BENZINDOLES 20.*

NITRATION OF 2,3-DIMETHYLBENZ[4,5]- AND 2,3-DIMETHYLBENZ[6,7]INDOLES

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Electrophilic substitution in the pyrrole part of the molecules of benz[4,5]- and benz[6,7]indoles has been widely investigated [2-4]. However, data on the introduction of substituents into the naphthalene part of the molecule are limited to a small amount of data on the bromination [5], acylation [6], and nitration [7, 8] of 2,3-disubstituted benz[4,5]- and benz[6, 7]indoles. The position of the substituent in nitration was not determined.

TABLE 1. Nitro Derivatives of 2,3-Dimethylbenz[4,5]- and 2,3-Dimethylbenz[6,7]indoles (III-VIII)

Compound		IR spectrum, ν, cm^{-1}			R_f	UV spectrum (alcohol solution)		Found, %			Molecular formula	Calculated, %			Yield, % (method of nitration)
		NH	NO₂			λ, nm	lg ε	C	H	N		C	H	N	
III	Vaseline oil	3408	1515	1328 1340 1368	0,62 (1) 0,16 (2)	235 325 400 430	4,73 4,14 3,51 3,34	70,1	5,2	11,9	$C_{14}H_{12}N_2O_2$	70,0	5,0	11,7	28 (1) 34 (2) 17 (3)
IV	KBr	3380	1504	1329	0,62 (1) 0,16 (2)	220 320 380	4,08 4,00 3,48	70,0	5,0	11,5	$C_{14}H_{12}N_2O_2$	70,0	5,0	11,7	26 (1) 27 (2) 15 (3)
	CHCl₃	3468	1553	1332											
V	KBr	3412	1528	1326 1360	0,70 (1) 0,21 (2)	245 305 410 440	4,30 3,66 3,60 3,60	70,0	5,1	11,8	$C_{14}H_{12}N_2O_2$	70,0	5,0	11,7	25 (1) 27 (2) 16 (3)
	CHCl₃	3469	1559	1310—1380											
VI	KBr	3360	1537 1510	1332	0,33 (1)	240 325 440	3,70 3,81 3,00	59,0	3,7	14,7	$C_{14}H_{11}N_3O_2$	59,0	3,9	14,7	1 (1) 1 (2) 6 (3)
	CHCl₃	3460	1560	1345											
VII	Vaseline oil	3437	1520	1320 1343	0,15 (2)	257 280 300 400	4,48 4,30 4,30 4,00	70,1	5,2	11,7	$C_{14}H_{12}N_2O_2$	70,0	5,0	11,7	6 (1) 7 (2) 5 (3)
VIII	Vaseline oil	3443	1512	1353	0,89 (2)	258 315 410 440	4,65 4,08 3,60 3,70	70,3	5,2	11,6	$C_{14}H_{12}N_2O_2$	70,0	5,0	11,7	45 (1) 51 (2) 20 (3)
	CHCl₃	3456	—	1340 1365											

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*For Communication 19, see [1].

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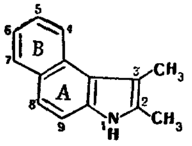
The purpose of the present work was to study nitration for the case of 2,3-dimethylbenz[4,5]- and 2,3-dimethylbenz[6,7]indoles (I, II), which were synthesized by the known scheme from naphthylamines [6, 9].

Nitration was realized by the action of sodium or potassium nitrate in concentrated sulfuric acid and with a mixture of concentrated sulfuric and nitric acids (d_4^{20} 1.35).



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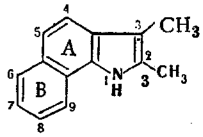

II

By treatment of benzindole (I) with nitrating agents we isolated the monosubstituted 4-nitro-, 6-nitro-, and 7-nitro-2,3-dimethylbenz[4, 5]indoles (III-V) in a ratio of 1:1:1 (according to PMR spectroscopy and to the product yields) and also a very low yield of the disubstitution product 4,6-dinitro-2,3-dimethylbenz[4,5]indole (VI). The overall yield of the nitration products with sodium and potassium nitrate amounted to 80 and 89% respectively (Table 1). The yield with the nitrating mixture was considerably lower (54%). The products (III-V) have almost identical chromatographic mobility (Table 1), and this greatly complicates their separation.

The nitration of the benzindole (II) also takes place ambiguously. From the reaction mixture we isolated the monosubstitution products 6-nitro- and 9-nitro-2,3-dimethylbenz[6, 7]indoles (VII) and (VIII).

The main product (up to 51%) is the 9-nitro derivative (VIII), which is easily separated from the other components of the reaction mixture by chromatography. The isomer (VII) was obtained in a mixture with a product of undetermined structure, from which it could be partially isolated in the pure form after additional purification. The overall yield of the products from nitration of 2,3-dimethylbenz[6,7]indole amounted to 51 and 58% with sodium nitrate and potassium nitrate respectively and 25% with the nitrating mixture.

Thus, the nitration of (I) and (II) occurs in the benzene ring (B) not fused with pyrrole. From the ratio of the yields of the mononitro derivatives it follows that the probability of attack at positions 4, 6, and 7 of 2,3-dimethylbenz[4, 5]indole (I) is approximately the same. For (II), in contrast to (I), substitution is observed at positions 6 and 9 with preferential orientation to position 9. The position of the nitro group was established by PMR spectroscopy (Table 2). The lines were assigned and identified by comparison with the PMR spectra of angular benzindoles and some of their derivatives [10] and also of substituted naphthalenes [11-13]. An assessment was first made of the multiplicity and chemical shift of each proton for all possible cases of substitution by the nitro group. The multiplicity of the signals was determined on the assumption of first-order spectra with the characteristic constants for benzene: $J_{ortho} = 6\text{-}9$, $J_{meta} = 1\text{-}3$, $J_{para} = 0\text{-}3$ Hz [14]. The sequence of the signals was determined from the chemical shifts of the protons of angular benzindoles [10] with allowance for the contributions from the nitro group to the chemical shift. These contribution were assumed to be equal to the values obtained for benzene derivatives [14]. Although it is approximate for the absolute values of the contributions to the chemical shift of the protons in the benzindoles, the last suggestion must, we consider, retain the same sequence for the signals in the second benzene ring of the benzindoles as in substituted benzene.

On the basis of the determinations, the spectra of compounds (III) and (V) correspond to substitution at positions 4 and 7 respectively. In the PMR spectrum of compound (V) (Fig. 1) for the signal of the 4-H proton with δ 8.72 ppm, apart from the constants $J_{4,5} = 7.7$ and $J_{4,6} = 1.1$ Hz, there is an additional constant $J = 0.5$ Hz. Examining the spin–spin coupling constants of substituted naphthalenes [11-13], we supposed that this is the spin–spin coupling constant of the 4-H and 8-H protons. From comparison of the chemical shifts of the 8-H and 9-H indole protons of compound (V) and of the initial compound (I) it is seen that the 8-H proton is greatly descreened ($\Delta\delta_8 \approx 30$ Hz) in compound (V). This is possible when the nitro group is at position 7.

There is also direct evidence for the analysis made above in the spectrum of compound

TABLE 2. PMR Spectra of the Nitro Derivatives of 2,3-Dimethylbenz[4,5]- and 2,3-Dimethylbenz[6,7]indoles (III-VIII) in Acetone-d_6

Compound	1-H	2-CH_3	3-CH_3	4-H	5-H	6-H	7-H	8-H	9-H	$\Delta\delta_{4,5}$, Hz	$\Delta\delta_{8,9}$, Hz	J, Hz
III	10,48	2,32	2,06	—	**7,79**	7,31	8,05	7,48	7,58	—	9,8	$J_{5,6}=7{,}7$; $J_{5,7}=1{,}1$; $J_{6,7}=8{,}0$; $J_{7,8}=0{,}2$; $J_{8,9}=8{,}5$
IV	10,52	2,41	2,54	8,78	8,17	—	8,53	7,66	7,64	—	24,0	$J_{4,5}=9{,}0$; $J_{4,7}=0{,}2$; $J_{4,8}=0{,}5$; $J_{5,7}=2{,}6$; $J_{7,8}=0{,}3$; $J_{8,9}=9{,}2$
V	10,53	2,40	2,53	8,72	7,54	7,88	—	7,81	7.66	—	15,0	$J_{4,5}=7{,}7$; $J_{4,6}=1{,}1$; $J_{4,8}=0{,}5$; $J_{5,6}=8{,}0$; $J_{8,9}=8{,}5$
IV	11,00	2,39	2,09	—	8,51	—	9,00	7,80	7,80	—	0	$J_{5,7}=2{,}2$; $J_{8,9}=8{,}5$
VI*	11,97	2,34	2,01	—	8,52	—	9,12	7,88	7,77	—	10,6	$J_{5,7}=2{,}4$; $J_{7,8}=0{,}2$; $J_{8,9}=8{,}8$
VII	10,89	2,38	2,20	7,73	**7,79**	—	7,86	7,49	8,49	4,0	—	$J_{1,4}=0{,}4$; $J_{4,5}=9{,}0$; $J_{5,9}=0{,}5$; $J_{7,8}=7{,}8$; $J_{7,9}=1{,}1$; $J_{8,9}=8{,}0$
VIII	9,69	2,40	2,33	7,69	7,53	8,17	7,36	8,01	—	15,0	—	$J_{1,4}=0{,}4$; $J_{4,5}=8{,}5$; $J_{6,7}=8{,}0$; $J_{6,8}=1{,}1$; $J_{7,8}=7{,}8$

*In DMSO-d_6.

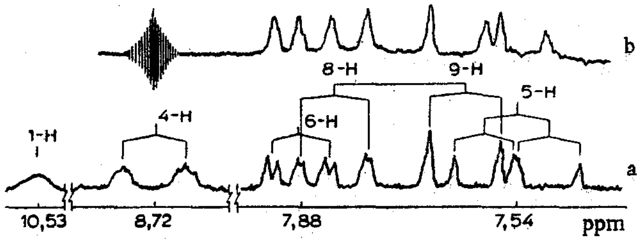

Fig. 1. Aromatic part of the PMR spectrum of compound (V): a) Single resonance spectrum; b) with suppression of the signal for the 4-H proton.

(III). The chemical shift of the methyl protons at position 3 changes greatly ($\sim$ 40 Hz) compared with the chemical shift of this methyl group in compound (I). The assignment of the methyl protons in all the investigated compounds was based on the results presented in Table 3. Here it was supposed that the chemical shift of the 2-CH_3 protons must be more sensitive to replacement of the solvent than the chemical shift of the 3-CH_3 protons [15]. In the spectrum of compound (III) it should be noted that there is an additional constant $J = 0.2$ Hz with one of the indole protons for the signal of the proton with $\delta = 8.05$ Hz. By analogy with substituted naphthalenes [12, 13] we suppose that this is the spin–spin coupling constant of the 7-H and 8-H protons. The assignment of the signals of the 5-H and 7-H protons in compound (III) was made on the basis of the fact that the $J_{6,5}$ constant is smaller than $J_{6,7}$ in all previously investigated benzindoles [10] and naphthalenes [14].

The spectrum of compound (VI) indicates dinitro substitution at position 4 and 6, since it contains two doublets with a characteristic meta constant $J_{\text{meta}} = 2.2$ Hz. They evidently belong to the protons arranged in the meta position in the benzene ring at which substitution occurs. In addition, in the spectrum of this compound, recorded in acetone-d_6, there is a singlet with double intensity at δ 7.8 ppm, which becomes an AB quartet when the solvent is substituted by DMSO-d_6. This makes it possible to assign it to the protons of the first benzene ring. The doublet at δ 9.12 ppm has an additional constant $J = 0.2$ Hz with one of the protons of the AB system. On the basis of data on substituted naphthalenes and of

TABLE 3. Chemical Shifts of the Methyl Groups in Substituted Benz[4,5]- and Benz[6,7]indoles (δ, ppm)

Compound	Solvent	$2\text{-}CH_3$	3-H, $3\text{-}CH_3$
2-Methylbenz[4,5]indole	CCl_4	2,27	6,47
	Acetone-d	2,44	6,67
2,3-Dimethylbenz[4,5]indole	CCl_4	2,24	2,48
	Acetone-d	2,37	2,52
	DMSO-d	2,33	2,48
2-Methylbenz[6,7]indole	CCl_4	2,34	6,11
	Acetone-d	2,43	6,22
2,3-Dimethylbenz[6,7]indole	CCl_4	2,25	2,17
	Acetone-d	2,36	2,19
	DMSO-d	2,30	2,11

comparison with the spectra of compounds (III) and (V) we suppose that this is $J_{7,8}$. The position of the signals for the methyl protons is close to their position in compound (III). All this confirms the assignment.

The spectrum of compound (IV) corresponds to 6-nitro-2,3-dimethylbenz[4,5]indole. The nitro group at position 5 would change the chemical shift of the 4-H proton more downfield than 8.78 ppm. In this case, according to the estimates which were made, the difference in the chemical shifts of the 4-H and 6-H protons amounted to 80 Hz. In the spectrum of compound (IV), however, the difference in the chemical shifts of the 4-H and 5-H protons is 25 Hz, and this corresponds to the calculated data for substitution at position 6. From the double resonance experiment we determined the spin–spin coupling constant of the 4-H and 8-H protons $J_{4,8}$ = 0.5 Hz.

The spectra of the nitro derivatives of 2,3-dimethylbenz[6,7]indole correspond to substitution at positions 6 for compound (VII) and 9 for compound (VIII). As expected, in compound (VIII) the nitro group has a significant effect in the chemical shift of the NH proton compared with (VII) [δ_{NH} = 10.89 for (VII) and 9.69 ppm for (VIII)]. At the same time, for compound (VII) the 5-H proton is the most sensitive to the nitro group [$\delta_{5\text{-}H}$ = 7.33 for (II) and 7.79 ppm for (VII)]. By a double resonance experiment at the NH proton of compound (VIII) it was possible to assign the signal with δ = 7.69 ppm to the 4-H proton ($J_{1,4}$ = 0.4 Hz). In addition, as we suppose, the presence of the constant $J_{5,9}$ = 0.5 Hz for (VIII) confirms the conclusion about the point of substitution.

It should be noted that in the spectra of all the investigated compounds there is a constant $J_{CH_3\text{-}CH_3}$ = 0.2 Hz, obtained by the double resonance method.

EXPERIMENTAL

The PMR spectra were obtained on a high-resolution Varian HA-100D spectrometer for solutions of the compounds in acetone-d_6 and in DMSO-d_6 at 31.5°C with HMDS as internal standard. The IR spectra were recorded on a UR-10 instrument. The UV spectra were recorded on a Shimadzu MPS-50 spectrophotometer for 2% solutions of the compounds in alcohol. The reaction mixtures were chromatographed on Silufol UV-254 plates in benzene (1) and in a 1:1 mixture of benzene and petroleum ether (2). The compounds were separated by column chromatography on Woelm TLC silica gel.

Nitration of 2,3-Dimethylbenz[4,5]indole (I). Method 1. To a solution of 5.0 g (25.6 mmole) of (I) in 20 ml of concentrated sulfuric acid, which had previously been cooled to −8°C, we added dropwise a solution of 2.25 g (25.6 mmole) of sodium nitrate in 20 ml of concentrated hydrochloric acid over 1 h 30 min so that the temperature did not rise above − 8°C. The mixture was then stirred at −8°C for 20 min. It was poured onto ice, and the precipitate was filtered off, washed on the filter to a neutral reaction with water, and dried in air. We obtained 5.33 g of dark-brown crystals. After separation of 1.0 g of the mixture of products (50-mg samples of the mixture of substances, with benzene as eluent) on a column (50 × 40 mm) of silica gel we obtained 0.26 g of (III) (mp 171-172°C, from benzene), 0.24 g of (IV) (mp 206-208°C, from benzene), 0.23 g of (V) (mp 164-166°C, from benzene), and 0.014 g (VI) (mp 263-266°C, from alcohol).

Method 2. Similarly, by nitration with potassium nitrate in concentrated sulfuric acid we obtained 0.3 g of (III), 0.25 g of (IV), 0.25 g of (V), and 0.015 g of (VI).

Method 3. To a previously cooled solution of 2.0 g (10.2 mmole) of (I) in 25 ml of concentrated sulfuric acid over 1 h we added dropwise 0.82 ml (10.2 mmole) of nitric acid (d_4^{20} 1.35) at a temperature not higher than −8°C. The mixture was stirred for 30 min. It was then treated as in method 1. We obtained 2.6 g of dark-brown crystals. After separation of the mixture we obtained 0.42 g of (III), 0.40 g of (IV), 0.41 g of (V), and 0.16 g of (VI).

Nitration of 2,3-Dimethylbenz[6,7]indole (II). Method 1. The reaction was realized by a method similar to that described above with 2.0 g of (II). We obtained 3.16 g of the crude product. After separation of 1.0 g of the reaction mixture on a column (100 × 60 mm) of silica gel (100-mg samples of the mixture of substances, with system 2 as eluent) we obtained 0.35 g of (VIII) (mp 123-124°C, from petroleum ether) and 0.047 g of (VII) (mp 204-206°C, from benzene).

Method 2. Similarly, by nitration with potassium nitrate in concentrated sulfuric acid we obtained 0.39 g of (VIII) and 0.048 g of (VII).

Method 3. Nitration was realized under the conditions described for 2,3-dimethylbenz[4,5]indole. The products were separated as in method 1, and 0.16 g of (VIII) and 0.04 g of (VII) were obtained.

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