REACTIONS OF HEXAFLUOROISOPROPYLIMINES WITH INDOLE*

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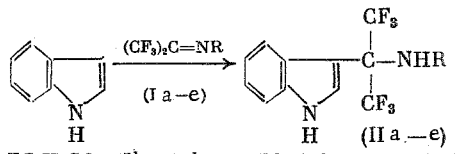
The methylenimines react with indoles in the presence of organic acids under the conditions required for the generation of iminium salts [2, 3]. The formation of 3-(α-aminoalkyl)-indole derivatives in this process confirms that the C-alkylation of the heterocycle occurs at the site of the highest electron density [4]. The data in [2] indicate that the alkylating properties of the methylenimines show up with a sharp increase in their π-acceptor character. This prompted the interest in investigation of the reaction between indole and such strong π-acids as methylenimines containing fluorine, which are by nature very similar to the iminium salts in a neutral nonaqueous environment.

The methylenimines containing fluorine have not been extensively studied in the C-alkylation reactions of aromatic and heterocyclic compounds. The feasibility of C-alkylation of substituted benzenes with hexafluoroisopropylimine (Ia) in the presence of Lewis acids was shown in [5]. The alkylation of N,N-dimethylaniline, anisole, and thiophene in the absence of N,N-dimethylaniline, anisole, and thiophene in the absence of a catalyst was accomplished with hexafluoroisopropylsulfonylimine [6, 7]. This work is concerned with the study of the reaction between indole and hexafluoroisopropylimine (Ia) and its derivatives (Ib-e).

The reaction of (Ia) with indole in the absence of catalyst takes place under pressure at only 120°C. The product, 3-(α-aminohexafluoroisopropyl)indole (IIa), is formed with 66% yield.



R = H (Ia), (IIa); *p*-FC_6H_4CO (Ib), (IIb); *o*-FC_6H_4CO (Ic), (IIc); $PhSO_2$ (Id), (IId); CF_3CO (Ie), (IIe).

The alkylation with fluorobenzoylimines (Ib, c) in $CHCl_3$ is completed after 12 h at 20°C, whereas the alkylation with benzenesulfonylimine (Id) takes only 1 h under the same conditions. In all cases high yields of C^3 alkylated indoles (IIb-e) were obtained.

Since the trifluoroacetylimine (Ie) is extremely active and reacts violently with indole at 20°C, the reaction was made to proceed at −20°C with subsequent warming up to 20°C. The progress of the reaction was followed easily by chromatography. The quantitative reaction gave 74% yield of the crystallized 3-(α-trifluoroacetamidohexafluoroisopropyl)indole (IIe).

Thus, the hexafluoroisopropylimines react with indole similarly to iminium salts. The reaction conditions strongly depend on the type of the substituent at N. The alkylating strength increases in the order imine, benzoylimines, sulfonylimines, hexafluoroisopropyl-perfluoroacylimines, i.e., the acidic properties of the hexafluoroisopropylimines are determined by the electron-acceptor effects of the substituent at N, as well as by the conjugation of the substituent with the C=N bond.

The indoles (IIa-e) are relatively stable in alkali medium. The trifluoroacetamide (IIe) is hydrolyzed only by boiling with 10% NaOH in aqueous alcohol giving (IIa) with 70% yield. The benzenesulfonylamide (IId) will not show any changes under these conditions.

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* For the preceding communication, see [1].

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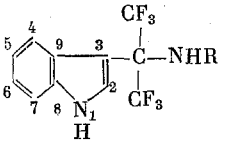
TABLE 1. PMR Spectra of Compounds (IIa-e)



Compound	δ, ppm*						$J^{\dagger}_{HN-CH'}$, Hz
	1	2	4	5	6	7	
(IIa)	11,3	7,56	8,00	7,24	7,13	7,54	1,98
(IIb)	11,55	7,53	7,62	7,12	7,00	7,47	1,98
(IIc)	11,55	7,53	7,77	7,16	7,06	7,49	1,98
(IId)	11,56	7,46	7,82	7,18	7,02	7,58	1,98
(IIe)	11,70	7,56	7,51	7,17	7,06	7,51	~2,00

* (IIb): AA'BB' substituent system (7.32 and 7.92 ppm); (IIc): ABCD substituent system (7.23-7.64 ppm); (IId): AA'BB'C substituent system (7.50-7.70 ppm).

† The spin–spin coupling constants for $^1H-^1H$ at carbon atoms 4, 5, 6, and 7 are not given since they do not differ from the known values and are independent of the nature of the substituent at C^3 [8].

The products (IIa-e) are compounds with high melting points and are easily soluble in polar organic solvents. The structures of (IIa-e) were confirmed by NMR, mass spectrometry, and microanalysis.

The PMR data (Table 1) indicate that the substitution takes place on one of the carbon atoms in the pyrrole ring. The δ_1, δ_2, and J_{NHCH} (IIa-e) values are practically the same and thus point to the regioselectivity of the substitution. At the same time, looking at the approximate parity of $^3J_{1,2}$ and $^4J_{1,3}$, the J_{NHCH} value (in conformance with [8]) cannot serve as evidence for the position of the substituent. To confirm the direction of substitution, the $^{13}C-\{^1H\}$ and ^{13}C (DEPT) (IIa) NMR spectra were obtained (δ, ppm; J, Hz): 126.28 (C^2, J_{CH} = 185.4), 105.58 (C^3), 121.6 (C^4 + C^5, J = 162.0), 119.55 (C^6, J = 162), 111.98 (C^7, J = 162.6), 136.7 (C^8), 125.4 (C^9), 124.75 (CF_3, $^1J_{^{13}C-^{19}F}$ = 286.3), 63.9 ($C(CF_3)_2$, J = 29.0). Comparison of the ^{13}C chemical shifts with the values for the unsubstituted indole [9] points to the C^3 substitution. This conclusion is verified also by the large spin–spin coupling constant of $^{13}C-H$ (185.4 Hz) characteristic for C atoms in α-position relative to N [10].

The mass spectra of (IIa-e) show the $M^{+\cdot}$ peaks. The general route of fragmentation appears to be the elimination of CF_3 and the NHR substituent. Apart from this, there is a range of specific routes of decomposition determined by the nature of R (see Experimental).

EXPERIMENTAL

The NMR spectra were obtained in DMSO-d_6 at 20°C on a Bruker WP-200 spectrometer [^1H 200, 13 MHz (one 90° pulse), ^{19}F 188.3 MHz (one 90° pulse), and ^{13}C 50.31 MHz (pulse duration 8 μsec, ~ 40°)]. The chemical shifts were measured relative to TMS (^1H, ^{13}C) and CF_3COOH (^{19}F) as external standards. The memory on SSI in all cases was 16 K; in some cases the mathematical line contraction was employed. The DEPT spectra was obtained using θ = 3/4 π with 90° pulse duration of 23.5 μsec for ^1H. The mass spectra were recorded on an AEI MS-30 spectrometer with direct sample inlet into the ion source, ionization potential 70 eV, and temperature of ionization chamber 250°C. The UV spectra were obtained on a Specord M-40 spectrometer in 96% EtOH. The R_f values were obtained on Silufol UV-250 plates made by Kavalier (Czechoslovakia) using the solvent system CCl_4-Me_2CO (3:1), with development under UV light.

3-(α-Aminohexafluoroisopropyl)indole (IIa). a) The imine (Ia, 19 g) was warmed with indole (5 g) in a sealed glass ampoule for 36 h at 120°C. The cooled ampoule was opened, and the excess of the imine (Ia) was removed at 40°C. The remainder was then recrystallized from hexane yielding 8 g (66.4%) of white crystalline product (IIa), mp = 100-101°C, R_f = 0.50. UV spectra (λ_{max}, nm): 268.4 (ε = 6276), 285.9 (ε = 4551). NMR ^{19}F spectra (δ, ppm):

−4.47. Mass spectra m/e (relative intensity, %): 282 M^+ (47), 266 $[M^+ - NH_2]^+$ (3), 243 $[M - HF_2]^+$ (8), 213 $[M - CF_3]^+$ (100), 166 $[M - C_2F_4NH_2]^+$ (9), 143 $[M - CF_3 - CF_3H]^+$ (13), 118 $[M - CF_3C(=NH)CF_3]^+$. Found, %: C 46.87; H 2.94; F 40.64. $C_{11}H_8N_2F_6$. Calculated, %: C 46.81; H 2.86; F 40.40.

b) Ethanol (7 ml), water (2 ml), and NaOH (1 g) were added to (IIe) (1 g) and the mixture was refluxed for 12 h. The resulting solution was neutralized with 0.1 N HCl and extracted with $CHCl_3$. The extract was washed with water, then dried over Na_2SO_4. The concentrated residue was recrystallized from hexane. Yield = 0.52 g (69.7%), mp = 100-101°C, R_f = 0.50.

3-(α-Fluorobenzoylamidohexafluoroisopropyl)indoles (IIb, IIc). Indole (2.16 g) was added with stirring to a solution of the acylimine (Ib) or (Ic) in pure $CHCl_3$ (12 ml). The mixture was then allowed to stand for 12 h at 25°C. The resulting precipitate was filtered off and recrystallized from $CHCl_3$. The white crystalline p-isomer (IIb) was obtained using (Ib) with 69.3% yield (5.7 g), mp = 185-187°C (decomp.), R_f = 0.51. UV spectra (λ_{max}, nm): 269.5 (ε = 5134), 286.5 (ε = 4113). ^{19}F NMR spectra (δ, ppm): 38, broad, singlet (1F), −2.0 (6F). Mass spectra m/e (relative intensity, %): 404 M^+ (17), 335 $[M - CF_3]^+$ (5), 266 $[M - NHCOC_6H_4F]^+$ (1), 202 M^{2+} (4), 123 $[FC_6H_4CO]^+$ (100), 95 $[FC_6H_4]^+$ (18). Found, %: C 53.02; H 2.70; N 6.77; F 33.25. $C_{12}H_{11}N_2O_7$. Calculated, %: C 53.48; H 2.74; N 6.93; F 32.91. The white crystalline o-isomer (IIc) was obtained using (Ic) with 70.6% yield (5.8 g), mp = 164-166°C, R_f = 0.51. UV spectra (λ_{max}, nm): 270.0 (ε = 8193), 286.2 (ε = 5922). ^{19}F NMR spectra (δ, ppm): 43.42 singlet (1F), −1.45 singlet (6F). Mass spectra m/e: 404 M^+, 355 $[M - CF_3]^+$, 266 $[M - NHCOC_6H_4F]^+$, 202 M^{2+}, 123 $[FC_6H_4CO]^+$, 95 $[FC_6H_4]^+$. Found, %: C 53.64; H 2.73; N 7.16; F 32.70. Calculated, %: C 53.48; H 2.74; N 6.93; F 32.91.

3-(α-Benzenesulfonylamidohexafluoroisopropyl)indole (IId). Indole (2.75 g) was added with stirring to a solution of (Id) (8.6 g) in pure $CHCl_3$ (10 ml) at 20°C. The mixture was then allowed to stand for 1 h. The resulting precipitate was filtered off and extracted with acetone (30 ml). The extract was concentrated by evaporation and the residue was recrystallized from $CHCl_3$. The yield of the beige crystalline product (IId) was 6.2 g (62.5%), mp = 181-182°C, R_f = 0.45. UV spectra (λ_{max}, nm): 265.8 (ε = 6774), 285.9 (ε = 4698). ^{19}F NMR spectra (δ, ppm): −2.32. Mass spectra m/e: 422 M^+, 353 $[M - CF_3]^+$. Found, %: C 48.51; H 2.81; S 7.26; F 27.21. $C_{17}H_{12}N_2O_2SF_6$. Calculated, %: C 48.36: H 2.84; S 7.58; F 27.00.

3-(α-Trifluoroacetamidohexafluoroisopropyl)indole (IIe). Indole (2.35 g) was added with stirring to a solution of (Ie) (6.3 g) in pure $CHCl_3$ (10 ml) at −20°C. The mixture was then allowed to stand for 30 min at 20°C. The resulting precipitate was filtered off and recrystallized from $CHCl_3$. The yield of the white crystalline product (IIe) was 5.6 g (73.8%), mp = 160-162°C, R_f = 0.53. UV spectra (λ_{max}, nm): 276.4 (ε = 4314), 285.9 (ε = 3649). ^{19}F NMR spectra (δ, ppm): −1.67, 2.80 (2:1). Mass spectra m/e (relative intensity, %): 378 M^+ (77), 309 $[M - CF_3]^+$ (100), 266 $[M - NHCOCF_3]^+$ (9), 239 $[M - CF_3 - CF_3H]^+$ (15), 166 $[M - NHCOCF_3 - C_2F_4]^+$ (13), 143 $[M - CF_3 - CF_3COCF_3]^+$ (39), 117 $[M - (CF_3)_2C=NCOCF_3]^+$ (58). Found, %: C 41.44; H 2.09; N 7.62; F 44.88. $C_{13}H_7N_2OF_9$. Calculated, %: C 41.28; H 1.87; N 7.41; F 45.21.

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CONCLUSIONS

1. The C-alkylation reactions of indole with fluorobenzoyl, benzenesulfonyl, trifluoroacetyl, and unsubstituted hexafluoroisopropylimines were studied. The reactions proceed without a catalyst. The regioselectivity for the C^3 indole atom was shown.

2. It was established that C-alkylation reaction of indole with imines containing fluorine is facilitated with increase in −I and −E effects of the substituent at the N atom of the imine.

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CYCLIZATION OF THE HYDRAZIDES OF VICINAL PHENYLETHYNYL DERIVATIVES OF N-METHYLPYRAZOLE-5-CARBOXYLIC AND BENZOIC ACIDS

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Intramolecular cyclization of vicinal functionally substituted aromatic acetylenic compounds has recently become increasingly important as a method for synthesis of heterocyclic condensed systems [1]. This type of heterocyclization of acetylenic derivatives of aromatic carboxylic acid hydrazides is not known. It could be possible to prepare multinuclear heterocyclic compounds which are difficult to obtain by other methods with this reaction.

Intramolecular cyclization of 4-phenylethynyl-1-methyl-pyrazole-5-carboxylic (I) and tolan-2-carboxylic (II) acid hydrazides in the presence of Cu(I) salts yields products which were described as diazepinones (III) and (IV) [2] based on the PMR data, IR spectra, and elementary analysis. However, it was subsequently shown that the compounds obtained in heating with an acid or a base do not undergo the constriction of the ring characteristic of diazepinones [3, 4].

A supplementary study of the reaction and properties of the products, which were reliably identified as 6,7-dihydro-1-methyl-4-benzylpyrazolo[3,4-d]pyridazin-7-one (V) and 1,2-dihydro-4-benzyl-1-phthalazinone (VI), is reported in the present article.

The starting hydrazide (I) was prepared by boiling the methyl ester of 4-phenylethynyl-1-methylpyrazole-5-carboxylic acid (VII) with an excess of $NH_2NH_2 \cdot H_2O$ in EtOH for 7 h with a yield of 90%. In contrast to (I), the hydrazide of tolan-2-carboxylic acid (II) undergoes cyclization into 2-amino-3-benzylideneisoindolin-1-one (IX) (yield of 70%) as ester (VIII) is formed in similar conditions. It is possible to suppress the secondary process and to obtain (II) (yield of ~ 55%) together with (IX) (~ 35%) at ~ 20°C.

We found that cyclic hydrazides of type (IX) are easily deaminated in oxidation with air in the presence of CuCl in DMF. The transformation of (IX) into the described 3-benzylideneisoindolin-1-one (X) by this method [5] and the nonidentity of (IX) with the alternative product of cyclization, 1,2-dihydro-2-amino-3-phenylisoquinolin-1-one [3, 6], and (X) with the also well-known product of deamination, 1,2-dihydro-3-phenylisoquinolin-1-one [6, 7] confirms its structure sufficiently convincingly. There is one singlet with δ 6.72 and 6.54 ppm, respectively, in the PMR spectra of (IX) and (X), assigned to the ethylene proton, which indicates the formation of only one geometric isomer (the configuration has not been established) during cyclization. Pyrazolecarboxylic acid hydrazide (I) is cyclized in conditions of basic catalysis with more difficulty than (II), and is transformed into pyridopyrazole

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