added, and the quinoline removed by steam distillation. The residue was extracted with ether, the ether dried (Na_2SO_4) and evaporated to give a brown oil (0.033 g) which solidified on cooling. This was chromatographed through a column of alumina (7 g); elution with benzene – light petroleum (1:3 v/v) gave benzo[c]phenanthridine (0.020 g), m.p. 135–135.5° (after recrystallization from aqueous ethanol). (Calc. for $C_{17}H_{11}N$: C, 89.05; H, 4.84. Found: C, 89.02; H, 5.09.) λ_{max} 265, 312, 343, 361 mμ; $10^{-3} \times \epsilon$ 80.5, 8.75, 5.60, 6.72 (in $CHCl_3$). Infrared spectrum (KBr disk): 1625 (m), 1270 (m), 824 (m), 798 (s), 760 (s), and 681 cm^{-1} (s). Whaley and Meadow (28) give m.p. 135° for benzo[c]phenanthridine.

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REFERENCES

1. R. H. F. Manske and H. L. Holmes. The Alkaloids. Vol. IV. Academic Press Inc., New York. 1954. p. 253; Vol. VII. 1960. p. 430.
2. A. S. Bailey, R. Robinson, and R. S. Staunton. J. Chem. Soc. 2277 (1950). A. S. Bailey and C. R. Worthing. J. Chem. Soc. 4535 (1956).
3. K. W. Gopinath, T. R. Govindachari, P. C. Parthasarathy, and N. Viswanathan. J. Chem. Soc. 4012 (1959). K. W. Gopinath, T. R. Govindachari, and N. Viswanathan. Tetrahedron, **14**, 322 (1961).
4. H. R. Arthur and Y. L. Ng. J. Chem. Soc. 4010 (1959).
5. A. L. Bluhm. Dissertation Abstr. **20**, 880 (1959).
6. T. Richardson, R. Robinson, and E. Seijo. J. Chem. Soc. 835 (1937).
7. C. R. Noller, R. O. Denyes, J. W. Gates, and W. L. Wasley. J. Am. Chem. Soc. **59**, 2079 (1937).
8. H. S. Forrest, R. D. Haworth, A. R. Pinder, and T. S. Stevens. J. Chem. Soc. 1311 (1949).
9. D. H. Hey and D. G. Turpin. J. Chem. Soc. 2471 (1954).
10. H. Plieninger and M. Schach von Wittenau. Ber. **91**, 1905 (1958).
11. D. H. Hey and J. M. Osbond. J. Chem. Soc. 3164 (1949).
12. R. A. Abramovitch, D. H. Hey, and R. D. Mulley. J. Chem. Soc. 4263 (1954).
13. R. A. Abramovitch. Can. J. Chem. **38**, 2273 (1960).
14. W. Hertz and D. R. K. Murty. J. Org. Chem. **26**, 418 (1961).
15. P. H. Leake. Chem. Rev. **56**, 27 (1956).
16. W. F. Beech. J. Chem. Soc. 1297 (1954).
17. J. J. Padbury and H. G. Lindwall. J. Am. Chem. Soc. **67**, 1268 (1945). C. F. Koelsch. J. Org. Chem. **10**, 34 (1945).
18. S. Okuda and M. M. Robison. J. Am. Chem. Soc. **81**, 742 (1959).
19. L. Friedman and H. Schechter. J. Org. Chem. **25**, 877 (1960).
20. H. S. Mosher and J. E. Tossieri. J. Am. Chem. Soc. **73**, 4925 (1951).
21. N. A. Coates and A. R. Katritzky. J. Org. Chem. **24**, 1836 (1959).
22. R. A. Abramovitch and K. A. H. Adams. Can. J. Chem. **39**, 2516 (1961).
23. R. Pschorr and H. Wolfe. Ber. **32**, 3402 (1899).
24. F. W. Bergstrom and J. H. Rodda. J. Am. Chem. Soc. **62**, 3030 (1940).
25. M. Harfeist, A. Bavely, and W. A. Lazier. J. Org. Chem. **19**, 1608 (1954).
26. S. J. Angyal, D. R. Penman, and G. P. Warwick. J. Chem. Soc. 1740 (1953).
27. J. Thiele and O. Dimroth. Ann. **305**, 114 (1899).
28. W. M. Whaley and M. Meadow. J. Org. Chem. **19**, 661 (1954).