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5-CHLORO- AND 5,7-DICHLOROISATIN BY CHLORINATION OF ISATIN WITH TRICHLOROISOCYANURIC ACID

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5-CHLORO- AND 5,7-DICHLOROISATIN

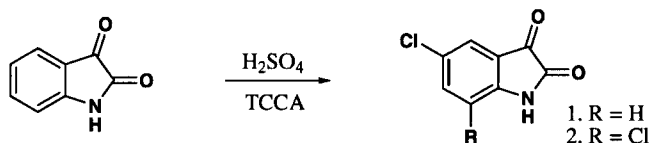
BY CHLORINATION OF ISATIN WITH TRICHLOROISOCYANURIC ACID

Submitted by N. M. Ribeiro*, B. V. da Silva, F. de Almeida Violante,
(12/27/04) C. M. Rezende and A. C. Pinto

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Isatin derivatives have important biological and pharmacological properties. In particular, ketals of 5-haloisatin exhibit anticonvulsant¹ and ansiolitic² activities. The classical method to prepare isatins first reported by Sandmeyer,^{3,4} requires several reagents and may produce hydrogen cyanide as a by-product,⁵ and the yields vary between 70 to 85%. 5-Chloroisatin and 5-bromoisatin can also be prepared from isatin using chlorine or bromine respectively, but these reagents are toxic, corrosive, and can lead to other products. Alternatively, halogenation of isatin can be performed by N-haloamides,⁶ N-haloimides⁷ or N-halosaccharins.⁸ As we needed large amounts of 5-chloroisatin to prepare derivatives for pharmacological tests, we evaluated the use of trichloroisocyanuric acid (TCCA), a safe, low-cost and efficient halogenating agent.⁹

We now report the reaction of isatin with TCCA to prepare 5-chloro- and 5,7-dichloroisatins. The solvent-free method is rapid, efficient and requires very simple manipulations. Trichloroisocyanuric acid reacts with isatin in the presence of sulfuric acid to produce 5-chloroisatin (1) or 5,7-dichloroisatin (2), depending mainly on the ratio of isatin:TCCA.



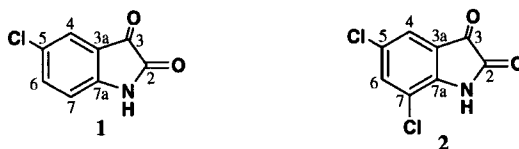
The use of a molar ratio 1:0.4 of isatin:TCCA furnishes the monohalogenated product (1) as the sole product while a molar ratio 1:1 of isatin:TCCA led to 5,7-dichloroisatin (2).

Halogenation occurs preferentially at positions 5 and/or 7, which are the most active for electrophilic aromatic substitution. Although it has been proposed that the aromatic halogenation by TCCA may occur *via* an electrophilic or a radical mechanism,¹⁰ in acidic medium the reaction

Table 1. Yields of **1** or **2** from the Reaction of Isatin with TCCA in Sulfuric Acid

Isatin (mol)	TCCA (mol)	Product	Yield (%)
20	9	1 (R = H)	97
20	20	2 (R = Cl)	93

probably proceeds by an electrophilic mechanism. Since the reaction is very exothermic, it is essential that the mixture be kept in a ice bath during the dropwise addition of sulfuric acid to the solid mixture of isatin and TCCA. The use of low temperature to complete the reaction suppresses the formation of the dichlorinated product (**2**) which is obtained when second phase of the reaction is performed at room temperature. Very pure crystals of the products are obtained by pouring the reaction mixtures over ice. The simplicity of this method and the excellent yields recommends this procedure as one of the best method for the preparation of 5-chloroisatin and 5,7-dichloroisatin selectively.

**Table 2.** ¹H NMR Data of 5-Chloroisatin and 5,7-Dichloroisatin

	NH	H4	H6	H7
1	11.1; 1H, sl	7.39; 1H, s	7.46; 1H, d, J = 8.2Hz	6.86; 1H, d, J = 8.2Hz
2	10.7; 1H, sl	7.13; 1H, d, J = 1.7Hz	7.01; 1H, d, J = 1.7Hz	----

Table 3. NMR ¹³C NMR Data of 5-Chloroisatin and 5,7-Dichloroisatin

	C2	C3	C3a	C4	C5	C6	C7	C7a
1	159.1	183.7	124.6	128.3	114.0	137.7	118.5	149.4
2	159.0	182.7	123.1	128.4	119.5	136.8	118.3	146.8

n

EXPERIMENTAL SECTION

Mps were determined in capillary tubes on a Mel-Temp II and are uncorrected. The IR spectra were obtained as KBr pellets on a Nicolet Magna IR 760. NMR spectra were recorded in CDCl₃-DMSO-d₆ using TMS as an internal standard on a Bruker DRX-200 spectrometer operating at 200 MHz for proton NMR and at 50 MHz for carbon NMR. Mass spectra were acquired on a Hewlett-Packard HP 5973 Mass Selective Detector coupled to a Hewlett Packard 6890 Series GC System controlled by standard Chem-Station G1701AA Ver. A03 (1996). Isatin and trichloroisocyanuric acid (TCCA) were used as received from Meck Co.

Preparation of 5-Chloro-1H-indole-2,3-dione (5-Chloroisatin).- To a mixture of isatin (2.94 g, 20 mmol) and 9 mmol of TCCA (2.09 g, 9 mmol) in an ice bath, 12 mL of H₂SO₄ was added dropwise over a 5 minute period with magnetic stirring. The mixture was kept in an ice bath under stir-

ring for 15 minutes. The mixture was then poured over cracked ice. The crystals were collected and washed with cold water to afford 3.51 g (97%) of 5-chloroisatin as an orange solid, mp. 240-242°C, *lit.*¹¹ 244-245°C. MS (70 eV): 183 (14), 181 (41), 153 (100), 125 (30), 110 (3), 98 (13), 90 (14), 75 (8), 63 (29). IR (cm⁻¹): 3495, 3181, 3080, 3002, 2922, 1752, 1709, 1618, 1451, 1276, 1125, 847, 702, 464.

Preparation of 5,7-Dichloro-1H-indole-2,3-dione (5,7-Dichloroisatin).- To a mixture of isatin (2.94 g, 20 mmol) and of TCCA (4.64 g, 20 mmol) in an ice bath, 12 mL of H₂SO₄ was added dropwise over a period of 5 minutes with magnetic stirring. The ice bath was removed, and the mixture was kept stirring for 30 minutes. The mixture was then poured over cracked ice. The crystals were collected and washed with cold water to yield of 3.98 g (93%) of 5,7-dichloroisatin as a brown solid, mp. 217-219°C, *lit.*¹¹ 223.5-225.5°C. MS (70 eV, m/z (%): 219 (4), 217 (16), 215 (33), 187 (100), 159 (42), 152 (5), 132 (8), 124 (18), 109 (6), 97 (21), 88 (20), 74 (10), 61 (13). IR (cm⁻¹): 3472, 3164, 3107, 3004, 2857, 1758, 1746, 1614, 1453, 1291, 1172, 874, 706, 593.

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