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CINNOLINE CHEMISTRY. I. SOME CONDENSATION REACTIONS OF 4-CHLOROCINNOLINE[1]

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It is well known that halogenated heterocyclic compounds in which the halogen atom is α or γ to the basic nitrogen atom are subject to attack by a variety of nucleophilic reagents with the elimination of a halide ion. The literature in this field has recently been summarized (1).

In order to extend the data on the susceptibility of 4-chlorocinnoline to nucleophilic attack, the condensation of the sodio-derivatives of phenylacetonitriles and 4-chlorocinnoline was studied. The conditions used by Cutler, Surrey, and Cloke (2) for 4,7-dichloroquinoline were adapted to 4-chlorocinnoline.

The condensation of 4-chlorocinnoline (I) with phenylacetonitrile (II) using sodium amide as the condensing agent gave a 94% yield of α-(4-cinnolyl)phenylacetonitrile (III) when the temperature was maintained at 25° or less during the condensation. When the condensation was carried out using sodium hydride as the condensing agent, the yield of III was 9%. Condensation of I with *m*-methoxyphenylacetonitrile and *p*-methoxyphenylacetonitrile gave 55% and 66% yields respectively of the corresponding condensation products. Several attempts to condense 4-chlorocinnoline with 3,4-dimethoxyphenylacetonitrile were unsuccessful. The difficulty appears to be in the formation of the sodio-derivative of the nitrile. Hartmann and Panizzon (3) reported the condensation product from 4-chloropyridine and 3,4-dimethoxyphenylacetonitrile in a patent. In our hands the corresponding condensation of 4-chlorocinnoline and 3,4-dimethoxyphenylacetonitrile using their conditions was unsuccessful.

4-Hydroxy-6,7-dimethoxycinnoline (VII) and 4-chloro-6,7-dimethoxycinnoline (VIII) were synthesized from 2-amino-4,5-dimethoxyacetophenone (VI) by the sequence of reactions shown in Chart II. VI was prepared essentially by the methods of Simpson (4). The 2-amino-4,5-dimethoxyacetophenone was converted smoothly into 6,7-dimethoxy-4-hydroxycinnoline in 67% yield. The 4-chloro-6,7-dimethoxycinnoline was prepared from the corresponding 4-hydroxy compound in 74% yield. In contrast to the unstable character of 4-chlorocinnoline (5), 4-chloro-6,7-dimethoxycinnoline is completely stable at room temperature.

4-Chloro-6,7-dimethoxycinnoline condensed smoothly with the sodio-derivative of phenylacetonitrile to produce a 40% yield of α-(6,7-dimethoxy-4-cinnolyl)-phenylacetonitrile. α-(4-Cinnolyl)phenylacetonitrile and α-(6,7-dimethoxy-4-cinnolyl)phenylacetonitrile were rapidly converted to the corresponding acetamides

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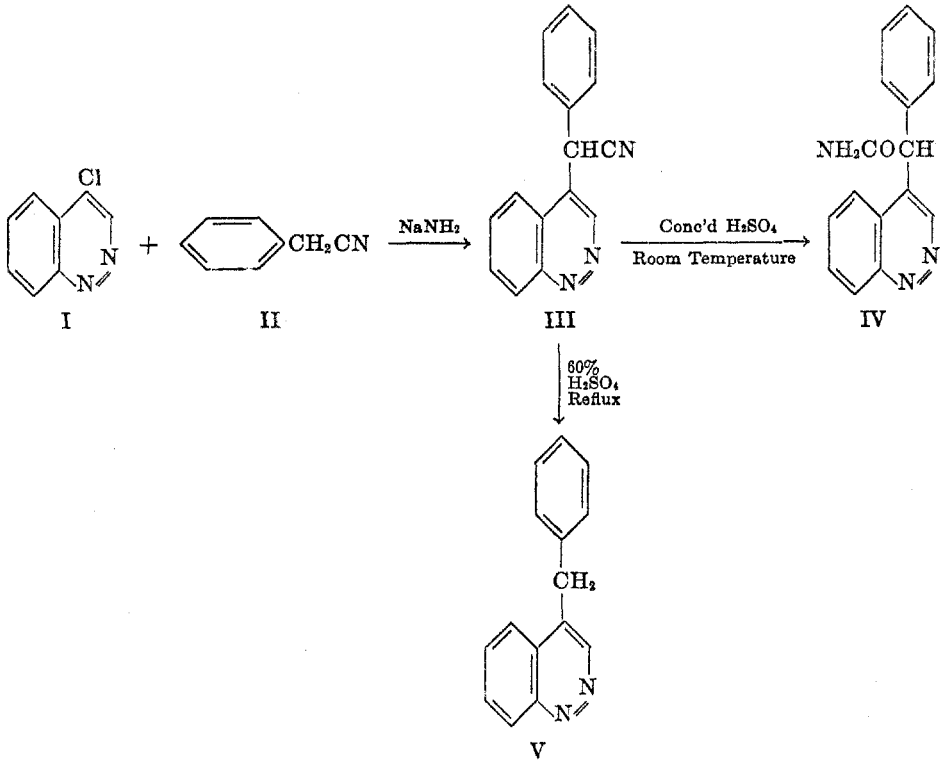
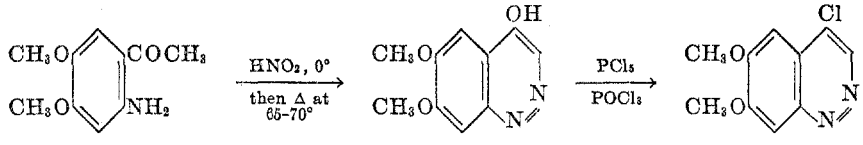
by allowing them to stand ten to twelve hours in concentrated sulfuric acid at room temperature. Yields of 93% and 18% of the acetamides were obtained respectively. The α-(4-cinnolyl)phenylacetonitrile was readily converted in 43% yield to 4-benzylcinnoline (V) by refluxing for one hour in 60% sulfuric acid.

CHART I



I II III IV V

CHART II



VI VII VIII

Attempts to condense 4-chlorocinnoline with sodio-derivatives of acetoacetic ester, malonic ester, malononitrile, benzoyl acetone, phenyl acetone, and ethyl cyanoacetate using a variety of condensing agents were unsuccessful. These attempted reactions are described briefly in the experimental part.

Some of the compounds prepared in this investigation have been submitted for physiological testing.

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EXPERIMENTAL

All melting points were taken with the Anschutz thermometers at total immersion, thus no stem correction was necessary, except where noted.

4-Chlorocinnoline was prepared by the procedure of Leonard and Boyd (6). 4-Chlorocinnoline is unstable (5) and thus was prepared in small quantities and used immediately upon purification by recrystallization from petroleum ether (b.p. 30–60°), pale yellow needles melting at 75–76.5°.

α-(4-Cinnolyl)phenylacetonitrile. To 13.0 g. of phenylacetonitrile in 70 ml. of dry benzene cooled in an ice-brine bath was added 6 g. of sodium amide. After stirring the mixture for one hour, 8.2 g. of 4-chlorocinnoline in 75 ml. of dry benzene was added over 15 minutes. The deep red color of the amide-nitrile mixture did not change upon the addition of 4-chlorocinnoline, although some orange solid began to appear. The mixture was stirred for an additional two hours at room temperature, then hydrolyzed with water, whereupon a voluminous yellow, curdy precipitate formed and remained suspended between the benzene and water layers. The precipitate was removed by filtration, and the benzene layer was separated, washed with water, dried over sodium sulfate, and evaporated to yield additional yellow solid. The accumulated yellow solids were recrystallized from aqueous ethanol yielding 11.5 g. (94%) of golden yellow plates melting at 197.5–198.5°.

Anal. Calc'd for $C_{16}H_{11}N_3$: C, 78.34; H, 4.52; N, 17.13.
Found: C, 78.09; H. 4.67; N, 16.77.

α-(4-Cinnolyl)-m-methoxyphenylacetonitrile. Following essentially the same procedure as above from 2.2 g. of 4-chlorocinnoline, 1.0 g. of sodium amide, and 4.0 g. of *m*-methoxyphenylacetonitrile, there was obtained 2.1 g. (55%) of deep orange-red plates melting at 194.5–195° after one crystallization from aqueous ethanol.

Anal. Calc'd for $C_{17}H_{13}N_3O$: C, 74.16; H, 4.76.
Found: C, 74.14; H, 4.94.

α-(4-Cinnolyl)-p-methoxyphenylacetonitrile. From 2.0 g. of 4-chlorocinnoline, 1.0 g. of sodium amide, and 4.0 g. of *p*-methoxyphenylacetonitrile, 2.5 g. (66%) of orange-red plates melting at 183–185° after one crystallization from aqueous ethanol was obtained.

Anal. Calc'd for $C_{17}H_{13}N_3O$: C, 74.16; H, 4.76.
Found: C, 74.36; H, 5.08.

α-(6,7-Dimethoxy-4-cinnolyl)phenylacetonitrile. From 2.5 g. of phenylacetonitrile, 1.0 g. of sodium amide, and 2.0 g. of 4-chloro-6,7-dimethoxycinnoline, 1.2 g. (40%) of orange-red plates melting at 220–221° after one crystallization from aqueous ethanol was obtained.

Anal. Calc'd for $C_{18}H_{15}N_3O_2$: C, 70.80; H, 4.95.
Found: C, 69.85; H, 5.10.

6,7-Dimethoxy-4-hydroxycinnoline. To a stirred solution of 5.2 g. of 2-amino-4,5-dimethoxyacetophenone in 185 ml. of concentrated hydrochloric acid and 26 ml. of water at −5° was added 1.85 g. of sodium nitrite in 8 ml. of water over 45 minutes. The mixture was stirred for an additional hour at 0° and then heated at 60–75° for four hours to effect ring closure. Crystals separated during the heating, and more were formed upon cooling the reaction mixture. The crystalline hydrochloride so obtained melted at 234° with decomposition (uncorr.). The free base was obtained by treatment with 10% sodium hydroxide. The base was purified by dissolving in dilute sodium hydroxide, boiling with charcoal, and precipitating with dilute hydrochloric acid. There was obtained 3.7 g. (67%) of white powder melting at 271–272°.

Anal. Calc'd for $C_{10}H_{10}N_2O_3$: C, 58.24; H, 4.89; N, 13.59.
Found: C, 58.15; H, 4.95; N, 13.79.

4-Chloro-6,7-dimethoxycinnoline. To 2.5 g. of 6,7-dimethoxy-4-hydroxycinnoline was added 5 ml. of phosphorus oxychloride and 3.5 g. of phosphorus pentachloride. The mixture was warmed for 15 minutes and then poured on crushed ice. After neutralization of the solution with sodium acetate to Congo Red, the precipitate was removed and recrystallized from ethanol. There was obtained 2.0 g. (74%) of hair-like, cream-colored needles melting at 195–196°.

Anal. Calc'd for $C_{10}H_9ClN_2O_2$: C, 53.46; H, 4.04; N, 12.47; Cl, 15.92.
Found: C, 54.37; H, 4.66; N, 12.53; Cl, 15.66.

α-(4-Cinnolyl)phenylacetamide. A mixture of 1.0 g. of α-(4-cinnolyl)phenylacetonitrile in 8 ml. of concentrated sulfuric was allowed to stand overnight at room temperature. It was then poured into a mixture of 25 ml. of concentrated ammonium hydroxide and 200 g. of crushed ice. An orange-yellow solid precipitated. It was washed with hot ethanol to remove unchanged nitrile and was purified by precipitation from a concentrated hydrochloric acid solution with dilute base. There was obtained 1 g. (93%) of pale yellow crystals melting at 248–249°.

Anal. Calc'd for $C_{16}H_{13}N_3O$: C, 72.98; H, 4.98.
Found: C, 72.75; H, 5.18.

α-(6,7-Dimethoxy-4-cinnolyl)phenylacetamide. By the procedure described above 0.35 g. of α-(6,7-dimethoxy-4-cinnolyl)phenylacetonitrile in 1.5 ml. of concentrated sulfuric acid was converted into the corresponding acetamide. After crystallization from aqueous ethanol there was obtained 66 mg. (18%) of white opaque crystals, melting at 234.5–236.5°, with initial softening at 228–232°.

Anal. Calc'd for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30.
Found: C, 66.83; H, 5.55.

4-Benzylcinnoline. A mixture of 4.0 g. of α-(4-cinnolyl)phenylacetonitrile, 8.0 ml. of concentrated sulfuric acid, and 8.0 ml. of water was refluxed for one hour. The cooled mixture was poured over crushed ice containing 25 ml. of concentrated ammonium hydroxide. The precipitated solid was dissolved in ether, dried, and the ether solution evaporated. The pale yellow, lath-shaped crystals were purified by crystallization from aqueous ethanol, yielding 1.6 g. (43%) of nearly colorless crystals melting at 104.5°.

Anal. Calc'd for $C_{15}H_{12}N_2$: C, 81.79; H, 5.49; N, 12.72.
Found: C, 81.77; H, 5.77; N, 12.53.

UNSUCCESSFUL ATTEMPTS TO CONDENSE *sodio-malonic ester* AND OTHER *enolic compounds* WITH *4-chlorocinnoline*

Malonic ester. To 5.0 g. of diethyl malonate in 100 ml. of dry ether was added 0.6 g. of sodium ribbon. After four hours stirring the sodio-malonic ester was a smooth white paste. To this paste was added 4.3 g. of 4-chlorocinnoline in 50 ml. of dry ether during a period of ten minutes. The mixture was heated until it was olive-green in color and then allowed to stand for ten hours. The mixture was hydrolyzed with water and then extracted with ether. The ether layer was washed with dilute hydrochloric acid, dilute sodium bicarbonate solution, and with water. The ether solution was dried over calcium sulfate, the ether removed by evaporation, and 4-chlorocinnoline recovered together with some tarry material, presumably from the decomposition of 4-chlorocinnoline.

Essentially the same procedure was followed in the attempted condensations of acetoacetic ester, ethyl cyanoacetate, benzoyl acetone, malononitrile, and phenyl acetone with 4-chlorocinnoline. Dry ether was always the solvent, and in some instances sodium hydride or sodium amide was used in place of sodium metal to prepare the sodio-derivatives. In all instances only 4-chlorocinnoline was recovered together with some tarry residue.

SUMMARY

The condensation of 4-chlorocinnoline with some phenylacetonitriles using sodium amide as the condensing agent has been studied. Two of the resulting

α-(4-cinnolyl)phenylacetonitriles have been hydrolyzed to the α-(4-cinnolyl)-phenylacetamides. α-(4-Cinnolyl)phenylacetonitrile was hydrolyzed to 4-benzylcinnoline. The synthesis of 6,7-dimethoxy-4-hydroxycinnoline and 4-chloro-6,7-dimethoxycinnoline has been accomplished. Of the cinnolines synthesized in this investigation only 4-chlorocinnoline has been previously reported.

Attempts to condense 4-chlorocinnoline with certain enolic compounds are described.

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