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REACTION OF 1-ALKYL-2-ARYL-3-(2-METHYL-2,3-EPOXYPROPIONYL)AZIRIDINES WITH BORON TRIFLUORIDE ETHERATE IN METHANOL

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UDC 547.422+547.717

The reaction of boron trifluoride etherate in methanol with trans-1-methyl(ethyl)- or cis-1-cyclohexyl-2-aryl-3-(2-methyl-2,3-epoxypropionyl)aziridines leads to the formation of the corresponding boron fluoride complexes on the nitrogen atom of the aziridine ring. Reaction with trans-1-cyclohexyl-2-phenyl-3-(2-methyl-2,3-epoxypropionyl)aziridines occurs with stereospecific opening of the aziridine ring to give diastereomeric 2-methyl-5-methoxy-5-phenyl-4-cyclohexylamino-1,2-epoxypentan-3-ones, as well as products from the opening of the epoxide and aziridine rings — tetrahydrofuranones and tetrahydropyranones.

The presence of the epoxide and aziridine rings in the epoxypropionylaziridine molecules makes it possible to compare their reactivity towards a number of reagents. It is known that Lewis acids are widely used as catalysts in reactions of oxiranes and ethyleneimines with nucleophilic reagents [1, 2]. In this connection, the conversions on treatment with boron trifluoride etherate in methanol of the diastereomeric 1-alkyl-2-aryl-3-epoxypropionylaziridines synthesized previously [3] are studied in the present work.

It has been established that the nature of the proeucts formed is dependent on the size of the alkyl substituent at the nitrogen atom of the aziridine ring, while in the case of

Scientific-Research Institute of Physicochemical Problems, V. I. Lenin Belorussian State University, Minsk. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 596-600, May, 1986. Original article submitted January 25, 1985.

0009-3122/86/2205-0485$12.50

TABLE 1. Physicochemical Properties of Compounds IV-VI, VIIIa,b, and Xa, b, to XXa,b

Compound	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
IV	125—126	54,5	5,4	4,7	$C_{13}H_{15}NO_2 \cdot BF_3$	54,8	5,3	4,9	61
V	117—118	47,2	4,4	8,3	$C_{13}H_{14}N_2O_4 \cdot BF_3$	47,3	4,3	8,5	52
VI	140—143	48,7	4,6	8,0	$C_{13}H_{16}N_2O_4 \cdot BF_3$	48,9	4,7	8,1	88
VIIIa	145—146	61,2	6,4	4,0	$C_{18}H_{23}NO_2 \cdot BF_3$	61,2	6,6	4,0	85
VIIIb	139—140	61,1	6,6	4,0					95
Xa	189—190	59,2	7,0	3,5	$C_{19}H_{27}NO_3 \cdot BF_3$	59,2	7,1	3,6	53
Xb	124—125	59,2	7,0	3,5					39
XI	177—179	59,1	7,0	3,5	$C_{19}H_{27}NO_3 \cdot BF_3$	59,2	7,1	3,6	38
XII	183—184	48,6	6,2	3,2	$C_{19}H_{28}BrNO_3 \cdot BF_3$	48,9	6,1	3,0	46
XIIIa	Oil	71,7	8,7	4,3	$C_{19}H_{27}NO_3$	71,9	8,6	4,4	99
XIIIb	Oil	71,8	8,7	4,3					99
XIV	Oil	71,8	8,5	4,4	$C_{19}H_{27}NO_3$	71,9	8,6	4,4	90
XV	139—140	70,1	8,1	3,8	$C_{21}H_{29}NO_4$	70,2	8,2	3,9	56
XVI	Oil	71,8	8,5	4,5	$C_{19}H_{27}NO_3$	71,9	8,6	4,4	26
XVII	116—117	70,1	8,1	3,8	$C_{21}H_{29}NO_4$	70,2	8,2	3,9	74
XVIII	84—86	67,4	7,6	5,5	$C_{14}H_{19}NO_3$	67,4	7,7	5,6	88
XIXa	99—100	59,2	7,0	3,6	$C_{19}H_{27}NO_3 \cdot BF_3$	59,2	7,1	3,6	29
XIXb	94—96	59,2	7,0	3,6					38
XXa	Oil	71,7	8,6	4,4	$C_{19}H_{27}NO_3$	71,8	8,6	4,4	80
XXb	Oil	71,7	8,6	4,3					88

bulky substituents there is a dependency on the configuration of the epoxypropionylaziridines. Thus, the trans-2-aryl-1-methyl(ethyl)-3-(2-methyl-2,3-epoxypropionyl)aziridines Ia, IIb, and IIIa, react readily with boron trifluoride etherate in methanol to form complexes on the nitrogen atom of the aziridine ring, IV-VI. On interaction of the cis-2-(2-methyl-2,3-epoxypropionyl)-3-phenyl-1-cyclohexylaziridines VIIa, b with boron trifluoride etherate, the analogous boron trifluoride complexes VIIIa, b are isolated in quantitative yield.

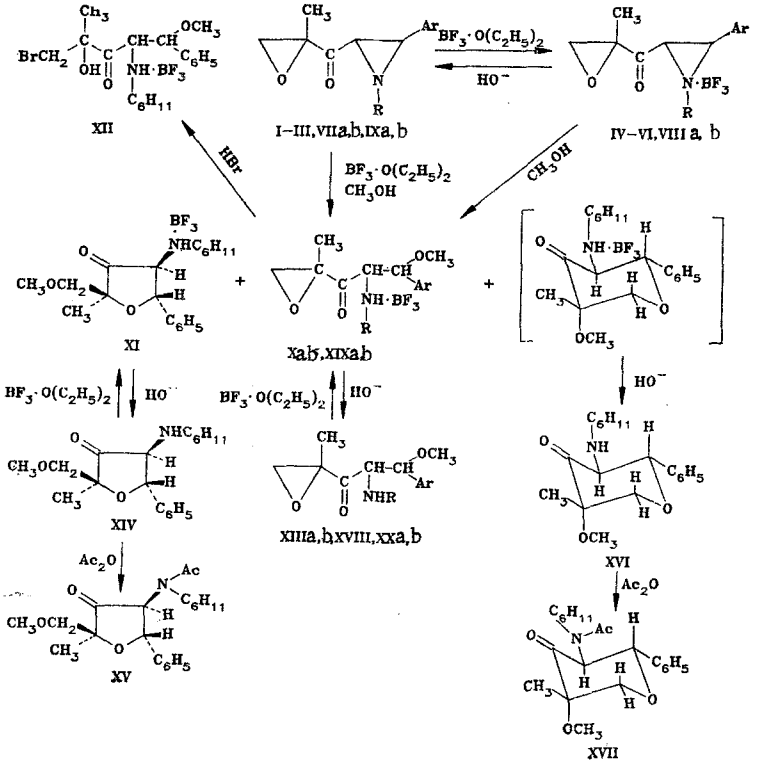
Unlike the cis-aziridines VIIa, b the interaction of boron trifluoride etherate in methanol with the trans-2-(2-methyl-2,3-epoxypropionyl)-3-phenyl-1-cyclohexylaziridines IXa, b gives a mixture of boron trifluoride complexes formed as a result of opening of the aziridine ring as well as both the epoxide and aziridine rings. In the case of the aziridinylepoxyketone IXa, a mixture of 2-methyl-5-methoxy-5-phenyl-4-cyclohexylamino-1,2-epoxypentan-3-one—boron trifluoride (Xa) and 2-methyl-2-methoxymethyl-5-phenyl-4—cyclohexylaminotetrahydrofuran-3-one—boron trifluoride (XI) is formed in the ratio 5:4. Compound Xa is obtained as a result of the stereospecific addition of methanol to the initially formed aziridinylepoxyketone—boron trifluoride. Opening of the aziridine ring takes place from the β-carbon atom in the aziridine ring, which is characteristic of reactions between aziridinylketones and nucleophilic reagents [4, 5]. Preservation of the epoxide ring in complex Xa is shown by reaction of the latter with hydrobromic acid, leading to the formation of the bromohydrin XII. On treatment with an alkaline solution the boron trifluoride complex Xa is converted to the corresponding unstable base XIIIa.

Formation of the cyclohexylaminotetrahydrofuranone—boron trifluoride XI indicates that in methanol as well as complex-formation on the nitrogen atom in the aziridine ring a competing alcoholysis of the epoxide ring, catalyzed by boron trifluoride, occurs with subsequent stereospecific opening of the aziridine ring from the β-carbon atom. Treatment of the boron trifluoride complex XI with an alkaline solution permits separation of the base XIV, which is converted to the acetamide XV by the action of acetic anhydride.

The reaction of boron trifluoride etherate in methanol with the diastereomer IXb, which differs from the trans-aziridinylepoxyketone IXa in the configuration of the chiral center of the epoxide ring, gives the boron trifluoride complex Xb (the corresponding base is XIIIb) which is a diastereomer of boron trifluoride complex Xa, and the cyclic compound XVI isolated and characterized as a base. It transpires that compound XVI is 5-methyl-5-methoxy-2-phenyl-3-cyclohexylaminotetrahydropyran-4-one, which is formed as a result of opening of the epoxide ring, catalyzed by boron trifluoride, from the α-carbon atom and the subsequent cyclization on the aziridine ring. The aminotetrahydropyran-4-one XVI is converted to the corresponding acetamide XVII by reaction with acetic anhydride.

Analysis of the chemical shifts from the aminotetrahydrofuranone XIV and aminotetrahydropyranone XVI and their acetamides XV and XVII, as well as the magnitudes of J_{vic} and J_{gem}

and the data from the nuclear Overhauser effect make it possible for the right configurations to be assigned unequivocally to the compounds just mentioned. Since on formation of the aminotetrahydrofuranone XIV during the reaction the α- and α'-carbon atoms of the epoxide and aziridine rings are unaffected, in the initial epoxypropionylaziridine IXa and R(S) configuration of the chiral center of the epoxide ring is combined with an RR(SS) configuration of the carbon atoms of the aziridine ring, while in the diastereomer IXb an R(S) configuration of the chiral center of the epoxide ring conforms to an SS(RR) configuration of the aziridine ring.



I, II, IV, V, XVIII R=CH_3, III, VI R=C_2H_5, VIIa,b—Xa,b, XIIIa,b, XIXa,b, XXa,b R=C_6H_{11}; I, IV, VIIa,b—Xa,b, XIIIa,b, XVIII, XIXa,b, XXa,b Ar=C_6H_5, II, III, V, VI Ar=4-$NO_2C_6H_4$

Thus, cyclization of the epoxypropionylaziridine IXa with an RRR(SSS) relative configuration of the chiral centers takes place as a result of opening of the epoxide ring from the β-carbon atom and gives the aminotetrahydrofuranone XIV, while cyclization of the diastereomer IXb with an RSS(SRR) configuration occurs by ring-opening from the α-carbon atom and gives the aminotetrahydropyranone XVI. Hence, the nature of the products formed is determined by the regioselectivity in opening the opoxide ring, which in turn depends on the relative configuration of the α-carbon atom of the neighboring heterocycle. These results are in agreement with the data obtained when studying the acetolysis of ketodiepoxides of a steroid series [6] and also the acid hydrolysis of α,β,α',β'-diepoxyketones [7], and indicates that the regioselectivity in opening the epoxide ring is determined by the configuration of the neighboring three-membered ring irrespective of the nature of the heteroatom.

Reaction occurs on boiling N-methylaziridinylepoxyketone—boron trifluoride IV in methanol for 5 min and gives the α-methylamino-β-methoxyketone XVIII. In the case of the cis-N-cyclohexylaziridine—boron trifluoride complexes VIIIa, b when boiled in methanol for 24 h a complex mixture of reaction products is formed, from which the α-cyclohexylamino—β-methoxyketone—boron trifluoride complexes XIXa, b are isolated with 30-38% yield and converted by the usual method to the corresponding bases XXa, b.

EXPERIMENTAL

IR spectra of the compounds in CCl_4 with concentration 10^{-1} moles/liter (thickness of layer 0.01 cm) and in KBr pellets were recorded on a Specord 75-IR spectrophotometer. PMR spectra of solutions of the compounds in CD_3OD and CCl_4 were measured on a Tesla BS-467-A spectrometer, the internal standard was HMDS.

TABLE 2. IR and PMR Spectra of Compounds IV, VIIIa,b, and Xa,b XXa,b

Compound	IR spectrum, ν, cm^{-1}; CCl_4 solution (KBr pellets)	PMR spectrum of complexes (in CD_3OD) and bases (in CCl_4), δ, ppm (J, Hz)
IV	(1705, C=O)	1,27, s (3H); 2,44, s (3H); 2,60, d 2,80, d (2H, 5,0); 4,30, d, 4,55, d (2H, 5,8); 7,35, s (5H)
VIIIa	(1705, C=O)	1,30, s (3H); 1,00—2,10, m (11H); 2,80, d, 2,98, d (2H, 5,0); 3,90, s (2H); 7,24, s (5H)
VIIIb		1,28, s (3H); 1,10—2,40, m (11H); 3,06, d, 3,55, d (2H, 5,0); 4,32, d, 4,56, d (2H, 9,5); 7,30, s (5H)
Xa	(1705, C=O; 3400, 3480, NH)	1,27, s (3H); 0,9—2,20, m (11H); 2,90, d, 3,10, d (2H, 5,0); 3,30, s (3H); 3,93, d, 4,60, d (2H, 6,0); 7,40, s (5H)
Xb		1,24, s (3H); 0,6—2,05, m (11H); 2,52, d 2,76, d (2H, 5,0); 3,00, s (3H); 4,20, d, 4,50, d (2H, 6,5); 7,30, s (5H)
XI		1,10, s (3H); 0,5—1,80, m (11H); 3,22, d, 3,46, d (2H, 10,0); 3,30, s (3H); 3,38, s (2H); 7,32, m (5H)
XII		1,38, s (3H); 0,7—2,30, m (11H); 3,26, s (3H); 3,48, d, 3,72, d (2H, 11,0); 5,07, d, 5,32, d (2H, 6,0); 7,40, s (5H)
XIIIa	1720, C=O;	1,37, s (3H); 0,8—2,10, m (12H); 2,63, s (2H); 3,01, s (3H); 3,56, d, 3,75, d (2H, 10,4); 7,20, m (5H)
XIIIb	3320, 3380, NH	1,36, s (3H); 0,6—2,20, m (12H); 2,70, d, 3,26, d (2H, 5,0); 2,91, s (3H); 3,36, d, 3,80, d (2H, 10,5); 7,15, s (5H)
XIV	1760, C=O; 3300, 3370, NH	1,00, s (3H); 0,45—2,40, m (12H); 3,30, d, 4,40, d (2H, 9,6); 3,30, s (3H); 3,35, s (2H); 7,20, m (5H)
XV	1770, 1640, C=O	1,28, s (3H); 0,6—2,00, m (11H); 2,00, s (3H); 3,20, d 5,20, d (2H, 9,0); 3,33, s (5H); 7,30, m (5H)
XVI	1728, C=O; 3360, NH	1,26, s (3H); 0,5—2,10, m (12H); 2,86, d, 4,26, d (2H, 8,0); 3,68, d, 4,12, d (2H, 9,0); 7,20, m (5H)
XVII	1730, 1640, C=O	1,38, s (3H); 0,6—1,50, m (11H); 1,87, s (3H); 2,82, d, 4,80, d (2H, 7,6); 3,42, s (3H); 3,60, d 4,50, d (2H, 8,5); 7,12, s (5H)
XVIII	1700, C=O; 3320, 3380, NH	1,42, s (3H); 2,02, s (3H); 2,75, d, 3,24, d (2H, 5,0); 3,02, s (3H); 3,28, d, 3,96, d (2H, 9,0); 7,20, s (6H)
XIXa		1,18, s (3H); 0,6—2,10, m (11H); 3,15, d, 3,28, d (2H, 5,0); 3,16, s (3H); 4,18, d, 4,42, d (2H, 9,0); 7,26, m (5H)
XIXb		1,05, s (3H); 0,8—2,20, m (11H); 2,88, s (2H); 3,20, s (3H); 4,36, d, 4,60, d (2H, 7,0); 7,35, s (5H)
XXa	1710, C=O; 3330, 3415, NH	1,20, s (3H); 0,6—2,10, m (11H); 2,36, s (2H); 3,16, s (3H); 3,90, s (2H); 7,08, m (5H)
XXb		1,35, s (3H); 0,6—2,10, m (11H); 2,70, s (2H); 3,38, d 4,44, d (2H, 3,5); 7,22, m (5H)

The properties of the compounds synthesized and their spectral data are given in Tables 1 and 2.

The synthesis and spectral properties of epoxypropionylaziridines I-III, VIIa, b, and IXa, b are described in [3, 8].

trans-1-Methyl(ethyl)- and cis-1-Cyclohexyl-2-aryl-3-(2-methyl-2,3-epoxypropionyl) aziridine—Boron Trifluoride Complexes (IV-VI, VIIIa, b). 10 mmoles of aziridines I-III and VIIa, b in 100 ml of methanol cooled to 0°C was mixed with 11 mmoles of boron trifluoride etherate. The reaction mixture was diluted with ether and after 2 h complexes IV-VI and VIIIa, b were filtered off. The mixture was made alkaline with a solution of sodium carbonate and aziridines IV-VI and VIIIa, b were extracted with ethers; their identity was confirmed from their melting points and by TLC.

2-Methyl-5-methoxy-5-phenyl-4-cyclohexlamino-1,2-epoxypentan-3-one—Boron Trifluoride Complexes (Xa, b), 2-Methyl-2-methoxy-5-phenyl-4-cyclohexylaminotetrahydrofuran-3-one—Boron Trifluoride (XI), and 5-Methyl-5-methoxy-2-phenyl-3-cyclohexylaminotetrahydropyran-4-one (XVI). 50 mmoles of aziridines IXa, b was dissolved in 100 ml of methanol, 55 mmoles of boron trifluoride etherate was added, and the reaction mixture was kept for 12 h at 18-20°C. The methanol was partially evaporated on a film evaporator, and ether was added. Complexes Xa, b crystallized out in the cold. The mother liquor was boiled off on a film evaporator, and the residue was crystallized from a 1:10 methyl ethyl ketone—ether mixture, separating boron trifluoride complex XI. After the crystals of Xb had been separated and the solvent evaporated, a solution of sodium carbonate was added to the residue, which was then extracted with ether, and the ether extract dried over sodium sulfate. The ether was evaporated and pyranone XVI was separated by chromatography on a silica gel column, the eluent being a 1:1 ether—hexane mixture.

1-Bromo-2-hydroxy-2-methyl-5-methoxy-5-phenyl-4-cyclohexylaminopentan-3-one—Boron Trifluoride (XII). 5 mmoles of complex Xa was dissolved in 20 ml of acetic acid and 1 ml of 47% hydrobromic acid was added. The crystals of compounds XII formed were filtered off and recrystallized from a methanol—methyl ethyl ketone mixture.

2-Methyl-5-methoxy-5-phenyl-4-cyclohexylamino-1,2-epoxypentan-3-ones (XIIIa, b) and 2-Methyl-2-methoxy-5-phenyl-4-cyclohexylaminotetrahydrofuran-3-one (XIV). To 20 mmoles of boron trifluoride complexes Xa, b and XI in 50 ml of water was added an aqueous solution of sodium carbonate or alkali, and the mixture was extracted with ether. After drying the ether was evaporated and compounds XIIIa, b and XIV were separated in the form of oils.

2-Methyl-2-methoxymethyl-5-phenyl-4-cyclohexylacetaminotetrahydrofuran-3-one (XV) and 5-Methyl-5-methoxy-2-phenyl-3-cyclohexylacetaminotetrahydropyran-4-one (XVII). 10 mmoles of amines XIV and XVI in acetic anhydride was kept for 1 h at room temperature. The reaction mixture was diluted with water, made alkaline with a solution of sodium carbonate, and extracted with ether. After partial removal of solvent acetamides XV and XVII were crystallized from an ether—hexane mixture.

2-Methyl-4-methylamino-5-methoxy-5-phenyl-1,2-epoxypentan-3-one (XVIII). 1.4 g (5 mmoles) of complex IV was boiled in methanol for 5 min. The alcohol was evaporated and the residue was made alkaline with an aqueous solution of sodium carbonate, extracted with ether, and the ether extracts were dried over potassium carbonate. After partial removal of ether compound XVIII crystallized out.

2-Methyl-5-methoxy-5-phenyl-4-cyclohexylamino-1,2-epoxypentan-3-one—Boron Trifluoride Complexes (XIXa, b) and Their Corresponding Bases (XXa, b). 3.53 g (10 mmoles) of complexes VIIIa, b was boiled in methanol for 24 h. The solvent was evaporated and complexes XIXa, b were crystallized from a 1:5 methyl ketone—ether mixture. Bases XXa, b were obtained from complexes XIXa, b by the usual method.

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