SYNTHESIS AND CONFIGURATION OF DIASTEREOMERIC 2-SUBSTITUTED 5-OXOQUINUCLIDINES

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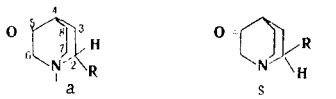
The individual diastereomers of 5-oxoquinuclidine-2-carboyxlic acid and its methyl ester and of 2-benzoyloxymethyl-5-oxoquinuclidine were obtained, and their stereochemistry and assignment to the quinine and quinidine series were given on the basis of the PMR spectra.

5-Hydroxyquinuclidine-2-carboxylic acid (I), which has reactive carboxyl and carbonyl groups in the 2 and 5 positions of the quinuclidine ring, can serve as the starting compound for the synthesis of diverse 2,5-disubstituted quinuclidines, including a number of natural alkaloids (quinine, cinchonine, cinchonamine, sarpagine, macusine, etc.).

The practicable method for the preparation of I from 2,4-lutidine that we previously developed [1] is associated with the generation of two asymmetrical centers in the course of the synthesis and with the formation of two diastereomeric forms – anti (Ia) and syn (Is)* – which are related, respectively, to the quinine and quinidine series:



a s

I R = COOH; II R = $COOCH_3$; VII R = CH_2OH; VIII R = $CH_2OCOC_6H_5$

A study of various routes for the preparation of pure syn- and anti-5-oxoquinuclidine-2-carboxylic acids has demonstrated that the simplest route is separation of the diastereomeric hydrochlorides of these compounds by crystallization from water. The hydrochloride of anti isomer Ia is less soluble in water and can be isolated in 70% yield by one crystallization. (The product contains 82% pure isomer.) The syn isomer (Is), containing 85% pure diastereomer, can be isolated in 85% yield from the mother liquor by fractional crystallization. The pure diastereomer with mp 297°, which is practically free of the hydrochloride of Is, can be obtained in an overall yield of 20% by two recrystallizations of the hydrochloride of Ia from water.

The analysis of the purity of the diastereomeric compounds and the establishment of their steric configurations using the hydrochlorides of oxo acids I causes difficulties. The PMR spectra do not contain distinctly expressed signals that can be rigorously assigned to the protons of one or the other diastereomer, and gas-liquid chromatography (GLC) also proved to be unsuitable in connection with the high melting points of the substances.

*Here and in what follows, we are considering the syn and anti orientation of the substituent attached to C_2 of the quinuclidine ring with respect to the links of the C_5–C_6 bicycle, which contains the carbonyl group.

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TABLE 1. PMR Spectra Parameters of 2-Substituted 5-Oxoquinuclidines

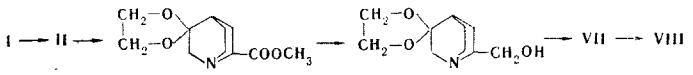
Compound	Chemical shifts, δ, ppm								J, Hz	
	2-H	3-H	3-H′	4-H	6-H	6-H′	7-H	8-H	$J_{3',8}$	$J_{2,3'}$
III	2,88	1,97		2,34	3,13		2,88	1,97		
VIIs	2,9	2,09	1,43	2,33	3,38	2,96	2,9	2,0	1,5	7,5
VIIa					3,23					
VIIIs	3,25	2,2	1,71	2,37	3,54	3,00	2,9	2,0	1,5	7,0
VIIIa		2,1	1,58	2,33	3,20		2,6—3,4	1,95	<0,5	7,5
Is					3,56	3,35				
Ia					3,39					
IIs	3,48	1,8—2,2		2,35	3,50	2,92	2,9	1,8—2,2		
IIa	3,49				3,15		2,6—3,2	1,8—2,4		

TABLE 2. Experimental and Calculated Changes in the Chemical Shifts of the C_6 Protons in VIIa and VIIs in Comparison with III

Change	VIIs		VIIa	
	syn-6-H*	anti-6-H′	syn-6-H	anti-6-H′
Measured	0,25	−0,17	0,10	0,10
Calc.	−0,04	−0,12	0,03	0,09

*Here and in what follows, syn and anti denote the orientation of the protons with respect to the $N-C_2-C_3-C_4$ link.

The corresponding methyl esters (IIa and IIs) were therefore used for the gas-chromatographic analysis of the purity of the stereoisomers of I and for their assignment, by means of their PMR spectra, to the quinine and quinidine series.

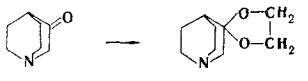


V VI

The esterification of I was carried out by twofold refluxing with methanolic hydrogen chloride with thorough azeotropic distillation of the water liberated in each step. Since the asymmetric center is not involved in the esterification, the pure diastereomer of the oxo ester of the quinine series (IIa) was obtained from the pure hydrochloride of Ia, while a 40:60 mixture of diastereomeric methyl esters IIa and IIs was obtained from a mixture of the hydrochlorides of Ia and Is. Diastereomeric oxo esters IIa and IIs were separated by means of preparative GLC, and their configurations were established on the basis of PMR spectroscopy, as was previously done for other 2,5-disubstituted quinuclidines [2]. Pure isomer IIa, which was isolated from the mixture, was identified from IIa obtained by the esterification of the pure hydrochloride of Ia.

The reduction of the ester function in II with prior protection of the ketone grouping was necessary to obtain 2-hydroxymethyl-5-oxoquinuclidines and their O-acyl derivatives.

The optimum conditions for ketal protection were worked out with unsubstituted 3-quinuclidone (III) with monitoring of the course of the reaction by GLC and paper chromatography (from the disappearance of the peak and spot, respectively, of III) and IR spectroscopy (from the disappearance of the $\nu_{C=O}$ band at 1730 cm^{-1}, characteristic for III).



III IV

The application of the reaction conditions worked out for the reaction of III with ethylene glycol in the presence of p-toluenesulfonic acid to a mixture of diastereomeric oxo esters IIa and IIs made it possible to accomplish the synthesis of the ethylene ketals of 2-methoxycarbonyl-5-oxoquinuclidines (Va and Vs) in yields of 92%.

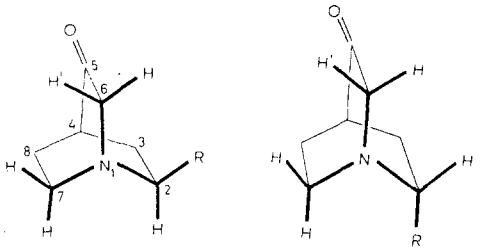


Fig. 1

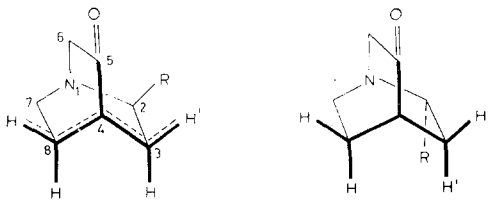


Fig. 2

Fig. 1. Relative orientation of the C_2 substituent and the C_6 protons in the diastereomers of I, II, VII, and VIII.

Fig. 2. Stereospecificity of the long-range spin–spin coupling constant of the 3-H' proton in the diastereomers of VII and VIII. (M is the path for transmission of the interaction through four σ bonds.)

The reduction of a mixture of Va and Vs with lithium aluminum hydride proceeded unambiguously without affecting the asymmetrical centers and resulted in a mixture of diastereomeric ethylene ketals of 2-hydroxymethyl-5-oxoquinuclidine (VIa and VIs). However, the removal of the ketal protection in VI required severe conditions: the reaction did not occur on prolonged refluxing with dilute sulfuric or hydrochloric acids but only as a result of heating at 160° for 12 h in a sealed tube with 18% hydrochloric acid to give 69% yields of 2-hydroxymethyl-5-oxoquinuclidines (VIIa and VIIs) in a mixture with the starting ethylene ketals (VIa and VIs) with a VII to VI ratio of 75 : 25. The pure syn isomer (VIIs) was isolated from this mixture due to the poor solubility of its hydrochloride in alcohol and the poor solubility of the base in anhydrous ether. The pure syn isomer of 2-benzoyloxymethyl-5-hydroxyquinuclidine (VIIIs) was obtained by the benzoylation of VIIs.

We subsequently demonstrated that a mixture of keto esters IIa and IIs can, without isolation of intermediates V, be converted in 30% yield to a mixture of diastereomeric VIIIa and VIIIs, during which the asymmetric centers are not affected in the course of the synthesis.

Owing to their different solubilities in ether, pure anti isomer VIIIa, which is related to the quinine series, and pure syn isomer VIIIs, which is related to the quinidine series, can be isolated from the mixture of diastereoisomers VIIIa and VIIIs.

The PMR spectral parameters used for the determination of the configurations of I, II, VII, and VIII are presented in Table 1.

For comparison, the chemical shifts of the protons of 3-quinuclidone (III) are also presented in Table 1. (In order to preserve the analogy with 2-substituted 5-oxoquinuclidines, the 2 and 3 positions in III are designated, respectively, as 6 and 5, and the 5 and 6 positions are designated as 3 and 2). The data in Table 1 demonstrate that the difference in the effects of the carbonyl group in III on the chemical shifts of the C_2, C_3, C_7, and C_8 protons in the syn and anti positions relative to the link of the $N-C_6-C_5-C_4$ bicycle with the C_5 carbonyl group is very insignificant. The insufficient stereospecificity of the effect of the C_5 carbonyl group on the chemical shifts of the C_2 proton is confirmed by the virtual coincidence of the chemical shifts of the C_2 protons in epimers IIa and IIs. Thus the chemical shifts of these protons cannot be used to establish the configuration of the compound.

The effect of the steric orientation of the C_2 substituents on the chemical shifts of the protons of the other fragments of the quinuclidine ring is exerted much more strongly. In Fig. 1 it is easy to see that the R substituent attached to C_2 in compounds of the syn series (Is, IIs, VIIs, and VIIIs) is adjacent to one of the C_6 protons, while in compounds of the anti series (Ia, IIa, VIIa, and VIIIa) it is adjacent to a C_7 proton.

The signals of the C_6 protons are the most convenient ones for observation, since they interact with one another to give a large geminal constant (~18 Hz) and interact with the remaining protons to give small long-range constants. (We will subsequently designate the C_6 proton as 6-H; its signal is found at weaker field than that of 6-H'.) Because of the presence of two asymmetrical centers in the molecule, the C_6 protons in 2-substituted 5-oxoquinuclidines are always nonequivalent, but the difference in the chemical shifts of the geminal protons ($\Delta\delta_{6\text{-}HH'} = \delta_{6\text{-}H} - \delta_{6\text{-}H'}$) depends markedly on the configuration of the diastereomer.

For the anti isomers of I, II, VII, and VIII, $\Delta\delta_{6\text{-}HH'}$ does not exceed 0.02 ppm, and one broad singlet with an intensity of two proton units is affiliated with the two C_6 protons. The $\Delta\delta_{6\text{-}HH'}$ values in the syn isomers of the same compounds are much larger (0.21-0.58 ppm). Thus the differences in the $\Delta\delta_{6\text{-}HH'}$ values in comparison with the effect of the C_2 substituents on the C_6 protons made it possible to assign the isomers of I, II, VII, and VIII to the syn and anti series.

It is interesting to note that, despite the different character of the C_2 substituents, the $\Delta\delta_{6\text{-}HH'}$ values for II, VII, and VIII lie in a narrow interval (0.42-0.58 ppm),* which makes it possible to limit the analysis of the reasons for this effect to the case of only one substituent – CH_2OH (in VII) – assuming that the effect of the remaining C_2 substituents will be qualitatively similar. The results of the calculation of the change in the chemical shifts of the C_6 protons in VIIa and VIIs as compared with III, which is caused by the difference in the anisotropy of the magnetic susceptibility of the C–H (in III) and C–C (in VII) bonds, with the use of the value $\Delta\chi_{CC}-\Delta\chi_{CH}=7\cdot10^{-30}$ cm^{-3} [3] and the results of the measurement of the experimental values are presented in Table 2.

As seen from Table 2, the most sizeable deviation between the calculated and experimental values consists in the observed weak-field shift of the syn-6-H signal in VIIs in place of the expected shift to strong field. This deviation is explained by the very small distance between the syn-6-H proton and the C_2 substituent, which, according to measurements on Dreiding molecular models, is 2.6 Å, i.e., 0.3 Å less than the sum of the van der Waals radii of the C and H atoms. At this distance, the chemical shifts can be substantially influenced by the fluctuating dipole effect [4], the evaluation of which from the formula $\Delta\delta = 163/R^6$ (where R is the distance in angstroms) [4] gives a shift of 0.5 ppm to weak field of the syn-6-H proton in VIIs. It is natural that the fluctuating dipole effect of the CH_2OH substituent on the syn-6-H proton is exerted more strongly than the anisotropic effects and determines the experimentally observed overall weak-field shift of syn-6-H in VIIs as compared with III. The fluctuating dipole effect does not have such significance for anti-6-H' in VIIs and both C_6 protons in VIIa because of the great distance between the C_2 substituent and the indicated proton. The experimental and calculated (with allowance for only the anisotropic effects) changes in the chemical shifts in these cases are therefore in qualitative agreement.

A characteristic feature of the PMR spectra of diastereomeric VII and VIII (as well as other quinuclidine derivatives with a CH_2R' grouping in the 2 position) is the shift of the signal of one of the β protons to strong field. On the basis of the magnitude of the vicinal spin–spin coupling constant (~7 Hz) of this proton with the C_2 protons, the indicated signal was assigned to the C_3 proton in the cis position relative to the R substituent attached to C_2. (It is designated as 3-H' in Table 1.) The character of the multiplet signal of this proton in the various isomers of VII and VIII additionally confirms the correctness of the assignment of the configurations of the diastereomers. The stereospecificity on the long-range spin–spin coupling constant through four σ bonds is well known [5]. In particular, these constants are ~1.7 Hz for quinuclidine derivatives for the M-path interaction and <0.5 Hz for the remaining long-range interactions of the β protons [6]. As shown in Fig. 2, the M path for transmission of the spin–spin coupling for the β proton in the cis orientation relative to the C_2 substituent is possible only for compounds of the syn series. In conformity with this, the peaks of the strongest-field multiplet in the PMR spectra of VIIs and VIIIs are additionally split by a long-range interaction that is absent in the spectrum of VIIIa.

EXPERIMENTAL

Analytical GLC was carried out with a Pye-Unicam series 104 chromatograph with a flame-ionization detector with a 2.1 m by 4 mm column packed with SE-30 silicone elastomer (10%) on silanized Diatomite S (100-120 mesh). The nitrogen flow rate was 30 ml/min, and the column temperature was 200°. The retention times in minutes were as follows: 5.4 for IIa, 6.0 for IIs, 2.2 for III, 3.9 for IV, 11.2 and 11.7 for Va and Vs, 9.5 for VIa and VIs, and 4.9 for VIIs.

Paper Chromatography. Descending paper chromatography on "for-chromatography" paper was carried out in a n-butanol–water–acetic acid (5:4:1) system. A 0.2% alcoholic ninhydrin solution was used to detect the hydrochlorides of acids Ia and Is, while the Dragendorf reagent was used for the remaining substances. The following R_f values were obtained (the color during detection is given in parentheses): 0.29

* Several deviations of this value that were observed in the case of I were caused by the fact that the PMR spectra of I were obtained from acid solutions (2N DCl), in which protonation of the nitrogen could be reflected in the conformation (and in the electric field effect) of the COOH group.

for Ia and Is (light blue), 0.63 for IIa and IIs (rose), 0.42 for III (lilac), 0.58 for IV (orange-rose), 0.72 for Va and Vs (orange-rose), 0.53 for VIa and VIs (orange), 0.42 for VIIs (rose), and 0.80 for VIIIa and VIIIs (orange).

The IR spectra of suspensions of the preparations in mineral oil were recorded with a UR-10 spectrometer.

The PMR spectra were recorded with a JNM-4H-100 spectrometer with an operating frequency of 100 MHz. Carbon tetrachloride was used as the solvent for II, III, VII, and VIII with tetramethylsilane as the internal standard. Deuterium oxide was used as the solvent for the hydrochlorides of Is and Ia with tert-butyl alcohol as the internal standard ($\delta = 1.20$).

anti-5-Oxoquinuclidine-2-carboxylic Acid (Ia). A 40.52-g (197 mmole) sample of a mixture of the diastereomeric hydrochlorides of 5-oxoquinuclidine-2-carboxylic acid [1] with mp 276-278° was crystallized from 100 ml of distilled water. The weight of the precipitated crystals after filtration and drying was 14.47 g, and they melted at 291°. These crystals were recrystallized from 50 ml of water to give 7.03 g of a substance with mp 296°. Three crystallizations from 40 ml of water gave 2 g of the pure anti isomer of the hydrochloride of acid I with mp 297°. Further crystallization did not raise the melting point. The mother liquors yielded an additional 5.97 g of a substance with mp 297° (dec.) after several recrystallizations from water. The overall yield of Ia was 7.97 g (19.6%). The colorless crystals were soluble in water, less soluble in methanol, slightly soluble in hot alcohol, and insoluble in the other ordinary organic solvents. IR spectrum: 1740-1760 cm^{-1} (CO, COOH). Found: C 46.7; H 5.7; Cl 17.4; N 6.5%. $C_8H_{11}NO_3 \cdot HCl$. Calculated: C 46.7; H 5.9; Cl 17.2; N 6.8%.

anti-2-Methoxycarbonyl-5-oxoquinuclidine (IIa). A 6.59-g (32.1 mmole) sample of the hydrochloride of acid Ia was refluxed for 4 h with 66 ml of methanol containing 10% hydrogen chloride. The reaction mass was evaporated to dryness, and water and alcohol residues were removed by two distillations with anydrous benzene. The esterification with alcoholic hydrogen chloride was repeated. The base was isolated by the addition of 50% potassium carbonate solution until the mixture was alkaline to phenolphthalein and extracted with ether. The extract was dried with potassium carbonate and vacuum-evaporated. The residue was fractionated at 98-100° (0.2 mm) to give 2.98 g (58%) of colorless crystals of IIa with mp 47.5-49.5°. The compound was quite soluble in the usual organic solvents, slightly soluble in water, and soluble in hot petroleum ether, hexane, and heptane. Gas-liquid chromatography gave one peak with a retention time of 5.4 min. IR spectrum: 1720-1740 cm^{-1} (C=O). Found: C 59.3; H 7.5; N 7.4%. $C_9H_{13}NO_3$. Calculated: C 59.0; H 7.1; N 7.7%.

syn- and anti-Isomers IIs and IIa. A mixture of diastereomeric 2-methoxycarbonyl-5-oxoquinuclidines obtained by the method in [1] was separated with a Pye-Unicam series 105 automatic preparative gas-liquid chromatograph with a flame-ionization detector and a 4.6 m by 8 mm column packed with SE-30 silicone elastomer (25%) on silanized diatomite S (60-72 mesh) at a nitrogen flow rate of 150 ml/min and a column temperature of 200°. A solution of 0.5 g (2.73 mmole) of a mixture of IIa and IIs in 1 ml of methanol was introduced into the column in six 100-μl portions. Fractions IIa were selected in the interval of retention times from 19.4-21.2 min, and fractions IIs were selected in the 25.3-27.4 min interval. The purities of the substances were monitored by analytical GLC. A total of 0.1 g of diastereomer IIa of no less than 93% purity and 0.05 g of diastereomer IIs of no less than 90% purity were collected. From the PMR spectrum and the retention time, the isolated diastereomer IIa was identical to IIa obtained by the esterification of pure diastereomer Ia.

3-Quinuclidone Ethyleneketal (IV). A total of 12.4 g (72 mmole) of p-toluenesulfonic acid and a solution of 6 g (48 mmole) of 3-quinuclidone (III) in 60 ml of anhydrous benzene were added to a solution of 3.58 g (58 mmole) of ethylene glycol in 40 ml of anhydrous benzene. The reaction mass was refluxed for 4 h with a Dean–Stark adapter until water liberation ceased, and it was then treated with 20 ml of 40% sodium hydroxide and extracted with benzene. The benzene extract was dried with potassium carbonate and vacuum-evaporated. The residue was distilled to give 7.38 g (88.3%) of IV, which, according to GLC, was 98.5% pure. The colorless viscous liquid had bp 82-84° (3 mm), n_D^{20} 1.4950, and was soluble in water and the usual organic solvents. IR spectrum: the ν_{CO} band at 1730 cm^{-1} was absent. Found: C 64.0; H 9.0; N 8.6%. $C_9H_{15}NO_2$. Calculated: C 63.9; H 8.9; N 8.3%.

Ethyleneketal of a Mixture of syn- and anti-2-Methoxycarbonyl-5-oxoquinuclidines (Vs and Va). A total of 11.7 g (68 mmole) of p-toluenesulfonic acid and 8.3 g (45 mmole) of a mixture of diastereomeric IIa and IIs in 100 ml of anhydrous benzene were added to a solution of 3.37 g (54 mmole) of ethylene glycol in 50 ml of anhydrous benzene. The reaction mass was refluxed with stirring for 2 h with a Dean–Stark adapter until water liberation ceased. For complete removal of moisture residues, 80 ml of the solvent was removed by distillation, 80 ml of anhydrous benzene was added, and the mixture was refluxed with stirring for 1 h. This operation was repeated, the mixture was cooled to room temperature, and 45 ml of 50% potassium carbonate solution was added. The precipitate was removed by filtration, and it and the aqueous layer were extracted thoroughly with benzene. The extract was dried with potassium carbonate and evaporated in vacuo. The residue (9.89 g), according to GLC, was a 96.1% mixture of diastereomeric Va and Vs (92.5% yield); two poorly separated peaks of the diastereomers with retention times of 11.2 and 11.7 min were observed on the chromatogram. The colorless liquid with bp 122-125° (0.7 mm) and n_D^{20} 1.4932 was soluble in the usual organic solvents and slightly soluble in water. Found: C 58.4; H 7.6; N 6.0%. $C_{11}H_{17}NO_4$. Calculated: C 58.1; H 7.5; N 6.2%.

Ethyleneketal of a Mixture of syn- and anti-2-Hydroxymethyl-5-oxoquinuclidines (VIs and VIa). A total of 3.95 g (17.4 mmole) of a mixture of diastereomeric Va and Vs in 50 ml of anhydrous ether was added gradually with stirring to a suspension of 3.3 g (87 mmole) of lithium aluminum hydride in 50 ml of anhydrous ether. The reaction mass was refluxed for 3 h and cooled with ice, and 10 ml of water was added gradually. The mixture was stirred for another 0.5 h, and the lithium and aluminum hydroxides were removed by filtration and washed with ether. The combined ether solutions were dried with magnesium sulfate and vacuum-evaporated. The residue [2.88 g [83.7%)] was ethyleneketal VI with bp 105-106° (0.5 mm) and n_D^{20} 1.5110. The colorless liquid was soluble in water and the usual organic solvents. IR spectrum: 3400 cm^{-1} (OH). Found: C 60.6; H 8.7; N 7.3%. $C_{10}H_{17}NO_3$. Calculated: C 60.3; H 8.6; N 7.0%.

syn-2-Hydroxymethyl-5-oxoquinuclidine (VIIs). A 4.82-g (25.2 mmole) sample of a mixture of diastereomeric VIa and VIs was heated with 52 ml of 18% hydrochloric acid in a sealed tube at 160° for 12 h. The solution was filtered and vacuum-evaporated, and the residue was dissolved in 5 ml of water. The solution was made alkaline with 50% potassium carbonate solution and extracted with chloroform. The extract was dried with potassium carbonate and vacuum-evaporated. The residue was distilled at 105-110° (0.8 mm) to give 3.49 g of a mixture, which, according to GLC, contained 24.5% of the starting ketal and 74.5% of 2-hydroxymethyl-5-oxoquinuclidine (69.3% yield). The latter was displayed on the chromatogram as a broad band (with an inflection) corresponding to the two diastereomers. A 3.49-g sample of this mixture was dissolved in 16.5 ml of anhydrous alcohol, and 7 ml of 20% alcoholic hydrogen chloride was added to it. The mixture was cooled, and the precipitated crystals were separated. The crystals (1.69 g, mp 260°) were made alkaline with 50% potassium carbonate solution and extracted with chloroform. The extract was dried with potassium carbonate and evaporated in vacuo. The residue was recrystallized from anhydrous ether to give 0.8 g (21% based on the mixture of starting diastereomeric ketals VIa and VIs) of VIIs as colorless crystals with mp 73-75° (from ether). The substance was quite soluble in water and chloroform, less soluble in the other ordinary organic solvents, soluble in hot ether, and less soluble in hot petroleum ether. IR spectrum: 1735 cm^{-1} (C=O), 1000, 1075, 3140-3200 cm^{-1} (OH). Found: C 61.6; H 8.3; N 8.7%. $C_8H_{13}NO_2$. Calculated: C 61.9; H 8.4; N 9.0%. The hydrochloride was obtained as colorless crystals with mp 261° (dec., from anhydrous alcohol). The substance was quite soluble in water, methanol, and hot anhydrous ethanol, and insoluble in the other ordinary organic solvents. Found: Cl 18.2; N 7.3%. $C_8H_{13}NO_2 \cdot HCl$. Calculated: Cl 18.5; N 7.3%.

syn-2-Benzoyloxymethyl-5-oxoquinuclidine (VIIIs). Benzoyl chloride [1.09 g (7.8 mmole)] was added gradually with ice cooling and stirring to a solution of 0.8 g (5.2 mmole) of VIIs in 10 ml of anhydrous distilled pyridine. The reaction mixture was stirred at 100° for 3 h and cooled, and 7 ml of water and 7 ml of a 50% potassium carbonate solution were added. The liberated base was extracted with benzene. The extract was dried with potassium carbonate and vacuum-evaporated. The residual pyridine was removed by distillation with anhydrous xylene to give 1.02 g (91.5%) of VIIIs as colorless crystals with mp 95-96.5°. The substance was soluble in the usual organic solvents, in hot ether and hexane, and insoluble in water. IR spectrum: 1710-1720 cm^{-1} (C=O, COOAr). Found: C 69.4; H 6.7; N 5.6%. $C_{15}H_{17}NO_3$. Calculated: C 69.5; H 6.6; N 5.4%. The hydrochloride was obtained as colorless crystals with mp 260° (dec.). The substance was soluble in water and insoluble in the usual organic solvents. Found: Cl 11.8; N 4.6%. $C_{15}H_{17}NO_3 \cdot HCl$. Calculated: Cl 12.0; N 4.7%.

syn- and anti-Isomers VIIIs and VIIIa. A 3.9-g sample of the mixture of substances obtained after distillation of the products of the saponification of ethyleneketal VI, which, according to GLC, contained 74.5% of diastereomeric 2-hydroxymethyl-5-oxoquinuclidines (18.7 mmole), was dissolved in 40 ml of anhydrous distilled pyridine. Benzoyl chloride [3.96 g (28.2 mmole)] was added with stirring to the ice-cooled solution. The reaction mass was stirred at 100° for 4 h and cooled, and 15 ml of water and 20 ml of 50% potassium carbonate solution were added. The liberated base was extracted with benzene, and the extract was dried with potassium carbonate and evaporated in vacuo. The residual pyridine was removed by distillation with anhydrous xylene. The residue was fractionated in vacuo twice to give 2.45 g of a mixture of diastereomers VIIIa and VIIIs with bp 170-175° (0.4 mm) as an oil that crystallized on standing. Thorough trituration with anhydrous ether and subsequent crystallization from ether gave 0.14 g of crystals of VIIIs with mp 91-93°; the compound crystallized out at room temperature after melting. Cooling of the ether mother-liquor precipitated 0.14 g of crystals of a mixture of VIIIa and VIIIs with mp 74-75°. The residual mother liquor was markedly diluted with anhydrous ether and carefully evaporated until crystallization commenced to give 0.07 g of colorless crystals of VIIIa with mp 86-89°. The crystals were soluble in the usual organic solvents, in hot ether and hexane, and insoluble in water. The melting point was depressed when the product was mixed with a sample of VIIIs (72-79°). IR spectrum: 1710-1720 cm^{-1} (C = O, COOAr); there are slight differences, as compared with the IR spectrum of VIIIs, at 1350, 1190, 1150, 905, and 760 cm^{-1}). Found: C 69.2; H 6.5; N 5.4%. $C_{15}H_{17}NO_3$. Calculated: C 69.5; H 6.6; N 5.4%.

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