INVESTIGATION OF 1-AZABICYCLES

X.* SYNTHESIS OF EPIMERIC 3-METHYLPYRROLIZIDINES BY CATALYTIC DEHYDRATION OF TETRAHYDROFURAN AMINES AND PYRROLIDINE ALCOHOLS.

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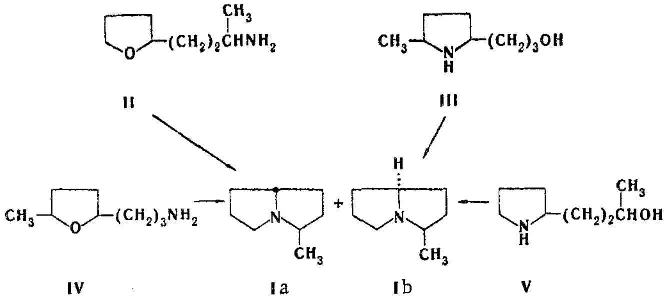
The composition of mixtures of epimeric 3-methylpyrrolizidines obtained by four methods was determined by gas-liquid chromatography (GLC). The data presented make it possible to select a method for the preparation of a mixture of isomers of 3-methylpyrrolizidine with predominance of trans- or cis-3,8-H-3-methylpyrrolizidine.

The investigation of the isomeric composition of alkylpyrrolizidines obtained by different methods may give information regarding the stereoselectivity of the process that makes it possible to determine the suitability of an individual method of synthesis for obtaining one or another isomer. The isomers of alkylpyrrolizidines are necessary for investigations involving the conformational analysis of these compounds, for some of their chemical transformations, and for the synthesis of physiologically active substances. Different methods for the synthesis of 3-methylpyrrolizidine (I) are described in the literature [2, 3], but these papers contain no accurate data regarding the ratio of epimers of the indicated compound – trans-3,8-H-3-methylpyrrolizidine (Ia) and cis-3,8-H-3-methylpyrrolizidine (Ib).



In the present communication, we examine four methods for the synthesis of I as well as different variants for the preparation of the starting compounds for two of the methods (Table 1). Dehydration of the tetrahydrofuran amine (II) obtained by the various methods (experiments 1-3) gives approximately the same result – a mixture of epimers with predominance of Ia. According to the data obtained in this research, it is still impossible to judge the stereochemistry of the catalytic dehydration of tetrahydrofuran amines itself, since the ratio of isomers in the starting amines is unknown, and, in addition, it has been established that passage of a mixture of Ia and Ib over Al_2O_3 under the dehydration reaction conditions is accompanied by only slight isomerization of Ib to Ia. However, markedly expressed stereoselectivity of the dehydration of tetrahydrofuran amines is undoubtedly absent, since the ratio of Ia and Ib proves to be dependent on the method of preparation of starting amine IV (experiments 5-7).

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* See [1] for communication IX.

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TABLE 1. Synthesis of trans- and cis-3,8-H-3-Methylpyrrolizidines (Ia and Ib)

Expt.	Starting compound	Conditions for obtaining the starting compound	Yield of Ia + Ib, % *	Ia : Ib ratio†
1	II[5]	Ni, H$_2$, alcohol 150°	69	67 : 33
2	II[5]	Ni, H$_2$, H$^+$, H$_2$O, 100°	62	70 : 30
3	II[6]	Ru/C, H$_2$, CH$_3$OH, 30°	45	67 : 33
4	III[7]	Ni, H$_2$, H$^+$, H$_2$O, 100°	67	32 : 68
5	IV	Ni, H$_2$, C$_2$H$_5$OH, 150°	21	45 : 55
6	IV	Ni, H$_2$, H$^+$, H$_2$O, 100°	19	64 : 36
7	IV	Ru/C, H$_2$, CH$_3$OH, 35–40°	42	27 : 73
8	V	Ni, H$_2$, H$^+$, H$_2$O, 100°	42	75 : 25

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* The yields in experiments 5 and 6 may be partially depressed because of the use of small amounts of IV in these experiments.

† The Ia : Ib ratio in the reaction mixture before distillation of the catalyzate is indicated.

According to the data of experiment 4, one can set up a qualitative representation regarding the isomer composition of the starting pyrrolidine alcohol (III), in which the isomer with cis-oriented methyl and γ-hydroxypropyl groups should prevail. This conclusion seems valid, since the asymmetric centers are not involved in the dehydration, and, in addition, the final product undergoes the Ib → Ia conversion, rather than the other way around. The ratio of the amount of trans isomer to the amount of cis isomer for the starting pyrrolidine alcohol should be lower than 32 : 68.

It must be noted that the successful conversion of III and V to I supports the representation of the mechanism of the catalytic dehydration of tetrahydrofuran amines in [4], according to which III and V may be intermediates in the examples of transformations of II and IV under consideration.

EXPERIMENTAL

The various samples of amine II were obtained via the methods in [5, 6], while alcohol III was obtained via the method in [7].

1-(5-Methyl-2-furyl)-3-aminopropane (VI).* This compound was prepared by reductive amination [8] of β-(5-methyl-2-furyl)acrolein [9] in 51% yield and had bp 88-90° (18 mm), d_4^{20} 0.9775, and n_D^{20} 1.4845 (bp 82° (6 mm), d_4^{20} 0.9578, and n_D^{20} 1.4840 [10]).

1-(5-Methyltetrahydro-2-furyl)-3-aminopropane (IV). This compound was obtained in 75% yield by hydrogenation of VI on Ru/C in methanol at 35-40° [6] and had bp 92-96° (18 mm) and n_D^{20} 1.4589. Found: C 67.5; H 11.5; N 10.0%. $C_8H_{17}NO$. Calculated: C 67.1; H 12.0; N 9.8%.

1-(α-Pyrrolidyl)-3-butanol (V). This compound was synthesized in 29% yield from VI via the method in [7] and had bp 129-130° (15 mm). Found: C 66.7; H 11.9; N 9.8%. $C_8H_{17}NO$. Calculated: C 67.1; H 12.0; N 9.8%. The other product of hydrogenation of VI in acid media was IV, which was obtained in 38% yield.

Aluminum oxide, prepared via the method in [11] and then calcined at 700° for 3 h, was used as the catalyst. The reactor was filled with Al_2O_3 granules ~3 mm in diameter. The dehydration of II-V was carried out as in [12] in a flow system at 320-340°; the space velocity for feeding of II-V was 0.1-0.18 h^{-1} (based on the liquid phase), and the rate of nitrogen flow through the reactor was 15.2-21.8 h^{-1}.

The mixtures of Ia and Ib were subjected to quantitative analysis by GLC with a KhL-4 chromatograph. Triethanolamine (6% on Inzenskii brick with 0.25-0.50-mm grains, processed according to the method in [13]) was used as the stationary phase. The column was 1 m long with an inner diameter of 6 mm. The column temperature was 100°. The carrier-gas (helium) flow rate was 5 liters/h. The peaks on the chromatogram were assigned on the basis of an analysis of mixtures in which the predominant component was determined by means of thin-layer chromatography and had a known configuration established by the quaternization method [14]. By this method it was found that isomer Ia has a lower retention time than isomer Ib on triethanolamine at 100°.

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* Synthesized by N. A. Buntyakova.

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