[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Naphthyridines. I. Synthesis of Some 1,7-Naphthyridines[1,2]

BY HENRY E. BAUMGARTEN AND ARTHUR L. KRIEGER[3]

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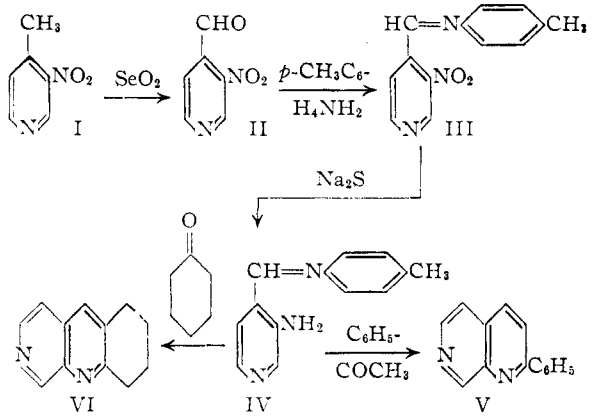
Oxidation of 3-nitro-4-picoline with selenium dioxide gave 3-nitro-4-pyridinecarboxaldehyde. Condensation of the aldehyde with *p*-toluidine gave N-(3-nitro-4-picolylidene)-*p*-toluidine (III), which was reduced to N-(3-amino-4-picolylidene)-*p*-toluidine (IV). Condensation of the latter with acetophenone and with cyclohexanone gave 2-phenyl-1,7-naphthyridine and 2,10-diaza-5,6,7,8-tetrahydroanthracene (VI), respectively. Reaction of 3-nitro-4-pyridinecarboxaldehyde with malonic acid gave β-(3-nitro-4-pyridyl)-acrylic acid, which was reduced to β-(3-amino-4-pyridyl)-acrylic acid, and the latter was cyclized to 2-hydroxy-1,7-naphthyridine. Fusion of the ammonium salt of β-homoquinolinic acid gave 6,8-dihydroxy-1,7-naphthyridine.

Of the six naphthyridine ring systems[4] some (*e.g.*, the 1,8-naphthyridines) have received considerable study while others have received little if any attention. The 1,7-naphthyridines fall in the latter group, for prior to 1945 no authentic 1,7-naphthyridine had been reported, and since that date only three synthetic studies[5-7a] have been described in which 1,7-naphthyridine derivatives have been prepared. This communication describes the synthesis of several 1,7-naphthyridines by three different routes, one of which shows promise of being general.

Inasmuch as 1,7-naphthyridine is an analog of both quinoline and isoquinoline, our first synthetic experiments have been patterned after known quinoline and isoquinoline syntheses. The first, and potentially most general, synthesis described below is based on the Borsche[8] modification of the Friedlander quinoline synthesis and is outlined in the sequence I → VI.



3-Nitro-4-pyridinecarboxaldehyde (II), which was required for the Borsche type synthesis, apparently has not been described previously, but its logical precursor, 4-methyl-3-nitropyridine (I), has been prepared by several investigators.[9-11] On the assumption that the behavior of I might be qualitatively analogous to that of 2,4-dinitrotoluene,[12] we first attempted to convert I into II by condensation with *p*-dimethylaminonitrosobenzene followed by hydrolysis of the resultant anil (similar in structure to III) much as is commonly done in the preparation of 2,4-dinitrobenzaldehyde.[13] Such a procedure would have had the advantage of giving directly the anil needed for the Borsche sequence. Unfortunately I failed to react satisfactorily under a variety of conditions with either *p*-dimethylaminonitrosobenzene or nitrosobenzene, giving only low yields of impure anil. The quaternary salt of I with benzyl bromide gave somewhat larger yields of the corresponding anil, but again these were too low and the product was too impure for preparative use. Recently Ockenden and Schofield[14] reported a similar low yield in the condensation of 3-nitrolepidine with *p*-dimethylaminonitrosobenzene.

If the assumed analogy of I with 2,4-dinitrotoluene were correct, the reaction of I with selenium dioxide should give no II, for Fisher[15] has found that 2,4-dinitrotoluene yielded no 2,4-dinitrobenzaldehyde when treated with selenium dioxide. However, treatment of I with selenium dioxide in boiling xylene did give II in 20–37% yield, further illustrating the failure of the analogy in the present example.

Condensation of II with *p*-toluidine gave N-(3-nitro-4-picolylidene)-*p*-toluidine (III) in nearly quantitative yield, and the latter was readily reduced with aqueous ethanolic sodium sulfide to N-(3-amino-4-picolylidene)-*p*-toluidine (IV) in 80% yield. Reaction of IV with acetophenone in the presence of aqueous ethanolic sodium hydroxide gave 2-phenyl-1,7-naphthyridine (V) in 84% yield. With cyclohexanone IV gave 2,10-diaza-5,6,7,8-tetrahydroanthracene (VI) in 66% yield. Based

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(3) Monsanto Chemical Company Fellow, 1952–1953.

(4) C. F. H. Allen, *Chem. Revs.*, **47**, 275 (1950).

(5) E. Ochiai, T. Ishida, H. Nomura, M. Hamana and K. Ishii, *J. Pharm. Soc. Japan*, **65**, 69 (1945); *C. A.*, **45**, 8018 (1951).

(6) V. A. Petrow, *J. Chem. Soc.*, 200 (1946).

(7) A. Albert and A. Hampton, *ibid.*, 4985 (1952).

(7a) NOTE ADDED IN PROOF.—A fourth study has been reported recently by J. G. Murray and C. R. Hauser, *J. Org. Chem.*, **19**, 2008 (1954).

(8) (a) W. Borsche, W. Doeller and M. Wagner-Roemich, *Ber.*, **76**, 1099 (1943); (b) W. Borsche and J. Barthenheier, *Ann.*, **548**, 50 (1941); (c) W. Borsche and W. Ried, *ibid.*, **554**, 269 (1943).

(9) E. Koenigs and A. Fulde, *Ber.*, **60**, 2106 (1927).

(10) H. E. Baumgarten, H. C. Su and A. L. Krieger, THIS JOURNAL, **76**, 596 (1954).

(11) E. V. Brown, *ibid.*, **76**, 3167 (1954).

(12) The generalization that pyridine and its derivatives react in a manner similar to that of nitrobenzene and the corresponding nitrobenzene derivatives has been noted by several authors. For example, see H. S. Mosher in R. C. Elderfield, "Heterocyclic Compounds," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1950, pp. 408 and 578.

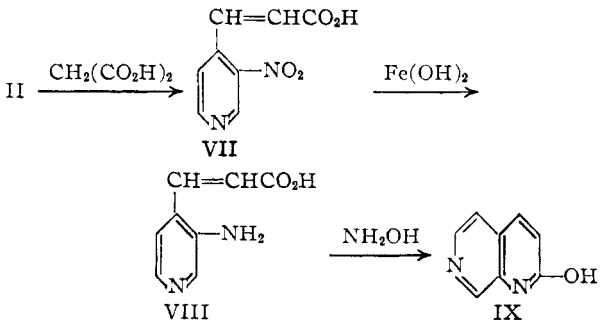
(13) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 223.

(14) D. W. Ockenden and K. Schofield, *J. Chem. Soc.*, 1915 (1953).

(15) C. H. Fisher, THIS JOURNAL, **56**, 2056 (1934).

on the demonstrated generality of the Borsche[8] quinoline synthesis, it seems that the condensation of IV with the appropriate aldehydes or ketones should afford a general synthesis for a number of substituted 1,7-naphthyridines.

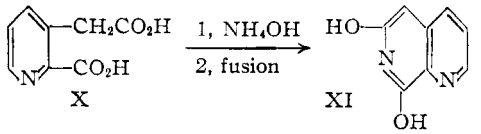
The second procedure developed in the present investigation was based on the Chiozza[16] synthesis of carbostyril *via* cyclization of *o*-aminocinnamic acid.



Condensation of crude II with malonic acid in the presence of pyridine and piperidine gave β-(3-nitro-4-pyridyl)-acrylic acid (VII) in 16% yield (based on I). Reduction of VII with ammoniacal ferrous hydroxide gave β-(3-amino-4-pyridyl)-acrylic acid (VIII) in 92% yield.

Attempts to cyclize VIII by heating in 50% sulfuric acid for two hours[17] or by heating in dilute hydrochloric acid for 72 hours[18] gave at best only traces of the expected 2-hydroxy-1,7-naphthyridine (IX). Cyclization by Posner's technique,[19] heating in methanolic hydroxylamine, gave IX in 30% yield.

Meyer and Vittenet[20] have reported the preparation of 1,3-dihydroxyisoquinoline by fusion of the ammonium salt of homophthalic acid. This procedure was used as the basis for the third 1,7-naphthyridine synthesis. The requisite homo-



phthalic acid analog, β-homoquinolinic acid (X), already has been described.[21] Fusion of the ammonium salt of X gave 6,8-dihydroxy-1,7-naphthyridine (XI) in 23% yield.

In addition to the three successful synthetic routes outlined above we made a number of attempts to prepare 1,7-naphthyridines from 3-aminoisonicotinic acid and 2,6-dimethyl-3-aminoisonicotinic acid. The latter substance had been used previously by Gulland and Robinson[22] in an unsuccessful effort to prepare 1,7-naphthyridines, and these authors had attributed their lack of success to the steric effect of the 2-methyl group. It seems probable that factors other than steric hindrance may be involved also, for in our hands both of the above aminoisonicotinic acids (and their methyl esters) failed to react with malonic ester, acetoacetic ester and methyl acetate under a variety of conditions, and 3-aminonicotinic acid, at least, is relatively unhindered. Especially disappointing was the failure of the two amino acids to react with methazonic acid, for the cyclization of the expected condensation products would have yielded the potentially useful 4-hydroxy-3-nitro-1,7-naphthyridines.[23]

(16) L. Chiozza, *Ann.*, **83**, 117 (1852).
(17) A. Feer and W. Koenigs, *Ber.*, **18**, 2388 (1885).
(18) F. Tiemann and J. Oppermann, *ibid.*, **13**, 2056 (1880).
(19) T. Posner, *Ann.*, **389**, 41 (1912).
(20) A. Meyer and R. Vittenet, *Ann. chim.*, [10] **17**, 291 (1932).
(21) K. Miescher and H. Kagi, *Helv. chim. Acta*, **24**, 1471 (1941).
(22) J. M. Gulland and R. Robinson, *J. Chem. Soc.*, **127**, 1493 (1925).

Experimental[24]

3-Nitro-4-pyridinecarboxaldehyde (II).—To a solution of 20.7 g. (0.15 mole) of 3-nitro-4-picoline[10] in 200 ml. of xylene heated nearly to boiling under reflux was added 16.6 g. (0.15 mole) of selenium dioxide in portions just large enough to keep the xylene boiling. After addition was complete, the reaction mixture was heated an additional hour, cooled, filtered from metallic selenium and extracted with 50% aqueous hydrochloric acid (3 × 100 ml.). The acidic solution was made basic with solid sodium carbonate and was chilled in ice. The crude solid aldehyde which separated was filtered off and the filtrate was extracted with ether. The solid aldehyde was dissolved in the ether, the solution was dried over magnesium sulfate and the ether was evaporated on the steam-bath. The yield of crude aldehyde (mixed with unreacted 3-nitro-4-picoline) was 16.9 g. (74%).

To 0.5 g. of the crude aldehyde in 20 ml. of hot 95% ethanol was added a solution prepared in the usual manner[25] from 0.4 g. of 2,4-dinitrophenylhydrazine, 2 ml. of concentrated sulfuric acid, 3 ml. of water and 10 ml. of 95% ethanol. **3-Nitro-4-pyridinecarboxaldehyde 2,4-dinitrophenylhydrazone** separated immediately as a bright yellow solid. Yield was 0.55 g. (50%), m.p. 258°, indicating that the yield of 3-nitro-4-pyridinecarboxaldehyde in the oxidation was at least 37%.

Anal. Calcd. for $C_{12}H_8O_6N_6$: C, 43.38; H, 2.43; N, 25.36. Found: C, 43.85; H, 2.71; N, 25.05.

For some experiments the crude aldehyde could be assayed in the above manner and used without further purification. However, for other experiments the pure aldehyde was required. Thus in one preparation (from 16 g. (0.12 mole) of 3-nitro-4-picoline) the crude solid aldehyde which separated from the aqueous sodium carbonate solution was recrystallized from water to yield 3.0 g. of **3-nitro-4-pyridinecarboxaldehyde dihydrate**, m.p. 91–93°. The sodium carbonate filtrate was extracted with ether, the ether was dried over magnesium sulfate and evaporated and the residue was recrystallized from the filtrate from the above recrystallization, yielding an additional 1.6 g. of the dihydrate. The total yield of pure 3-nitro-4-pyridinecarboxaldehyde dihydrate was 4.6 g. (20%).

Anal. Calcd. for $C_6H_8N_2O_5$: N, 14.89. Found: N, 15.12.

The dihydrate was sublimed twice at 60 mm. pressure and dried over phosphorus pentoxide at 30° for 24 hours, giving 3-nitro-4-pyridinecarboxaldehyde, m.p. 53–54°. The progress of the dehydration was followed by analyzing for nitrogen after each treatment.

Anal. Calcd. for $C_6H_4N_2O_3$: C, 47.37; H, 2.65; N, 18.42. Found: C, 47.58; H, 3.11; N, 18.23.

N-(3-Nitro-4-picolylidene)-*p*-toluidine (III) proved to be rather unstable toward storage and normally was not isolated. In one experiment a solution of 0.100 g. (0.00066 mole) of 3-nitro-4-pyridinecarboxaldehyde and 0.072 g. (0.00066 mole) of *p*-toluidine in 1 ml. of ethanol was heated under reflux for one hour, diluted to 4 ml. with ethanol, treated with a small amount of charcoal, chilled and filtered, giving 0.150 g. (95%), m.p. 92–93°, of N-(3-nitro-4-picolylidene)-*p*-toluidine as bright yellow needles. The product was recrystallized from ethanol with little loss and no

(23) K. Schofield and R. S. Theobald, *ibid.*, 395 (1950).
(24) Melting points are corrected.
(25) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1948, p. 171.

change in melting point, dried quickly at room temperature *in vacuo* and analyzed immediately. On standing exposed to light the color of the product changed from bright yellow to bright red.

Anal. Calcd. for $C_{13}H_{11}N_3O_2$: N, 20.09. Found: N, 19.87.

N-(3-Amino-4-picolylidene)-*p*-toluidine (IV).—A solution of 0.75 g. (0.0040 mole) of 3-nitro-4-pyridinecarboxaldehyde dihydrate and 0.43 g. (0.0040 mole) of *p*-toluidine in 4 ml. of ethanol was heated under reflux for one hour. To the hot solution was added a solution of 1.9 g. (0.0079 mole) of sodium sulfide nonahydrate in 2 ml. of 50% ethanol. On cooling, the amine precipitated as tan plates, which were filtered, washed with cold, dilute ethanol and dried, giving 0.65 g. (77%) of N-(3-amino-4-picolylidene)-*p*-toluidine, m.p. 146–148°, which was satisfactory for use without further purification. For analysis the product was recrystallized from dilute ethanol giving light yellow plates, m.p. 146–148°.

Anal.[26] Calcd. for $C_{13}H_{13}N_3$: C, 73.89; H, 6.20; N, 19.89. Found: C, 74.25; H, 6.24; N, 19.44.

2-Phenyl-1,7-naphthyridine (V).—A mixture of 0.264 g. (0.00125 mole) of N-(3-amino-4-picolylidene)-*p*-toluidine, 0.150 g. (0.00125 mole) of acetophenone, 1 ml. of 2 *N* sodium hydroxide and 3 ml. of ethanol was heated under reflux on the steam-bath for eight hours. The alcohol and *p*-toluidine were distilled with steam. After cooling the product was collected by filtration, dried and dissolved in the minimum amount of methanol. The methanol solution was freed from a small amount of insoluble material by filtration, heated on the steam-bath, diluted with water to incipient cloudiness and chilled. The pale tan needles (0.215 g. (84%), m.p. 112–114°) which formed were collected and recrystallized from dilute methanol (using charcoal), giving a 90% recovery of 2-phenyl-1,7-naphthyridine, m.p. 113.8–114.8°, as white needles.

Anal.[26] Calcd. for $C_{14}H_{10}N_2$: C, 81.53; H, 4.89; N, 13.59. Found: C, 81.57; H, 4.71; N, 13.40.

2,10-Diaza-5,6,7,8-tetrahydroanthracene (VI).—A mixture of 0.264 g. (0.00125 mole) of N-(3-amino-4-picolylidene)-*p*-toluidine, 0.12 g. (0.0012 mole) of cyclohexanone, 1 ml. of 2 *N* sodium hydroxide and 3 ml. of ethanol was heated under reflux on the steam-bath for eight hours and the alcohol and *p*-toluidine were removed by steam distillation. The crude product which separated from the cooled aqueous solution proved to be too soluble for satisfactory recrystallization from dilute methanol but was readily recrystallized from petroleum ether (30–60°), giving 0.15 g. (66%) of 2,10-diaza-5,6,7,8-tetrahydroanthracene, m.p. 89.5–91°.

Anal.[26] Calcd. for $C_{12}H_{12}N_2$: C, 78.22; H, 6.57; N, 15.21. Found: C, 78.28; H, 6.74; N, 14.91.

β-(3-Nitro-4-pyridyl)-acrylic Acid (VII).—A mixture of 15.2 g. (0.05 mole) of crude 3-nitro-4-pyridinecarboxaldehyde (assay: 50% aldehyde), 10.4 g. (0.10 mole) of malonic acid and two drops of piperidine in 10 ml. of pyridine was heated under reflux on the steam-bath for two hours. The reaction mixture was poured into 150 ml. of cold water and glacial acetic acid was added until the product precipitated. The crude, dark colored solid (4.2 g., 43%) was recrystallized twice from ethanol with about 85% recovery, giving β-(3-nitro-4-pyridyl)-acrylic acid as fine off-white crystals, m.p. 250–251°.

(26) Analysis by Clark Microanalytical Laboratory, Urbana, Illinois.

Anal. Calcd. for $C_8H_6N_2O_4$: C, 49.48; H, 3.09; N, 14.42. Found: C, 49.01; H, 3.45; N, 14.48.

β-(3-Amino-4-pyridyl)-acrylic Acid (VII).—A solution of 19 g. of ferrous sulfate in 100 ml. of water was heated to boiling and saturated with gaseous ammonia. To this solution was added a solution of 2.2 g. (0.011 mole) of β-(3-nitro-4-pyridyl)-acrylic acid in 20 ml. of concentrated ammonium hydroxide, and the mixture was heated for 10 minutes on the steam-bath. The hot solution was filtered and concentrated under reduced pressure. The cold solution was acidified with acetic acid and filtered, giving 1.7 g. (92%) of greenish-yellow solid, m.p. 242–243° dec. A small portion of the product was recrystallized from water for analysis, giving small yellow prisms, m.p. 242–243° dec., of β-(3-amino-4-pyridyl)-acrylic acid.

Anal. Calcd. for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.13; H, 5.24; N, 16.82.

2-Hydroxy-1,7-naphthyridine (IX).—To a solution of 0.58 g. (0.0084 mole) of hydroxylamine hydrochloride in 6 ml. of absolute methanol was added a solution of 0.45 g. (0.0084 mole) of sodium methoxide in 3 ml. of methanol. The precipitated sodium chloride was filtered off and washed with 1 ml. of methanol. To the filtrate was added 0.30 g. (0.0018 mole) of β-(3-amino-4-pyridyl)-acrylic acid and the resultant mixture was heated under reflux on the steam-bath overnight. The methanol was evaporated and the residue was washed with 5 ml. of cold 5% sodium bicarbonate. The insoluble residue was recrystallized twice from water (10 ml.), giving 0.075 g. (29%) of matted, pale yellow needles, m.p. 282–284°. The product was dried to constant weight at 80° *in vacuo* for analysis (approximately 10 hours required), during which time the melting point rose to 291–292°.

Anal.[26] Calcd. for $C_8H_6N_2O$: C, 65.74; H, 4.14; N, 19.17. Found: C, 65.81; H, 4.44; N, 18.92.

In another experiment 1.0 g. of β-(3-amino-4-pyridyl)-acrylic acid was heated with 4 ml. of concentrated hydrochloric acid in 50 ml. of water under reflux for 72 hours. The solution was neutralized with ammonium hydroxide and concentrated while successive crops of crystals were collected. From the last crops a small amount of 2-hydroxy-1,7-naphthyridine, m.p. 290–291°, was isolated by repeated recrystallization from water. In a similar experiment using 50% sulfuric acid (9 ml.) for 2 hours rather than hydrochloric acid, none of the 2-hydroxy-1,7-naphthyridine could be isolated.

6,8-Dihydroxy-1,7-naphthyridine (XI).—β-Homoquinolinic acid was prepared essentially as described by Miescher and Kagi[21] and, after recrystallization from methanol, was found to melt at 190–191° (lit.[21] m.p. 182–183°).

Anal. Calcd. for $C_8H_7NO_4$: N, 7.74. Found: N, 7.63.

The over-all yield based on quinolinic acid was 22%.

A solution of 2 g. of β-homoquinolinic acid in an excess of 28% ammonium hydroxide was evaporated to dryness and the residual solid was fused and held at 180–200° until the evolution of ammonia ceased. The dark residue was extracted with 100 ml. of ethanol. The ethanolic solution was treated with charcoal, concentrated, cooled and filtered, giving 0.4 g. of gray solid, m.p. 270–280° dec. After two recrystallizations from ethanol and one from chloroform, 6,8-dihydroxy-1,7-naphthyridine was obtained as white needles, m.p. 275° dec.

Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.25; H, 3.71; N, 17.28. Found: C, 59.54; H, 4.02; N, 17.30.

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