SYNTHESIS OF AZETIDIN-3-ONES BY HETEROCYCLIZATION OF α-CYCLOHEXYLAMINO-α',β'-EPOXY KETONES

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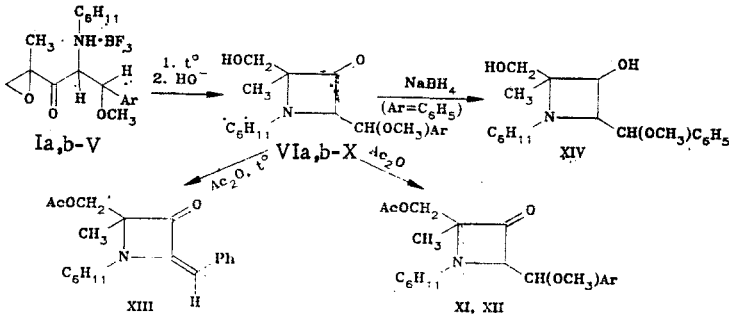
The stereospecific cyclization of 5-aryl-2-methyl-5-methoxy-4-cyclohexylamino-1,2-epoxypentan-3-one borofluorides on heating in acetone or in acetonitrile leads to 4-arylmethoxymethyl-2-hydroxymethyl-2-methyl-1-cyclohexylazetidin-3-ones. Certain chemical transformations of the latter have been studied. It was shown that, in contrast to the borofluoride complex, 2-methyl-5-methoxy-5-phenyl-4-cyclohexylamino-1,2-epoxypentan-3-one cyclizes into a mixture of diastereomeric 2-(cyclohexylamino)tetrahydrofuran-3-ones.

Despite interest in the chemistry of azetidinones [1], only a few papers have been published dealing with the synthesis of azetidin-3-ones [2-6]. In the present work, a new method is proposed for the synthesis of substituted azetidin-3-ones by cyclization of borofluoride complexes of α-cyclohexylamino-α',β'-epoxy ketones.

We have already described the synthesis of epoxypropionylaziridines [7] and studied their reaction with methanol in the presence of boron trifluoride etherate [8]. Together with other products, disasteromeric borofluorides of erythro-α-cyclohexylamino-α',β'-epoxy ketones (Ia,b) have been isolated and characterized. The borofluoride complexes II-V with a substituent in the benzene ring were obtained in a similar way.

It was found that when borofluorides Ia,b-V are heated in an aprotic solvent (acetone, acetonitrile), 4-arylmethoxymethyl-2-hydroxymethyl-2-methyl-1-cyclohexylazetidin-3-ones (VIa, b-X) are formed, which are isolated when the reaction mixture is made alkaline. When the polar aprotic solvent is replaced by methanol or toluene, there is no cyclization.



Ia,b, VIa,b, XI Ar=C_6H_5; II, VII Ar=4-BrC_6H_4; III, VIII, XII Ar=3-BrC_6H_4; IV, IX Ar=2-$CH_3OC_6H_4$; V, X Ar=4-ClC_6H_4

The structure of the synthesized compounds was confirmed by spectral data. In the IR spectra of compounds VIa,b-X there is an intense band at 1800-1805 cm^{-1}, characteristic of the C=O group in azetidin-3-ones [9]. The band at 3630 cm^{-1} (CCl_4, 10^{-3} mole/liter) indicates the presence of a free hydroxyl group. In the mass spectra of compounds VIa,b there are peaks of the molecular ion with m/z 317, as well as the fragmentary ions with m/z 289 ($[M - C{=}O]^+$), characteristic of cyclic carbonyl compounds. A special feature of the PMR spectrum of azetidinone VIa in DMSO is the presence of a triplet signal of the hydroxyl proton (J = 4.0 Hz) and two quadruplets of methylene group protons (J = 4.0 and 11.0 Hz), which indicates the presence of a primary hydroxyl group in the molecule.

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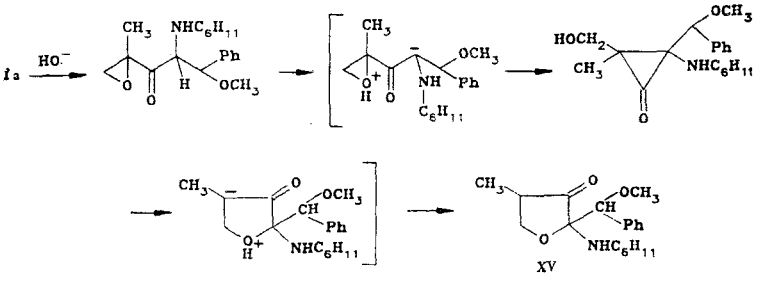
We took diastereomeric borofluorides Ia,b as an example, and found that the reaction is stereospecific and leads to the formation of diastereomeric azetidin-3-ones VIa,b, respectively, differing in the configuration of the $C_{(2)}$ atom. It is clear that the stereospecific cyclization of borofluorides Ia,b-V into azetidin-3-ones presumes an intramolecular α-opening of the epoxy ring by the amino group. When borofluorides Ia,b-V are heated in acetone or acetonitrile, the ammonium complex partially dissociates. Subsequent coordination of boron trifluoride is possible at the oxygen atom of the epoxy ring, which catalyzes the opening of the latter during a nucleophilic attack. The direction of the epoxide opening [10, 11], and also the stereochemistry of the process indicate that the reaction proceeds by the S_N2 mechanism. It should also be noted that the cyclization of borofluorides Ia,b-V conforms also with the Baldwin's steric rules, describing it as a 4-exo-sp^3 process [12]. The formation of an oxonium complex is probably the necessary condition for cyclization, since heating of α-cyclohexylamino-α',β'-epoxy ketones, isolated from the corresponding complexes in acetone or acetonitrile, does not lead to azetidin-3-ones.

The synthesized azetidin-3-ones enter into reactions at the functional groups with retention of the four-membered heterocyclic ring. Thus, at a temperature of 20°C, azetidin-3-ones VIa and VIII are acetylated by acetic anhydride to form acetates XI and XII. In the IR spectra of acetates XI and XII, the OH group band disappears and the ester group band appears at 1740 cm^{-1}.

When azetidinone VIa is boiled in a mixture of acetic acid with acetic anhydride, the acetylation is accompanied by splitting of methanol and the formation of an unsaturated ketone XIII. The relative intensity of the $\nu_{C=O}$ and $\nu_{C=C}$ bands in the IR spectrum of compound XIII at 1750 and 1635 cm^{-1} indicates the presence of an s-cis-fragment of a saturated ketone in the molecule. The E-configuration of the exocyclic double bond in azetidinone XIII is confirmed by the chemical shift of the benzylidene proton [13, 14] and agrees with the stereochemistry of trans-elimination of methanol from azetidinone, obtained from erythro-α-cyclohexylamino-β-methoxyepoxy ketone.

The reduction of azetidinone VIa by sodium borohydride in methanol proceeds stereospecifically and leads to one diastereomer of 2-hydroxymethyl-2-methyl-4-phenylmethoxymethyl-1-cyclohexylazetidin-3-ol (XIV) with a trans-orientation of the hydroxyl and hydroxymethyl groups. The configuration of the diol was established from measuring the Overhauser effect.

In contrast to the borofluoride complexes, α-cyclohexylamino-α',β'-epoxy ketones were found to be unstable. Thus, 2-methyl-5-methoxy-5-phenyl-4-cyclohexylamino-1,2-epoxypentan-3-one, isolated from borofluoride Ia, decomposes on storage or on heating to form a mixture of products, from which diastereomeric 4-methyl-2-phenylmethoxymethyl-2-cyclohexylaminotetrahydrofuran-3-ones (XV) were isolated by chromatography:



In the IR spectrum of tetrahydrofuran-3-one XV bands of the $\nu_{C=O}$ (1765 cm^{-1}) and ν_{NH} (3340 cm^{-1}) groups are observed. In the mass spectrum of aminofuranone XV there are peaks of molecular ion with m/z 317 and of main fragmentary ions with m/z 289 $[M - C{=}O]^+$; 196 $[M - CH(OCH_3)C_6H_5]^+$; 121 $[CH(OCH_3)C_6H_5]^+$. A characteristic feature of the PMR spectrum of aminofuranone XV is the presence of a doublet of the methyl group protons (J = 6.6 Hz), a multiplet of the 4-H proton, and two quadruplets of methylene protons (J = 9.8, 7.8, and 7.5 Hz).

The proposed scheme of transformation of 2-methyl-5-methoxy-5-phenyl-4-cyclohexylamino-1,2-epoxypentan-3-one into aminotetrahydrofuranone XV incldues the formation of a cyclopropane intermediate, which as a result of an intramolecular nucleophilic substitution transforms into tetrahydrofuran-3-ones. It should be noted that no appreciable amounts of nitrogen-containing heterocyclic compounds, products of opening of the epoxy ring by the cyclohexylamino group, were detected in the reaction mixture.

TABLE 1. Physicochemical and Spectral Characteristics of Compounds II-XV

Compound	mp, °C	PMR spectrum,* ppm (J, Hz)	Found, %			Empirical formula	Calculated, %			Yield, %
			C	H	N		C	H	N	
II	164—165	1,30 (s, 3H); 1,74 (m, 11H); 2,90, 3,05 (two d, 2H, J=5,0); 3,27 (s, 3H); 4,45, 4,78 (two d, 2H, J=6,0); 7,40 (s, 4H)	49,1	5,5	3,0	$C_{19}H_{26}BrNO_3 \cdot BF_3$	49,2	5,7	3,0	48
III	187—188	1,24 (s, 3H); 1,60 (m, 11H); 2,88, 3,03 (two d, 2H, J=5,0); 3,28 (s, 3H); 4,56, 4,93 (two d, 2H, J=6,0); 7,46 (m, 4H)	49,2	5,6	3,1	$C_{19}H_{26}BrNO_3 \cdot BF_3$	49,2	5,7	3,0	45
IV	156—158	1,03 (s, 3H); 1,50 (m, 11H); 2,64, 2,80 (two d, 2H, J=5,0); 3,18 (s, 3H); 3,75 (s, 3H); 4,48, 5,00 (two d, 2H, J=6,0); 7,02 (m 4H)	57,7	4,9	3,2	$C_{20}H_{29}NO_4 \cdot BF_3$	57,8	4,9	3,4	51
V	177—178	1,30 (s, 3H); 1,55 (m, 11H); 2,90, 3,05 (two d, 2H, J=5,0); 3,27 (s, 3H); 4,45, 4,78 (two d 2H, J=6,0); 7,40 (s, 4H)	54,5	6,2	3,4	$C_{19}H_{26}ClNO_3 \cdot BF_3$	54,4	6,3	3,3	49
VIa	121—122	1,24 (s, 3H); 1,35—1,85 (10H); 2,00 (s, H); 3,10 (t, H, J=10,0); 3,32 (s, 3H); 3,77, 3,80 (two d, 2H, J=11,0); 4,30, 4,47 (two d, 2H, J=1,8); 7,35 (m, 5H)	71,8	8,4	4,3	$C_{19}H_{27}NO_3$	71,9	8,6	4,4	70
VIб	136—138	1,16 (s, 3H); 1,33—1,90 (m, 10H); 2,78 (t, H, J=10,0); 3,27 (s, 3H); 3,35, 3,67 (two d, 2H, J=11,0); 4,31, 4,39 (two d, 2H, J=2,0); 7,36 (m, 5H)	72,0	8,5	4,4	$C_{19}H_{27}NO_3$	71,9	8,6	4,4	60
VII	162—163	1,16 (s, 3H); 1,32—1,82 (m, 10H); 1,98 (s, H); 3,09 (t, H, J=10,0); 3,30 (s, 3H); 3,37, 3,81 (two d, 2H, J=11,0); 4,23, 4,42 (two d, 2H, J=1,8); 7,25, 7,45 (two d, 4H, J=9,0)	57,4	6,5	3,3	$C_{19}H_{26}BrNO_3$	57,6	6,6	3,5	61

VIII	127—128	1,17 (s, 3H); 1,34—1,83 (m, 10H); 2,08 (s, H); 3,11 (t, H, J=10,0); 3,33 (s, 3H); 3,37, 3,84 (two d, 2H, J=11,0); 4,23, 4,45 (two d, 2H, J=1,8); 7,22, 7,34, 7,41, 7,51 (m, 4H)	57,6	6,5	3,5	$C_{19}H_{26}BrNO_3$	57,6	6,6	3,5	71
IX	116—118	1,28 (s, 3H); 1,36—2,01 (m, 10H); 2,76 (s, H); 3,16 (t, H, J=10,0); 3,40 (s, 3H); 3,74, 3,76 (two d, 2H, J=11,0); 3,78 (s, 3H); 4,40, 4,70 (two d, 2H, J=1,8); 6,82, 6,98, 7,22, 7,51 (m, 4H)	69,0	8,4	4,0	$C_{20}H_{29}NO_4$	69,1	8,4	4,0	76
X	132—134	1,00 (s, 3H); 1,36—1,90 (m, 10H); 3,09 (t, H, J=10,0); 3,15 (s, H); 3,24 (s, 3H); 3,72, 3,80 (two d, 2H, J=11,0); 4,22, 4,37 (two d, 2H, J=2,0); 7,28 s (4H)	72,1	8,2	4,5	$C_{19}H_{26}ClNO_3$	72,2	8,3	4,4	65
XI	104—105	1,25 (s, 3H); 0,9—2,50 (m, 11H); 1,98 (s, 3H); 3,20 (s, 3H); 4,17 (s, 2H); 4,17, 4,38 (two d, 2H, J=1,8); 7,30 (m, 5H)	70,1	8,1	3,8	$C_{21}H_{29}NO_4$	70,2	8,2	3,9	79
XII	101—102	1,02 (s, 3H); 1,00—2,50 (m, 11H); 1,89 (s, 3H); 3,18 (s, 3H); 3,94, 4,18 (two d, 2H, J=11,0); 4,00, 4,24 (two d, 2H, J=1,8); 7,17 (m, 4H)	57,4	6,6	3,2	$C_{21}H_{28}BrNO_4$	57,5	6,5	3,2	83
XIII	154—155	1,40 (s, 3H); 0.7—2,50 (m, 11H); 2,06 (s, 3H); 4,18, 4,24 (two d, 2H, J=7,0); 6,20 (s, H); 7,32, 7,68 (m, 5H)	73,3	7,7	4,2	$C_{20}H_{25}NO_3$	73,4	7,7	4,4	75
XIV	142—144	1,26 (s, 3H); 1,19—2,78 (m, 10H); 2,40 (s, H); 2,79 (t, H, J=10,0); 3,38 (s, 3H); 3,55, 3,57 (two d, 2H, J=11,1); 3,76 (q, H, J=1,8, J=7,0); 4,32 (q, H, J=7,0, J=10,3); 4,57 (d, H, J=1,8); 4,79 (d, H, J=10,3); 7,27, 7,35, 7,41 (m, 5H)	71,3	9,2	4,4	$C_{19}H_{29}NO_3$	71,4	9,2	4,4	90
XV**	86—87	1,06 (d, 3H, J=6,6); 0,55—1,80 (m, 11H); 2,26 (m, 2H, J=6,6); 3,00 (s, 3H); 3,38 (q, H, J=9,8; J=7,8); 4,34 (q, H, J=9,8, J=7,5); 4,40 (s, H); 7,33 (s, 5H)	71,8	8,4	4,5	$C_{19}H_{27}NO_3$	71,9	8,6	4,4	73

*The PMR spectra were measured on a Tesla BS-467-A spectrometer in CD_3OD (II-V), in CCl_4 (XI, XII), in $CDCl_3$ (XIII), XV), and on a Bruker WM-360 spectrometer in $CDCl_3$ (VIa,b – X, XIV).

**The characteristics of one diastereomer are given.

Thus, the heterocyclization of borofluorides of α-cyclohexylamino-α',β'-epoxy ketones on heating in acetone or acetonitrile leads to azetidin-3-ones, while the corresponding bases convert into aminotetrahydrofuran-3-ones.

EXPERIMENTAL

The IR spectra of the compounds in CCl_4 at a concentration of 10^{-1} M (optical path 0.01 cm) and 10^{-3} M (optical path 1 cm) were run on a Specord 75 IR spectrophotometer. The PMR spectra of the solutions of the compounds in CCl_4, $CDCl_3$, CD_3OD, and DMSO were measured on Tesla BS 467A and Bruker WM-360 spectrometers, using HMDS as internal standard. The mass spectra of the compounds were obtained on a Varian MAT-311 A mass spectrometer.

The characteristics of the synthesized compounds are listed in Table 1.

5-Aryl-2-methyl-5-methoxy-4-cyclohexylamino-1,2-epoxypentan-3-one Borofluorides (II-V). A 55 mmole portion of boron trifluoride etherate is added to a solution of 50 mmoles of trans-1-cyclohexyl-2-aryl-3-(2-methyl-2,3-epoxypropionyl)aziridine [7] in 80-120 ml of methanol, and the reaction mixture is held for 12-24 h at 18-20°C. Methanol is partially evaporated, and an equal volume of ether is added to the residue. Complexes II-V crystallize on cooling.

4-Arylmethoxymethyl-2-hydroxymethyl-2-methyl-1-cyclohexylazetidin-3-ones (VIa,b-X). A 10 mmole portion of complex Ia,b-V is placed in an ampule, 30-50 ml of acetone or acetonitrile are added, and the solution is purged with argon. The ampule is sealed and heated on a water bath for 6-10 h. The ampule is then opened, the solvent is evaporated on a film evaporator. Water is added to the residue, the mixture is made alkaline by adding sodium carbonate solution or triethylamine, and extracted by ether. The ether extract is dried over sodium sulfate. After the removal of ether, azetidinones VIa,b-X are crystallized from an ether–hexane mixture (1:1)-(1:3).

4-Arylmethoxymethyl-2-acetoxymethyl-2-methyl-1-cyclohexylazetidin-3-ones (XI, XII). A 5 mmole portion of azetidinone VIa is held in 7 ml of acetic anhydride at 20°C for 3 h. The reaction mixture is poured into water, made alkali by adding a sodium carbonate solution, and extracted by ether. The ether extract is washed with water and dried over sodium sulfate. After removal of ether, acetates XI and XII are crystallized from a 1:2 ether–hexane mixture.

2-Acetoxymethyl-4-benzylidene-2-methyl-1-cyclohexylazetidin-3-one (XIII). A 1.5 g (5 mmoles) portion of azetidinone VIa is boiled for 30 min in 10 ml of a 1:1 mixture of acetic acid and acetic anhydride. The reaction mixture is treated as in the preceding experiment. On evaporation of ether, azetidinone XIII crystallizes.

2-Hydroxymethyl-2-methyl-4-phenylmethoxymethyl-1-cyclohexylazetidin-3-ol (XIV). A 0.2 g portion of sodium borohydride is added to a solution of 1.5 g (5 mmoles) of azetidinone VIa in 15 ml of methanol. After 30 min, the solvent is evaporated, the residue is diluted with water and the mixture is extracted by ether. The mixture is dried, ether is partially evaporated, and azetidinol XIV crystallizes.

4-Methyl-2-phenylmethoxymethyl-2-(cyclohexylamino)tetrahydrofuran-3-one (XV). A 10 mmole portion of 2-methyl-5-methoxy-5-phenyl-4-cyclohexylamino-1,2-epoxypentan-3-one [8] is held for 3 days at 20°C, or is boiled in acetone for 10 h. The solvent is evaporated, and the oily residue is separated on a column with silica gel (eluent, a 1:2 mixture of ether and hexane). A diastereomeric mixture of XV crystallizes from hexane.

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TRANSFORMATION OF ALKYL ESTERS OF 4-OXO-3-PHENYLTHIOALKANOIC ACIDS INTO SUBSTITUTED 4-PHENYLTHIO-2(5H)-FURANONES AND 3-PHENYLTHIOFURANS

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When the solutions of methyl and ethyl esters of 4-oxo-3-phenylthioalkanoic acids are boiled in toluene in the presence of p-toluene sulfonic acid, substituted 4-phenylthio-2(5H)-furanones are formed in good yields. In the reaction with diisobutylaluminum hydride or organomagnesium compounds, the latter convert into the corresponding 3-phenylthiofurans.

4-Oxoalkaloic acids are successfully used in the synthesis of compounds in the furan series [1, 2]. Information on the use of this class of compounds in the synthesis of alkylthio- and aryl-thiofurans and their derivatives, representatives of which have interesting chemical [3-5] and biological properties [6, 7], is limited to examples of the preparation of substituted 4-phenylthiotetrahydro-2-furanones [5, 8]. In the present work, conditions were found for converting esters of 4-oxo-3-phenylthioalkanoic acids (Ia-i) [9] into substituted 4-phenylthio-2(5H)-furanones (IIa-i) and 3-phenylthiofurans (IIIa-h).

TABLE 1. Physicochemical Characteristics of Compounds Synthesized

Compound	mp, °C [bp, °C]	n_D^T	T, °C	Found, %		Empirical formula	Calculated, %		Yield, %
				C	H		C	H	
IIa	69—70*			64,1	5,0	$C_{11}H_{10}O_2S$	64,1	4,9	56
IIb	35—36*			65,6	6,0	$C_{12}H_{12}O_2S$	65,4	5,5	95
IIc		1,5782	16	66,4	6,2	$C_{13}H_{14}O_2S$	66,6	6,0	85
IId	[171—172 (2 hPa)	1,5592	17	68,8	7,0	$C_{15}H_{18}O_2S$	68,7	6,9	94
IIe	42—43*			71,8	5,3	$C_{17}H_{14}O_2S$	72,3	5,0	85
IIf		1,5763	16	65,5	5,6	$C_{12}H_{12}O_2S$	65,4	5,5	85
IIg	[169—170 (2 hPa)	1,5526	17	66,7	6,1	$C_{13}H_{14}O_2S$	66,6	6,0	81
IIh		1,5528	20	67,4	6,6	$C_{14}H_{16}O_2S$	67,7	6,5	80
IIi		1,5506	20	68,2	7,1	$C_{15}H_{18}O_2S$	68,7	6,9	71
IIIa		1,5411	17	71,1	6,4	$C_{13}H_{14}OS$	71,5	6,5	35
IIIb		1,5917	15	70,2	5,9	$C_{12}H_{12}OS$	70,5	5,9	40
IIIc		1,5547	18	72,8	7,4	$C_{15}H_{18}OS$	73,1	7,4	45
IIId		1,5738	17	71,0	6,4	$C_{13}H_{14}OS$	71,5	6,5	86
IIIe		1,5682	17	72,0	7,1	$C_{14}H_{16}OS$	72,4	6,9	88
IIIf	63—64*			76,9	5,8	$C_{18}H_{16}OS$	77,1	5,7	75
IIIg		1,5478	17	74,7	8,0	$C_{17}H_{22}OS$	74,4	8,1	82
IIIh		1,6108	15	78,0	6,9	$C_{21}H_{22}OS$	78,2	6,9	90

*From 2-propanol.

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