RESEARCH ON 1-AZA TWO-RING SYSTEMS.

20.* SYNTHESIS AND STEREOCHEMISTRY OF 3(5)-(3-HYDROXYPROPYL)PYRROLIZIDINES

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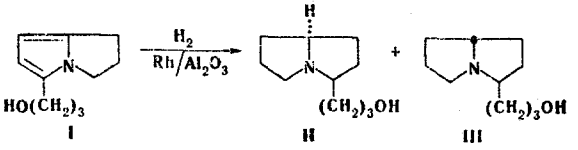
UDC 541.634:542.941.7:547.759.5:543.544

The catalytic hydrogenation of 5-(3-hydroxypropyl)-1,2-dihydropyrrolizines gave a mixture of stereoisomers of 3(5)-(3-hydroxypropyl)pyrrolizidines, which was separated successfully. The stereochemistry of the compounds obtained was determined by means of the IR and ^{13}C NMR spectra. The presence of strong intramolecular hydrogen bonds was detected. The basicities of the compounds obtained were determined.

We have previously proposed methods for the synthesis and investigation of the stereochemistry of 3(5)-hydroxymethyl- [2] and 1- and 3(5)-(2-hydroxyethyl)pyrrolizidines [3]. In the present communication we examine the preparation of 3(5)-(3-hydroxypropyl)pyrrolizidines by catalytic hydrogenation of 5-(3-hydroxypropyl)-1,2-dihydropyrrolizines [4] and the separation of the isomeric pyrrolizidine alcohols and their stereochemistry. As a result of hydrogenation at room temperature on 5% Rh/Al_2O_3, 5-(3-hydroxypropyl)-1,2-dihydropyrrolizine (I) is converted to a mixture of cis- (II) and trans-3,8-H-3-(3-hydroxypropyl)pyrrolozidine (III) in 66% average yield.



The percentages of isomers II and III in the mixture are, respectively, 95 and 5%, and these figures are similar to the ratio of cis and trans isomers obtained as a result of hydrogenation of 5-hydroxymethyl-1,2-dihydropyrrolizine [2] through primarily cis addition of hydrogen. The configurational assignment of epimers II and III was made on the basis of a combination of data obtained by nonspectroscopic methods [17]. In the case of hydrogenation on Raney nickel at 90-115°C we observed an increase in the percentage of one of the isomers from 11 to 91% in the mixture of amino alcohols II and III, and trans configuration III was assigned to it as a consequence of its being the thermodynamically more stable form. As in the case of other 3-hydroxyalkylpyrrolizidines [2, 3], analysis by gas-liquid chromatography (GLC) showed that the epimer with trans configuration III has a shorter retention time than the epimer with cis configuration II.

The catalytic hydrogenation of 3-methyl-5-(3-hydroxypropyl)-1,2-dihydropyrrolizine (IV) gives a mixture of all four possible diastereomers, viz., cis-3,8-H-3-methyl-cis-5,8-H- (V), trans-3,8-H-3-methyl-cis-5,8-H- (VI), cis-3,8-H-3-methyl-trans-5,8-H- (VII), and trans-3,8-H-3-methyl-trans-5,8-H-5-(3-hydroxypropyl)pyrrolizidine (VIII), in 64% average yield.

The percentages of isomers V-VIII in the mixture are, respectively, 59, 24, 5, and 12%. This stereochemical result of the hydrogenation of IV is very similar to the quantitative distribution of the analogous isomeric 3-methyl-5-hydroxymethylpyrrolizidines obtained in the hydrogenation of 3-methyl-5-hydroxymethyl-1,2-dihydropyrrolizine [2].

As a result of the assignments made in analogy with those in [2], configuration V was assigned to the isomer that predominates quantitatively in the catalyzate and has the short-

*See [1] for Communication 19.

N. G. Chernyshevskii Saratov State University, Saratov 410601. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 63-67, January, 1980. Original article submitted July 26, 1978.

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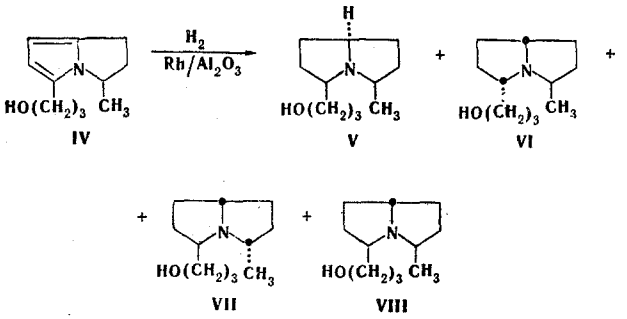
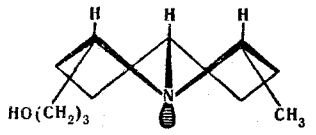


est emergence time during GLC. Since the γ-hydroxypropyl group takes up more space than the methyl group, V, like cis-3,8-H-cis-5,8-H-3,5-dimethylpyrrolizidine (IX) [5], evidently should exist primarily in trans-fused form VA.



VA

In this case, in analogy with IX [6], one should expect that amino alcohol V will have the lowest basicity of all the isomers, and this was observed experimentally. Compound V, being the weakest base, was isolated from the mixture of isomers by incomplete neutralization of the mixture with an acid. The high percentage of trans-fused form VA in the equilibrium mixture of conformations of V was confirmed by data from the IR and ^{13}C NMR spectra. As in the case of the spectrum of primarily trans-fused IX [5], Bohlmann bands are observed in the IR spectrum of V at 2710 (medium), 2760 (shoulder), and 2800 cm^{-1} (strong). The chemical shift of the C_8 atom in the ^{13}C NMR spectrum of isomer V has a value (72.5 ppm) that is typical for strained pyrrolizidines with predominant trans fusion of the rings [7]. It is characteristic that the signal of the C_8 atom in the ^{13}C NMR spectrum of isomer VIII has a value (65.6 ppm) that is normal for primarily cis-fused pyrrolizidines that do not have substituents in the 1 or 7 position [7].

Isomers that have a nitrogen atom with a more shielded electron pair react with alkyl iodides more slowly than other isomers during competitive quaternization of mixtures of isomeric pyrrolizidines [17]. Structure VIII was therefore assigned to the isomer whose relative percentage in solution increases during the reaction of a mixture of isomers VI-VIII with ethyl or methyl iodide.

A trans configuration at the C_3 atom (exo orientation of the methyl group) of VIII is confirmed by the data from the ^{13}C NMR spectrum: the chemical shift of the CH_3 group has a value (21.3 ppm) that is close to the value observed for analogously oriented methyl groups in trans-3,8-H-trans-5,8-H-3,5-dimethylpyrrolizidine (X) [7]. If the methyl group were endo-oriented, as a consequence of the effect of mutual steric compression [8] of the C_5 atoms and the CH_3 group in the γ position, the signal of this group would be found at stronger field, as, e.g., in the case of cis-3,8-H-3-methylpyrrolizidine (17.2 ppm). For the same reasons, the magnitude of the chemical shift of the C_3 atom (61.7 ppm), which is the same as in the case of base X [7], constitutes evidence for the absence of steric interaction between the 5-CH_2 group and the 3-H atom and, consequently, for an exo orientation of the hydroxypropyl group, i.e., a relative trans configuration of the C_5 atom.

The tentative configurational assignment of amino alcohols VII and VI, which emerge as the third and fourth peaks, respectively, during chromatography, was made on the basis of the fact that predominant cis addition of hydrogen, which leads primarily to compounds with a relative cis configuration at the C_8 and C_5 [2, 3], C_6 [9], or C_7 atom [10], is observed in the 1,2-dihydropyrrolizine series under mild conditions. With respect to its quantitative percentage (24%), isomer VI is second after isomer V (59%).

By means of a study of the concentration dependence of the IR sepctra in the region of the stretching vibrations of the hydroxy group [11] we showed that amino alcohols II, III, V, and VIII form an intramolecular hydrogen bond. The high $\Delta\nu_{OH}$ values (457-500 cm^{-1}) indicate considerable strength of the intramolecular hydrogen bonds. This fact is explained,

TABLE 1. 3-(3-Hydroxypropyl)- (II, III) and 3-Methyl-5-(3-hydroxypropyl)pyrrolizidines (V, VIII)

Compound	bp, °C (mm)	n_D^{20}	IR spectrum[a]			Found, %			Empirical formula	Calc., %		
			ν_{OH}, cm^{-1} (ε^a, liters·mole^{-1}·cm^{-1})	ν_{OH}, cm^{-1} (ε^a, liters·mole^{-1}·cm^{-1})	$\Delta\nu_{OH}$, cm^{-1}	C	H	N		C	H	N
II[b]	118—119 (1)	1,5000	3645 (15)	3188 (45)	457	70,9	10,8	8,3	$C_{10}H_{19}NO$	71,0	11,3	8,3
III[c]	102,5 (1)	1,4933	3640 (9)	3145 (28)	495	71,4	11,6	8,2	$C_{10}H_{19}NO$	71,0	11,3	8,3
V[d]	114—115 (2)	1,4931	3635 (17)	3170 (39)	465	71,4	11,4	7,4	$C_{11}H_{21}NO$	72,1	11,6	7,6
VIII[e]	121 (4)	1,4884	3630 (7)	3130 (40)	500	72,0	11,5	7,2	$C_{11}H_{21}NO$	72,1	11,6	7,6

[a]In all cases the concentration was $2\cdot10^{-3}$ mole/liter, and the cuvette length was 5 cm. [b]d_4^{20} 1.0190. Found: MR_D 48.85. Calculated: MR_D 49.44. [c]d_4^{20} 1.0059. Found: MR_D 48.93. Calculated: MR_D 49.44. [d]The isomeric purity was 99%. [e]The isomeric purity was 98%.

on the one hand, by the favorable geometry of the resulting seven-membered ring with a hydrogen bridge [11] and, on the other hand, by the high basicity of the nitrogen atom in the cis-fused pyrrolizidines [6, 12]. To monitor the latter property we determined the basicities of isomers II and III in aqueous solution at 25°C. The pK_a values for these isomers are, respectively, 11.48 ± 0.04 and 11.17 ± 0.05.

Compound V has the highest $\varepsilon^a/\varepsilon^{a'}$ ratio among amino alcohols II, III, V, and VIII [for isomers V and VIII it differs by a factor of more than two (Table 1)]. This difference is evidently due to the weaker basic properties of the nitrogen atom in primarily trans-fused V as compared with amino alcohol VIII. It is known that a decrease in the basicity of the nitrogen atom, other things being equal, causes weakening of a hydrogen bond of the N···HO type [13, 14] and, consequently, an increase in the percentage of free hydroxy groups.

EXPERIMENTAL

The IR spectra of thin layers and CCl_4 solutions (in cuvettes with NaCl windows) of amino alcohols II, III, V, and VIII were recorded with a UR-20 spectrometer. The accuracies in the determination of the maxima of the absorption bands of the stretching vibrations of free and associated hydroxy groups were, respectively, ±2 and ±10 cm^{-1}. The ^{13}C NMR spectra* of V and VIII in 18.8 and 11.6% solutions in benzene were recorded with a Varian CFT-20 spectrometer (20 MHz) under conditions of suppression of the $^{13}C-^{1}H$ spin coupling by noise modulation, under incomplete double resonance conditions, and under pulse accumulation conditions with subsequent Fourier transformation. The resonance conditions were stabilized with respect to the deutermium nuclei in D_2O. The chemical shifts were measured relative to the signal of benzene, and their values with respect to tetramethylsilane (TMS) were found from the formula $\delta(TMS) = 128.53 + \delta(C_6H_6)$. The assignment of the signals was made on the basis of the data in [7] and application of the technique of incomplete $^{13}C-\{^{1}H\}$ double resonance.

Chromatographic analysis of the mixtures of isomers II and III was accomplished with an LKhM-8M chromatograph with a thermal-conductivity detector. Polyethylene glycol 20000 (10%) applied to silanized N-AW-HMDS Chromaton (Chemapol, Czechoslovakia) (0.20-0.25 mm) was used as the stationary phase for filling the steel column (2900 by 3); the column temperature was 191°C, and the carrier-gas (hydrogen) flow rate was 100 ml/min. Mixtures of amino alcohols V-VIII were analyzed with a model 5 LKhM-8MD chromatograph with a flame-ionization detector. Steel columns (2000 by 3), which were filled with 6% polyethylene glycol 20000 on N-AW-HMDS Chromaton (0.125-0.16 mm) or 10% lucoprene on the same support, were used. Isomers V and VIII were partially separated when polyethylene glycol was used as the stationary phase at 201°C and a carrier-gas (argon) flow rate of 60 ml/min, whereas isomers VI and VII were separated completely. Better separation of isomers V and VIII was achieved on lucoprene at 151°C and an argon flow rate of 24 ml/min; however, in this case isomer VII, which was superimposed on the peak of isomer VI and was present in the smallest amounts (∿5%), was not detected. Lucoprene was used for observation of the course of the configurational catalytic isomerization and for monitoring the purity of isomer V.

*The authors thank O. A. Subbotin for recording the ^{13}C NMR spectra.

The pK_a values were determined by potentiometric titration (pH-340 potentiometer). The experimental procedures and methods used to treat the results were similar to those in [12].

3-(3-Hydroxypropyl)pyrrolizidines II and III. A rotary 150-ml autoclave was charged with 9.6 g (57 mmole) of I [4], 67 ml of methanol, and 9.6 g of 5% Rh/Al_2O_3 catalyst [2]. The initial hydrogen pressure was 120 atm. Hydrogenation was carried out at room temperature for 3 h, after which the hydrogenation product was removed from the catalyst by filtration, the solvent was removed by distillation, and the residue was distilled at reduced pressure with collection of the fraction with bp 125°C (1.5 mm). According to the GLC data, the product (6.9 g) contained 97% of a mixture of isomers II and III and 3% starting I. Two more hydrogenation experiments were carried out, and the combined products were purified to remove I by the addition of 10% HCl solution to pH 4-5, during which amino alcohols II and III were tied up in the water-soluble hydrochlorides, while starting I was removed by successive extraction with ether and benzene. Free bases II and III were isolated from the aqueous solution by alkalization (with cooling) with solid KOH up to the saturation point, and the liberated oil was extracted with ether. The extracts were dried with solid KOH, the ether was removed by distillation, and the residue was distilled at reduced pressure to give 16.4 g (56%) of a mixture of isomers II (95%) and III (5%) with bp 120-122°C (1 mm) and n_D^{20} 1.4933. When a more efficient 5% Rh/Al_2O_3 catalyst was used, we were able to hydrogenate I virtually completely to amino alcohols II and III, avoid operations involving purification of the product through the hydrochloride, and obtain the product in up to 81% yields.

cis-3,8-H-3-(3-Hydroxypropyl)pyrrolizidine (II). A total of 4 g of II was isolated from 16.4 g of a mixture of isomers II (95%) and III (5%) by fractional distillation at reduced pressure.

trans-3,8-H-3-(3-Hydroxypropyl)pyrrolizidine (III). A 160-ml rotary autoclave was charged with 8 g of a mixture of isomers II (89%) and III (11%), 16 g of Raney nickel [15], and 25 ml of methanol, and hydrogen was pumped in up to a pressure of 20 atm. The autoclave was heated initially at 90-95°C for 3 h and at 110-115°C for another 4.5 h. A mixture of epimers II (9%) and III (91%), from which 0.7 g of pure amino alcohol III was isolated by means of fractional distillation, was obtained.

3-Methyl-5-(3-hydroxypropyl)pyrrolizidines (V-VIII). These compounds were obtained by hydrogenation of IV [4] and isolation of the mixture of isomers by a method similar to the method described above for the synthesis of pyrrolizidine alcohols II and III. The average yield of the mixture of isomers V-VIII was 64%.

cis-3,8-H-3-Methyl-cis-5,8-H-5-(3-hydroxypropyl)pyrrolizidine (V). A 5.4 N solution of HCl was added with stirring to a solution of 10.6 g of a mixture of isomers V (57%), VI (23%), VII (7%), and VIII (13%) in 50 ml of ether until isomers VI-VIII vanished in the ether solution, according to the GLC data (7.7 ml of acid was required for this). The ether layer was separated, and the aqueous solution was saturated with potassium chloride and extracted with ether. The extracts were combined with the separated ether layer and dried with solid KOH, the solvent was removed by distillation, and the residue was distilled at reduced pressure to give 2 g (33%) of amino alcohol V. ^{13}C NMR spectrum* (multiplicity of the signal in the incomplete $^{13}C-\{^1H\}$ double resonance spectrum) (ppm): *26.2* t, *25.7* t (C_1, C_7); *38.5* t, *34.8* t (C_2, C_6); 55.9 d (C_3); 59.5 d (C_5); 72.5 d (C_8); 21.4 q (CH_3); 62.4 t (OCH_2) [16].

Catalytic Isomerization of a Mixture of Amino Alcohols V-VIII. A solution of 7.3 g of a mixture of isomers V (32%), VI + VII (55%), and VIII (13%) in 25 ml of methanol and 15 g of Raney nickel were sealed in a 120-ml glass ampul, and the contents were shaken periodically (with caution to prevent breaking of the ampul) and heated on a boiling-water bath for 11 h. The catalyst was removed by filtration, the solvent was removed by distillation, and the residual mixture (5.7 g) of isomers V (0.5%), VI + VII (45%), and VIII (54.5%) was used for the subsequent isolation of VIII.

trans-3,8-H-3-Methyl-trans-5,8-H-5-(3-hydroxypropyl)pyrrolizidine (VIII). A 3-g (16 mmole) sample of the mixture of isomers V-VIII prepared as a result of isomerization was dissolved in 30 ml of ether, and 11.6 g (82 mmole) of methyl iodide was added to the solution. The course of the reaction was monitored by chromatography. Virtually only amino alcohol

*The tentative assignment of the individual pairs of signals is given in italics here and in the description of the spectrum of VIII.

VIII remained in solution after 45 min. The precipitate was separated rapidly, 4 ml of water was added to the ether solution, and the mixture was acidified to pH 1-2 with 18% HCl. The aqueous layer was separated and saturated with solid KOH, and the liberated base was extracted with ether. The extract was then worked up in the usual way. The experiment was repeated, and 1 g of VIII was ultimately obtained. ^{13}C NMR spectrum (multiplicity of the signal in the incomplete $^{13}C-\{^1H\}$ double resonance spectrum) (ppm): 32.5 t, 32.1 t (C_1, C_7); 34.7 t, 34.1 t (C_2, C_6); 61.7 d (C_3); 64.5 d (C_5); 65.6 d (C_8); 21.3 q (CH_3); 63.1 t (OCH_2).

LITERATURE CITED

1. I. M. Skvortsov and I. V. Antipova, Khim. Geterotsikl. Soedin., No. 1, 58 (1979).
2. I. M. Skvortsov and S. A. Kolesnikov, Khim. Geterotsikl. Soedin., No. 4, 484 (1976).
3. I. M. Skvortsov and V. M. Levin, Khim. Geterotsikl. Soedin., No. 7, 947 (1973).
4. I. M. Skvortsov, L. N. Astakhova, S. N. Kuz'min, and I. Ya. Evtushenko, Khim. Geterotsikl. Soedin., No. 3, 359 (1978).
5. Yu. A. Pentin, I. M. Skvortsov, and I. A. Antipova, Dokl. Akad. Nauk SSSR, 230, 617 (1976).
6. I. V. Antipova and I. M. Skvortsov, in: Research on the Synthesis and Catalysis of Organic Compounds [in Russian], Saratov (1975), p. 31.
7. I. M. Skvortsov and O. A. Subbotin, Zh. Org. Khim., 13, 466 (1977).
8. J. B. Grutzner, M. Jautelat, J. B. Dence, R. A. Smith, and J. D. Roberts, J. Am. Chem. Soc., 92, 7107 (1970).
9. J. Schnekenburger and H. Vollhardt, Arch. Pharm., 310, 186 (1977).
10. M. T. Pizzorno and S. M. Albonico, J. Org. Chem., 39, 731 (1974).
11. M. Tichý, Adv. Org. Chem., 5, 115 (1965).
12. I. M. Skvortsov and I. V. Antipova, Khim. Geterotsikl. Soedin., No. 8, 1060 (1976).
13. P. J. Krueger and H. D. Mettee, Can. J. Chem., 43, 2970 (1965).
14. M. Tamres, S. Searles, E. M. Leighly, and D. W. Mohrman, J. Am. Chem. Soc., 76, 3983 (1954).
15. A. N. Kost (ed.), General Laboratory Manual of Organic Chemistry [Russian translation], Mir, Moscow (1965), p. 615.
16. J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reich, J. Am. Chem. Soc., 92, 1338 (1970).
17. I. M. Skvortsov, V. M. Levin, S. A. Kolesnikov, and I. V. Antipova, in: Problems in Stereochemistry [in Russian], Vol. 3, Kiev (1973), p. 27.