ate was removed by filtration, washed with acetic acid and ether, and vacuum dried. A 10- to 20-ml sample of a 10% solution of $ZnCl_2$ in CH_3COOH was added to a hot saturated solution of the chloride in acetic acid, and the mixture was cooled after a certain time to precipitate the corresponding chlorozincate, which was washed with acetic acid and ether and vacuum dried (Table 1).

Kinetics of the Reaction of 6-Methoxy- and 6-Chlorobenzo-1,2,3-dithiazolium Chlorides with Aniline. The kinetics were studied by spectrophotometry with an SF-4A spectrophotometer at 25°. An 0.5-ml sample of a $2 \cdot 10^{-3}$ M solution of the salt in CH_3COOH was added to 19.5 ml of a 1 M solution of aniline in CH_3COOH (for the 6-methoxy derivative) or was injected into an acetic acid solution of aniline in the spectrophotometer cuvette (for the 6-chloro derivative). It was shown by preliminary experiments that the reaction goes to completion and that the concentration of the resulting 6-phenylamino derivative is equal to the concentration of the 6-chloro and 6-methoxy derivative used for the investigation. The rate constants calculated for the pseudomolecular reactions were $(1.58 \pm 0.04) \cdot 10^{-2}$ liter$\cdot$sec$^{-1}\cdot$mole^{-1} and $(1.24 \pm 0.03) \cdot 10^{-3}$ liter$\cdot$sec$^{-1}\cdot$mole^{-1} for the 6-chloro (Ia) and 6-methoxy (Ic) derivatives, respectively.

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SATURATED NITROGEN-CONTAINING HETEROCYCLES.

VIII.* SYNTHESIS AND PROPERTIES OF SOME SUBSTITUTED PYRROLIDYLALKANOLS

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UDC 547.743.1:547.722:547.584:
547.495.1

Phenyl-substituted pyrrolidylalkanols were synthesized by hydrogenation of the corresponding furan amines in acidic aqueous solution in the presence of nickel on diatomaceous earth. Terephthalates, carbamates, and other pyrrolidylalkanol derivatives were obtained. The ability of (2-pyrrolidyl)-3-alkanols to form an intramolecular hydrogen bond was studied by IR spectroscopy.

We have previously reported a new method for the synthesis of (2-pyrrolidyl)-3-alkanols with alkyl substituents in various positions of the pyrrolidine ring by hydrogenation of the corresponding furan amine in acidic aqueous solution in the presence of metal catalysts [1, 2]. The pyrrolidine alcohols are most smoothly obtained in 50-60% yields in the presence of an industrial nickel catalyst on diatomaceous earth. The utilization of this catalyst made it possible to extend the reaction to the synthesis of the previously undescribed phenyl-substituted pyrrolidylalkanols. The latter, in analogy with the structurally similar N-aralkyl-N-alkylaminoalkyl alcohols, may be used for the synthesis of possible neurotropic preparations [3].

We used furan amines (I-III) containing a phenyl ring in the side chain with respect to the furan ring as the starting compounds. The amines were hydrogenated in hydrochloric acid solution (pH 4) at 90°C and an initial hydrogen pressure of 75 atm. The principal reaction

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*See [1] for communication VII.

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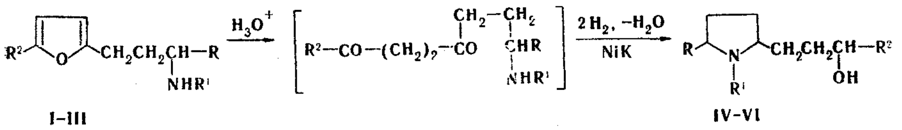
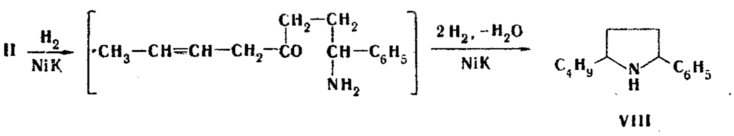
under these conditions was hydrolytic cleavage of the furan ring, as a result of which pyrrolidine alcohols were formed via the mechanism previously examined in [4].



I, IV R=C_6H_5, R^1=R^2=H; II, V R=C_6H_5, R^1=H, R^2=CH_3; III, VI R=R^2=H. R^1=C_6H_5

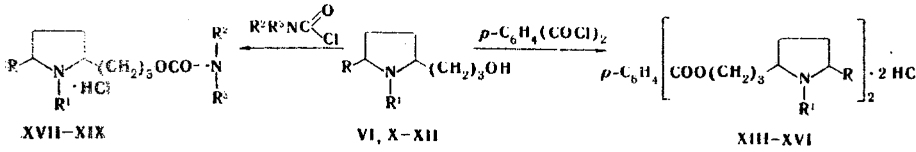
The corresponding tetrahydrofuran amine (VII), amine II, and 2-butyl-5-phenylpyrrolidine (VIII), which is probably formed by hydrogenolysis of the furan ring at the 1,5 bond in agreement with the literature data [5, 6], were isolated as side products of hydrogenation of amine I.



In the case of amine III, which has weak basic properties and is only slightly soluble in mineral acids, the reaction was carried out in dioxane—hydrochloric acid and was accompanied by hydrogenolysis of the amine at the C—N bond. As a result, aniline (up to 50%) was detected in the reaction products.

An increase in the hydrogenation temperature from 90 to 120° led to considerable resinification of the reaction products. An increase in the initial hydrogen pressure from 75 to 110 atm promoted an increase in the yields of VII and VIII.

A number of terephthalate hydrochlorides (XIII-XVI) and carbamate hydrochlorides (XVII-XIX) were synthesized by acylation of nitrogen-substituted pyrrolidine alcohols with terephthaloyl and carbamoyl chlorides.



VI, XIII R=H, R^1=C_6H_5; X, XIV R=C_6H_5, R^1=CH_3; XI, XV R=H, R^1=CH_3; XII, XVI R=iso-C_4H_9, R^1=CH_3; XVII R=R^3=C_6H_5, R^1=R^2=CH_3; XVIII R=H, R^1=R^2=CH_3, R^3=C_6H_5; XIX R=*iso*-C_4H_9, R^1=R^2=CH_3, R^3=C_6H_5

N-Acetyl and N,O-diacetyl derivatives of II-VIII were also obtained. Acetylation of alcohol V proceeds only at nitrogen to give IX, whereas the other pyrrolidylalkanols that we previously obtained give N,O-diacetyl derivatives under these conditions [4]. An examination of Stuart—Briegleb models showed that this is possible only for the cis isomer of alcohol V, in which the oxygen atom of the hydroxyl group is sterically hindered with respect to nucleophilic attack. It is well known that the formation of monocyclic disubstituted and higher substituted systems by catalytic hydrogenation on metals frequently takes place stereospecifically to give mainly the cis isomers [7]. On the basis of the results of gas—liquid chromatography (GLC), it may be supposed that the formation of pyrrolidine alcohols from furan amines is also a stereospecific reaction. The principal diastereomeric form is realized to the extent of 80-90% and was isolated by fractional distillation.

The presence of a phenyl ring is detected in the IR spectra of II-V from the characteristic absorption bands at 3000-3100, 1470-1600, and 690-760 cm^{-1}. The IR spectra of N-acetyl derivatives of II, III, V, VII, and VIII contain intense absorption at 1640-1660 cm^{-1} (amide $\nu_{C=O}$). Bands of stretching vibrations of a carbonyl group in esters at 1730-1750 cm^{-1} and of a C-O single bond at 1250-1260 cm^{-1} appear in the spectra of N,O-diacetyl derivatives of alcohol IV, terephthalates XIII-XVI, and carbamates XVII-XIX.

Several communications dealing with the determination of the strength of the intramolecular hydrogen bond of various amino alcohols by IR spectroscopy have appeared in recent years [8-10]. We have not found similar information relative to pyrrolidyl-3-alkanols.

TABLE 1. Synthesized Compounds

Compound	bp, °C (mm); mp, °C	n_D^{20}	d_4^{20}	MR_D		Empirical formula	Found, %			Calc., %			Yield, %
				ou	calc.		C	H	N	C	H	N	
II	138—140 (2)	1,5440	1,047	65,31	65,18	$C_{14}H_{17}NO$	77,9	7,9	6,5	78,1	7,9	6,5	70
III	162—164 (7)	1,5647	0,998	61,62	60,74	$C_{13}H_{15}NO$	77,9	7,5	7,0	77,6	7,5	6,9	44
IV	158—160 (1)	1,5345	1,029	62,00	61,56	$C_{13}H_{19}NO$	75,7	9,7	6,8	76,1	9,3	6,8	37
V	138—140 (2,5)	1,5319	1,025	66,38	66,08	$C_{14}H_{21}NO$	77,1	9,9	6,8	76,8	9,7	6,4	33
VI	175—180 (4)	1,5510	1,045	62,70	61,90	$C_{13}H_{19}NO$	76,6	9,3	6,9	76,1	9,3	6,8	35
VII	144—146 (1)	1,5195	1,011	61,69	61,50	$C_{13}H_{19}NO$	75,6	10,0	6,8	76,1	9,3	6,8	14
VIII	123—125 (3)	1,5144	0,946	64,71	64,65	$C_{14}H_{21}N$	82,8	10,2	7,2	82,8	10,3	6,9	33
IX	210 (4)	1,5337	—	—	—	$C_{16}H_{23}NO_2$	74,0	8,7	5,4	73,6	8,9	5,4	80
X	152 (2)	1,5162	0,993	66,75	66,52	$C_{14}H_{21}NO$	76,4	10,1	6,5	76,8	9,7	6,4	45
XIV	141—142	—	—	—	—	$C_{36}H_{44}N_2O_4 \cdot 2HCl$	67,2	7,1	4,3	67,4	7,2	4,4	55
XV	145	—	—	—	—	$C_{24}H_{36}N_2O_4 \cdot 2HCl$	58,7	7,6	5,6	58,9	7,7	5,7	77
XVI	180—181	—	—	—	—	$C_{32}H_{52}N_2O_4 \cdot 2HCl$	63,6	8,8	4,8	63,8	9,0	4,7	73

TABLE 2. Shift of the ν_{OH} Frequency during the Formation of an OH...N Intramolecular Hydrogen Bond in (2-Pyrrolidyl)-3-alkanols at Concentrations of 0.01 mole/liter

Compound	ν_{OH}, cm^{-1}	ν_{HB}cm^{-1}	Δν, cm^{-1}	$D_{OH}=\lg\frac{I_0}{I}$	$D_{HB}=\lg\frac{I_0}{I}$	$\frac{D_{OH}}{D_{HB}}$
VI	3645	3415	230	0,208	0,035	5,8
IX	3454	3360	94	0,358	0,009	4
X	3640	3190	450	0,081	0,086	1,04
XI	3642	3180	462	0,112	0,198	0,565
XII	3640	3170	470	0,066	0,208	0,335

We recorded the IR spectra of liquid films of alcohols VI and IX-XII and solutions of them in CCl_4 at various concentrations at 3000-3650 cm^{-1}. The spectra of the liquids contain a broad intense band at 3200-3400 cm^{-1} related to the stretching vibrations of an associated OH group. This band is shifted hypsochromically, and its intensity falls in the spectra of solutions of the alcohols as the concentration decreases. Two absorption bands that do not sustain a change in the position of their maxima on further dilution are present in the spectra of the alcohols at concentrations beginning with 0.01 mole/liter, and this made it possible to assign the band of the highest-frequency absorption to vibrations of a free OH group and the band in the longer-wavelength region exclusively to a hydroxyl group with an intramolecular hydrogen bond [11]. The results of the measurements are presented in Table 2. The error in the determination of ν was ±2 cm^{-1}. If the low-frequency shift $\Delta\nu_{OH}$ is taken as a measure of the strength of the intramolecular hydrogen bond, as assumed in [8-10], in this series of compounds, pyrrolidyl-3-alkanols X-XII, which form seven-membered rings, give strong hydrogen bonds, and this is in complete agreement with the data for aliphattic dialkylamino alcohols [8-10]. The presence of a phenyl group or an acetyl group attached to the nitrogen atom of the pyrrolidine ring in alcohols VI and IX leads, as expected, to a considerable decrease in the strength of the intramolecular bond.

EXPERIMENTAL

The IR spectra of capillary layers of CCl_4 solutions and mineral oil and hexafluorobutadiene suspensions of the compounds (1300-1500 cm^{-1}) were recorded with a UR-10 spectrometer. The individuality of amines I-III was monitored by thin-layer chromatography (TLC) on activity-II aluminum oxide [benzene—hexane (1:1), development with iodine vapors]. The purity of alcohols IV-VI and X-XII was determined by GLC with a Chrom-31 chromatograph with a flame-ionization detector. A 3.6-m by 6-mm column was filled with Apiezon-L applied (in 15 wt.% quantities) on a TND-TS-M support previously treated with a 2% solution of potassium hydroxide in alcohol. The carrier-gas (helium) flow rate was 1.8 liters/h, and the column temperature was varied from 170 to 210°.

3-(2-Furyl)-1-phenylpropylamine (I). This compound was obtained by the method in [12].

3-(5-Methyl-2-furyl)-1-phenylpropylamine (II). A 610-ml autoclave was charged with 60 g (0.28 mole) of 5-methylfurfurylideneacetophenone [13], 250 ml of methanol containing 38 g of ammonia, and 6 g of Raney nickel. The initial hydrogen pressure was 120 atm, the temperature was 100°, and the reaction was complete after 15 h. The hydrogenolysis product was freed from the catalyst by filtration, and the methanol was removed by distillation at reduced pressure. A dilute solution of hydrochloric acid (1:4) was added to the residue until it gave an acid reaction with respect to Congo Red, after which the nitrogen-free impurities were extracted with ether. The calculated amount of solid alkali was then added to a solution of the amine salt, and the liberated amine was separated and dissolved in ether. The ether solution was dried with granulated potassium hydroxide, and the mixture was vacuum distilled to give 41 g of amine II (Table 1). The N-acetyl derivative of II had bp 203-205° (3 mm) and mp 68.5-70°. Found, %: N 5.5. $C_{16}H_{19}NO_2$. Calculated, %: N 5.4.

N-Phenyl-3-(2-furyl)propylamine (III). This compound was obtained in 40-44% yield by reductive aminoarylation of furylacrolein in a solution of ethanol in an autoclave under a hydrogen pressure of 100 atm at 50° in the presence of Raney nickel. The N-acetyl derivative of III had bp 150-153° (2 mm) and n_D^{20} 1.5380. Found, %: N 5.8. $C_{15}H_{17}NO_2$. Calculated, %: N 5.7.

3-(5-Phenyl-2-pyrrolidyl)-1-propanol (IV) and 3-(2-Tetrahydrofuryl)-1-phenylpropylamine (VII). A solution of 20 g of amine I in 60 ml of dilute hydrochloric acid (pH 4) was hydrogenated in a 150-ml autoclave in the presence of 15% (with respect to the weight of the amine) nickel on diatomaceous earth. (The industrial catalyst was subjected to prior reduction in a stream of hydrogen at 220° and cooled in an atmosphere of carbon dioxide.) The initial hydrogen pressure was 75 atm and the temperature was 90°. The reaction was complete after 20 h. The calculated amount of sodium hydroxide was added to the hydrogenolysis product after removal of the catalyst, and the mixture was allowed to stand for several hours until liberation of the amine above the aqueous layer was complete. The amine was dried in ether with solid KOH, and the mixture was vacuum distilled to give 2.8 g (14%) of amine VII with bp 144-146° (1 mm), and 7.4 g (37%) of alcohol IV with bp 158-160° (1 mm). The N-acetyl derivative of VII had bp 195° (3 mm) and mp 68-69°. Found, %: N 5.8. $C_{15}H_{21}NO_2$. Calculated, %: N 5.7. The N,O-diacetyl derivative of IV had bp 215-217° (3 mm) and n_D^{20} 1.5186. Found, %: N 4.8. $C_{17}H_{23}NO_3$. Calculated, %: N 4.8.

2-Butyl-5-phenylpyrrolidine (VIII) and 4-(5-Phenyl-2-pyrrolidyl)-2-butanol (V). These compounds were similarly obtained by hydrogenation of amine II. The N-acetyl derivative of VIII had bp 190-191° (3.5 mm) and n_D^{20} 1.5277. Found, %: N 6.0. $C_{16}H_{23}NO$. Calculated, %: N 5.7. See Table 1 for the physical characteristics of the N-acetyl derivative (IX) of V.

Pyrrolidylalkanols XI and XII, data on which were reported in [2, 4], were obtained from the appropriate furan amines via the method described above in 50 and 60% yields, respectively.

3-(1-Phenyl-2-pyrrolidyl)-1-propanol (VI). This compound was obtained by hydrogenation of amine III in dioxane–hydrochloric acid (pH 4) in the presence of nickel on diatomaceous earth under an initial hydrogen pressure of 60 atm at 70-85°. The N-acetyl derivative of VI had bp 173-175° (9 mm) and n_D^{20} 1.5290. Found, %: N 6.0. $C_{15}H_{21}NO_2$. Calculated, %: N 5.6.

3-(1-Methyl-5-phenyl-2-pyrrolidyl)-1-propanol (X). A 10-ml sample of 80% formic acid and 10 ml of formalin were added with cooling to 5 g of alcohol IV, after which the mixture was refluxed for 10 h. The calculated amount of hydrochloric acid was then added, and the solvent was removed by distillation at reduced pressure. A 10-ml sample of 50% NaOH solution was added to the residue, and the mixture was allowed to stand for several hours. The liberated amine salt was separated, dried in ether with solid potassium hydroxide, and vacuum distilled to give 2.4 g (45%) of product.

Bis[3-(1-phenyl-2-pyrrolidyl)propyl] Terephthalate Dihydrochloride (XIII). This compound, with mp 129-131°, was obtained in 40% yield by mixing equimolar amounts of ether solutions of alcohol VI and terephthaloyl chloride. Found, %: Cl 11.2; N 4.7. $C_{34}H_{40}N_2O_4 \cdot 2HCl$. Calculated, %: Cl 11.4; N 4.6.

Bis[3-(1-methyl-5-phenyl-2-pyrrolidyl)propyl] Terephthalate Dihydrochloride (XIV), Bis-[3-(1-methyl-2-pyrrolidyl)propyl] Terephthalate Dihydrochloride (XV), and Bis[3-(1-methyl-5-isobutyl-2-pyrrolidyl)propyl] Terephthalate Dihydrochloride (XVI). These compounds were similarly obtained (see Table 1).

3-(1-Methyl-5-phenyl-2-pyrrolidyl)propyl N-Methylphenylcarbamate Hydrochloride (XVII). A mixture of 1.7 g (8 mmole) of alcohol X was stirred thoroughly with 2 g (12 mmole) of N-methylphenylcarbamoyl chloride, after which the mixture was heated at 110-120° for 4 h. It was then cooled, and the resulting viscous oil was triturated with ether to isolate crystals of salt XVII with mp 110° in 50% yield. Found, %: Cl 9.2; N 6.7%. $C_{22}H_{28}N_2O_2 \cdot HCl$. Calculated, %: Cl 9.4; N 7.2.

3-(1-Methyl-2-pyrrolidyl)propyl N-Methylphenylcarbamate Hydrochloride (XVIII). This compound, with mp 113-115°, was similarly obtained in 80% yield from alcohol XI. Found, %: Cl 10.4. N 8.9. $C_{16}H_{24}N_2O_2 \cdot HCl$. Calculated, %: Cl 10.1; N 8.9.

3-(1-Methyl-5-isobutyl-2-pyrrolidyl)propyl N-Methylphenylcarbamate Hydrochloride (XIX). This compound, with mp 97-98°, was similarly obtained in 70% yield from alcohol XII. Found, %: Cl 9.2; N 7.4. $C_{20}H_{32}N_2O_2 \cdot HCl$. Calculated, %: Cl 9.6; N 7.6.

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SYNTHESIS OF N-SUBSTITUTED INDOLES BY EXTRACTIVE ALKYLATION

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A method was developed for the N-alkylation of indole and its derivatives by alkyl halides in the presence of sodium hydroxide and catalytic amounts of trimethylbenzylammonium chloride.

N-Alkylindoles are used for the preparation of indomethacin analogs that have antiphlogistic activity [1, 2], and also in diverse syntheses in the indole series.

The alkylation of indole itself is realized through its metallated derivatives. The natures of the metal and the solvent have the greatest effect on the direction of alkylation (at N or in the 3 position). An increase in the ionic character of the nitrogen–metal bond by utilization of alkali metals (Na and K) [3] and strongly dissociating solvents [dimethyl

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