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SATURATED NITROGENOUS HETEROCYCLES.

10.* SYNTHESIS AND EXAMINATION OF THE STEREOISOMERS OF 3-(5-ALKYL-2-PYRROLIDYL)ALKANOLS

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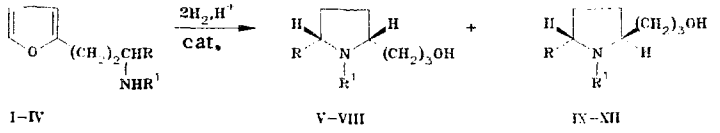
UDC 547.743,1'722:542.97:541.634

Methods have been developed for the synthesis of cis- and trans-3-(5-alkyl-2-pyrrolidyl)alkanols. The catalyst isomerization of the stereoisomers has been studied, and configurational assignments of the isomers made on the basis of x-ray structural examinations, NMR spectroscopy, and comparison of physicochemical properties. A relationship has been found between the more characteristic signals in the NMR spectra of the pyrrolidylalkanols and their spatial structures.

It has been previously reported that alkylated pyrrolidylalkanols, which are of interest for the synthesis of biologically active compounds, can be obtained by the stereochemically directed catalytic hydrogenation of the appropriate amines of the furan series in acidic media. X-ray structural analysis has shown that in the case of 5-methylpyrrolidylalkanols the principal isomer possesses the cis-configuration [1].

When the catalyst employed is nickel promoted by ruthenium [2], the formation of pyrrolidylalkanols is less stereospecific, and when an alkyl substituent is present in the 3-position of the side chain in the original amines, in addition to the cis-pyrrolidylalkanols (V-VIII), there are formed in yields up to 35% the lower-boiling trans-pyrrolidylalkanols (IX-XII).



I-IV V-VIII IX-XII

I, V, IX R=CH_3, R^1=H; II, VI, X R=R^1=CH_3; III, VII, XI R=i-C_4H_9, R^1=H; IV, VIII, XII R=i-C_4H_9, R^1=CH_3

When the reaction is carried out at 60°C under a hydrogen pressure of 60-70 atm, the ratio of the cis- and trans-isomers in the catalyzate is, according to GLC, the same throughout the reaction. At a temperature of 100°C, reversible catalytic isomerization begins, with the establishment of a constant ratio of cis- and trans-isomers, the latter predominating. The composition of the mixtures obtained is independent of temperature over the range 100-120°C. At higher temperatures, partial resinification occurs. The same ratio of isomers is established within 7-8 h in randomly selected samples, enriched in one or other of the isomers, when kept under the isomerization conditions.

*For Communication 9, see [1].

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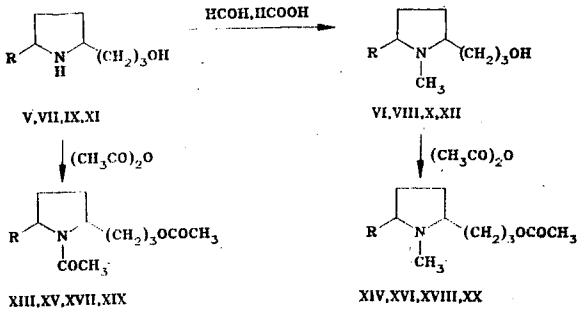
0009-3122/84/2012-1357$08.50

When hydrogenation was carried out at 100°C, instead of the expected mixture of pyrrolidylalkanols enriched in the trans-isomers, the main reaction products were the tetrahydrofuran amine starting materials [3].

Thus, for the preparative synthesis of the cis-isomers it is desirable to carry out the reaction at 60°C, and of the trans-isomers, to maintain the hydrogenation mixture at 100-120°C for 7-10 h after the end of the reaction.

Isomerization occurs only under hydrogen pressure. In the presence of nitrogen or air, degradation of both the cis- and trans-isomers occurs with the formation of low-boiling products of unknown structure. In the absence of a catalyst, the pyrrolidylalkanols are stable on heating in nitrogen or air as well as hydrogen. These findings are in accordance with known behavior on catalytic isomerization [4].



XIII, XIV —cis , R=CH_3; XV, XVI — cis, R=i-C_4H_9; XVII, XVIII — trans, R=CH_3; XIX, XX — trans, R=i-C_4H_9

The N-methylpyrrolidylalkanols (VI), (VIII), (X), and (XII) were obtained directly by methylation with formaldehyde in the presence of formic acid of the appropriate N-unsubstituted pyrrolidylalkanols.

Reaction of the alcohols (V-XII) with acetic anhydride gave 80-90% yields of the acetates and N-acylacetates (XIII-XX).

The IR spectra of (V-XII) show strong absorption at 3400-3200 cm^{-1}, with maxima at 3360-3390 cm^{-1}, characteristic of stretching vibrations of the associated OH group, together with other bands characteristic of OH vibrations (1310, 1265, and 1080 cm^{-1}). The spectra of VI, VIII, X, XII, XIV, XVI, XVIII, XX contain a narrow band at 2780 cm^{-1} [$\nu CH_3(N)$]. Characteristic of (XIII-XX) is strong absorption at 1720-1730 and 1250-1230 cm^{-1} (ester C=O). In the spectra of the N-acylacetates (XIII), (XV), (XVII), and (XIX), in addition to ester group absorption, there was strong absorption at 1670-1630 cm^{-1} (C=O in tertiary amides).

The cis-configuration of the pyrrolidylalkanols (V) and (VI) was established by x-ray structural analysis of the dihydrate of the acid tartrate of (VI), and by the chemical conversion V→VI [1]. The pyrrolidylalkanols (IX) and (X) have the same chemical structure as (V) and (VI), but they differ from the latter in their physical properties, and are therefore the trans-isomers.

The pyrrolidine alcohols (V-VIII) possess higher boiling points and refractive indices than the isomers (IX-XII).

From a comparison of the physical constants of the compounds obtained (Table 1), we have made a tentative assignment of the pyrrolidylalkanols (VII) and (VIII) as the cis-, and (XI) and (XII) as the trans-isomers. The results are in agreement with the Auwers—Skita rule, according to which in uncharged five-membered rings the trans-isomers boil at lower temperatures, and have lower refractive indices than the corresponding cis-compounds.

We have found that the trans-isomers are more weakly hydrogen-bonded than the cis-isomers [5], and have lower retention times on a variety of sorbents used in GLC (Table 1).

One of the most characteristic features of the ^{13}C NMR spectra is the signal for the carbon of the CH_2OH group, the chemical shift of which is highly dependent on the steric structure of (V) and (VII-XII). Thus, in the cis-isomers this signal occurs at higher field (61-62 ppm), indicating steric deformation in the cis-isomers [6], and for the corresponding trans-isomers at 67-68 ppm, the position of this signal in both geometrical forms being largely independent of the presence of substituents either on the nitrogen atom, or at $C_{(5)}$ of the pyrrolidine ring.

TABLE 1. Stereoisomeric 3-(5-Alkyl-2-pyrrolidyl)propanols

Compound	Bp (mp), °C (pressure, hPa)	n_D^{20}	GLC; retention time, min		Found, %			Empirical formula	Calculated, %		
			Apiezon	SE-30	C	H	N		C	H	N
V	116—117 [20—21] (9,3)	1,4750	21,0	18,8	67,2	12,3	9,5	$C_8H_{17}NO$	67,2	12,0	9,7
IX	91—92 (6,7)	1,4558	10,5	8,2	67,1	12,1	9,6	$C_8H_{17}NO$	67,2	12,0	9,7
VI	113 (8)	1,4680	18,0	10,5	68,3	12,2	8,9	$C_9H_{19}NO$	68,8	12,1	8,9
X	98 (4)	1,4508	12,2	6,5	68,4	12,2	8,8	$C_9H_{19}NO$	68,8	12,1	8,9
VII	160—162 [32] (21,3)	1,4689	22,5	17,5	71,2	12,6	7,5	$C_{11}H_{23}NO$	71,3	12,5	7,6
XI	116—118 (6,7)	1,4538	12,8	11,0	71,6	12,3	7,6	$C_{11}H_{23}NO$	71,3	12,5	7,7
VIII*	114—116 (4)	1,4679	19,5	9,2	72,5	12,7	7,5	$C_{12}H_{25}NO$	72,4	12,6	7,0
XII†	133—135 (16)	1,4509	16,2	8,0	72,3	12,5	7,0	$C_{12}H_{25}NO$	72,4	12,6	7,0

*PMR spectrum: δ 0.81 (3H, d, CH_3), 0.85 (3H, d, CH_3), 2.20 (3H, s, CH_3—N), 2.12 (1H, m, 5-H), 2.30 (1H, m, 2-H), 3.52 ppm (2H, m, CH_2—O).

†PMR spectrum: δ 0.81 (6H, d, $2CH_3$), 2.14 (3H, s, CH_3—N), 2.12 (1H, m, 5-H), 2.20 (1H, m, 2-H), 3.67 ppm (2H, m, CH_2—O).

In the PMR spectra of the N-methylpyrrolidylalkanols, the signals for the methylene protons of the CH_2OH group occur as a multiplet at 3.52-3.67 ppm. It is likely that owing to the presence of strong intramolecular hydrogen bonding exchange of the OH group protons is slow, and the signal for the CH_2OH protons is split both as a result of interaction with the protons of neighboring CH_2 groups, and with the OH protons.

The PMR spectrum of the cis-isomer of (VIII) differs from that of the trans-isomer in the type of absorption of the methyl groups in the isobutyl radical. In the spectrum of cis-(VIII), each methyl groups is split by the methine proton into a doublet (J = 6.0 Hz). In the spectrum of the trans-isomer, a single doublet (J = 6.3 Hz) is observed in the region of absorption of $(CH_3)_2CH$.

EXPERIMENTAL

IR spectra were obtained on a UR-20 instrument as suspensions in vaseline oil and hexachlorobutadiene in the case of crystalline solids, and in thin layers for liquids. PMR spectra were obtained on a Varian XL-100 spectrometer in solution in $CDCl_3$ or CCl_4. ^{13}C NMR spectra were measured on a Varian FT-80 A (20 MHz) spectrometer in $CDCl_3$, in the impulse accumulation mode followed by Fourier transformation. GLC analyses were carried out on an LKhM-8MD chromatograph with a flame ionization detector, 3.6 m × 0.6 cm column, sorbent Inzensk brick TND-TS-M, modified with 2% KOH and soaked in 15% Apiezon L; 1 m × 0.3 cm column, sorbent Cellite C, treated with 15% of SE-30, temperture 140-250°C, carrier gas (argon) flow rate 1.2 liter/h.

3-(2-Phrrolidyl)propanol (XXI) and 3-(1-methyl-2-pyrrolidyl)propanol (XXII) were obtained as described in [3].

trans-3-(5-Isobutyl-2-pyrrolidyl)propanol (VII). In a rotary autoclave of 250 ml capacity was placed 20 g (0.1 mole) of the amine (III), and diluted (1:3) hydrochloric acid was added to bring the pH to 4, followed by 2 g of Ni/Ru. The initial hydrogen pressure was 60 atom, and temperature 60-70°C. When the calculated amount of hdyrogen has been absorbed (5.5 liter), the catalyst was filtered off and the filtrate neutralized with an excess of solid NaOH. The oil which separated was isolated, and the aqueous layer extracted with ether. The ether extracts were combined with the oil, and dried over solid KOH. The ether was distilled off. According to GLC, the hydrogenation product contained 50% of isomer (VII) and 36% of isomer (XI). On distillation *in vacuo*, 6.4 g (32%) of (XI) was collected over the temperature range 116-118°C (6.7 hPa). The aminoalcohol (VII) (4.3 g, 23%) distilled over at 160-162°C (21.3 hPa).

Similarly obtained were the trans-pyrrolidylpropanols (IX), (X), and (XII), and the cis-pyrrolidylpropanols (V), (VI), and (VIII).

Catalytic Isomerization of 3-(5-Isobutyl-2-pyrrolidyl)propanols. A. In an autoclave was placed 20 g (0.1 mole) of the amine (III), and the pH was brought to 4 with diluted (1:3) hydrochloric acid, followed by the addition of 2 g of Ni/Ru. The initial hydrogen pressure was 60 atm, and the temperature 60-70°C. After absorption of the calculated amount of hydro-

gen over a period of 10 h, the hydrogenation products, according to GLC, contained 50% of the cis-isomer (VII) and 36% of the trans-isomer (XI). The remaining 14% consisted of impurities of unknown structure. The temperature was raised to 100°C, whereupon after 1 h, according to GLC, the mixture contained 40% of the cis-isomer and 46% of the trans-isomer.

B. An autoclave was charged with a prepared mixture of isomers of 3-(5-isobutyl-2-pyrrolidyl)propanol, containing 75% of the cis and 25% of the trans-isomer. Dilute hydrochloric acid (1:3) was added to bring the pH to 4, followed by 2 g of Ni/Ru. The hydrogen pressure was 60 atm, temperature 100°C. According to GLC, after 7 h the mixture contained 50 ± 2% of the trans-isomer, after 10 h 40 ± 2% cis and 60 ± 2% trans, and after 14 h the composition of the mixture was unchanged.

C. An autoclave was charged with a mixture of isomers of 3-(5-isobutyl-2-pyrrolidyl)propanol containing 17% of the cis-isomer (VII) and 83% of the trans-isomer (XI). Dilute (1:3) hydrochloric acid was added to bring the pH to 4, followed by 2 g of Ni/Ru. The hydrogen pressure was 60 atm, and the temperature 100°C. After 14 h, the composition of the mixture remained constant at 40 ± 2% of the cis-isomer (VII), and 60 ± 2% of the trans-isomer.

3-(5-Alkyl-2-pyrrolidyl)propanols (VI), (VIII), (X), and (XII) were obtained by direct synthesis by methylation with formalin and formic acid of the 3-(5-alkyl-2-pyrrolidyl)propanols (V), (VII), (IX), and (XI), as described in [7].

The acetyl derivatives (XIII)-(XX) were obtained as described in [3].

cis-3-(1-Acetyl-5-methyl-2-pyrrolidyl)propyl Acetate (XIII). Bp 201-203°C (6.6 hPa); n_D^{20} 1.4716. Found: C 63.3; H 9.4; N 6.2%. $C_{12}H_{21}NO_3$. Calculated: C 63.4; H 9.3; N 6.1%.

cis-3-(1-Acetyl-5-isobutyl-2-pyrrolidyl)propyl Acetate (XV). Bp 174-175°C (6.6 hPa); n_D^{20} 1.4705. Found: C 67.3; H 10.4; N 5.7%. $C_{15}H_{27}NO_3$. Calculated: C 67.0; H 10.0; N 5.2%.

trans-3-(1-Acetyl-5-methyl-2-pyrrolidyl)propyl Acetate (XVII). Bp 178-179°C (2.7 hPa); n_D^{20} 1.4689. Found: C 63.8; H 9.6; N 6.3%. $C_{12}H_{21}NO_3$. Calculated: C 63.4; H 9.3; N 6.1%.

trans-3-(5-Isobutyl-1-methyl-2-pyrrolidyl)propyl Acetate (XX). Bp 118-119°C (9.3 hPa); n_D^{20} 1.4470. Found: C 72.4; H 11.6; N 6.0%. $C_{14}H_{27}NO_2$. Calculated: C 72.7; H 11.6; N 6.0%.

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