SYNTHESIS AND STEREOCHEMISTRY OF 1-ALKYL-2-ARYL-3-(2-METHYL-2,3-EPOXYPROPIONYL) AZIRIDINES

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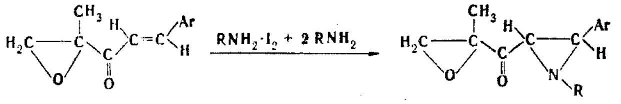
Two diastereoisomeric 1-alkyl-2-aryl-3-(2-methyl-2,3-epoxypropionyl)aziridines with an E configuration of the aziridine ring were obtained by the reaction of 2-methyl-2-cinnamoyoxiranes with iodine–methylamine and iodine–ethylamine complexes. The relative configuration of the chiral centers of the synthesized compounds was established by means of spectral data. The predominant formation of diastereomers with the RRR (SSS) relative configuration is explained by the effect of steric factors in the diastereomeric chelated amino enols that precede the formation of the epoxy keto aziridines.

It has been shown [1, 2] that cinnamoyloxiranes in aprotic solvents add amines exclusively at the double bond and that the formation of products of double addition with subsequent cyclization of the latter to stereoisomeric 3-hydroxy-4-piperidones is possible in protic solvents.

In a continuation of our research on the reactivities of cinnamoyloxiranes in order to synthesize biologcially active compounds, in the present research we studied their reaction with primary amines in aprotic solvents in the presence of iodine. The reaction of 2-methyl-2-cinnamoyloxiranes I with iodine–methylamine and iodine–ethylamine complexes in the presence of excess amine in benzene or ether leads to mixtures of two stereoisomeric E-aziridinyl epoxy ketones IIa,b–VIa,b, the ratio of which was determined from the PMR spectra of the reaction mixtures (Table 1). The absence in the IR spectra of absorption bands of OH and NH groups at 3200-3600 cm^{-1} and the disappearance of the band of stretching vibrations of a double bond (1620 cm^{-1}) that is characteristic for cinnamoyloxiranes indicate the formation of an aziridine ring and retention of the epoxide ring. The intense absorption of the carbonyl group of IIa,b–VIa,b (1690-1695 cm^{-1}) is close to the carbonyl absorption of cinnamoyloxiranes (1680 cm^{-1}), and this constitutes evidence for the existence of hyperconjugation of the ethyleneimine ring and the π bond of the C=O group [3]. Two AB spin systems that belong to the geminal protons of the epoxide ring (J = 5.0 Hz) and to the vicinal protons of the aziridine ring



I

II–VI a,b

TABLE 1. Characteristics of the Synthesized Compounds

Compound	Ar	R	mp, °C	R_f	N found, %	Empirical formula	N calc., %	b : a ratio	Yield, %
IIa	C_6H_5	CH_3	65—67	0,39	6,3	$C_{13}H_{15}NO_2$	6,4	1 : 1,5	28
IIb	C_6H_5	CH_3	75—76	0,45	6,4	$C_{13}H_{15}NO_2$	6,4		19
IIIa	4-$NO_2C_6H_4$	CH_3	117—118	0,39	10,7	$C_{13}H_{14}N_2O_4$	10,7	1 : 1,7	42
IIIb	4-$NO_2C_6H_4$	CH_3	99—111	0,33	10,5	$C_{13}H_{14}N_2O_4$	10,7		25
IVa	2-$CH_3OC_6H_4$	CH_3	oil	0,28	5,6	$C_{14}H_{17}NO_3$	5,7	1 : 1,2	23
IVb	2-$CH_3OC_6H_4$	CH_3	84—85	0,34	5,6	$C_{14}H_{17}NO_3$	5,7		19
Va	C_6H_5	C_2H_5	oil	0,51	6,0	$C_{14}H_{17}NO_2$	6,1	1 : 1,8	36
Vb	C_6H_5	C_2H_5	oil	0,57	6,1	$C_{14}H_{17}NO_2$	6,1		20
VIa	4-$NO_2C_6H_4$	C_2H_5	58—59	0,47	9,9	$C_{14}H_{16}N_2O_4$	10,1	1 : 2,0	47
VIb	4-$NO_2C_6H_4$	C_2H_5	89—90	0,49	10,0	$C_{14}H_{16}N_2O_4$	10,1		24

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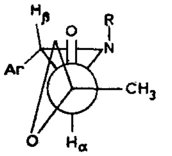
TABLE 2. Parameters of the PMR Spectra

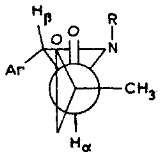
Compound	δ, ppm				H′gem	H″gem	$\Delta(H_\beta-H_\alpha)$, Hz	$\Delta(H''-H')$, Hz
	CH_3	$N-CH_3$	H_α	H_β				
IIa	1,20	2,40	2,96	3,07	2,18	2,54	11	36
IIb	1,18	2,50	2,80	2,98	2,01	2,18	18	17
IIIa	1,20	2,30	2,78	2,85	2,12	2,48	7	36
IIIb	1,20	2,40	2,67	2,87	2,05	2,20	20	15
IVa	1,18	2,48	3,00	3,60	2,12	2,56	60	44
IVb	1,20	2,60	2,78	3,50	2,14	2,42	72	28
Va	1,24	—	3,00	3,14	2,28	2,72	14	44
Vb	1,20	—	2,78	3,12	2,10	2,25	34	15
VIa	1,22	—	2,84	2,98	2,24	2,66	14	42
VIb	1,18	—	2,60	2,92	2,02	2,18	32	16

(J = 2.3-3.0 Hz) are present in the PMR spectra of the compounds obtained (Table 2). The observed spin–spin coupling constants (SSCC) are characteristic for E-aziridinyl ketones [4]. The signals of the protons of the α- and β-carbon atoms were assigned on the basis of exchange of the α proton of the aziridine ring with deuterium.

An analysis of the spectral data makes it possible to assign the relative configuration to the chiral centers of the synthesized 1-alkyl-2-aryl-3-(2-methyl-2,3-epoxypropionyl)aziridines. On the basis of the cisoid orientation of the C = O group and the aziridine ring, a study of the Overhauser effect, and the difference in the chemical shifts of the vicinal and geminal protons, the most stable conformations of the diastereomeric E-aziridinyl epoxy ketones can be represented as follows:



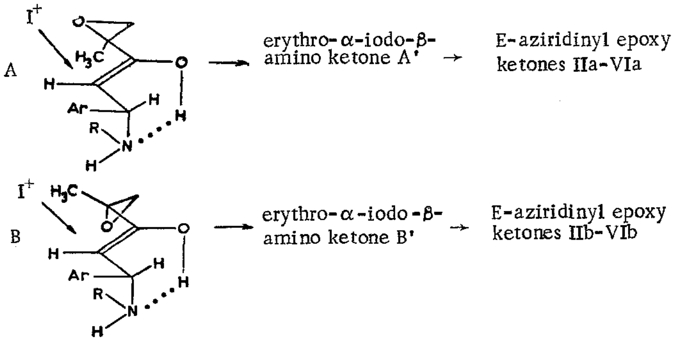
IIa-VIa



IIb-VIb

Thus, irradiation of the resonance frequency of the Hβ proton of the aziridine ring in IIb gives rise to a 14% increase in the signal of the geminal protons of the epoxide ring, while irradiation of the protons of the C-methyl group does not lead to an appreciable change in the signals of the protons of the aziridine and epoxide rings. The difference in the chemical shifts of the Hβ and Hα protons in the spectra of IIa-VIa is smaller than in the spectra of IIb-VIb as a consequence of the effect of the oxygen atoms of the C = O group and the epoxide ring. The signals of the geminal protons in IIa-VIa appear at weaker field than in the case of IIb-VIb, and the difference in the chemical shifts of H'' and H' in the spectra of IIa-VIa is greater owing to the deshielding effect of the C = O group. The methyl group in both diastereomers absorbs at the same field, i.e., the magnetic environments of the C-methyl groups are virtually identical. Thus the enumerated data make it possible to assign the R(S) configuration to the chiral center of the epoxide ring of diastereomers IIa-VIa with respect to the RR(SS) configuration of the ethyleneimine ring and the S(R) configuration correspondingly to the chiral center of the epoxide ring in IIb-VIb relative to the RR(SS) configuration of the aziridine ring.

The observed ratios of the products in the reaction of 2-methyl-2-cinnamoyloxiranes with iodine–alkylamine complexes can be explained by the effect of steric factors of the groups in the intermediate chelated amino enols that are formed as a result of 1,4 addition of the amine to the α,β-unsaturated system [5]. The stereochemistry of epoxy keto aziridines will be determined in the step involving the iodination of diastereomeric enols A and B presented below:



The formation of two aziridinyl epoxy ketones with an E configuration is explained by the participation of only chelated conformations of the intermediate diastereomeric amino enols in the reaction, owing to which attack by the iodinating agent is realized on one side of the chelate ring. The primary formation of IIa-VIa with an RRR(SSS) relative configuration is due to the fact that the iodination of enol B is less favorable as a consequence of steric hindrance created by the methyl group of the epoxide ring of the attacking agent.

EXPERIMENTAL

The IR spectra of solutions (10^{-1} mole/liter) of the compounds in CCl_4 were recorded with a UR-20 spectrometer (the layer thickness was 0.1 mm). The PMR spectra of solutions of the compounds in benzene were recorded with a Varian HA-100 D-15 spectrometer with hexamethyldisiloxane as the internal standard. The Rf values of the compounds were determined on Silufol UV-254 plates by elution with petroleum ether–ether (1:1).

1-Alkyl-2-aryl-3-(2-methyl-2.3-epoxypropionyl)aziridines (IIa,b-VIa,b). A 0.05-mole sample of iodine was added to a solution of 0.05 mole of 2-methyl-2-cinnamoyloxirane I in benzene, and the mixture was saturated at 10°C with gaseous methylamine or ethylamine until the solution became colorless. The benzene solution was diluted with ether, washed with water, and dried with magnesium sulfate. The solvent was removed by distillation, and the residual diastereomeric epoxy keto aziridines IIa and IIb were separated by fractional crystallization from petroleum ether–ether (1:1). Compounds IIIa and IIIb and VIa and VIb were crystallized from petroleum ether–ether (1:2) and CCl_4–hexane (1:1), respectively. The mixtures of diastereomers IVa and IVb and Va and Vb were separated by chromatography on L40/100 silica gel; the sorbent to substance ratio was 100:1, and the eluent was linear gradient petroleum ether–ether (1:1).

Deuterium Exchange of 1-Methyl-2-phenyl-3-(2-methyl-2,3-epoxypropionyl)aziridines (IIa,b). Catalytic amounts of CD_3ONa were added to 0.2 g of IIa or IIb in $CD_3OD-(CD_3)_2SO_4$ (4:3), and the mixture was allowed to stand for 5 h. It was then diluted with D_2O and extracted with benzene. The extract was dried with potassium carbonate and evaporated, and the PMR spectrum of the residue was recorded (65% of the deuteration product was present).

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