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REACTION OF 1-HALO-3-METHYL-2,3-EPOXYBUTANES WITH SECONDARY AMINES

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UDC 547.717'233.2.07:541.621.2:543.422.25

1-Chloro(bromo)-2,3-epoxybutanes react with secondary amines at the C—halogen bond to give amino derivatives in high yields. It was established that under the influence of $BF_3\cdot OEt_2$ the latter undergo isomerization to amino ketones, which were also synthesized from 1-bromo-3-methyl-2-butanones.

Owing to the development of a new convenient method for the synthesis of dimethylvinylcarbinol [1] its derivatives have become accessible intermediates in organic synthesis. The latter include 1-chloro- and 1-bromo-3-methyl-2,3-epoxybutanes and 2-methyl-2-chloro-3,4-epoxybutane (I-III), efficient methods for the preparation of which from dimethylvinylcarbinol are widely known [2]. However, the number of reagents that have been subjected to reaction with these halides is rather limited: Reactions involving the participation of methanol [3], alkoxides [4], acetoacetic ester, and a number of other compounds with active methylene groups [5] are known. It was noted that their reactions with the indicated reagents are far from trivial. Thus 1-bromo-3-methyl-2,3-epoxybutane reacts with alcohols in the presence of alkaline agents to give epoxy ethers without involving the epoxide ring [4], whereas in the absence of bases this epoxide reacts with methanol, for example, to give a product of addition to the epoxide ring, just like ordinary epoxy halides [3]. The reaction with acetoacetic ester also evidently commences at the C—Br bond [5].

In the light of the data set forth above it became of interest to conduct systematic studies of the regiochemistry of the reactions of these epoxides with various reagents. In the present communication we present data on the reaction with amines. The studies showed that halides I and II react with secondary amines to give products of replacement of the halogen atom in high yields. The course of the reaction can be expressed by two schemes that include initial attack by the amine at the carbon atom of the C—Br bond with the direct formation of epoxy amines IV or at the epoxy group with ring opening and the subsequent formation of oxygen-containing heteroring V. The amino oxides obtained do not give a positive reaction with a concentrated solution of sodium chloride [6]; refluxing with excess amounts of amines and with lithium aluminum hydride in ether does not lead to opening of the oxygen ring. All of this would seem to indicate the existence of an oxetane structure. In view of the fact that their PMR spectra did not give reliable information regarding the structures of the amines obtained, we also studied the reaction of the amines with epoxy chloride III, since the latter could react either at the C—Cl bond or with opening of the oxide ring in accordance with the Krasuskii rule with the subsequent formation of oxirane IV rather than oxetane V. We found that epoxy chloride III forms a mixture of isomeric amines that contains 60% amine IV [according to gas-liquid chromatography (GLC)], which was identical to a sample obtained from oxide I. These results make it possible to exclude the formation of an oxetane amine. Consequently, the formation of epoxy amines IV takes place as a result of direct replacement of the halogen atoms in epoxy halides I and II without involvement of the epoxide ring, in contrast to the known scheme that includes its opening and subsequent closing [6].

An additional confirmation of the assumptions made above was conversion of amino epoxide IVb to allylamine VI under the influence of zinc in the presence of sodium iodide

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0009-3122/83/1909-0934$07.50

TABLE 1. Amino Epoxides IV and Amino Ketones VII

Compound	bp, °C (mm)	n_D^{20}	d_4^{20}	Found, %			Empirical formula	Calc., %			Yield,[a] %
				C	H	N		C	H	N	
IVa	143—144 (650)	1,4200	0,8721	65,4	11,4	10,8	$C_7H_{15}NO$	65,1	11,6	10,8	90
IVb	69—70 (14)	1,4295	0,8627	68,7	12,2	9,0	$C_9H_{19}NO$	68,8	12,1	8,9	82
IVc	121—122 (14)	1,4390	0,8583	73,4	12,5	6,6	$C_{13}H_{27}NO$	73,2	12,7	6,5	83
IVd	99—100 (14)	1,4609	0,9286	70,0	11,5	8,1	$C_{10}H_{19}NO$	71,0	11,2	8,3	82 (78)[b]
IVe	108 (13)	1,4620	1,0039	63,5	9,9	8,2	$C_9H_{17}NO_2$	63,2	9,9	8,2	91 (83)[b]
VIIa	149—150 (650)	1,4230	0,8649	65,4	11,4	10,6	$C_7H_{15}NO$	65,1	11,6	10,8	80
VIIb	69—71 (12)	1,4320	0,8623	68,6	12,4	9,1	$C_9H_{19}NO$	68,8	12,1	8,9	78
VIIc	115—117 (12)	1,4400	0,8517	73,6	12,8	6,2	$C_{13}H_{27}NO$	73,2	12,2	6,6	82
VIId	94—96 (13)	1,4570	0,9258	70,9	11,3	8,4	$C_{10}H_{19}NO$	71,0	11,2	8,3	81
VIIe	108—111 (12)	1,4610	1,0004	63,3	10,2	8,5	$C_9H_{17}NO_2$	63,2	9,9	8,2	85

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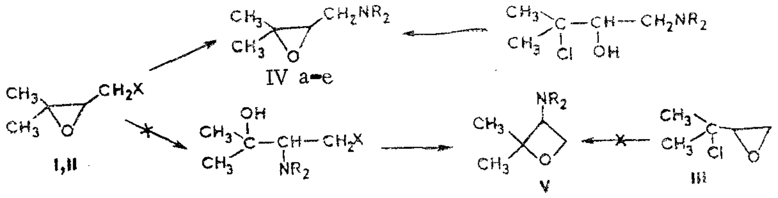
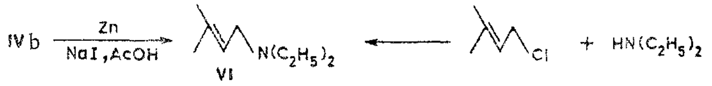
[a] Based on the converted halide (10-15% was recovered).
[b] The yield from epoxy chloride I is indicated in parentheses.

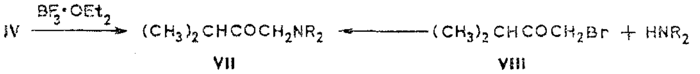


X=Cl, Br; IV a R=CH_3; b R=C_2H_5; c R=C_4H_9; d R—R=—$(CH_2)_5$—; R—R= =—$(CH_2)_2O(CH_2)_2$—

and acetic acid [7]; the product was identical (according to GLC and PMR) to a sample obtained from prenyl chloride and diethylamine [8].

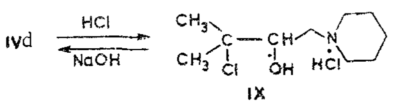


In addition, it was shown that amino epoxides IV upon reaction with boron trifluoride etherate undergo partial transformation to 1-dialkylamino-3-methyl-2-butanones (VII). The structure of the latter was proved by alternative synthesis from 1-bromo-3-methyl-2-butanol [9].



$$\text{IV} \xrightarrow{BF_3\cdot OEt_2} \underset{\text{VII}}{(CH_3)_2CHCOCH_2NR_2} \longleftarrow \underset{\text{VIII}}{(CH_3)_2CHCOCH_2Br} + HNR_2$$

In contrast to nucleophilic agents, opening of the epoxide ring of IVd by means of hydrogen chloride proceeds exceptionally easily; upon treatment of the resulting chlorohydrins with a base the oxide ring is restored.



EXPERIMENTAL

The PMR spectra of solutions of the compounds in CCl_4 were recorded with a Perkin-Elmer R-12B spectrometer with tetramethylsilane as the internal standard. The purity and identity of the synthesized compounds were determined by GLC with an LKhM-8MD chromatograph with a catharometer and a 2-m long column packed with 5% SE-30 on Chromaton N-AW-HMDS; the carrier-gas (helium) flow rate was 40-60 ml/min, and the temperature was 120-170°C.

<u>1-Amino-3-methyl-2,3-epoxybutanes (IVa-e, Table 1).</u> A 50-mmole sample of halide I or II was added dropwise at room temperature to 100 mmole of the amine in 20 ml of benzene or ether, and the mixture was heated at 50-60°C for 4 h. The precipitated salt was removed by filtration and washed thoroughly with ether, and the filtrate was distilled.

In the preparation of the dimethylamino derivative dry dimethylamine was passed into an ether solution of the halide.

PMR spectra: IVa: 1.20 (d, CH_3), 2.18 [s, $(CH_3)_2N$], 3.38 (m, CH_2), and 2.66 ppm (m, CH); IVd: 1.16 (d, CH_3), 1.45 and 2.32 [m, $(CH_2)_5N$], and 2.19-2.73 ppm (m, CH, CH_2); IVe: 1.16 (d, CH_3), 2.62 (m, CH), 3.53 [t, $(CH_2)_2O$], and 2.21-2.62 ppm [m, $(CH_2)_3N$].

1-Amino-3-methyl-2-butanones (VIIa-e, Table 1). A) These compounds was obtained from amines and bromo ketone VIII by a procedure similar to that used to obtain IV.

B) A 2-ml sample of $BF_3 \cdot OEt_2$ was added slowly dropwise with stirring to 3.38 g (20 mmole) of amino epoxide IVd in 10 ml of benzene. At the end of the exothermic reaction, the mixture was refluxed for another 2 h, after which it was cooled and treated with sodium carbonate solution and ether. Distillation yielded 1.2 g (35%) of amino ketone VIId. Compound IVd could not be recovered; resinification was observed during workup.

PMR spectra: VIIa: 0.98 (d, CH_3), 3.05 (s, CH_2), 2.20 [s, $(CH_3)_2N$], and 2.73 ppm (m, CH); VIIb: 1.02 (d, 3-CH_3), 3.13 (s, CH_2), 2.54 [q, $(CH_2)_2N$], 0.96 (t, β-CH_3), and 2.73 ppm (m, CH)]; VIId: 0.98 (d, CH_3), 3.00 (s, CH_2), 1.45 and 2.31 [m, $(CH_2)_5N$], and 2.73 ppm (m, CH); VIIe: 0.98 (d, CH_3), 3.08 (s, CH_2), 2.39 [m, $(CH_2)_2N$], 3.58 [m, $(CH_2)_2O$], and 2.73 ppm (m, CH).

3-Methyl-1-piperidino-3-chloro-2-butanol Hydrochloride (IX). A cooled 20-ml sample of dry ether was saturated with gaseous HCl, after which 8.5 g (50 mmole) of amino epoxide IVd was added at room temperature, and a moderate stream of HCl was passed into the mixture in the course of 2 h. The resulting salt was removed by filtration and air dried to give 11.7 g (97%) of salt IX with mp 152°C. IR spectrum: 3330 cm^{-1} (OH). Found: C 49.9; H 8.6; Cl 29.1; N 5.7%. $C_{10}H_{20}ClNO \cdot HCl$. Calculated: C 49.6; H 8.7; Cl 29.6; N 5.8%. Amino epoxide IVd was regenerated by treatment of salt IX with 50% NaOH solution.

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