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HETEROCYCLIC COMPOUNDS WITH A PHARMACOPHORIC HALOSUBSTITUTED GROUP. 1. 2-BROMO-1,1-DIFLUORO-2-CHLOROETHYLATION OF HETEROCYCLIC COMPOUNDS WITH TWO HETEROATOMS

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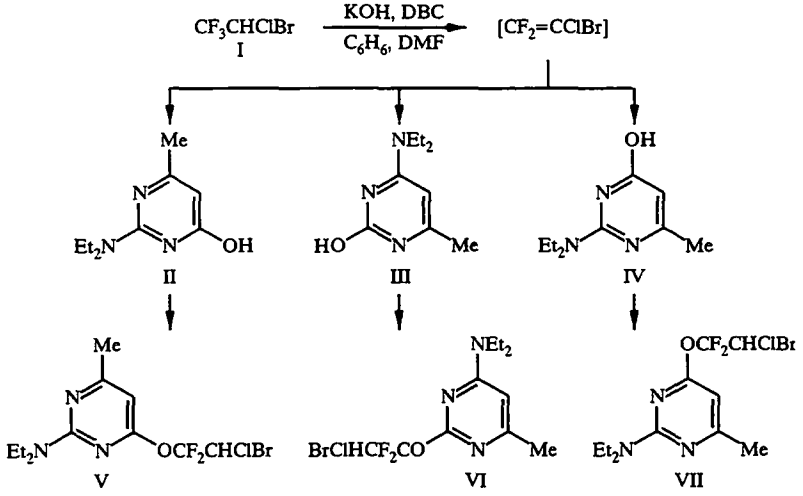
A study was carried out on the reactions of the available inhalation anesthetic halothane with pyrimidines, uracils, and benzimidazole under various conditions. The products structures were determined using IR and PMR spectroscopy.

The use of fluorine-containing synthones in the synthesis of biologically-active molecules holds considerable promise [1]. The introduction of fluorine-containing fragments into a molecule leads to enhanced lipid solubility and, in many cases, more efficient drugs due to facilitation of their transport into the organism [2].

We have already reported a convenient method for the preparation of aliphatic alkynes and alkadiynic acids with the pharmacophoric $OCF_2CHClBr$ group, in which the inhalation anesthetic, 1-bromo-1,1,1-trifluoro-2-chloroethane (halothane, I), is used as the synthone [3]. The fluoroalkynes obtained display bactericidal, diuretic, or antidiuretic activity.

This reaction may be extended to heterocyclic compounds and provides a new strategy for the synthesis of polyfunctional molecules. Furthermore, the preparation of new potential antitumor agents and antiseptics is possible when uracils, pyrimidines, and benzimidazole are used as reagents.

The reaction was carried out in the benzene – dimethylformamide – powdered potassium hydroxide – dibenzo-18-crown-6 system.



The reaction of halothane I with base proceeds with elimination of hydrogen fluoride and generation of 2-bromo-1,1-difluoro-2-chloroethylene as an intermediate [4].

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TABLE 1. Indices of V-VII, IX, X, XIV-XVI, and XVIII-XIX

Compound	Chemical formula	Found, % / Calculated, %			mp, °C	IR spectrum (KBr), cm^{-1}			PMR spectrum (DMSO-d_6), δ, ppm (J, Hz)	Yield, %
		C	H	N		ν_{C-F}	ν_{Alk}	$\nu_{C=O}$		
V	$C_{11}H_{15}BrClF_2N_3O$	36,6 36,8	4,3 4,2	10,3 11,7	108...112	1170, 1220	2853, 3000	—	1,072 (6H, t, $2CH_3$, $J_{H,H}$ = 4,4); 2,048 (3H, s, CH_3); 3,352...3,418 (4H, m, $2CH_2$); 5,715 (1H, s, $C_{(5)}$–H); 7,16 (1H, t, CHClBr, $J_{H,Hal}$ = 5,9)	40
VI	$C_{11}H_{15}BrClF_2N_3O$	36,0 36,8	3,9 4,2	10,9 11,7	102...105	1170, 1220	2853, 3000	—	1,074 (6H, s, $2CH_3$, $J_{H,H}$ = 4,3); 2,056 (3H, s, CH_3); 3,29...3,38 (4H, m, $2CH_2$); 5,619 (1H, s, $C_{(5)}$–H); 7,18 (1H, t, CHClBr, $J_{H,Hal}$ = 5,9)	48
VII	$C_{11}H_{15}BrClF_2N_3O$	37,0 36,8	4,6 4,2	12,0 11,7	100...105	1170, 1230	2850, 3001	—	1,07 (6H, s, $2CH_3$, $J_{H,H}$ = 4,49); 2,05 (3H, s, CH_3); 3,358...3,4 (4H, m, $2CH_2$); 5,16 (1H, c, $C_{(5)}$–H); 7,16 (1H, t, CHClBr, $J_{H,Hal}$ = 5,9)	35
IX	$C_9H_6BrClF_2N_2$*2	36,0 36,5	2,1 2,0	9,6 9,5	200...203	1170, 1250	—	—	7,27 (1H, t, BrClBrCH, $J_{H,F}$ = 5,8); 7,282...8,914 (5H, d, C_6H_4, $J_{H,H}$ = 7,4, N=CH)	30
X	$C_{16}H_{10}BrClN_4$	51,5 54,4	3,0 2,7	15,0 14,9	222...225	—	—	—	7,29...8,91 (5H, d, C_6H_4, $J_{H,H}$ = 7,4, N=CH)	45
XIV	$C_{12}H_{10}BrClN_4O_4$	37,3 37,0	3,1 2,6	15,0 14,4	285...287	—	2800, 3000	1710, 1750	1,734 (6H, s, $2CH_3$); 7,257 (2H, s, $2C_{(6)}$–H); 11,0 (2H, s, $2N_{(3)}$–H)	22
XV	$C_{10}H_4Br_3ClN_4O_4$	22,8 23,0	1,0 0,8	11,0 10,8	235...237	—	—	1710, 1750	7,9 (2H, s, $2C_{(6)}$–H); 11,52 (2H, br. s, $2N_{(3)}$–H)	30
XVI	$C_{12}H_{10}BrClN_4O_4$	37,8 37,1	3,0 2,6	14,8 14,4	295...300	—	2800, 3000	1710, 1750	2,01 (6H, s, $2CH_3$); 5,313 (2H, s, $2C_{(5)}$–H); 10,83 (2H, s, $2N_{(3)}$–H)	26
XVIII	$C_7H_8BrClN_2O_3$*3	30,0 29,9	2,2 2,2	9,9 10,0	272...276	—	2800, 3010	1650, 1750	1,74 (3H, s, CH_3); 7,26 (1H, s, $C_{(6)}$–H); 10,62 (1H, s, $N_{(3)}$–H); 11,03 (1H, s, OH)	28
XIX	$C_6H_4BrClN_2O_3$*3	27,0 26,9	1,6 1,5	10,5 10,5	280...283	—	—	1650, 1750	5,460 (1H, d, $C_{(5)}$–H, $J_{H,H}$ = 7,3); 7,365 (1H, d, $C_{(6)}$– H $J_{H,H}$ = 7,3); 10,81 (1H, s, $N_{(3)}$– H); 10,99 (1H, s, OH)	25

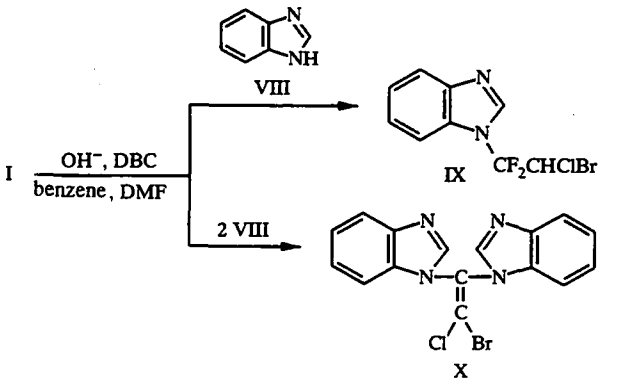
*The ν_{C-Br}, ν_{C-Cl}, and ν_{Ar} stretching bands of all the products appear in the proper spectral region.

*2PMR spectrum taken in $CFBr_3$.

*3In the IR spectrum, ν_{OH} 3200-3400 cm^{-1}.

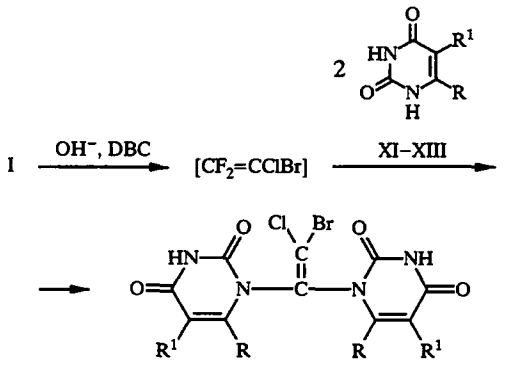
Pyrimidines containing a hydroxyl group in the heterocyclic ring (II-IV) behave in this reaction as phenols and add 2-bromo-1,1-difluoro-2-chloroethylene to give the corresponding ethers V-VII. Facility in carrying out this reaction and a simple work-up of the final products are advantages of this approach.

In contrast to aliphatic alcohols and pyrimidines containing a hydroxyl group, benzimidazole VIII acts as a stronger nucleophile to also give products of fluorine substitution in the halothane molecule, namely, X.



Benzimidazole IX, similar to pyrimidines V-VII, has a chiral site and its PMR spectrum has a triplet at 7.2 ppm corresponding to the proton of the alkyl substituent at $N_{(1)}$.

Uracils XI-XIII react analogously to benzimidazole VIII. This reaction is carried out in 5:2 benzene–DMF in the presence of dibenzo-18-crown-6 in an alkaline medium.

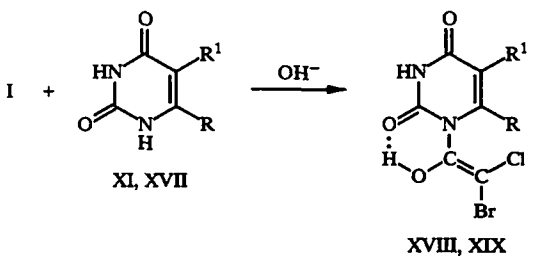


XIV–XVI

XI, XII, XIV, XV, XVIII R = H; XIII, XVI R = Me; XI, XIV, XVIII R^1 = Me; XII, XV R^1 = Br; XIII, XVI R^1 = H

Products XIV-XVI were found to be unstable upon attempts to recrystallize them and starting uracils XI-XIII were isolated.

The reaction of equimolar amounts of halothane I and uracils XI and XVII in an alkaline medium and in the presence of a phase transfer catalyst or using only calcined potassium carbonate leads to uracils XVIII and XIX, which give a positive test for the presence of chloride and bromide ions upon reaction with silver nitrate and a negative test for fluoride ion [5].



XI, XVII

XVIII, XIX

XVII, XIX R = R^1 = H

The IR spectra of XVIII and XIX have a strong band at 3200-3400 cm^{-1}, corresponding to the ν_{OH} stretching vibration. These products display a PMR singlet at 10.994-11.07 ppm, assigned to the hydroxyl group proton, which disappears upon dissolving the compound in D_2O [6].

The assignment of all remaining signals is indicated in Table 1.

EXPERIMENTAL

The PMR spectra of V-VII, IX, X, XIV-XVI, XVIII, and XIX were taken on a Bruker WP-200 spectrometer at 200-132 MHz for solutions in DMSO-d_6 or $CFBr_3$ with TMS as the internal standard. The IR spectra were taken on a UR-20 spectrophotometer. Thin-layer chromatography was carried out on Silufol plates.

The physicochemical and spectral indices and yields of products V-VII, IX, X, XIV-XVI, XVIII, and XIX are given in Table 1.

2-Diethylamino-4-methyl-6-(2′-bromo-1′,1′-difluoro-2′-chloroethoxy)pyrimidine (V, $C_{11}H_{15}BrClF_2N_3O$). A mixture of 7 mmoles halothane I and 7 mmoles pyrimidine II dissolved in a minimal volume of dimethylformamide was added dropwise with stirring to a mixture of 7 mmoles powdered potassium hydroxide and 7 mmoles dibenzo-18-crown-6 in 20 ml absolute benzene. The temperature was gradually raised to 80°C and the mixture was maintained at this temperature for 5-6 h. After cooling, the resultant precipitate was filtered off. The solvent was distilled off and cold 1:1 ether–hexane was added to the residue. The precipitate was filtered off and recrystallized from benzene to give V. Complete precipitation was achieved by adding hexane.

Analogously, VI ($C_{11}H_{15}BrClF_2N_3O$) and VII ($C_{11}H_{15}BrClF_2N_3O$) were obtained from halothane I and pyrimidines III and IV, respectively (Table 1).

1-(2′-Bromo-1′,1′-difluoro-2′-chloroethyl)benzimidazole (IX, $C_9H_6BrClF_2N_2$). A sample of 3 mmoles halothane I was added dropwise with stirring to a mixture of 3 mmoles powdered potassium hydroxide, 3 mmoles dibenzo-18-crown-6, and 3 mmoles benzimidazole in 10 ml absolute benzene. The mixture was stirred for 10 h at 80°C. The cooled solution was filtered. The solvent was distilled off and the yellow crystalline residue was washed with hexane and dried in the air to give IX (Table 1).

Analogously, X ($C_{16}H_{10}BrClN_4$) was obtained from 3 mmoles halothane I, 6 mmoles benzimidazole VIII, 6 mmoles potassium hydroxide, and crown ether (Table 1).

Analogously, we obtained bicyclic derivatives of halothane I: XIV ($C_{12}H_{10}BrClN_4O_4$), XV ($C_{10}H_4Br_3ClN_4O_4$), and XVI ($C_{12}H_{10}BrClN_4O_4$) (Table 1).

$N_{(1)}$-(2′-Bromo-1′-hydroxy-2′-chloroethyl)-5-methyluracil (XVIII, $C_7H_6BrClN_2O_3$). A mixture of 7 mmoles halothane I and 7 mmoles uracil XI dissolved in a minimal volume of dimethylformamide was added dropwise with stirring to a mixture of 7 mmoles powdered potassium hydroxide and 7 mmoles dibenzo-18-crown-6 in 20 ml benzene and stirred for 7 h at 80°C. After cooling, the resultant precipitate was filtered off. The solvent was distilled off to give an oil, which was crystallized from 1:1 ether–hexane. The precipitate was filtered off and dried in the air to give XVIII (Table 1).

This reaction may be carried out in DMSO in the presence of calcined potassium carbonate.

Analogously, XIX ($C_6H_4BrClN_2O_3$) was obtained from halothane I and uracil XVII.

REFERENCES

1. N. Ishikawa (ed.), Fluorine Compounds. Synthesis and Applications [Russian translation], Mir, Moscow (1990), Ch. 5, p. 265.
2. L. M. Yagupol'skii, Aromatic and Heterocyclic Compounds with Fluorine-Containing Substituents [in Russian], Naukova Dumka, Kiev (1988), p. 90.
3. E. V. Proshakova, O. A. Radchenko, and A. Ya. Il'chenko, Zh. Org. Khim., **28**, 1120 (1992).
4. I. I. Gerus, M. T. Kolycheva, Yu. L. Yagupol'skii, and V. P. Kukhar', Zh. Org. Khim., **25**, 2020 (1989).
5. S. Weibel, Identification of Organic Compounds [in Russian], Izd. Inostr. Lit. (1957), p. 269.
6. V. A. Mironov and S. A. Yankovskii, Spectroscopy in Organic Chemistry [in Russian], Khimiya, Leningrad (1985), p. 80.