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SATURATED NITROGEN HETEROCYCLES.

11.* CATALYTIC SYNTHESIS OF 2-PYRROLIDYLALKANOLS

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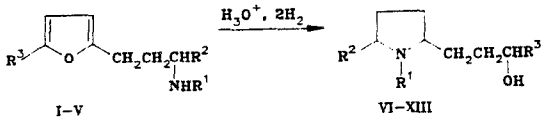
UDC 547.741'722:542.97

Furylakylamines have been catalytically converted into novel isomers of 2-pyrrrolidylalkanols bearing a secondary alcohol group in the aliphatic chain, or a tert-butyl group attached to the heterocycle.

Continuing studies of the conversion of furylakylamines into pyrrolidylalkanols by hydrogenation in acid media in the presence of ruthenium-promoted nickel [1], preparative methods have been developed for obtaining secondary pyrrolidylalkanols and primary alcohols containing the bulky tert-butyl radical in the 5-position of the pyrrolidine ring.



I–V VI–XIII

I, VI $R^1=R^2=H$, $R^3=CH_3$; II, VII $R^1=R^3=CH_3$, $R^2=H$; III, VIII (trans), IX (cis) $R^1=H$, $R^2=R^3=CH_3$; IV, X (trans), XI (cis) $R^1=R^2=R^3=CH_3$; V, XII (trans), XIII (cis) $R^1=R^3=H$; $R^2=t\text{-}C_4H_9$

Alcohols (VI-XIII) were obtained in acidic solution (pH 4) in the presence of skeletal nickel containing 1% of ruthenium, with an initial hydrogen pressure of 50-60 atm [2].

The presence of a methyl group in the 5-position of the furan ring reduces the rate of the reaction, so that the hydrogenation of amines (I-IV) was carried out at 70-80°C, i.e., 10-20°C higher than the other amines [1].

In the case of starting compounds (III-V), which contain an alkyl substituent in the 3-position of the side chain, both the cis- and trans-isomers are obtained, in accordance

*For Communication 10, see [1].

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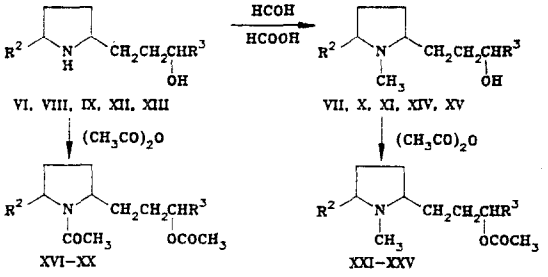
 0009-3122/88/2408-0870$12.50

with previously obtained information on the catalyzed hydrogenation of furylalkylamines [1]. With amines (III) and (IV), the hydrogenate contained predominantly the cis-pyrrolidinols, according to GC. The hydrogenation of (V) resulted in the preferential formation of the trans-isomer (XII) (53-55%), apparently as a result of the presence of the bulky tert-butyl substituent adjacent to the nitrogen atom involved in cyclization [3].

The use of ruthenium-promoted nickel enabled the yield of 4-(5-methyl-2-pyrrolidyl)butan-2-ol to be increased from 12% [3] to 50% (overall yield cis- and trans- isomers). As in the method employed in [3], in the present case small amounts (up to 8%) of the corresponding aminodiol were formed.

N-Methylpyrrolidylalkanols (VII), (X), and (XI) were obtained by hydrogenating the appropriate N-methylfurylamines, or by direct synthesis by methylating the nitrogen-unsubstituted pyrrolidylalkanols with formaldehyde in the presence of formic acid. Alcohols (XIV) and (XV) were obtained by methylating (XII) and (XIII), respectively.

The structures of the alcohols (VI-XV) were established by their conversion into the acetyl derivatives (XVI-XXV).



XIV, XIX, XXIV (trans), XV, XX, XXV (cis) R^2=*t*-C_4H_9, R^3=H; XVI, XXI R^2=H, R^3=CH_3; XVII, XXII (trans), XVIII, XIII (cis) R^2=R^3=CH_3

The pure isomers (VIII-XI) were isolated from the hydrogenate by vacuum fractionation, with a chromatographic purity of 96-99%.

In the case of (5-tert-butyl-2-pyrrolidyl)propanols (XII) and (XIII), fractionation gave a mixture enriched in the cis- or trans- forms. The trans-isomers always contained as impurity the difficultly separable tetrahydrofurylamines. The pure compounds were obtained by fractional crystallization of the tartrates as described in [4], from fractions enriched in the trans-isomer. Configurational assignment of the isomers was made by comparison of their physicochemical properties (Tables 1 and 2) and spectral characteristics with those of known stereoisomers, using previously established criteria [1, 5]. The cis-pyrrolidine alcohols (IX, XI, XIII, XV) have higher boiling points and refractive indices, and longer retention times on various sorbents used in GC than the trans-compounds (VIII, X, XII, XIV).

In the IR spectra of alcohols (VI-XV), strong absorption is seen at 3600-3200 cm^{-1} with maxima at 3320-3400 cm^{-1}, together with other bands (1310, 1260, 1075, and 950 cm^{-1}) characteristic of hydroxyl group vibrations. In the spectra of (VII), (X), (XI), (XIV), and (XV), narrow absorption is seen at 2790-2780 cm^{-1} ($\nu_{CH_3N<}$). The presence of the tert-butyl radical in (XII-XIV), (XIX-XX), and (XXIV-XXVI) is shown by a doublet at 1395-1365 cm^{-1} (δ_{CH_3}) with an intensity ratio of 1:2. In the case of compounds (XXI-XXV), strong absorption is present at 1740-1720 cm^{-1} and 1250-1235 cm^{-1} (ester $\nu_{C=O}$), and in the N-acylacetates (XVI-XX), in addition to ester group absorption, strong absorption is present at 1680-1640 cm^{-1} (tertiary amide $\nu_{C=O}$).

One of the most characteristic signals in the ^{13}C NMR spectrum of the 2-pyrrolidylalkanols is that for the CH_2OH carbon atom, the chemical shift of which is highly dependent on the steric structure of the molecule [1]. In the spectra of the secondary alcohols (VI-XI), the signal for the carbon atom bound to the hydroxyl group is shifted to lower field by 4-6 ppm by the α-effect, as compared with the similar carbon atoms in primary alcohols. A similar difference in chemical shifts persists in the acetyl derivatives (XVI),(XVII), and (XXI-XXIII).

The splitting of the signals in the ^{13}C NMR spectra of the alcohols (VI-XI) shows that the latter exist in the erythro- and threo- forms, which we were unable to separate in consequence of the closeness of their physical properties.

TABLE 1. Properties of Compounds Obtained

Compound	bp, °C (pressure, hPa)	n_D^{20}	Found, %			Empirical formula	Calculated, %			Yield, %
			C	H	N		C	H	N	
VI	105...106 (5,3) [30...32]	—	67,0	11,9	9,9	$C_8H_{17}NO$	67,1	11,9	9,8	35
VII	84...85 (6,6)	1,4624	68,9	12,0	8,8	$C_9H_{19}NO$	68,8	12,1	8,9	42
VIII	96...97 (8)	1,4555	68,7	12,2	8,8	$C_9H_{19}NO$	68,8	12,1	8,9	25
IX	115...116 (9,3) [43...44]*	1,4648**	68,6	12,0	8,7	$C_9H_{19}NO$	68,8	12,1	8,9	35
X	96...97 (5,3)	1,4502	70,3	12,3	8,3	$C_{10}H_{21}NO$	70,2	12,3	8,2	28
XI	100...101 (5,3)	1,4585	70,2	12,3	8,1	$C_{10}H_{21}NO$	70,2	12,3	8,2	37
XII	95...96 (13)	1,4570	71,3	12,4	7,9	$C_{11}H_{23}NO$	71,4	12,4	7,6	38
XIII	115...116 (13)	1,4682	71,3	12,1	7,8	$C_{11}H_{23}NO$	71,4	12,4	7,6	23
XIV	114...115 (13)	1,4532	72,1	12,3	7,2	$C_{12}H_{25}NO$	72,4	12,6	7,0	70
XV	88...89 (7)	1,4635	72,0	12,2	7,2	$C_{12}H_{25}NO$	72,4	12,6	7,0	13
XVI	158...159 (5,3)	1,4716	63,4	9,2	6,2	$C_{12}H_{21}NO_3$	63,4	9,3	6,2	82
XVII	170...171 (4)	1,4670	64,6	9,7	5,8	$C_{13}H_{23}NO_3$	64,7	9,5	5,8	86
XVIII	168...169 (2,6)	1,4710	64,8	9,4	5,9	$C_{13}H_{23}NO_3$	64,7	9,5	5,8	92
XIX	155 (13)	1,4635	66,8	9,9	5,4	$C_{15}H_{27}NO_3$	66,9	10,0	5,2	88
XX	159 (11)	1,4743	66,5	9,9	5,6	$C_{15}H_{27}NO_3$	66,9	10,0	5,2	76
XXI	89...90 (6,6)	1,4540	66,2	10,5	7,0	$C_{11}H_{21}NO_2$	66,3	10,6	7,0	80
XXII	115...116 (12)	1,4460	67,5	10,8	6,5	$C_{12}H_{23}NO_2$	67,6	10,8	6,6	84
XXIII	112...113 (6,6)	1,4530	67,7	10,4	6,6	$C_{12}H_{23}NO_2$	67,6	10,8	6,6	79
XXIV	129...130 (21)	1,4508	69,4	11,0	6,0	$C_{14}H_{27}NO_2$	69,7	11,2	5,8	80
XXV	134...135 (21)	1,4542	69,5	11,0	5,6	$C_{14}H_{27}NO_2$	69,7	11,2	5,8	82

*According to [6], bp 109-111°C (5 mm), mp 43-45°C.
**For the supercooled liquid.

TABLE 2. ^{13}C NMR Spectra of Pyrrolidylalkanols

Compound	Chemical shifts, δ, ppm									
	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	$C_{(7)}$	$C_{(8)}$	R^1	R^2	R^3
VI	59,42	32,80	25,35	46,09	32,10	37,40	66,85	—	—	23,61
	58,90	32,10		46,01	31,51	36,73	66,37			23,50
VII	65,86	29,81	21,10	56,36	28,96	35,31	66,86	39,51	—	23,02
	65,24	29,34			28,62	35,07	66,24	39,01		
IX	59,88	33,12	33,27	54,64	32,10	37,18	67,04	—	21,12	23,58
	59,07	32,58	33,22	54,39	30,94	36,34	66,79		21,01	
XI	67,85	29,82	31,42	62,73	26,51	35,49	66,72	38,67	19,07	23,97
	67,26	29,30	31,26	62,57	25,77	34,85	66,31	38,05	18,58	23,60
XIII	58,98	33,29	25,96	68,66	31,40	30,22	62,20	—	26,52 (CH_3)	—
									34,51 (C)	
XV	68,54	29,85	25,85	76,71	31,20	28,69	63,01	44,65	27,12 (CH_3)	—
									35,25 (C)	

EXPERIMENTAL

IR spectra were obtained on a UR-20 instrument, for solids as a paste in vaseline oil and hexachlorobutadiene, and for liquids in thin films. ^{13}C NMR spectra were recorded on a Varian FT-80A spectrometer (20 MHz) in $CDCl_3$ in pulse accumulation mode followed by Fourier transmission. GC analyses were carried out on an LKhM-8MD chromatograph with a flame ionization detector, column 1.0 × 0.3 m, sorbent Inzensk brick TMD-TS-M modified with 2% KOH and soaked in 15% Apiezon L, temperature 140-150°C, carried gas (argon) flow rate 1.2 liter/h.

The (2-furyl)alkylamines (I-IV) were obtained as described in [3].

1-(2-Furyl)-4,4-dimethyl-3-aminopentane (V). In a steel rotary autoclave of 610 ml capacity were placed 32 g (0.17 mole) of α-furfurylidenepinacoline, 180 ml of methanol saturated with ammonia at 0°C, and 4 g of skeletal nickel. The initial hydrogen pressure was 100 atm, and the temperature 110-120°C. When uptake of hydrogen had ceased (5 h), a further 2 g of skeletal nickel and 80 ml of methanol saturated with ammonia at 0°C were added, and hydroamination continued for 6 h. The hydrogenate was worked up as described in [3]. Vacuum distillation gave 13 g (39%) of (V), bp 108°C (13.13 hPa), n_D^{20} 1.4750. Found: C 72.7; H 10.4; N 7.9%. $C_{11}H_{19}NO$. Calculated: C 72.9; H 10.5; N 7.7%.

4-(trans-5-Methyl-2-pyrrolidyl)butan-2-ol (VIII) and 4-(cis-5-Methyl-2-pyrrolidinyl)-butan-2-ol (IX). A solution containing 15 g (0.1 mole) of 1-(5-methyl-2-furyl)-3-aminobutane (III), 40 ml of dilute hydrochloric acid (pH 4.0), and 2 g of skeletal nickel/1% Ru was hydrogenated in a steel rotary autoclave of 250 ml capacity at 80°C, initial hydrogen pressure 50 atm. When uptake of hydrogen had ceased (25 atm), the hydrogenate was worked up as described in [2]. Vacuum distillation gave 3.75 g (25%) of (VIII), GC (min) 0.4, 5.25 g (35%) of (IX), GC (min 1.0, and 1.2 g (8%) of aminononane-5,8-diol, bp 146°C (2.7 hPa), n_D^{20} 1.4804 [3].

4-(2-Pyrrolidinyl)butan-2-ol (VI), 4-(1-methyl-2-pyrrolidyl)butan-2-ol (VII), 4-(trans-1,5-dimethyl-2-pyrrolidyl)butan-2-ol (X), and 4-(cis-1,5-dimethyl-2-pyrrolidyl)butan-2-ol (XI) were obtained similarly.

3-(trans-5-tert-Butyl-2-pyrrolidyl)propan-1-ol (XIII). A solution containing 18 g (0.1 mole) of the amine (V), 45 ml of dilute (1:2) hydrochloric acid (pH 4.0), and 2 g of skeletal Ni/1% Ru was hydrogenated in a rotary steel autoclave of 250 ml capacity with an initial hydrogen pressure of 50 atm at 60-70°C. Uptake of hydrogen (27 atm) was complete in 5 h. Vacuum distillation gave 11 g (62%) of a fraction containing 76% of the trans-isomer (XII) and 6.6 g (32%) of a fraction containing 70% the cis-isomer (XIII). To the first mixture was added a solution of 9 g of (+)-tartaric acid in 20 ml of absolute ethanol, and the (XII) tartrate crystallized out as in [4], yield 10 g (65%), mp 121°C. Found: C 53.3; H 8.7; N 4.4%. $C_{11}H_{23}NO \cdot C_4H_6O_6$. Calculated: C 53.7; H 8.6; N 4.1%. Treatment of the tartrate with alkali gave 6.8 g (38%) of the trans-isomer (XII), GC (min) 0.5, purity 97%. Addition of alkali to the mother liquor gave the cis-isomer (XIII), yield 4.1 g (23%), GC (min) 1.5, purity 95%.

(1-Methyl-2-pyrrolidyl)propan-1-ols (XIV) and (XV) were obtained by methylating (XII) and (XIII), respectively, with formalin and formic acid, as described in [6]. Acetates (XXI-XXV) and N-acylacetates (XVI-XX) were obtained as in [3].

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