INDOLE DERIVATIVES

XC.* PREPARATION OF INDOLES WITH A SUBSTITUENT IN THE BENZENE RING FROM THE CORRESPONDING 2-NAPHTHOLS

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7-Nitroindole, 5-methoxyindole, and 6-methoxyindole were synthesized by oxidation of 2-naphthol derivatives with hydrogen peroxide to the corresponding o-carboxycinnamic acids and cyclization of their amides under the conditions of the Hofmann reaction.

We have previously reported [2] a new method for the preparation of indole and 5-bromoindole by oxidative opening of the hydroxyl-containing ring of the corresponding 2-naphthols with subsequent closing of the heterocycle. This method seems of promise to us in connection with the accessibility of naphthalene derivatives and the possibility of obtaining indoles with a strictly determined position of the substituent by this method.

In the present research we have studied the possibility of extending the method, having selected as starting materials 6-, 7-, and 8-substituted 2-naphthols with substituents (nitro and methoxy groups) that differ sharply with respect to their electronic effect on the aromatic system.

The oxidative cleavage of 8-nitro-2-naphthol (Ia) with hydrogen peroxide in acetic acid proceeds smoothly. Acid IIa, which is converted to lactone Va only on heating, is formed in high yield. Previously [2], in an attempt to obtain the isomeric 6-nitro acid we isolated only the corresponding lactone; this indicates the substantial steric strain [3] in the molecules of this acid because of disruption of the coplanarity of the system. Oxidation of methoxynaphthols (Ib, c) does not proceed so unambiguously. The yields of the corresponding acids (IIb, c) are low, although they may be raised somewhat if the reaction is carried out at lower temperatures. A low yield for 2,6-dihydroxynaphthalene and its monomethyl ether was also noted in [4]. The presence of electron-donor substituents in the naphthol molecule apparently hinders the production of the corresponding o-carboxycinnamic acids.

Two doublets from vinyl protons with the spin–spin coupling constant ($J = 16$ Hz) characteristic for trans-o-carboxycinnamic acids [3] are observed in the PMR spectra of IIa, c.

When acids IIa,b,c are fused with phosphorus pentachloride and then treated with ammonia, they are converted to trans-diamides (IIIa,b,c), which cyclize to indoles (IVa,b,c) under the conditions of the Hofmann reaction. This transformation can also be realized through a step involving the urethane (VI). In the succeeding steps of the synthesis, i.e., in the II → IV conversion, we did not note a substantial effect of the substituent on the course of the process.

Thus the proposed method for the synthesis of substituted indoles from 2-naphthols is sufficiently general for the preparation of indoles with different substituents in the 5, 6, and 7 positions. The possibility of its practical realization depends primarily on the ease of formation of o-carboxycinnamic acids by oxidative cleavage of the naphthols. There are also quite convenient methods [5] for the synthesis of 5- and 7-substituted indoles, but the proposed method is simpler than the known methods [5, 6] in the synthesis of 6-substituted indoles. The question of the use of this method for the preparation of 4-substituted indoles

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*See [1] for communication LXXXIX.

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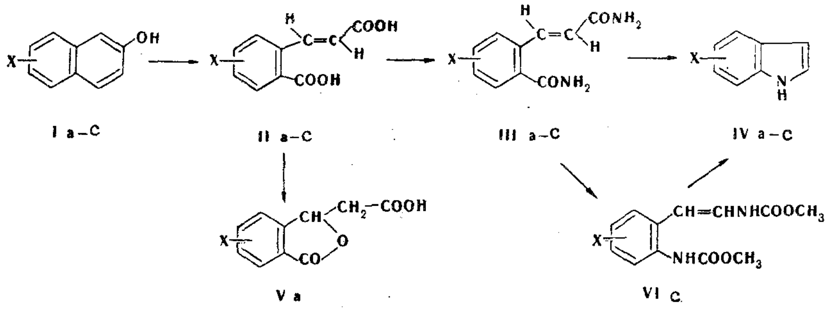

I a $X=8-NO_2$, b $X=c-OCH_3$, c $X=7-OCH_3$; II a $X=3-NO_2$, b $X=5-OCH_3$, c $X=4-OCH_3$;

III a $X=3-NO_2$, b $X=5-OCH_3$, c $X=4-OCH_3$; IV a $X=7-NO_2$, b $X=5-OCH_3$, c $X=6-OCH_3$;

V a $X=3-NO_2$; VI c $X=4-OCH_3$;

remains open despite an unsuccessful attempt [2] to synthesize 4-nitroindole and will be the subject of special investigations.

As demonstrated by our experiments, in contrast to the literature data [7], not only 5- and 8-nitro-2-naphthylamines but also 4-nitro-2-naphthylamine and 4,5-dinitro-2-naphthylamine are formed in the nitration of 2-naphthylamine.

EXPERIMENTAL

The IR spectra of mineral oil suspensions were recorded with a UR-10 spectrometer. The PMR spectra of deuterodimethyl sulfoxide solutions were recorded with a C-60-HL spectrometer with an operating frequency of 60 MHz with tetramethylsilane as the internal standard.

3-Nitro-2-carboxycinnamic Acid (IIa). A total of 40 ml of 40% H_2O_2 was added to a solution of 3.8 g (0.02 mole) of Ia and 60 mg of Na_2MoO_4 in 50 ml of acetic acid, and the mixture was allowed to stand at 40° for 4 days. It was then vacuum evaporated at 30° to 5 ml, 40 ml of water was added, and after 30 min at about 0°, as in [2], 2.7 g (57%) of IIa with mp 193-194° was obtained. IR spectrum: 1670, 1740 (CO) cm^{-1}. PMR spectrum: doublet at 6.5 ppm (1 H, J = 16 Hz) and doublet at 8.1 ppm (1 H, J = 16 Hz). Found, %: C 50.5; H 3.2; N 6.0. $C_{10}H_7NO_6$. Calculated, %: C 50.6; H 3.0; N 5.9. According to [4], this compound has mp 188-189°.

γ-Lactone of 3-Nitro-2-carboxycinnamic Acid (Va). A solution of 0.2 g (0.001 mole) of acid IIa in 10 ml of acetic acid was heated at 55-60° for 1 h, after which it was vacuum evaporated to 3 ml and filtered to give 0.13 g (63%) of Va with mp 157-158° (from water). IR spectrum: 1750, 1780 (CO) cm^{-1}. Found, %: C 50.4; H 2.8; N 6.0. $C_{10}H_7NO_6$. Calculated, %: C 50.6; H 3.0; N 5.9.

5-Methoxy-2-carboxycinnamic Acid (IIb). As in the preceding experiment, 7 ml of 93% H_2O_2 in 7 ml of acetic acid was added to a solution of 2.8 g (0.016 mole) of Ib in 40 ml of acetic acid, after which the mixture was allowed to stand at 25° for 3 days and worked up to give 1.4 g (40%) of IIb with mp 206-207°. IR spectrum: 1675, 1695 (CO) cm^{-1}. Found, %: C 69.6; H 4.5. $C_{11}H_{10}O_5$. Calculated, %: C 59.5; H 4.5. According to [4], this compound has mp 186-187°.

4-Methoxy-2-carboxycinnamic Acid (IIc). As in the preceding experiment, 6 g (0.037 mole) of Ic was oxidized with 15 ml of 93% H_2O_2, and the reaction mixture was allowed to stand at 25-28° for 3 days and worked up to give 3.3 g (43%) of IIc with mp 195-196° (dec.). IR spectrum: 1690, 1710 (CO) cm^{-1}. PMR spectrum: doublet at 6.3 ppm (1 H, J = 16 Hz) and doublet at 8.3 ppm (1 H, J = 16 Hz). Found, %: C 59.3; H 4.3. $C_{11}H_{10}O_5$. Calculated, %: C 59.5; H 4.5.

Diamide of 3-Nitrocarboxycinnamic Acid (IIIa). This compound, with mp 306-308° (dec., from alcohol), was obtained in 81% yield by the method in [2] by fusing IIa with PCl_5 at 110°. IR spectrum: 1630, 1675 (CO), 3370, 3405, 3180 (NH) cm^{-1}. Found, %: C 50.8; H 4.0; N 17.6. $C_{10}H_9N_3O_4$. Calculated, %: C 51.0; H 3.9; N 17.9.

Diamide of 5-Methoxy-2-carboxycinnamic Acid (IIIb). This compound, with mp 237.5-238° (from water), was obtained in 66% yield by fusing IIb with PCl_5 at 115°. IR spectrum: 1670, 1695 (CO), 3200, 3330, 3410 (NH) cm^{-1}. PMR spectrum: doublet at 6.6 ppm (1 H, J = 16 Hz) and doublet at 7.9 ppm (1 H, J = 16 Hz). Found, %: C 60.0; H 5.5; N 12.5. $C_{11}H_{12}N_2O_3$. Calculated, %: C 60.0; H 5.5; N 12.7.

Diamide of 4-Methoxy-2-carboxycinnamic Acid (IIIc). This compounds, with mp 224-225° (from water), was obtained in 86% yield by fusing IIc with PCl_5 at 80°. IR spectrum: 1665, 1695 (CO), 3200, 3330, 3400 (NH) cm^{-1}. PMR spectrum: doublet at 6.4 ppm (1 H, J = 16 Hz) and doublet at 7.7 ppm (1 H, J = 16 Hz). Found, %: C 60.2; H 5.5; N 12.8. $C_{11}H_{12}N_2O_3$. Calculated, %: C 60.0; H 5.5; N 12.7.

4-Methoxy-N,N'-dicarbomethoxy-2,ω-diaminostyrene (VIc). As in [2], 0.3 g (0.001 mole) of IIIc gave 0.08 g (30%) of VIc with mp 180-181° (from water). IR spectrum: 1710, 1720 (CO), 3330, 3410 (NH) cm^{-1}. Found, %: C 55.5; H 5.74; N 10.2. $C_{13}H_{16}N_2O_5$. Calculated, %: C 55.7; H 5.8; N 10.0.

7-Nitroindole (IVa). This compound, with mp 95-97° was obtained in 60% yield by the method in [2]. IR spectrum: 3400 (NH) cm^{-1}. According to [7], this compound has mp 95-97°.

5-Methoxyindole (IVb). This compound was obtained from IIIb by the method in [2]. Compound IVb could be isolated from the reaction mass after treatment with NaOCl by steam distillation or extraction with chloroform or benzene. The yield was 42%. The product did not depress the melting point of an authentic sample and had a completely identical IR spectrum: 3400 (NH) cm^{-1}.

6-Methoxyindole (IVc). This compound, with mp 91.5-92°, was obtained in 36% yield from IIIc as in the preceding experiment. IR spectrum: 3400 (NH) cm^{-1}. According to [9], this compound has mp 92°.

6-Methoxy-2-naphthol (Ib). Absolute tetrahydrofuran (20 ml) and 4.74 g (0.02 mole) of 6-bromo-2-naphthol methyl ether were added successively to 0.61 g (0.025 mole) of Mg activated with iodine, after which the mixture was heated until an exothermic reaction began. At the end of spontaneous refluxing, the mixture was heated for another 15-20 min, cooled to −8 to −10°. Air, purified by passing through granulated KOH, was then passed through the mixture for 2 h, and it was then poured into 150 ml of water. The aqueous mixture was acidified with HCl and extracted with ether. The ether extract was extracted repeatedly with 5% KOH, and CO_2 was bubbled into the alkaline extracts until the pH was about 8. The mixture was filtered to give 1.2 g (36%) of Ib with mp 147-148° (from alcohol) (mp 145-147° [10], mp 150-151° [11]).

7-Methoxy-2-naphthol (Ic). A 6.25 ml (0.064 mole) sample of dimethyl sulfate was added dropwise to a solution of 10 g (0.063 mole) of 2,7-dihydroxynaphthalene in 36 ml of water and 65 ml of 1 N NaOH, after which the mixture was stirred for 6 h and allowed to stand overnight. The precipitate was removed by filtration and stirred with 5% KOH. The alkaline mixture was filtered, and the alkaline filtrate was acidified. The precipitate was removed by filtration and dried to give 5.08 g (47%) of Ic with bp 189° (3 mm) and mp 117-117.5° (aqueous alcohol) (mp 117° [12]).

8-Nitro-2-naphthalene, 4-Nitro-2-naphthylamine, and 4,5-Dinitro-2-naphthylamine. The sulfuric acid mother liquor after separation of the precipitated 5-nitro-2-naphthylamine obtained by nitration [2] of 5 g of 2-naphthylamine was neutralized at 0° with 25% NH_4OH. The precipitate was removed by filtration and extracted with 0.1 N HCl. The acid extract was neutralized with ammonia, and the precipitate (1.2 g) was placed in a column filled with 70 g of Al_2O_3 and eluted successively with ether−petroleum ether (10 : 1) to give 0.6 g (8.2%) of 8-nitro-2-naphthylamine with mp 103-104° (the acetyl derivative had mp 195.5°), 0.2 g (overall yield 21.2%) of 5-nitro-2-naphthylamine with mp 144-145° (the acetyl derivative had mp 185.5), 0.1 g (1.5%) of 4-nitro-2-naphthylamine with mp 96-98° (the acetyl derivative had mp 241°), and 0.15 g (2.3%) of 4,5-dinitro-2-naphthylamine had mp 230-232° (the acetyl derivative had mp 296-297°). According to [13], 8-nitro-2-naphthylamine has mp 103.5-105° (the acetyl derivative has mp 195.5°), 4-nitro-2-naphthylamine has mp 98.5° (the acetyl derivative has mp 241°), and 4,5-dinitro-2-naphthylamine has mp 232° (the acetyl derivative has mp 296°).

8-Nitro-2-naphthol (Ia). This compound, with mp 143-144° (mp 144-145° [13]), was obtained in 70% yield by the method in [14].

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