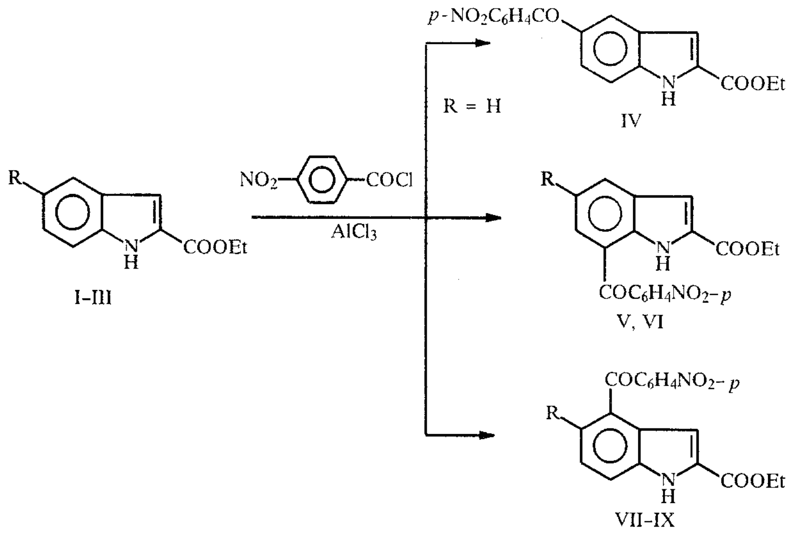
INDOLE DERIVATIVES.
140.* FRIEDEL–CRAFTS ACYLATION OF SOME 5-SUBSTITUTED 2-(ETHOXYCARBONYL)INDOLES BY p-NITROBENZOYL CHLORIDE

I. Sh. Chikvaidze, É. O. Gogrichiani, L. N. Kurkovskaya,
L. V. Baramidze, Sh. A. Samsoniya, and N. N. Suvorov

It was shown that Friedel–Crafts acylation of 5-methyl-2-(ethoxycarbonyl)indole by p-nitrobenzoyl chloride occurs predominantly in the 4 and 7 positions, and that of the 5-methoxy derivative occurs in the 4 position.

In [2], Murakami et al. described the acylation of 2-(ethoxycarbonyl)indole (I) by acid anhydrides and chlorides under conditions of the Friedel–Crafts reaction in the presence of $AlCl_3$ with boiling in 1,2-dichloroethane. The ratio of the resulting 3-, 5-, and 7-acyl derivatives changed in relation to the strength of the corresponding acid. Acylation by derivatives of stronger acids occurred with an increasing fraction of 5-substituted isomers. During acylation by p-nitrobenzoyl chloride, these derivatives formed in a 9:72:19 ratio, respectively, in 68% total yield, i.e., substitution occurred predominantly in the 5 position of 2-(ethoxycarbonyl)indole (I).

We investigated the possibility of a change of the direction of the p-nitrobenzoylation using 5-substituted 2-(ethoxycarbonyl)indoles. For that purpose, we carried out p-nitrobenzoylation of 2-(ethoxycarbonyl)-5-methylindole (II), 2-(ethoxycarbonyl)-5-methoxyindole (III), and, for comparison, 2-(ethoxycarbonyl)indole (I).



I, V R = H; II, VI, VII R = CH_3; III, VIII R = OCH_3; IX R = OH

During acylation of 2-(ethoxycarbonyl)indole (I), 5- and 7-acylindoles IV and V formed in a 49:1 ratio in total yield 75%. The predominant formation of the 5-acyl derivative was probably due to the fact that when a strong acylating agent, p-

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*See [1] for Communication 139.

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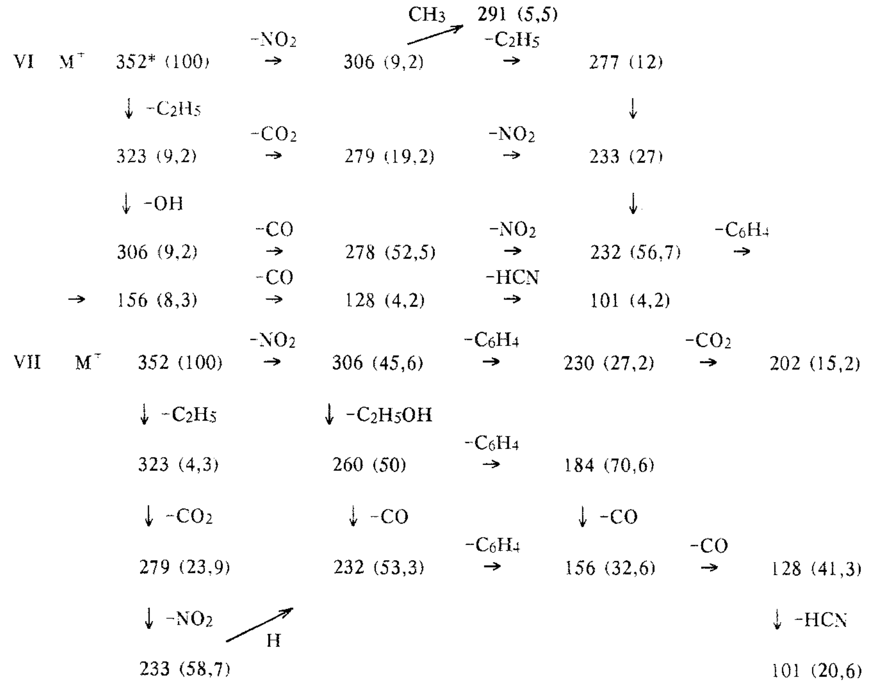
nitrobenzoyl chloride, was used, the direction of the reaction was governed not by electronic factors, but by steric factors. In the remaining cases, 4- and 7-substituted compounds VI-IX were obtained in 56-62% total yields. Whereas the 4- and 7-acyl derivatives of 2-(ethoxycarbonyl)-5-methylindole (II) formed in a 1:1 ratio (compounds VI and VII), for 2-(ethoxycarbonyl)-5-methoxyindole (III) the 7 isomer was absent, probably because of the strong orienting effect of the OCH_3 group. The product of acidolysis of compound VIII, 2-(ethoxycarbonyl)-4-(p-nitrobenzoyl)-5-hydroxyindole (IX), was recovered unexpectedly in high yield [3].

In the IR spectra of all acylation products IV-IX, not only absorption bands characteristic of the C=O ester group in the region of 1710-1700 and the N−H group in the region of 3460-3310 cm^{-1}, but also bands of stretching vibrations in the region of 1650-1610 cm^{-1} appeared, which is characteristic of the Ar−CO−Ar group (Table 1).

The substitution sites were determined by comparison of the PMR spectra of acyl derivatives VI-IX and starting compounds II and III. The spectra of compounds VII-IX contained no peaks of 4-H protons that were contained in the spectra of compounds II and III at 7.42 and 7.21 ppm, respectively, and the spectrum of compound VI contained no 4-H proton peak that appeared in the spectrum of compound II at 7.35 ppm. All spectra contained peaks in the form of two doublets characteristic of protons of p-disubstituted benzenes. In addition, the peaks of all indole protons were shifted to the region of weak fields because of the electron-acceptor effect of the introduced substituent. The significant strong-field shift of the peaks of 3-H (compounds VII-IX) and 1-H (compound VI) protons can be explained by anisotropy of the neighboring $CO-C_6H_4-NO_2$ group (Table 2).

The molecular mass numbers of compounds VI-IX, determined mass-spectrometrically, corresponded to calculations, and the nature of subsequent fragmentation did not contradict the proposed structures:



In the mass spectra of compounds VI-VII the maximum intensity was observed in the case of peaks of molecular ions with mass 352, and in the spectra of compounds VIII and IX the maximum intensity was observed in the case of peaks of ions obtained after abstraction of NO_2 groups from the molecular ions. This fact indicates that the molecular ions are more stable in the first cases. Under electron impact, the molecular ion of compound VI decomposed with subsequent abstraction of C_2H_5, OH, CO, NO_2, C_6H_4, and HCN groups, i.e., first the ester group was abstracted, and then the p-nitrobenzoyl group. This is indicated by the high intensity of the peaks corresponding to mass numbers 323, 306, 278, 232, and 156 in comparison with the others. Fragmentation of molecular ion VII occurred in two directions, i.e., with abstraction of nitrobenzoyl and ester groups. In the mass spectra of compounds VIII and IX, the maximum intensity was observed in the case of peaks of ions with

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*The m/z values are presented, and the relative intensities with respect to the maximum ion current are presented in parentheses.

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	mp, °C	R_f*	IR spectrum, ν, cm⁻¹	UV spectrum, λ_{max}, nm (log ε)	Yield, %
VI	$C_{19}H_{16}N_2O_5$	149...151	0,86	3460 (NH), 1710 (CO, ester), 1640 (C=O)	202 (4,43), 263 (4,26), 364 (3,94)	30
VII	$C_{19}H_{16}N_2O_5$	176...178	0,47	3350 (NH), 1710 (CO, ester), 1620 (C=O)	203 (4,42), 222 (4,33), 265 (4,13), 298 (4,05)	31
VIII	$C_{19}H_{16}N_2O_5$	215...217	0,49	3350 (NH), 1710 (CO, ester), 1650 (C=O)	204 (4,34), 219 (4,36), 269 (4,14)	10
IX	$C_{18}H_{14}N_2O_6$	218...220	0,47	3310 (NH), 1700 (CO, ester), 1610 (C=O), 3135 (OH)	205 (4,32), 219 (4,25), 264,5 (4,21)	46

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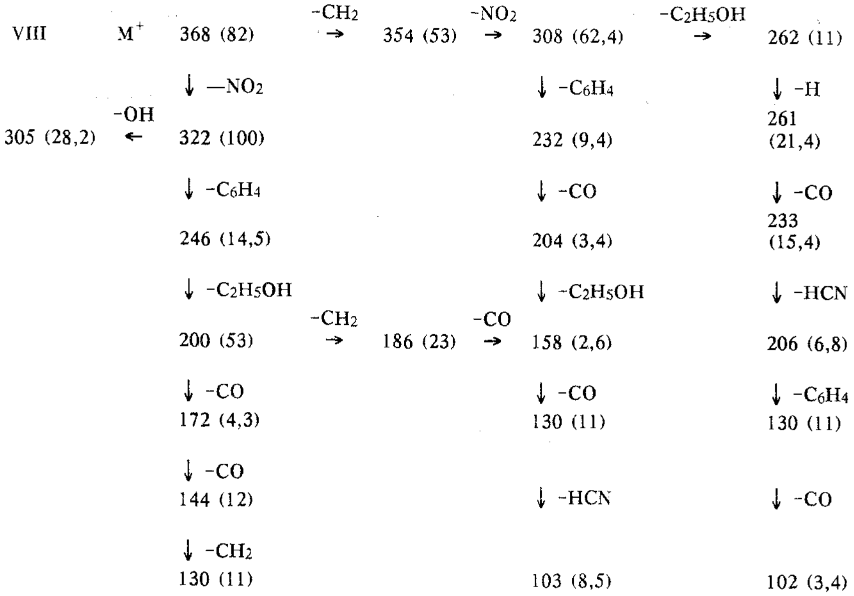
*Benzene–acetone, 10:1.



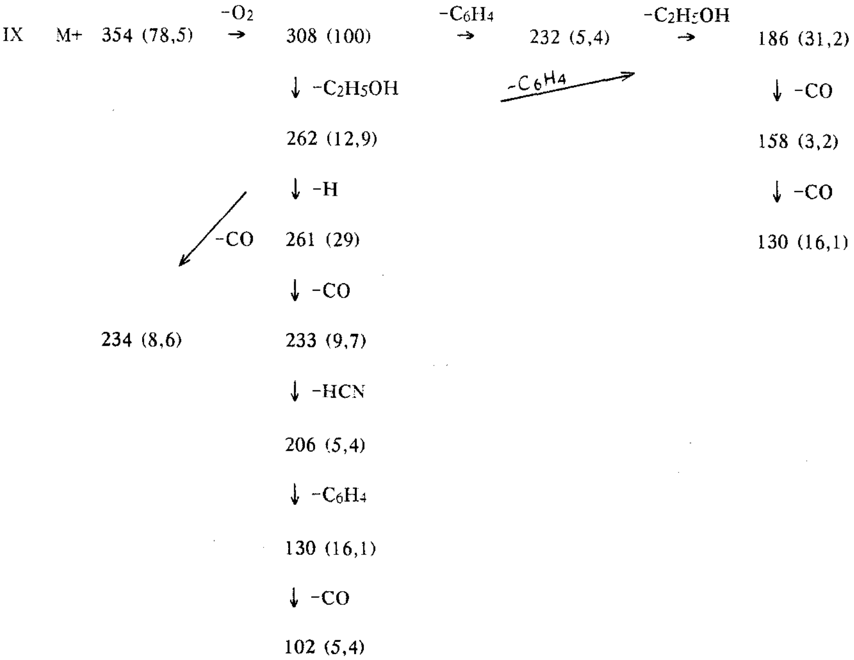


TABLE 2. PMR Spectra of Compounds II, III, and VI-IX

Compound	Chemical shifts, δ, ppm	SSCC, J, Hz
II	11,74 (1H, s, 1-H); 7,05 (1H, br.s, 3-H); 7.42 (1H, d. 4-H); 7,08 (1H, d.d , 6-H); 7,35 (1H, d, 7-H); 2,36 (3H, § 5-CH_3); 4,33 (2H, q $\underline{CH_2}CH_3$); 1,34 (3H, t, $\underline{CH_3}CH_2$)	$J_o = 8,4$; $J_m = 1,1$
III	11,76 (1H, s 1-H); 7.07 (1H, br.s, 3-H); 7,11 (1H, d. 4-H); 6,94 (1H, d.d 6-H); 7,38 (1H, d, 7-H); 3,77 (3H, s. $O\underline{CH_3}$); 4.34 (2H, q, $\underline{CH_2}CH_3$); 1,35 (3H, t. CH_3CH_2)	$J_o = 8,8$; $J_m = 2,2$
VI	10,96 (1H, s. 1-H); 7.31 (1H, d, 3-H); 7.43 (1H, d. 4-H); 7.91 (1H, d, 6-H); 2,41 (3H, s, 5-CH_3); 4,38 (2H, q, $\underline{CH_2}CH_3$); 1,36 (3H, t, $\underline{CH_3}CH_2$); 8,01 (1H, d A-H); 8,41 (1H, d, B-H)	$J_m = 1,1$; $J_{AB} = 8.4$ $J_{13} = 1,1$
VII	12,20 (1H, s, 1-H); 6,56 (1H, br. s, 3-H); 7,29 (1H, d.d, 6-H); 7.60 (1H, d, 7-H); 2,23 (3H, s. 5-CH_3); 4.28 (2H, q, $\underline{CH_2}CH_3$); 1,27 (3H, t, $\underline{CH_3}CH_2$); 7,93 (1H, d. A-H); 8.36 (1H, d. B-H)	$J_o = 8,6$; $J_{AB} = 8.4$
VIII	12,15 (1H,s , 1-H); 6,96 (1H, d ,3-H); 7,29 (1H, d 6-H); 7,71 (1H, d 7-H); 3,62 (3H,s, OCH_3); 4,32 (2H, q, $\underline{CH_2}CH_3$); 1,31 (3H, t, $\underline{CH_3}CH_2$); 7,89 (1H, d, A-H); 8,33 (1H, d, B-H)	$J_o = 8,8$; $J_{AB} = 8.4$ $J_{13} = 1,5$
IX	12,07 (1H, s, 1-H); 6,87 (1H, br. s, 3-H); 7,00 (1H, d. 6-H); 7,59 (1H, d 7-H); 10,03 (1H, s. OH); 4,30 (2H, q., $\underline{CH_2}CH_3$); 1,30 (3H, t, $\underline{CH_3}CH_2$); 7,91 (4H, d. A-H); 8.33 (1H, d, B-H)	$J_o = 8,8$; $J_{AB} = 8.4$

mass numbers 322 and 308, respectively, which probably corresponds to initial abstraction of NO_2 groups from molecular ions with mass numbers 368 and 354, and subsequent fragmentation of these ions occurred with simultaneous decomposition of benzoyl and ester groups.

EXPERIMENTAL

Monitoring of the course of the reaction and the purity of the compounds, as well as determination of the R_f values were carried out on Silufol UV-254 plates. The sorbent for column chromatography was silica gel with particle size 100-250 μm.

The UV spectra were recorded in ethanol with a Specord spectrophotometer, the IR spectra were recorded in white mineral oil with a UR-20 instrument, and the PMR spectra were recorded with a WP-200 SY spectrometer. Chemical shifts were measured with respect to TMS as the internal standard with accuracy 0.01 ppm, and the spin–spin coupling constants were measured with accuracy 0.1 Hz. The mass spectra were measured with a Ribermag 10-10-B spectrometer, and the energy of the ionizing electrons was 70 eV.

The data of elemental analysis of compounds VI-IX for C, H, and N corresponded to the calculated values.

General Acylation Method [4]. A solution of 7.42 g (40 mmoles) of p-nitrobenzoyl chloride in 40 ml of 1,2-dichloroethane and then a solution of 20 mmoles of a derivative of 2-(ethoxycarbonyl)indole II or III in 40 ml of 1,2-dichloroethane were added dropwise with cooling to a solution of 10.68 g (80 mmoles) of $AlCl_3$ in 80 ml of 1,2-dichloroethane. The whole was boiled for 3 h. (In the case of 2-(ethoxycarbonyl)-5-methoxyindole (III), the reaction was carried out at 60°C.) The reaction material was poured into 500 ml of ice water, acidified with HCl to pH 1, and extracted with chloroform, and the extract was washed with water, a 2% sodium hydroxide solution, and again with water and dried with anhydrous Na_2SO_4. The solvent was evaporated under vacuum, and the residue was separated on a column with a benzene eluent.

REFERENCES

1. E. N. Gordeev, V. E. Zhigachev, and M. M. Kuznetsov, Khim. Geterotsikl. Soedin., No. 1, 46 (1992).
2. Y. Murakami, M. Tani, K. Tanaka, and Y. Yokoyama, Heterocycles, 22, 241 (1984).
3. L. Gutterman and G. Wieland, Practical Studies in Organic Chemistry [Russian translation], Goskhimizdat, Moscow–Leningrad (1948), p. 187.
4. A. N. Kost (ed.), General Practical Course in Organic Chemistry [Russian translation], Mir, Moscow (1965), p. 308.