ISOMERIZATIONAL RECYCLIZATION OF PYRIDYLETHYLATED CYCLANONES.

A NEW METHOD FOR THE SYNTHESIS OF SUBSTITUTED POLYHYDROACRIDINES

AND THEIR ANALOGS

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Mixtures of cis and trans isomers of 1,2,3,4,9,10,9a,10a-octahydroacridines are formed in the recyclization of quaternary salts of pyridylethylated alicyclic ketones. The 1,2,3,4,9,10-hexahydro-1-acridone skeleton was obtained in the recyclization of the quaternary salt of pyridylethylated dimedone, whereas a noncyclic amino ketone was isolated from the products of recyclization of the quaternary salt of pyridylethylated camphor. The structures of the compounds obtained were confirmed by means of data from the IR, UV, and PMR spectra.

We have recently described a method for the construction of a quinoline ring on the basis of the Kost-Sagitullin reaction [1, 2] starting from pyridylethylated aliphatic and arylaliphatic ketones [3, 4]. In the present research this method was extended to carbocyclic carbonyl compounds, which made it possible to obtain a series of derivatives of polyhydroacridines and their analogs, the synthesis of which by traditional reduction or condensation methods [5-8] is difficult or impossible.

The starting pyridylethylated cyclanones II were obtained by the usual method by refluxing a mixture of the corresponding ketone with 2-vinylpyridine in the presence of sodium metal (Scheme 1).



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Com-	Base, bp.	Derivative,	UV spec-	IR spec-	Fou	nd,	Fmpirical	Cal	c.,	- - -
pound	•C (mm)	mp, °C	λ_{\max} , nm (log el	cm=1 (C=0)	с	н	formula	с	н	Yiel
lla	180—185 (7)	5657 ^a	204 (3,80), 256 (3,50)	1720	52,4	4,8	C19H20N4O8	52,8	4,8	70
		124—125 ^b	262 (3,60), 268 (3,47)				P			
IIb	170—172 (7)	130—131 ^c	204 (3,75), 256 (3,50), 262 (3,58), 268 (3,43)	1720	60,8	5,6	C ₂₀ H ₂₃ N ₅ O ₄	60,5	5,8	50
IIc	195—200 (8)	149—150 ^C	203 (3,87), 256 (3,46), 262 (3,53), 268 (3,40)	1720	60,2	5,7	C ₂₀ H ₂₃ N ₅ O ₄	60,5	5,8	50
IIq	180—182 (7)	90—91 ^a 223—224 ^b	202 (3,80), 256 (3,49), 262 (3,51), 268 (3,46)	1710	53,5	4,9	$C_{20}H_{22}N_4O_8$	53,8	4,9	70
He	87—88 ^d	_	-	1715	73,8	8,0	C ₁₅ H ₁₉ NO ₂	73,4	7,8	70
Ilf	189—190 (7)	180—181 ^a 260—261 ^b	202 (3,80), 255 (3,52), 260 (3,57), 268 (3,48)	1730	56,2	5,3	C ₂₃ H ₂₆ N ₄ O ₈	56,8	5,5	50
Hg	218––220 (15)	98—99 a 104—105b	202 (3,80), 256 (3,50), 261 (3,53), 267 (3,45)	1720 1750	47,5	5,6	C ₁₆ H ₂₂ INO ₃	47,6	5,4	70
IIh	170—171 (8)	127—128 ^b	202 (3,82), 256 (3,51), 261 (3,54), 268 (3,42)	1720	46,9	5,2	C ₁₃ H ₁₈ INO	47,1	5,4	84
¹ Picrate. ^b Methiodide. ^c 2,4-Dinitrophenylhydrazone.										

TABLE 1. Properties of the Pyridylethylcyclanones

^dPicrate. ^DMethiodide. ²,4-Dinitrophenylhydra: ^dMelting point.

TABLE 2. tion of 1	Properties of th Pyridylethylated C	e Isolated yclanones	Products	of Recycl:	iza-
Compound	mp, °C	Found, %	Empirical	Calc., %	Yield

Compound	mp,	Found, %		Empirical	Calc., %		Yield	
Compound	base	picrate	СН		formula	с	н	%
trans-Va cis-Va trans-Vb cis-Vb Wb (mix- ture of cis and trans) trans-Vc cis-Vc Vd (mix- ture of cis and trans)	62—63 ^a Oil 60—61 Oil 73—74 Oil Oil ^d	137-138 171-172b 260-261c 150-151 160-161 230-231c 130-131	83,5 56,1 53,9 83,2 53,6 	9,9 5,5 6,4 9,5 6,3 	$\begin{array}{c} C_{14}H_{19}N\\ C_{20}H_{22}N_4O_7\\ \hline \\ \\ C_{16}H_{24}IN\\ C_{15}H_{21}N\\ C_{16}H_{24}IN\\ \end{array}$	83,6 55,8 53,8 83,7 53,8 	9,4 5,1 6,7 9,8 6,7	26 20 35 35 70 35 35 35 33
IVa VI VII VIII XI XI XI	$\begin{array}{c} 75-76\\ 53-54^e\\ 160-161\\ 89-90\\ 37-38\\ 67-68\end{array}$	$ \begin{array}{c}$	79,7 — 86,5 80,0 63,6 —	9,8 7,5 8,7 9,0 	$\begin{array}{c} C_{18}H_{25}NO\\\\ C_{15}H_{15}N\\ C_{16}H_{19}NO\\ C_{9}H_{15}NO_{2}\\\\ \end{array}$	79,6 — 86,1 79,1 63,9 —	9,2 7,1 8,3 9,0 	$ \begin{array}{r} 32 \\ 15 \\ 10 \\ 30 \\ 46 \\ \end{array} $

^aAccording to the data from [11], the base had mp 64-65°C, and the picrate had mp 136-138°C. ^bAccording to the data from [10], the picrate had mp 172-173°C. ^cThe methiodides of the mixture of isomers. ^dSee Table 4 for the mass spectrum. Compound Vd was described in [15]; however, no mention was made of any of the constants. ^eAccording to [12], the base had mp 55°C, and the picrate had mp 218°C.

TABLE 3. UV and PMR Spectra of IVf, Va-d, and VIII

Compound	UV spec- trum,	PMR spectrum, δ , ppm (in CCl ₄)								
Compound	\max , init (log ε)	N—CH3 S	4a-H, m	9-H	9-H R—H		aliphatic ring H, m			
trans-Va	216 (4,14), 300 (3,55)	2,85	3,10	2,50 (d)		6,40—7,10	1,00-2,00			
cis- Va	257 (4,16), 307 (3,54)	2,80	3,10	2,20— 2,70 (m)		6,30-7,10	7,00-2,00			
tr a ns-Vb	260 (4,23), 306 (3,54)	2,90	3,15	2,20 (s)	9a-CH₃ 0,95 (\$)	6,20-7,00	1,00-2,00			
cis-Vb	236 (4,23), 312 (3,58)	2,75	3,10	2,30 (s)	9a-CH3 0,85 (s)	6,20-7,00	1,00-2,00			
trans-Vc	260 (4,17), 300 (3,65)	2,85	3,15	2,50 (d .)	2-CH ₃ 1,00 (d)	6,30-7,10	1,20—2,10			
cis-Vc	248 (4,19), 295 (3,76)	2,80	3,20	2,2 0 —2,60 (m)	2-CH₃ 0,90 (d)	6,30-7,10	1,20-2,10			
Vd (mix- ture of cis and trans)	234 (4,25), 360 (3,70)	2,80	3,10	2,20— 2,50 (m)		6,00-7,00	1,00-2,00			
VIII	$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	3,15		3,45 (s,	3(CH ₃) ₂ 1,00 (s)	6,50—7,10	2H-2,00			
IVf	$\begin{array}{c} 204 \ (4,6), \\ 244 \ (4,03), \\ 295 \ (3,48) \end{array}$	$ \begin{vmatrix} 0,75 & (s, 3H); & 0,80 & (s, 3H); & 0,90 & (s, 3H) \\ 1,10-2,10 & (m, 6H); & 2,65 & (d, 2H); & 2,75 & (s, 3H) \\ 6,40-7,10 & (m, 4H); & 7,25 & (s, 1H) \end{vmatrix} 4H-2,25 & (s, 2H) $								
TABLE 4. Mass Spectra ^a of IVf. Va-d. VI-VIII. and X-XII										

TABLE 4.	Mass	Spectra ^a	of	IVf, Va-d,	VI-VIII,	and 1	X-XII
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Compound	m/z (relative intensity in %)	$\frac{I_{156}}{I_{\mathrm{M}}}$	$\frac{I_{145}}{I_{\rm M}}$	$\frac{I_{144}}{I_{\rm M}}$
IVf	271 (20), 243 (13), 228 (13), 160 (14), 121 (10), 120 (100), 118 (16), 107 (84), 91 (36), 77 (16),			
trans-Va	65 (17), 55 (30), 41 (61) 201 (33), 159 (25), 158 (92), 146 (17), 145 (84), 144 (100), 143 (17), 130 (25), 120 (13), 118 (13),	2,8	2,5	3,0
cis-Va	91 (10), 78 (7), 77 (13) 201 (67), 200 (78), 159 (25), 158 (100), 157 (13), 145 (17), 144 (55), 143 (11), 130 (7), 120 (3), 118	1,5	0,3	0,8
trans-Vb	(8), 91 (11), 77 (3) 215 (58), 200 (17), 172 (6), 159 (40), 158 (100), 157 (10), 145 (8), 144 (17), 130 (5), 120 (7), 118	1,7	0,2	0,3
cis-Vb	(7), 91 (10), 77 (8) 215 (70), 200 (18), 172 (6), 159 (24), 158 (100), 157 (6), 145 (6), 144 (17), 130 (5), 120 (12), 118	1,4 •	0,1	0,2
trans-Vc	(7), 91 (6), 77 (4) 215 (20), 200 (15), 159 (22), 158 (100), 145 (25), 144 (22), 130 (20), 120 (15), 118 (45), 93 (25), 91	5,0	1,3	⁻ 1,3
cis-Vc	(20), 77 (20), 73 (35) 215 (60), 200 (10), 159 (20), 158 (100), 145 (35), 144 (40), 130 (15), 120 (60), 118 (35), 93 (20), 91	1,7	0,6	0,7
Vd	$ \begin{array}{c} (25), 77 & (17), 73 & (22) \\ 215 & (18), 214 & (40), 202 & (60), 200 & (100), 186 & (40), \\ 173 & (55), 158 & (70), 121 & (65), 120 & (50), 107 & (60), 91 \\ \end{array} $			
VI	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$			
VII	77 (25), 76 (27), 73 (25) 209 (50), 208 (100), 207 (35), 193 (38), 192 (22), 191 (15), 120 (10), 118 (4), 104,5 (10), 103,5 (25),			
VIII	95,5 (11), 83,5 (20), 73 (24) 241 (50), 240 (40), 239 (8), 226 (11), 224 (100), 210 (13), 209 (7), 196 (7), 180 (8), 157 (12), 134			
X	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$			
XI	$ \begin{array}{cccccccccccccccccccccccccccccccccccc$			
XII	56 (10), 53 (25) 237 (25), 220 (9), 209 (7), 208 (5), 195 (15), 194 (100), 193 (16), 180 (11), 179 (5), 167 (4), 162 (7), 161 (8), 151 (4)			

^aThe molecular ion and the 12 most intense peaks are presented.

Compound IIh can be obtained by direct pyridylethylation of cyclopentanone or by acidic hydrolysis of keto ester IIg, but the latter variant gives a better yield. The properties and yields of IIa-h are presented in Table 1.

The bases obtained were converted by treatment with methyl iodide to methiodides IIIa-h, the recyclization of which was realized by heating in an ampul with an excess amount of an aqueous solution of methylamine sulfite at 130-140°C for 10-50 h. Preliminary evaluation of the composition of the reaction mixture in its benzene extract was accomplished by chromato-graphic mass spectrometry, after which the principal individual reaction products detected in it were isolated by traditional methods and by preparative chromatography.

As a result of our study, we established that the principal products of recyclization of IIIa-d are octahydroacridines Va-c, which are produced in the form of mixtures of approximately equal amounts of the cis and trans isomers (Table 2), and 2,3-pentamethylene-1,2,3,4tetrahydroquinoline (Vd). In addition, 1,2,3,4-tetrahydroacridine (VI) (15%) was detected among the products of recyclization of salt IIIa and was isolated in individual form, whereas 2,10-dimethyl-9,10-dihydroacridine (VII) was formed in the recyclization of salt IIIc. The principal product in the recyclization of salt IIIe was 3,3,10-trimethyl-1,2,3,4,9,10-hexahydro-1-acridone (VIII).

As we have already mentioned above, the recyclization of salts IIIa-c leads to mixtures of geometrical isomers Va-c, from which individual compounds with cis- and trans-fused rings were isolated by preparative chromatography.* Singlets of the protons of NCH₃ groups, the chemical shifts of which in the case of the trans isomers lie at somewhat weaker field, are characteristic for their PMR spectra (Table 3). In the PMR spectra of the same isomers the signals of the 9-H protons are observed in the form of a doublet with a spin-spin coupling constant (SSCC) of 8 Hz due to coupling with the 9a-H proton, which is axially oriented with respect to the cyclohexane ring (A). The signals of the same protons (9-H) in the case of cis-fused rings, in agreement with the data of Booth and co-workers [9, 10], show up in the PMR spectrum in the form of a multiplet, since an equatorial orientation of the 9a-H proton with respect to the A ring promotes its resonance with the 9-H protons.

In the case of the cis and trans isomers of Vb the signals of the 9-H protons have the form of singlets, but the chemical shifts of the 9-H protons of the trans isomers are smaller than in the case of the cis configuration. On the other hand, the signal of the protons of the methyl group in the 9a position in the case of trans fusion (an axial CH_3 group) is observed at weaker field than in the case of the cis isomer.

Two absorption maxima are observed in the UV spectra of Va-c (Table 3); in the case of the trans isomers these bands are drawn together (the distance between the maxima is 39-46 nm), whereas in the spectra of the cis-fused compounds these bands generally are farther away from one another (the distance between the maxima is 47-76 nm).

Under the influence of electronimpact, Va-d form rather stable molecular ions, which undergo fragmentation via three principal pathways (Scheme 2). The first pathway (A) is characterized by retrodiene fragmentation of the B ring, which takes place with the transfer of one hydrogen atom to either the resulting fragment (the 120 ion)⁺ or to the fragment that is split out (the 118 ion). The other two fragmentation pathways (B and C) involve prior cleavage of the C_4-C_{10a} bond in the molecular ion, which is characteristic for perhydroquinoline derivatives [13], and subsequent fragmentation of this ion radical with the loss of the C_1-C_4 atoms (pathway B) or the C_2-C_4 atoms with the transfer of the 9a-H atom (when R = H) to the chain that is split out (pathway C).

*We were unable to separate the mixture in the case of Vd. †Here and subsequently, the m/z values are given for the ion peaks. Scheme 2



The mass spectra of the cis- and trans-isomeric compounds are similar to one another (Table 4); however, they do differ quantitatively. In contrast to the mass-spectrometric behavior of perhydroquinolines [13], the molecular ions of trans-fused Va-c are less stable, and the intensities of the peaks of the fragment ions in them are, correspondingly, higher than in the case of the cis isomers. As a result, the $I_{15\,8}/I_M$, I_{145}/I_M , and I_{144}/I_M ratios in the mass spectra of the trans isomers are always higher than in the case of the cis-fused compounds (Table 4). The presence of an annelated benzene ring evidently stabilizes the cis configuration (but not the trans configuration) of the octahydroacridine to a greater degree. At the same time, in the latter the axially oriented 9a-H atom should migrate via pathway C, leading to the 158 ion, with greater ease in the primary ion radical.

The structure of VIII is confirmed by the mass spectrum (the 240, 239, and 224 ions; Scheme 3), the IR spectrum (the characteristic C=O absorption band at 1680 cm⁻¹), and the PMR spectrum, in which the chemical shifts are similar to those described in the literature for N-methyl-1,4-dihydroquinoline but not to those described for 1,2-dihydroquinoline [14].

Scheme 3



Thus, as in the case of pyridylethylated carbonyl compounds with an open chain [3, 4], in the recyclization of the salts of most of the pyridylethylated cyclanones the process does not stop at the step involving the formation of anilino ketones IV, inasmuch as they undergo cyclization to the corresponding derivatives of di- or tetrahydroquinolines. In the case of salt IIIe appreciable amounts of N-methylaniline were formed along with acridine VIII; this indicates parallel (to recyclization) cleavage of quaternary salt IIIe. It is possible that this is associated with the greater steric hindrance in salt IIIe, as well as the greater ease of cleavage of β -diketones.



The role of steric factors is displayed to an even greater degree in the case of salt IIIf, which contains a camphor residue. Completely stable anilino ketone IVf was obtained in 32% yield as a result of its recyclization. Absorption bands at 1740 (C==0) and 3420 cm⁻¹ (N-H) are present in its IR spectrum, and its dissociative ionization is characterized, on the one hand, by retrodiene cleavage of the camphor ring (the 243 and 160 ions) or "benzyl" cleavage of the side chain (the maximum peak is that of the 120 ion, Scheme 4).

N-Acetyl derivative IX was obtained by heating amino ketone IVf with acetic anhydride; this also confirms the noncylic structure of IVf. The formation of acridine X was established qualitatively (by mass spectrometry) when IVf was heated with phosphoric anhydride.

Attempts to accomplish the recyclization of pyridylethylated cyclopentanone salt IIIh were unsuccessful. Products with basic character were not detected in the reaction mixture even after heating for 60 h, and only starting salt IIIh was isolated from the aqueous layer after it was evaporated.

When the process was carried out with salt IIIg, the only isolated reaction product was 2-N-methylamino-1-ethoxycarbonylcyclopentene (XI, in 46% yield), the formation of which is apparently also associated with cleavage of the quaternary salt to give the "starting" components with subsequent reaction of the resulting 2-ethoxycarbonylcyclopentanone with excess methylamine.

Thus in our research we have found a new rather general method for the synthesis of 2,3-polymethylene-1,2,3,4-tetrahydroquinolines that makes it possible to obtain various substituted compounds of this series.

EXPERIMENTAL

The chromatographic mass spectra were recorded with a Varian MAT-111 apparatus with a 1.5-m-long column (with an inner diameter of 3.5 mm); the liquid phase was 5% SE-30 on Poropak, the carrier gas was helium, and the thermostat was used for programmed heating from 100 to 250°C at a rate of 10°C/min. The mass spectra were recorded at an ionization energy of 80 eV. The mass spectra of the solid compounds were obtained with a Varian MAT-44S spectrometer at an ionization energy of 70 eV and with an MKh-1303 spectrometer at 50 eV. The PMR spectra of solutions of the compounds in CCl₄ were recorded with Varian T-60 and Tesla BS-497 (100 MHz) spectrometers with hexamethyldisiloxane as the internal standard. The UV spectra of solutions in ethanol were recorded with a Cary (Varian) spectrophotometer at 200 to 500 nm. The IR spectra were obtained with a UR-20 spectrometer. The individuality of the compounds was verified by means of thin-layer chromatography (TLC) on Silufol UV-254 or by means of chromatographic mass spectrometery.

Pyridylethylation of Cyclanones (General Method). A 0.1-mole sample of freshly distilled 2-vinylpyridine, 0.2 mole of the cyclanone, 0.02 mole of sodium metal in the form of small pieces, and 0.1 g of hydroquinone were placed in a three-necked flask equipped with a stirrer, a reflux condenser, and a thermometer, and the mixture was heated with vigorous stirring at 140-150°C for 5-6 h. It was then cooled and treated with 20% hydrochloric acid solution, and

the oily layer was separated. The acidic layer was washed with benzene and made alkaline with 30% aqueous sodium hydroxide solution. The oily layer was separated, the aqueous layer was extracted with benzene, and the extract was combined with the oil and dried with anhydrous magnesium sulfate. The solvent was removed by distillation, and the residue was distilled *in vacuo*. The constants, spectral data, and yields of IIa-h are given in Table 1. Methiodides IIIa-h were obtained by heating bases IIa-h with excess methyl iodide in a sealed ampul at 100-110°C. The melting points of the crystalline salts are presented in Table 1.

Recyclization of Methiodides IIIa-H (General Method). A solution of 0.01 mole of the corresponding methiodide dissolved in the minimum amount of water, 5 ml of 25% aqueous methylamine solution, and 3 ml of 25% aqueous methylamine saturated with sulfur dioxide were heated in a sealed ampul at 120-140°C for 10-60 h (10-20 h for salts IIIa-c, 40 h for salts IIId-g, and 60 h for salt IIIh). The reaction mixture was then cooled to room temperature and treated with benzene. The extract was analyzed with a chromatographic mass spectrometer, after which the compounds that were identified in the mixture were isolated by column chromatography (on L 40/100 silica gel) or by chromatography on a plate (on aluminum oxide) in a benzene methanol system (9:1).

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