FLUORINE-CONTAINING AZOLES.

2.* REACTION OF IMIDAZOLE, BENZIMIDAZOLES, AND PERIMIDINES WITH DIFLUOROCARBENE

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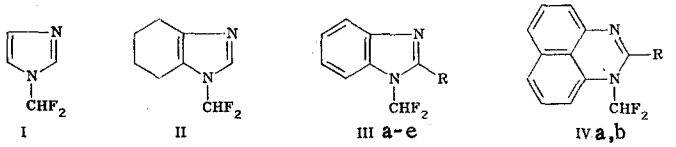
The reaction of difluorocarbene, generated from difluorochloromethane in an alkaline medium or from sodium trifluoroacetate in a neutral medium, with imidazole, tetrahydrobenzimidazole, benzimidazoles, and perimidines leads to the production of their N-difluoromethyl-substituted derivatives.

In contrast to dichlorocarbene, little study has been devoted to the reactivity of difluorocarbene with respect to heterocycles. It is known, for example, that 2,3-dimethylindole adds difluorocarbene in the 3 position to give 2,3-dimethyl-3-difluoromethyl-3H-indole [2]. We recently [1] established that N-difluoromethyl-substituted derivatives are formed in good yields by the action of difluorocarbene on benzimidazole and 2-methylbenzimidazole. The aim of the present research consisted in a more detailed study of this reaction and its extension to other benzimidazoles, perimidines, and imidazole. An investigation of imidazole seemed of particular interest, since it has been previously shown that dichlorocarbene reacts with it to give a mixture of 5-chloropyrimidine and 2-chloropyrazine [3].

Difluorocarbene was generated by two methods: by the action of a concentrated solution of KOH on difluorochloromethane (method A) and by thermal decomposition of sodium trifluoroacetate (method B). We recently proposed the latter method and used it for the difluoromethylation of phenols [4]. It is important to note that in both methods for the generation of difluorocarbene its subsequent reaction with the heterocyclic compound proceeds in a two-phase system: aqueous alkali–acetone in method A and water–diglyme in method B.

We have found that difluorocarbene generated by method A reacts with benzimidazole, 2-alkylbenzimidazoles, tetrahydrobenzimidazole, and imidazole to give N-difluoromethyl-substituted derivatives (I-III) in 37-87% yields. Products (IV) of N-difluoromethylation of perimidines are formed in low yields; this is evidently due to the very facile self-oxidizability of perimidines with a free NH group in an alkaline medium [5], as well as to the instabilities of IV. In fact, it was noted that IV decomposes slowly during storage under ordinary conditions, whereas I-III are completely stable. N-Difluoromethylation of the imidazole ring is also observed in the generation of difluorocarbene by method B; however, the yield is considerably lower in this case (Table 1).



I II III a-e IV a,b

III, IV a R=H; b R=CH_3; III c R=C_2H_5; d R=C_3H_7; e R=C_9H_{19}

It is apparent from Table 1 that there is a rather distinct tendency for an increase in the yield of the N-difluoromethyl-substituted compound as the lipophilicity of the starting heterocyclic compound increases. Thus the highest yield was obtained in the case of 2-nonylbenzimidazole, although one might have expected that a bulky substituent in the 2

*See [1] for communication 1.

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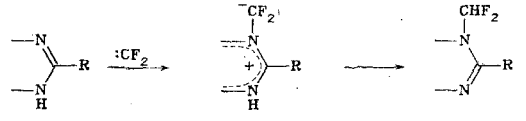
TABLE 1. Characteristics of the Synthesized Compounds

Compound	bp, °C (mm)	mp, °C	n_D^{20}	Found, %		Empirical formula	Calc., %		Yield, %	
				F	N		F	N	A	B
I	155—156 (740)	—	1,4300	32,0	23,8	$C_4H_4F_2N_2$	32,3	23,7	37	12
II	57—58 (5)	79—80	—	22,4	16,3	$C_8H_{10}F_2N_2$	22,1	16,3	44	—
IIIa	102—103 (2)	42—43	—	—	—	—	—	—	62	43
IIIb	120—121 (4)	62—63	—	—	—	—	—	—	70	60
IIIc	99—101 (2)	—	1,5340	19,7	14,5	$C_{10}H_{10}F_2N_2$	19,4	14,3	57	—
IIId	106—107 (2)	—	1,5270	17,9	13,5	$C_{11}H_{12}F_2N_2$	18,1	13,3	61	—
IIIe	92—93 (2)	—	1,5075	12,6	9,7	$C_{17}H_{24}F_2N_2$	12,9	9,5	87	—
IVa	—	74—76[a]	—	17,3	13,0	$C_{12}H_8F_2N_2$	17,4	12,8	7	1
IVb	—	74—75[b]	—	16,5	12,4	$C_{13}H_{10}F_2N_2$	16,3	12,1	9	—

[a]Purified by sublimation at 90°C (6 mm). [b]Purified by sublimation at 120°C (2 mm).

position should hinder the addition of difluorocarbene as compared with benzimidazole itself. This fact undoubtedly constitutes evidence for the realization of interphase catalysis in the addition of difluorocarbene, as in the case of dichlorocarbene [6]. It is logical to assume that difluorocarbene is generated in the organic layer (acetone or dioxane [1]). An increase in the lipophilicity of the substrate, which is particularly pronounced for 2-nonylbenzimidazole, should promote its passage into the organic layer both in the form of an anion and in the form of a base, which will lead to a pronounced increase in the reaction rate. Moreover, a significant amount of imidazole, which has low nucleophilicity, evidently is found in the aqueous layer, and its reaction with difluorocarbene takes place only at the interface. The available data are not sufficient to enable one to express a well-reasoned opinion as to whether the heterocyclic compound reacts with difluorocarbene in the form of the N anion or just as it is. On the one hand, it is difficult to assume that heterocycles with NH acidity over the range pK_a 13-14 [7] can remain undissociated in the presence of alkali. On the other hand, passage of the heterocycle into the organic layer may prevent such ionization. In one of our experiments we established that in the difluoromethylation of 2-methylbenzimidazole by method A an increase in the potassium hydroxide concentration from 43% to 50% led to a decrease in the yield of IIIb from 70% to 11%. We were unable to realize the reaction of difluorocarbene with the sodium salt of 2-methylbenzimidazole. When we heated the latter with sodium trifluoroacetate at 160°C in anhydrous diglyme, we isolated the starting compound in almost quantitative yield. These results would appear to constitute evidence that the reaction proceeds through the undissociated form, which can be represented by the scheme



Compound IIIa is formed instead of the expected 1-difluoromethyl-2-trifluoromethylbenzimidazole in the reaction of 2-trifluoromethylbenzimidazole with difluorocarbene (method A). We established that the trifluoromethyl group of 2-trifluoromethylbenzimidazole does not undergo any changes under the conditions of the synthesis even in the case of heating to 160°C in aqueous diglyme in an alkaline medium. This fact makes it possible to assume that the CF_3 group is hydrolyzed to a carboxy group (see [8]) with subsequent decarboxylation only after incorporation of the difluoromethyl group into the 2-trifluoromethylbenzimidazole molecule.

The structures of the synthesized compounds were confirmed by the results of elementary analysis and data from the IR, PMR, and mass spectra. The absorption band of the C—H bond is shifted to 3070-3130 cm^{-1} in the IR spectra of I-IV (Table 2), which indicates its stronger polarization as compared with compounds of the aliphatic series [9]. Three absorption bands that are characteristic for the imidazole ring [10, 11] are present at 1500-1640 cm^{-1} in the spectra of I-III, whereas a very intense doublet that is characteristic for N-substituted perimidines [5] is observed in the spectra of IV. Absorption bands of a C—F bond that are characteristic for polyfluoroalkyl substituents are present at 1110-1190 cm^{-1} in the spectra of all of the compounds.

TABLE 2. IR Spectra of the Synthesized Compounds

Compound	ν_{C-H}, cm^{-1} (CHF_2 group)	$\nu_{C=N/C=C}$, cm^{-1}
I	3130	1630, 1560, 1525
II	3100	1610, 1590, 1500
IIIa	3075	1610, 1590, 1510
IIIb	3075	1615, 1585, 1550
IIIc	3070	1615, 1595, 1545
IIId	3070	1615, 1595, 1540
IIIe	3075	1610, 1590, 1540
IVa	3070	1640, 1590
IVb	3070	1635, 1585

In the PMR spectra of I and IVa, b the proton of the CHF_2 group gives, respectively, a triplet at 7.12, 7.55, and 6.95 ppm with a spin–spin coupling constant (SSCC) of 59 Hz.

Thus our investigation showed that difluorocarbene is capable of adding extremely smoothly to the NH group of imidazole systems, as a result of which previously unknown and difficult-to-obtain N-difluoromethylimidazoles and N-difluoromethylbenzimidazoles can be synthesized.

EXPERIMENTAL

The IR spectra of solutions of the compounds in CCl_4 were recorded with a UR-20 spectrometer. The PMR spectra of 0.04 mole/liter solutions of the compounds in CCl_4 or CF_3COOH were obtained with Tesla BS-467 (60 MHz) and Tesla BS-487 (80 MHz) spectrometers with hexamethyldisiloxane as the internal standard. The mass spectra were recorded with a Jm-10-JC-2 mass spectrometer with direct introduction of the samples into the ion source at an ionization energy of 75 eV. The course of the reactions and the purity of the compounds were monitored by means of thin-layer chromatography (TLC) (activity IV Al_2O_3 and Silufol UV-254) in chloroform.

N-Alkylation with Difluorocarbene. A) 1-Difluoromethylimidazole (I), 1-Difluoromethyltetrahydrobenzimidazole (II), and 1-Difluoromethyl-2-alkylbenzimidazoles (IIIa-e). A 3.36-liter (0.15 mole) sample of difluorochloromethane was passed with vigorous stirring at 40-50°C in the course of 3 h into a two-phase system containing 0.1 mole of the corresponding NH azole, 0.2 mole of KOH, 30 ml of acetone, and 15 ml of water, after which the organic layer was separated and distilled to give I, II, and IIIa-e (see Tables 1 and 2). Mass spectrum of 1-difluoromethylimidazole, m/z^+ (relative intensity, %): 118 (100), 80 (1.1), 78 (2.0), 68 (22.8), 67 (3), 51 (7.7), 41 (4.7), and 40 (7.8).

1-Difluoromethylbenzimidazole (IIIa). A 3.36-liter (0.15 mole) sample of difluorochloromethane was passed with vigorous stirring at 40-50°C in the course of 3 h into a mixture consisting of 0.1 mole of 2-trifluoromethylbenzimidazole, 0.2 mole of KOH, 30 ml of acetone, and 15 ml of water, after which the organic layer was separated, the solvent was evaporated, and the residue was distilled *in vacuo* at 102-103°C (2 mm) to give 8.7 g (37%) of product.

1-Difluoromethylperimidine (IVa) and 1-Difluoromethyl-2-methylperimidine (IVb). A reaction flask containing a solution of 0.024 mole of perimidine in 100 ml of acetone was purged with argon until traces of oxygen had been removed, a solution of 0.03 mole of KOH in 5 ml of water was introduced into the flask in a stream of argon, the contents were heated to 40°C, and 0.67 liter (0.03 mole) of difluorochloromethane was passed into the mixture in the course of 2 h. The acetone was removed by distillation in a stream of argon in the vacuum created by a water aspirator, and the residue was chromatographed. The isolated reaction product was additionally purified by vacuum sublimation. Mass spectrum of IVb, m/z^+ (relative intensity, %): 233 (17.9), 232 (100), 182 (26.4), 181 (14.3), and 127 (2.4).

B) 1-Difluoromethylimidazole (I), 1-Difluoromethylbenzimidazole (IIIa), 1-Difluoromethyl-2-methylbenzimidazole (IIIb), and 1-Difluoromethylperimidine (IVa).* A 0.1-mole sample of the corresponding NH azole and 50 ml of diglyme were added to a solution of sodium trifluoroacetate obtained by neutralization of 0.3 mole of trifluoroacetic acid with 0.3

*The synthesis of IVa was carried out in a stream of argon.

mole of sodium hydroxide dissolved in 25 ml of water, and the mixture was heated to the boiling point. As the water was removed by distillation, the temperature of the reaction mixture increased from 110°C to 160°C. The mixture was maintained at this temperature for 11 h, after which it was cooled and treated with 100 ml of water, and the product was extracted with chloroform. Compound IVa was isolated by chromatography, and I and IIIa, b were isolated by distillation (see Tables 1 and 2).

Compounds I, IIIa, b, and IVa obtained by methods A and B were identical according to their boiling and melting points and TLC and IR spectral data.

Difluoromethylation of the Sodium Salt of 2-Methylbenzimidazole. A mixture of 1.54 g (0.01 mole) of the sodium salt of 2-methylbenzimidazole, 4.08 g (0.03 mole) of sodium trifluoroacetate, and 20 ml of anhydrous diglyme was stirred at 150-160°C for 11 h, after which the diglyme was removed by distillation, and the dry residue was treated with chloroform. Thin-layer chromatography on aluminum oxide indicated the absence of a difluoromethylation product (IIIb).

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