Pyridylethylation of Mesitylene. A concentrated reaction mixture (25 g) was obtained from 1256 g (10.5 moles) of mesitylene and 10.5 g (0.1 mole) of 2-VP. Vacuum distillation (6 mm) gave two fractions: The first fraction (11.4 g) had bp 160-170°C, while the second fraction (3.3 g) had bp 175-190°C.

Compounds I-VII with Ar = o-, m-, and p-$CH_3C_6H_4$ and 3,5-$(CH_3)_2C_6H_3$ were isolated preparatively from the pyridylethylation of the xylenes and mesitylene. The PMR and mass spectra of these compounds are similar in character to the corresponding spectra of I-VII with Ar = C_6H_5. The characteristics of the principal reaction products are given in Table 2.

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SYNTHESIS AND THREE-DIMENSIONAL STRUCTURES OF 3-(α-AMINO- and α-HYDROXYBENZYL)QUINUCLIDINES

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UDC 547.834.4.07:541.63:543.422.25

3-Substituted quinuclidines that contain a hydroxy or amino group in the side chain were synthesized by reduction of 3-benzoyl- and 3-benzoylmethylquinuclidines and their oximes. It is shown that the reduction of the ketones takes place stereospecifically to give one diastereomeric alcohol in both cases, whereas mixtures of diastereomeric 3-(α-aminobenzyl)quinuclidines are formed in the hydrogenation of their oximes. The configurations of the substances obtained were established on the basis of data from the PMR spectra.

The high biological activity of arylalkanolamines and arylalkylideneamines, which include noradrenaline, ephedrine, propanolol, etc., is widely known.

In a number of cases the activity is also retained when fragments that correspond to these compounds are included in mono- and bicyclic systems. The previously described 3-hy-

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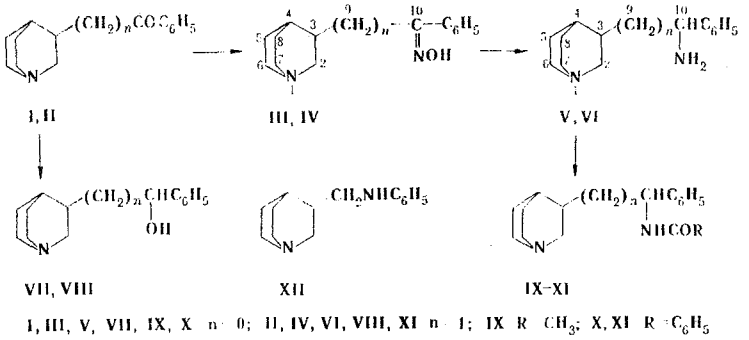
TABLE 1. Chemical Shifts (ppm) of III-X*

Compound	2,6,7-H	3,5,8-H	4-H	3-R
III	2,7—3,4; 4,09 K	1,3—2	1,82	7,3—7,5 (C_6H_5)
IV	2,3—3,5	1,0—2,1		7,3—7,7 (C_6H_5); 2,3—3,5 (9-H)
Va	2,4—3,3	1,4—2,2	1,20	3,90 (10-H), $J_{3\text{-H},\ 10\text{-H}} \approx 10{,}5$ Hz; 7,2—7,3 (C_6H_5)
Vb	2,6—3,0	1,5—2,1	2,27	3,76 (10-H), $J_{3\text{-H},\ 10\text{-H}} \approx 10{,}5$ Hz; 7,2—7,3 (C_6H_5)
VI	2,4—3,2	1,3—2,3		3,78 t (10-H), $\Sigma J \approx 14$ Hz; 1,3—2,3 (9-H); 7,2—7,4 (C_6H_5)
VII	2,3—2,7	1,3—2,1	2,12	4,39 d (10-H), $J_{3\text{-H},\ 10\text{-H}} \approx 10$ Hz; 7,2—7,3 (C_6H_5)
VIII	2,2—3,2	1,4—1,9		1,4—2,9 (9-H); 4,6 t (10-H), $\Sigma J \approx 13$ Hz; 7,2—7,3 (C_6H_5)
IX	2,5—3,2	1,2—2,4		4,96 d, 4,94 d (10-H); 7,2—7,4 (C_6H_5); 1,9 s, 1,93 s ($NCOCH_3$)
X	2,5—3,0	1,4—2,5		5,14 d (10-H), $J_{3\text{-H},\ 10\text{-H}} \approx 11$ Hz; 7,2—7,8 (C_6H_5, COC_6H_5)

*The solvents were CD_3OD for VIII-X and $CDCl_3$ for the remaining compounds; the internal standard was tetramethylsilane. The signals whose multiplicities are not indicated are multiplets.

droxy-3-arylquinuclidines and 3-arylaminoquinuclidines that contain the indicated fragments have displayed a number of interesting pharmacological properties [1, 2]. Compounds of the quinuclidine series that are derivatives of arylpropylenediamines and arylpropanolamines have been unknown up until now.

We have accomplished the synthesis of substances of this type, viz., 3-(α-aminobenzyl)- (V) and 3-(α-hydroxybenzyl)quinuclidines (VII) and the corresponding derivatives at the amino group (IX and XI). Amine V was obtained by reaction of 3-benzoylquinuclidine (I) with hydroxylamine hydrochloride and subsequent hydrogenation of oxime III in the presence of a Raney nickel catalyst, while carbinol VII was previously synthesized by reduction of ketone I catalytically (in the presence of platinum) or with lithium aluminum hydride [3]. The presence in V and VII of two asymmetric carbon atoms required the determination of the configuration and stereospecificity of their formation. We solved these problems by means of PMR spectroscopy.



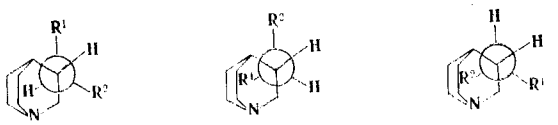
I, III, V, VII, IX, X n = 0; II, IV, VI, VIII, XI n = 1; IX R = CH_3; X, XI R = C_6H_5

Our investigation showed that the reduction of oxime III proceeds nonstereospecifically to give approximately equal amounts of diastereomeric amines Va,b. A mixture of isomeric amines V is formed along with 3-(phenylaminomethyl)quinuclidine (XII) when oxime III is treated with lithium aluminum hydride. The formation of XII is evidently associated with Beckmann rearrangement of oxime III and with subsequent reduction of the resulting quinuclidine-3-carboxylic acid aniline by lithium aluminum hydride.

According to data from the PMR spectra (Table 1), oxime III was isolated in the form of an individual isomer. Evidence for this is provided by the presence in the spectra recorded in various solvents of a single set of signals, particularly a quartet at ∿4 ppm (1H), which corresponds to one of the protons in the 2 position of the quinuclidine ring.

In addition to multiplet signals of the protons of the quinuclidine and phenyl rings, two doublets (at 3.7-3.8 ppm), which correspond to the 10-H proton in each of two possible diastereomeric amines Va,b (in a 55:45 ratio in the mixture), are observed in the PMR spectrum of the mixture of amines Va,b.

The mixture of diastereomeric amines V was separated into individual diastereomers Va,b by chromatography on plates, while the configurations were established on the basis of the peculiarities of the PMR spectra. First, it was found that the spin–spin coupling constants (SSCC) of the vicinal 3-H and 10-H protons are extremely high for both isomers and amount to ≈10.5 Hz. The $J_{3\text{-H},10\text{-H}}$ value can be linked with the populations of the conformers relative to the C_3—C_{10} bond, about which free rotation is possible.



T G1 G2

$R^1 = C_6H_5$, $R^2 = NH_2$: configuration *RS/SR*.
$R^1 = NH_2$, $R^2 = C_6H_5$: configuration *RR/SS*

Since it should be expected that $J_{3\text{-H},10\text{-H}} \approx 3$-4 Hz [3] for individual gauche conformers G1 and G2, the much higher value of the observed SSCC indicates the existence of each of the Va,b isomers mainly in the form of conformer T with a transoid orientation of the 3-H and 10-H protons.

A second peculiarity of the PMR spectra of diastereomeric amines V was the significant difference in the chemical shifts of the 4-H protons, the signal of which in the spectrum of isomer Va is shifted almost 1 ppm to strong field as compared with isomer Vb and is observed at stronger field than in the other previously investigated quinuclidine derivatives [4, 5]. This strong-field shift is evidently determined by the fact that the 4-H proton in the predominant (transoid) conformer of isomer Va is situated close to the phenyl ring and is located in its shielding region. It follows from an examination of molecular models that this sort of drawing together and the corresponding mutual spatial orientation of the phenyl ring and the 4-H proton are possible only when $R^1 = C_6H_5$ and $R^2 = NH_2$ (structure T), which corresponds to an RS/SR configuration for isomer Va and, correspondingly, and RR/SS configuration for isomer Vb.

We used the above-noted peculiarities of the PMR spectra of diastereomeric amines Va,b to establish the configurations of 3-(α-hydroxybenzyl)quinuclidine (VII). Carbinol VII is an individual substance, which constitutes evidence for the stereospecificity of the reduction of ketone I [6]. In the PMR spectrum of carbinol VII the signal of the 10-H proton is a doublet with $J_{3\text{-H},10\text{-H}} \approx 10$ Hz, while the signal of the 4-H proton is observed at 2.12 ppm, i.e., the strong-field shift that is characteristic for amine Va is absent. In conformity with the material set forth above, the same configuration as that for amine Vb, i.e., RR/SS, can be assigned to VII.

In addition to amine V and carbinol VII, we obtained quinuclidine derivatives with the same functional groups but with an additional methylene link between the benzyl group and the bicyclic ring.

3-(β-Amino-β-phenylethyl)quinuclidine (VI) and 3-(β-hydroxy-β-phenylethyl)quinuclidine (VIII) were synthesized on the basis of 3-benzoylmethylquinuclidine (II) [7] by the methods used for the preparation of V and VII. Ketone I was converted to oxime, which was then reduced to amine VI. We were unable to solve the problem of the configurational purity of oxime IV by PMR spectroscopy because of marked overlapping of the multiplets corresponding to different protons. In the spectrum of amine VI the signal of the 10-H proton, which is a triplet, is not overlapped with the remaining signals. However, in the spectra recorded in the presence of the Eu(DPM)$_3$ shift reagent this signal is doubled and is converted to two triplets with an intensity ratio close to 1:1, which indicates that product VI exists in the form of an equimolar mixture of diastereomers VIa,b.

The reduction of ketone with lithium aluminum hydride or the reduction of its hydrochloride catalytically in the presence of platinum (Adams) to carbinol VIII proceed stereospecifically, as evidenced by the presence in the PMR spectrum of VIII of a lone signal (a triplet) corresponding to the 10-H proton. As indicated above, a similar pattern is also observed in the reduction of ketone I.

Mixtures of diastereomeric amines V and VI were subjected to acylation. A mixture of diastereomeric 3-(α-acetamidobenzyl)quinuclidines (IX) was obtained from the mixture of amines Va,b by heating with acetic anhydride; this was confirmed by the presence in the PMR

spectrum of IX of two singlets of acetyl groups. Heating amines V and VI with benzoyl chloride in benzene in the presence of triethylamine led, respectively, to mixtures of diastereomeric 3-(α-benzamidobenzyl)- and 3-(β-benzamido-β-phenylethyl)quinuclidines (X, XI).

EXPERIMENTAL

The PMR spectra were recorded with JNM-4H-100 and XL-200 spectrometers with operating frequencies of 100 and 200 MHz, respectively.

Compounds I and VII were obtained by the method in [6], while II was obtained by the method in [7].

3-Benzoylquinuclidine Oxime (III). A mixture of 4.3 g (20 mmole) of 3-benzoylquinuclidine (I) [6], 1.4 g (20 mmole) of hydroxylamine hydrochloride, and 30 ml of ethanol was refluxed for 15 h, after which the solution was evaporated *in vacuo*, and the residue was dissolved in 20 ml of water. A 30-ml sample of a 50% solution of potassium carbonate was added, and the mixture was extracted with chloroform. Workup of the extract gave 3.3 g (72%) of a product with mp 192-194°C (from ethanol). Found: C 73.0; H 8.0; N 12.0%. $C_{14}H_{18}N_2O$. Calculated: C 73.0; H 7.8; N 12.2%.

3-Benzoylmethylquinuclidine Oxime (IV). This compound, with mp 176-178°C (from ethyl acetate), was similarly obtained from 3-benzoylmethylquinuclidine [7]. Found: C 73.6; H 8.2; N 11.7%. $C_{15}H_{20}N_2O$. Calculated: C 73.7; H 8.2; N 11.6%.

Diastereomeric 3-(α-Aminobenzyl)quinuclidines (Va,b). A 3.7-g (16 mmole) sample of oxime III was reduced in 50 ml of ethanol in the presence of 4 g of Raney nickel at 40°C and an initial hydrogen pressure of 40 atm. After two equivalents of hydrogen had been absorbed, the catalyst was removed by filtration. The alcohol was removed from the filtrate by distillation, and the residue was distilled *in vacuo* to give 3.04 g (87%) of a product with bp 134-136°C (0.5 mm). The resulting mixture of diastereomeric amines was separated on plates with a fixed layer of silica gel with methanol as the mobile phase by elution with chloroform. Amine Va had mp 48-50°C. Found: C 77.7; H 9.4; N 12.7%. $C_{14}H_{20}N_2$. Calculated: C 77.7; H 9.3; N 13.0%. Amine Vb had mp 85-87°C. Found: C 77.9; H 9.2; N 13.1%. $C_{14}H_{20}N_2$. Calculated: C 77.7; H 9.3; N 13.0%.

3-(β-Amino-β-phenylethyl)quinuclidines (VIa,b). These compounds were obtained by reduction of oxime IV under the conditions described above. The yield of the mixture of diastereomeric amines, with bp 148-152°C (0.5 mm), was 75%. Found: C 78.3; H 9.4; N 12.0%. $C_{15}H_{22}N_2$. Calculated C 78.2; H 9.6; N 12.2%.

3-(β-Hydroxy-β-phenylethyl)quinuclidine (VIII). A) A mixture of 2 g (8.8 mmole) of 3-benzoylmethylquinuclidine (II) [7], 20 ml of ethanol, and 0.2 g of platinum oxide was shaken with hydrogen. After one equivalent of hydrogen had been absorbed, the platinum was removed by filtration, and the alcohol solution was evaporated *in vacuo*. The residue was triturated with ether to give 1.3 g (64%) of a product with mp 127-129°C (from acetone). Found: C 78.1; H 9.2%. $C_{15}H_{21}NO$. Calculated: C 77.9; H 9.2%. The hydrochloride had mp 175-177°C. Found: Cl 13.1%. $C_{15}H_{21}NO \cdot HCl$. Calculated: Cl 13.2%.

B) A solution of 1.6 g (7 mmole) of ketone II was added to a suspension of 1.5 g (40 mmole) of lithium aluminum hydride in 20 ml of ether, and the mixture was refluxed with stirring for 5 h. It was then cooled and treated with 3 ml of water, and the precipitate was removed by filtration and washed thoroughly with chloroform. The combined extracts were evaporated, and the residue was triturated with ether to give 1.2 g (75%) of a product with mp 127-129°C (from acetone).

The substances obtained by the two methods were identical, and no melting-point depressions were observed for mixtures of the samples.

3-(α-Acetamidobenzyl)quinuclidines (IXa,b). A solution of 2 g (9.3 mmole) of the mixture of diastereomeric amines Va,b in 20 ml of acetic anhydride was heated at 100°C for 5 h, after which it was evaporated *in vacuo*, and the residue was dissolved in 10 ml of water. The solution was made alkaline with potassium carbonate and extracted with chloroform. The chloroform was removed, and the residue was triturated with acetone to give 1.7 g (72%) of a mixture of diastereomeric IXa,b with mp 138-141°C (from acetone). Found: C 69.6; H 8.7; N 10.1%. $C_{16}H_{22}N_2O \cdot H_2O$. Calculated: C 69.5; H 8.7; N 10.1%.

3-(α-Benzamidobenzyl)quinuclidines (Xa,b). A solution of 3.47 g (16 mmole) of the mix-

ture of diastereomeric amines Va,b, 2.26 g (16 mmole) of benzoyl chloride, and 1.62 g (16 mmole) of triethylamine in 30 ml of benzene was refluxed for 10 h, after which it was extracted with 17% hydrochloric acid. The hydrochloric acid solution was made alkaline with potassium carbonate and extracted with chloroform. The chloroform was removed by distillation, and the residue was recrystallized from ethyl acetate to give 1.85 g (36%) of a mixture of diastereomeric Xa,b with mp 150-151°C. Found: C 74.6; H 7.8; N 8.4%. $C_{21}H_{24}N_2O$. Calculated: C 74.5; H 7.7; N 8.7%.

3-(β-Benzamido-β-phenylethyl)quinuclidines (XIa,b). The reaction with 2 g (8.7 mmole) of the mixture of amines VIa,b, 1.22 g (8.7 mmole) of benzoyl chloride, and 0.88 g (8.7 mmole) of triethylamine in 20 ml of benzene was carried out as described in the preceding experiment. The residue obtained after evaporation of the chloroform extract was dissolved in 10 ml of acetone, and the acetone solution was acidified with an alcohol solution of hydrogen chloride and diluted with ether until it became turbid. The liberated oil was triturated with ether to give 2.3 g (68%) of a mixture of the diastereomeric hydrochlorides of XIa,b with mp 45-47°C (dec.). Found: C 68.2; H 7.3; Cl 9.2%. $C_{22}H_{26}N_2O \cdot HCl \cdot H_2O$. Calculated: C 68.0; H 7.5; Cl 9.1%.

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REACTION OF 1-AMINOBENZIMIDAZOLES WITH β-DIKETONES. SYNTHESIS OF PYRIDAZINO[1,6-a]BENZIMIDAZOLES

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The action of acetyl- and benzoylacetone on 1-aminobenzimidazoles in the presence of catalytic amounts of zinc chloride was used to synthesize 1-ylidene derivatives, which at higher temperatures undergo thermal cyclization to 2,4-disubstituted pyridazino[1,6-a]benzimidazoles.

In contrast to α-amino derivatives of nitrogen heterocycles, the reaction of which with β-dicarbonyl compounds is quite widely known [1], the analogous reactions for N-amines of the azole series have remained almost undescribed [2, 3]. In the present research we investigated the behavior of 1-aminobenzimidazoles with respect to 1,3-diketones.

Considering the fact that 1-aminobenzimidazoles condense with ketones only upon prolonged heating (150-160°C) in the presence of catalytic amounts of zinc chloride [4], the β-diketones were subjected to reaction under similar conditions. We found that, depending on the structure of the starting amines, this reaction has its own peculiarities. Thus 1-amino- (Ia) and 1-amino-2-methylbenzimidazole (Ib) react with acetylacetone to give ketimines IIa,b. Under the same conditions 1-amino-5,6-dimethylbenzimidazole (Ic) undergoes cyclization to py-

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