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PYRROLOINDOLES. 18*. AN UNEXPECTED CHLORINATION REACTION DURING THE SYNTHESIS OF 2,7-DIETHOXYCARBONYL-1H,8H-PYRROLO[3,2-*g*]INDOLE

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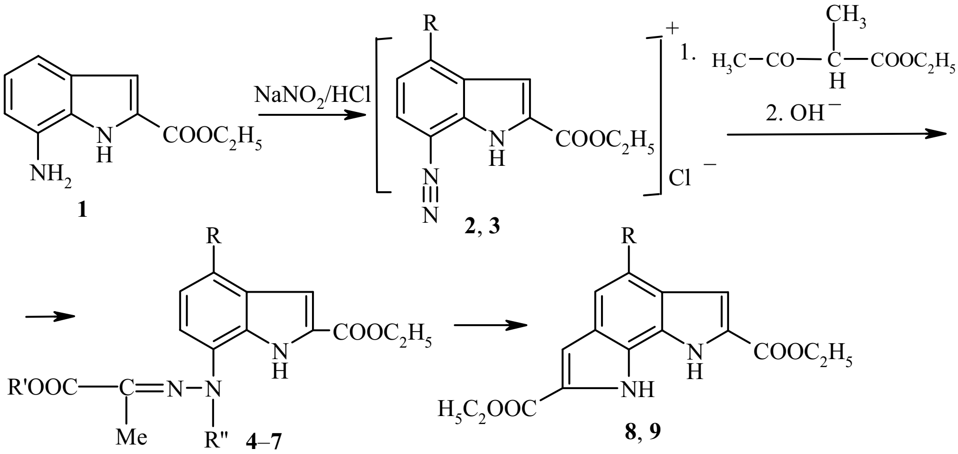
During the E. Fischer type synthesis of 2,7-diethoxycarbonyl-1H,8H-pyrrolo[3,2-g]indole there was discovered an unusual chlorination reaction of the benzene ring in 7-amino-2-ethoxycarbonylindole. It is suggested that the reaction occurs via an electrophilic substitution mechanism.

Keywords: pyrroloindoles, Fischer synthesis, chlorination, electrophilic substitution.

The synthesis of 2,7-diethoxycarbonyl-1H,8H-pyrrolo[3,2-*g*]indole *via* annelation of a second pyrrole ring to the benzene ring of 7-amino-2-ethoxycarbonylindole (**1**) has been reported in the literature [2]. We have shown [3] that diazotation of amine **1** in the reported conditions [2] ($NaNO_2$ / 50% HCl; 0°C) occurs to give a complex mixture of products and the starting compound, the main part of which is unreacted even after 5 h. Complete conversion of amine **1** occurs only at 45°C but with significant tarring. The stages of linking with methylacetoacetic ester and hydrolysis of azoester takes place under standard conditions. Instead of the expected hydrazone **4** we separated from the reaction mixture the chloro compounds **5-7** in 25% overall yield. Indolization of ethyl pyruvate 4-chloro-2-ethoxycarbonylindol-7-ylhydrazone (**5**) gives 5-chloro-2,7-diethoxycarbonyl-1H,8H-pyrrolo[3,2-*g*]indole (**9**) in 8% yield.



2, **8** R = H; **3**, **9** R = Cl; **4** R = R'' = H, R' = C_2H_5; **5** R = Cl, R' = C_2H_5, R'' = H;
6 R = Cl, R' = R'' = H; **7** R = Cl, R' = R'' = C_2H_5

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* For Communication 17 see [1].

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Based on the reaction conditions it can be assumed that chlorination occurs in the starting aminoindole **1** *via* an electrophilic substitution mechanism by chlorine which is generated *in situ* as a result of the reaction of nitrite ion or HNO_2 with excess HCl.

We consider the alternative radical or nucleophilic substitution variant less likely. It has been noted that, in these conditions, chlorination does not occur either in 2-ethoxycarbonylindole (**10**) or in its 7-nitro- (**11**), 7-methyl-, or 5-*p*-aminophenyl derivatives. To rationalize these results we have carried out quantum-chemical calculations of the distribution of electron density in 2-ethoxycarbonylindole **10** and its 7-amino and 7-nitro derivatives using the MNDO AM1 method [4].

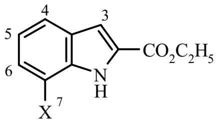
From the data in Table 1 it is evident that the electron density on the C_4 and C_6 atoms in amine **1** is higher, and in nitroindole **11** lower, than in 2-ethoxycarbonylindole **10**. Hence the electrophilic substitution will in fact be directed to positions 4 and 6 in amine **1** and should not occur in nitro indole **11**. The position of substitution was determined on the basis of the ^{1}H NMR spectra of hydrazones **5-7** and the chlorinated pyrroloindole **9**.

In the ^{1}H NMR spectrum of hydrazone **5** the signals in the region 10.30 (s) and 11.73 (d) are assigned to the hydrazone and indole NH group protons respectively. The doublet at 7.11 ppm was assigned to the 3-H proton and the two doublets at 7.10 and 7.14 ppm (with a spin-spin coupling interaction J_o = 8.4 Hz typical of *o*-protons) to the 5-H and 6-H protons respectively. Hence the chlorine atom is situated at position 4 of the indole ring. A similar picture is also observed in the aromatic region in the spectra of hydrazones **6, 7**.

With an orientation of the chlorine atom at position 6 of the indole ring, it would be possible to assign these signals to the 4-H and 5-H protons. Hence, from the overall picture of the ^{1}H NMR spectra for hydrazones **5-7** it is impossible to assign unambiguously the position of substitution by the chlorine atom (4 or 6). We give a preference to structures **5-7** since the 4-H proton signals in similar indole derivatives are best characterized by a chemical shift around 8 ppm [5, 6]. The absence in the spectra of signals with such a chemical shift is, in our view, a significant proof that the chlorine atom is actually at position 4 of the indole ring and thus, at the same time, *para* positioned to the amino group in compound **1**.

The ^{1}H NMR spectrum of compound **9** shows two singlets at 11.65 and 11.86 ppm which we assign to the signals of the NH group protons. The signals of the CH_2 and CH_3 appear as two quartets (4.39 and 4.37) and two triplets (1.39 and 1.37 ppm) respectively. Two doublets at 7.20 and 7.24 ppm are assigned to the 3-H and 6-H protons respectively. The solitary singlet signal at 7.37 ppm is assigned to the 4-H proton. The position 4 in the hydrazone **5** accordingly to systematic nomenclature becomes position 5 in its cyclization product **9**.

TABLE 1. Quantum-chemical Calculations for the Distribution of Electron Density in 2-Ethoxycarbonylindole (**10**), 7-Amino-2-ethoxycarbonylindole (**1**), and 2-Ethoxycarbonyl-7-nitroindole (**11**)*



X	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$
H	4.1257 (-0.1118)	4.0715 (-0.0715)	4.1636 (-0.1636)	4.0948 (-0.0948)	4.1524 (-0.1524)
NH_2	4.1299 (-0.1299)	4.1223 (-0.1223)	4.1212 (-0.1212)	4.1701 (-0.1701)	3.8942 (+0.1038)
NO_2	4.1239 (-0.1239)	4.0217 (-0.0217)	4.1803 (-0.1803)	4.0277 (-0.0277)	4.1406 (-0.1406)

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* Overall electron density is reported and the π-electron density is given in parentheses.

TABLE 2. Physicochemical and Spectroscopic Properties of Compounds **5-7**, **9**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, nm (log ε)	^{1}H NMR spectrum		Yield, %
		C	H	N	Cl				δ, ppm	spin-spin coupling, Hz	
5	$C_{16}H_{18}N_3O_4Cl$	$\frac{54.9}{54.7}$	$\frac{5.1}{5.1}$	$\frac{12.3}{12.0}$	$\frac{10.2}{10.0}$	142-143	3410, 3290 (NH), 1730, 1700 (ester CO), 1640 (N=C)	206 (4.44) 242 (4.35) 303 (4.10) 365 (4.10)	1.34; 1.36 (6H, t, $CH_2\underline{CH_3}$); 2.14 (3H, s, CH_3); 4.32; 4.38 (4H, q, $\underline{CH_2}CH_3$); 7.02 (1H, d, 5-H); 7.11 (1H, d, 3-H); 7.14 (1H, d, 6-H); 10.30 (1H, s, NH); 11.73 (1H, d, 1-H)	J_{13} = 2.40 J_{56} = 8.40	10
6	$C_{14}H_{14}N_3O_4Cl$	$\frac{52.5}{52.3}$	$\frac{4.2}{4.4}$	$\frac{13.4}{13.1}$	$\frac{10.8}{10.9}$	218-219	3460, 3390 (NH), 3145 (OH), 1730 (ester CO), 1660 (N=C)	208 (4.09) 245 (4.33) 305 (4.80)	1.35; 1.36 (3H, t, $CH_2\underline{CH_3}$); 2.42 (3H, s, CH_3); 4.37; 4.38 (2H, q, $\underline{CH_2}CH_3$); 7.01 (1H, br. s, 3-H); 7.14 (1H, d, 6-H); 7.31 (1H, d, 5-H); 9.88 (1H, s, NH); 12.78 (1H, s, 1-H)	J_{56} = 8.10	8
7	$C_{18}H_{22}N_3O_4Cl$	$\frac{57.3}{57.0}$	$\frac{5.9}{5.8}$	$\frac{11.3}{11.1}$	$\frac{9.6}{9.2}$	140-141	3390 (NH), 1720 (ester CO), 1630 (N=C)	202 (3.96) 208 (4.12) 238 (4.46) 307 (4.00)	1.31; 1.35; 1.36 (9H, t, $CH_2\underline{CH_3}$); 2.32 (3H, s, CH_3); 4.38; 4.39; 4.48 (6H, q, $\underline{CH_2}CH_3$); 7.16 (1H, br. s, 3-H); 7.21 (1H, d, 6-H); 7.39 (1H, d, 5-H); 11.60 (1H, s, 1-H)	J_{56} = 8.50	7
9	$C_{16}H_{15}N_2O_4Cl$	$\frac{58.0}{57.5}$	$\frac{4.8}{4.5}$	$\frac{8.2}{8.4}$	$\frac{10.8}{10.5}$	270-272	3350, 3290 (NH), 1720, 1690 (ester CO)	208 (4.40) 270 (4.53) 385 (3.95)	1.34; 1.39 (3H, q, $CH_2\underline{CH_3}$); 4.35; 4.40 (2H, q, $\underline{CH_2}CH_3$); 7.20 (1H, d, 3-H); 7.24 (1H, d, 6-H); 7.37 (1H, s, 4-H); 11.65 (1H, s, 1-H); 11.86 (1H, s, 8-H)	J_{13} = 2.37 J_{68} = 2.34	8

TABLE 3. Mass Spectra of Compounds **5-7***

Com-pound	Fragments						
	M$^+$	Φ$_1$	Φ$_2$	Φ$_3$	Φ$_4$	Φ$_5$	Φ$_6$
5	351 (43)	237 (50)	191 (100)	163 (12)	128 (11)	102 (8)	101 (9)
6	323 (35)	237 (57)	191 (100)	163 (12)	128 (11)	102 (8)	101 (9)
7	379 (32)	265 (10)* 237 (48)	191 (100)	163 (12)	128 (11)	102 (8)	101 (9)

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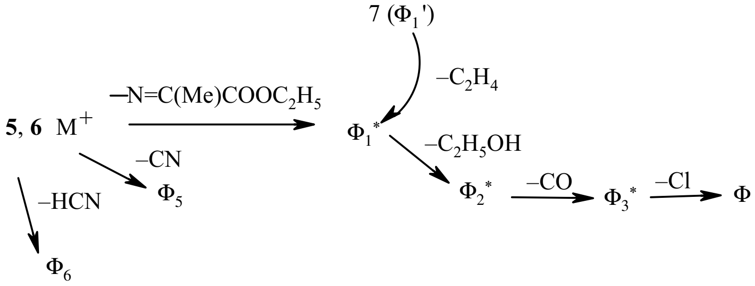
* Values of *m/z* are reported and the intensities are given in parentheses relative to the maximum ion peak.

The mass spectra of hydrazones **5-7** (Table 2) and pyrroloindole **9** show peaks for the molecular ions and peaks for (M+2). The ratio of the intensities of these peaks (M / M+2) is about 3: 1 in all cases and this is in good agreement with the natural isotopic composition of the element chlorine. Fragmentation of the molecular ions for all three hydrazones occurs almost identically. After fission of the N–N bond, ethanol is eliminated to give the fission ion Φ$_2$* (here and subsequently the ions containing the ^{35}Cl isotope are indicated by stars). Upon fragmentation of the molecular ion for compound **7** the ion Φ$_1$' first eliminates a C_2H_4 fragment to form the ion Φ$_1$*.



As other 2-ethoxycarbonylindoles, the molecular ion of compound **9** [334 (48)] eliminates consecutively two molecules of ethanol [ions 288* (100) and 242* (72)], then two molecules of CO [ions 214* (6) and 186* (28)], and only after this loses chlorine [ion 151 (7)] or CN and HCN [ions 160* (6) and 134* (3)].

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument using vaseline oil, UV spectra on a Specord spectrophotometer with ethanol solvent, and ^{1}H NMR spectra on Bruker 500 and 300 MHz spectrometers with DMSO-d$_6$ solvent and TMS internal standard. Mass spectra were taken on a Ribermag 10-10-B spectrometer with an ionization energy of 70 eV. Monitoring of the course of the reaction, compound purity, and the R_f value was performed on Silufol UV-254 TLC plates. Silica gel (particle size 100-250 microns) was used as sorbent for column chromatography.

Ethyl Pyruvate 4-Chloro-2-ethoxycarbonylindol-7-ylhydrazone (5), Pyruvic Acid 4-Chloro-2-ethoxycarbonylindol-7-ylhydrazone (6), and Ethyl Pyruvate 4-Chloro-2-ethoxycarbonyl-N-ethylindol-7-ylhydrazone (7). An aqueous solution of $NaNO_2$ (0.33 g, 5 mmol) was added to a suspension of amine hydrochloride **1** (1.17 g, 4.9 mmol) in HCl (50%, 6 ml) at room temperature thus increasing the temperature to 40-45°C and then stirred for 30 min. The reaction mixture was cooled and methylacetoacetic ester (1 ml, 7 mmol) and KOH (50%, 2.5 ml) in ethanol (7.5 ml) were added at 0-5°C. The mixture was stirred for 1 h, left overnight, extracted with ether, and the extract dried over anhydrous $CaCl_2$. Solvent was evaporated to leave a viscous red mass which was column chromatographed using benzene eluent to give compound **5** (0.2 g), compound **6** (0.14 g), and compound **7** (0.17 g).

5-Chloro-2,7-diethoxycarbonyl-1H,8H-pyrrolo[3,2-*g*]indole (9). Several drops of conc. H_2SO_4 were added to a solution of hydrazone **5** (1 g, 3 mmol) in ethanol (50 ml). The mixture was refluxed for 25 h, evaporated to one third volume, and diluted with water. The precipitated crystals were filtered off, washed with water to neutrality, and dried. The product was purified on a column using benzene eluent.

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REFERENCES

1. Sh. A. Samsoniya, M. V. Trapaidze, N. A. Kurpashvili, D. S. Zurabishivili,, and N. N. Suvorov, *Khim. Geterotsikl. Soedin.*, 942 (1998).
2. H. A. Katti and S. Siddappa, *Indian. J. Chem.*, **22B**, 1205 (1983).
3. I. Sh. Chikvaidze, Sh. A. Samsoniya, N. L. Targamadze, and N. Lomadze, *Khim. Geterotsikl. Soedin.*, 1145 (1994).
4. M. I. Dewar, E. G. Zoelisch, E. F. Healy, and J. P. Stewart, *J. Amer. Chem. Soc.*, **107**, 3902 (1985).
5. W. H. Houlihan (editor), *Indoles*, John Wiley and Sons, New York (1972), Part 1, p. 33.
6. S. P. Hiremath and R. S. Hosmane, *Adv. Heterocycl. Chem.*, **15**, 350 (1973).