SOME REACTIONS OF 2-(2-HYDROXYHEXA-FLUORO)ISOPROPYL-5-METHYLFURAN

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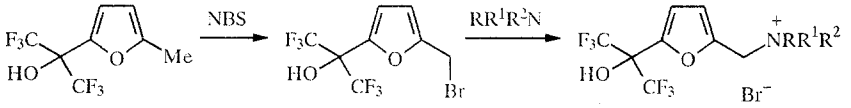
The bromination of 2-(2-hydroxyhexafluoro)isopropyl-5-methylfuran at the methyl group and subsequent reaction with nitrogen nucleophiles gave some secondary amines and quaternary salts.

2-(2-Hydroxyhexafluoro)isopropyl-5-methylfuran (I), which is readily available by the reaction of α-methylfuran with hexafluoroacetone [1] is an extremely attractive reagent for synthetic studies in light of its polyfunctional nature.

In previous work [2], we showed that nucleophilic substitution of the OH group in furan I proceeds only with difficulty. The hydrogen atom in this group, on the other hand, displays pronounced acidity upon reactions with metals, amines, and alkali solutions. The alcoholates have low activity in alkylation and acylation reactions [2].

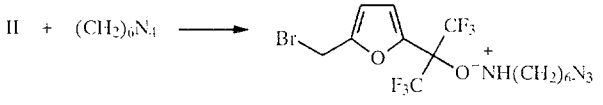
In the present work, we studied the synthetic possibilities of furan I due to the presence of a labile hydrogen atom in the methyl group. This hydrogen atom may be readily replaced by bromine upon treatment with N-bromosuccinimide. In turn, bromide II forms the corresponding salts III-XX with a series of aromatic and heterocyclic amines (Table 1).



I II III-XIX

The PMR spectra of salts III-XIX all have signals for furan protons (6.9 ppm), the methylene group (6.0 ppm), and signals characteristic for protons of the starting amine. Depending on the amine used, the synthesis is carried out at room temperature or on a steam bath.

In the case of a more basic amine such as urotropine, this reaction proceeds unusually at the hydroxyl group without affecting the bromine atom.



XX

The IR spectrum of product XX lacks the hydroxyl group band and its PMR spectrum has signals for two types of urotropine methylene protons (4.4 and 5.5 ppm) and a signal for the proton at the ammonium nitrogen atom (8.7 ppm).

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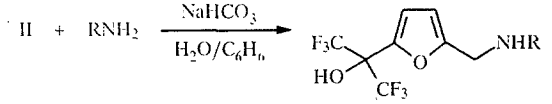
TABLE 1. Synthesis of N—R—N—R^1—N—R^2-(2-[5-(2-Hydroxyhexafluoro)isopropylfuryl])methylammonium Bromides III-XX

Compound	R	R^1	R^2	Chemical formula	Solvent	mp, °C	Yield, %
III	C_6H_5	H	H	$C_{14}H_{12}BrF_6NO_2$	C_6H_6	200	80
IV	3-$NO_2C_6H_4$	H	H	$C_{14}H_{11}BrF_6N_2O_4$	$CHCl_3$	160 (dec.)	14
V	4-$NO_2C_6H_4$	H	H	$C_{14}H_{11}BrF_6N_2O_4$	$(C_2H_5)_2O$	195 (dec.)	20
VI	2-ClC_6H_4	H	H	$C_{14}H_{11}BrClF_6O_2$	C_6H_6	200	14
VII	3-HOC_6H_4	H	H	$C_{14}H_{12}BrF_6NO_3$	$(C_2H_5)_2O$	196	21
VIII	2,4-$(NO_2)_2C_6H_5$	H	H	$C_{14}H_{10}BrF_6N_3O_6$	C_6H_6	175	25
IX	1-Phenyl-2,3-dimethyl-5-pyrazolidon-4-yl	H	H	$C_{19}H_{18}BrF_6N_3O_3$	$CHCl_3$	200	30
X	4-N-(4-Nitrophenylamino)-2-thiazolyl	H	H	$C_{17}H_{13}BrF_6N_4O_4S$	$(CH_3)_2CO$	167 (dec.)	18
XI	1-Phenyl-3-pyrazalidone	—	—	$C_{17}H_{15}BrF_6N_2O_3$	$CHCl_3$	119...120	27
XII	Pyridine	—	—	$C_{13}H_{10}BrF_6NO_2$	C_6H_6	145	90
XIII	4-Pyridinaldoxime	—	—	$C_{14}H_{11}BrF_6N_2O_3$	C_6H_6	185	85
XIV	2-Bromopyridine	—	—	$C_{13}H_9Br_2F_6NO_2$	C_6H_6	113	67
XY	2-Aminopyridine	—	—	$C_{13}H_{11}BrF_6N_2O_2$	$CHCl_3$	157	15
XVI	4-Aminopridine	—	—	$C_{13}H_{11}BrF_6N_2O_2$	C_6H_6	154	69
XVII	3-(1,3-Dioxan-2-yl)pyridine	—	—	$C_{17}H_{16}BrF_6NO_4$	C_6H_6	164	29
XVIII	Quinoline	—	—	$C_{17}H_{12}BrF_6NO_2$	C_6H_6	155	64
XIX	8-Hydroxyquinoline	—	—	$C_{17}H_{12}BrF_6NO_3$	C_6H_6	45	41
XX	Urotropine	—	—	$C_{14}H_{17}BrF_6N_4O_2$	CH_3CN	160	55

TABLE 2. Synthesis of 2-(2-Hydroxyhexafluoro)isopropyl-5-N-R-aminomethylfurans (XXI)-(XXIII)

Compound	R	Time, h	mp, °C	Yield, %
XXI	C_6H_5	0,5	82	39
XXII	3-$NO_2C_6H_4$	1,0	103	19
XXIII	4-$NO_2C_6H_4$	2,0	109	10

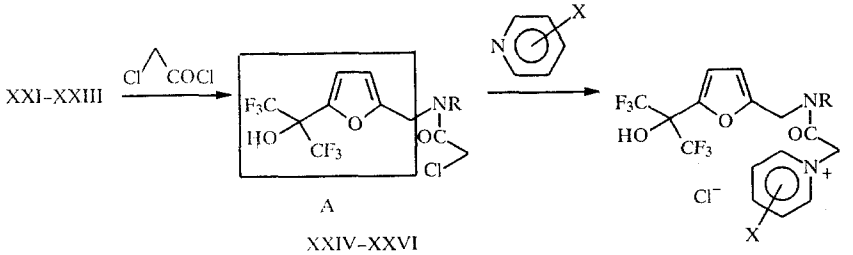
The reaction of bromide II with aromatic amines in the presence of $NaHCO_3$ in water—benzene heterophase system leads to N-alkylation of these amines.



XXI-XXIII

On the whole the yield of products XXI-XXIII increases with increasing basicity of the amines used (Table 2).

The secondary amino group in XXI-XXIII is acylated by chloroacetyl chloride to give XXIV-XXVI in moderate yields. These acyl derivatives, in turn, are converted to pyridinium salts XXVII-XXXII upon treatment with the corresponding bases (Table 3).



XXIV-XXVI

XXVII-XXXII

TABLE 3. Synthesis of 2-(2-Hydroxyhexafluoro)isopropyl-5-R-N-chloroacetylaminomethylfurans and Their Pyridinium Salts XXIV-XXXII

Compound	R	X	mp, °C	Yield, %
XXIV	C_6H_5	—	94	40
XXV	$3\text{-}NO_2C_6H_4$	—	96	25
XXVI	$4\text{-}NO_2C_6H_4$	—	165	16
XXVII	C_6H_5	H	196	67
XXVIII	C_6H_5	4-CH=NOH	65	40
XXIX	C_6H_5	3-(1,3-Dioxan-2-yl)	80	31
XXX	$3\text{-}NO_2C_6H_4$	H	200	34
XXXI	$3\text{-}NO_2C_6H_4$	4-CH=NOH	200	41
XXXII	$4\text{-}NO_2C_6H_4$	H	200	53

Hence, the bromination of furan I with subsequent substitution of the bromine atom is a convenient preparative method for the introduction of structural fragment A into various nitrogen nucleophiles.

EXPERIMENTAL

The PMR spectra were taken on a Tesla BS-487C spectrometer at 60 MHz with HMDS as the internal standard. The IR spectra were taken in Vaseline mulls on a UR-20 spectrophotometer.

A sample of 2-(2-hydroxyhexafluoro)isopropyl-5-bromomethylfuran was obtained according to a standard procedure [3].

Synthesis of Salts III and VI-XX. A mixture of equimolar amounts of bromide II and the corresponding amine in a minimal volume of solvent (5 ml per 3 mmoles amine) was left at 20°C for 24 h. The product was separated by adding 20 ml ether or hexane, filtered, and crystallized (Table 1).

Synthesis of Salts IV and V. A mixture of equimolar amounts of bromide II and the corresponding amine in a minimal volume of solvent (5 ml per 3 mmole amine) was heated on a steam bath for 6 h and cooled. The precipitate was filtered off and crystallized (Table 1).

Synthesis of 2-(2-Hydroxyhexafluoro)isopropyl-5-N-R-aminomethylfurans XXI-XXIII. A sample of 8 g bromide II was added dropwise with stirring to a mixture of 0.024 mole amine (0.096 mole when R = H), 8 g (0.06 mole) $NaHCO_3$, 6 ml water, and 20 ml benzene at reflux and heated for 0.5-2 h at reflux. After cooling, the precipitate was filtered off and the filtrate was neutralized by the addition of 10% sulfuric acid. The organic layer was separated, washed with saturated aqueous NaCl, dried over Na_2SO_4, and filtered. The solvent was distilled off. When R = H, the excess aniline was removed by vacuum distillation. The product was separated from the vat residue by crystallization from hexane (Table 2).

Synthesis of 2-(2-Hydroxyhexafluoro)isopropyl-5-N-R-chloroacetylaminomethylfurans XXIV-XXVI. A sample of 1 mmole chloroacetyl chloride was added dropwise with stirring to a mixture of 1 mmole amine, 1 mmole potassium carbonate, and 10 ml benzene and heated at reflux for 2 h. After cooling, the precipitate was filtered off. The filtrate was washed with water and dried over Na_2SO_4. Benzene was distilled off. The residue was crystallized from hexane (Table 3).

Synthesis of Pyridinium Salts XXVII-XXXII from XXIV-XXVI. A mixture of 1 mmole XXIV-XXVI and 1 mmole pyridine in 5 ml benzene was maintained for 24 h at 20°C and 20 ml hexane was added. The mixture was filtered and the precipitate was crystallized. In the case of 4-pyridinaldoxime, 1 mmole of this reagent and 1 mmole XXIV or XXV in 5 ml ethanol was heated at reflux for 5 h and cooled. The unreacted oxime was removed and the residue was crystallized (Table 3).

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2. S. P. Gavrilova, L. A. Badovskaya, V. G. Glukhovtsev, and G. I. Nikhishin, Zh. Org. Khim., **26**, 2420 (1990).
3. Weygand-Hilgetag, Experimental Methods in Organic Chemistry [Russian translation], Khimiya, Moscow (1969), p. 138.