SATURATED NITROGEN-CONTAINING HETEROCYCLES

III*. CATALYTIC SYNTHESIS OF PYRROLIDINYLALKAN-3-OLS AND CYCLOALKANOPYRROLIDINYLALKAN-3-OLS AND THEIR REACTIONS

A. A. Ponomarev, A. P. Kriven'ko,
and M. V. Noritsina

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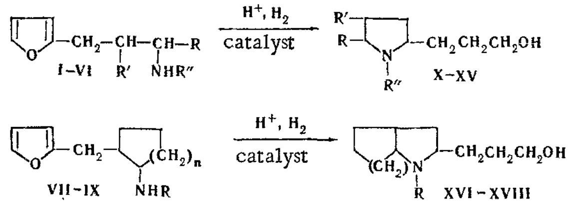
The method for the preparation of hydroxyalkyl derivatives of pyrrolidine and cycloalkanopyrrolidines developed previously has been improved by the replacement of the Raney nickel catalyst by Raney cobalt or partially deactivated palladized carbon. The synthesis of N-methylpyrrolidinylpropanols and cyclopentano[b]pyrrolidinylpropanols and their esterification with some aromatic acids have been performed.

We have previously reported a new method for synthesizing pyrrolidine and cyclo-alkanopyrrolidine alcohols by the hydrogenation of furan amines in the presence of Raney nickel catalyst [1-3]. The yields of heterocyclic alcohols varied from 18 to 70% according to the structure of the initial amine, the lowest yield (18-32%) being found in the case of furan amines with an unbranched side chain. A by-product of the reaction was the corresponding tetrahydrofuran amine.

In order to increase the yields of alcohols of the type mentioned above, studies have been made of new catalysts for this reaction. The best results have been achieved by using Raney cobalt and palladized carbon containing 10% of metallic palladium partially deactivated by the action of air. These catalysts are less effective than Raney nickel in the hydrogenation of the multiple bonds of the furan ring and thereby lead to its more complete hydrolytic cleavage, i.e., in the final account, to an increase in the yields of the desired products.

Primary and secondary furan amines with the amino group in an aliphatic side chain or in an alicycle were subjected to hydrogenation.



I R = R′ = R″ = H; II R = R′ = H, R″ = CH$_3$; III R = CH$_3$, R′ = R″ = H; IV R = i-C$_4$H$_9$, R′ = R″ = H; V R = R″ = H, R′ = C$_2$H$_5$; VI R = R″ = H, R′ = i-C$_3$H$_7$; VII n = 1, R = H; VIII n = 1, R = CH$_3$; IX n = 2, R = H; X R = R′ = R″ = H; XI R = R′ = H, R″ = CH$_3$; XII R = CH$_3$, R′ = R″ = H; XIII R = i-C$_4$H$_9$, R′ = R″ = H; XIV R = R″ = H, R′ = C$_2$H$_5$; XV R = R″ = H, R′ = i-C$_3$H$_7$; XVI n = 1, R = H; XVII n = 1, R = CH$_3$; XVIII n = 2, R = H

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*For Communication II, see [3].

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TABLE 1. Yields of Pyrrolidine and Cycloalkanopyrrolidine Alcohols on Various Catalysts

Compound	Obtained from	Yield, %		
		Raney Ni	Raney Co	palladium on carbon
X	I	18	—	53
XI	II	21	40	—
XII	III	20	43	47
XIII	IV	29	—	56
XIV	V	30	—	61
XV	VI	46	—	60
XVI	VII	10	32	—
XVII	VIII	10	27	—
XVIII	IX	18	48	—

TABLE 2. Pyrrolidine and Cyclopentanopyrrolidine Alcohols and Their Derivatives

Compound	Obtained from	Bp, °C (pressure, mm)	Mp, °C	n_D^{20}	d_4^{20}	MR_D		Empirical formula	Found, %			Calculated, %			Yield, %
						found	calc.		C	H	N	C	H	N	
XVII*	VIII	125—128 (5)	—	1,4906	0,9840	53,91	54,06	$C_{11}H_{21}NO$	71,58	11,71	7,39	72,08	11,55	7,64	
XIX	XII	95—98 (3)	—	1,4680	0,9338	46,80	47,02	$C_9H_{19}NO$	68,27	12,17	8,91	68,78	12,10	8,69	72
XX	XIII	114—116 (3)	—	1,4679	0,9120	60,62	60,88	$C_{12}H_{25}NO$	72,49	12,72	7,00	72,42	12,66	7,02	70
XXI	XIV	115—116 (5)	—	1,4700	0,9273	51,83	51,65	$C_{10}H_{21}NO$	69,75	12,24	8,30	70,00	12,28	8,19	72
XXII†	XIX	—	145—146	—	—	—	—	$C_{16}H_{23}NO_2 \cdot HCl$	64,25	8,17	4,98	64,50	8,15	4,72	75
XXIII†	XX	—	132—133	—	—	—	—	$C_{19}H_{29}NO_2 \cdot HCl$	67,52	8,66	4,37	67,11	8,90	4,12	77
XXIV†	XXI	—	100—101	—	—	—	—	$C_{17}H_{25}NO_2 \cdot HCl$	65,12	8,31	4,40	65,45	8,40	4,49	72
XXV†	XVII	—	112—114	—	—	—	—	$C_{21}H_{31}NO_5 \cdot HCl$	61,14	8,21	3,60	60,91	7,79	3,38	59
XXVI	XVII	184—185 (5)	—	1,5228	1,0826	89,54	89,19	$C_{19}H_{27}NO_2$	71,77	8,45	4,48	71,90	8,57	4,41	30
XXVII	XVII	180—182 (3)	—	1,5172	1,0523	82,85	82,95	$C_{18}H_{25}NO_2$	75,27	8,80	4,49	75,23	8,78	4,48	50

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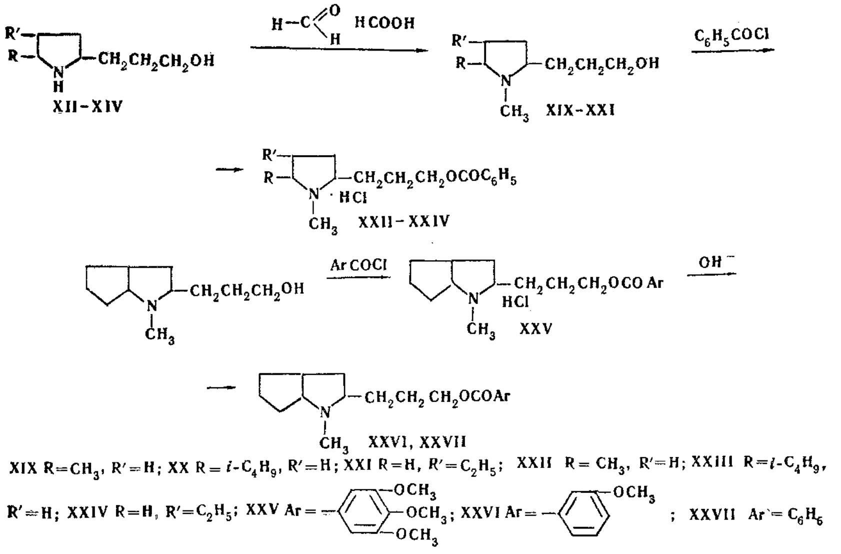
*For yields, see Table 1.

† Figures given for the hydrochloride.

Hydrogenation in the presence of the Raney cobalt catalyst was carried out under the same conditions as for the Raney nickel (acidic aqueous solution of the amine with pH 4, temperature ~100°C, initial pressure of hydrogen ~100 atm); when palladized carbon was used, the optimum conditions were: pH of the solution 4, temperature ~130°C, initial pressure of hydrogen ~50 atm. Table 1 gives the comparative yields of pyrrolidinylalkanols and cycloalkanopyrrolidinylalkanols using the various catalysts.

It follows from Table 1 that the replacement of Raney nickel by Raney cobalt or palladized carbon leads to an increase in the yields of the hydroxyalkyl derivatives of pyrrolidine and cycloalkanopyrrolidines by a factor of 1.5-3, which is very important in the preparative respect and also because of the value of these compounds in the synthesis of biologically active substances [6-8].

Some substances with a possible physiological action have been synthesized from the heterocyclic alcohols obtained. For this purpose, compounds XII-XIV were methylated by the Leukart reaction and the pyrrolidinyl- and cyclopentano[b]pyrrolidinylpropanols alkylated at the nitrogen atom were esterified with benzyoyl, m-methoxybenzoyl, and 3,4,5-trimethoxybenzoyl chlorides. Information on the new compounds obtained is given in Table 2.



The IR spectra of the amino alcohols XI, XVII, and XIX-XXI show the frequency of the stretching vibrations of the N–CH_3 bond at 2795-2798 cm^{-1}, and compounds XXII-XXVII each exhibit a strong absorption band at 1752-1757 cm^{-1} which is characteristic for an ester group.

The pharmacological activity of the esters obtained is being studied.

EXPERIMENTAL

The initial furan amines I-XI were obtained by methods described previously [2,3,9-12]. The previously unknown 1-furfuryl-2-methylaminocyclopentane (VIII) was obtained in analogy with previous work [2] by the reductive methylamination of monofurfurylidenecyclopentanone with a yield of 48%. Liquid with bp 126-127°C (22 mm); d_4^{20} 1.0050; n_D^{20} 1.4960. Found, %: C 73.64; H 9.51; N 7.50; MR_D 52.11. $C_{11}H_{17}NO$. Calculated, %: C 73.70; H 9.55; N 7.81; MR_D 52.91.

N-Acetyl-VIII. Liquid with bp 165-166°C (6 mm); n_D^{20} 1.5138. Found, %: C 70.51; H 8.75; N 5.90. $C_{13}H_{19}NO_2$. Calculated, %: C 70.59; H 8.59; N 6.33.

3-(2'-Octahydroindol-2'-yl)propan-1-ol (XVIII). A 610-ml autoclave was charged with a hydrochloric acid solution of 1-amino-2-furfurylcyclohexane (IX) with pH 4 (35 g of amine in 80 ml of dilute hydrochloric acid) and 3.5 g of Raney cobalt [4]. The initial pressure of hydrogen was 100 atm and the temperature 100°C. The reaction was complete after 12 h, when 2 moles of hydrogen per mole of amine had been ascribed. The hydrogenizate was filtered from the catalyst and neutralized with an excess of solid caustic soda. The oil that separated out was removed, and the aqueous layer was extracted with ether. The ether was distilled off, and vacuum distillation yielded XVIII, bp 152-154°C (5 mm). Yield 17 g (48%).

Compounds XI, XII, XVI, and XVII were obtained similarly.

3-(4'-Ethylpyrrolidin-2'-yl)propan-1-ol (XIV). A 250-ml autoclave was charged with a hydrochloric acid solution of 1-amino-2-ethyl-3-(α-furyl)propane (V) with pH 4 (15 g of the amine in 30 ml of dilute hydrochloric acid) and 1.5 g of palladium on carbon [5]. The initial pressure of hydrogen was 50 atm, and the temperature 120°C. After 9 h, the calculated amount of hydrogen had been absorbed. The hydrogenizate was treated as described above. Vacuum distillation yielded 9.4 g (61%) of XIV.

The pyrrolidinylpropanols X, XII, XIII, and XV were obtained under similar conditions.

3-(4'-Ethyl-1'-methylpyrrolidine-2'-yl)propan-1-ol (XXI). With cooling, 20 ml of 80% formic acid and 20 ml of formaline were added to 10 g of fused 3-(4'-ethylpyrrolidin-2'-yl)propan-1-ol (XIV). The mixture was boiled for 10 h, and then the calculated amount of hydrochloric acid was added and the solvent was distilled off under reduced pressure. The residue was treated with 20 ml of 50% caustic potash solution, the amine layer was separated off, and the aqueous layer was extracted with ether. The ethereal extracts were combined with the amine and dried with granulated KOH. The solution was filtered, the ether was evaporated off, and the residue was distilled in vacuum, a fraction with bp 115-116°C (5 mm) being collected. Yield 7.8 g (72%).

Compounds XIX and XX were obtained similarly.

3-(N-Methylcyclopentano[6]pyrrolidin-2'-yl)propyl Benzoate (XXVII). Solutions of 4 g (0.02 mole) of XVII in 20 ml of absolute benzene and of 2.8 g (0.02 mole) of benzoyl chloride in absolute benzene were mixed and allowed to stand at room temperature for 2-3 h, after which the precipitate of the hydrochloride of XXVII was filtered off. Yield 4 g (57%). mp 140-142°C (ethanol–ether). Found, %: N 4.93. $C_{18}H_{25}NO_2 \cdot HCl$. Calculated, %: N 4.32.

The hydrochlorides of the esters XXII-XXV were obtained similarly. The free ester XXVII was isolated by treating the corresponding hydrochloride with a saturated solution of sodium carbonate. The ester XXVI was obtained by heating (80°C) benzene solutions of XVII and m-methoxybenzoyl chloride [13].

The IR absorption spectra were recorded on a H-800 double-beam spectrophotometer (Hilger) using a sodium chloride prism.

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