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Abstract

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A NEW METHOD FOR THE SYNTHESIS OF INDOLES SUBSTITUTED IN THE BENZENE NUCLEUS

In connection with the discovery of serotonin and the search for its antimetabolites, a large number of studies have appeared in the field of indoles substituted in the benzene nucleus. However, the synthesis of such indoles is very difficult. Usually the Reissert method is used, but in this case one must carry out a multistage route starting from substituted *o*-nitrotoluenes, which are often difficult to obtain, and the resulting derivatives of α-indolylcarboxylic acids are usually decarboxylated in low yields. The Fischer synthesis is complicated by the fact that many phenylhydrazines (for example, *p*-methoxyphenylhydrazine, etc.) and, especially, the corresponding phenylhydrazones are very unstable. In re—

[[reaction scheme shown: transformations of indole derivatives labeled I–X, with yields indicated as 85%, 80%, 100%, 90%, 76%, 78%, 58%, 100%, 63%, 80%, and 100%; substituents shown include CH_3, O_2N, H_2N, C_6H_5CONH, and $C_6H_5(CO)_2N$.]]

cent times it has become possible to introduce nitrophenylhydrazones of ketones into the Fischer reaction; however, the cyclization of nitrophenylhydrazones of aldehydes to indoles proceeds with great difficulty. In the case of *m*-nitrophenylhydrazones, a mixture of isomers is formed. The synthesis of indoles from substituted anilines and α-bromoketones (the Bischler method) leads to indoles containing substituents not only in the benzene nucleus, but also in the α- and β-positions. For indole homologs with aliphatic substituents this method is applicable only in a limited number of cases. Indole itself cannot be obtained in this way.

In the present work a new method is proposed for the synthesis of indoles substituted in the benzene nucleus. Indole (or its homolog) is reduced with forma-

of indoline, which is an aromatic amine, and substituents are introduced into the benzene ring by ordinary reactions. The substituted indoline is dehydrogenated to give the corresponding substituted indole. It should be noted that, both for the synthesis of derivatives of indole itself and of derivatives of its N- or β-homologues, the starting material is indole itself.

We obtained 6-nitro-1-methylindole, 6-amino-1-methylindole, and its benzoyl and phthalyl derivatives (see the scheme on p. 94).

Methylation of indole and preparation of 1-methylindoline I were carried out by the method described in the literature ([1],[2]). In its properties I is very close to N,N-dimethyl-*o*-toluidine. Under conditions analogous to those under which dimethyltoluidine is nitrated ([3]), I was nitrated and 6-nitro-1-methylindoline II was isolated. Dehydrogenation of II was carried out by boiling in xylene with chloranil. (In a similar manner, Julian and Printy dehydrogenated 1-methyl-5-methoxyindoline ([4]).) The yield of 6-nitro-1-methylindole III is 61%, calculated on indole, and 72%, calculated on 1-methylindole.

On oxidation of III with chromic acid, nitromethylisatin IV was obtained; its melting point differs sharply from that of 5-nitro-1-methylisatin described in the literature ([5]). Thus, the nitro group in the nitroindole obtained does not occupy position 5. By analogy with the nitration of N,N-dimethyl-*o*-toluidine and tetrahydroquinoline ([6]), we consider that the indole synthesized by us is 6-nitro-1-methylindole. Brown ([7]) likewise believes that, in the nitration of indoline derivatives, the nitro group enters position 6.

Reduction of 6-nitro-1-methylindole with hydrazine hydrate in the presence of Raney nickel gave 6-amino-1-methylindole V. The yield of V is 49%, calculated on indole.

6-Amino-1-methylindole was also obtained by another route. On reduction of 6-nitro-1-methylindoline II with stannous chloride, 6-amino-1-methylindoline VI was isolated. The substance is very close in its properties to 1,1-dimethyl-*m*-phenylenediamine. Heating VI with phthalic anhydride gave 6-phthalimino-1-methylindoline VII. VII was dehydrogenated by boiling with palladium black and cinnamic acid in xylene (see the dehydrogenation of indoline ([8])). On heating with hydrazine hydrate, 6-phthalimino-1-methylindole VIII gave 6-amino-1-methylindole V. The benzoyl derivative prepared from V obtained from 6-nitro-1-methylindole III, and that prepared from V obtained from 6-phthalimino-1-methylindole VIII, proved to be identical (no depression of the melting point of the mixed sample). 6-Benzoylamino-1-methylindole X was also obtained in the dehydrogenation of 6-benzoylamino-1-methylindoline. Dehydrogenation with chloranil in boiling xylene gave X in 80% yield; dehydrogenation with palladium black and cinnamic acid, in 67% yield.

Experimental Part

6-Nitro-1-methylindoline II. To 28.9 g of 1-methylindoline I, with cooling below +3° and vigorous stirring, 200 ml of conc. H_2SO_4 are added. Then a mixture of 9.5 ml of conc. HNO_3 (*d* 1.5) and 50 ml of conc. H_2SO_4 is slowly added dropwise (vigorous stirring, cooling below +3°). After 0.5 h the reaction mass is poured onto ice (1 kg). On gradual neutralization with soda, 38.5 g (quantitative) of 6-nitro-1-methylindoline II are obtained; the substance is bright red, m.p. 49.5-50.5° (from aqueous methyl alcohol).

Found, %: C 60.67; H 5.84; N 15.72
$C_9H_{10}O_2N_2$. Calculated, %: C 60.66; H 5.65; N 15.73

6-Nitro-1-methylindole III—15.7 g of II and 21.5 g of chloranil are dissolved in 300 ml of xylene and boiled for 7 h. After cooling, the solution is washed with 30% alkali, filtered, and washed several more times with alkali,

then with water and dilute hydrochloric acid (1:3). It is washed with water and the xylene is removed in vacuo. After recrystallization from alcohol, 14 g of III (90%) is obtained—a bright-yellow substance, mp 76.5–78.5° (from petroleum ether).

Found, %: C 61.43; H 4.79; N 16.02
$C_9H_8O_2N_2$. Calculated, %: C 61.35; H 4.57; N 15.90

The substance does not form picrates.

6-Amino-1-methylindole V. 15.7 g of III is dissolved in 150 ml of methyl alcohol, 5 g of Raney nickel is added, and 50 ml of hydrazine hydrate is added dropwise. Warming of the reaction mixture to 60° and vigorous evolution of gas are observed. After an hour, the reaction mixture is cautiously heated to 60°, then filtered, and the methyl alcohol is evaporated in vacuo. V is distilled. Yield 10 g of V (78%). Bp 156° at 3 mm. A viscous yellow liquid. Decomposes on storage.

Found, %: C 73.69; H 7.26;
$C_9H_{10}N_2$. Calculated, %: C 73.93; H 6.89

6-Amino-1-methylindole hydrochloride was obtained by passing a stream of dry hydrogen chloride into a solution of V in benzene. It gradually darkens on heating above 100°. Decomposes on attempted recrystallization. Hygroscopic in the presence of alcohol.

Found, %: C 58.91; H 6.30
$C_9H_{11}N_2Cl$. Calculated, %: C 59.17; H 6.07

On benzoylation of V by the Schotten–Baumann method, 6-benzoylamino-1-methylindole X was obtained. The yield was quantitative. Mp 159.5–160.5° (from alcohol, then from benzene, then from xylene).

Found, %: N 11.01
$C_{16}H_{14}ON_2$. Calculated, %: N 11.20

The picrate of 6-benzoylamino-1-methylindole is an orange substance. Obtained in ether. Mp 151–152° (from benzene).

Found, %:	N 14.55
$C_{22}H_{17}O_8N_5$. Calculated, %:	N 14.61

6-Amino-1-methylindoline VI. 17.9 g of II is dissolved in 100 ml of conc. HCl and 80 g of stannous chloride is added. An almost colorless salt of 6-nitro-1-methylindoline and stannous chloride precipitates. On heating on a boiling water bath, the crystalline precipitate of the double salt dissolves. After heating for 3 hours, the reaction mixture is cooled and 40% alkali is cautiously added until a strongly alkaline reaction is reached. The reaction product is extracted with benzene, the benzene is removed in vacuo, and the resulting substance is distilled. 8.7 g of VI is obtained, bp 143–144° at 6 mm. Mp 42–43°. It darkens rapidly in air.

Found, %:	C 73.09; H 8.38
$C_9H_{12}N_2$. Calculated, %:	C 72.93; H 8.16

The benzoyl derivative IX was obtained in quantitative yield by benzoylation by the Schotten–Baumann method. Mp 149.3–149.6° (from ethyl alcohol).

Found, %:	C 76.09; H 6.49; N 11.13
$C_{16}H_{16}ON_2$. Calculated, %:	C 76.16; H 6.39; N 11.12

IX dissolves in conc. HCl; after a day, 6-benzoylamino-1-methylindoline hydrochloride precipitates from the solution. Mp 255.5–256.5° (from alcohol).

Found, %:	C 66.41; H 6.27; N 9.65
$C_{16}H_{17}ON_2Cl$. Calculated, %:	C 66.54; H 5.94; N 9.70

6-Phthalimino-1-methylindoline VII. 5.5 g of 6-amino-1-methylindoline VI and 5.5 g of phthalic anhydride are heated in a bath at 200° for 30 min. After recrystallization from alcohol, 10.2 g of VII is obtained (quantitative yield). M.p. 160–162°.

Found, %:	C 73.28; H 5.26; N 10.08
$C_{17}H_{14}O_2N_2$. Calculated, %:	C 73.36; H 5.07; N 10.06

6-Phthalimino-1-methylindole VIII. 2.78 g of VII are boiled for 5 hr in 5 ml of xylene with 2.96 g of cinnamic acid and 0.1 g of palladium black in a stream of carbon dioxide. After cooling the reaction mixture, the solution is decanted from the palladium black, washed with 30% alkali, filtered, washed with alkali, then with water and dilute acid (1 : 3). After washing with water, the xylene solution is evaporated in vacuo to give 1.7 g (63%) of 6-phthalimino-1-methylindole VIII. M.p. 189–190° (from benzene and alcohol).

Found, %: C 73.60; H 4.80
$C_{17}H_{12}O_2N_2$. Calculated, %: C 73.89; H 4.38

6-Amino-1-methylindole V from VIII. 1 g of VIII is dissolved in 15 ml of methyl alcohol and heated with 1 g of hydrazine hydrate to boiling. After 1 hr the alcoholic solution of IV is filtered and poured into water. It is extracted with ether, dried over $MgSO_4$, and distilled off in vacuo. IV is obtained as an oil. On benzoylation of it, 0.6 g of 6-benzoylamino-1-methylindole X was obtained, m.p. 158–160°.

6-Nitro-1-methylisatin IV. To a solution of 4.5 g of III in 180 ml of acetic acid, with stirring, is added dropwise a solution of 5.2 g of CrO_3 in 15 ml of water. After 0.5 hr, 500 ml of water is added and IV is extracted with benzene. After evaporation of the benzene, 4 g of IV (76%) is obtained. The crystals are bright orange. M.p. 180–180.5° (from benzene).

Found, %: C 52.54; H 3.11; N 13.62
$C_9H_6O_4N_2$. Calculated, %: C 52.43; H 2.88; N 13.59

Phenylhydrazone IV is a dark-red substance. M.p. 225–226° (from acetic acid).

Found, %: C 60.78; H 4.39; N 18.90
$C_{15}H_{12}O_3N_4$. Calculated, %: C 60.81; H 4.08; N 18.91

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Note: Figure translations are in progress. See original paper for figures.

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