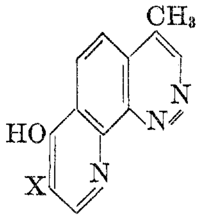
[CONTRIBUTION FROM AVERY LABORATORY OF THE UNIVERSITY OF NEBRASKA]

THE SYNTHESIS OF SOME SUBSTITUTED PYRIDO[3,2-*h*]CINNOLINES

LESTER MCKENZIE AND CLIFF S. HAMILTON

Received May 4, 1951

One of the methods of producing an N-heterocyclic ring involves the condensation of ethoxymethylenemalonate with a primary amine and subsequent ring closure. This method has been employed with 8-amino-4-methylcinnoline in the synthesis of substituted pyrido[3,2-*h*]cinnolines.



VI X = $CO_2C_2H_5$
VII X = CO_2H
VIII X = H

4-Methylcinnoline (I) was prepared, in good yield, according to the directions of Jacobs, *et al.* (1). Nitration of I (2) gave 4-methyl-8-nitrocinnoline (II). Reduction of II was accomplished by three different methods: A. Stannous chloride and hydrochloric acid (3); B. "Etched" iron and aqueous ethanol (4); C. Raney nickel and hydrogen at 45 pounds pressure. The best yields were obtained using the stannous chloride procedure; however, the ease of isolating the product made the "etched" iron method preferable when large amounts of nitro compound were used.

It was found that the color and crystalline form of 8-amino-4-methylcinnoline (III) is identical with that described in the literature (3) but the melting point is 133–134°, compared to the literature value of 126–127°. The structure of III was proved therefore by the conversion of it *via* the Sandmeyer reaction to 8-chloro-4-methylcinnoline (IV), a yellow crystalline product melting at 124–125° (m.p. of picrate 177–178°). 8-Chloro-4-methylcinnoline, prepared by an independent method (3) is reported to have m.p. 126–127° (m.p. of picrate 179–180°).

The reaction of III with diethyl ethoxymethylenemalonate gave 8-(2,2-dicarbethoxyvinylamino)-4-methylcinnoline(V). Cyclization of V was carried out in hot diphenyl ether to form 3-carbethoxy-4-hydroxy-7-methylpyrido[3,2-*h*] cinnoline (VI). Hydrolysis of VI in aqueous sodium hydroxide gave 3-carboxy-4-hydroxy-7-methylpyrido[3,2-*h*]cinnoline (VII). Decarboxylation of VII by heating the dry acid to its melting point did not proceed satisfactorily. There was considerable decomposition and only a low yield of an impure hydroxy compound could be isolated. The decarboxylation proceeded smoothly in good yield when the acid was heated with benzophenone at 265–275° (5).

The ultraviolet absorption spectra of III, V, and VI were determined in ethanol. The curves are shown in Fig. 1. 8-Amino-4-methylcinnoline shows maxima at 415 and 332 mμ, while 8-(2,2-dicarbethoxyvinylamino)-4-methylcinnoline has peaks at 387, 335, and 298 mμ. The maxima for 3-carbethoxy-4-hydroxy-7-methylpyrido[3,2-*h*]cinnoline occur at 347 and 276 mμ.

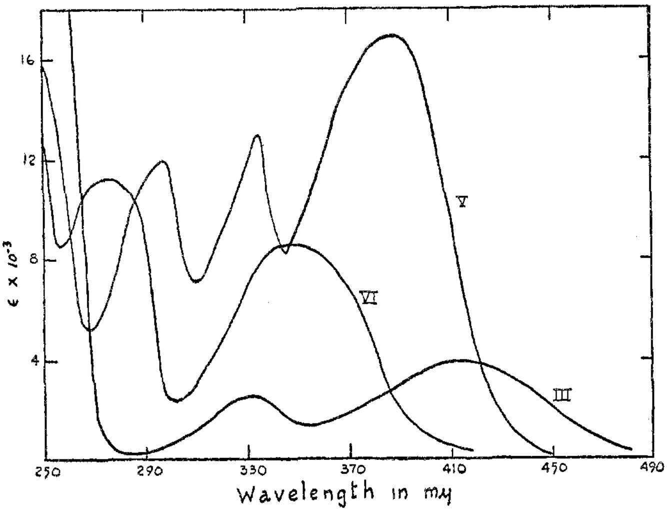


FIGURE 1. ULTRAVIOLET ABSORPTION SPECTRA OF 8-Amino-4-methylcinnoline (III), 8-(2,2-Dicarbethoxyvinylamino)-4-methylcinnoline (V), and 3-Carbethoxy-4-hydroxy-7-methylpyrido[3,2-*h*]cinnoline (VI) in ethanol.

EXPERIMENTAL

All observed melting points are uncorrected.

4-Methylcinnoline (I). This compound was prepared according to the procedure of Jacobs, *et al.* (1). The yield of crude product (m.p. 64–70°), based on methyl anthranilate, was 74%. The recrystallized product melted at 73–74°.

4-Methyl-8-nitrocinnoline (II). The method of Johnson and Hamilton (2) developed for the nitration of 2-chloro-4-methylquinoline was employed. Compound I (10 g.) was dissolved in 40 ml. of cold concentrated sulfuric acid. The solution was stirred vigorously and the temperature kept below 0° during the addition of the cinnoline. The solution was then cooled to −8° and 20 ml. of a nitrating mixture consisting of 16.3 ml. of conc'd sulfuric acid and 3.7 ml. of nitric acid (*d.* 1.5) was added dropwise. The rate of addition was adjusted to maintain the temperature below 0°. The solution was stirred for 30 minutes at 0° and for 2 hours at room temperature. The reaction mixture was poured on ice and neutralized to *p*H 7 with dilute ammonium hydroxide. The brown solid was removed and recrystallized from methanol. The yield was 4.6 g. (35%) of yellow crystalline material melting at 137–138° (dec.).

8-Amino-4-methylcinnoline (III). The procedure giving the best yield was the stannous chloride method described by Schofield and Swain (3). The product when recrystallized from benzene gave a 70% yield of orange crystals, m.p. 128–130°. Further recrystallization from ether-petroleum ether (40–60°) produced an analytical sample, m.p. 133–134°.

8-Chloro-4-methylcinnoline (IV) (3). The Sandmeyer reaction on III gave a product which produced yellow needles, melting at 124–125° after recrystallization from ligroin (b.p. 90–120°). A small amount of this compound was converted to the picrate, m.p. 177–178°.

3-(2,2-Dicarbethoxyvinylamino)-4-methylcinnoline (V). Compound III (9 g., 0.056 mole) was dissolved in 40 ml. of benzene by warming on the steam-bath. To this solution, in a 250-ml. suction flask, was added 13.6 g. (0.063 mole) of diethyl ethoxymethylenemalonate. A stream of dry air was drawn over the reaction mixture at 20–30 mm. pressure, while the flask was heated at 40–50° in a water-bath. The reduced pressure and temperature were held for a total of 8 hours. The solid residue remaining in the flask was recrystallized from absolute ethanol; yield, 14.65 g. (78%), m.p. 150–153°. The analytical sample was recrystallized from ethanol, m.p. 155–156°.

Anal. Calc'd for $C_{17}H_{19}N_3O_4$: C, 61.99; H, 5.81; N, 12.76.
Found: C, 62.05; H, 6.04; N, 13.05.

3-Carbethoxy-4-hydroxy-7-methylpyrido[3,2-h]cinnoline (*VI*). Diphenyl ether (315 g.) was heated to 245°. The solvent was stirred vigorously while 12.46 g. (0.0378 mole) of finely divided V was added portionwise over a period of 10 minutes. The temperature then was maintained at 245° for 20 minutes. The solution was cooled to room temperature and two volumes of ligroin (b.p. 90–120°) were added to the mixture. The solid which separated was removed, triturated twice with hot ligroin, and washed several times on the filter with the same solvent. The crude product was recrystallized twice from 95% ethanol yielding 3.35 g. (31%) of a light tan crystalline hygroscopic solid, m.p. 245–248°. The analytical sample was prepared by recrystallizing two times from 95% ethanol yielding pale yellow needles, m.p. 257–258°.

Anal. Calc'd for $C_{15}H_{13}N_3O_3$: C, 63.59; H, 4.62; N, 14.83.
Found: C, 63.55; H, 4.63; N, 15.09.

3-Carboxy-4-hydroxy-7-methylpyrido[3,2-h]cinnoline (VII). A mixture of 2.75 g. (0.0097 mole) of VI and 52 ml. of 2% aqueous sodium hydroxide was heated under reflux for 6.5 hours. The reaction mixture was cooled to room temperature, diluted to 100 ml. with water, then cooled in an ice-bath and made acidic to Congo Red with 0.5 *N* hydrochloric acid. The white precipitate was removed and dried in a vacuum-desiccator. The yield was quantitative, m.p. 313–314° (dec.).

4-Hydroxy-7-methylpyrido[3,2-h]cinnoline (VIII). A mixture of 1.35 g. (0.0053 mole) of VII and 7.0 g. of benzophenone was placed in a wide-mouth test tube. The tube was flushed with nitrogen and fitted with a stopper carrying a small glass tube. The test tube was heated to 265–275° for 1½ hours or until the evolution of carbon dioxide had ceased. The melt was cooled and treated with two volumes of ether. The brown solid which separated was removed and dried in a vacuum-desiccator. The weight was 1.05 g. (93%), m.p. 323–325°. The analytical sample was prepared by recrystallization from 95% ethanol in which it is sparingly soluble. The product separated as a light tan amorphous powder, m.p. 325–326°.

Anal. Calc'd for $C_{12}H_9N_3O$: C, 68.23; H, 4.29; N, 19.90.
Found: C, 68.08; H, 4.49; N, 20.17.

SUMMARY

1. The synthesis of several substituted pyrido[3,2-*h*]cinnolines is reported.
2. The ultraviolet spectrum of three cinnoline derivatives in ethanol solution is given.

LINCOLN, NEBRASKA

REFERENCES

(1) JACOBS, WINSTEIN, HENDERSON, AND SPAETH, *J. Am. Chem. Soc.*, **68**, 1310 (1946).
(2) JOHNSON AND HAMILTON, *J. Am. Chem. Soc.*, **63**, 2867 (1941).
(3) SCHOFIELD AND SWAIN, *J. Chem. Soc.*, 1367 (1949).
(4) CLEMO AND LEGG, *J. Chem. Soc.*, 539 (1947).
(5) ASHWORTH, DAFFERN, AND HAMMICK, *J. Chem. Soc.*, 809 (1939).