SYNTHESIS AND STEREOCHEMISTRY OF 3-HYDROXY-6-PERFLUOROALKYL-2,3-DIHYDRO-4-PYRONES

V. I. Tyvorskii, L. S. Stanishevskii, and I. G. Tishchenko

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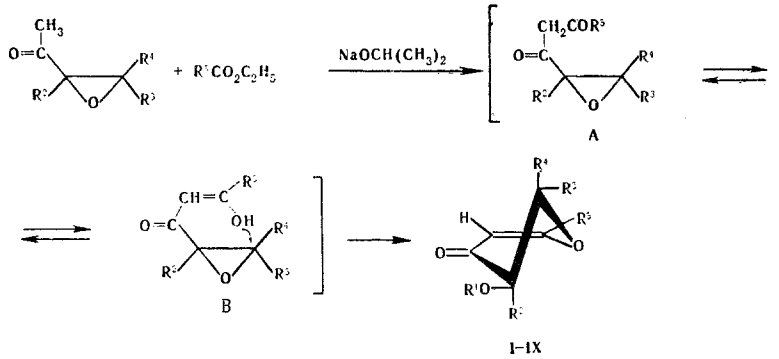
The reaction of a number of aliphatic and alicyclic acetloxiranes with perfluoroalkanoic acid esters was studied. It is shown that substituted 3-hydroxy-6-perfluoroalkyl-2,3-dihydro-4-pyrones are formed. The reverse reaction scheme, including the formation of an intermediate β-diketone and cyclization of its enol form to a dihydropyrone, was confirmed in the case of the condensation of 3-methyl-2,3-epoxycyclohexanone with ethyl trifluoroacetate. The stereochemistry of the reaction products, which exist in a half-chair confirmation with a pseudoequatorial hydroxyl group, was examined by means of PMR spectroscopy.

We have previously shown [1] that the reaction of some acetyloxiranes with perfluoroalkanoic acid esters under the conditions of the Claisen condensation leads to 3-hydroxy-2,3-dihydro-4-pyrone derivatives.

To ascertain the stereochemistry of the products of the indicated reaction, in the present research we studied the reaction of a number of aliphatic and alicyclic acetyloxiranes with ethyl trifluoroacetate and ethyl n-heptafluorobutyrate in dimethoxymethane in the presence of an equivalent amount of sodium alkoxide. This procedure gave substituted 3-hydroxy-6-perfluoroalkyl-2,3-dihydro-4-pyrones (I-IX) in up to 78% yields:

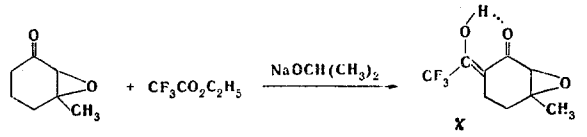


I–IX

I–IX R^1=H; I, III, V, VII, IX R^5=CF_3; II, IV, VI, VIII R^5=n-C_3F_7; I, II R^2=CH_3, R^3=R^4=H; III, IV R^2=R^4=H, R^3=CH_3; V, VI R^2=H, R^3=R^4=CH_3; VII, VIII R^2=R^3=CH_3, R^4=H; IX R^2R^3=$(CH_2)_4$, R^4=H

According to the results of thin-layer chromatography (TLC) [on Silufol, ether–hexane (1 : 1)], the condensation is virtually complete in 30 min, and β-diketone A, which has very low chromatographic mobility, is formed; it is gradually converted through enol form B to the corresponding dihydropyrone I-IX (cyclization is completed during isolation of the reaction products). In this connection, condensation intermediates cannot be obtained in the individual state.

To confirm the above reaction scheme, we studied the reaction, under the same conditions, of 3-methyl-2,3-epoxycyclohexanone (X), since the subsequent cyclization presupposes the existence of a double bond attached to the nodal bridge atom:



X

V. I. Lenin Belorussian State University, Minsk 220080. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 897-900, July, 1978. Original article submitted June 14, 1977.

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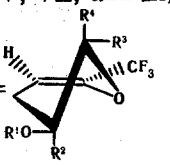
TABLE 1. Parameters of PMR Spectra of 3-Hydroxy-6-trifluoromethyl-2,3-dihydro-4-pyrones* (I, III, V, VII, and IX) and Their Acetates (Ia, IIIa, Va, VIIa, and IXa) 

Compound	R¹	R²	R³	R⁴	Chemical shifts, δ, ppm					SSCC, Hz	
					R¹	R²	R³	R⁴	5-H	$J_{R^2R^3}$	$J_{R^3R^4}$
I	H	CH_3	H	H	3,92 s	1,33 s	4,22 d + 4,38 d		5,78 s	—	12
Ia	CH_3CO	CH_3	H	H	2,08 s	1,53 s	4,23 d	5,14 d	5,83 s	—	12
III	H	H	CH_3	H	3,72 d †	4,00 dd†	1,67 d	4,34 dq	5,88 s	12	6
IIIa	CH_3CO	H	CH_3	H	2,15 s	5,20 d	1,55 d	4,64 dq	5,84 s	12	6
V	H	H	CH_3	CH_3	3,64 s	4,20 s	1,28 s + 1,66 s		5,85 s	—	—
Va	CH_3CO	H	CH_3	CH_3	2,18 s	5,38 s	1,40 s + 1,57 s		5,83 s	—	—
VII	H	CH_3	CH_3	H	3,64 s	1,21 s	1,53 d	4,38 q	5,83 s	—	6
VIIa	CH_3CO	CH_3	CH_3	H	2,07 s	1,36 s	1,44 d	5,40 q	5,81 s	—	6
IX	H	$(CH_2)_4$		H	3,53 s	1,40—2,23 m		4,32—4,38 m	5,85 s	—	—
IXa	CH_3CO	$(CH_2)_4$		H	2,06 s	1,58—2,10 m		5,18—5,24 m	5,76 s	—	—

* Replacement of the trifluoromethyl group by an n-heptafluoropropyl group has virtually no effect on the parameters of the PMR spectra of the investigated compounds.

† $J_{3-H,OH} = 2$ Hz.

Diketone X gives intense coloration with a dilute methanol solution of ferric chloride and readily forms a chelate complex on reaction with copper acetate. Absorption bands at 1640 and 1590 cm^{-1}, which are characteristic for the enol form of β-diketones [2], are observed in the IR spectrum of X; adsorption bands of the diketo form are absent. The PMR spectrum (the signal of an enol OH group at 14.81 ppm) also indicates virtually complete enolization of trifluoroacetylcyclohexanone X in the direction of the trifluoroacetyl group; this is characteristic for partially fluorinated β-diketones [3-5].

Opening of the epoxide ring on the β-carbon atom side during intramolecular cyclization of the intermediate enol form B is confirmed by the presence in I-XI of an α-ketol grouping, according to the results of oxidation with periodic acid, and also by comparison of the PMR spectra of the latter and their acetates IA, IIIa, Va, VIIa, and IXa (I, III, V, VII, and IX $R^1 = CH_3CO$) (Table 1). Thus the signal of the 3-H proton in the PMR spectrum of III is a quartet due to coupling with the 2-H and OH protons. The latter type of coupling is absent in acetate IIIa, and the signal of the 3-H proton in the PMR spectrum appears as a doublet that is shifted (1.2 ppm) to weak field as compared with the spectrum of III due to the effect of the secondary acetoxy group [6]. A similar shift (1.18 ppm) of the signal of the 3-H signal is observed on passing from the PMR spectrum of V to the spectrum of its acetate (Va). In the PMR spectrum of acetate Ia the signal of one of the protons of the 2-CH_2 group is shifted significantly to weak field as compared with the spectrum of nonacetylated I, and the chemical shift of the other proton of the same methylene group remained virtually unchanged. This indicates the absence in I of the primary hydroxyl group that would have been formed in the case of opening of the oxirane ring of B during cyclization on the part of the α-carbon atom [6].

The transformation of intermediate enol form B to dihydropyrones I-IX should be accompanied by inversion of the configuration of the β-carbon atom of the epoxide ring,* as previously proposed for the similar (with respect to mechanism) intramolecular cyclization of epoxides of trans-2-acetoxychalcones, which leads to dihydroflavonols [7]. In fact, the vicinal $J_{2-H,3-H}$ constant in the PMR spectrum of III is 12 Hz, which indicates a pseudoxial orientation (a trans orientation) of the 2-H and 3-H protons in the half-chair conformation of the dihydropyrone ring [8-11] and confirms inversion of the starting configuration of the epoxide ring in the B form. The $J_{2-H,3-H}$ constant in the PMR spectrum of acetate IIIa remains the same; i.e., the conformation with a pseudoequatorial hydroxy (acetoxy) group is retained on passing from hydroxy derivative III to its acetate (IIIa).

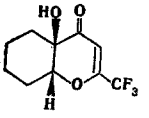
* In the condensation we used acetyloxiranes with a known configuration, which is indicated in the general scheme of the reaction.

TABLE 2. Characteristics of the Compounds

Compound	bp (mm) or mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	F		C	H	F	
I	67 (12)[a]	42,7	3,4	29,6	$C_7H_7F_3O_3$	42,9	3,6	29,1	66
Ia	62 (3)[b]	45,5	3,7	23,5	$C_9H_9F_3O_4$	45,4	3,8	23,9	52
II	82 (12), 24	36,4	2,4	45,2	$C_9H_7F_7O_3$	36,5	2,4	44,9	54
III	75	42,9	3,6	29,3	$C_7H_7F_3O_3$	42,9	3,6	29,1	25
IIIa	60	45,5	3,8	24,2	$C_9H_9F_3O_4$	45,4	3,8	23,9	65
IV	76	36,6	2,4	45,0	$C_9H_7F_7O_3$	36,5	2,4	44,9	20
V	70	45,4	4,2	26,9	$C_8H_9F_3O_3$	45,7	4,3	27,1	55
Va	26	47,9	4,5	23,1	$C_{10}H_{11}F_3O_4$	47,6	4,4	22,6	58
VI	65	38,9	3,2	42,8	$C_{10}H_9F_7O_3$	38,7	2,9	42,9	34
VII	64 (10)[c]	45,6	4,2	27,2	$C_8H_9F_3O_3$	45,7	4,3	27,1	78
VIIa	48	47,7	4,5	22,8	$C_{10}H_{11}F_3O_4$	47,6	4,4	22,6	74
VIII	76 (12)[d]	39,0	3,2	43,1	$C_{10}H_9F_7O_3$	38,7	2,9	42,9	75
IX	44	50,7	4,9	24,5	$C_{10}H_{11}F_3O_3$	50,9	4,7	24,1	67
IXa	79	51,6	4,7	20,7	$C_{12}H_{14}F_3O_4$	51,8	4,7	20,5	65
X	62—65 (2)[e]	48,8	4,2	26,0	$C_9H_9F_3O_3$	48,7	4,1	25,7	47

[a] d_4^{20} 1.3581 and n_D^{20} 1.4265. Found: MR_D 37.0. Calculated: MR_D 35.5. [b] d_4^{20} 1.3287 and n_D^{20} 1.4325. Found: MR_D 45.7. Calculated: MR_D 44.8. [c] d_4^{20} 1.2947 and n_D^{20} 1.4230. Found MR_D 41.3. Calculated: MR_D 40.1. [d] d_4^{20} 1.4386 and n_D^{20} 1.3912. Found: MR_D 51.2. Calculated: MR_D 49.8. [e] d_4^{20} 1.3456 and n_D^{20} 1.4620. Found: MR_D 45.4. Calculated: MR_D 43.3.

The 1-H proton shows up in the form of a weakly resolved quartet with a width of 6 Hz in the PMR spectra of 6-hydroxy-3-trifluoromethyl-2-oxabicyclic[4.4.0]dec-3-en-5-one (IX) and its acetate (IXa), and this constitutes evidence for its equatorial orientation in the cyclohexane ring.



IX

The cis fusion (which is the only possible fusion in this case) of the cyclohexane and dihydropyrone rings and the pseudoequatorial orientation of the hydroxyl group in the latter follow from this.

A conformation with a pseudoequatorial hydroxyl group and R^3 substituent can be similarly assigned to I, II, and IV-VIII either on the basis of the identical character of the substitution with dihydropyrones III or IX or on the basis of the characteristic (for acetylation) shift of the signal of the 2-H proton to weak field in the PMR spectra.

Absorption bands of a hydroxyl group at 3500 cm^{-1}, of stretching vibrations of C—H attached to a double bond at 3100 cm^{-1}, and of a conjugated carbonyl group and double bond at 1690-1700 and 1620-1630 cm^{-1}, respectively, are observed in the IR spectra of dihydropyrones I-IX. The constant and characteristic [11] position of the band of hydroxyl absorption also indirectly confirm the identical character of the conformation of I-IX.

EXPERIMENTAL

The IR spectra of solutions of I-X in CCl_4 were obtained with a UR-20 spectrometer at 400-3700 cm^{-1}. The PMR spectra of 10% solutions of I-X in carbon tetrachloride were recorded with a Varian HA-100 spectrometer with an operating frequency of 100 MHz with tetramethylsilane as the internal standard.

The physicochemical constants of the compounds are presented in Table 2.

3-Hydroxy-6-perfluoroalkyl-2,3-dihydro-4-pyrones (I-IX). A mixture of 0.2 mole of the corresponding acetyloxirane and 0.2 mole of perfluoroalkanoic acid ester was added with stirring and cooling to −10°C to a

suspension of 0.2 mole of sodium isopropoxide in 500 ml of absolute dimethoxymethane. After 30 min, 0.2 mole of glacial acetic acid was added, the solvent was removed by distillation, and the residue was treated with 100 ml of water. The aqueous mixture was extracted with ether (four 100-ml portions), and the ether extract was dried with anhydrous sodium sulfate. The ether was removed by distillation, and the residue was vacuum fractionated. Compounds II and VI were crystallized from pentane, and III-V and IX were crystallized from hexane.

3-Methyl-6-trifluoroacetyl-2,3-epoxycyclohexanone (X). This compound was obtained by the above method, but the temperature of the reaction mixture was raised to 18-20°C after the addition of the reagents to the sodium isopropoxide, and stirring was continued for another 2 h. PMR spectrum of X: 1.49 (3H, s, CH_3), 1.57-2.49 (4H, m, CH_2CH_2), 3.19 (1H, s, 2-H), and 14.81 ppm (1H, s, =COH). The copper complex was obtained by the method in [12] and was crystallized from ethanol to give a product with mp 225°C (dec.).

3-Acetoxy-6-trifluoromethyl-2,3-dihydro-4-pyrones (Ia, IIIa, Va, VIIa, and IXa). A solution of 0.01 mole of I, III, V, VII, or IX in 20 ml of acetyl chloride was allowed to stand at 18-20°C for 24 h, after which the acetyl chloride was removed by distillation, and the residue was dissolved in 30 ml of ether. The ether solution was washed with a saturated solution of sodium bicarbonate and dried with sodium sulfate, the ether was removed by distillation, and the residue was vacuum distilled (Ia, Va) or crystallized from hexane (IIIa, VIIa, IXa).

The α-ketol grouping in I-IX was determined by oxidation with periodic acid by the method in [13].

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