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SYNTHESIS OF NITRO- AND AMINOINDOLES

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Optimal conditions are proposed for the direct nitration of 2,3-dimethylindoles containing methyl and methoxy groups in the benzene ring. In contrast to 5- and 6-methylindoles and 5- and 6-methoxyindoles, nitration of 7-methyl- and 7-methoxy-2,3-dimethylindoles proceeds differently under the same conditions. A series of previously unreported aminoindoles was obtained by reduction of the nitroindoles.

Indoles with nitro group in the benzene ring are used to prepare benzaminoindoles, which are employed for the construction of an additional heterocyclic ring and, thus, new heterocyclic systems.

Analysis of the literature data allows to suggest three major pathways for the preparation of nitroindoles: 1) electrophilic introduction of nitro group into the benzene ring of the indole molecule, 2) introduction of nitro group into the benzene ring of indoline with subsequent dehydrogenation to indole, and 3) preparation of indoles with nitro group in the benzene ring using the Fischer reaction.

The selection of a particular method is a function of the nitroindole isomer desired. We carried out a comparative analysis of the literature data [1-9] and the results of our studies on the synthesis of nitroindoles by direct nitration of the corresponding indoles. We should note that the well-known acidophobic nature of indoles requires careful selection and strict maintenance of the conditions for direct nitration. Thus, in the present work, we present several methods for nitration of indoles differing from those reported in the literature, which insure success of this reaction.

The yield and purity of nitroindoles formed depend largely on the purity of the starting indoles. Thus, freshly-distilled or freshly-crystallized indoles should be used for nitration. The sulfuric acid concentration also affects the yield and should be taken in accord with the basicity of the starting compound. 2-Methyl-, 2-aryl-, and 2,3-dimethylindoles are nitrated in good yield in concentrated sulfuric acid, while 2,3,6-trimethyl- and 2,3-dimethyl-6-methoxyindoles are best nitrated in 89% sulfuric acid. Change in the acid concentration leads to side-reactions, which reduce the yield and leads to contamination of nitroindoles produced. Nitration has usually been carried out at from -25° to 0°C depending on the structure of indole used with the aim to prevent resinification of the reaction mixture [3, 9]. Our data suggest that nitration of indoles is best carried out at 0-5°C. We used some special methods for strict maintenance of this temperature range. The quantity of starting indole sample must not exceed 1-1.5 g. Use of solution of indole in 25 ml of sulfuric acid cooled to 0°C and solution of equimolar amount of KNO_3 in the same volume of acid is optimal. In this case, there is virtually no increase in the temperature of the reaction mixture even upon rapid mixing of the reagents. We should note the necessity of rapid extraction of the nitroindoles formed from the acidic reaction medium by rapid filtration of coarse crystalline precipitate or rapid extraction of fine crystalline precipitate with chloroform. Maintenance of these conditions leads to rather pure 5-nitroindoles. Additional purification of 5-nitroindoles prior to reduction was carried out by chromatography (see Experimental).

An advantage of this method of direct nitration for 2-methyl-, 2-phenyl-, and 2,3-dimethylindoles is its regiospecificity. The formation of the 5-nitro isomer occurs since the indoles are nitrated in protonated form under these conditions [10]. When there is a substituent in the benzene ring of 2-substituted or 2,3-disubstituted indoles, the direction of nitration is entirely a function of this substituent although dependence on the pH of the medium is

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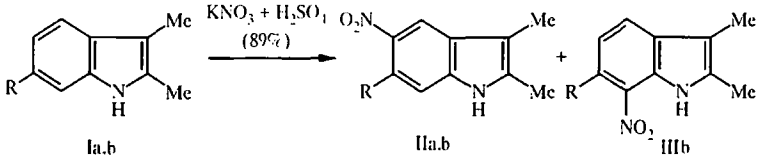
not excluded. When there is a donor substituent in the indole benzene ring, the nitration proceeds in the *ortho* position relative to this substituent. Thus, the nitration of 5-methoxy-2,3-dimethyl- and 2,3,5-trimethylindoles in 95% sulfuric acid by nitrating mixture leads to formation of two isomeric 4- and 6-nitroindoles with predominance of the latter. The nitro group is introduced predominantly at $C_{(6)}$ into 2,3-dimethylindoles with occupied position 5 under conditions of electrophilic attack in acid media.



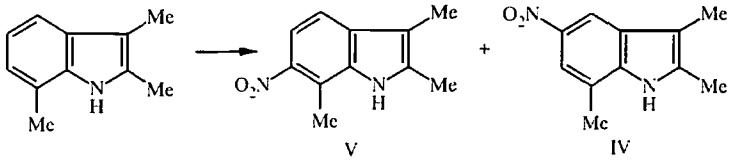
Ia,b IIa,b IIIb

I, II, III a R = Me, b R = OMe

We have found exactly the same behavior for nitration of 2,3-dimethylindoles containing electron-donor substituents at $C_{(6)}$. For example, formation of 7- and 5-nitro products with predominance of the latter is observed in the course of nitration of 2,3-dimethyl-6-methoxyindole Ib in 89% sulfuric acid. Pure 2,3-dimethyl-6-methoxy-5-nitroindole (IIb) was obtained by crystallization from benzene. 2,3-Dimethyl-6-methoxy-7-nitroindole IIIb was isolated by preparative chromatography on thick layer of alumina using chloroform as the eluent.

The structure of the formed isomeric nitroindoles was unequivocally confirmed by PMR spectroscopy (see Table 1). While singlets for the two isolated protons 4-H and 7-H are observed for 5-nitroindoles II, a clear AB system is seen for the *ortho* 4-H and 5-H protons (two doublets) in the case of 7-nitroindole.

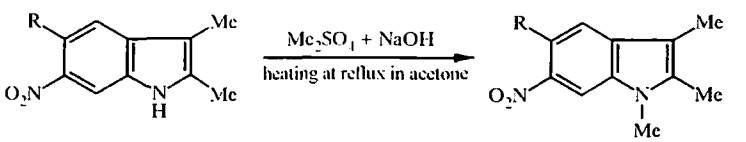
We should note that nitration proceeds differently for analogous indoles containing methoxy and methyl group at $C_{(7)}$ under the same conditions. While, 2,3-dimethyl-7-methoxyindole gives mainly 2,3-dimethyl-7-methoxy-6-nitroindole with a small admixture of 4-nitro isomer [9], 2,3,7-trimethylindole is converted into a mixture of 5- and 6-nitro derivatives with identical content of isomers IV and V.



V IV

In light of the equal solubility of these products, their separation by crystallization proved impossible and, thus, preparative thick-layer chromatographic separation was carried out on alumina plate with chloroform as the eluent. According to Kost et al. [10], 5-nitro isomers may be distinguished from 6-nitro analogs by their UV spectra, in which a bathochromic shift of the long-wavelength band is found for 6-nitro derivatives. The nitroindoles examined in this work conform to this behavior and the long-wavelength band in the UV spectrum of 2,3,7-trimethyl-6-nitroindole is shifted to longer wavelengths in comparison with 5-nitro derivative (Table 1). The aromatic region of the PMR spectrum of 5-nitroindole IV features two doublets for protons 4-H and 6-H with coupling constant of about 2 Hz, characteristic for the coupling of *meta*-situated protons. The structure of 6-nitroindole V is confirmed by occurence of the AB system for 4-H and 5-H protons in the PMR spectrum. Thus, under our conditions, the direct introduction of nitro group into 2,3-dimethylindoles with a methyl or methoxy group in the benzene ring may be used for the preparative synthesis of 5- and 6-nitro isomers in yields of≥50%.

Methylation of the corresponding NH-indoles by dimethyl sulfate in alkaline medium (KOH in acetone or water) was used to obtain N-methylnitroindoles.



VI R = Me; VII R = H VI, VII

TABLE 1. Nitro- and Aminoindoles I–XV

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	PMR spectrum, δ, ppm	UV spectrum		Yield, %
		C	H	M			λ_{max}	log ε	
1	2	3	4	5	6	7	8	9	10
IIa	$C_{11}H_{12}N_2O_2$			204 204	162-163	7.10 (1H, s, 7-H); 11.00 (1H, s, 1-H)	217 273 335	4.40 4.23 3.80	79
IIb	$C_{11}H_{12}N_2O_3$	59.6 60.0	5.5 5.5	220 220	150-152	7.10 (1H, s, 7-H); 8.10 (1H, s, 4-H); 11.10 (1H, s, 1-H)	220 270 345	4.42 4.12 3.61	66
IIIb	$C_{11}H_{12}N_2O_3$			220 220	191-192	7.10 (1H, d, 5-H, $J_{5,4}$ = 9 Hz); 7.83 (1H, d, 4-H, $J_{4,5}$ = 9 Hz); 11.02 (1H, s, 1-H)	260 385	4.10 3.81	8
V	$C_{11}H_{12}N_2O_2$	64.5 64.7	5.7 5.9		206	2.13 (3H, s, 3-CH_3); 2.30 (3H, s, 2-CH_3); 2.40 (3H, s, 7-CH_3); 7.50 (1H, d, 6-H, $J_{6,4}$ = 2 Hz); 7.95 (1H, d, 4-H, $J_{4,6}$ = 2 Hz); 10.75 (1H, s, 1-H)	215 267 339	4.14 4.01 3.73	25
IV	$C_{11}H_{12}N_2O_2$	64.4 64.7	5.6 5.9		198-199	2.00 (3H, s, 3-CH_3); 2.20 (3H, s, 2-CH_3); 2.55 (3H, s, 7-CH_3); 6.97 (1H,d, 4-H, $J_{4,5}$ = 9 Hz); 7.50 (1H, d, 5-H, $J_{5,4}$ = 9 Hz); 10.77 (1H, s, 1-H)	222 260 363	4.18 3.74 3.60	28
VI	$C_{12}H_{14}N_2O_2$	65.9 66.1	6.2 6.4		111-112	2.12 (3H, s, 3-CH_3); 2,27 (3H, s, 2-CH_3); 2.56 (3H, s, 5-CH_3); 3.54 (3H, s, 1-CH_3); 7.05 (1H, s, 4-H); 7.83 (1H, s, 7-H)			67
VII	$C_{11}H_{12}N_2O_2$	64.4 64.7	6.2 5.9		135-136		218 254 276	4.32 3.90 3.85	95
VIII	$C_{11}H_{14}N_2$			174 174	221-223	2.02 (3H, s, 3-CH_3); 2.12 (3H, s, 2-CH_3); 2.18 (3H, s, 6-CH_3); 2.97 (2H, s, 5-NH_2); 6.43 (1H, s, 4-H); 6.76 (1H, s, 7-H); 9.02 (1H, s, 1-H)	207 235 294	3.99 4.08 3.43	90

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10
IX	$C_{11}H_{14}N_2O$			190 190	203-204	1.97 (3H, s, 3-CH_3); 2.13 (3H, s, 2-CH_3); 3.58 (2H, s, 5-NH_2); 3.67 (3H, s, 6-OCH_3); 6.48 (2H, s, 4-H, 7-H); 9.42 (1H, s, 1-H)	208 232 280 (sh) 311	4.22 4.29 3.60 3.82	95
X	$C_{11}H_{14}N_2$	75.4 75.9	7.6 8.0		169-170	1.98 (3H, s, 3-CH_3); 2.18 (6H, s, 2,7-CH_3); 3.28 (2H, s, 5-NH_2); 6.03 (1H, s, 6-H); 6.76 (1H, s, 4-H); 9.10 (1H, s, 1-H)	214 (sh) 232 282 303 (sh)	4.19 4.33 3.78 3.63	73
XI	$C_{11}H_{14}N_2$	76.0 75.9	7.9 8.0	174 174	156-157	2.15 (6H, s, 2,5-CH_3); 2.06 (3H, s, 3-CH_3); 3.53 (2H, s, 6-NH_2); 6.35 (1H, s, 7-H); 6.84 (1H, s, 4-H); 8.96 (1H, s, 1-H)	213 (sh) 234 276 306	4.19 4.29 3.61 3.73	75
XII	$C_{12}H_{16}N_2$	76.5 76.5	8.3 8.5		118-119	2.07 (3H, s, 3-CH_3); 2.13 (6H, s, 2,5-CH_3); 3.35 (3H, s, 1-CH_3); 3.46 (2H, s, 6-NH_2); 6.30 (1H, s, 7-H); 6.87 (1H, s, 4-H)	213 (sh) 236 290 (sh) 308	4.14 4.25 3.63 3.72	67
XIII	$C_{11}H_{14}N_2O$	69.3 69.5	7.1 7.4		130-131	2.12 (3H, s, 3-CH_3); 2.23 (3H, s, 2-CH_3); 3.50 (2H, s, 6-NH_2); 3.80 (3H, s, 5-OCH_3); 6.46 (1H, s, 7-H); 6.62 (1H, s, 4-H); 9.05 (1H, s, 1-H)	213 (sh) 232 286 (sh) 312	4.10 4.15 3.39 3.77	79
XIV	$C_{11}H_{14}N_2$			174 174	154-155	1.98 (3H, s, 3-CH_3); 2.13 (3H, s, 2-CH_3); 2.17 (3H, s, 7-CH_3); 3.12 (2H, s, 6-NH_2); 6.20 (1H, d, 5-H, $J_{5,4}$ = 9 Hz); 6.89 (1H, d, 4-H, $J_{4,5}$ = 9 Hz); 8.78 (1H, s, 1-H)	208 (sh) 231 275 303	4.13 4.38 3.71 3.37	65
XV	$C_{11}H_{14}N_2O$	69.1 69.5	7.0 7.4		150-151	2,13 (3H, s, 3-CH_3); 2,27 (3H, s, 2-CH_3); 3.70 (3H, s, 7-OCH_3); 3.43 (2H, s, 6-NH_2); 5.80 (1H, d, 5-H, $J_{5,4}$ = 9 Hz); 6.10 (1H, d, 4-H, $J_{4,5}$ = 9 Hz); 9.27 (1H, s, 1-H)	227 272 300 (sh)	4.58 3.93 3.79	80

We have found that the benzene ring nitro group enhances the NH-acidity of indoles and significantly facilitates N-methylation. While methylation of nitroindoles proceeds with yields of about 90% and is complete in 2-4 h, methylation of indoles lacking a nitro group does not proceed to completion over a long period even in the presence of sodium hydride [9].

The nitroindoles obtained were converted into the corresponding aminoindoles. Hydrazine hydrate in the presence of Raney nickel was used in all cases to reduce the nitro compounds. The reaction was carried out in methanol using freshly-prepared catalyst and concentrated aqueous hydrazine hydrate over 1 h.

VIII–XV

VIII 5-NH_2, R = 6-Me, R^1 = H; IX 5-NH_2, R = 6-OMe, R^1 = H; X 5-NH_2, R = 7-Me, R^1 = H; XI 6-NH_2, R = 5-Me, R^1 = H; XII 6-NH_2, R = R^1 = Me; XIII 6-NH_2, R = 5-OMe, R^1 = H; XIV 6-NH_2, R = 7-Me, R^1 = H; XV 6-NH_2, R = 7-OMe, R^1 = H

The amines are usually obtained as rather pure samples when chemically pure nitro compounds are used. After drying in the air, these amine products are used in subsequent reactions without purification. In isolating the aminoindoles, we should bear in mind their sensitivity toward oxidation in solution. N-Methylaminoindoles are quite sensitive to the action of oxygen in solution. Methyl and methoxy groups in the benzene ring stabilize the amines relative to oxidation and these derivatives are usually obtained as the purest products.

The PMR spectra of aminoindoles VIII-XV (see Table 1) show characteristic signals for the amino group protons at 2.97-3.58 ppm, depending on the structure of the compound, and for the α,β-methyl group protons at 1.97-2.27 ppm. For aminoindoles not substituted at the nitrogen atom of pyrrole ring a singlet for 1-H is observed at low field (8.78-9.42 ppm), while a singlet for the N–CH_3 group at 3.35 ppm is found for methyl-substituted derivatives such as compound XII. The mutual arrangement of the amino and methyl or amino and methoxy groups may be determined using the pattern of the two benzene ring protons. Thus, two clear singlets in the aromatic region are found for aminoindoles VIII, IX, XI, and XII, which confirms the *para* arrangement of the aromatic protons. The broad signals at 6.03 and 6.23 ppm for aminoindole X indicate the occurrence of *meta* interacting protons, while the two doublets with J = 9 Hz in the spectra of XIV and XV indicate *ortho*-unsubstituted position in the benzene ring.

The electronic spectra of all the obtained aminoindoles (Table 1) show strong short-wavelength band at 230-240 nm, which is characteristic for compounds with pyrrole ring. One or two maxima are seen in the long-wavelength region with lower intensity depending on the position of the amino group probably related to electron transitions in the benzene moiety. Thus, the spectra of 5-aminoindoles VIII-X feature one maximum, while the spectra of 6-aminoindoles XI-XV have two maxima, one of which sometimes appears as a shoulder.

EXPERIMENTAL

The PMR spectra were taken on Varian S-60T, Tesla BS-467C spectrometers at 60 MHz for solutions in DMSO for I-III, in DMSO-d_6 for IV-VII (relative to TMS), in 10:1 CCl_4-DMSO-d_6 for VIII-XV (HMDS as the internal standard). The electronic absorption spectra were taken on Cary-219 and Specord spectrometers for ethanol solutions. The spectral data and other indices for nitro- and aminoindoles are given in Table 1.

Nitroindoles (General Method). Cold solution of potassium nitrate (10.08 mol) in 89-96% sulfuric acid (25 ml) was added with cooling and stirring to cooled solution (0°C) of freshly-purified indole (10.03 mol) in sulfuric acid of the same concentration (25 ml) at a rate such that the temperature of the mixture did not exceed 10°C. After 10-15 min, the reaction mixture was poured onto ice. When a precipitate with coarse particles formed,

the products were filtered, washed repeatedly with water, and dried in the air. When nitroindole was obtained as a fine crystalline dispersion, chloroform (200 ml) was added. After all the nitroindole dissolved, the chloroform layer was separated, washed twice with 10-12% aqueous ammonia, two or three times with water, and dried over Na_2SO_4. Chloroform was then distilled off.

2,3,6-Trimethyl-5-nitroindole (Ia) was obtained from 2,3,6-trimethylindole. Nitration was carried out in 89% sulfuric acid. Nitroindole Ia was purified by chromatography on a column packed with silica gel LP 100/160 using chloroform as the eluent.

6-Methoxy-2,3-dimethyl-5-nitro- (IIb) and 2,3-Dimethyl-6-methoxy-7-nitroindole (IIIb) were obtained analogously from 2,3-dimethyl-6-methoxyindole. The mixture of the two isomers was separated preparatively by thick-layer chromatography on a plate with loose layer of alumina with Brockman II activity using chloroform as the eluent.

2,3,7-Trimethyl-6-nitro- (V) and 2,3,7-Trimethyl-5-nitroindole (IV) were obtained from 2,3,7-trimethylindole. Nitration was carried out in 96% sulfuric acid. PMR spectroscopy indicated a 1:1 isomer mixture. This mixture was separated preparatively by thick-layer chromatography on a plate with loose layer of neutral alumina with Brockman I activity using chloroform as the eluent.

1,2,3,5-Tetramethyl-6-nitroindole (VI). Sample of 2,3,5-trimethyl-6-nitroindole (6.3 mmol) was dissolved in acetone (40 ml). Then, dimethyl sulfate (32 ml), water (0.4 ml), and potassium hydroxide (32 mmol) were added. The reaction mixture was heated at reflux for 2-4 h. At the end of the reaction determined by chromatographic monitoring, water (100 ml) was added. The precipitate formed was filtered, washed repeatedly with water, dried, and recrystallized from heptane.

1,2,3-Trimethyl-6-nitroindole (VII) was obtained analogously from 2,3-dimethyl-6-nitroindole and recrystallized from a mixture of benzene and heptane.

Aminoindoles (General Method). Sample of concentrated hydrazine hydrate (8 ml) and a catalytic amount of freshly-prepared Raney nickel were added to solution of nitroindole (5 mmol) in absolute methanol (100 ml). The reaction mixture was stirred with heating for 1-1.5 h. At the end of the reaction determined by chromatographic monitoring, the still hot mixture was filtered to remove the catalyst. Methanol was distilled off to leave a minimal volume and water (50 ml) was added. The aminoindole precipitate formed was filtered off, washed repeatedly with water, and dried.

5-Amino-2,3,6-trimethylindole (VIII) was obtained from 2,3,6-trimethyl-5-nitroindole and purified by crystallization from aqueous ethanol.

5-Amino-2,3-dimethyl-6-methoxyindole (IX) was obtained from 6-methoxy-2,3-dimethyl-5-nitroindole and purified by crystallization from aqueous ethanol.

5-Amino-2,3,7-trimethylindole (X) was obtained from 2,3,7-trimethyl-5-nitroindole and purified by crystallization from benzene.

6-Amino-2,3,5-trimethylindole (XI) was obtained from 2,3,5-trimethyl-6-nitroindole and purified by crystallization from a mixture of benzene and petroleum ether.

6-Amino-1,2,3,5-tetramethylindole (XII) was obtained from 1,2,3,5-tetramethyl-6-nitroindole and purified by crystallization from petroleum ether.

6-Amino-5-methoxy-2,3-dimethylindole (XIII) was obtained from 5-methoxy-2,3-dimethyl-6-nitroindole and purified by crystallization from aqueous ethanol.

6-Amino-2,3,7-trimethylindole (XIV) was obtained from 2,3,7-trimethyl-6-nitroindole and purified by crystallization from benzene.

6-Amino-7-methoxy-2,3-dimethylindole (XV) was obtained from 7-methoxy-2,3-dimethyl-6-nitroindole and purified by crystallization from a mixture of benzene and petroleum ether.

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