THE REACTION OF 2,3-EPOXYBUTYRALDEHYDE WITH α-AMINOISOBUTYRONITRILE AND ITS N-ALKYL AND N,N-DIALKYL DERIVATIVES

L. A. Yanovskaya, B. I. Kozyrkin,
and V. F. Kucherov

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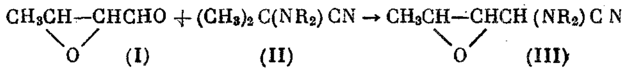
We have shown that N-alkyl- and N,N-dialkylaminoisobutyronitriles react with saturated, aromatic, and α,β-unsaturated aldehydes forming aminonitriles, Schiff bases, cyano-enamines or α-cyanimines depending on the structure of the starting aminonitrile and aldehyde. In actual fact a mixture of geometric isomers of the cyano-enamine is formed on reacting an α,β-unsaturated aldehyde with an N,N-dialkylaminoisobutyronitrile but an α-cyanimine is formed on reaction with an N-alkylaminoisobutyronitrile. It was of interest to study the reaction between aminonitriles and 2,3-epoxybutyric aldehyde to ascertain the influence of the oxide ring, which imitates a double bond in many ways, on the course of the reaction.

The reaction between aminoisobutyronitrile and 2,3-epoxybutyraldehyde was carried out by two routes: 1) the equivalent quantity of aminoisobutyronitrile (which can readily be obtained from acetone cyanohydrin and the corresponding amine [1]) was added to the aldehyde at room temperature or under cooling at 0-5°, the mixture was kept 3-24 h, checking the course of the reaction with the aid of gas-liquid chromatography (GLC) or thin-layer chromatography (TLC), and at the end of the reaction the product was isolated by distillation: 2) an equivalent amount of amine was added to a mixture of aldehyde and acetone cyanohydrin at room temperature or with cooling, after separation of water the product was dried over $MgSO_4$ and distilled. The yield of product by both variations proved to be approximately equal (Table 1).

As was to be expected, the reaction of 2,3-epoxybutyraldehyde (I) with N,N-dialkyl-α-aminoisobutyronitrile (II) (or acetone cyanohydrin and a secondary amine) led to N,N-dialkyl-2-amino-3,4-epoxyvaleronitrile (III) in high yield.

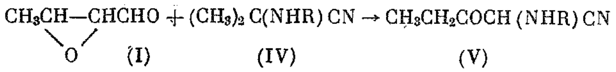


$$\underset{\text{(I)}}{CH_3\underbrace{CH-CH}_{O}CHO} + \underset{\text{(II)}}{(CH_3)_2C(NR_2)CN} \rightarrow \underset{\text{(III)}}{CH_3\underbrace{CH-CH}_{O}CH(NR_2)CN}$$

$R=CH_3$ (a); C_2H_5 (b); n-C_4H_9 (c); $CH_2CH=CH_2$ (d); $CH_2C_6H_5$ (e)

Structure (III) was confirmed by elemental analytical data, by the presence of one active hydrogen atom, and by IR spectra. By heating in a sealed ampule (III) reacts with amines, forming hydroxydiaminonitriles.

The reaction of (I) with N-monoalkyl-α-aminoisobutyronitrile (IV) (or with acetone cyanohydrin and a primary amine) takes place with isomerization of the α-oxide ring as a result of which the corresponding N-alkyl-2-amino-3-ketovaleronitrile (V) is formed.



$$\underset{\text{(I)}}{CH_3\underbrace{CH-CH}_{O}CHO} + \underset{\text{(IV)}}{(CH_3)_2C(NHR)CN} \rightarrow \underset{\text{(V)}}{CH_3CH_2COCH(NHR)CN}$$

$R=C_2H_5$ (a); n-C_4H_9 (b); n-C_6H_{13} (c)

The structure of (V) was confirmed by elemental analytical data, by the presence of two active hydrogen atoms, by the immediate formation of a 2,4-dinitrophenylhydrazone by the action of 2,4-dinitrophenylhydrazine hydrochloride solution [compounds (III) also form 2,4-dinitrophenylhydrazones, but only on long standing for 7-10 days due to isomerization of the α-oxide ring], and by IR and UV spectra. Oxidation of (Va) with aqueous potassium permanganate solution gave propionic acid identified as its S-benzylthiouronium salt which unambiguously shows the position of the keto group in the compounds obtained.

$$CH_3CH_2COCH(NHR)CN \xrightarrow[(KMnO_4)]{O_2} CH_3CH_2COOH$$

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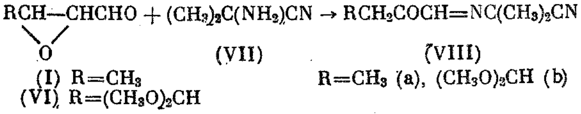
TABLE 1. Yields, Constants and Analytical Data of Epoxyaminonitriles (III)

Substance	Yield by method		bp, °C (p, mm Hg)	n_D^{20}	IR spectrum, ν, cm^{-1}	Found H_{active}	Found, %			Calculated, %		
	A	B					C	H	N	C	H	N
IIIa	—	60	56–57 (0.4)	1.4400	1265 s $\underset{\diagdown O \diagup}{(CH{-}CH)}$	—	60.30	8.87	20.23	59.97	8.63	19.99
					2312 w 2222 w (CN)		60,27	8.60	20.46			
IIIb	50	91	73–74 (0.5)	1.4440	1248 s $\underset{\diagdown O \diagup}{(CH{-}CH)}$	1.10	64.20	9.73	16.78	64.25	9.59	16.65
					2350 w 2226 w (CN)		64.01	9,58	16,72			
IIIc	—	87	76–77 (0.1)	1.4445	1246 s $\underset{\diagdown O \diagup}{(CH{-}CH)}$	1,04	69.75	10.51		69.60	10.78	—
					2350 w 2224 w (CN)		69.99	10.62				
IIId	—	82	74–75 (0.25)	1.4665	1263 s $\underset{\diagdown O \diagup}{(CH{-}CH)}$	1,15	68.50	8.40		68.72		
					1648 s (CH=CH) 2350 w 2224 w (CN)		68.20	8.26	—		—	—
IIIe	—	66	155–158 (0.3)	1.5625	1244 s $\underset{\diagdown O \diagup}{(CH{-}CH)}$				9.29			
					2344 w 2202 w (CN)				9.04		—	9.58

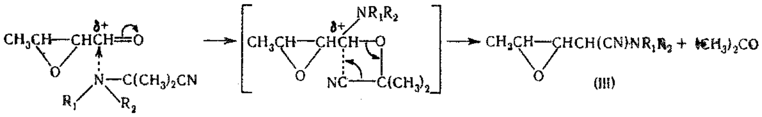
TABLE 2. Yields, Constants and Analytical Data of Ketoaminonitriles (V)

Substance	Yield by method		bp, °C (p, mm Hg)	n_D^{20}	IR spectrum, ν, cm^{-1}	UV spectrum, λ_{max}, mμ (ε)	Mol. wt. (cryoscopic in benzene)	Found H_{active}	Found, %		Calculated, %	
	A	B							C	H	C	H
Va	54.3	—	78 (0.3)	1.4490	1682 s (CO) 2217 w (CN)	261 (364)	148; 152	2.12; 2.01	59.94 59,95	8.47 8.25	59.97	8.63
Vb	47.5	57	87–89 (0.2)	1.4538	1680 s (CO) 2217 w (CN)	262 (1140)	177; 172	1.89; 1.95	64.37 64.40	9.51 9.64	64.25	9.54
Vc	52.5	52	100–101 (0.4)	1.4570	1676 s (CO) 2224 w (CN)	265 (735)		1.98; 2.05	67.96 67.58	10.50 10.20	67.30	10.27

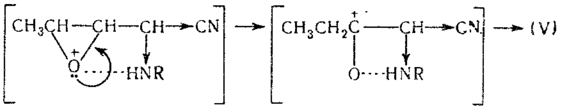
In contrast to the reaction described above, (I) and 4,4-dimethoxy-2,3-epoxybutyraldehyde (VI) interact with α-aminoisobutyronitrile (VII) forming Schiff bases (VIII), while in this instance the reaction is accompanied by isomerization of the α-oxide ring into a keto group.



The structure of (VIII) was confirmed by elemental analytical data, by the absence of active hydrogen atoms and by IR and UV spectra. (VIIIa) gave with 2,4-dinitrophenylhydrazone hydrochloride solution, a 2,4-dinitrophenylhydrazone corresponding in structure to the hydrazone of the respective α-keto aldehyde. The presence in the IR spectrum of (VIIIa) and (VIIIb) of weak absorption bands at 1730-1735 cm^{-1} indicates possible contamination by the isomeric ketone. This contamination is obviously very small since GLC data on these substances do not support contamination though by the method of thin layer chromatography on Al_2O_3 in various solvent systems it is possible to record traces of impurity in addition to the basic spots. The formation of various reaction products, depending on the structure of the aminoisobutyronitrile, is understandable if the usual reaction scheme for (I) is considered in all three cases.

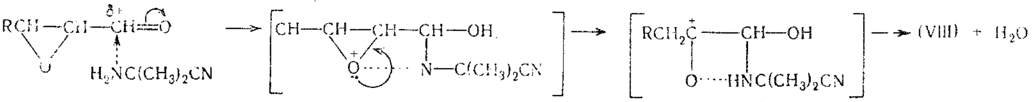


In the case of N,N-dialkylaminoisobutyronitrile the reaction is of course completed at the stage of formation of (III). However in the case of N-alkylaminoisobutyronitriles, when R_1 or R_2 = H in (III), the situation is different. The presence of an acidic hydrogen atom in the aminonitrile (III, R_1 = H) [2, 3] capable of establishing a hydrogen bond with the oxygen of the oxide ring, and the presence in the immediate vicinity of the oxide ring of two electron accepting substituents instrumental in drawing off the free electron pair of the oxygen must undoubtedly facilitate and bring about a redistribution of the electron density in the molecule, i.e., it



must lead to isomerization according to the mechanism of the usual intramolecular acid isomerization of oxides [4]. It is quite possible that the formation of aminonitrile and isomerization take place simultaneously in a single reaction complex.

The formation of (VIII) by the reaction of α-aminoisobutyronitrile and 2,3-epoxybutyraldehyde can be explained by the following scheme.



In this case the reaction undoubtedly takes place in a single reaction complex since Schiff bases of 2,3-epoxybutyraldehyde, which are readily formed by the action of primary amines on the aldehyde [5], are stable enough compounds having no tendency towards isomerization. Thus the isomerization is brought about by the presence of an acidic hydrogen in the aminonitrile molecule.

EXPERIMENTAL

GLC analysis of the compounds obtained was carried out on a column of length 2 m with 1% silicone elastomer on NaCl. For TLC plates a binder-free layer of Al_2O_3 (activity II) was used, solvent mixtures were of ether and n-hexane in ratios 1 : 9, 1 : 5, 5 : 1 and 9 : 1 by volume. IR spectra were taken on an IKS-14 instrument in capillary films; UV spectra were taken on an SF-4A instrument with alcohol as solvent.

2-Dimethylamino-3,4-epoxyvaleronitrile (IIIa). To a mixture of 3.4 g 3,4-epoxybutyraldehyde (I) and 4.25 g acetone cyanohydrin, 7.9 g 30% aqueous dimethylamine solution was added. The mixture became slightly warm. After 1 h Na_2SO_4 was added and was filtered off the next day. By distillation 4.2 g (IIIa) was isolated, the constants, IR spectrum, and elemental analysis of which are given in Table 1. The product gave a single peak on GLC (145°, N_2 flow rate 32 ml/min) and a single spot on an Al_2O_3 plate.

2-Diethylamino-3,4-epoxyvaleronitrile (IIIb). A. To 4.3 g (I) 7 g (IIb) was added. On the following day 4.2 g (IIIb) was isolated by distillation, the constants, IR spectrum, and elemental analysis of which are given in Table 1. The product gave a single peak on GLC (140°, N_2 32 ml/min) and a single spot on an Al_2O_3 plate.

B. To a mixture of 6.5 g (I) and 6.4 g acetone cyanohydrin, 5.6 g diethylamine was added with cooling. After 1 h $MgSO_4$ was introduced and on the following day 11.5 g (IIIb) was isolated by distillation identical to that described above.

A mixture of 5 g (IIIb) and 3 g diethylamine was heated in a metal tube at 120° for 23 h. After cooling, 2 g (28%) product with bp 85-88° (0.25 mm) was isolated with n_D^{18} 1.5030, giving a single basic spot on a plate. 0.4 g product was dissolved in 300 ml absolute ether and to the solution an excess of ether saturated with hydrogen chloride was added. After 10 days 0.3 g (61%) dihydrochloride was obtained with mp 216-219° (with decomposition). Found %: N 14.08, 13.88. $C_{13}H_{28}ON_2Cl_2$. Calculated %: N 14.08.

Aminonitriles (IIIc), (IIId) and (IIIe) were obtained by method B. Their constants, IR spectra, and elemental analytical data are given in Table 1. They each gave one peak on GLC and a single spot on Al_2O_3 plates.

2-Ethylamino-3-ketovaleronitrile (Va). 4.3 g (I) was mixed with 5.4 g (IV, $R = C_2H_5$) and after several minutes an exothermic reaction was observed. On the following day 3.8 g (Va) was isolated by distillation. Constants, IR and UV spectra and elemental analytical data are given in Table 2.

1 g (Va) was oxidized in an aqueous emulsion with 5% potassium permanganate solution (added until the pink color failed to disappear). The filtrate was concentrated in vacuum, the residue acidified with H_2SO_4 and steam distilled. A saturated solution of benzylthiouronium chloride was added to the distillate. On standing, the S-benzylthiouronium salt of propionic acid was precipitated with mp 147-150°, giving no depression of melting point on admixture with an authentic specimen.

Ketoaminonitriles (Vb) and (Vc) were obtained similarly (see Table 2).

α-Cyano-α,α-dimethylmethyliminobutan-2-on-1-al (VIIIa). 4.2 g (VII) was added to 4.3 g (I). The mixture became very warm and turbid, and after 1 h Na_2SO_4 was added. Next day 3.35 g (44%) Schiff base (VIIIa) was isolated by distillation with bp 97-99° (13 mm): n_D^{20} 1.4475. Found %: C 62.70, 62.67; H 7.91, 7.88; N 18.78, 18.78. $C_8H_{12}ON_2$. Calculated %: C 63.13; H 7.95; N 18.41. IR spectrum (ν, cm^{-1}): 1628 (C=N), 1668 (conjugated CO), 1730 w (saturated CO), 2312, 2225 w (CN) (VIIIa) gave a single peak on GLC (102°, N_2 25 ml/min) and a single spot on an Al_2O_3 plate. With 2,4-dinitrophenylhydrazine hydrochloride solution, the hydrazone precipitated immediately retaining the keto group, mp 237.5-239° (from benzene), λ_{max} 396 mμ. Found %: N 21.30, 21.49. $C_{10}H_{10}O_5N_4$. Calculated %: N 21.05.

In a similar manner to (VIIIa), (VIIIb) was obtained from (VI) in 46% yield, bp 84-85° (0.4 mm); n_D^{18} 1.4520. Found %: C 56.65, 56.44; H 7.64, 7.71; N 13.26, 13.33. $C_{10}H_{16}O_3N_2$. Calculated %: C 56.59; H 7.60; N 13.20. λ_{max} 217.5 mμ (ε 2,610). IR spectrum (ν, cm^{-1}): 1628 (C=N), 1688 s (CO conjugated), 1735 w (CO saturated), 2315, 2224 w (CN).

CONCLUSIONS

1. N,N-Dialkylaminoisobutyronitriles were reacted with 2,3-epoxybutyric aldehyde forming previously unknown 2-N,N-dialkylamino-3,4-epoxyvaleronitriles.

2. The reaction of 2,3-epoxybutyric aldehyde with N-alkylaminoisobutyronitriles was accompanied by isomerization of the oxide ring and led to 2-N-alkylamino-3-ketovaleronitriles.

3. α-Aminoisobutyronitrile and 2,3-epoxybutyric aldehyde gave a Schiff base with isomerization of the oxide ring.

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