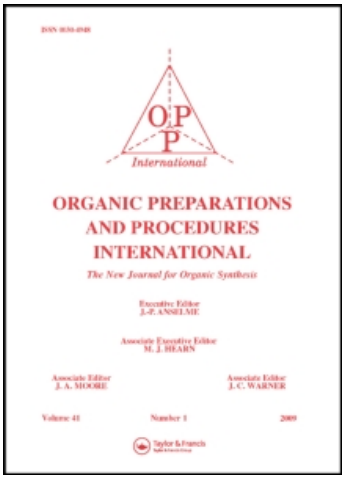

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SYNTHESIS OF 3,4-DIHYDROXYCINNOLINE AND A CONVENIENT PREPARATION OF N-AMINOOXINDOLE

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SYNTHESIS OF 3,4-DIHYDROXYCINNOLINE AND A CONVENIENT PREPARATION OF N-AMINOOXINDOLE

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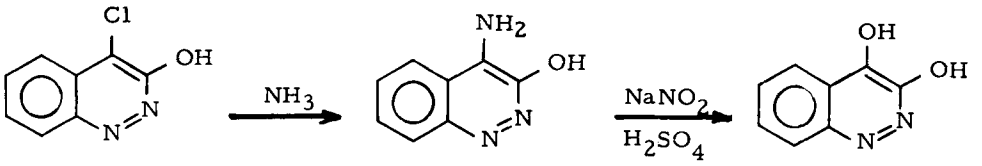
In connection with our work on diketocinnolines,[1] it was necessary to synthesize 3,4-dihydroxycinnoline(III), a compound not previously described in the literature.

The first method investigated for the synthesis of III involved the diazotization of the hitherto unknown 4-amino-3-hydroxycinnoline (II) followed by hydrolysis of the diazonium

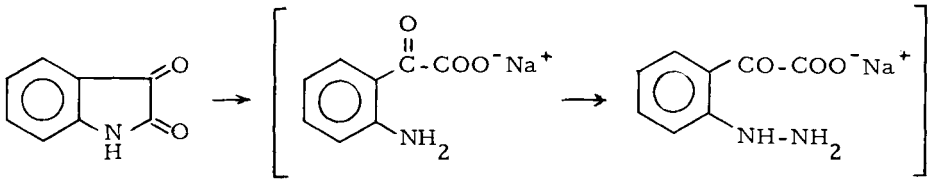


I II III

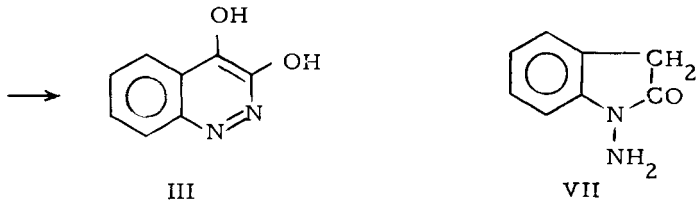
salt to give 3,4-dihydroxycinnoline(III), mp. 253-254° in 60% yield. The required 4-amino-3-hydroxycinnoline(II) was prepared by amination of the 4-chloro-3-hydroxycinnoline(I) with ammonia in methanol under pressure (50 atm) at 160-200°.

An alternative synthesis with a better yield (80%) was accomplished by a modification of the procedure used by Zey[2] for the preparation of 3-cinnolinol. Basic hydrolysis of isatin (IV) afforded the sodium o-aminophenylglyoxylate which

was diazotized without isolation. Reduction with stannous chloride in hydrochloric acid resulted in the formation of III, mp. 253°, identical in all respects with the compound obtained by the above procedure. The yield was dependent of the amount of stannous chloride ($SnCl_2 \cdot 2H_2O$) used. When a 1:2 molar ratio



IV V VI



III VII

of isatin/stannous chloride was used, III was obtained in 80% yield, while a mixture of III (11%) and of N-aminooxindole (VII, 81%) was obtained with a 1:4 molar ratio of isatin/stannous chloride. A more practical procedure for the preparation of VII (61%) involves the prior catalytic reduction of the sodium salt of o-aminophenylglyoxylate, followed by diazotization and reduction with stannous chloride.

EXPERIMENTAL

4-Amino-3-hydroxycinnoline (II).- A suspension of 4 g (0.02 mole) of 4-chloro-3-hydroxycinnoline (I)[3] in methanol (50 ml) saturated with ammonia, was heated in a pressure bomb at 160-200° (25-50 atm.) for 28 hrs. The precipitated 4-amino-3-

hydroxycinnoline was removed by filtration. Evaporation of the filtrate left a residue which was treated with chloroform. Recrystallization from water afforded 2.15 g (61% yield) of pure II, mp. 294°, as yellow plates.

Anal. Calcd. for $C_8H_7N_3O$: C, 59.61; H, 4.37; N, 27.07: Found: C, 59.58; H, 4.59; N, 26.33.
IR (KBr; cm^{-1}): 740, 770, 890, 1110 (s), 1180 (w), 1415 (s), 1530, 1595, 1620, 1670 (vs), 2860 (broad and difuse), 3200 (s), 3320, 3370 (w). NMR (DMSO-d_6; δ): 6.8-7.6 (3H, m, H-5, H-6, H-7), 7.7-8.0 (1H, m, H-8); 11.5 (1H, m, O-H). Mass spectra: m/e 161 (M^+), 133 (22%), 116 (13%), 104 (17%), 77 (12%), 67 (11%), 51 (13%).

3,4-Dihydroxycinnoline (III)

Method A.- To a solution of 1.0 g (0.0062 mole) of II in 60 ml of 5N sulfuric acid, cooled to -5° (ice salt bath) was added dropwise a solution of 0.42 g (0.0062 mole) of sodium nitrite in 100 ml of water. The solution, which turned a red color, was stirred at 0° for 1 hr. After the addition of 100 ml of water, evolution of nitrogen and development of a yellow color were observed. The mixture was stirred at 50° for 2 hrs. and after cooling, was extracted several times with chloroform. The yellow solid obtained after evaporation of the solvent, was recrystallized from water or ethyl acetate/petroleum ether (bp. 50-60°) to give 0.5 g (60%) of III, mp. 253-254°.

Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.25; H, 3.73; N, 17.27. Found: C, 59.31; H, 3.66; N, 16.99.
IR: (KBr; cm^{-1}): 730, 775 (s), 1160 (w), 1240 (s), 1470, 1480

(s), 1690 (vs), 2000-3600 (broad). NMR (DMSO-d_6; δ): 7.2-8.0 (3H, m, H-6, H-7, H-8), 8.0-8.3 (1H, m, H-5), 12.2 (2H, m, disappears on addition of D_2O). Mass spectra: m/e 162 (M^+), 145 (32%), 118 (30%), 91 (25%), 90 (21%), 88 (19%), 63 (13%), 58 (21%), 43 (49%).

Method B.- To a solution of 5 g (0.034 mole) of isatin (IV) in 50 ml of conc. sodium hydroxide in a round-bottomed flask equipped with a thermometer and an efficient magnetic stirrer, cooled to -5° (ice-salt bath) was added dropwise a solution of 2.34 g (0.034 mole) of sodium nitrite in 10 ml of water. The solution was then added in small portions to 100 ml of conc. hydrochloric acid previously cooled to below 0°, and the mixture was stirred for 1 hr. The diazonium salt solution was then added dropwise to a solution of 15.15 g (0.068 mole) of stannous chloride dihydrate in 100 ml of conc. hydrochloric acid previously cooled to below 0°. During the addition, a yellow precipitate appeared. This was filtered and recrystallized from water to give 4.40 g (80%) of a compound which was identical in all respects to that obtained by method A (mixed mp., IR and NMR).

N-Aminooxindole.- A solution of 37 g (0.25 mole) of isatin (IV) in 160 ml of concentrated sodium hydroxide was hydrogenated in the presence of 10% Pd/C catalyst at 25° and 4 atm. The catalyst was removed by filtration and a solution of 17.2 g (0.25 mole) of sodium nitrate in 100 ml of water was added. The resulting solution was then slowly added with stirring to 300 ml of conc. hydrochloric acid under cooling (ice-bath) and the mixture was stirred for one hour.

The diazonium salt solution was then added dropwise to a solution of 222.65 g (1 mole) of stannous chloride dihydrate in 300 ml of conc. hydrochloric acid previously cooled to below 0°. During the addition, a yellow precipitate appeared. The insoluble solid was removed by filtration and recrystallized from water to give 5 g (11%) of 3,4-dihydroxycinnoline identical in all the respects with that obtained above.

The filtrate was neutralized with sodium hydroxide and extracted with chloroform. The combined extracts were dried over anhydrous sodium sulfate and the solvent was evaporated. The residue was recrystallized from water or benzene to give 25 g (61%) of N-aminooxindole, mp. 125-126°.

Anal. Calcd. for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.90. Found: C, 64.62; H, 5.20; N, 19.04.
IR (KBr; cm^{-1}): 3300, 3200 (s); 3425 (s); 1680 (vs); 750 (vs). NMR (Cl_3Cd, δ): 3.55 (2H, s, $-CH_2-CO$); 4.08 (2H, s, NH_2); 7-7.5 (4H, m, arom.).

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