BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN VOL. 42 3016—3017 (1969)

Synthesis of 5-Chloro-6-Methoxy-*N*-Methylisatin

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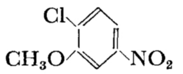
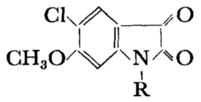
(Received March 27, 1969)

In connection with the investigation of melanin precursors, we have reported the synthesis of the DOPA dimer[1] and pipataline.[2] These substances are interesting as model compounds of melanin precursors. This paper will be concerned with the synthesis of 5-chloro-6-methoxy-*N*-methylisatin (IV), which would make a black pigment upon oxidative polymerization. The compound has been identified with a metabolite of *Micromonospora carbonacea* reported by Reimann and Jaret.[3]

Compound IV was prepared as follows. The chlorination of the diazonium salt obtained from 5-nitro-*o*-anisidine gave 2-chloro-5-nitroanisole (I) in the presence of cuprous chloride. The reduction of I with stannous chloride and hydrochloric acid afforded the corresponding amine; the amine was then converted to 4-chloro-3-methoxyisonitrosoacetanilide (II). After the cyclization of II into 5-chloro-6-methoxyisatin (III), it was methylated with methyl iodide to give IV. The spectral data (IR, UV, and NMR) of the synthetic substance are in good agreement with those of the natural substance, but the melting point of the synthetic substance is lower than that of the natural one.



I



II

III R=H
IV R=CH_3

Experimental

All the melting points are uncorrected.

2-Chloro-5-nitroanisole (I). 5-nitro-*o*-anisidine (20 g), suspended in concentrated hydrochloric acid (50 m*l*) and water (40 m*l*), was diazotized at 0—6°C with sodium nitrite (9 g) in water (50 m*l*). Then the cold diazonium solution was rapidly stirred into an ice-cooled cuprous chloride solution. As the commercial cuprous chloride considerably diminished the yield, it was freshly prepared.[*1] The reaction proceeded very vigorously, with the release of nitrogen gas and the separation of the precipitates. The mixture was stirred for 1.5 hr at room temperature, warmed for 30 min at 50—60°C, and then heated to 80°C for 15 min to decompose the addition product completely. By the steam distillation of the reaction mixture, 2-chloro-5-nitroanisole (19 g, yield 85%) was obtained; mp 84—85°C (lit[4] mp 83°C).

4-Chloro-3-methoxyisonitrosoacetanilide (II). *a) Reduction of 2-Chloro-5-nitroanisole.* A solution of I (20 g) in glacial acetic acid (50 m*l*) was boiled. The heat was removed from the solution of I, to which stannous chloride (104 g) dissolved in concentrated hydrochloric acid was gradually added. A stannic chloride compound of the amine then began to crystallize. After the addition of the stannous chloride solution, the mixture was heated gently for 30 min and then cooled with ice water. The separated crystals were filtered and dried. The yield was 33 g.

b) 4-Chloro-3-methoxyisonitrosoacetanilide. To a solution of chloral hydrate (17 g) in water (200 m*l*), there were added, in order: crystallized sodium sulfate (240 g), a solution of the amine obtained above (32 g) in water (200 m*l*), and finally a solution of hydroxylamine hydrochloride (21 g) in water (90 m*l*). While the mixture was gently boiled for 1.5 hr, the precipitates of the isonitrosoacetanilide separated. After cooling with water, the precipitates were filtered, dried, and extracted with ethyl acetate. The removal of the solvent gave the crude isonitrosoacetanilide (17 .2g), which was reprecipitated from ethanol-water; mp 185°C.

Found: C, 47.40; H, 3.98; N, 12.32%. Calcd for $C_9H_9O_3N_2Cl$: C, 47.27; H, 3.97; N, 12.25%. UV $\lambda_{\max}^{\text{EtOH}}$ nm (ε) 215—220 (17800, sh), 290 (9600, sh), and 300 (10000). IR ν^{KBr} cm^{-1} 3305, 2860, 1620, 1603, 1549, 1289, 1257, and 1066.

5-Chloro-6-methoxyisatin (III). According to the method of the literature,[5] II (15 g) was treated with concentrated sulfuric acid (50 m*l*) to produce the corresponding isatin. The crude product was then purified by dissolving it in aqueous sodium hydroxide and by then slowly adding dilute hydrochloric acid. The

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[1] a) Y. Omote, Y. Fujinuma and N. Sugiyama, *Chem. Commun.*, **1968**, 190. b) Y. Omote, Y. Fujinuma and N. Sugiyama, This Bulletin, **42**, 1752 (1969).

[2] Y. Omote, H. Tazawa, Y. Fujinuma and N. Sugiyama, This Bulletin, **42**, 569 (1969).

[3] H. Reimann and R. Jaret, *Chem. & Ind.*, **1967**, 2173.

[*1] A solution of cuprous chloride was prepared from crystallized copper sulfate (13 g), copper powder (7 g), sodium chloride (6 g) and concentrated hydrochloric acid (40 m*l*).

[4] E. L. Holmes and C. K. Ingold, *J. Chem. Soc.*, **1926**, 1684.

[5] C. S. Marvel and G. S. Hiers, "Organic Syntheses," Coll. Vol. I, p. 327 (1956).

yellow precipitates that separated at first were filtered at once. The pale orange filtrate was acidified to congo red paper with hydrochloric acid. The solution was then cooled, and the isatin (III) which separated (2.3 g) was collected by filtration; mp 278°C.

Found: C, 50.16; H, 3.02; N, 6.96%. Calcd for $C_9H_6O_3NCl$: C, 51.09; H, 2.86; N, 6.62%.

UV λ_{max}^{EtOH} nm (ε) 220 (16500), 267 (25800), 273 (25100), 317 (7400), and 418 (110). IR ν^{KBr} cm^{-1} 3235, 1764, 1614, 1488, 1447, and 1038. This compound produced a black pigment when it was treated with hydrobromic acid.

5-Chloro-6-methoxy-*N*-methylisatin (IV). To a suspension of III (0.3 g) in methanol (3 m*l*) there was added a solution of sodium methoxide (0.12 g) in methanol (3 m*l*). After the mixture had been stirred for 10 min, the sodium salt precipitated was collected. The sodium salt suspended in methyl iodide (6 m*l*) was heated at 100°C for 2 hr in a sealed tube. After the removal of the excess methyl iodide under reduced pressure, the residue was purified in the manner described for the preparation of III. The yield was 0.08 g; mp 242—243°C.

Found: C, 52.92; H, 3.68; N, 6.13%. Calcd for $C_{10}H_8O_3NCl$: C, 53.24; H, 3.57; N, 6.21%.

UV λ_{max}^{EtOH} nm (ε) 221 (17400), 270 (27200), 276 (26400), 319 (6900), and 430 (800). IR ν^{KBr} cm^{-1} 3100, 1745, 1613, 1587, 1493, and 1248.

NMR δ (d_6-DMSO) 3.15 (s, $ArNCH_3$), 4.02 (s, $ArOCH_3$), 6.88 (s, ArH), and 7.52 (s, ArH).