INDOLE DERIVATIVES.

131.* REACTION OF 1-ACYLINDOLES WITH ACETYLCHLORIDE AND CHLOROACETYLCHLORIDE UNDER FRIEDEL–CRAFTS CONDITIONS

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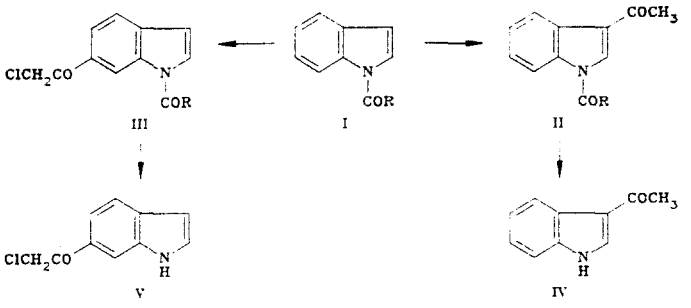
Acylation of 1-acylindoles by acetylchloride and chloroacetylchloride in the presence of aluminum chloride leads to formation of 3-acetyl- and 6-chloroacetyl-1-acylindoles, respectively.

Acylation of 1-acylindoles under Friedel–Crafts conditions is little studied. It is known [2] that introduction of a substituent into the 3 position is preferred and if it is occupied the 2 position is easily attacked. 2,3-Disubstituted 1-acylindoles are acylated in the 6 position [3-5]. Acylation of compounds not containing substituents on the $C_{(2)}$ and $C_{(3)}$ atoms have not been studied.

In this work, the acylation of 1-acylindoles, I, by acetylchloride and chloroacetylchloride in the presence of aluminum chloride is studied. The reaction direction does not depend on the nature of the N-acyl substituent but is determined by the newly entering substituent. All the 1-acylindoles, Ia-c, upon reaction with acetylchloride form the 3-acylderivatives IIa-c and with chloroacetylchloride, the 6-indolylketones IIIa-c.

The structure of compounds IIa-c were established by hydrolysis of the known 3-acyl derivative. The position of the substituent on $C_{(6)}$ in compounds IIIa-c was assumed based on their PMR spectra (Table 1), where a shift to weak field of the signal from proton 7-H through the influence of the two magnetically anisotropic carbonyl groups on $C_{(6)}$ and the nitrogen atom is observed. Hydrolysis of compounds IIIa-c leads to formation of the 6-indolylketone V.

The observed difference in the orientation of the newly entering substituent is explained by the more voluminous chloroacetyl substituent being introduced in the less hindered 6 position. In every case, the formation of compound III does not occur as a result of secondary migration processes of the chloroacetyl substituent since in separate experiments with heating of 1-chloroacetylindole (Ib) and 1,3-bischloroacetylindole with aluminum chloride in methylene chloride, compounds III and V were not observed by TLC in the reaction products.



I—IIIa R = CH_3, b R = CH_2Cl, c R = C_6H_5

*For Communication 130, see [1].

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TABLE 1. PMR Spectra of the Synthesized Compounds

Compound	δ, ppm (SSCC, Hz)							
	2-H	3-H	4-H	5-H	7-H	H	N—R, s	$C_{(3)}$—R, s
IIa*	8,04 s	—	8,36 m		~8,36m	—	2,73	2,58
IIIb**	7,65 d (3,8)	6,79 d (3,8)	7,69 d (8,3)	7,98 q (3,8, 1,6)	9.06 s br.	—	4,62	—
IV	7,90 d (3,0)	—	8,43 m	7.30 m	7,45m	8,77 br.	—	2,57
V	7,46 q (2,5; 3,1)	6,64 m	~7,71m		8,15s br.	8,68 br.		

*δ 7.42 ppm (6-H, m).
**δ 4.82 ppm ($C_{(6)}$—R, s).

EXPERIMENTAL

IR spectra were taken (in vaseline) on Perkin—Elmer 457 and Perkin—Elmer 599 instruments, PMR spectra (in $CDCl_3$) used a Varian XL-200 instrument and an internal standard of TMS. The reaction and purity of compounds was monitored by TLC on Silufol UV-254 plates. A column with silica gel L 40/100 was used for preparative separation.

Elemental analyses corresponded to those calculated for C, H, and N.

1,3-Diacetylindole (IIa, $C_{12}H_{11}NO_2$). To a solution of 1.59 g (10 mmole) 1-acetylindole Ia [6] in 10 ml acetylchloride at 10-15°C were added in portions 5 g aluminum chloride. The mixture was stirred for 0.5-1 h, diluted with 200 ml water, and the precipitate filtered. Yield of IIa 1.72 g (85%), mp 152-153°C (from acetonitrile). IR spectrum: 1650, 1705 cm^{-1} (C=O).

3-Acetyl-1-chloroacetylindole (IIb, $C_{12}H_{10}ClNO_2$) was obtained analogously as above from 1.32 g (6.8 mmole) 1-chloroacetylindole Ib [7] and 3.5 g aluminum chloride in 7 ml acetylchloride. Yield 1.6 g (97%), mp 196-198°C (from acetonitrile). IR spectrum: 1655, 1730 cm^{-1} (CO).

1-Acetyl-6-chloroacetylindole (IIIa, $C_{12}H_{10}ClNO_2$) was obtained analogously as above from 7.95 g (50 mmole) 1-acetylindole Ia and 20 g aluminum chloride in 50 ml chloroacetylchloride. Yield 11.3 g (95%), mp 182-183°C (from acetonitrile). IR spectrum: 1680, 1670 cm^{-1} (C=O).

1,6-Bischloroacetylindole (IIIb, $C_{12}H_9Cl_2NO_2$) was obtained analogously as above from 7.4 g (38 mmole) 1-chloroacetylindole Ib and 18.5 g aluminum chloride in 52 ml chloroacetylchloride. Yield 9.1 g (88%), mp 165-167°C (from toluene or acetonitrile). IR spectrum: 1690, 1710 cm^{-1} (C=O).

3-Acetyl-1-benzoylindole (IIc, $C_{17}H_{13}NO_2$). To a solution of 2.21 g (10 mmole) 1-benzoylindole Ic [6] and 2.36 g acetylchloride in 20 ml dry methylene chloride at 5-10°C were added in portions over 10 min 4 g aluminum chloride. The mixture was stirred for 20 min while heating to 20°C and after 0.5 h at this temperature, was poured into 200 ml ice water and extracted with 2 × 150 ml chloroform. The combined extracts were successively washed with water, $NaHCO_3$ solution, and water, dried and evaporated in vacuum, and the residue recrystallized from alcohol. Yield 2 g (76%) of IIc, mp 126-128°C. IR spectrum: 1670, 1703 cm^{-1} (C=O).

1-Benzoyl-6-chloroacetylindole (IIIc, $C_{17}H_{12}ClNO_2$) was obtained analogously to IIc. To 2.21 g (10 mmole) 1-benzoylindole Ic in 20 ml dry methylene chloride were added 3.39 g chloroacetylchloride and 4 g aluminum chloride. The residue after evaporation of the extract was placed on a column with 150 g silica gel and eluted with a mixture of chloroform—hexane, 1:1, and then 2:1. The solvent was evaporated from the eluent and 1.52 g (51%) of IIIc, mp 116-118°C (from alcohol) was obtained. IR spectrum: 1690, 1703 cm^{-1} (C=O).

3-Acetylindole (IV, $C_{10}H_9NO$). To a suspension of 0.5 g (2.5 mmole) IIa in 25 ml methanol was added a solution of 0.5 g potash in 5 ml water. The mixture was stirred 15 min at 20°C until dissolution and neutralized with acetic acid. The methanol was evaporated in vacuum, 15 ml water added to the residue, and the precipitate filtered and recrystallized

from dilute alcohol. Yield 0.28 g (83%) IV, mp 190-192°C. According to [8], mp 190-191°C; according to [9], 194°C.

6-Chloroacetylindole (V, $C_{10}H_8ClNO$). Analogously to the above, 0.5 g (2.1 mmole) IIIa were hydrolyzed. Yield 0.3 g (73%) V, mp 128-129°C (from diluted alcohol). IR spectrum: 1670 (C=O), 3350 cm^{-1} (NH).

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MASS SPECTROMETRY AND STRUCTURE OF HETEROCYCLIC IONS BY COLLISIONAL ACTIVATION.

3.* DIMETHYLNITROINDOLIZINES

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The fragmentation of isomeric dimethylnitroindolizines due to electron impact was studied by collisional activation and high resolution mass spectroscopy. The $[M - OH]^+$ ion which is formed as a result of the ortho-effect was found to have a variable structure. In the case of 2,8-dimethyl-1-nitroindolizine, one of the main fragmentation processes of $[M - OH]^+$ is the elimination of an H_2O molecule.

Recently, dissociation by collisional activation (DCA) has been widely applied for study of the structure of ions and their fragmentation processes. Basic aspects of the DCA method and its possibilities for identification of organic compounds have been reviewed by Levsen [2] and Holmes [3]. This method has been widely used for studying the structure of ions which are formed in the gas phase and the fragmentation of indole [4], pyrazine [5], piperidine [6], benzimidazole and indazole [7], and quinoline and isoquinoline [8] due to electron impact. However, disregarding the great possibilities of this method for the analysis of isomers, efforts toward the application of DCA for the study of the ortho-effect of substituents in a series of hetarenes are practically absent.

We studied the fragmentation features of isomeric monomethylnitroindolizines due to electron impact; in particular, using DCA it was shown that the $[M - OH]^+$ ion, which is formed as a result of the ortho-effect during decomposition of 2-methyl-3- and 1-nitroindolizines, has a variable structure [9].

*For Communication 2, see [1].

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