INVESTIGATION OF 1-AZABICYCLIC COMPOUNDS

IX.* CONDENSATION OF 1,2-DIHYDROPYRROLIZINES WITH ETHYLENE OXIDE

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The conditions for carrying out the condensation of 1,2-dihydropyrrolizine, 2-methyl-1,2-dihydropyrrolizine, and 3-methyl-1,2-dihydropyrrolizine with ethylene oxide were investigated. The NMR spectra indicated that hydroxyethylation proceeds at the 5 and 7 positions of the 1,2-dihydropyrrolizine system.

The reactions of α-oxides with compounds containing various functional groups and with aromatic and several heterocyclic compounds of aromatic character are described in [2, 3]. For pyrroles, 2-hydroxyethylation was accomplished through the organomagnesium derivatives [4]. Direct hydroxyethylation of pyrrole itself was unsuccessful [5].

In this communication we present the results of investigations of the reaction of 1,2-dihydropyrrolizine [6] (I), 2-methyl-1,2-dihydropyrrolizine [7] (II), and 3-methyl-1,2-dihydropyrrolizine [8] (III) with ethylene oxide (IV). The conditions for the synthesis were selected in experiments using III and IV as model compounds.

The reaction was carried out in a 50-ml steel autoclave at 190-200°C (the optimum temperature interval was determined experimentally) and a III to IV molar ratio of 3 : 1. The degree of filling of the autoclave was held constant at 43 ml in all the experiments (except No. 15).

Examination of the experimental data presented in Table 1 indicates that the best results in neutral, acidic, and alkaline media under the studied conditions are obtained when approximately 1 g of water is introduced into the reaction mixture. The reaction does not proceed at all with dry reagents without a third component (No. 1). A regular increase in the yields of the reaction products (IX + X) on passing from an alkaline medium through a neutral medium to an acidic medium (compare experiments Nos. 9, 7, 4, and 10) is apparent from Table 1. This enables one to suppose that the reaction is catalyzed by hydrogen ions. Water is apparently important in the transformation, although it is not the only possible component serving as a proton donor. Acetic acid fulfills this role in experiment No. 13. The decrease in yields on increasing the water content is probably explained by the increase in the relative weight of the side reactions of ethylene oxide with water.

The experiments indicated that the degree of filling of the autoclave, which apparently determines the amount of ethylene oxide in the liquid phase (compare Nos. 11 and 15), also affects the yields.

Condensation of I and II with IV was carried out under the conditions of experiment No. 11. The reaction products are light-yellow, viscous liquids with a weak characteristic odor which give acylation products with acetic anhydride.

The IR and PMR spectral data of the reaction products make it possible to assume the following scheme for the transformations:

*For Communication VIII, see [1].

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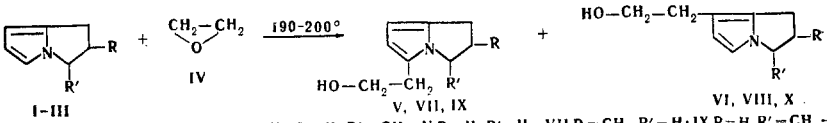
TABLE 1. Conditions for Hydroxyethylation of 3-Methyl-1,2-dihydropyrrolizine

Expt. No.	3-Methyl-1,2-dihydropyrrolizine (III), g (mole)	Ethylene oxide (IV), g (mole)	Catalyst, g	Water added, g	Yield of reaction products (IX+X) based on ethylene oxide, %
1	36,36 (0,3)	4,4 (0,1)	—	—	—
2	36,36 (0,3)	4,4 (0,1)	—	0,025	5
3	36,36 (0,3)	4,4 (0,1)	—	0,5	20
4	36,36 (0,3)	4,4 (0,1)	—	1	31
5	35,36 (0,291)	4,28 (0,097)	—	2	28
6	34,54 (0,285)	4,18 (0,09)	—	3	29
7	36,36 (0,3)	4,4 (0,1)	K_2CO_3 (2)	1	28
8	34,54 (0,285)	4,18 (0,09)	K_2CO_3 (2)	3	13
9	36,36 (0,3)	4,4 (0,1)	KOH (2)	1	—
10	36,36 (0,3)	4,4 (0,1)	CH_3COOH (0,009)	1	39
11	36,36 (0,3)	4,4 (0,1)	CH_3COOH (0,078)	1	39
12	34,54 (0,285)	4,18 (0,09)	CH_3COOH (0,027)	3	28
13	36,36 (0,3)	4,4 (0,1)	CH_3COOH (1)	—	32
14	36,36 (0,3)	4,4 (0,1)	H_2SO_4 (0,0004)	1	42
15	18,18 (0,15)	2,2 (0,05)	CH_3COOH (0,035)	0,5	33

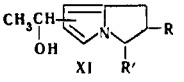


I-III IV V, VII, IX VI, VIII, X

I R=H, R'=H; II R=CH_3, R'=H; III R=H, R'=CH_3; V R=H, R'=H; VII R=CH_3, R'=H; IX R=H, R'=CH_3; VI R=H R'=H; VIII R=CH_3, R'=H; X R=H, R'=CH_3

The pyrrole ring is detected in the paired mixtures (V + VI, VII + VIII, and IX + X) by the presence in the IR spectra of characteristic vibrations peculiar to the pyrroles. An absorption band from 3093 to 3090 cm^{-1}, which is characteristic for the stretching vibrations of the C–H bond of pyrroles [9, 10], is present in the spectra obtained in a capillary layer. The two bands at 1508 and 1564-1570 cm^{-1} were ascribed to the stretching vibrations of the pyrrole ring [11]. The strong absorption at 1293-1298 cm^{-1} and the band at 751-757 cm^{-1} were assigned to the stretching vibration of the N–C_3 bond [12] and to the in-plane deformation vibrations of the C–H bond of the pyrrole ring [10], respectively. In addition, a broad and intense absorption with a maximum at 3380 cm^{-1}, which is peculiar to the hydroxyl group in intermolecular associates, and a strong band at 1050 cm^{-1}, which corresponds to the stretching vibrations of the C–O bonds [13], are present in the spectra.

It is well known that ethylene oxide undergoes isomerization to acetaldehyde with acidic catalysts under rather mild conditions [14, 15]. The formation of structures of the XI type with secondary alcohol groups (products of the reaction of acetaldehyde and 1,2-dihydropyrrolizines) was excluded on the basis of the NMR data from the absence of a signal from the protons of the methyl group in the case of V + VI.



XI

The problem of the position of the 2-hydroxyethyl group in the reaction products was solved by an NMR method in the case of V + VI and IX + X.

Four doublets with chemical shifts of 6.38 ppm ($J_{5,6}$ = 2.7 Hz), 5.88 ppm ($J_{5,6}$ = 2.7 Hz), 5.75 ppm ($J_{6,7}$ = 3.2 Hz), and 5.51 ppm ($J_{6,7}$ = 3.2 Hz) are present in the spectrum of V + VI, and the intensity of the first signal is equal to the intensity of the second signal, while the intensity of the third signal is equal to that of the fourth signal.

A similar picture is observed in weak field for IX + X. The positions of the signals (doublets) are as follows: 6.25 ppm ($J_{5,6}$ = 2.6 Hz) and 5.78 ppm ($J_{5,6}$ = 2.6 Hz) (equal intensities), 5.65 ppm ($J_{6,7}$ = 3.2 Hz) and 5.43 ppm ($J_{6,7}$ = 3.2 Hz) (equal intensities). Two doublets are found at strong field at 1.32 and 1.25 ppm (J is 6.3 Hz in both cases) and are assigned to the methyl groups.

The signals in the spectra of V + VI and IX + X were assigned on the basis of the literature data [16, 17] and a comparison of the spectra of V + VI and IX + X with the PMR spectra of I and 3,5-dimethyl-1,2-dihydropyrrolizine [8] (XII) in the region of the signals from pyrrole protons. The spectrum of 1,2,5-trimethylpyrrole, obtained in CCl_4 at 60 MHz with tetramethylsilane (TMS) as internal standard, has signals from the protons attached to the 3- and 4-carbon atoms at 330.3 Hz (5.50 ppm) [16] or at 5.52 ppm [17]. Under similar conditions, 1,2-dimethylpyrrole has the following positions of the signals of the pyrrole protons: 3-H (5.67 ppm), 4-H (5.77 ppm), and 5-H (6.30 ppm) [17]. It was found that the chemical shifts of the pyrrole protons are almost independent of the solution concentration [16]. The PMR spectrum of I in the weak-field region has three signals of equal intensity at 6.37, 5.98, and 5.60 ppm which, on the basis of data for 1,2-dimethylpyrrole [17], should be assigned to 5-H, 6-H, and 7-H, respectively. Compound XII has two doublets ($J_{6,7}$ = 3.0 Hz) at 5.60 and 5.40 ppm, which are assigned to 6-H and 7-H (the affiliation of each signal with a definite proton was not determined). The difference in the chemical shifts of the indicated protons is 0.20 ppm. The protons of the 3-methyl group give a signal at 1.27 ppm.

The set of the above-presented experimental and literature data indicates that V + VI and IX + X are mixtures of isomers with a 2-hydroxyethyl group in the 5 and 7 positions.

The first two signals at weaker field in the spectra of V + VI and IX + X are assigned to 5-H and 6-H of the isomer with the 2-hydroxyethyl group in the 7 position, while the next two signals in the direction of increasing field belong to 6-H and 7-H of the isomer with the hydroxyethyl group in the 5 position; splitting of the signals in the latter case is similar to that observed for 6-H and 7-H in XII, viz., 0.24 ppm for V + VI and 0.22 ppm for IX + X.

Since the 5, 6, and 7 positions of the 1,2-dihydropyrrolizine system correspond to the 2, 3, and 4 positions of pyrrole, the above assignment of the signals from the chemical shifts is confirmed by assignment according to the spin-spin coupling constants [22].

For V + VI the chief isomer is an alcohol with the 2-hydroxyethyl group in the 5 position (the isomer content is 62% V and 38% VI according to the integral intensities), while for IX + X the major component of the mixture is the isomer with the 2-hydroxyethyl group in the 7 position (55% X and 45% IX).

It should be noted that the presence of isomers with the 2-hydroxyethyl group in the 6 position was not detected in V + VI and IX + X by the NMR method. The presence of 6-(2-hydroxyethyl)-1,2-dihydropyrrolizine and, accordingly, 3-methyl-6-(2-hydroxyethyl)-1,2-dihydropyrrolizine, should have led to the appearance in these spectra of two signals of equal intensity from 5-H and 7-H ($J_{5,7} \approx 1.4$ Hz) [22].

The isomer ratio in the hydroxyethylation products was also determined by gas-liquid chromatography. The data on the isomer content obtained by the NMR and GLC methods are in satisfactory agreement.

In the case of the reaction of III and IV, it was found that the isomer ratio is independent of the temperature from 160 to 200°. A more detailed study of the effect of the hydroxyethylation conditions and the structural peculiarities of the starting 1,2-dihydropyrrolizines on the isomeric composition of the reaction products will be the subject of further investigations.

EXPERIMENTAL

Ethylene oxide (IV) was distilled over KOH and analyzed for water [18] and acetaldehyde content [19]. It was found to contain 0.025% water and 0.014% acetaldehyde.

3-Methyl-5-(2-hydroxyethyl)-1,2-dihydropyrrolizine (IX) and 3-Methyl-7-(2-hydroxyethyl)-1,2-dihydropyrrolizine (X). A 50-ml autoclave was charged with 36.36 g (0.3 mole) of III, 4.4 g (0.1 mole) of IV, 1 g of water, and 0.009 g of acetic acid. The autoclave was heated at 190-200° for 5 h. The reaction mixture was discharged from the autoclave, washed with three 50-ml aliquots of water, 100 ml of ether was added, and the ether solution was dried over potassium hydroxide for 24 h. The ether was then removed, and the residue was distilled at reduced pressure to give 26.85 g of unchanged III and 6.42 g of IX + X (50% yields based on the III consumed and 39% based on the IV consumed).

V + VI and VII + VIII were similarly obtained. The data are presented in Table 2.

The IR spectra were obtained with a UR-10 spectrophotometer in a capillary layer.*

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TABLE 2. Properties and Analysis of the Products of Hydroxyethylation of 1,2-Dihydropyrrolizines

Comp. of the isomer mixture, %		mp, (pressure, mm)	d_4^{20}	n_D^{20}	MR_D		Empirical formula	Found, %			Calc., %			Yield, %
from GLC	from NMR				found	calc.		C	H	N	C	H	N	
V 66 VI 34	V 62 VI 38	121—122 (5)	1,0855	1,5432	43,92	43,89	$C_9H_{13}NO$	71,60 71,61	8,70 8,80	8,97 9,01	71,49	8,67	9,26	33
VII 65 VIII 35	—	104—105,5 (2)	1,0466	1,5277	48,59	48,51	$C_{10}H_{15}NO$	72,76 72,72	9,26 8,98	8,72 8,76	72,69	9,15	8,48	65
IX 47 X 53	IX 45 X 55	103—104 (1)	1,0587	1,5315	48,32	48,51	$C_{10}H_{15}NO$	72,48 72,52	9,07 9,28	8,32 8,25	72,69	9,15	8,48	50

The NMR spectra were obtained under the following conditions: V + VI, 1.55 mole/liter solution in CCl_4, hexamethyldisiloxane internal standard, 60 MHz, RS-60 spectrometer; IX + X, 10-15% solution in CCl_4, hexamethyldisiloxane internal standard, 60 MHz, Varian DA-60 spectrometer; I and XII, 0.97 mole/liter and 0.88 mole/liter solutions in CCl_4, TMS internal standard, 60 MHz, JEOL C-60 spectrometer.

The chromatographic analysis of the mixtures of isomeric 2-hydroxyethyl-1,2-dihydropyrrolizines was carried out with a UKh-2 chromatograph with a thermal conductivity detector. Polyethylene glycol 20,000, applied in 15% quantities on Inzenskii brick and processed successively by the method in [20, 21] was used as the stationary phase. The support grain size was 0.25-0.50 mm, the column was 1.4 m long and had an inner diameter of 4 mm. The column temperature was 237°, 231°, and 237° for the analysis of V + VI, VII + VIII, and IX + X, respectively, while the gas-carrier (helium) rate was 100, 77, and 100 ml/min, respectively.

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