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Naphthyridines. III.

Synthetic Experiments in the 1,5-Naphthyridine Series (1,2)

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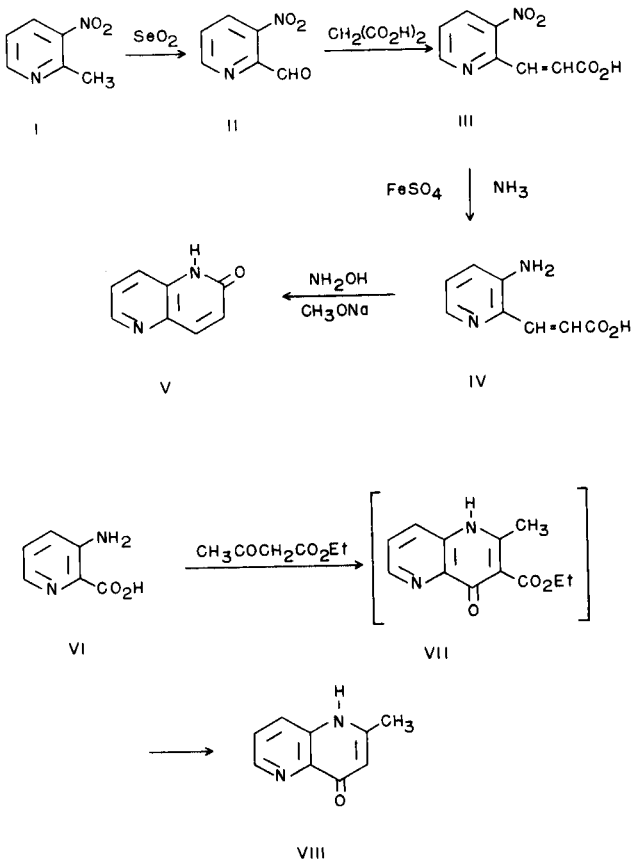
Most synthetic routes to the naphthyridine ring systems are patterned after quinoline syntheses (3). We have examined several such syntheses with the objective of preparing 1,5-naphthyridine derivatives. As is the frequent experience with attempted naphthyridine syntheses (3), some of our proposed synthetic schemes were and others were not effective.

One successful and potentially useful procedure is illustrated in the sequence I-V. Oxidation of 3-nitro-2-picoline (I) with selenium dioxide gave 50-55% yields of mixtures of 3-nitro-2-pyridinecarboxaldehyde (II) and I, which contained about 30-50% of II. Reaction of crude II with malonic acid gave a 10% yield (based on I) of 3-(3-nitro-2-pyridyl)-acrylic acid (IV). Cyclization of IV with hydroxylamine and sodium methoxide (Posner's technique (4)) afforded 1,5-naphthyridin-2(1*H*)-one (2-hydroxy-1,5-naphthyridine) (V) in 31% yield. Although the use of II as a synthetic intermediate was not studied further, earlier studies in this Laboratory (1) on the reactions of 3-nitro-4-pyridinecarboxyaldehyde suggest that II could be used in a number of Friedlander-like syntheses of 1,5-naphthyridines.

A second moderately successful 1,5-naphthyridine synthesis was based on the Niementowski quinoline synthesis (5). When 3-aminopicolinic acid (VI) was heated with ethyl acetoacetate, 2-methyl-1,5-naphthyridine-4(1*H*)-one (VIII) could be isolated in 13% yield. The intermediate ester VII was not isolated but must have been hydrolyzed and decarboxylated during the heating period.

A number of unsuccessful attempts were made to extend the Kulisch (7,8) synthesis of quinoline to the reaction of 3-amino-2-picoline with glyoxal, glyoxal sodium bisulfite addition product, or biacetyl. Finally, an attempt was made to duplicate Kulisch's original work. A long series of experiments at various temperatures and pressures failed to yield any quinoline from *o*-toluidine and glyoxal.

A large number of experiments were directed toward extending the Pfitzinger quinoline synthesis to 1,5-naphthyridines. Although 5-isonitrosoacetamino-2-picoline could be obtained in 73-79% yield from 5-amino-2-picoline, chloral hydrate, and hydroxylamine, attempted ring closure (10) of the oxime to the isatin analog could not be effected. 3-Isonitrosoacetamino-2-picoline also failed to cyclize. From 3-aminopyridine-1-oxide no isonitrosoacetamino derivative could be obtained.



EXPERIMENTAL

3-Nitro-2-pyridinecarboxaldehyde (II).

To a boiling mixture of 2.1 g. of selenium dioxide in 45 ml. of xylene 2.75 g. (0.02 mole) of 3-nitro-2-picoline (10) was added through the reflux condenser. The mixture was refluxed for 2 hours. The cooled solution was filtered and the filtrate was extracted with dilute hydrochloric acid (1:1). The hydrochloric acid extract was neutralized with solid sodium carbonate and the red precipitate which formed was filtered off. The filtrate was extracted with ether. The ethereal extracts were dried over anhydrous magnesium sulfate and then evaporated, giving a yellowish brown oil, 1.74 g. The oil was a mixture of 3-nitro-2-pyridinecarboxaldehyde and unreacted 3-nitro-2-picoline.

The content of 3-nitro-2-pyridinecarboxaldehyde could be estimated by n.m.r. spectroscopy (-CHO at δ 6.02, $-CH_3$ at δ 2.87) or often more satisfactorily but less rapidly by assay (11) of the mixture with 2,4-dinitrophenylhydrazine. Most samples contained 30-50% of the aldehyde.

A small portion of the yellowish brown oil was dissolved in alcohol and a solution of about two equivalents of 2,4-dinitrophenylhydrazine in sulfuric acid in ethanol-water (11) was added. After the mixture

had stood for two hours, the precipitated 2,4-dinitrophenylhydrazone was collected as a bright yellow solid, m.p. 210-211°.

Anal. Calcd. for $C_{12}H_8N_6O_6$: C, 43.37; H, 2.41; N, 25.30. Found: C, 43.63; H, 2.95; N, 25.16.

β-(3-Nitro-2-pyridyl)acrylic acid (III).

A mixture of 1.7 g. of the crude 3-nitro-2-pyridinecarboxaldehyde, 1.6 g. (0.015 mole) of malonic acid, 1.5 ml. of pyridine, and 1 drop of piperidine was heated on the steam bath for 2 hours. The dark liquid was poured into 20 ml. of water and stirred well. The solution was cooled in ice and acidified with acetic acid until precipitation was complete. A brown solid, 0.6 g., was obtained. This solid was recrystallized from ethanol (charcoal), giving 0.37 g. (10% based on 3-nitro-2-picoline) of III, m.p. 192.5-194°.

Anal. Calcd. for $C_8H_6N_2O_4$: C, 49.48; H, 3.09; N, 14.43. Found: C, 49.28; H, 3.78; N, 14.82.

β-(3-Amino-2-pyridyl)acrylic acid (IV).

Ammonia was passed into a boiling solution of 6.45 g. of ferrous sulfate (0.023 mole) in 30 ml. of water until the solution was saturated. To this solution was added a solution of 0.75 g. of β-(3-nitro-2-pyridyl)acrylic acid in 7 ml. of concentrated ammonium hydroxide. The blue-green color immediately changed to brown. The mixture was heated on the steam bath for 10 minutes and filtered. The blue solution was concentrated to a volume of *ca.* 20 ml. under reduced pressure and made acidid with acetic acid. A small amount of tarry material was removed by treatment with charcoal and filtered. The solution was concentrated to a volume of 10 ml. and chilled in an ice-salt mixture, giving 0.33 g. (57%) of green-yellow needles, m.p. 205-208°. A 30-mg. sample was twice recrystallized from 2 ml. of water for analysis giving 0.015 g. of bright yellow needles, m.p. 207-208° (Kofler hot stage).

Anal. Calcd. for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.05; H, 4.66; N, 16.91.

1,5-Naphthyridin-2(1*H*)-one (V).

To a solution of 0.58 g. of hydroxylamine hydrochloride in 6 ml. of absolute methanol was added a solution of 0.45 g. of sodium methoxide in 3 ml. of methanol. The precipitated salt was removed by filtration and washed with 1 ml. of methanol. To the filtrate was added 0.27 g. of β-(3-amino-2-pyridyl)acrylic and the mixture was refluxed on the steam bath overnight. The methanol was evaporated and the residue was washed with 3 ml. of 5% aqueous sodium bicarbonate and filtered. The crude product (0.110 g.) was recrystallized from 6 ml. of water (charcoal) giving 0.075 g. (31%) of colorless needles, m.p. 260-261° (Kofler hot stage, change of crystal form to large flat colorless plates at about 220°) (lit. (12,13) m.p. 256°, 259°); infrared peaks ($CHCl_3$) at 3400 (NH), 1662 (C=O) cm^{-1}.

5-Isonitrosoacetamino-2-picoline.

The procedure reported by Marvel and Hiers (9) for the preparation of isonitrosoacetanilide was adapted for the preparation of 5-isonitrosoacetamino-2-picoline.

To a solution of 1.8 g. (0.011 mole) of chloral hydrate in 25 ml. of water were added in order: 26 g. of crystalline sodium sulfate; a solution of 1.08 g. (0.01 mole) of 5-amino-2-picoline in 6 ml. of water and 1.7 ml. (0.021 mole) of concentrated hydrochloric acid; and finally a solution of 2.2 g. (0.032 mole) of hydroxylamine hydrochloride in 10 ml. of water. The mixture was then heated over a burner to vigorous boiling which was continued for 1-2 minutes. The solution was cooled, made slightly basic with anhydrous sodium carbonate, and filtered, giving 1.1-1.2 g. (73-79%) of the isonitrosoacetamino compound as a fine gray powder. Recrystallization from ethanol (charcoal) gave a white powder, m.p. 181-182°.

Anal. Calcd. for $C_8H_9N_3O_2$: C, 53.63; H, 5.03; N, 23.46. Found: C, 53.53; H, 5.32; N, 23.00.

3-Isonitrosoacetamino-2-picoline.

3-Isonitrosoacetamino-2-picoline was prepared by the procedure described above for 5-isonitrosoacetamino-2-picoline. The crude product was obtained as a yellow powder in 47% yield. After recrystallization from methanol (charcoal) white needles, m.p. 189-190° (dec.), were obtained.

Anal. Calcd. for $C_8H_9N_3O_2$: C, 53.63; H, 5.03; N, 23.46. Found: C, 53.86; H, 5.29; N, 22.86.

When the filtrate from the yellow powder was extracted with chloroform, it led to a 24% recovery of the 3-amino-2-picoline.

2-Methyl-1,5-naphthyridine-4(1*H*)-one (VIII).

A mixture of 1.0 g. (0.007 mole) of 3-aminopicolinic acid in a large excess (5-10 ml.) of ethyl acetoacetate was heated under reflux for 4 hours. A brown solution with a green fluorescence formed. The liquid was set in the refrigerator for 3 days. The solid which formed was collected and washed with water, giving a brown solid, m.p. 252-255°. This solid was dissolved in chloroform, treated with charcoal twice, and evaporated to dryness. This solid residue was washed several times with ether and dried, giving 0.15 (13%) of nearly colorless crystals, m.p. 254-256°; infrared bands ($CHCl_3$) at 3408 (NH), 1664 (C=O) cm^{-1}; and n.m.r. peaks ($CDCl_3$, 60 mc.) at 158 c.p.s. (singlet, 3H, CH_3), 409 c.p.s. (singlet, 1H, H-3), 440-480 c.p.s. (multiplet, 3H), 516 c.p.s. (broad singlet, 1H, N-H). In four other experiments yields of purified product were 2-10%; additional quantities of less pure product could be obtained by exhausive fractionation of the ethyl acetoacetate filtrate.

Anal. Calcd. for $C_9H_8N_2O$: C, 67.50; H, 5.00; N, 17.50. Found: C, 67.01; H, 5.18; N, 17.46.

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Received June 18, 1966

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