SATURATED NITROGEN-CONTAINING HETEROCYCLES. 15.* CATALYTIC SYNTHESIS AND ISOMERIZATION OF 9-SUBSTITUTED 10-METHYLPERHYDROACRIDINES

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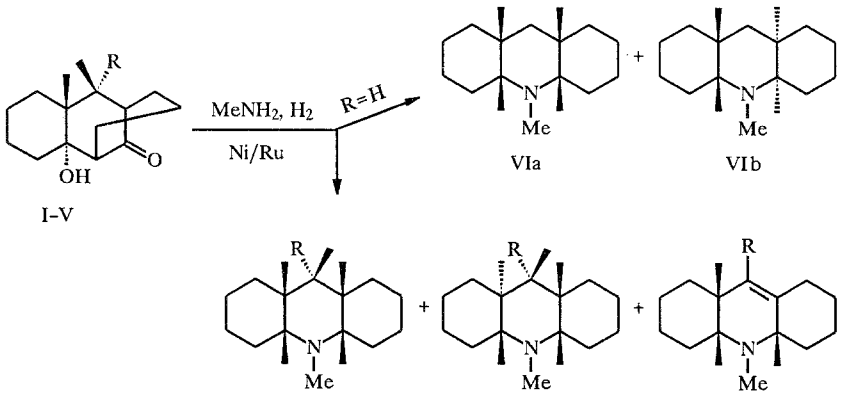
In the catalytic hydromethylamination of 8-substituted 2-hydroxytricyclo[7.3.1.0^{2,7}]tridecane-13-ones they are converted into 9-substituted 10-methyl-$\Delta^{9,9a}$-dodecahydroacridines and 10-methylperhydroacridines with trans,anti,cis- *and* cis,syn,cis-*conformation. The ability of the latter to isomerize into the* trans,cis,trans-*form has been established.*

In the catalytic reductive amination of 8-substituted 2-hydroxytricyclo[7.3.1.0^{2,7}]tridecan-13-ones (I-V), which are accessible products of intramolecular aldol condensations of methylene(alkylidene, arylidene)dicyclohexanones, 9,10-disubstituted perhydroacridines are formed [2, 3]. It has been shown, from their ^{13}C NMR spectra and x-ray analysis, that 10-substituted perhydroacridines which do not have a substituent on the $C_{(9)}$ carbon are formed as two isomers with *cis,syn,cis-* and *cis,anti,cis-*configuration (VIa, b) [4].

The present study was undertaken with the object of examining the stereoisomeric composition of 9,10-substituted perhydroacridines formed in the catalytic hydromethylamination of 8-alkyl(phenyl,2-furyl)-2-hydroxytricyclo[7.3.1.0^{2,7}]trideca-13-ones (II-V), and the possibility of the directed synthesis of individual isomers of 9-substituted 10-methylperhydroacridines.

It has been established that under the conditions of the reaction (a five-times excess of methylamine, 100°C, hydrogen pressure 10 mPa, catalyst Raney nickel modified with ruthenium) the β-cycloketones II-V are converted into *cis,syn,cis-* and *trans,anti,cis-*perhydroacridines (VIIa-Xa and VIIb-Xb respectively). In addition, the partially unsaturated azaheterocycles $\Delta^{9,9a}$-dodecahydroacridines XI-XIV were detected in yields of 17-20% (by GLC) in the hydrogenation products



I, VI R=H; II, VII, XI R=Me; III, VIII, XII R=Et; IV, IX, XIII R=Ph; V, Xa, c XIV R=2-furyl

The formation of *cis,syn,cis*-perhydroacridines VIa-Xa can be considered as taking place through a stage of retrodecomposition of β-cycloketones to the corresponding 1,5-diketones, azacyclization of the latter to intermediates† with a 1,4-dihydropyridine fragment and subsequent catalytic *cis*-addition of hydrogen. The appearance of *trans,anti,cis*-perhydroacridines VIIb-Xb is apparently the result of isomerization of the intermediate 1,4-dihydropyridine system into the corresponding 1,2-dihydropyridine. The isomerization hypothesis is supported by the formation of dodecahydroacridines XI-XIV, which contain a double bond stabilized by the substituent at $C_{(9)}$. In this connection it is important to note that in the hydroamination of the unsaturated β-cycloketone

*For Communication 14, see [1].

†Isolation of the 1,4-dihydropyridines will be reported in a subsequent communication.

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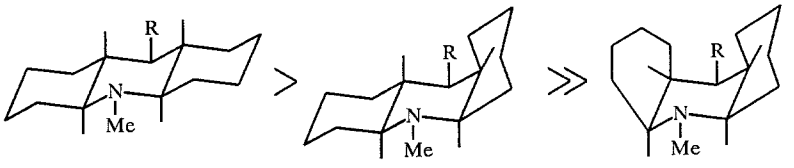
TABLE 1. Carbon-13 NMR Spectra of Perhydroacridines VIIa-c and Xa-c (δ ppm, $CDCl_3$)

Compound	$C_{(1)}$, $C_{(8)}$	$C_{(2)}$, $C_{(7)}$	$C_{(3)}$, $C_{(6)}$	$C_{(4)}$, $C_{(5)}$	$C_{(9)}$	$C_{(4a)}$, $C_{(10a)}$	$C_{(8a)}$, $C_{(9a)}$	$C_{(11)}$
VIIa	25,27	27,73	21,27	31,20	38,89	66,11	43,82	35,69
VIb *	21,33; 31,29	27,05; 26,07	20,39; 26,07	30,08; 30,90	40,11	64,62; 70,06	43,06; 44,43	35,52
VIIc	30,40	26,05	26,26	31,47	41,54	68,08	45,91	34,89
VIIIa	25,31	27,82	21,32	31,29	46,11	66,22	41,79	35,82
VIIIb*	21,09; 29,80	27,08; 26,01	20,51; 26,19	31,05; 31,55	46,60	64,68; 70,20	39,24; 42,33	36,66
VIIIc*	29,82	26,12	26,50	31,56	46,41	68,34	41,50	35,38
IXa	25,78	27,73	21,31	31,39	50,37	66,72	41,98	35,58
IXb	23,03; 30,97	26,71; 25,86	20,12; 26,22	30,97; 31,25	53,96	64,80; 70,41	39,41; 44,78	36,48
Xa	25,81	26,46	21,13	31,16	45,67	65,91	36,49	35,64
Xb	22,95; 30,94	27,55; 26,12	20,00; 26,74	31,16	47,26	63,76; 70,20	41,46; 43,34	36,36

*Spectra of isomers individually isolated.

I; dodecahydroacridines and the isomeric acridines with *trans*-articulation of the ring are not formed [4].

We have established by special tests that isomerization of the final reaction products VIIa, b-Xa, b does not occur under the conditions of the hydromethylamination. Taking the 9-alkyl-10-methylhydroacridines VIIa, b, VIIIa, b, XI, and XII as an example, it has been shown that isomerization conversion takes place only on increasing the temperature to 160-180°C. At 120°C only hydrogenation of the double bond of the dodecahydroacridines XI and XII occurs and the catalyzates contain a mixture of saturated bases VIIa, b and VIIIa, b. On increasing the temperature to 160°C, 9,10-dimethyl-*cis,syn,cis*-perhydroacridine (VIIa) (over 10-12 h) and 10-methyl-9-ethyl-*cis,syn,cis*-perhydroacridine (VIIIa) (over 6-7 h) are completely converted into the *trans,anti,cis*-isomers VIIb and VIIIb. After 6-7 h further heating at 180°C the latter is isomerized into the thermodynamically more stable *trans,syn,trans*-forms (VIIIc) (completely) and VIIc (to ~70%). The mixture of isomers of 10-methylperhydroacridine VIa and VIb is unchanged at these temperatures. Thus, it is possible to arrange the 9,10-substituted perhydroacridines according to their relative stability in the following series, which is in agreement with the well-known Johnson rule [5]:



VIIc, VIIIc VIIb, VIII b VIIa VIIIa

R=Me, Et

This information on the isomerization makes it possible to forecast the conditions for the synthesis of 9,10-substituted perhydroacridines of given structure by varying the reaction temperature: 160°C for the *trans,anti,cis*-configuration and 180°C for *trans,cis,trans*. Thus, in the hydromethylamination of the β-cycloketone III at 160°C (10 h reaction time), 10-methyl-9-ethyl-*trans,anti,cis*-perhydroacridine (VIIIc) was isolated in 90% yield.

The composition and spatial structure of the reaction products were determined from the ^{13}C NMR spectra of the hydrogenation products, mixtures obtained as a result of fractionation of the products, and the pure isomers (Table 1). Assignment of the signals was effected on the basis of known increments [6] and characteristic data [4].

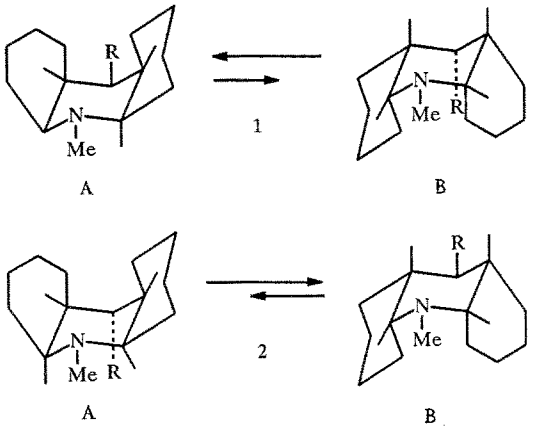
Examination of the hydrogenation products, obtained by the hydromethylamination of the β-cycloketone II, using chromatograph-mass spectrometry showed the presence of two molecular ions of mass 210 corresponding to 9,10-dimethylperhydroacridines VIIa and b, and a third with mass 219 from which was inferred the presence of 9,10-dimethyldodecahydroacridine XI. Carbon-13 NMR spectroscopy confirmed the presence of a double bond in compound XI (signals at 130.88 and 127.84 ppm) and made it possible to determine its location. Signals at 66.67 and 57.96 ppm, belonging to the $C_{(4a)}$ and $C_{(10a)}$ atoms, showed that the double bond did not affect them. The considerable difference in the chemical shifts of the carbon of the methyl group on $C_{(9)}$ in the spectra of perhydroacridine VIIa and dodecahydroacridine XI (16.70 and 21.33 ppm respectively) provides evidence that

the double bond is located at $C_{(9)}$—$C_{(9a)}$. A full-strength signal at 19.92 ppm characterizes *cis*-articulated carbo- and heterocycles. The $C_{(4a)}$—N bond apparently takes up an equatorial position since in any other case closure of the hydropyridine ring would be difficult. Since isomers VIIa and b are formed in the hydrogenation of dodecahydroacridine XI one can conclude that the hydrogens at $C_{(4a)}$ and $C_{(10a)}$ are also *syn*-located one to another.

From the similar chemical shifts of the α-carbons of the heterocycle (66.69 and 58.46 ppm for XII, 66.72 and 58.55 ppm for XIII, 67.42 and 57.77 ppm for XIV) one can conclude that the structures of compounds XI-XIV are of the same type.

The existence of signals at 70.06 and 64.22 ppm and an upfield signal at 20.39 ppm in the spectrum of a mixture of 9,10-dimethylperhydroaridines VIIa,b and dodecahydroacridine XI confirms the presence of isomer VIIb with *trans,anti,trans*-configuration in the hydrogenation products; the signal at 66.11 ppm points to the presence of isomer VIIa with *cis,syn,cis*-structure. A similar approach was used in the analysis of the spectra of mixtures of VIIIa, b and XII, IXa, b and XIII, and Xa, b and XIV.

A feature of perhydroacridines of *cis,cis* type is their conformational mobility [4]. 9,10-Substituted *cis,syn,cis*-perhydroacridines can exist in two isomeric forms (1 and 2) with different orientation of the substituent on $C_{(9)}$:



The *cis,syn,cis*-perhydroacridines VIIa-Xa were isolated in form 1, stabilized conformation A, the signals of the $C_{(9)}$ carbon, and the carbon of the methyl group being evidence of this (Table 1). The chemical shifts of these compounds differed by 2-3 ppm from those observed (39.00 ppm) for N-methyl-*cis,syn,cis*-perhydroacridine stabilized as conformer B [4].

In the ^{13}C NMR spectra of 9,10-dialkylperhydroacridines VIIc and VIIIc there are seven resonance lines corresponding to the perhydroacridine skeleton which provides support for its symmetrical structure, and the positions of the signals of the angular carbons at 68.08 and 45.91 ppm for isomer VIIb, and 68.34 and 41.50 ppm for VIIIb point to a *trans,syn,trans*-configuration (Table 1).

All the perhydroacridine isomers considered have an equatorial orientation of the substituent on $C_{(9)}$ since with an axial disposition of the latter the signals of carbons $C_{(4a)}$ and $C_{(10a)}$ would be shifted upfield by 4-6 ppm as a result of 1,3-diaxial interactions.

Thus, for 2-hydroxytricyclo[7.3.1.$0^{2,7}$]tridecane-13 ones substituted in position 8 it is characteristic that, under conditions of catalytic hydromethylamination, there should be formed not only 9-substituted 10-methyl-*cis,syn,cis*-perhydroacridines but also the *trans, anti, cis* forms. The ability of the latter to isomerize at higher reaction temperatures is employed for the directed synthesis of the individual *trans,syn,trans*- and *trans,anti,cis*-isomers.

EXPERIMENTAL

Gas chromatography was carried out on an LKhM-8MD chromatograph using a flame-ionization detector and a column 5 m in length packed with "inzenskii" brick modified with 3% KOH and impregnated with 5% Apiezon L. Column temperature was 200-220°C and flow rate of the helium carrier gas 1.2 liter/h. Carbon-13 NMR spectra were run on a Varian FT-80A instrument in deuterochloroform with TMS internal standard. Mass spectra were recorded on a Varian MAT 212 (80 eV).*

Catalytic hydromethylamination of the β-diketones II-V was carried out by the method of [2] in the presence of Raney nickel modified with ruthenium and a five-times excess of methylamine. The hydrogenation products, separated from catalyst and solvent, were fractionally distilled in vacuum at 2.66 hPa.

*The authors are grateful to N. S. Kulikova of Moscow University for carrying out the chromatography-mass spectrometry studies.

Isomerization of the mixtures VIa and VIb; VIIa, VIIb, and XI; VIIIa, VIIIb, and XII was effected in an autoclave in methanol in the presence of Ni/Ru under a hydrogen pressure of 10 mPa inn the temperature range 120-180°C. Samples were removed at the end of each 6-7 h period and the temperature then increased by 20°. The samples, after removal of catalyst and solvent, were analyzed by GLC and ^{13}C NMR spectroscopy.

The results of elemental analysis for C, H, N for compounds VIIb and VIIIb were in agreement with the calculated results.

Characteristics of the isomers of the 9,10-substituted perhydroacridines which we isolated are given below.

9,10-Dimethyl-*trans,anti,cis*-perhydroacridine (VIIb, $C_{15}H_{27}N$). Bp 131-132°C/5.32 hPa, n_D^{20} 1.5125. **10-Methyl-9-ethyl-*trans,anti,cis*-perhydroacridine (VIIIb, $C_{16}H_{29}N$):** Bp 116-118°C/2.66 hPa, n_D^{20} 1.5150. **10-Methyl-9-ethyl-*trans,syn,trans*-perhydroacridine (VIIIc, $C_{16}H_{29}N$):** Bp 124-126°C/2.66 hPa, n_D^{20} 1.5168.

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