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SATURATED NITROGEN-CONTAINING HETEROCYCLES. 19.* CATALYTIC REDUCTION OF 10- AND 9,10-SUBSTITUTED *sym*-OCTAHYDROACRIDINIUM SALTS

R. V. Seller, P. V. Reshetov, S. S. Seller, and A. P. Kriven'ko

10-Methyl(phenyl)- and 9,10-diphenylperhydroacridines have been obtained by the catalytic reduction of 10- and 9,10-substituted sym-octahydroacridinium salts. Selective reduction of the furan ring occurred in the case of 9-(2-furyl)-10-phenyl-sym-octahydroacridinium perchlorate. The stereoisomeric composition of the reaction products has been established and a probable scheme for their formation has been proposed.

Keywords: perhydroacridines, hydroacridinium salts, catalytic reduction, stereostructure.

Catalytic reduction of pyridinium salts is one of the methods used to prepare azaheterocycles of the piperidine series [2-5], however this method has been little studied for polysubstituted pyridinium salts and their condensed analogs. In the present work examples of the catalytic hydrogenation of 10R- and 9R-10R^1-*sym*-octahydroacridinium salts were examined and a possible scheme for the formation of substituted perhydroacridines in the reaction studied was proposed on the basis of the new and previously obtained data [6, 7].

10- And 9-10-substituted *sym*-octahydroacridinium salts **1-5** were obtained by the reaction of *sym*-octahydroacridine with methyl iodide, by boiling 8R-2-hydroxy-13-oxotricyclo[7.3.1.0^{2,7}]tridecanes (R = H, 2-Fur) with aniline in acetic acid with subsequent addition of $NaClO_4$ [8], and by recyclization of pyrilium salts in the presence of aniline or saturated ethanolic methylamine [6, 7]. Since the nature of the anion did not affect hydrogenation of the salt, iodides, tetrafluoroborates, and perchlorates can participate in the reaction with equal success.

The required products were obtained in good yield at 100°C and hydrogen pressure of 10 MPa in the presence of an equimolar amount of an amine (methylamine or aniline) to prevent hydrogenolysis of the C–N bond [6]. Nickel modified with ruthenium was used as the catalyst. Change in these conditions (increase in temperature, absence of amine) caused the reaction to slow or side reaction to occur to give a complex mixture of products.

The results obtained permitted the conclusion that the direction and stereochemical results of the reaction were determined by the number and nature of the substituent groups (Me, Ph, 2-Fur) in the heterocyclic substrate. For example, catalytic reduction of the 10-R^1-substituted (R^1 = Me, Ph) *sym*-octahydroacridinium salts **1** and **2** gave saturated products with the *cis-cis*-structure. Under the conditions described 10-methyl-*sym*-octahydroacridinium iodide **1** was converted into the corresponding *cis-syn-cis*-10-methylperhydroacridine (**4**) in 74% yield whereas hydrogenation of perchlorate **2** led to a mixture of *cis-syn-cis*- and *cis-anti-cis*-10-phenylperhydroacridines (**7**, **8**) in an overall yield of 58%.

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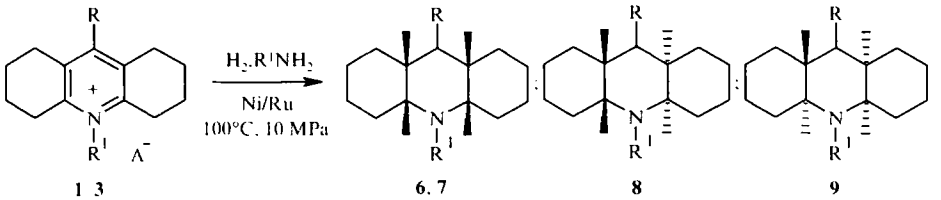
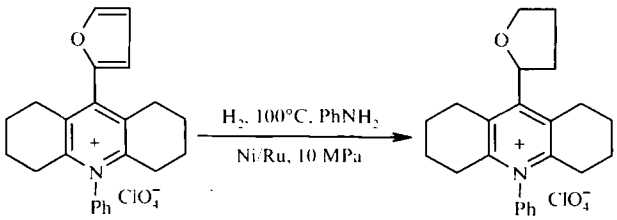
The stereodirection of the reaction changed when a phenyl substituent was introduced at position 9 in the salt molecules. For example, *trans-anti-cis*-9,10-diphenylperhydroacridine (**9**) was prepared in 58% yield from 9,10-diphenyl-*sym*-octahydroacridinium tetrafluoroborate (**3**).



1, 3 6, 7 8 9

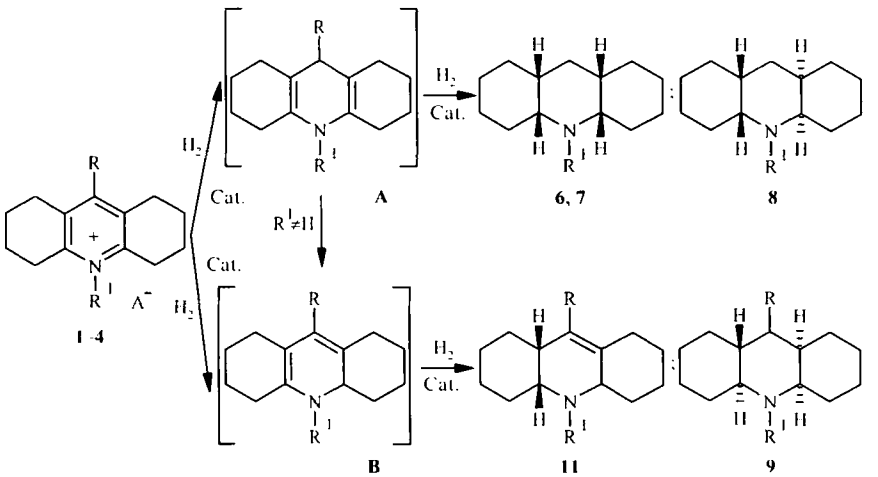
1, **6** R = H, R^1 = Me, A = I; **2**, **7**, **8** R = H, R^1 = Ph, A = ClO_4;
3, **9** R = R^1 = Ph, A = BF_4

An unexpected result was obtained on hydrogenation of *sym*-octahydroacridinium salt **5**, which contains a furyl substituent. Under the reaction conditions selective hydrogenation of the furyl ring occurred with retention of the pyridine ring to give 9-(tetrahydrofuryl)-10-phenyl-*sym*-octahydroacridinium perchlorate (**10**) in 41% yield. This result may be explained by predominant absorption of salt **5** on the catalyst *via* the furan unit.



5 **10**

The results of the hydrogenation of *sym*-octahydroacridinium salts **1-4** are indicated by the differences in the configurations of the products. To explain this fact we used data we had obtained previously that hydrogenation of pyridinium salts may occur via 1,2- and 1,4-dihydropyridine intermediates [6], and a scheme is proposed for the formation of the isomeric perhydroacridines **6-9** *via* intermediate products **A** and **B** of analogous structure:



1-4 **A** **6, 7** **8** **B** **11** **9**

4, **11** R = Ph, R^1 = Me, A = BF_4

Formation of products with a *cis-cis*-configuration occurs in the case of *sym*-octahydroacridinium salts **1,2** which have no substituent 9 *via* intermediate **A** with either planar (compounds **6,7**) or edge (compound **8**) adsorption and *cis*-addition of hydrogen, which is characteristic for the hydrogenation reaction. *trans-anti-cis*-Perhydroacridine **9** can only be obtained from 1,2-dihydropyridine of type **B**. Apparently the formation of the 1,4-dihydropyridine intermediate **A** occurs by additional addition of a hydrogen atom at the unsubstituted γ-position of the salt; if this position is occupied, attack at the α-position is more favorable. If a substituent is present at position 9 of the substrate it is impossible to exclude the possibility of isomerization of dihydropyridine **A** into compound **B**. The proposed scheme is confirmed by the stereoisomeric composition of the reaction products and also the isolation, along with perhydroacridines **6-9**, of a product of the incomplete hydrogenation of intermediate **B**, 10-methyl-9-phenyl-1,2,3,4,4a,6,7,8,8a,10,10a-dodecahydroacridine (**11**).

The spatial structure of the compounds synthesized was established using ^{13}C NMR spectroscopy. The spectroscopic data for perhydroacridines **6-8** coincide with the analogous characteristics of stereoisomers prepared by reductive amination of 8R-2-hydroxy-13-oxotricyclo[7.3.1.$0^{2,7}$]tridecanes [6, 9]. The common mechanisms for the described catalytic syntheses of perhydroacridines determines the uniform stereochemical results [10]. We have described the spatial structures of 9,10-diphenylperhydroacridine **9** and dodecahydroacridine **11** previously [6, 7]. The ^1H NMR spectrum of 9-(2-tetrahydrofuryl)-10-phenyl-*sym*-octahydroacridinium perchlorate (**10**) includes signals for the α- and β-protons of the tetrahydrofuran ring at 4.20 and 5.31 ppm respectively.

In conclusion, catalytic reduction of *sym*-octahydroacridinium salts is a method for the stereodirected synthesis of perhydroacridines and permits the preparation of alkyl- and aryl-substituted perhydroacridines with a given stereochemistry depending on the number and type of the substituents on the heterocycle.

EXPERIMENTAL

^1H and ^{13}C NMR spectra of $CDCl_3$ solutions with TMS as internal standard were recorded with a Varian FT-80A instrument (working frequencies 80 and 20 MHz respectively). TLC was carried on Silufol UV-254 plates, with 4:1:1 hexane–ether–acetone as eluant, and development with iodine vapor.

***trans-anti-cis*-9,10-Diphenylperhydroacridine (9)** was described previously [7].

10-Methyl-9-phenyl-1,2,3,4,4a,5,6,7,8,8a,10,10a-dodecahydroacridine 11 was described previously [6].

10-Methyl-*sym*-octahydroacridinium Iodide (1). A solution of *sym*-octahydroacridine (5 g, 27 mmol) in CH_3I (15 ml) was kept for a day at room temperature. The precipitated crystals of product **1** were filtered off and washed with ether. Yield 62%; mp 80-82°C (acetone). ^1H NMR spectrum ($CDCl_3$): 1.97 (8H, m, CH_2); 2.91 (4H, t, CH_2); 3.18 (4H, t, CH_2); 4.17 (3H, s, N–CH_3); 7.83 ppm (1H, s, CH). Found, %: C 51.58; H 6.25; N 4.31. $C_{14}H_{20}IN$. Calculated, %: C 51.06; H 6.07; N 4.25.

***sym*-Octahydroacridinium Perchlorates 2** and **5** were synthesized by method [8]. **Salts 3** and **4** were synthesized from 9-phenyl-*sym*-octahydroxanthylium tetrafluoroborate by a known method [6].

***cis-cis-cis*-10-Methylperhydroacridine (6).** Salt **1** (3.29 g, 10 mmol), Ni/Ru (1 g), and ethanol (80 ml) saturated with methylamine (0.31 g, 10 mmol) were placed in an autoclave (volume 150 ml). The initial hydrogen pressure was 10 MPa and the temperature 100°C. The reaction mixture was cooled after 7 h, the catalyst was filtered off, alcohol evaporated, and the crystals of product **6** were filtered off. Yield 74%; mp 64-66°C (ethanol). ^{13}C NMR spectrum ($CDCl_3$): 32.34 ($C_{(1)}$, $C_{(8)}$, t); 22.69 ($C_{(2)}$, $C_{(7)}$, t); 25.66 ($C_{(3)}$, $C_{(6)}$, t); 25.98 ($C_{(4)}$, $C_{(5)}$, t); 61.03 ($C_{(4a)}$, $C_{(10a)}$, d); 37.73 ($C_{(8a)}$, $C_{(9a)}$, d); 26.85 ($C_{(9)}$, d); 39.20 ppm (N–CH_3, q). Found, %: C 81.52; H 12.27; N 7.10. $C_{14}H_{25}N$. Calculated, %: C 81.09; H 12.15; N 6.75.

***cis-syn-cis*- (7) and *cis-anti-cis*- (8) 10-Phenylperhydroacridines** were obtained analogously by hydrogenation of salt **2** in the presence of aniline. Overall yield 58%.

Compound 7. ^{13}C NMR spectrum ($CDCl_3$): 32.51 ($C_{(1)}$, $C_{(8)}$, t); 21.81 ($C_{(2)}$, $C_{(7)}$, t); 26.24 ($C_{(3)}$, $C_{(6)}$, t); 26.24 ($C_{(4)}$, $C_{(5)}$, t); 53.65 ($C_{(4a)}$, $C_{(10a)}$, d); 37.67 ($C_{(8a)}$, $C_{(9a)}$, d); 26.24 ppm ($C_{(9)}$, d).

Compound 8. ^{13}C NMR spectrum ($CDCl_3$): 30.09 ($C_{(1)}$, $C_{(8)}$, t); 22.12 ($C_{(2)}$, $C_{(7)}$, t); 24.04 ($C_{(3)}$, $C_{(6)}$, t); 32.51 ($C_{(4)}$, $C_{(5)}$, t); 55.86 ($C_{(4a)}$, $C_{(10a)}$, d); 32.51 ($C_{(8a)}$, $C_{(9a)}$, d); 27.05 ppm (C(9), d).

9-(2-Tetrahydrofuryl)-10-phenyl-*sym*-octahydroacridinium Perchlorate (10) was prepared analogously to compound **6** by hydrogenation of salt **5** in the presence of aniline. Yield 41%; mp 150-152°C (ethyl acetate). ^{1}H NMR spectrum ($CDCl_3$): 1.79-1.85 (8H, m, CH_2); 2.48 (4H, t, CH_2); 2.96 (4H, t, CH_2); 4.20 (4H, m, CH_2); 5.31 (3H, t, CHO); 7.69 ppm (5H, m, C_6H_5). Found, %: C 63.54; H 6.39; N 3.76. $C_{23}H_{28}ClNO_5$. Calculated, %: C 63.67; H 6.46; N 3.23.

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