INDOLE DERIVATIVES

LXXXIII.* PREPARATION OF INDOLE AND 5-BROMOINDOLE FROM 2-NAPHTHOL AND 6-BROMO-2-NAPHTHOL

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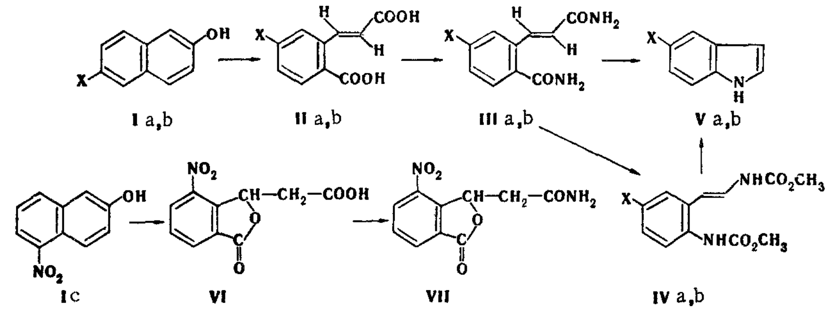
The o-carboxycinnamic acids obtained in the oxidation of 2-naphthol and 6-bromo-2-naphthol were converted to the amides, which give indole and 5-bromoindole, respectively, under the conditions of the Hofmann reaction. Oxidation of 5-nitro-2-naphthol gives the γ-lactone of 6-nitro-2-carboxycinnamic acid rather than the acid itself.

In the present communication we propose a new synthesis for the preparation of indole (Va) and 5-bromoindole (Vb) from 2-naphthol (Ia) and 6-bromo-2-naphthol (Ib). Using this method, one can apparently obtain diverse indoles with a fixed position of the substituent in the benzene ring.



I, II, III, IV, V a X=H; b X=Br

The data available in the literature [2-8] regarding the oxidation of 2-naphthol with peracetic acid made it possible to assume that this process is quite general in character. We carried out the oxidation of naphthols Ia,b by a method similar to that in [5] by somewhat modifying the conditions used to carry out the reaction and the method used to isolate the products. Naphthol Ib is oxidized more rapidly and gives higher yields: side products (coumarins), the formation of which is characteristic [3, 5] for the oxidation of naphthol Ia, were not found in the reaction mass after its oxidation.

Two doublet signals from vinyl protons are observed in the PMR spectra of the oxidation products (IIa,b): at 6.46 and 8.61 ppm for IIa (in deuterodimethylformamide), and at 6.31 and 8.29 ppm for IIb (in deuterodimethyl sulfoxide). The spin–spin coupling constant (J = 16 Hz) corresponds to a trans orientation of the substituents (carboxyl and phenyl) attached to the ethylene bond of the o-carboxycinnamic acids [8].

On treatment with PCl_5 and then ammonia, the carboxylic acids obtained (IIa,b) give the corresponding diamides IIIa,b. We studied their conversion under the conditions of the Hofmann reaction [9]. In the course of this reaction, the cinnamic acid amide is converted to phenylacetaldehyde [10]. Diamides IIIa,b probably similarly form o-aminophenylacetaldehydes which are then converted [11] to the corresponding indoles (Va,b). When the reaction was carried out in methanol [10], we isolated urethanes (IVa,b), which also smoothly form indoles (Va,b) on hydrolysis.

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* See [1] for communication LXXXII.

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In contrast to Ia and Ib, the oxidation of nitronaphthol Ic with peracetic acid gives the γ-lactone (VI). Two groups of signals of the protons of the ABX system of the aliphatic portion of the molecule are observed in its PMR spectrum (in deuteropyridine): the proton of the lactone ring gives a quartet (6.55 ppm, 1H), while the protons of the α-CH_2 group give an octet centered at 3.13 ppm (2H), in which $J_{gem} = 19$ Hz, $J_{vic} = 3$ Hz, and $J'_{vic} = 7$ Hz can be isolated.

Elvidge and Jones [8] link the intramolecular γ-lactonization of o-carboxycinnamic acids with steric effects. In fact, when one examines the molecular models of lactone VI and the corresponding dicarboxylic acid IIc, it can be noted that acid IIc in the coplanar anti-trans and(or) syn–trans conformations (according to the nomenclature in [8]) should experience considerable steric strain; at the same time, such hindrance is almost absent in lactone VI. The lactone form for the oxidation product is probably so much more favorable that we were unable to open the lactone ring even with concentrated alkali or ammonium hydroxide solutions. Amide VII was obtained by successive treatment of lactone VI with PCl_5 and ammonia.

Thus the use of 2-naphthol derivatives for the synthesis of indoles is limited to a considerable degree by the possibility of obtaining the o-carboxycinnamic acids.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were obtained with a UR-10 spectrophotometer, while the PMR spectra were obtained with a C-60 HL spectrometer with an operating frequency of 60 MHz and tetramethylsilane as the internal standard.

o-Carboxycinnamic Acid (IIa). A 30-mg sample of Na_2MoO_4 was added to a solution of 4 g (28 mmole) of Ia in 45 ml of glacial acetic acid, after which 30 ml of 40% H_2O_2 was slowly added dropwise to the mixture. It was then stirred at 30-40° for 4 days, after which 50 ml of water was added, and the mixture was cooled with an ice–salt mixture. The precipitate that formed after 1.5 h was removed by filtration and dissolved in saturated $NaHCO_3$ solution. The solution was filtered to remove the undissolved 4-(2-carboxyphenyl)-5,6-benzocoumarin (mp 280-281°). The filtrate was acidified with dilute HCl, and the precipitate was removed by filtration,washed with cold water to pH 6-7, and dried to give 3.2 g (67.2%) of IIa with mp 203° (from dilute alcohol); IR spectrum: 1680, 1695 (CO) cm^{-1} (mp 170.5-205° [12]).

5-Bromo-2-carboxycinnamic Acid (IIb). As in the preceding experiment, a warm solution of 5 g (22 mmole) of Ib [13] and 30 mg of Na_2MoO_4 in 38 ml of acetic acid was oxidized with 27 ml of 40% H_2O_2 to give 4.27 g (71%) of IIb as a cream-colored powder with mp 183-185° (dec.): IR spectrum: 1685, 1691 (CO) cm^{-1}. Found: C 44.5; H 2.7; Br 29.6%. $C_{10}H_7BrO_4$. Calculated: C 44.3; H 2.6; Br 29.6%.

o-Carboxycinnamic Acid Diamide (IIIa). A mixture of 1 g (6 mmole) of IIa and 2.3 g (11 mmole) of PCl_5 was fused at 90-100° until HCl evolution ceased, after which the yellow melt was dissolved in 20 ml of absolute ether, and the solution was added dropwsie with stirring to 50 ml of liquid ammonia. The ammonia was evaporated, and the residue was allowed to stand at 20° for 4 h. The white precipitate was removed by filtration, washed with 30 ml of cold water, and dried to give 0.42 g (42%) of IIIa with mp 240-242° (from alcohol); IR spectrum: 1645, 1670 (CO), 1620, 970 (C=C), 3400, 3330, and 3200 (NH) cm^{-1} (mp 200 and 230° [8]). Found: C 63.2; H 5.2; N 14.8%. $C_{10}H_{10}N_2O_2$. Calculated: C 63.2; H 5.3; N 14.7%.

5-Bromo-2-carboxycinnamic Acid Diamide (IIIb). A mixture of 6.9 g (25 mmole) of IIb and 11.6 g (55 mmole) of PCl_5 was fused at 50-55°, and the melt was held at this temperature for another hour until HCl evolution ceased. The melt was dissolved in 70 ml of absolute ether, and the solution was added to 300 ml of liquid ammonia to give 5.7 g (82.6%) of IIIb with mp 261-262° (dec., from alcohol); IR spectrum: 1650, 1672 (CO), 1625, 975 (C=C), 3430, 3353, 3170 (NH), cm^{-1}. Found: C 45.1; H 3.3; Br 29.6; N 10.3%. $C_{10}H_9BrN_2O_2$. Calculated: C 45.4; H 3.3; Br 29.7; N 10.4%.

N,N'-Dicarbomethoxy-2,ω-diaminostyrene (IVa). A total of 6 ml of NaOCl solution (here and elsewhere, 1.52 N) was added in portions with stirring to a suspension of 0.8 g (3.2 mmole) of IIIa in 35 ml of methanol, and the mixture was rapidly heated to boiling, refluxed for another 15 min, and cooled with an ice–salt mixture for 4 h. The precipitate was removed by filtration, washed with 20 ml of cold water–methanol (1 : 1), and dried to give 0.52 g (50%) of IVa with mp 168.5-170° (from water); IR spectrum: 1696, 1720 (CO), 3325 (NH) cm^{-1} (mp 168.5-170° [14]).

5-Bromo-N,N'-dicarbomethoxy-2,ω-diaminostyrene (IVb). As in the preceding experiment, 0.65 g of IVb was obtained from 1 g (3 mmole) of IIIb and 12 ml of NaOCl in 60 ml of methanol; evaporation of the mother liquor gave 0.12 g of IVb for an overall yield of 64.8% [mp 186-187° (from dilute methanol)]; IR spectrum: 1700, 1725 (CO), and 3330 (NH) cm^{-1}. Found: C 43.7; H 4.0; Br 24.1; N 8.4%. $C_{12}H_{13}BrN_2O_4$. Calculated: C 43.8; H 4.0; Br 24.3; N 8.5%.

Indole (Va). A. A mixture of 0.95 g (5 mmole) of IIIa and 8 ml of NaOCl was stirred at 40° for 2 h, after which 5 ml of 7% KOH was added and the mixture was slowly steam-distilled until indole was no longer detected in the distillate (test with Ehrlich's reagent). The distillate was extracted with benzene to give 0.327 g (49.7%) of Va, which was identical to an authentic sample.

B. A suspension of 0.5 g (2 mmole) of IVa in 40 ml of 7% KOH was steam-distilled as in the preceding experiment to give 0.21 g (90%) of Va.

5-Bromoindole (Vb). A. A 12-ml sample of cold NaOCl was added in portions to a suspension of 1 g (4 mmole) of IIIb in 15 ml of methanol, and the mixture was refluxed for 35 min, after which 10 ml of 7% KOH was added, and the mixture was steam-distilled as in the preceding experiment. The distillate was filtered to give 0.346 g (55%) of Vb with mp 90.5-91° (mp 90.5-91° [15]). The picrate had mp 136-137° (dec., from methanol) (mp 137-138° [15]).

B. As in the preparation of Va, 0.5 g (1.5 mmole) of IVb was hydrolyzed to give 0.28 g (95.4%) of Vb.

5-Nitro-2-naphthylamine (VIII). A 2.5-g (40 mmole) sample of urea and 5 g (35 mmole) of 2-naphthylamine were dissolved successively in 35 ml of ~100% H_2SO_4, and a cooled solution of 5 g (72 mmole) of sodium nitrate in 70 ml of concentrated sulfuric acid was added dropwise to the viscous mass. After 4 h at −5°, the mixture was poured onto 400 g of finely crushed ice, and the ice mixture was allowed to stand in a refrigerator overnight. The precipitate was removed by filtration, washed with 20 ml of aqueous H_2SO_4 (2 : 1), squeezed thoroughly, and recrystallized from water. A suspension of the precipitate in water was made alkaline with dilute ammonium hydroxide, and the mixture was stirred for another 2 h. The precipitate was removed by filtration, washed with water, and recrystallized three times from alcohol to give 1.2 g of VIII with mp 145-146° (mp 146° [2]). The acetyl derivative had mp 185-186° (from alcohol) (mp 185.5° [2]).

5-Nitro-2-naphthol (Ib). This compound, with mp 147-148° (mp 147-149° [2]), was obtained in 60% yield from VIII by the method in [16].

γ-Lactone of 5-Nitro-2-carboxycinnamic Acid (VI). The oxidation of 2.7 g (14 mmole) of Ic was carried out via the method used to synthesize IIa to give 2.6 g (77%) of VI with mp 194-195.5°; IR spectrum: 1772, 1790, 1765 (CO) cm^{-1}. Found: C 50.6; H 3.0; N 5.9%. $C_{10}H_7NO_6$. Calculated: C 50.6; H 3.0; N 5.9%.

Amide of 5-Nitro-2-carboxycinnamic Acid γ-Lactone (VII). This compound, with mp 250-252° (from alcohol), was obtained in 50% yield from 0.23 g (1 mmole) of VI by the method used to prepare IIIa; IR spectrum: 1770, 1790 (lactone CO), 1692 (amide CO), 3220, and 3370-3410 (NH) cm^{-1}. Found: C 50.5; H 3.4; N 12.0%. $C_{10}H_8N_2O_5$. Calculated: C 50.8; H 3.4; N 11.9%.

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