REACTION OF INDOLES WITH TRIFLUOROACETIC ACID

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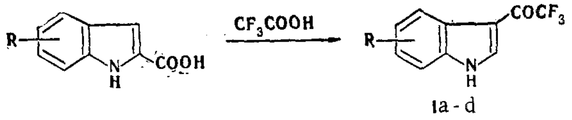
3-Trifluoroacetyl indoles are formed by the action of trifluoroacetic acid on indole-2-carboxylic acid and its benzo-substituted derivatives. When unsubstituted indole is refluxed with trifluoroacetic acid, it gives 3-trifluoroacetylindole in 30% yield.

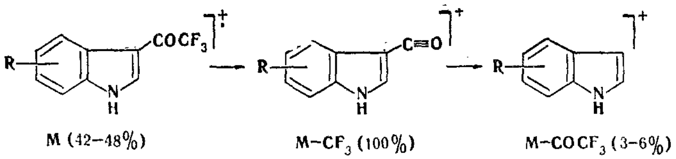
2-Alkyl- and 2-arylindoles are protonated in trifluoroacetic acid solution [1]; this is easily detected by PMR spectroscopy. When 2-acylindoles are refluxed in trifluoroacetic acid [2, 3], the acyl group migrates from the 2 position to the 3 position.

We have investigated the behavior of indole-2-carboxylic acids in the case of refluxing in trifluoroacetic acid for many hours. We found that considerable resinification occurs under these conditions, but we were able to isolate individual compounds, which proved to be 3-trifluoroacetylindoles, from the reaction mixtures by crystallization or chromatography.



I a R=H; b R=4-CH_3; c R=6-Br; d R=7-C_6H_5

A band at 1650-1665 cm^{-1}, which is characteristic for 3-acylindoles, is observed in the IR spectra of the compounds obtained. A multiplet (splitting by ^{19}F nuclei) is present in the PMR spectra (Table 1) at 8.3-8.4 ppm. Under the influence of electron impact indoles Ia-d undergo fragmentation with the initial ejection of a trifluoromethyl group and subsequent ejection of CO; this is followed by the fragmentation that is typical for the indole ring.



These data constitute unambiguous evidence for the structure of the 3-trifluoroacetylindoles obtained. In addition, unsubstituted indole Ia is readily obtained as a result of the reaction of indole and trifluoroacetic anhydride [4]. It proved to be identical to the product obtained from indole-2-carboxylic acid.

TABLE 1. Chemical shifts in the PMR Spectra of 3-Trifluoroacetylindoles

Compound	δ, ppm				
	2-H	4-H	5-H	6-H	7-H
Ia	8,38	8,40	7,10—7,80		
Ib	8.33	—	7,35	7,13	6,95
Ic	8,42	8,14	7,42	—	7,78

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*Deceased.

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TABLE 2. 3-Trifluoroacetylindoles

Compound	R	Reaction time, h	mp, °C	R_f[a]	M[b]	ν_{CO}, cm^{-1}	Yield, %
Ia	H	13	208—211[c]	0,76	213	1650, 1590 shoulder	10
Ib	4-CH_3	16	165—167[d]	0,79	227	1665	27
Ic	6-Br	26	254—256[e]	0,80	291[f], 293	1650	12
Id	7-Ph	26	173—174[e]	0,77	289	1650	3

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[a] On Silufol UV-254 [elution with benzene—ethyl acetate (1:1)]. [b] Determined by mass spectrometry. [c] From a mixture of ether with benzene. [d] From a mixture of methylene chloride with hexane. [e] After chromatographic purification with a column [SiO_2 (100/160 μ), benzene]. [f] Two values because of bromine isotopes.

4-Nitroindole-2-carboxylic, pyromucic, and benzofuran-2-carboxylic acids do not react under these conditions.

The formation of the 3-trifluoroacetylindoles apparently occurs as a consequence of acylation of the indoles formed as a result of decarboxylation of the acids. In fact, indole-2-carboxylic acids are decarboxylated under acidic conditions [5], and donor substituents in the benzene ring facilitate this process, whereas acceptor substituents hinder it. At the same time, trifluoroacetic acid is a moderate acylating agent [6]. In fact, when indole is refluxed in trifluoroacetic acid solution for 3 h, 3-trifluoroacetylindole is formed in 30% yield. In this case the yields of 3-trifluoroacetylindoles depend on the ability of the indolecarboxylic acids to undergo decarboxylation. For example, if decarboxylation occurs by using ethyl indole-2-carboxylate, the latter does not undergo trifluoroacetylation. 4-Nitroindole-2-carboxylic acid behaves similarly. Trichloroacetic acid is weaker than trifluoroacetic acid, and the trichloroacetylation of indole-2-carboxylic acid naturally proceeds with considerably greater difficulty in it.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in $(CD_3)_2CO$ were recorded with a Varian T-60 spectrometer with hexamethyldisiloxane as the internal standard. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The mass spectra were obtained with MKh-1303 and Varian MAT-111 spectrometers at energies of 50 and 80 eV with direct introduction of the substances into the ion source.

Reaction of Indole-2-carboxylic Acids with Trifluoroacetic Acid. A solution of 1-8 mmole of the corresponding indole-2-carboxylic acid in 8 ml of trifluoroacetic acid was placed in a flask equipped with a reflux condenser fitted with a calcium chloride tube, and the flask was heated on a water bath at 80°C for 13-26 h. The reaction was monitored by thin-layer chromatography (TLC) on Silufol with development in UV light. At the end of the reaction the trifluoroacetic acid was removed by distillation, cold water was added to the residue, and the precipitated crystals of Ia-d were removed by filtration and purified by recrystallization or column chromatography.

The characteristics of the trifluoroacetylindoles obtained are presented in Table 2.

Reaction of Indole-2-carboxylic Acid with Trifluoroacetic Acid. A mixture of 1.25 g (8 mmole) of indole-2-carboxylic acid with 5 g of trifluoroacetic acid was heated on a water bath at 80°C in a flask equipped with a reflux condenser fitted with a calcium chloride tube for 19 h, after which the mixture was poured into ice water, as a result of which dark crystals precipitated. Two purifications with a chromatographic column [SiO_2 (100/160 μ), benzene] gave 8 mg (0.4%) of 3-trichloroacetylindole with mp 235-237°C (mp 235°C [7]).

Acylation of Indole with Trifluoroacetic Acid. A mixture of 0.23 g (2 mmole) of indole and 14 ml of trifluoroacetic acid was refluxed for 3 h in a flask equipped with a reflux condenser, after which the excess acid was removed by vacuum distillation, and 3 ml of methylene chloride was added to the residue. Recrystallization of the precipitated crystals from benzene gave 0.12 g (30%) of 3-trifluoroacetylindole with mp 210-212°C (mp 209-212°C [4]).

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BROMINATION OF PYRIDINE IN THE PRESENCE OF SOME LEWIS ACIDS

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The bromination of pyridine in the form of complexes with some Lewis acids and in the presence of catalytic amounts of the latter was studied. It is shown that bromination takes place readily at ∿100°C in the presence of catalysts such as $AlCl_3$, $ZnCl_2$, $CuCl_2$, $SbCl_3$, $InCl_3$, $TeCl_4$, and $HgCl_2$. The principal bromination products are 3-bromopyridine and 3,5-dibromopyridine. The problem of the possibility of so-called π back-bonding in the case of elements of the higher periods (particularly In, Te, and Sb) is discussed.

It is well known that specific difficulties are encountered in the case of electrophilic substitution in the pyridine series: electrophilic attack on the π-deficient system requires activation; however, the aprotic and protic acids that are ordinarily employed as catalysts form complexes with pyridines that are even more inert than the free bases. An increase in the amount of the catalyst most often has no effect, since, for example, in the case of bromination it promotes a shift not only in equilibrium (1) to favor the active electrophile particle, which is depicted in this case as a polarized complex of bromine with the Lewis acid, but also in equilibrium (2) to favor the deactivated nv complex:

$$Br_2 + MX_n \rightleftarrows Br \ldots\ldots Br \cdot MX_n \tag{1}$$

$$C_5H_5N + MX_n \rightleftarrows C_5H_5N \cdot MX_n \tag{2}$$

The utilization of salts of metals of higher periods, particularly and especially mercury, most often gives a positive effect, which is usually explained by so-called "back-bonding" [1], i.e., by transfer of the electron density from the central metal atom to the π system of the pyridine ring. It should be emphasized that the explanation of the catalytic effect of aluminum halides that is sometimes encountered in the literature (for example, see review [2, 3]) is absolutely invalid: The aluminum atom, being an element of the third period, simply does not contain in its outer shell free electrons that could be transferred to the π system of the pyridine ring.

The aim of the present research was to study the catalytic activity in the bromination of pyridine of a number of Lewis acids, the central atoms of which belong to different periods of the Mendeleev system.* In the first stage of this research we studied the bromination at 80-100°C of previously prepared complexes in which, depending on the nature of element M, the MX_n:pyridine ratio was 1:1 or 1:2. The results of the experiments are presented in Table 1.

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*The contents of this paper were presented in part in [4].

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