nitrogen atmosphere. For the potentiometric titration we used a circuit consisting of a glass electrode and silver chloride electrode with potassium chloride saturated in methanol. The glass electrode was first immersed in 0.1 N aqueous hydrochloric acid over 24 h and then for about this duration in distilled water, while it was immersed prior to operation in DMF for about 1 h. Measurement of the electromotive force of the circuit in a buffer solution consisting of benzoic acid and sodium benzoate ($c_{acid} = c_{salt} = 1$ mM) was used to follow the state of the glass electrode. A weighed sample of the compound studied was dissolved in 15 ml DMF. Then, 1 eq. 0.01 N sodium methylate solution was added. The mixture was thoroughly stirred using a magnetic stirrer and the pH was measured thrice on a 362 pH-meter. Benzoic acid, which was used as the standard, was titrated with sodium methylate under analogous conditions.

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CATALYTIC REDUCTION OF 4-(3-OXOQUINUCLIDYL-2-METHYLIDENE)-6-METHOXYQUINOLINE AND ITS ETHYLENEKETAL

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An examination was carried out on the catalytic reduction of 4-(3-oxoquinuclidyl-2-methylidene)-6-methoxyquinoline, its ethyleneketal, and the ethyl ester of 6-(3,4-dimethoxystyryl)picolinic acid. Stepwise nature was shown for the hydrogenation of the pyridine and quinoline rings, side chains, and catalytic demethoxylation using PMR spectroscopy, mass spectrometry, and gas–liquid chromatography.

In a search for new cardiovascular drugs, we studied the catalytic reduction of possible intermediates in their synthesis, namely 4-(3-oxoquinuclidyl-2-methylidene)-6-methoxyquinoline (I) and its ethyleneketal (V). PMR spectroscopy, mass spectrometry, and gas–liquid chromatography were used to study the stepwise hydrogenation of the exocyclic double bond and the different fragments and the catalytic demethoxylation (see scheme at top of following page).

Quinoline (I) was obtained according to Bender [1] by the condensation of 3-quinuclidone with quinaldehyde and its structure was confirmed by PMR spectroscopy (Table 1). Similarly to analogously synthesized 2-arylidene- and 2-heteroarylidene-3-oxoquinuclidines [2-4], I is

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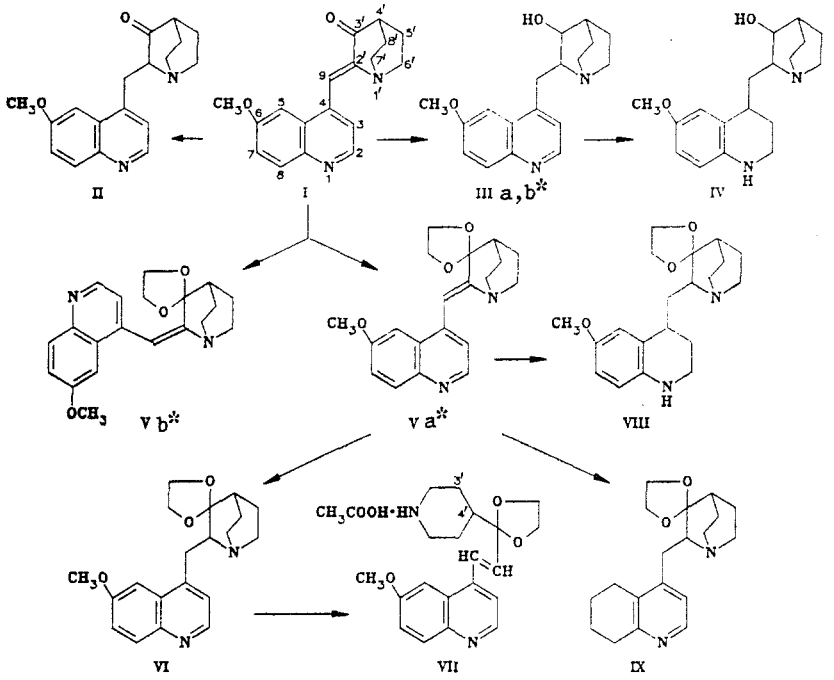
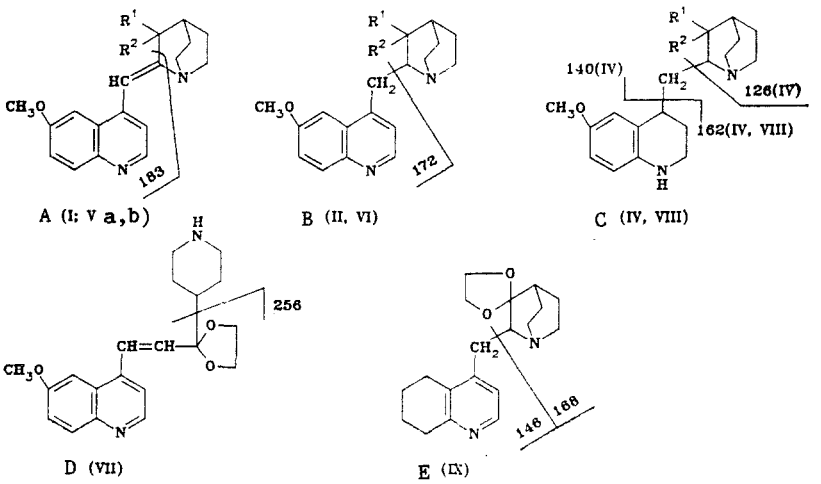


a Z isomer but undergoes Z–E isomerization in acid medium as indicated by the appearance of a second set of PMR peaks in a spectrum taken in CD_3OD. The mass spectrum of I (Table 2, scheme A) shows a strong molecular ion peak 294† and fragments of stepwise bond dissociation in the quinuclidine system: $[M - CO]^+$ 266, $[M - HCO]^+$ 265, $[M - COCH_3]^+$ 251, $[M - CO - C_2H_4]^+$ 238, $[M - COC_2H_5]^+$ 237, and also the 183 ion, whose formation is a consequence of the conjugation of the exocyclic double bond with the 6-methoxyquinoline ring. The catalytic reduction of I in the presence of palladium on activated charcoal at room temperature led to a 61.5% yield of (3'-oxoquinuclidyl-2')(6-methoxyquinolyl-4)methane (II). The PMR spectrum of (II) lacks the singlet for the proton at $C_{(9)}$, while multiplets arise at 2.8-3.8 ppm corresponding to 9-H and 2'-H with an integral intensity of three proton units. The oxo group at $C_{(3')}$ of the quinuclidine system as indicated by the chemical shift of the proton at $C_{(4')}$ (2.55 ppm) [5]. The mass spectrum shows a molecular ion peak at 296, corresponding to the addition of two hydrogen atoms to unsaturated ketone I and a strong peak for the 172 ion, indicating reduction of the exocyclic double bond with retention of the 6-methoxyquinoline ring (Table 2; scheme B).

Major pathways for the mass spectrometric decomposition of I-IX



A, B, C I, II $R^1 R^2$ = O; III, IV R^1 = OH, R^2 = H; Va, b, VI, VIII $R^1 R^2$ = OCH_2CH_2O

*The letters a and b in the scheme indicate structural isomers of the same compounds.
†Here and below, the m/z values are given.

TABLE 1. PMR Spectra of I-IX (δ-scale, ppm)

Compound*	Quinuclidine (or piperidine) fragment**		Quinoline system							Linking chain	Ketal protective group
	3'-H	4'-H	2	3	4	5	6 (OCH_3), s	7	8		
I	—	2,73 qn	8,80 d	8,09 d	—	7,31 d	3,98	7,39 q	8,03 d	7,70 s	
II	—	2,55 qn	8,67 d	7,25...7,45	—	7,25...7,45	3,96	7,25...7,45	8,03 d	2,7...3,8	
III	3,90***, 4,05 q	1,96 m	8,48; 8,37	7,2...7,4	—	7,2...7,4	3,92 3,93	7,2...7,4	7,9...8,0	2,7...3,4	
IV	3,80***, 3,94 q	1,9 m	2,5...3,5	1,4...2,0		6,4...6,8	3,74	6,4...6,8		2,5...3,5	
Va	—	2,09 qn	8,74 d	7,73 d	—	7,27 d	3,95	7,36 q	8,0 d	6,97 s	4,0...4,4
Vb	—	1,91 qn	8,70 d	7,43 q	—	7,17 d	3,91	7,35 q	7,98 d	6,99 d	3,1...3,2; 3,6...3,7
VI	—	1,89 m	8,66 d	7,2...7,4	—	7,2...7,4	3,95	7,2...7,4	8,0 d	3,13 q; 3,31 q	3,6...4,0
VII	1,65...3,05		8,72 d	7,42 d	—	7,26 d	3,96	7,40 q	8,04 d	7,33 d; 6,27 d (J = 16 Hz)	4,03 m
VIII	—	~1,99	2,6...3,35	1,4...2,25		6,75 d	3,79	6,65 q	6,50 d	2,6...3,35	3,80...4,05
IX	—	1,83	8,22 d	6,97 d	—	2,4...3,05	1,3...2,15		2,4...3,05	2,4...3,0	3,6...4,05

*Compounds III and IV were studied as diastereomer mixtures; VII was studied as its acetic acid salt, δ_{COCH_3} 1.92 ppm.
**The signals for the protons at the α- and β-positions relative to the nitrogen atom of the quinuclidine and piperidine groups appear as overlapping multiplets at 2.4-3.8 and 1.30-2.25 ppm, respectively.
***The multiplicity was not determined due to overlap with the OCH_3 group signal.

TABLE 2. Mass Spectra of I-IX*

Compound	m/z (I_{rel}, %)
I	294 (100), 279 (10), 266 (30), 265 (27), 251 (23), 238 (40), 237 (33), 197 (13), 183 (27), 140 (10)
II	296 (4), 268 (100), 267 (22), 253 (59), 240 (39), 227 (80), 199 (11), 184 (16), 173 (39), 172 (86), 96 (16)
IV	302 (55), 271 (18), 245 (55), 194 (16), 162 (100), 160 (55), 140 (58), 126 (67), 98 (14), 82 (15)
Va	338 (100), 323 (12), 266 (14), 265 (19), 251 (19), 238 (25), 237 (20), 224 (11), 197 (7), 183 (16)
Vb	338 (100), 323 (8), 266 (13), 265 (20), 251 (20), 238 (17), 237 (18), 224 (8), 197 (9), 183 (13)
VI	340 (62), 268 (31), 267 (14), 253 (37), 240 (35), 227 (55), 173 (40), 172 (100), 168 (54), 156 (24)
VII	340 (19), 259 (17), 258 (89), 257 (21), 256 (100), 211 (13), 182 (11), 172 (14), 171 (25), 82 (10)
VIII	344 (8), 256 (22), 237 (18), 183 (13), 172 (32), 162 (57), 160 (33), 110 (100), 99 (37), 69 (46), 55 (90)
IX	314 (94), 242 (56), 241 (25), 227 (19), 202 (100), 168 (44), 158 (44), 146 (38), 130 (12), 96 (88)

*The ten strongest and weakest molecular ion peaks are given.

The catalytic reduction of unsaturated ketone I in the presence of Raney nickel at room temperature and 196-294 Pa hydrogen pressure also gave II (in 31% yield). The yield of II is reduced to 20% at 40°C and 70 atm.

More vigorous hydrogenation conditions (H_2/Ni, 40°C, 100 atm) gave a mixture in which IIIa and IIIb are the major products as indicated by PMR spectroscopy and mass spectrometry (the content of the other compounds did not exceed 5%). This is supported by the absence of the signal for 9-H at the double bond, an upfield shift of the signal for 4'-H to 1.95 ppm, and the appearance of signals at 3.9-4.0 ppm assigned to the 3'-H protons of the two diastereomers. Similar values of the chemical shifts of 3-H and 4-H protons were observed in our previous work in the PMR spectra of 2-carboxy-3-oxoquinuclidines [6]. An analogous sequence of reduction of the exocyclic double bond in position 2 and of the keto group at position 3 in the quinuclidine system has been described for other compounds [7, 8].

The hydrogenation of the mixture of diastereomers IIIa and IIIb at 100°C and 120 atm over nickel led to the formation mainly of diastereomers IV. However, this reaction is accompanied by tar formation and the preparative separation of the products is difficult. The PMR spectrum of IV lacks signals for pyridine ring protons, while the signals for the benzene ring and OCH_3 group protons are found at higher field than in IIIa and IIIb. The signals at 3.8-3.95 ppm may be assigned to the 3'-H protons of diastereomers IV. The mass spectrum of IV has molecular ion 302. A characteristic feature of the mass spectral decomposition of IV is the lack of ions 183 and 172 and presence of strong peaks 162, 140, and 126, which indicates the reduction of the pyridine ring in the quinoline portion of the molecule in addition to the exocyclic double bond and the keto group (Table 1; scheme C).

In order to avoid the reduction of the carbonyl group in I and simplify the stereochemistry of the reactions, unsaturated ketone I was converted to its ethyleneketal V by heating this ketone with ethylene glycol in the presence of p-toluenesulfonic acid in benzene at reflux with the azeotropic distillation of water. This reaction is accompanied by the partial isomerization of the Z-isomer of unsaturated ketal Va to E-isomer Vb. These isomers could be preparatively separated due to their different solubility in ether. The less-soluble E-isomer Vb (Table 1) is characterized by a strong upfield shift in the PMR signals of the ketal protective group protons in comparison with the analogous protons of Z-isomer Va, which has better solubility in ether. This shift may be attributed to the magnetic anisotropy effect of the quinoline fragment, which is close to the ketal protective group protons in the E-isomer. The same anisotropic effect may be used to explain the greater difference in the chemical shifts of the pairwise equivalent protons of the ketal protective group in E-isomer Vb in comparison with Z-isomer Va.

The marked difference in the long-range $^4J_{93}$ coupling constants for Va ($\leq$0.5 Hz) and Vb (1.2 Hz) is a feature of these PMR spectra, which supports the hypothesis of a different orientation of the quinoline system relative to the double bond in isomers Va and Vb. The total yield of ketals Va and Vb is 62 and 28%, respectively.

Isomeric ketals Va and Vb have mass spectra, which differ only slightly in the relative intensities of the major ions. The only slight difference in these mass spectra is apparently related to fragmentation of Va and Vb after opening of the molecular ion at the $C_{(2')}$–$C_{(3')}$ bond (Table 2, scheme A).

The reduction of unsaturated ethyleneketal Va in the presence of a Pd/C catalyst at room temperature proceeds, as in the case of unsaturated ketone I, only at the exocyclic C=C bond and leads to (3',3'-ethylenedioxyquinuclidyl-2')(6-methoxyquinolyl-4)methane (VI). The PMR spectrum of VI (Table 1) lacks the singlet for the protons at the double bond of the side chain, which is characteristic for Va and Vb, but shows quartets for the two inequivalent 9-H protons at 3.13 and 3.31 ppm. The mass spectrum (Table 2; scheme B) has molecular ion 340 and a strong ion peak 172, which is also seen for II.

Further reduction of VI on a platinum catalyst in methanol at pH 8 does not proceed, while reduction in 60% acetic acid gives the acetate of 4-[3"-(piperidyl-4')-3",3"-ethylenedioxypropen-1"-yl-1"]-6-methoxyquinoline (VII). The formation of VII is not relative to the hydrogenation reaction and is attributed to opening of the quinuclidine fragment by the action of acetic acid (similar reactions are discussed by Mikhlina and Yakhontov [9]). Upon prolonged standing of a solution of VI in glacial acetic acid at room temperature it is also converted to VII. The finding of a trans-disubstituted double bond is indicated by the presence of two downfield doublets in the PMR spectrum (Table 1) with splitting of $\sim$16 Hz. Upfield

TABLE 3. Retention Time (t) and Mass Spectral Characteristics of X-XVa, b

Compound	t, min	m/z (I_{rel}, %)			
		M^+	$M-COOC_2H_5^-$	$M-CH_2CH_2A^{+*}$	CH_2A^{+*}
X	10,4	313 (80)	240 (20)	—	—
XI	4,8	267 (1)	194 (100)	156 (67)	—
XII	8,5	315 (90)	248 (2)	—	151 (100)
XIII	8,0	321 (17)	248 (100)	156 (56)	151 (35)
XIV	7,0	327 (1)	254 (70)	156 (100)	—
XVa	5,8	297 (1)	224 (70)	156 (100)	—
XVb	6,2	297 (1)	224 (70)	156 (100)	—

** XI $A=C_6H_{11}$; XII, XIII $A=C_8H_9O_2$; XIV $A=C_8H_{15}O_2$; XVa,b $A=C_7H_{13}O$.

signals are found, which are characteristic of 4-substituted piperidines: major doublet of the equatorial protons and major triplet of axial protons 2'-H and 6'-H and also the complex multiplet of highly coupled protons 3'-H, 5'-H, and 4'-H. We should note the absence of the equidistant quintet with splitting of about 3 Hz in the PMR spectrum, which is characteristic for the spectra of 3,3-disubstituted quinuclidines. The mass spectrum of VII with retention of the molecular ion mass of 340 a.u. differs markedly from the mass spectra of quinuclidine compounds (Table 2; scheme D). This spectrum lacks the characteristic fragments 268 and 172, but shows strong peaks 256 and 258. According to the DADI spectrum, ion 256 is formed directly upon the decomposition of the molecular ion and corresponds to elimination of the piperidine ring with charge stabilization on the ethyleneketal group oxygen atoms. At the onset of evaporation, the mass spectrum shows peaks of the acetic acid spectrum [60 (M^+), 45 $(M - CH_3)^+$, 43 $(M - OH)^+$], supporting the salt-like nature of VII.

The reduction of Va on a nickel catalyst under the conditions for the conversion of I to 6-methoxy-1,2,3,4-tetrahydroquinoline derivative IV (100°C, 120 atm) gives a mixture of compounds. PMR spectrum indicated that the major product is (3',3'-ethylenedioxyquinuclidyl-2')(6-methoxy-1,2,3,4-tetrahydroquinolyl-4)methane (VIII), which was not isolated preparatively. The PMR spectrum shows signals for the protons of the benzene ring, methoxy group, and partially reduced quinoline ring (Table 1). The mass spectrum (Table 2, scheme C) shows molecular ion 344, corresponding to the addition of six hydrogen atoms to Va and strong fragment peak 162, which is common with the fragment obtained upon the decomposition of IV due to electron impact.

The reduction of Va in anhydrous ethanol, containing an equimolar amount of hydrogen chloride using a platinum catalyst at 90-95°C and 196-294 Pa hydrogen pressure proceeds entirely in a different manner. Reduction of the benzene fragment and catalytic demethoxylation occur in addition to the hydrogenation of the exocyclic double bond. The PMR spectrum of the product, (3',3'-ethylenedioxyquinuclidyl-2')-(5,6,7,8-tetrahydroquinolyl-4)methane (IX) (Table 1) at low field shows only two doublets, corresponding to pyridine ring protons. The signal for OCH_3 group protons is lacking. Signals for the individual protons of the quinuclidine system and methylene protons of the ketal protective group may be identified at higher field. The signals of most of the quinuclidine fragment protons are overlapped by two strong multiplets of equal intensity centered at 1.80 and 2.70 ppm, which correspond to the alicyclic protons of the 5,6,7,8-tetrahydroquinoline fragment. The mass spectrum of IX (Table 2) has molecular ion peak 314 and lacks the fragment peak 162, characteristic for 1,2,3,4-tetrahydroquinoline derivatives. The formation of observed peaks 146 and 168 is illustrated in scheme E.

There has been a report of the catalyzed demethoxylation only for ortho-methoxyphenols with their conversion into the corresponding cyclohexanols [10].

We obtained the ethyl ester of 6-(2-cyclohexylethyl)pipecolinic acid (XI) in the reduction of the ethyl ester of 6-(3,4-dimethoxystyryl)picolinic acid (X), which was identical to the product of the catalytic reduction of the ethyl ester of 6-styrylpicolinic acid under the same conditions [11].

In light of the hydrogenation of the benzene ring with concurrent catalytic demethoxylation in the preparation of IX from Va, we undertook a detailed study of the analogous transformation of X to XI. For this purpose we carried out the hydrogenation of styryl derivative

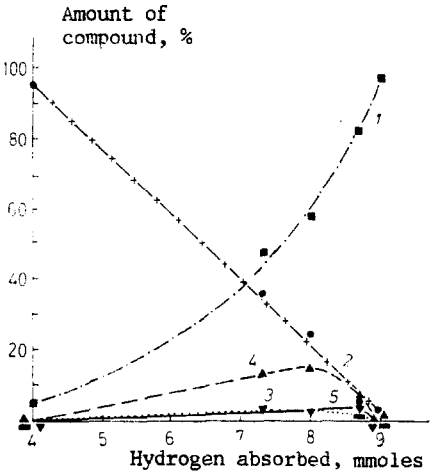
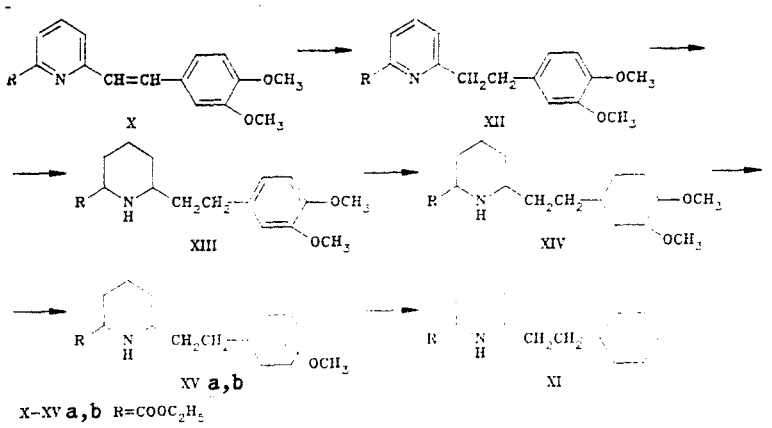


Fig. 1. Dependence of the amounts of XI and XIII-XVa, b formed in the hydrogenation of X over platinum in ethanolic HCl at 20°C and 196-294 Pa hydrogen pressure on the amount of hydrogen absorbed: 1) XI; 2) XIII; 3) XIV; 4) XVa; 5) XVb.

X under the conditions described in our previous work [11] using an Adams platinum catalyst in ethanolic hydrogen chloride at 20°C and 196-294 Pa hydrogen pressure. In contrast to our previous procedure [11], the hydrogenation was stopped after the absorption of given amounts of hydrogen and the composition of the products was studied by gas–liquid chromatography and chromato-mass spectrometry (Table 3).

According to the data obtained, the conversion of X to XI proceeds through the following scheme:



The finding of a strong peak 151 $(CH_2A)^+$ in the mass spectrum of XII and XIII characterizes their benzylic decomposition and indicates reduction of the double bond of the styryl fragment up to the conversion of the benzene ring to a cyclohexane ring. On the other hand, the strong peaks for $(M - CO_2C_2H_5)^+$ and $(M - CH_2CH_2R)^+$ in the mass spectra of XIII-XVa, b and XI indicates hydrogenation of the pyridine ring. These results indicate that the hydrogenation of the pyridine ring in XIII precedes reduction of the benzene ring. The mass number 327 in the mass spectra of XIV corresponds to the product of the hydrogenation of the benzene and pyridine rings with retention of the methoxy groups. Compounds XVa, XVb, and XI have peaks for the molecular ions and $(M - CO_2C_2H_5$ fragments, corresponding to hydrogenation of the exocyclic ethylene group and benzene and pyridine rings as well as the consecutive replacement of one (in XVa and XVb) or both methoxy groups (in XI) by hydrogen. The positions of the methoxy groups in monomethoxy derivatives XVa and XVb were not established. The conversion of X to XI by the above scheme was also indicated by the curves for the dependence of the amount of each compound in the reaction mixture (Fig. 1) on the amount of hydrogen consumed in the hydrogenation.

EXPERIMENTAL

The IR spectra were taken on a Perkin–Elmer 599 spectrometer in Vaseline mull. The UV spectra were taken on a Perkin–Elmer 575 spectrometer in ethanol.* The PMR spectra were taken on a Varian XL-200 spectrometer at 200 MHz in $CDCl_3$ with TMS as the internal standard. The

*The IR and UV spectra were taken and interpreted by N. M. Rubtsov and T. Yu. Kurbatova, to whom the authors express their gratitude.

mass spectra and DADI spectra were taken on a Varian MAT-112 mass spectrometer with direct sample inlet into the source and with inlet through a chromatograph (X-XVa, b). The ionizing electron energy was 70 eV. The chromatography was carried out on a Varian Aerograph 1440 with helium as the gas carrier. The helium flow rate was 20 ml/min. The work was carried out on a 2000 × 2 mm column packed with 3% OV-101 on Chromosorb W (80-100 mesh). The injector temperature was 230°C and the evaporator temperature was 250°C. The temperature programming of the column was from 150 to 250°C at 20°C/min. The reaction course and purity of the compounds obtained were monitored by thin-layer chromatography on Silufol UV-254 plates with development in UV light and eluents: A) 20:1 methanol—ammonia and B) 15:1 chloroform—methanol. The gas—liquid chromatography for I, II, Va, Vb, VI, and IX was carried out on a Khrom-5 chromatograph using a flame ionization detector, 40 ml/min helium gas carrier flow rate, and 1000 × 3 mm column packed with 5% OV-17 on Chromatone NHMDS (80-100 mesh) at 260°C. The gas—liquid chromatography of X-XVa, b was carried out on a Varian 3700 chromatograph using a katharometer detector, 35 ml/min helium gas carrier flow rate, and 500 × 1 mm column packed with 3% OV-10 on Chromosorb (100-120 mesh) with temperature programming of the column from 140 to 220°C at 20°C/min. The elemental analysis data for C, H, and N corresponded to the calculated values.

(3'-Oxoquinuclidyl-2')(6-methoxyquinolyl-4)methane (II, $C_{18}H_{20}N_2O_2$). A. A sample of 35 ml 1 N HCl was added to a solution of 2 g (6.8 mmoles) 4-(3-oxoquinuclidyl-2-methylidine)-6-methoxyquinoline (I) [1] in 50 ml water and the mixture was hydrogenated in the presence of 0.2 g 5% palladium on activated charcoal at 20°C and 196-294 Pa hydrogen pressures until starting I [R_f 0.77 (A), 0.66 (B), gas—liquid chromatography 6.83 min, IR spectrum: 1698, 1610 cm^{-1} (C=O), UV spectrum: λ_{max} (log ε): 366 (4.29), 338 nm (4.28)] disappeared as indicated by thin-layer chromatography. The catalyst was filtered off. The filtrate was made basic by the addition of 50% aqueous potassium carbonate to pH 9 and extracted with four 50-ml portions of ether. The ethereal extract was dried over potassium carbonate and evaporated. The residue was recrystallized from ethanol to give 1.24 g (61.5%) II as yellow crystals, mp 91-93°C (after prolonged drying in a vacuum desiccator over calcium chloride). The product is soluble in hot alcohols and ether, but has very limited solubility in hot heptane and hexane and is insoluble in acetone, ethyl acetate, benzene, and chloroform, R_f 0.60 (A), gas—liquid chromatography: 6.33 min. IR spectrum: 1716 cm^{-1} (C=O). UV spectrum, λ_{max} (log ε): 331 (4.18), 280 nm (4.08).

B. A solution of 5 g (17 mmoles) ketone I in 450 ml methanol was hydrogenated in the presence of 1 g Raney nickel catalyst at 20°C and 196-294 Pa until I had disappeared as indicated by thin-layer chromatography. The residue was recyrstallized from heptane and ethanol to give 1.57 g (31.2%) II, which was identical in its R_f value and IR spectrum to the product obtained according to procedure A and does not give a depressed mixed melting point.

The analogous hydrogenation of I in methanol in the presence of Raney nickel catalyst at 40°C and 70 atm hydrogen gave II in 20.5% yield.

(3'-Hydroxyquinuclidyl-2')(6-methoxyquinolyl-4)methane (III). A solution of 6.5 g (22.1 mmoles) ketone I in 200 ml methanol was hydrogenated in the presence of 9 g Raney nickel catalyst at 40°C and 100 atm. The reaction was monitored by IR spectroscopy until the carbonyl band at 1716 cm^{-1} disappeared. The catalyst was filtered off. The filtrate was evaporated. The oily product (5.7 g) is largely a mixture of diastereomeric IIIa and IIIb, which could not be preparatively separated by chromatography. These compounds were identified by thin-layer chromatography, PMR spectroscopy, and mass spectrometry.

(3'-Hydroxyquinuclidyl-2')(6-methoxy-1,2,3,4-tetrahydroquinolyl-4)methane (IV). The mixture of diastereomers IIIa and IIIb obtained in the previous experiment was hydrogenated over a Raney nickel catalyst in methanol at 100°C and 120 atm. The catalyst was filtered off and the filtrate was evaporated to give 5.5 g an oily yellow product, which was a mixture of diastereomers of IV as indicated by PMR spectroscopy. Preparative separation of these diastereomers by column chromatography using various adsorbents and solvents or by thin-layer chromatography proved impossible.

4-(3,3-Ethylenedioxyquinuclidyl-2-methylene)-6-methoxyquinolines ($C_{20}H_{22}N_2O_3$; isomers Z-Va and E-Vb). A mixture of 3.05 g (49 mmoles) ethyleneglycol, 19.8 g (115.2 mmoles) p-toluenesulfonic acid, and 12.0 g (40.8 mmoles) I in 200 ml anhydrous benzene was heated at reflux with rapid stirring in a flask equipped with a Dean—Stark trap until no further water was separated (about 0.5 ml). Then, 40 ml water and 40 ml 20% NaOH were added to the reaction mass. The aqueous layer was separated and extracted with eight 50-ml portions of

methylene chloride. The benzene solution and organic extracts were combined, dried over magnesium sulfate, and evaporated in vacuum to give 13.7 g residue, which was shown by gas–liquid chromatography to be a 2:1:1 mixture of ketals Va and Vb and ketone I. This residue was heated at reflux with 400 ml anhydrous ether. Then, 0.51 g Vb was filtered off as yellow crystals, mp 136-137°C (from hexane), which are soluble in hexane, ethyl acetate, acetone, chloroform, and hot alcohols but are insoluble in water. R_f 0.71 (A), 0.41 (B). Gas–liquid chromatography: 5.5 min. IR spectrum: 1140, 1100, 1025, 1000 cm^{-1} (C–O–C–O–C).

p-Toluenesulfonate of Vb, $C_{20}H_{22}N_2O_3 \cdot C_7H_8O_3S$ was obtained as colorless crystals, mp 203-204°C (from anhydrous ethanol). This compound is soluble in water, alcohols, and chloroform, but insoluble in acetone, ethyl acetate, and benzene.

The ethereal mother liquor after the separation of Vb was concentrated to 100 ml and 5.4 g Va was filtered off, mp 156-158°C (from anhydrous ethanol). This compound is soluble in benzene, chloroform, methylene chloride, and hot acetone, ethyl acetate, alcohols, and ether but insoluble in water. R_f 0.74 (A), 0.48 (B). Gas–liquid chromatography: 9.33 min. IR spectrum: 1230, 1150, 1030, 1000 cm^{-1} (C–O–C–O–C). UV spectrum, λ_{max} (log ε): 336 (4.28), 310 nm (4.18).

Dihydrochloride-dihydrate of Va, $C_{20}H_{22}N_2O_3 \cdot 2HCl \cdot 2H_2O$ was obtained as colorless crystals, mp 235-237°C (from 80% aqueous ethanol), which are soluble in water and alcohols but insoluble in acetone, ethyl acetate, and benzene.

p-Toluenesulfonate of Va, $C_{20}H_{22}N_2O_3 \cdot C_7H_8O_3S$ was obtained as greenish crystals, mp 194-196°C (from anhydrous ethanol), which are soluble in water, chloroform, methylene chloride, and hot alcohols but insoluble in benzene, acetone, and ethyl acetate.

The ethereal mother liquor after the separation of Va and Vb was evaporated to dryness. The residue (6.89 g) was subjected to repeated ketalization under the described conditions to give an additional 7 g of 1:1.1 mixture of ketals Va and V as indicated by gas–liquid chromatography, which did not contain a trace of ketone I. The total yield of ketals Va (8.5 g, 62%) and Vb (3.9 g, 28%) were calculated relative to I.

(3',3'-Ethylenedioxyquinuclidyl-2')(6-methoxyquinolyl-4)methane (VI, $C_{20}H_{24}N_2O_3$). A solution of 4 g (11.8 mmoles) ketal Va in 250 ml methanol was hydrogenated in the presence of 0.4 g 5% palladium on activated charcoal by analogy with the procedure for II (method A). After separation of the catalyst and evaporation of the reaction mass, the residue (4.08 g) was dissolved in 10 ml 10:1 chloroform–methanol and placed onto a 850 × 30 mm column packed with 200 g silica gel (L 40/100 μm). Elution with this solvent gave 2.64 g of a product, which was recrystallized from 200 ml hexane to give 1.87 g (46.4%) VI as yellow crystals, mp 158-158.5°C (from 2-propanol), which are soluble in methanol, ethanol, acetone, chloroform, ethyl acetate, hot 2-propanol, hot benzene, and hot hexane, but insoluble in water. R_f 0.51 (A). Gas–liquid chromatography: 8.16 min. IR spectrum: 1150, 1100, 1010 cm^{-1} (C–O–C–O–C).

4-[3"-(Piperidyl-4')-3",3"-ethylenedioxypropen-1"-yl-1"]-6-methoxyquinoline Acetate (VII, $C_{20}H_{24}N_2O_3 \cdot CH_3CO_2H$. A solution of 1.5 g (4.4 mmoles) quinuclidine ethyleneketal VI in 40 ml 60% acetic acid was hydrogenated in the presence of 0.2 g Adams platinum catalyst at 20°C and 196-294 Pa. The catalyst was filtered with activated charcoal. The filtrate was evaporated in vacuum and the residue was recrystallized from 2-propanol to give 0.43 g (24.3%) VII light yellow crystals, mp 171-173°C, which are soluble in methanol, ethanol, hot 2-propanol, hot water, hot acetic acid, and hot chloroform but insoluble in benzene, ethyl acetate, chloroform, and acetone. R_f 0.08 (A). IR spectrum: 2600-2400 (NH_2^+), 1620 (C=C), 1230, 1030 cm^{-1} (C–O–C–O–C).

(3',3'-Ethylenedioxyquinuclidyl-2')(5,6,7,8-tetrahydroquinolyl-4)methane (IX, $C_{19}H_{26}N_2O_2$). A solution of 3.58 g (0.01 mmole) ethyleneketal Va in 160 ml anhydrous ethanol containing 0.4 g (0.011 mmole) hydrogen chloride was hydrogenated with 0.4 g Adams platinum catalyst at 90-95°C and 196-294 Pa until the starting compound had disappeared as indicated by thin-layer chromatography [R_f 0.74 (A), 0.48 (B)]. The catalyst was filtered off and the filtrate was evaporated in vacuum. The residue (3.38 g) was made basic with 25% aqueous sodium carbonate to pH 9 and extracted with four 50-ml portions of ether. After removal of the solvent, the residue was recrystallized from ether to give 1.95 g (59.7%) IX as colorless crystals, mp 126-127°C, which are soluble in organic solvents and hot heptane, but insoluble in water. R_f 0.59 (A), 0.34 (B). Gas–liquid chromatography: 3.83 min. IR spectrum: 1140, 1075, 1020 cm^{-1} (C–O–C–O–C). UV spectrum, λ_{max} (log ε): 267 nm (2.36).

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PURINES, PYRIMIDINES, AND CONDENSED SYSTEMS BASED ON THEM.

6.* REACTIVITY OF 7- AND 9-AMINOXANTHINES TOWARD OXIDIZING AGENTS AND SOME ELECTROPHILES. SYNTHESIS OF THE ANTIBIOTICS FERVENULIN AND RHEUMYCIN

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The action of various oxidizing agents on 7- and 9-aminotheophyllines and also on 1-methyl-9-aminoxanthine was studied. 7-Aminotheophyllines are oxidized by almost all the oxidizing agents to 6,8-dimethylpyrimido[4,5-e]-as-triazine-5, 7(6H,8H)-dione (40-90%). 1-Methyl-9-aminoxanthine and 9-aminotheophylline are oxidized with greater difficulty. The best results are obtained with hydrogen peroxide, which transforms these amines with yields of ~40% into the antibiotics rheumycin and fervenulin, respectively. Under certain conditions the action of bromine and nitric acid leads to the bromination and nitration of the N-aminoxanthines at position 8. A series of the physicochemical characteristics of the N-aminoxanthines were investigated. The factors which affect their behavior toward oxidizing agents and electrophiles are discussed.

Earlier we showed that 7-aminotheophylline (I) and other 7-aminoxanthines [2, 3] are oxidized by lead tetraacetate, forming good yields of pyrimido[4,5-e]-as-triazine-5,7-dione derivatives such as isofervenulin (III). In the present work we attempted to introduce the recently synthesized [4] 1-methyl-9-aminoxanthine (IVa) and 9-aminotheophylline (IVb) into an analogous reaction. It was assumed that the transformation products in these cases would be the antibiotic rheumycin (VIa) and fervenulin (VIb) (see scheme on following page).

It was found that the amines (IVa,b) are not oxidized by lead tetraacetate. At the same time the action of potassium chlorate, periodic acid, or potassium permanganate leads

*For Communication 5, see [1].

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