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SATURATED NITROGEN-CONTAINING HETEROCYCLES. 17*. SYNTHESIS AND CATALYTIC HYDROGENATION OF 9,10-SUBSTITUTED DECAHYDROACRIDINES (MECHANISM OF HYDROAMINATION OF β-CYCLOKETOLS)

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The synthesis of 9,10-substituted decahydroacridines was carried out, and their catalytic hydrogenation was studied. The participation of these compounds as intermediates in the formation of perhydroacridines in the reaction of catalytic hydroamination of 8-R-2-hydroxy-13-oxotricyclo[7.3.1.0^{2,7}]tridecanes was established. The ^{1}H and ^{13}C NMR spectra of the synthesized compounds are given.

We have shown previously that catalytic reductive amination of 1,5-diketones and their synthetic equivalents, β-cycloketols, is a preparative method of synthesizing saturated azaheterocycles of the series of piperidine and its condensed analogs [2]. As possible intermediates of the reaction studied, we considered compounds containing the 1,4-dihydropiperidine fragment. Formation of the latter compounds was indicated by indirect data, i.e., the evolution of oxazolohydropyridines during the catalytic hydroethanolamination of semi- and acyclic 1,5-diketones [3], as well as by the stereochemical result of the reactions, i.e. formation of cis-linked condensed azaheterocycles [4, 5].

Continuing studies begun earlier, aimed at confirming the participation of 1,4-dihydropyridines in hydroamination reactions, we synthesized certain compounds of this series and studied their catalytic hydrogenation.

As the model compounds we chose 8-R-2-hydroxy-13-oxotricyclo[7.3.1.0^{2,7}]tridecanes (I, II)—the products of intramolecular aldolization of benzylidene(furfurylidene)dicyclohexanes. The aminating agents were methylamine and aniline.

It was found that β-cycloketols I, II acted on by methylamine with strict preservation of hydroamination reaction conditions (methanol, 5-fold excess of methylamine, 100°C, 10 mPa) but in the absence of a catalyst (to prevent hydrogenation of the intermediates), are converted with a 65% to 70% yield to the corresponding 9-phenyl- and 9-(2-furyl)-10-methyl-$\Delta^{4a,8a,9a,10a}$-decahydroacridines (III, IV).

The presence of a 1,4-dihydropyridine ring in compounds III, IV is confirmed by the presence in their IR spectra of two absorption bands of the stretching vibrations of isolated C=C bonds in the range 1620-1700 cm^{-1}, as is consistent with the data of [6]. This is also indicated by the data of NMR spectroscopy. Thus, in the ESR spectra, in addition to the proton signals of the methylene units in the range 1.51-2.22, there is also a proton singlet in the 9 position at 3.45 ppm (compound III) or at 3.65 ppm (compound IV). The presence in the ^{13}C NMR spectrum of product III of seven resonance signals of decahydroacridine carbon atoms indicates symmetry of the structure and a 1,4 arrangement of the double bonds in the dihydropyridine nucleus (see Experimental section).

*For report 16, see [1].

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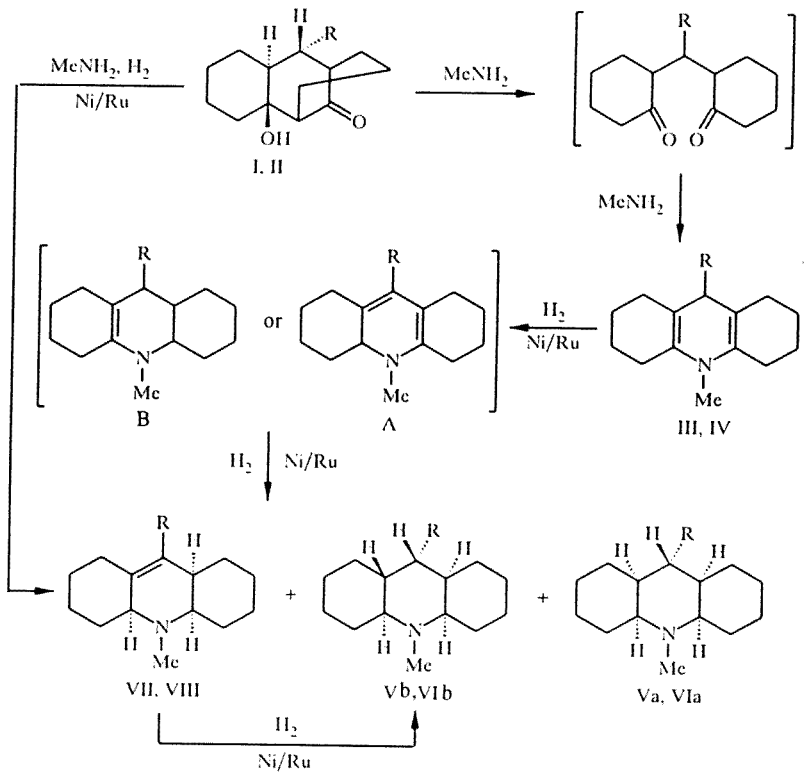


I, III, Va, VIa, VII R = Ph; II, IV, Vb, VIb, VIII R = 2- furyl

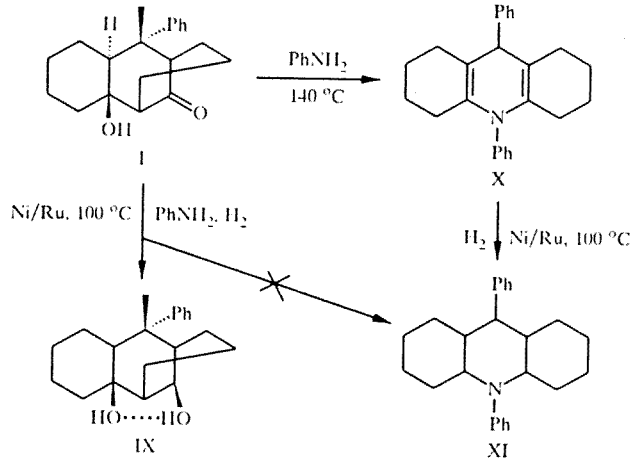
Hydrogenation of compounds III, IV and direct hydromethylamination of β-cycloketols I, II were carried out under identical conditions (5-fold excess of methylamine in methanol, 100°C, 10 mPa, ruthenium-modified nickel catalyst). Analysis of ^{13}C NMR spectra of the products thus obtained showed them to be completely identical. In both cases, cis-syn-cis (Va, VIa) and trans-anti-cis (Vb, VIb) isomers of 9-R-10-methylperhydroacridines were formed with a small amount of 9-R-10-methyl-$\Delta^{8a,9}$-dodecahydroacridines (VII, VIII) present as impurities. In [7], we gave a detailed description of the assignment of signals in the ^{13}C NMR spectra of compounds V-VIII.

Formation of isomers Va, VIa probably results from cis-addition of hydrogen to intermediates III, IV containing the 1,4-dihydropyridine fragment in a single event of adsorption. Trans-anti-cis isomers Vb, VIb may be formed as a result of isomerization of intermediates of dicyclohexa-1,4-dihydropyridines III, IV to the corresponding dicyclohexa-1,2-dihydropyridines A, followed by cis-addition of hydrogen in accordance with the rib doublet scheme via the stage of formation of dodecahydroacridines VII, VIII. In the latter compounds, the double bond is stabilized and screened by the substituent of the $C_{(9)}$ atom; this slows the rate of its hydrogenation and makes it possible to record the formation of these compounds. Also possible is a partial reduction of intermediate III, IV to $\Delta^{8a,10a}$-dodecahydroacridines B and subsequent displacement of the double bond to the 8a, 9 position with formation of products VII, VIII.

Thus, step-by-step hydroamination of β-cycloketols I, II and a study of the geometry of the end products make it possible to treat this reaction as a process taking place via the steps of retroaldol splitting of β-cycloketols to the corresponding 1,5-diketones, amination of the latter with formation of 1,4-dihydropyridine systems, catalytic isomerization and hydrogenation of the deca- and dodecahydroacridine intermediates being formed, with cis-addition of hydrogen characteristics of catalytic reactions.

Our data made it possible to account for the fact that under ordinary conditions (100°C), under action of aromatic amines no hydroamination of ketols I, II takes place; rather, products of their catalytic reduction, of the type of IX, are formed [8]. We found that retroaldol splitting of ketol I acted on by a weak base — aniline — takes place under more severe conditions (at 140°C) and with a lower yield (45%) of the target product — the familiar 9,10-diphenyl-$\Delta^{4a,8a,9a,10a}$-decahydroacridine (X), the characteristics of which are consistent with those cited in the literature [6]. Hydrogenation of compound X (methanol, 100°C, 10 mPa) on ruthenium-modified nickel produced 9,10-diphenylperhydroacridine (XI), formed with a 77% yield as a

single isomer (ESR data). Direct hydroarylamination of cycloketol I at 140°C is complicated by reduction of the phenyl substituents with formation of a complex mixture of products



The results obtained show the possibility of synthesizing 9-R-N-arylperhydroacridines by successively carrying out the reactions of arylamination of β-cycloketols and catalytic hydrogenation of the N-aryldecahydroacridines formed. Let us note that this was the first time we carried out the hydrogenation of decahydroacridines of the indicated structure; the reaction takes place smoothly, with high yields of perhydroacridines. In view of the fact that complex metal hydrides (KBH_4, $LiAlH_4$) do not reduce these compounds even under severe conditions, and in the presence of other reductants — formic acid, mixture of dimethylformamide with HCOOH or HCl — this proportionation takes place in addition to the reduction [9], the method of catalytic hydrogenation of decahydroacridines to perhydroacridines has distinct advantages.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded with a Varian FT-80 A instrument in $CDCl_3$, with TMS as the internal standard. The IR spectra were recorded with a Specord M-80 spectrometer (suspension in vaseline oil or hexachlorobutadiene). TLC was carried out on Silufol UV-254 plates: 3:1:1 hexane–ether–acetone eluent; development with iodine vapor.

Data of ultimate analysis of the newly synthesized compounds III, IV, XI for C, H, N correspond to the calculated data.

10-Methyl-9-phenyl-$\Delta^{4a,8a,9a,10a}$-decahydroacridine (III). A mixture of 6.16 g (0.021 mole) of cycloketol I and 100 ml of methanol, saturated with 3.25 g (0.1 mole) of methylamine, is kept in a 250-ml autoclave for 6 h at 100°C and a hydrogen pressure of 10 mPa. After the solvent is evaporated (~2/3 of the volume), the precipitate is filtered off and washed with cold methanol. Compound III is obtained in an amount of 3.92 g (65%). MP 73-74°C (from ethanol). IR spectrum: 1665, 1690 (C=C), 2835 (NMe), 2875, 2950 (CH_2), 3020-3080 cm^{-1} (=CH). ^1H NMR spectrum: 1.50-2.20 (16 H, m, 8 CH_2); 2.90 (3H, s, NMe); 3.45 (1H, s, 9-H); 7.19-7.23 ppm (5H, m, H_{Ph}). ^{13}C NMR spectrum: 22.79 ($C_{(3)}$, $C_{(6)}$), 23.10 ($C_{(2)}$, $C_{(7)}$), 25.10 ($C_{(4)}$, $C_{(5)}$), 26.60 ($C_{(1)}$, $C_{(8)}$), 32.16 ($C_{(Me)}$); 51.80 ($C_{(9)}$), 109.02 ($C_{(8a)}$, $C_{(9a)}$), 125.78 ($C_{(Ph\text{-}p)}$), 128.30 and 128.80 ($C_{(Ph\text{-}o\ and\ m)}$), 132.60 ($C_{(4a)}$, $C_{(10a)}$), 147.01 ppm. ($C_{(Ph\text{-}unco)}$). Found, %: C 86.29; H 8.56; N 5.08. $C_{20}H_{25}N$. Calculated, %: C 86.02; H 8.86; N 5.02.

By a similar method, starting from cycloketol II and methylamine, cycloketol I and aniline, compounds IV and X are respectively obtained.

10-Methyl-9-(2-furyl)-$\Delta^{4a,8a,9a,10a}$-decahydroacridine (IV). Yield, 70%. MP 54-55°C (for methanol). IR spectrum: 1620, 1665 (C=C), 2810 (NMe), 2850, 2910 (CH_2), 3100 cm^{-1} (=C–H). ^1H NMR spectrum: 1.51-2.22 (16 H, m, 8 CH_2), 2.88 (3 H, s, NMe), 3.65 (1 H, s, 9-H), 5.95 (1 H, d.d., 3′-H_{furyl}, $J_{3'4'}$ = 3.5 Hz), 6.23 (1 H, d.d., 4′-H_{furyl}, $J_{4'5'}$ = 2.2 Hz), 7.27 ppm (1 H, d.d., 5′-H_{furyl}, $J_{3'5'}$ = 1.0 Hz). Found %: C 79.93; H 7.94; N 5.87. $C_{18}H_{23}NO$. Calculated: %: C 80.3; H 8.55; N 5.20.

9,10-Diphenyl-$\Delta^{4a,8a,9a,10a}$-decahydroacridine (X). Yield, 45%. MP 93-95°C. Lit. MP 95-96°C [6]. IR spectrum: 1670, 1700 (C=C) 2875, 2955 (CH_2), 3025-3080 cm^{-1} (=CH). ^1H NMR spectrum: 1.37-2.40 (16 H, m, 8 CH_2), 3.62 (1 H, s, 9-H), 7.00-7.29 (10 H, m, H_{Ph}).

Catalytic Hydrogenation of Decahydroacridines III, IV and Hydromethylamination of Cycloketols I, II. The reactions are carried out in accordance with the method of [10]; products V-VIII are identified from the data of ^{13}CNMR spectra. Listed below are the most characteristic resonance signals of carbon atoms in the ^{13}C NMR spectra of compounds V-VIII. (For a complete assignment of the signals, see [7]).

Compound Va: 35.58 (NMe); 41.98 ($C_{(8a)}$, $C_{(9a)}$); 50.37 ($C_{(9)}$); 66.72 ppm ($C_{(4a)}$, $C_{(10a)}$).

Compound Vb: 36.48 (NMe); 39.41 ($C_{(8a)}$); 44.78 ($C_{(9a)}$); 53.95 ($C_{(9)}$); 64.80 ($C_{(4a)}$); 70.41 ppm ($C_{(10a)}$).

Compound VIa: 35.64 (NMe); 36.49 ($C_{(8a)}$, $C_{(9a)}$); 45.67 ($C_{(9)}$); 65.91 ppm ($C_{(4a)}$, $C_{(10a)}$).

Compound VIb: 36.35 (NMe); 41.46 ($C_{(8a)}$); 43.34 ($C_{(9a)}$); 47.26 ($C_{(9)}$); 63.76 ($C_{(4a)}$); 70.20 ppm ($C_{(10a)}$).

Compound VII: 38.59 (NMe); 44.73 ($C_{(9a)}$); 58.54 ($C_{(4a)}$); 66.63 ($C_{(10a)}$); 133.92 ($C_{(8a)}$); 135.62 ppm ($C_{(9)}$).

Compound VIII: 57.77 ($C_{(4a)}$); 67.42 ppm ($C_{(10a)}$).

9,10-Diphenylperhydroacridine (XI). A mixture of 3.5 g (0.01 mole) of decahydroacridine X, 70 ml of methanol and ~0.5 g of ruthenium-modified nickel is kept in a 250-ml autoclave at 100°C and an initial hydrogen pressure of 10 mPa. The reaction ends 5 to 6 h after absorption of the calculated amount of hydrogen (0.02 mole). The catalyst is filtered off, and the solvent is driven off at reduced pressure; the residue is crystallized. Compound XI is obtained in an amount of 2.7 g (77%). MP 134-135°C (for methanol). IR spectrum: 2870, 2950 (CH_2), 3020-3080 cm^{-1} (=CH). ^1H NMR spectrum: 1.05-2.19 (20 H, m, 8 CH_2, 4CH); 2.40-2.43 (1H, t, 9-H); 7.10-7.26 ppm (10 H, m, H_{Ph}). Found: %: C 86.53; H 9.06; N 4.35. $C_{25}H_{31}N$. Calculated: %: C 86.95; H 8.98; N 4.95.

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