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SYNTHESIS, STRUCTURE, AND PROPERTIES OF PYRAZOLO[4,3-b]QUINUCLIDINE DERIVATIVES

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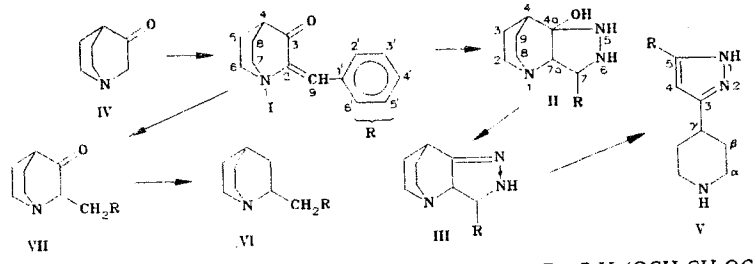
It was shown by means of ^{1}H and ^{13}C NMR spectroscopy that the reaction of 2-arylmethylene-3-oxoquinuclidines with hydrazine hydrate gives 4a-hydroxy-7-aryl-4a,5,7,7a-tetrahydropyrazolo[4,3-b]quinuclidines, which are stable in the crystalline state but undergo dehydration to the corresponding 7-aryl-6H-7,7a-dihydropyrazolo[4,3-b]quinuclidines in solutions. The latter undergo cleavage to 3-(4-piperidyl)-5-arylpyrazoles when they are heated in an alkaline medium.

We have previously shown that the reactions of 2-arylmethylene-3-oxoquinuclidines with hydrazine hydrate lead to 7-aryl-6H-7,7a-di-hydropyrazolo[4,3-b]quinuclidines [1]. In expanding our research in this direction we have accomplished the synthesis of new 2-arylmethylene-3-oxoquinuclidines (I), have studied their reaction with hydrazine hydrate under various conditions, and have established the structure of the resulting compounds, viz., 4a-hydroxy-7-aryl-4a,5,7,7a-tetrahydropyrazolo[4,3-b]quinuclidines (II), the products of the transformation of which are 7-aryl-6H-7,7a-dihydropyrazolo[4,3-b]-quinuclidines (III). We also investigated the properties of these substances.



I, II, V, VI, VII a R=$C_6H_3(OCH_3)_2$-3,4, b R=$C_6H_4OCH_3$-4, c R=$C_6H_4(OCH_2CH_2OC_6H_5)$-4, d R=$C_{10}H_7$-1; I, II, III e R=C_6H_4Cl-2; III c R=$C_6H_4(OCH_2CH_2OC_6H_5)$-4; VI f R=$C_6H_3(OH)_2$-3,4, g R=C_6H_4OH-4

Unsaturated ketones Ia-e were synthesized by condensation of 3-oxoquinuclidine (IV) with the corresponding aromatic aldehydes in the presence of sodium hydroxide [2, 3]. The structures of ketones I — individual geometrical isomers Ia-c,e and a mixture of Id isomers — were confirmed by data from the ^{1}H and ^{13}C NMR spectra (Table 1). The configurations of ketones Ia-c,e were established on the basis of the spectra recorded in aqueous acetone

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1248-1256, September, 1985. Original article submitted October 1, 1984.

solutions with the successive addition of hydrochloric acid. In conformity with the data in [4], the signals that appeared under these conditions and became more intense were assigned to the trans isomers, and starting ketones Ia-c,e were consequently the individual cis isomers.* It should be noted that a comparison of the chemical shifts of the $C_{(9)}$ atom in the ^{13}C NMR spectra of Ia,b (124.4 and 124.7 ppm) with the corresponding values for the geometrical isomers of 2-benzylidene-3-oxoquinuclidine (124.9 ppm for the cis isomer and 136.1 ppm for the trans isomer [2]) confirms the cis configuration of Ia,b and indicates the possibility of the independent establishment of the configurations of isomers of 2-arylidene-3-oxoquinuclidines on the basis of the chemical shifts of the $C_{(9)}$ atom.

The reaction of Ia-e with excess hydrazine hydrate in ethanol takes place in heterogeneous medium, during which a change in the color of the solid phase from bright-yellow (ketones I) to colorless is observed. At 50-60°C the reaction is complete in 2-3 h, whereas at 20°C the reaction proceeds slowly and cannot be made to go to completion. It was shown by means of the ^1H and ^{13}C NMR spectra (Table 2) that the resulting compounds, which were isolated directly from the reaction masses, are tetrahydropyrazolo[4,3-b]quinuclidine derivatives II. In solutions that do not contain hydrazine hydrate II undergo dehydration quite rapidly, and an attempt to recrystallize IIc,e led to the isolation of the corresponding dihydropyrazolo[4,3-b]-quinuclidines IIIc, e; we were unable to isolate crystalline substances in attempts to recrystallize IIa,b,d. In all cases the ^1H and/or ^{13}C NMR spectra make it possible to detect the conversion of II to III, which commences immediately after dissolving and is complete, depending on the substance and the solvent, in from 10 min to 1 day. In the case of IIa it was shown that a similar conversion also occurs in water. The presence of catalytic amounts of hydrochloric acid in the solution markedly accelerates the dehydration; a high concentration of hydrazine hydrate, on the other hand, slows the reaction down, and this explains the possibility of the isolation of II in crystalline form from the reaction masses. It should be noted that we were unable to find examples in the literature of compounds with a hydrated C=N bond for either dihydropyrazoles or for hydrazones, which, with respect to the electronic properties of this bond, can be regarded as acyclic analogs of dihydropyrazoles.

A relatively low value of the SSCC of the 7-H and 7a-H protons ($J_{7,7a}$ 5-7 Hz) and a relatively strong-field position of the 4-H signal at ~2.0 ppm, which constitutes evidence for sp^3 hybridization of the $C_{(4a)}$ atom of the three-ring system [5], are characteristic for the ^1H NMR spectra of II. This conclusion was confirmed by the presence in the ^{13}C NMR spectra of a signal at 92 ppm, which corresponds to the $C_{(4a)}$ atom — a quaternary carbon atom with two electronegative substituents.

Doublets† with a much larger SSCC ($J_{7,7a}$ = 12.5 Hz) than in II correspond to the 7-H and 7a-H protons in the ^1H NMR spectra of III. The signal of the 4-H proton in the spectra of III, which is overlapped in neutral media with the signal of the 2- and 8-CH_2 groups, was identified by means of two-dimensional (2DJ) spectroscopy (Fig. 1). In spectra of this type (when 45° projection is used) the spin-spin couplings lead to splitting of the signal of the proton to give a multiplet, the components of which are characterized by the same abscissa (δ) but different ordinates (J) [6]. According to 2DJ spectrum of IIIe, the 4-H signal is a quintet with characteristic (for quinuclidine derivatives) constant $J_{\beta\gamma} \approx 3$ Hz; the weak-field shift of this signal (up to 2.9 ppm) as compared with II constitutes evidence for sp^2 hybridixation of the $C_{(4a)}$ atom in III. This is also indicated by data from the ^{13}C NMR spectra of three-ring systems III, in which the signal at 165 ppm, which is comparable to the values 150-160 ppm observed for the carbon atom of the C=N bond in oximes [7], corresponds to the $C_{(4a)}$ atom.

A peculiarity of the ^{13}C NMR spectra of dihydropyrazolo[4,3-b]-quinuclidines III is an appreciable difference in the ^{13}C chemical shifts not only in the pair of $C_{(2)}$ and $C_{(8)}$ atoms but also in the pair of $C_{(3)}$ and $C_{(9)}$ atoms. The difference between the $C_{(2)}$ and $C_{(8)}$ chemical shifts in III can be explained by interaction of the spatially drawn together 8-CH_2 and 7-CHR groups, which, according to [8], is responsible for the shift of the $C_{(8)}$ signal to strong field. A similar effect of a strong-field shift of one of the two unsubstituted α (or β)-carbon atoms when a single substituent is attached to the tertiary α (or, respectively, β)-carbon atom that has retained sp^3 hybridization is characteristic for other quinuclidine derivatives; for example, see the $C_{(6)}$ and $C_{(7)}$ chemical shifts for VIa and

*Here and subsequently, the orientation in which the aryl substituent and the nitrogen atom of the quinuclidine ring come closer together was taken as the cis orientation.
†In the spectrum of IIIe (in d_6-DMSO) the signal of the 7-H proton is a quartet as a consequence of additional coupling with the 6-H proton.

TABLE 1. ^{1}H and ^{13}C NMR Spectra of Quinuclidine Derivatives I, IV, and VI-VIII

Compound[a]	NMR spectrum[b]	δ,[c] ppm (the absence of a letter denotes a multiplet)											
		2	3	4	5, 8	6, 7	9	1′	2′	3′ (OCH_3)	4′ (OCH_3)	5′	6′
Ia	^{1}H			2,62	1,95—2,10	2,90—3,25	6,96 s		7,99 d	3,89 s	3,91 s	6,86 d	7,81 q
Ib	^{1}H			2,61	1,95—2,10	2,90—3,25	6,98 s		8,03	6,89	3,83	6,89	8,03
Ic	^{1}H			2,62	1,95—2,19	2,90—3,25	6,99 s		8,04	6,94	—d	6,94	8,04
Id	^{1}H			2,69[f] 2,62[f]	1,95—2,15 — g	2,90—3,30 — g	7,92 s[f] 7,19 s[f]				—e		
Ie	^{1}H			2,65	1,95—2,10	2,90—3,25	7,48 s			7,20—7,45			8,49
VIa	^{1}H	3,75	1,5—2,05	2,12	1,50—2,05	3,10—3,60	2,99 d		6,96 d	3,83 s	3,85 s	7,00 d	6,90 q
VIb	^{1}H	3,75	1,5—2,0	2,11	1,50—2,00	3,10—3,60	3,00 d		7,28	6,99	3,82 s	6,99	7,28
VIIa	^{1}H	4,51		2,88	1,95—2,45	3,30—3,70	3,0—3,5		7,00 d	3,838 s	3,842 s	7,01 d	6,95 q
VIIc	^{1}H	3,33		2,45	1,90—2,10	2,85—3,25	2,75—3,20				—h		
Ia	^{13}C	142,6	205,2	39,9	25,7	47,2	124,4	126,7	114,2	148,2 (55,3)	149,4 (55,3)	110,4	160,0
Ib	^{13}C	142,7	205,7	40,3	26,0	47,5	124,7	126,7	133,7	113,7	160,5 (55,1)	113,7	133,7
IV	^{13}C	62,1	218,5	29,1	25,1	46,1							
VIa	^{13}C	59,9	30,6	20,9	22,7; 23,4	49,7; 42,5	38,2	129,0	113,4	148,2 (56,6)	149,2 (56,6)	112,9	122,6
VIIa	^{13}C	71,4	208,2	38,4	20,5—21,3	49,7; 42,7	33,2	127,6	113,1	148,6 (56,6)	149,3 (56,6)	113,0	122,6

	J_{HH}, Hz
Ia VIa VIIa	45, 48 3,1; 2′6′ 2,0; 5′6′ 8,3 29 8,0, 2′6′ 2,0; 5′6′ 8,3 $29H_A$ 10,2; $29H_B$ 5,8 45, 48 3,1; $9H_A$ $9H_B$ 15,3; 2′6′ 2,1; 5′6′ 8,3

	J_{CH}, Hz
Ib	$C_{(4)}$4-H 142,5; $C_{(5)}$5-H, $C_{(8)}$8-H 130; $C_{(6)}$6-H, $C_{(7)}$7-H 137,5; $C_{(9)}$9-H 152,0; $C_{(9)}$2′H-, $C_{(9)}$6′H 4,3; $C_{(2')}$2′-H, $C_{(3')}$3-H 162—164; $C_{(1')}$3′-H, $C_{(1')}$5′-H 7,7′; 4′-OCH_3 ($^{1}J_{CH}$) 144
IV	$C_{(2)}$2-H 139,5; $C_{(4)}$4-H 144; $C_{(5)}$5-H, $C_{(8)}$8-H 131; $C_{(6)}$6-H, $C_{(7)}$7-H 139

[a]Compounds VIa,b and VIIa were studied in the form of their hydrochlorides. [b]The assignment of the signals in the $C(_2')$ and $C(_5')$ and $C(_3')$ and $C(_4')$ pairs can possibly be reversed in the ^{13}C NMR spectra of Ia, VIa, and VIIa. [c]The solvents (standards) were $CDCl_3$ [tetramethylsilane (TMS)] for Ia-e, IV, and VIIc and D_2O (dioxane, 3.74 ppm) for the hydrochlorides of VIa,b and VIIa. [d]Signals at 4.35 ppm (4′-OCH_2CH_2) and 6.9-7.3 ppm ($O-C_6H_5$). [e]Signals at 7.45-8.45 ppm from the protons of the naphthyl ring. [f]The δ values for the less preferred cis isomer. [g]The signals are hidden by the more intense signals of the trans isomer. [h]Signals at 6.85-7.35 ppm from the protons of the phenyl rings; 4.30 ppm (4′—O—CH_2—CH_2).

TABLE 2. ^{1}H and ^{13}C[a] NMR Spectra of Pyrazolo[4,3-b]quinuclidines II and III

Compound[b]	NMR spectrum	δ, ppm											
		2, 8	3, 9	4	4a	7	7a	1′	2′	3′	4′	5′	6′
IIa	^{1}H	2,7—3,2	1,4—2,0	2,09		4,20d	3,28d		7,00d	3,87s	3,89s	6,85 d	7,02q
IIb	^{1}H	2,6—3,2	1,4—2,20			4,19d	3,26d		7,37	6,85	3,81s	6,85	7,37
IIc	^{1}H	2,7—3,1	1,4—1,95	2,08		4,19d	3,26d		7,37	6,93	—c	6,93	7,37
IId	^{1}H	2,55—3,3	1,3—2,1	1,94		4,81d	3,24d				—d		
IIe	^{1}H	2,45—3,1	1,3—2,0	1,91	—e	4,50d	2,95d				7,3—7,45		7,65
IIIa[f]	^{1}H	2,5—3,2	1,4—2,0	2,9		4,78d	3,71d		7,14d	3,87s	3,91s	6,83d	6,98q
IIIb[f]	^{1}H	2,6—3,2	1,4—2,2	2,9		4,77d	3,71d		7,39	6,85	3,81s	6,83	7,39
IIIc	^{1}H	2,8—3,3	1,55—2,1	2,9		4,77d	3,69d		7,42	6,94	—e	6,94	7,42
IIId[f]	^{1}H	2,8—3,5	1,6—2,0	2,85		5,49q[g]	3,75d[i]				—h		
IIIe		2,8—3,35	1,7—1,95	2,92		5,34d	3,86q[i]			7,36	7,15—7,3		7,82
II a	^{13}C	48,9 40,5	23,3 22,0	30,7	92,0	67,0	80,3	133,1	111,2	147,9j	148,7j	111,9	119,2
II d	^{13}C	48,7 40,4	23,1 22,0	31,8	92,3	63,5	79,5			—k			
IIIa[f]	^{13}C	48,7 42,3	31,6 22,6	27,1	164,2	66,5	74,7	133,5	110,9	147,9j	148,5j	111,7	119,1
IIId[f]	^{13}C	48,2 42,2	32,1 22,7	27,2	163,3	64,1	75,2			—l			
IIIe	^{13}C	48,8 42,5	31,2 22,5	27,1	165,8	64,4	74,3	134,0	136,6	126,7	127,8	128,5	129,3

J_{HH}, Hz

IIa	7*a* 6,2($CDCl_3$), 6,8 (ДМСО-D_6), 7,3 (D_2O); 5′6′ 8,5; 2′6′ 2,3
IIb IIc	7*a* 6,4
IId	7*a* 4,8
IIe	43, 49 3,0; 7*a* 6,7
IIIa	7*a* 12,5, 5′6′ 8,4; 2′6′ 2,2
IIIc	7*a* 12,5
IIId	7*a* 12,3
IIIe	43, 49 3,2; 7*a* 12,8

J_{CH}, Hz

IId	$C_{(2)}$2-H 137; $C_{(3)}$3-H 129; $C_{(4)}$4-H 138,5; $C_{(7)}$7-H 138,5; $C_{(7a)}$7*a*-H 142; $C_{(9)}$9-H 130
III e	$C_{(2)}$2-H 140; $C_{(3)}$3-H 131; $C_{(4)}$4-H 144; $C_{(7)}$7-H 135; $C_{(7a)}$7*a*-H 139; $C_{(8)}$8-H 138,5; $C_{(9)}$ 9-H 131,5; $C_{(3')}$3′-H, $C_{(4')}$4′-H, $C_{(5')}$5′-H, $C_{(6')}$6′-H 161—165

[a]In the case of the ^{13}C NMR spectra we did not assign the signals in the $C(_2')$, $C(_5')$ and $C(_3')$, $C(_4')$ (IIa, IIIa), $C(_1')$, $C(_2')$ and $C(_3')$, $C(_6')$ (IIIe) and $C(_1')$, $C(_1'a)$, $C(_4'a)$, and $C(_2')$–$C(_8')$ (IId and IIId) groups. [b]For IIa-c and IIIa-c,e the solvent was $CDCl_3$, and the standard was tetramethylsilane (TMS); for IId,e and IIId the solvent was d_6-DMSO, and the standard was TMS; for IIa,d and IIIa,d (^{13}C NMR spectra) the solvent was d_6-DMSO, the signal of which (39.6 ppm) was adopted as the standard. [c]Signals (ppm) at 4.31 broad s (4′-OCH_2CH_2—) and 6.9-7.3 (—OC_6H_5). [d]Signals of naphthyl ring protons at 7.45-8.40 ppm. [e]Signals of a 4a-OH group and 5-H and 6-H protons at 5.13, 4.74, and 4.09 ppm (all broad s). [f]Studied without isolation as the product of transformation of II. [g]Signal of a 6-H proton at 6.85 d with J_{67} = 6.4 Hz. [h]Signals of naphthyl ring protons at 7.45-8.25 ppm. [i]Long-range coupling (SSCC ^{4}J = 0.7 Hz) with one of the protons in the 2 position. [j]Signal of an OCH_3 group at 55.6 ppm. [k]Signals (ppm) of the carbon atoms of the naphthyl ring: 137.7, 133.5, 131.7 [$C(_1')$, $C(_1'a)$, $C(_4'a)$]; 128.5, 127.2, 126.0, 125.6, 125.5, 124.2, 123.2 [$C(_2')$–$C(_8')$]. [l]Signals (ppm) of the carbon atoms of the naphthyl ring: 137.7, 133.4, 131.5 [$C(_1')$, $C(_1')$, $C(_4'a)$]; 128.2, 127.3, 125.6, 125.5, 125.4, 124.4, 123.9 [$C(_2')$–$C(_8')$].

TABLE 3. ^{1}H and ^{13}C NMR Spectra of 3-(4-Piperidyl)-5-aryl-pyrazoles V

Compound	NMR spectrum[a]	δ, ppm											
		3	4	5	α[b]	β[b]	γ	1′	2′	3′	4′	5′	6′
Va	^{1}H		6,31 s		2,76 (3,20)	1,65 (2,00)	2,83		7,26 d	3,91 s	3,93 s	6,90 d	7,25q
Vb	^{1}H		6,27 s		2,68 (3,14)	1,70 (2,00)	2,77		7,62	6,89	3,81 s	6,89	7,62
Ve	^{1}H		6,51 s		2,74 (3,17)	1,70 (2,01)	2,84			7,45	7,25—7,30		7,70
Ve	^{13}C	150,0	102,2	145,5	45,8	32,6	33,9	130,8	131,9	127,1	128,7	130,1	130,2
	J_{HH}, Hz												
Va Ve	$\alpha_a\alpha_e$ 12,2; $\alpha_a\beta_a$ 12,3; $\alpha_a\beta_e$ 2,5; $\alpha_e\beta_a$ 3,5; $\beta_a\gamma$ 11,7; $\beta_e\gamma$ 3,8; 2′6′ 2,0; 5′6′ 8,2 $\alpha_a\alpha_e$ 12,4; $\alpha_a\beta_a$ 12,1; $\alpha_a\beta_e$ 2,3; $\alpha_e\beta_a$ 3,8; $\beta_a\beta_e$ 12,0; $\beta_e\gamma$ 4,0												
	J_{CH}, Hz												
Ve	$C_{(4)}$4-H 175; $C_{(\alpha)}\alpha$-H 133; $C_{(\beta)}\beta$-H 127; $C_{(\gamma)}\gamma$-H 125; $C_{(3')}$3′-H, $C_{(4')}$4′-H, $C_{(5')}$5′-H, $C_{(6')}$6′-H 162—166; $C_{(4)}\gamma$-H 3; $C_{(5)}$4-H, $C_{(5)}$6′-HS; $C_{(3')}$5′-H, $C_{(4')}$6′-H, $C_{(5')}$3′-H; $C_{(6')}$4′-H 7—8												

[a]For Va,b,e (^{1}H NMR spectra) the solvent was $CDCl_3$, and the standard was tetramethylsilane (TMS); for Ve (^{13}C NMR spectrum) the solvent was d_6-DMSO, the signal of which (39.6 ppm) was adopted as the standard; the signals in the $C(_1')$, $C(_2')$, and $C(_3')$–$C(_6')$ groups were not assigned. [b]The δ_H values correspond to the axial protons; the values in parentheses correspond to the equatorial protons.

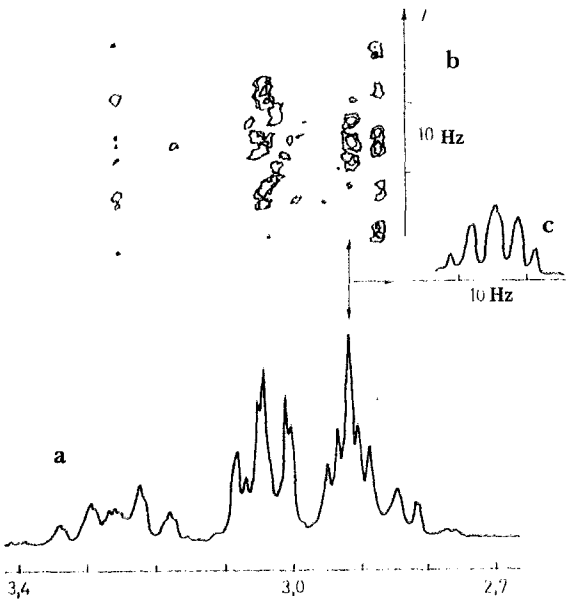


Fig. 1. Spectra of IIIe: a) fragment of the ^1H NMR spectrum of IIIe in $CDCl_3$ (over the range 2.7-3.4 ppm); b) 2DJ spectrum of this range, 45° projection, cross section parallel to the Jδ plane (the signals of the 4-H proton are indicated by an arrow; the δ scale is the same in spectra a and b); c) cross section of the 2DJ spectrum perpendicular to the δ axis at point δ = 2.92 ppm, which illustrates the multiplicity of the 4-H signal (in the absence of superimposition of the signals of other protons).

VIIa (Table 1) and the $C(_2)$ and $C(_8)$ chemical shifts for IIa and IId (Table 2), as well as [9, 10]. However, in view of the sp^2 hybridization of the $C(_{4a})$ atom, the difference between the $C(_3)$ and $C(_9)$ chemical shifts for III cannot be explained by this effect. It might be assumed that this difference (up to $\Delta\delta \approx 9$ ppm) is associated with distortions of the bond angles in the tricyclic dihydropyrazolo[4,3-b]quinuclidine system III, which is sterically strained as a consequence of the different hybridizations of the bridge $C(_{4a})$ and $C(_{7a})$ atoms, the rigidity of the quinuclidine ring, and the reduced flexibility of the five-membered ring because of the presence of a double bond in it.

The IR spectra of crystalline IIb,d and IIIc,e confirm their structures. A band of medium intensity at 1650 cm^{-1} (C=N) and a lone narrow band at ~3300 cm^{-1} (NH) are characteristic for the IR spectra of dihydropyrazolo[4,3-b]quinuclidines IIIc,e. The IR spectra of 4a-hydroxy-7-aryl-4a,5,7,7a-tetrahydropyrazolo[4,3-b]-quinuclidines IIb,d do not contain a band at 1650 cm^{-1}; the narrow bands at 3250-3350 cm^{-1} and the broad band at 3050 cm^{-1} correspond to the vibrations of NH and OH groups.

The above-presented $J_{7,7a}$ SSCC in the ^1H NMR spectra of II and III make it possible to draw a conclusion regarding the configuration of the pyrazolo[4,3-b]quinuclidines obtained. According to the data in [11], vicinal constant $J_{7,7a} \approx 12.5$ Hz in the spectra of III can correspond only to an anti-periplanar orientation of the coupling protons (with a dihedral angle close to 180°). An examination of molecular models shows that this orientation of the 7-H and 7a-H protons is possible only in the case of an RS/SR configuration of III.

The ease of conversion of tetrahydro derivatives II to the corresponding dihydro derivatives III and the absence of exchange of the 7-H or 7a-H protons for deuterium in a medium that contains labile deuterons (CD_3OD, D_2O) constitute evidence for the same (RS/SR) configuration of the indicated compounds with respect to the $C(_7)$ and $C(_{7a})$ centers. The low value of the $J_{7,7a}$ constant (≈5-7 Hz) in the case of compounds of the II series (with retention of the trans orientation of the protons) therefore indicates a significant increase in the flexibility of the tetrahydropyrazole ring in three-ring system II as compared with the dihydropyrazole ring in three-ring system III. One consequence of this increased flexibility

TABLE 4. Constants of the Synthesized Compounds

Compound	mp, deg C		Found, %			Empirical formula	Calculated, %			Yield, %
	base	hydrochloride	C	H	N(Cl)		C	H	N(Cl)	
Ia	112—114	207—209	70,4	7,2	5,2	$C_{16}H_{19}NO_3$	70,3	7,0	5,2	79
Ic	175—177	194—196	75,4	6,6	4,0	$C_{22}H_{23}NO_3$	75,6	6,6	4,0	97
Id	150—152	192—193	82,1	6,4	5,4	$C_{18}H_{17}NO$	82,1	6,5	5,3	80
Ie	136—137	195—197	67,7	5,7	5,5	$C_{14}H_{14}ClNO$	67,9	5,7	5,7	75
IIa	105—107	—	63,2	7,5	13,6	$C_{16}H_{23}N_3O_3$	62,9	7,6	13,6	65
IIc	137—140	—	69,2	7,2	11,0	$C_{22}H_{27}N_3O_3$	69,3	7,1	11,0	77
IId	112—114	—	73,2	7,2	14,2	$C_{18}H_{21}N_3O$	73,2	7,4	14,2	98
IIe	141—143	—	60,2	6,6	15,2	$C_{14}H_{18}ClN_3O$	60,1	6,5	15,0	90
IIIc	149—151	—	72,8	7,0	11,6	$C_{22}H_{25}N_3O_2$	73,1	7,0	11,8	90
IIIe	218—220	241—243[a]	66,6	7,3	14,4	$C_{16}H_{21}N_3O_2$	66,9	7,4	14,6	85
Vb	170—172	230—231[a]	69,9	7,4	16,4	$C_{15}H_{19}N_3O$	70,0	7,4	16,3	88
Vc	177—179	290—292[a]	72,7	7,0	11,5	$C_{22}H_{25}N_3O_2$	72,8	7,0	11,6	81
Vd	80—82	245—247[a]	72,9	7,2	14,5	$C_{18}H_{19}N_3 \cdot H_2O$	73,2	7,2	14,2	76
Ve	160—162	236—238[a]	64,2	6,3	16,1	$C_{14}H_{16}ClN_3$	64,2	6,2	16,0	68
VIa	—	234—236	64,5	8,3	(11,9)	$C_{16}H_{23}NO_2 \cdot HCl$	64,5	8,1	(11,9)	66
VIb	—	226—228	67,2	8,1	(13,5)	$C_{15}H_{21}NO \cdot HCl$	67,2	8,3	(13,4)	77
VIc	—	245—247	70,6	7,4	9,3	$C_{22}H_{27}NO_2$	70,5	7,5	9,5	57
VId	—	246—248	74,8	7,7	(12,2)	$C_{18}H_{21}N \cdot HCl$	75,1	7,7	(12,3)	51
VIf	—	260—262	61,9	7,6	(12,9)	$C_{14}H_{19}NO_2 \cdot HCl$	62,3	7,4	(13,1)	78
VIg	—	333—335	66,1	7,7	(5,3)	$C_{14}H_{19}NO \cdot HCl$	66,3	7,9	(5,5)	74
VIIa	—	192—194	61,6	7,1	(11,3)	$C_{16}H_{21}NO_3 \cdot HCl$	61,6	7,1	(11,4)	90
VIIb	83—85	184—186	—	—	(12,3)	$C_{15}H_{19}NO_2 \cdot HCl$	—	—	(12,6)	91
VIIc	—	250—252	—	—	(8,9)	$C_{22}H_{25}NO_3 \cdot HCl$	—	—	(8,9)	92
VIId	—	278—279	71,5	6,5	(11,6)	$C_{18}H_{19}NO \cdot HCl$	71,6	6,7	(11,7)	75

[a]The dihydrochloride.

is conformational lability of the tetrahydropyrazole ring in II, which is manifested in the dependence of the $J_{7,7a}$ constant not only on the aryl substituent (5.8 Hz for IId and 6.8 Hz for IIa with d_6-DMSO as the solvent) but also on the solvent (6.2 Hz in $CDCl_3$ and 7.3 Hz in D_2O in the case of IIa). An examination of molecular models shows that this conformational lability is in better agreement with cis fusion of the quinuclidine and tetrahydropyrazole rings than with trans fusion* of these rings. In the latter case the conformational lability of the five-membered ring would be markedly restricted by the rigidity of the quinuclidine system. The data presented above make it possible to arrive at the conclusion that II are cis-fused 4a,7,7a(RRS/SSR)-4a-hydroxy-7-aryl-4a,5,7,7a-tetrahydropyrazolo[4,3-b]-quinuclidines.

The chemical properties of the pyrazolo[4,3-b]quinuclidines provide evidence for the instability of these compounds. In addition to three-ring systems II and III, products of cleavage of the pyrazoloquinuclidines at the $N(_1)$—$C(_{7a})$ bond develop in the reaction of ketones Ia-e with hydrazine hydrate at 50-60°C. The resulting 3-(4-piperidyl)-5-arylpyrazoles V become the only reaction products in the case of refluxing mixtures of ketones I with hydrazine hydrate in alcohol or in the case of heating these mixtures in diethylene glycol with potassium hydroxide. Under these conditions the initially formed pyrazolo[4,3-b]quinuclidines evidently undergo cleavage to 3,5-disubstituted pyrazoles V under the influence of alkaline reagents. The instability of III in an alkaline medium was confirmed by their cleavage upon heating in alcohol in the presence of potassium hydroxide (2.5% solution) or in hydrazine hydrate.

The structure of V follows from their ^1H and ^{13}C NMR spectra (Table 3). A peculiarity of the ^1H NMR spectra of these compounds is the multiplicity of the signal of the γH proton of the piperidine ring, which is a triplet of triplets with clearly isolable axial-axial ($J \approx 12$ Hz) and axial-equatorial ($J \approx 4$ Hz) couplings. In the spectra of quinuclidine derivatives I-IV, VI, and VII and other quinuclidine derivatives [12] the signal of the 4-H proton is a multiplet with close constants that do not, as a rule, exceed 5.5 Hz. In the ^{13}C NMR spectra of V the absence of a quinuclidine ring is attested to by a decrease in the $^1J_{C\gamma H}$ SSCC to 125 Hz, which is close to the $^1J_{CH}$ value in the spectrum of cyclohexane (124.6 Hz [13]) and differs appreciably from the anomalously high "quinuclidine" SSCC $^1J_{C(_4)H} > 138$ Hz in the spectra of I-IV (Tables 1 and 2). The decrease in the number of signals in the ^{13}C NMR spectra of γ-substituted piperidines V as compared with the corresponding

*trans-Fused condensed systems based on quinuclidine have not been described in the literature.

unsymmetrical quinuclidine derivatives II or III is also significant.

In addition to our investigation of the reactions of 2-aryl-idene-3-oxoquinuclidines I with hydrazine hydrate, we developed a simple method for the preparation of 2-benzylquinuclidines VI, which consists in the two-step reduction of I, initially catalytically in the presence of palladium on carbon to 2-benzyl-3-oxoquinuclidines VII and then via the Wolff–Kishner reaction by heating with hydrazine hydrate in the presence of potassium hydrozide to give VI. Compounds VIf and VIg, which contain hydroxy groups in the aromatic part of the molecules, were obtained by hydrolysis of the corresponding methoxy derivatives VIa and VIb with hydrochloric acid. The structures of VI and VII were confirmed by the ^{1}H and ^{13}C NMR spectra (Table 1).

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded with Varian XL-100A and XL-200 spectrometers with operating frequencies of, respectively, 100 and 200 MHz for the protons and 25.2 and 52.3 MHz for the ^{13}C nuclei. The two-dimensional (2DJ) spectrum of IIIe was recorded with an XL-200 spectrometer with the aid of the HOM2DJ program that enters into the standard set of programs for the spectrometer.

The constants and yields of I-III and V-VII are presented in Table 4.

2-(3,4-Dimethoxyphenylmethylene)-3-oxoquinuclidine (Ia). A 15-g (120 mmole) sample of 3-oxoquinuclidine and 19.9 g (120 mmole) of veratraldehyde were added to a solution of 0.2 g (5 mmole) of sodium hydroxide in 60 ml of ethanol, and the mixture was then refluxed for 5 h and allowed to stand at 20°C for 16 h. The precipitate was removed by filtration and washed with ethanol and water.

Compounds Ic-e were similarly obtained using the corresponding aldehydes. The reaction time for Id was 12 h. Compound Ib was obtained by the method in [3].

For purification, Ia, Ic, Id, and Ie were crystallized from 2-propanol, dimethylformamide, methanol, and ethanol, respectively.

4a-Hydroxy-7-(3,4-dimethoxyphenyl)-4a,5,7,7a-tetrahydropyrazolo[4,3-b]quinuclidine (IIa). A mixture of 5 g (18.3 mmole) of Ia, 20 ml of hydrazine hydrate, and 30 ml of ethanol was heated at 60°C for 2 h, during which the bright-orange starting ketone gradually became colorless. The reaction mass was allowed to stand at 4°C for 20 h, after which the precipitate was removed by filtration and washed with water and isopropyl alcohol.

Compounds IIb [1] and IIc-e were similarly obtained. Recrystallization of II resulted in the formation of 7-substituted 6h-7,7a-dihydropyrazolo[4,3-b]quinuclidines III; IIIc (from benzene) and IIIe (from 2-propanol) were isolated in the individual state.

3-(4-Piperidyl)-5-(3,4-dimethoxyphenyl)pyrazole (Va). A) A 0.5-g (1.64 mm) sample of IIa was added to a solution of 0.05 g (1.25 mmole) of sodium hydroxide in 20 ml of ethanol, and the mixture was refluxed for 6 h. The alcohol was removed by distillation *in vacuo* and the residue was stirred with water. The aqueous mixture was extracted with chloroform, the chloroform was removed by distillation, and the residue was triturated with ether. Cleavage of three-ring system IIa was accelerated when the potassium hydroxide concentration was increased.

B) A mixture of 1 g (3.28 mmole) of IIa and 5 ml of hydrazine hydrate was heated at 100°C. After 2 h, the development of pyrazole derivative Va was observed; the process was complete after 10 h. The precipitate was removed by filtration and washed with water, 2-propanol, and ether.

C) A mixture of 5 g (16.4 mmole) of ketone Ia, 10 ml of hydrazine hydrate, 10 g of potassium hydroxide, and 50 ml of diethylene glycol was heated at 165-170°C (bath temperature) for 7 h, after which the excess hydrazine hydrate and diethylene glycol were removed by distillation, and the residual mass was cooled and triturated with 100 ml of water. The precipitate was removed by filtration and washed with water.

Compounds Vb-e were synthesized from ketones Ib-e via method C.

For purification, Va, Vb, Vc, Vd, and Ve, respectively, were crystallized from 2-propanol–acetone, ethyl acetate, ethanol, 50% ethanol, and acetone.

2-(3,4-Dimethoxybenzyl)-3-oxoquinuclidine (VIIa). A 63-ml sample of methanol and 1 g of 5% palladium on charcoal were added to a suspension of 10 g (37 mmole) of Ia in 37 ml of 1 N hydrochloric acid, and the mixture was shaken with hydrogen at 20°C. After one equivalent of hydrogen had been absorbed, the catalyst was removed by filtration, the solution was evaporated *in vacuo*, and the residue was recrystallized from isopropyl alcohol.

Compounds VIIb,d were similarly obtained and purified by recrystallization from isopropyl alcohol.

2-[4-(β-Phenoxyethoxy)benzyl]-3-oxoquinuclidine (VIIc). A solution of 2 g (5.7 mmole) of Ic in 200 ml of methanol was treated with 2 ml of a 20% alcohol solution of hydrogen chloride, 0.3 g of 5% palladium on charcoal was added, and the mixture was shaken with hydrogen. After one equivalent of hydrogen had been absorbed, 50 ml of methanol was added, and the mixture was heated on a water bath until the precipitate had dissolved. The catalyst was removed by filtration, the solution was evaporated to 50 ml, and the concentrate was allowed to stand at 4°C for 16 h. The colorless precipitate was removed by filtration and washed with ether.

2-(3,4-Dimethoxybenzyl)quinuclidine (VIa). A mixture of 5 g (18 mmole) of base VIIa, 10 ml of hydrazine hydrate, 10 g of potassium hydroxide, and 50 ml of diethylene glycol was heated at 165-170°C (bath temperature) for 5 h, after which the excess hydrazine hydrate and water were removed by distillation, during which the bath temperature was raised gradually to 195°C. The residue was dissolved in 80 ml of water, and the aqueous solution was extracted with benzene. The solvent was removed by distillation, and the residue was dissolved in 20 ml of isopropyl alcohol. The solution was acidified with an alcohol solution of hydrogen chloride, and the precipitate was removed by filtration and washed with 2-propanol and acetone.

Compounds VIb-d were similarly obtained. Bases VIb,d were extracted with chloroform, and the hydrochlorides were isolated from ether solutions of the bases. For purification, VIa and VIb were crystallized from 2-propanol.

2-(3,4-Dihydroxybenzyl)quinuclidine (VIf). A solution of 2 g (6.7 mmole) of the hydrochloride of VIIa in 10 ml of concentrated hydrochloric acid was refluxed for 10 h, 10 ml of acid was added, and heating was continued for 12 h. Another 10 ml of acid was added, and the mixture was refluxed for 12 h. It was evaporated to half its original volume, and the concentrate was decolorized with charcoal and allowed to stand at 4°C for 15 h. The precipitate (0.62 g) was removed by filtration, and the filtrate was evaporated to a volume of 10 ml. This concentrate was cooled to give another 0.7 g of substance. The product was recrystallized from 95% ethanol.

Compound VIg was similarly obtained.

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REACTIONS OF N-ALKYLAZINIUM CATIONS. 3.* QUATERNARY PTERIDINIUM SALTS. SYNTHESIS, STRUCTURE, AND REACTIONS WITH SIMPLE NUCLEOPHILES

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UDC 547.859:543.422.25

4-Morpholinopteridine reacts with triethyloxonium tetra-fluoroborate to give two types of isomeric quaternary salts, viz., 1-ethyl- and 8-ethyl-4-morpholinopteridinium tetrafluoroborates. The structures of the pteridinium cations were proved by the ^1H and ^{13}C NMR spectra and also by chemical transformations in reactions with simple nucleophiles.

The chemistry of pteridines has undergone significant development because of the important role of derivatives of this series in biochemical processes [2, 3]. Reactions of pteridines with diverse N, O, S, and C nucleophiles are known [2, 3], and the phenomenon of covalent hydration of protonated forms of the pteridinium ion has been studied thoroughly [4]; however, the literature contains no information regarding quaternary pteridinium salts or their reactions with nucleophiles.

The aim of the present research was to obtain quaternary N-alkylpteridinium salts and to study their structures and reactivities with respect to simple nucleophiles.

Considering the ease with which protonated forms of pteridine are hydrated in both the pyrimidine and pyrazine rings [5], the preparation of stable pteridinium cations seemed possible only when mesomeric-donor substituents, which participate in declocalization of the positive charge, are present. Alkoxy, alkylmercapto, or dialkylamino groups could have been substituents of this sort, since the alkylation of pteridines with free hydroxy and amino groups, even though it does take place at one of the ring nitrogen atoms, leads to uncharged oxo or imino derivatives as a result of deprotonation of these groupings [6, 7]. Starting from these premises and taking into account the fact that the pyrimidine ring, particularly the $C(_4)$ atom, is most vulnerable to the formation of covalent hydrates, in the present research we investigated the quaternization of 4-morpholinopteridine (I), which was obtained from 4-methylthiopteridine [8].

Since pteridines have low basicities and attempts to obtain quaternary salts by reaction with methyl iodide were unsuccessful [9], the quaternization of pteridine I was carried out with triethyloxonium tetrafluoroborate at 40°C in methylene chloride. Under these conditions 4-morpholinopteridine (I) forms two types of stable pteridinium salts with quaternary nitrogen atoms in the 1 (II) and 8 (III) positions, which were synthesized preparatively in 77% and 8% yields, respectively (Tables 1 and 2). It is known [3] that the basicities of the nitrogen atoms in unsubstituted pteridine decrease in the order $N_3 > N_1 > N_5 > N_8$. It is therefore not surprising that alkylation of the sterically accessible and more basic N_1 atom of the pyrimidine ring as compared with the N_8 atom of the pyrazine ring is the preferred quaternization pathway.

*See [1] for communication 2.

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 0009-3122/85/2109-1048$09.50