INDOLE CHEMISTRY

XXI.* NITRATION OF 3-ACYLINDOLES

L. G. Yudin, A. I. Pavlyuchenko,
V. A. Budylin, V. I. Minkin,
and A. N. Kost

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In the nitration of 3-acyl- and 3-carbethoxyindoles with various nitrating agents, the ratio of substitution of the hydrogen atoms in the 4 or 6 positions or the replacement of the acyl group in the 3 position by a nitro group depend on the conditions. Replacement of the carbethoxy group in the 3 position is not observed. The experimental data were compared with the reactivity indexes calculated by the LCAO MO method. It was concluded that replacement of the hydrogen atoms in the benzene ring of the investigated models proceeds as electrophilic attack of an unprotonated molecule of the indole compound.

Electrophilic reagents preferably attack the 3 position during reaction with indole structures. The resulting carbonium ion is stabilized by adding an anion [addition at the $C_{(2)}-C_{(3)}$ double bond], splits out the substituent in the 3 position (substitution in the pyrrole ring), and attacks another indole molecule (formation of dimers and trimer) or undergoes repeated electrophilic attack with replacement of the hydrogen atoms in the benzene ring. Protonation of the pyrrole portion does not have a substantial effect on the total electron density in the benzene ring but does change its distribution (especially on the boundary orbitals), so that the orientation of the entry of substituents changes on protonation [2]. Most electrophilic substitution reactions proceed in acidic media, in which the indole molecule undergoes competitive attack by a proton or, for example, a nitronium ion. In the process, the proton, which has the minimum steric requirements, is more likely to attack the 3 position than the nitronium ion. In 3-acylindoles, the conjugation of the electron pair of the ring nitrogen atom through the multiple bond with the carbonyl group is markedly expressed; this affects the IR spectra (see [3], for example) and results in rather facile deacylation in acidic media [4]. The side replacement of a 3-acyl group by a nitro group was noted under nitration conditions [5, 6].

In the present research, we made a systematic study of the nitration of a number of 3-acylindoles and, for comparison purposes, 3-carbethoxyindoles. Calculations of the electron density, carried out with Hückel approximation by the LCAO MO method, attest to the fact (see Table 1) that the total charge in 3-acyl- and 3-carbethoxyindoles is a maximum in the 3 position, and, despite the electron-acceptor effect of the acyl group, primary electrophilic attack in the 3 position is consequently the most probable reaction. The electron densities on the boundary orbital are also evidence of this. The total charge is higher on $C_{(5)}$ than on $C_{(4)}$ and $C_{(6)}$ (if there is no substituent in the 7 position), but the density on the boundary orbital in the 5 position is minimal. It is precisely this latter index rather than the charge that determines the direction of substitution during the nitration of alkylindoles in strong acids [2].

The chief process in the nitration of 3-formyl- and 3-acetylindoles and their 1-methyl derivatives in acetic acid, which cannot protonate such weak bases as indole, is substitution of the acyl group to form 3-nitroindole, accompanied by nitration of the benzene ring in the 6 and 4 positions (see Table 1).

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*See [1] for communication XX.

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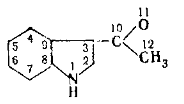
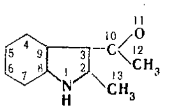
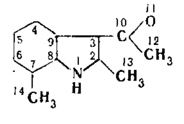
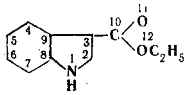
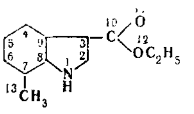
TABLE 1. Charge and Density on the Boundary Orbitals and Multiplicity of the Bonds of 3-Acyl- and 3-Carbethoxyindoles*

Indole	Atom No.	Total charge	Dens. on the boundary orbital	Bond multiplicity
1	2	3	4	5
	1	+0,269	0,080	N—C$_2$ 0,481
	2	+0,186	0,338	C$_2$—C$_3$ 0,696
	3	−0,113	0,374	C$_3$—C$_9$ 0,420
	4	−0,016	0,306	C$_9$—C$_4$ 0,600
	5	−0,023	0,001	C$_4$—C$_5$ 0,692
	6	−0,016	0,289	C$_5$—C$_6$ 0,640
	7	−0,028	0,114	C$_6$—C$_7$ 0,685
	8	+0,007	0,082	C$_7$—C$_8$ 0,624
	9	−0,032	0,177	C$_8$—C$_9$ 0,648
	10	+0,330	0,028	C$_{10}$—O$_{11}$ 0,729
	11	−0,576	0,242	
	12	+0,011	0,000	
	1	+0,265	0,067	N—C$_2$ 0,480
	2	+0,202	0,337	C$_2$—C$_3$ 0,688
	3	−0,122	0,385	C$_3$—C$_9$ 0,419
	4	−0,017	0,293	C$_9$—C$_4$ 0,601
	5	−0,024	0,000	C$_4$—C$_5$ 0,691
	6	−0,018	0,291	C$_5$—C$_6$ 0,640
	7	−0,028	0,126	C$_6$—C$_7$ 0,685
	8	+0,006	0,094	C$_7$—C$_8$ 0,625
	9	−0,032	0,122	C$_8$—C$_9$ 0,656
	10	+0,327	0,030	C$_{10}$—O$_{11}$ 0,724
	11	−0,585	0,248	
	12	+0,012	0,000	
	13	+0,010	0,006	
	1	+0,265	0,073	N—C$_2$ 0,481
	2	+0,202	0,320	C$_2$—C$_3$ 0,688
	3	−0,122	0,380	C$_3$—C$_9$ 0,419
	4	−0,023	0,312	C$_9$—C$_4$ 0,600
	5	−0,023	0,001	C$_4$—C$_5$ 0,692
	6	−0,026	0,296	C$_5$—C$_6$ 0,640
	7	−0,016	0,140	C$_6$—C$_7$ 0,683
	8	0,000	0,078	C$_7$—C$_8$ 0,625
	9	−0,031	0,116	C$_8$—C$_9$ 0,651
	10	+0,327	0,029	C$_{10}$—O$_{11}$ 0,725
	11	+0,012	0,001	
	12	−0,580	0,244	
	13	+0,010	0,006	
	14	+0,007	0,003	
	1	+0,264	0,084	N—C$_2$ 0,472
	2	+0,0169	0,352	C$_2$—C$_3$ 0,712
	3	−0,121	0,387	C$_3$—C$_9$ 0,426
	4	−0,017	0,310	C$_9$—C$_4$ 0,600
	5	−0,024	0,001	C$_4$—C$_5$ 0,694
	6	−0,017	0,290	C$_5$—C$_6$ 0,639
	7	−0,029	0,145	C$_6$—C$_7$ 0,687
	8	+0,006	0,083	C$_7$—C$_8$ 0,623
	9	−0,031	0,114	C$_8$—C$_9$ 0,652
	10	+0,329	0,023	C$_{10}$—O$_{11}$ 0,682
	11	−0,628	0,200	
	12	+0,098	0,009	
	1	+0,264	0,091	N—C$_2$ 0,472
	2	+0,169	0,333	C$_2$—C$_3$ 0,712
	3	−0,121	0,382	C$_3$—C$_9$ 0,426
	4	−0,022	0,330	C$_9$—C$_4$ 0,599
	5	−0,023	0,002	C$_4$—C$_5$ 0,694
	6	−0,026	0,296	C$_5$—C$_6$ 0,638
	7	−0,016	0,161	C$_6$—C$_7$ 0,685
	8	0,000	0,067	C$_7$—C$_8$ 0,621
	9	−0,031	0,107	C$_8$—C$_9$ 0,649
	10	+0,329	0,023	C$_{10}$—O$_{11}$ 0,681
	11	−0,628	0,199	
	12	+0,098	0,009	
	13	+0,007	0,002	

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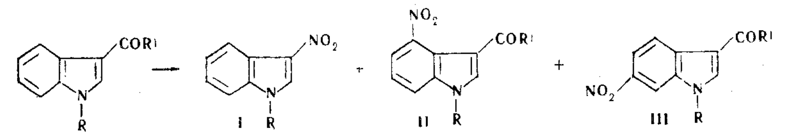
* The following parameters were used for the calculations:

$h_{NH}=1,5$ $h_{O(C=O)}=1$ $h_{CH_3}=4$
$K_{C-N}=0,8$ $K_{C=O}=1$ $K_{C-CH_3}=0,45$

TABLE 2. Nitration of 3-Acylindoles with Nitric Acid (Method A), a Mixture of Nitric Acid and Acetic Acid (Method B), or with Nitrogen Pentoxide in Acetonitrile Containing Triethylamine (Method C)



Starting 3-acylindole		Nitration products											
		I				II				III			
		yield, %			mp, °C	yield, %			mp, °C	yield, %			mp, °C
R	R′	A	B	C		A	B	C		A	B	C	
H	H	0	18	22	210[9]	0	0	—	—	32	29	8	300—302[8]
CH_3	H	—	15	17*	156—157[5]	—	8	6*	232—233[5]	—	14	13*	200—203[5]
H	CH_3	0	24	16	210[9]	0	<1	—	—	30	18	17	340[6]
CH_3	CH_3	3	32	35	156—157[5]	10	5	13	209—210	28	17	14	216—217

* Data on nitration with benzoyl nitrate.

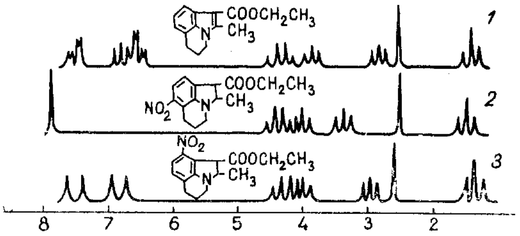
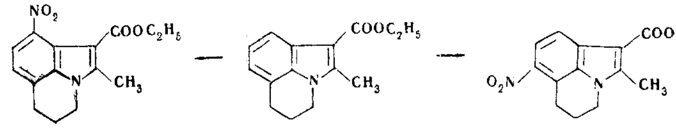


Fig. 1. PMR Spectra: 1) 2-methyl-2-carbethoxy-1,7-trimethyleneindole (V); 2) 4-nitro-V; 3) 6-nitro-V.

If only nitric acid (sp. gr. 1.49), which itself acts as a solvent, is used for the nitration, not even traces of the corresponding 3-nitroindoles can be detected even during a thorough chromatographic study of the reaction mixture. The reaction products proved to be the 4- and 6-nitro derivatives. The side formation of insignificant amounts of 1-methyl-3-nitroindole could be detected only in the case of 1-methyl-3-nitroindole.

The reaction of acetyl and benzoyl nitrates, a solution of nitrogen pentoxide in acetonitrile, or even nitric acid in acetonitrile with 3-acylindoles proceeds just as in the nitration with nitric acid in acetic acid; i.e., the major process proves to be substitution of the acyl group. In all of the cases examined, the orientation during substitution of the hydrogen atom in the benzene ring does not change (the 4- and 6-nitro isomers are always formed), and it can therefore be assumed that a neutral, unprotonated molecule of the indole compound undergoes attack. In fact, in the nitration of 1-methyl-3-acetylindole with nitrogen pentoxide in the presence of triethylamine (which should tie up protons), we obtained the same mixture of nitration products as in acetic acid. We were unable to note replacement of the carbethoxy group by a nitro group in 3-carbethoxyindoles, which also form 4- and 6-nitro derivatives under various conditions.

In all cases, we separated the reaction products preparatively by chromatography on a thin layer of aluminum oxide. Some of the substances had been previously prepared, and they were identified by comparing them with samples of known structure. In the case of 1-methyl-3-acetylindole, the structures of the compounds obtained were proved by methylation of the known 4- and 6-nitro-3-acetylindoles [6] with dimethyl sulfate in alkaline media. The position of the nitro group for the products of the nitration of 1,2-dimethyl-3-carbethoxyindole (IV) was established by means of saponification and decarboxylation to the known 4- and 6-nitro-1,2-dimethylindoles. In the case of 2-methyl-3-carbethoxy-1,7-trimethyleneindole (V), the structures of the reaction products were established by examining the PMR spectra (see Fig. 1). The aromatic region in the spectrum of the 4-nitro isomer is represented as a quartet corresponding to a typical AB system. Only a singlet with an intensity of two protons is found at weak field in the spectrum of the 6-nitro derivative. The nitro group apparently strongly deshields the $C_{(5)}$ proton and less strongly deshields the $C_{(4)}$ proton, which is found at weaker field in the spectrum of the starting indole. The effect of



4-nitro-V V 6-nitro-V

the nitro group equalizes the chemical shifts of both protons, and they become practically magnetically equivalent. One's attention should be drawn to the fact that the signal of the methylene group bonded to the benzene ring is shifted sharply to weak field (0.5 ppm) in the case of the 6-nitro isomer. A similar phenomenon was observed in 6-nitro-2,3-dimethyl-1,7-trimethyleneindole [7].

The difference in the behavior of the 3-acyl- and 3-carbethoxyindoles may be explained by the high stability of the acylium cation that is detached. If this is so, the introduction of a methyl group into the 1 or 2 position should stabilize the transition state and, as a result, raise the yield of the 3-nitro derivative. This is in agreement with both the experimental data obtained in this study and that in the literature [5].

The examination of the mechanism of electrophilic attack on our models should be made with allowance for the possibility of protonation at the oxygen atom, the electron density on which is extremely high, judging from the calculated data. However, a number of problems that require special study arise when this is done.

EXPERIMENTAL

Chromatographic Separation of the Reaction Products. A 0.7-0.8-mm layer of activity II (Brockmann classification) aluminum oxide was applied to an 18 by 24 cm glass plate. A 1-cm-wide layer was removed along the broad side of the plate at a distance of 1.5-2 cm from the edge. The aluminum oxide thus removed was mixed with a solution of the substance to be separated in ether or acetone. The solvent was evaporated until the residue was dry, and the residue was placed in an even layer on the former site on the plate. A benzene–acetone mixture was used as the system for the separation. The colored bands of nitro compounds were removed from the plate and eluted with acetone. The acetone was removed to obtain the pure reaction products.

Monitoring of the Reaction. This was accomplished by analytical thin-layer chromatography, since the R_f values of the starting acylindoles and their nitro derivatives differ appreciably [benzene–acetone (1 : 1)].

The PMR spectra of deuterochloroform solutions were recorded with an RS-60 spectrometer with hexamethyldisiloxane as the internal standard.

Nitration of 3-Acylindoles. A) With nitric acid. A solution of 2.56 g (16.1 mmole) of 3-acetylindole in 40 ml of concentrated nitric acid (sp. gr. 1.42) was stirred initially at 0° for 0.5 h and then at room temperature for 0.5 h and poured into water. The resulting precipitate was removed by filtration and recystallized initially from ethanol and then from acetone to give 0.75 g (23%) of 6-nitro-3-acetylindole with mp 340° [6]. Other nitro compounds could not be detected by chromatography.

B) With nitric acid–acetic acid. A total of 0.16 ml (3.26 mmole) of nitric acid (sp. gr. 1.475) was added dropwise at room temperature to 0.5 g (3.12 mmole) of 3-acetylindole in 8 ml of 95% acetic acid, and the mixture was heated on a boiling-water bath until the starting indole disappeared (as monitored by chromatography). The reaction mass was cooled and diluted with water. The precipitate was removed by filtration, dried, and subjected to chromatographic separation to give 114 mg (18%) of 6-nitro-3-acetylindole with mp 340° [6] and 120 mg (24%) of 3-nitroindole with mp 210° [9].

C) With nitrogen pentoxide in acetonitrile. Triethylamine [0.3 g (3.0 mmole)] was added to 0.5 g (2.79 mmole) of 1-methyl-3-acetylindole in 20 ml of dry acetonitrile, the reaction mixture was cooled to 0°, and a solution of 0.6 g (5.6 mmole) of nitrogen pentoxide in 8 ml of acetonitrile was added dropwise. The mixture was warmed to room temperature and stirred until the starting indole had vanished. The mixture was worked up as in the previous experiment to give 90 mg (14%) of 6-nitro-1-methyl-3-acetylindole with mp 216-217° (Found: C 60.59; H 4.70%. $C_{11}H_{10}N_2O_3$. Calculated: C 60.55; H 4.56%); 81 mg (13%) of 4-nitro-1-methyl-3-acetylindole with mp 209-210° (Found: C 60.35; H 4.59%. $C_{11}H_{10}N_2O_3$. Calculated: C 60.55; H 4.56%); and 165 mg (32%) of 3-nitro-1-methylindole with mp 156-157° [5]. All three of these compounds were obtained with identical melting points and chromatographic mobilities by methylation of the appropriate nitroindoles with dimethyl sulfate in alkaline media.

In a similar experiment, 55 mg (9%) of 6-nitro-1-methyl-3-acetylindole, traces of 4-nitro-1-methyl-3-acetylindole, and 150 mg (30%) of 3-nitro-1-methylindole were obtained by the reaction of 0.5 g of 1-methyl-3-acetylindole with 0.5 g of acetyl chloride and 1 g of silver nitrate in 20 ml of acetonitrile (initially at -10°, and then at room temperature).

Nitration of 1,2-Dimethyl-3-carbethoxyindole (IV). A total of 0.12 ml (2.3 mmole) of nitric acid (sp. gr. 1.475) was added dropwise at room temperature to 0.5 g (2.3 mmole) of IV in 35 ml of 95% acetic acid, and the mixture was heated on a boiling-water bath until the starting indole had vanished (as monitored by chromatography). The mixture was cooled and poured into water. The precipitate was separated chromatographically to give 145 mg (24%) of 6-nitro-1,2-dimethyl-3-carbethoxyindole (6-nitro-IV) with mp 200-201° [Found: C 59.42; H 5.46%; $C_{13}H_{14}N_2O_4$. Calculated: C 59.54; H 5.32%] and 90 mg (15%) of 4-nitro-1,2-dimethyl-3-carbethoxyindole (4-nitro-IV) with mp 145° [Found: C 59.47; H 5.34%. $C_{13}H_{14}N_2O_4$. Calculated: C 59.54; H 5.32%].

Similarly, 142 mg (24%) of 6-nitro-IV and 100 mg (17%) of the 4-nitro isomer were obtained from 0.5 g of IV and 0.5 g (4.6 mmole) of nitrogen pentoxide in 28 ml of acetonitrile and 0.3 g (3.0 mmole) of triethylamine (initially at 0°, and then at room temperature) after removal of the solvent and preparative chromatography in a thin layer of aluminum oxide.

6-Nitro-1,2-dimethylindole. A mixture of 100 mg of 6-nitro-IV, 3 ml of 95% acetic acid, and 0.4 ml of concentrated sulfuric acid was refluxed for 20 min, cooled, and poured into water. The resulting precipitate was washed with water and chromatographed to give 10 mg (15%) of 6-nitro-1,2-dimethylindole with mp 105° [10].

4-Nitro-1,2-dimethylindole. This compound [5 mg (8%)] was similarly obtained from 100 mg of 4-nitro-IV and had mp 93-95° [10].

Nitration of 2-Methyl-3-carbethoxy-1,7-trimethyleneindole (V). A total of 0.1 ml (2 mmole) of nitric acid (sp. gr. 1.475) was added dropwise at room temperature to a solution of 0.5 g (2 mmole) of V in 10 ml of glacial acetic acid, and the mixture was heated on a boiling-water bath until the starting indole had vanished (as monitored by chromatography). The mixture was cooled and poured into water. The resulting precipitate was chromatographed to give 179 mg (30%) of 6-nitro-2-methyl-3-carbethoxy-1,t-trimethyleneindole (6-nitro-V) with mp 178-180° [Found: C 62.45; H 5.62%. $C_{15}H_{16}N_2O_4$. Calculated: C 62.50; H 5.56%] and 155 mg (26%) of 4-nitro-2-methyl-3-carbethoxy-1,7-trimethyleneindole (4-nitro-V) with mp 142-143° [Found: C 62.32; H 5.57%. $C_{15}H_{16}N_2O_4$. Calculated: C 62.50; H 5.56%].

Similarly, 59 mg (17%) of 6-nitro-V and 18 mg (5%) of 4-nitro-V were obtained from 0.3 g (1.2 mmole) of V, 0.5 g of silver nitrate, and 0.5 g of benzoyl chloride in 20 ml of acetonitrile (initially at -5°, and then at room temperature) after separation of the AgCl, vacuum evaporation, and chromatographic separation.

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