MECHANISM OF RING OPENING OF cis- AND trans-1-METHYL-2-ARYL-3-AROYLAZIRIDINE PERCHLORATES UNDER THE INFLUENCE OF ALCOHOLS

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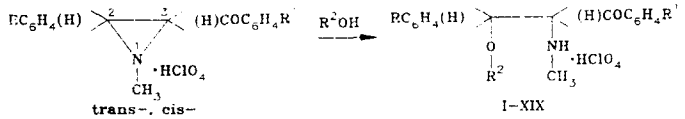
The corresponding threo- and erythro-1,3-diaryl-3-alkoxy-2-N-methylamino-1-propanones, which are formed regio- and stereospecifically, were obtained by the reaction of cis- and trans-1-methyl-2-aryl-3-aroylaziridine perchlorates with alcohols.

The corresponding derivatives of oxazolidines and 2-imidazolines are formed in the action of acetone [1] and acetonitrile [2] on 1-methyl-2-aryl-3-aroylaziridine borotrifluorides; the reaction proceeds regio- and stereospecifically with attack by the nucleophile on the β-carbon atom of the aziridine ring. The same thing is also observed in the reaction of a number of compounds of aziridine-2-carboxylic acid and alcohols under acid-catalysis conditions [3, 4]. In this connection it was logical to study opening of the aziridine ring in the salt form under the influence of alcohols in the case of derivatives of 3-aroylaziridines.

Heating trans-1-methyl-2-aryl-3-aroylaziridine perchlorates with methanol leads to the formation of the corresponding 1,3-diaryl-3-methoxy-2-N-methylamino-1-propanones I-VII in 70-90% yields (Table 1). According to the results of analysis of the reaction mixtures by means of TLC and PMR spectroscopy, the reaction proceeds without any side products.

Other alcohols – ethanol, isopropyl alcohol, and tert-butyl alcohol – also react similarly with trans-3-aroylaziridine perchlorates to give the corresponding 1,3-diaryl-3-alkoxy-2-N-methylamino-1-propanone derivatives VIII-X (Table 1). The reaction rate depends substantially on the size of the alkyl substituent and decreases in the order CH_3 > C_2H_5 > iso-C_9H_7 > tert-C_4H_9.



A molecular-ion peak ($[M]^+$) with m/z 333 (5) and high intensity $[M - 148]^+$ [m/z 183 (100)] and $[M - 183]^+$ [m/z 148 (25)] peaks, which correspond to cleavage of the molecule at the $C_{(2)}$–$C_{(3)}$ bond, are observed in the mass spectrum of VIII. This shows that the attack by alcohols is directed exclusively at the $C_{(2)}$ atom, i.e., as in [1, 2].

Absorption bands of C–H vibrations at 3100, 3000, and 2800 cm^{-1}, of a carbonyl group at 1680 cm^{-1} with a small shoulder at 1690 cm^{-1}, and of R^2–O (~1100 cm^{-1}) and $R_2NH_2^+$ (2750 cm^{-1}) bonds are observed in the IR spectra of I-X.

In the PMR spectra of I-VII (Table 1) neither the 2-H proton nor the NH_2^+–CH_3 methyl groups are additionally split by the NH_2^+ protons. This probably indicates the sufficiently rapid exchange of the protons attached to the nitrogen atom. However, if the reaction involving opening of the trans-3-aroylaziridine perchlorates is carried out not in the pure alcohol but in alcohol–chloroform (1:10), the product is precipitated from the reaction mixture by means of ether, and its PMR spectrum is recorded under the same conditions as in the previous case; significant broadening of both the signal of the protons of the NH_2^+–CH_3 methyl group and the signal of the 2-H proton is observed in it. It might be assumed that prior to recrystallization the carbonyl group is oriented in such a way that the

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TABLE 1. Characteristics of 1,3-Diaryl-3-alkoxy-2-N-methylamino-1-propanone Perchlorates

Compound*	R**	R^2	Empirical formula	Reaction time, h	mp, °C	δ, ppm					$J_{2,3}$, Hz	Yield, %
						OR^{2***}	NCH_3	3-H	2-H	H_{arom}		
I	H	CH_3	$C_{19}H_{19}ClNO_6$	20 min	176	3,20	2,96	5,08	5,58	6,83 ... 7,41	3,9	70
II	*p*-Cl	CH_3	$C_{17}H_{19}Cl_2NO_6$	0,25	196	3,20	2,96	5,07	5,56	6,83 ... 7,36	4,0	74
III	*p*-Br	CH_3	$C_{17}H_{19}BrClNO_6$	0,25	208	3,20	2,96	5,07	5,56	6,86 ... 7,40	3,9	78
IV	*m*-NO_2	CH_3	$C_{17}H_{19}Cl_2N_2O_8$	5 ... 6	211	3,30	3,06	5,33	5,66	7,00 ... 7,73	4,0	76
V	H	CH_3	$C_{17}H_{19}Cl_2NO_6$	0,25	192	3,16	2,93	5,08	5,54	6,81 ... 7,40	4,0	79
VI	H	CH_3	$C_{17}H_{19}BrClNO_6$	0,50	191	3,18	2,95	5,07	5,52	6,84 ... 7,30	3,9	93
VII	*p*-CH_3	CH_3	$C_{18}H_{22}ClNO_6$	0,25	186	3,13	2,88	5,01	5,51	6,63 ... 7,45	3,9	89
VIII	*n*-Cl	*p*-C_3H_7	$C_{19}H_{23}Cl_2NO_6$	1	168	3H, t, 1,08; 2H, q, 331	2,89	5,17	5,53	6,90 ... 7,46	4,1	72
IX	*p*-Cl	C_2H_5	$C_{18}H_{21}Cl_2NO_6$	0,50	170	3H, d, 1,10; 3H, d, 0,95; 1H, m, 3,43	2,88	5,18	5,53	6,83 ... 7,40	4,0	75
X	*p*-Cl	*t*-C_4H_9	$C_{20}H_{25}Cl_2NO_6$	4 ... 5	195	1,00	2,80	5,33	5,51	6,96 ... 7,63	4,2	81
XI	H	CH_3	$C_{19}H_{19}ClNO_6$	10 ... 11	141	3,06	2,80	4,51	5,50	6,90 ... 7,58	7,8	71
XII	*p*-Cl	CH_3	$C_{17}H_{19}Cl_2NO_6$	5 ... 6	193	3,10	2,85	4,56	5,53	6,96 ... 7,61	8,0	78
XIII	*p*-Br	CH_3	$C_{17}H_{19}BrClNO_6$	9 ... 10	212	3,13	2,86	4,56	5,53	7,05 ... 7,63	8,0	93
XIV	*m*-NO_2	CH_3	$C_{17}H_{19}ClN_2O_8$	8 ... 9	168	3,16	2,90	4,78	5,65	7,16 ... 7,93	7,9	88
XV	H	CH_3	$C_{17}H_{19}Cl_2NO_6$	7 ... 8	151	3,10	2,85	4,53	5,49	6,93 ... 7,60	8,0	84
XVI	H	CH_3	$C_{17}H_{19}BrClNO_6$	10 ... 11	159	3,12	2,85	4,57	5,51	7,01 ... 7,63	7,9	89
XVII	*p*-CH_3	CH_3	$C_{18}H_{22}ClNO_6$	9	210	3,06	2,80	4,49	5,48	6,78 ... 7,60	7,8	86
XVIII	*p*-Cl	*p*-C_3H_7	$C_{19}H_{23}Cl_2NO_6$	11 ... 12	139	3H, d, 0,87; 3H, d, 0,95; 1H, m, 3,30	2,73	4,87	5,50	7,00 ... 7,73	6,4	45
XIX	*p*-Br	*p*-C_3H_7	$C_{19}H_{23}BrClNO_6$	11 ... 12	157	3H, d, 0,90; 3H, d, 0,96; 1H, m, 3,34	2,75	4,90	5,50	7,04 ... 7,81	6,3	40

*Compounds I-X had an erythro configuration, while XI-XIX had a threo configuration.
**I-IV, VII-XIV, XVII-XIX R^1 = H, V, XV R^1 = p-Cl, VI, XVI R^1 = p-Br.
***J = 6.0 Hz for VIII, IX, XVIII, and XIX.

TABLE 2. Overhauser Nuclear Effect (ONE) of III and XIII

Irradiated group	Chemical shift		Observed proton	ONE, %	
	III	XIII		III	XIII
o-H	Ar, 7,18	Ar, 7,37	2-H	0	11
o-H	Ar, 7,18	Ar, 7,37	3-H	18	23
CH_3—O	3,37	3,27	2-H	0	0
CH_3—O	3,37	3,27	3-H	10	11
CH_3—NH_2^+	3,10	2,98	2-H	0	10
CH_3—NH_2^+	3,10	2,98	3-H	0	0

electron pairs of the oxygen atom interact with the positively charged nitrogen atom, as a result of which exchange of the protons attached to the nitrogen atom is hindered, and we observe broadening of the signals of the 2-H proton and the protons of the $CH_3NH_2^+$ group. Acetonitrile solvates the nitrogen atom and pushes out the carbonyl group, which occupies a different conformation. The energy barrier between these conformations is quite high and hinders free rotation of the carbonyl group. According to [5, p. 170], the ratio of the skew conformation to the cisoid conformation in phenacyl bromides is 4.4, as compared with 1.6 in phenacyl chlorides, i.e., it depends markedly on the volume of the substituents in the α position relative to the carbonyl group. The amino group is approximately equal in size to the bromine atom. This is also confirmed by the IR spectral data. It is known that the presence in the α-position relative to the carbonyl group of an electron acceptor atom that is eclipsed by it leads to an increase in the frequency of the vibration of this carbonyl group [6]. This was also observed for I-X. Thus, for example, in the IR spectrum of II prior to recrystallization from acetonitrile we observed two bands of vibrations of a carbonyl group with different intensities (1680, 1690 cm^{-1}), whereas after crystallization, as we have already noted, we observed one band (1680 cm^{-1}) and a small shoulder on it (1690 cm^{-1}).

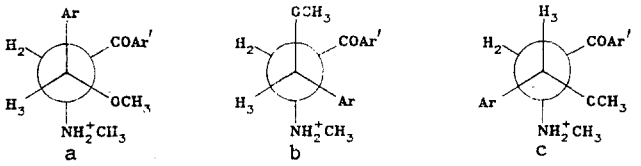
In contrast to trans-3-aroylaziridine borotrifluorides, their cis analogs behave somewhat differently in reactions involving expansion of the three-membered ring [1, 2]. In this connection we studied the behavior of cis-3-aroylaziridine perchlorates with alcohols. The three-membered ring opened easily with the formation of only (TLC, PMR) 1,3-diaryl-3-methoxy-2-N-methylamino-1-propanones XI-XVII in high yields (Table 1). The rates of the reaction of cis-3-aroylaziridine perchlorates with alcohols are substantially lower than the rates of the corresponding trans analogs. Ring opening and the formation of normal products also occur in the reaction with isopropyl alcohol (Table 1); however, in addition to them, products of destruction of the aziridine ring at the $C_{(2)}$—$C_{(3)}$ bond – substituted benzaldehydes and ω-N-methylaminoacetophenone – were detected in the reaction mixture. However, the reaction with tert-butyl alcohol gives only destruction products. The different behavior of alcohols and acetone [1] can be explained either by the greater nucleophilicities of alcohols as compared with acetone or by the different structures of the borotrifluoride and perchlorate complexes of cis-3-aroylaziridines.

Absorption bands of C—H vibrations (2800-3100 cm^{-1}), a carbonyl group (1685 cm^{-1}), an R^2—O bond (1100 cm^{-1}), and an NH_2^+ group (2760 cm^{-1}) are observed in the IR spectra of XI-XIX.

As in the case of products I-X, the CH_3—NH_2^+ methyl group and the 2-H methylidyne proton of XI-XIX recrystallized from acetonitrile do not interact with the protons of the NH_2^+ group. However, recording of the PMR spectra of the same compounds isolated directly from the reaction mixture shows that the signals of the $CH_3NH_2^+$ and 2-H protons are substantially broadened and in some samples are also altogether split (J = 6.0 Hz), i.e., for the products of the reaction of cis-3-aroylaziridine perchlorates with alcohols exchange of the protons in the NH_2^+ group is retarded to an even greater extent. In this case we probably have a more pronounced interaction of the π electrons of the oxygen atom of the carbonyl group with the positively charged nitrogen atom. In the opinion of Tarburton and coworkers [7], the result of a similar difference in the relationship of the carbonyl group to the nitrogen atom of the aziridine ring in 3-aroylaziridine bases is that the sterically more hindered cis-3-aroylaziridines are thermodynamically more stable than the corresponding trans analogs.

Since the literature does not contain the vicinal constants of the 2-H and 3-H protons for erythro- and threo-3-alkoxy-2-N-methylamino-1-propanones in the salt form, they were converted to the corresponding bases in the case of II and XII. In the PMR spectra of these compounds the vicinal constants of the 2-H and 3-H protons were 6.8 and 5.8 Hz, respectively. Such close values of the constants do not make it possible to draw a conclusion regarding the relative configurations of II and XII, for the determination of which we investigated the Overhauser nuclear effect (ONE) [8]. For this, we irradiated alternately the ortho protons of the aryl ring and the protons of the CH_3–O and NH_2^+–CH_3 groups of III and XIII and observed the changes in the intensities of the 2-H and 3-H protons (Table 2).

An analysis of the results of the study of the ONE for III shows that it is either the erythro isomer, which exists in conformation a of the Newman projection, or the threo isomer in conformation b.



However, conformation b is less acceptable than a, since interaction between the free electron pairs of the oxygen atom of the methoxy group and the positively charged nitrogen atom, which leads to the energetically more stable conformer, can occur in a. In fact, an analysis of the PMR spectra of VIII and XVIII, which contain an isopropoxy group, shows that its methyl substituents are not equivalent and show up in the form of two doublets. In the free bases the R^2–O and CH_3–NH groups are not attracted to one another but rather repulse one another. This should lead to a change in the conformation of the molecule relative to the $C_{(2)}$–$C_{(3)}$ bond in such a way that the isopropyl groups of VIII and XVIII prove to have greater free rotation. In fact, in the PMR spectra of bases VIII and XVIII the methyl substituents of the isopropyl group are equivalent and one can confidently assign an erythro configuration to III; conformation a will be preferable for it in the salt form. Similar reasoning, as well as the regularities in the PMR spectra, makes it possible to assign a threo configuration to XIII; conformation c will be the preferred conformation for it (Table 1).

EXPERIMENTAL

The course of the reactions and the individuality of the compounds obtained were monitored by means of TLC on Silufol plates (ether–hexane). The IR spectra of solutions of the compounds in $CHCl_3$ were recorded with an IR-75 spectrometer; the thickness of the absorbing layer was 0.507 mm. The PMR spectra of 5-10% solutions of the reaction products were recorded with a Tesla BS 467 spectrometer (60 MHz) with hexamethyldisiloxane (HMDS) as the internal standard. The experiments on the Overhauser nuclear effect (ONE) were carried out using previously degassed 5-7% solutions of the compounds in $(CD_3)_2CO$. The mass spectra were recorded with a Varian MAT-311 mass spectrometer; the ionizing voltage was 70 eV, and the temperature of the sample-input system was 125°C.

The characteristics of I-XIX are presented in Tables 1 and 2. The results of elementary analysis for C, H, and N were in agreement with the calculated values.

cis- and trans-1-Methyl-2-aryl-3-aroylaziridine Perchlorates. A 0.12-mole sample of perchloric acid was added at −20°C (0°C for the cis compounds) to a solution of 0.1 mole of the cis- and trans-1-methyl-2-aryl-3-aroylaziridine in 150 ml of alcohol [alcohol–ether (2:1) for the cis compounds] while maintaining the temperature at no higher than 0°C (10°C for the cis compounds). The resulting salt was precipitated slowly from the solution by means of ether, removed by filtration, and air dried. The crystals obtained were reprecipitated from acetonitrile–ether and dried over P_2O_5. The yields were 87-96%.

erythro- and threo-1,3-Diaryl-3-alkoxy-2-N-methylamino-1-propanone Perchlorates(I-XVII). A 25-ml sample of alcohol was added to 4 g (~0.02 mole) of trans- or cis-1-methyl-2-aryl-3-aroylaziridine perchlorate, and the mixture was refluxed from 15 min to 5 h (5-11 h for the cis isomers). At the end of the reaction the alcohol was evaporated at reduced pressure, the residue was diluted with ether until the reaction mixture was obtained, and the latter

was allowed to stand at room temperature. As the crystals precipitated, the reaction mixture was gradually diluted with ether until the product had precipitated completely. The precipitate was removed by filtration, washed with ether, and reprecipitated from acetonitrile–ether. The yields were 68-89%.

Reaction of cis-1-Methyl-2-aryl-3-benzoylaziridine Perchlorates with Isopropyl Alcohol (XVIII, XIX). A solution of 4 g (~0.02 mole) of cis-1-methyl-2-aryl-3-benzoylaziridine perchlorate in 12 ml of isopropyl alcohol was refluxed for 12 h. At the end of the reaction the alcohol was evaporated at reduced pressure, the residue was diluted with dry ether, and the mixture was allowed to stand at room temperature for 3 days. The precipitated crystals were removed by filtration, washed on the filter with dry ether, and dissolved in chloroform. The undissolved ω-N-methylaminoacetophenone perchlorate was removed by filtration. The filtrate was gradually diluted with dry ether until the precipitation of 3-isopropoxy-2-N-methylamino-3-aryl-1-phenyl-1-propanone perchlorate was complete, and the precipitated product was removed by filtration and reprecipitated from acetonitrile–ether. The yields were 40-45%.

Reaction of cis-1-Methyl-2-(p-chlorophenyl)-3-benzoylaziridine with tert-Butyl Alcohol. A solution of 3.7 g (0.02 mole) of cis-1-methyl-2-(p-chlorophenyl)-3-benzoylaziridine perchlorate in 12 ml of tert-butyl alcohol was refluxed for 12 h, after which the alcohol was evaporated at reduced pressure. The residue was diluted with ether, and the mixture was allowed to stand at room temperature for 2 days. The precipitated crystals were removed by filtration, washed on the filter with dry ether, and air dried. The yield of ω-N-methylaminoacetophenone perchlorate was 82%.

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