SATURATED NITROGEN-CONTAINING HETEROCYCLES.
16.* CATALYTIC SYNTHESIS OF N-ARYLPERHYDROACRIDINES

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Catalytic hydroamination of methylene-2,2'-dicyclohexanone in the presence of substituted anilines or nitrobenzenes involves the formation of N-arylperhydroacridines. The stereoisomeric composition and yields of the latter are determined by the nature and position of the substituent in the aromatic ring of the aminating agent. The structure of isomeric N-arylperhydroacridines was established from data of ^{13}C *NMR spectroscopy and x-ray diffraction analysis.*

Reductive amination of 1,5-diketones is a convenient method of synthesizing substituted piperidines and their condensed analogs [2]. However, aromatic amines as aminating agents have found little use in the indicated reaction. It is well known that the reaction of methylene-2,2'-dicyclohexanone (I) with aniline in the presence of formic acid leads to the formation of three stereoisomers of N-phenylperhydroacridine [3], one of which had the trans-syn-trans configuration [4]. Previously, we isolated cis-syn-cis- and cis-anti-cis-N-phenylperhydroacridines in a catalytic hydroarylamination [5].

In order to synthesize N-arylperhydroacridines containing different types of substituents in the aromatic ring and study their influence on the stereoisomeric composition of the reaction products, we investigated the catalytic hydroamination of methylenedicyclohexanone I in the presence of functionally substituted anilines and nitrobenzenes.

The reaction was carried out in methanol (or hexane) solution in an autoclave at an equimolar ratio of the reactants at a hydrogen pressure of 10 mPa and 100°C in the presence of skeleton nickel modified by ruthenium. The aminating agents used were p-aminophenol, p-anisidine, p-aminobenzoic acid, and o- and p-phenylenediamines; nitroarenes — nitrobenzene, o- and p-nitrophenols, m-nitrobenzoic acid, and p-nitroaniline — were used for the first time. The choice of these nitroarenes was due to their availability, stability to oxidation, and ease of reduction to the corresponding anilines in the presence of heterogeneous catalysts. We should also note the preferability of the simultaneous introduction of the nitroarene and substrate into the process as compared to a stepwise introduction.

Under the selected conditions, diketone I was used to synthesize N-arylperhydroacridines II-IX, whose yields and stereoisomeric composition are influenced by the nature and position of the substituent in the aromatic amine.

The reaction takes place most readily when p-amino- and m-nitrobenzoic acids are used. N-(p-Carboxyphenyl)- and N-(m-carboxyphenyl)perhydroacridines (VI, VII) were isolated in quantitative yields (Table 1). This result can be explained by acid activation of the carbonyl group of the substrate. In the presence of p-aminophenol and p-anisidine, heavy resinification of the hydrogenates was observed. The yields of N-(p-hydrophenyl)- and N-(p-methoxyphenyl)perhydroacridines (III-V) did not exceed 10-29%. This was successfully raised to 40-42% when the solvent, i.e., methanol, was replaced by hexane (Table 1). The use of nitroarenes instead of the readily oxidizable anilines is preferable and independent of the solvent polarity. Thus, diketone I reacting with nitrobenzene, o- and p-nitrophenols and hydrogen is converted into N-phenyl-, N-(p-hydroxyphenyl)- and N-(o-hydroxyphenyl)perhydroacridines I, III, IV in 45-76% yields (Table 1). Hydroamination of diketone I in the presence of o- and p-phenylenediamines and p-nitroaniline takes place with difficulty and is accompanied by heavy resinification. N-(o-

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*For Communication 15, see [1].

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TABLE 1. Hydroarylamination of Methylene-2,2'-dicyclohexanone (I) (Ni/Ru, 100°C, P_{H_2}, 10 mPa)

Aminating agent	Solvent	Reaction products	Yield, %
$C_6H_5NO_2$	Methanol	IIa + IIb	50
	Hexane	IIa + IIb	50
p-$HOC_6H_4NH_2$	Methanol	III	29
	Hexane	III	42
p-$HOC_6H_4NO_2$	Hexane*	III	45
o-$HOC_6H_4NO_2$	Methanol	IV	76
p-$CH_3OC_6H_4NH_2$	Methanol	V	18
	Hexane	V	40
p-$HOOCC_6H_4NH_2$**	Methanol	VI	95
m-$HOOCC_6H_4NO_2$**	Methanol	VII	95
o-$NH_2C_6H_4NH_2$	Hexane*	VIII	7

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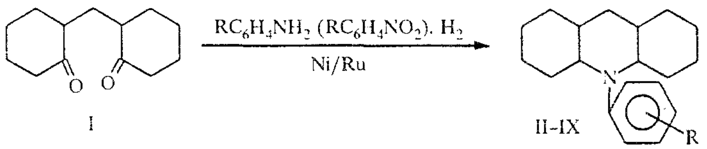
*When methanol was used, the products were not isolated because of heavy resinification.

**Insoluble in hexane.

TABLE 2. Characteristics of Synthesized N-Arylperhydroacridines III-VIII

Compound	T_m, °C	IR spectrum, cm^{-1}
III	192...194 (with decomp.)	3100...3450 (ν_{OH} assoc.) 3020...3060 ($\nu_{=CH}$), 2935 ($\nu^{as}CH_2$), 2860 (νCH_2), 835 ($\delta_{=CH}$)
IV	79...80	3150...3400 (ν_{OH} assoc.) 3030...3060 ($\nu_{=CH}$), 2910 ($\nu^{as}CH_2$), 2850 ($\nu^{s}CH_2$), 750 ($\delta_{=CH}$)
V	170...171	3020...3080 ($\nu_{=CH}$), 2860 ($\nu^{s}OCH_3$), 2220...2240 ($\nu_{=C\text{-}OCH_3}$), 835 ($\delta_{=CH}$)
VI	220...225 (with decomp.)	1600 ($\nu^{as}COO$-), 1380 ($\nu^{s}COO$-), 3030...3080 ($\nu_{=CH}$), 2940 ($\nu^{as}CH_2$), 2860 ($\nu^{s}CH_2$), 825, 835 ($\delta_{=CH}$)
VII	212...214 (with decomp.)	3150...3500 (ν_{OH}), 1700 ($\nu_{C=O}$), 1570 ($\nu^{as}COO$-), 1380 ($\nu^{s}COO$-), 3060...3090 ($\nu_{=CH}$), 2950 ($\nu^{as}CH_2$), 2870 ($\nu^{s}CH_2$), 755...810 ($\delta_{=CH}$)
VIII	130...132	3360,3460 (νNH_2), 3020...3080 ($\nu_{=CH}$), 2935 ($\nu^{as}CH_2$), 2860 ($\nu^{s}CH_2$), 845 ($\delta_{=CH}$)



I

II-IX

II R = H, III R = p-OH, IV R = o-OH, V R = p-CH_3O, VI R = p-HOOC, VII R = m-HOOC,
VIII R = o-NH_2, IX R = p-NH_2

Aminophenyl)perhydroacridine (VIII) was successfully isolated in 7% yield after the removal of resinlike products on a column packed with γ-Al_2O_3. The formation of N-(p-aminophenyl)perhydroacridine (IX) was recorded only by TLC.

The IR and ^{13}C NMR spectra of N-arylperhydroacridines III-VIII are shown in Tables 2 and 3. In the IR spectra of compounds III and IV, the stretching vibrations of the associated hydroxyl group are located in the 3100-3450 cm^{-1} region, and those of the methoxy substituent in compound V, at 2860 cm^{-1}; the primary amino group in the o-phenylene fragment of the base VIII shows up in the form of two absorption bands at 3360 and 3460 cm^{-1}. The absence in the spectrum of N-(p-carboxyphenyl)perhydroacridine (VI) of bands characterizing the hydroxyl group of carboxyl as well as a sharp increase in band strength around 1600 cm^{-1} ($\nu_{COO^-}{}^{as}$) indicates the existence of the latter in the form of an inner salt. Based on the spectrum

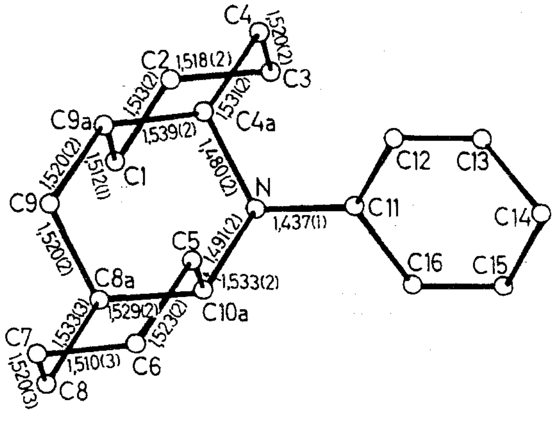
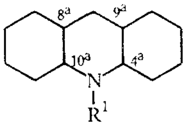


Fig. 1. Geometry of the cis-anti-cis-N-phenylperhydroacridine (IIb) molecule with interatomic distances.

TABLE 3. ^{13}C NMR Spectra of N-Arylperhydroacridines IIa-d, V, VIII



Compound	Chemical shifts (δ; ppm) in $CDCl_3$						
	$C_{(1)}$, $C_{(8)}$	$C_{(2)}$, $C_{(7)}$	$C_{(3)}$, $C_{(6)}$	$C_{(4)}$, $C_{(5)}$	$C_{(9)}$	$C_{(8a)}$, $C_{(9a)}$	$C_{(4a)}$, $C_{(10a)}$
IIa*	32,46	21,62	26,11	26,11	26,02	37,49	55,43
IIb*	29,87	22,06	23,79	25,75	27,07	32,29	55,71
IIc	32,90	25,47	25,86	31,98	40,13	42,23	67,82
IId	26,87	26,87	19,92	30,46	39,04	37,33	60,83
	33,16	25,47	25,85	32,45		37,33	68,85
V	29,42	23,18	23,64	24,31	30,40	33,98	56,82
VIII	29,66	20,86	27,00	20,14	31,70	31,05	49,25
	31,05	25,92	27,00	18,28		37,40	59,40

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*Described previously [5].

of N-(m-carboxyphenyl)perhydroacridine (VII), one can postulate the presence of equilibrium between the polyassociate and the inner salt (ν_{OH} at 3150-3500 cm^{-1}, $\nu_{C=O}$ at 1700 cm^{-1}, and ν_{COO^-} at 1380 cm^{-1}).

To study the spatial structure of the N-arylperhydroacridines obtained, it was necessary to have a wide range of isomers. Therefore, isomeric N-phenylperhydroacridines (II) were synthesized by the Leuckart reaction [3].

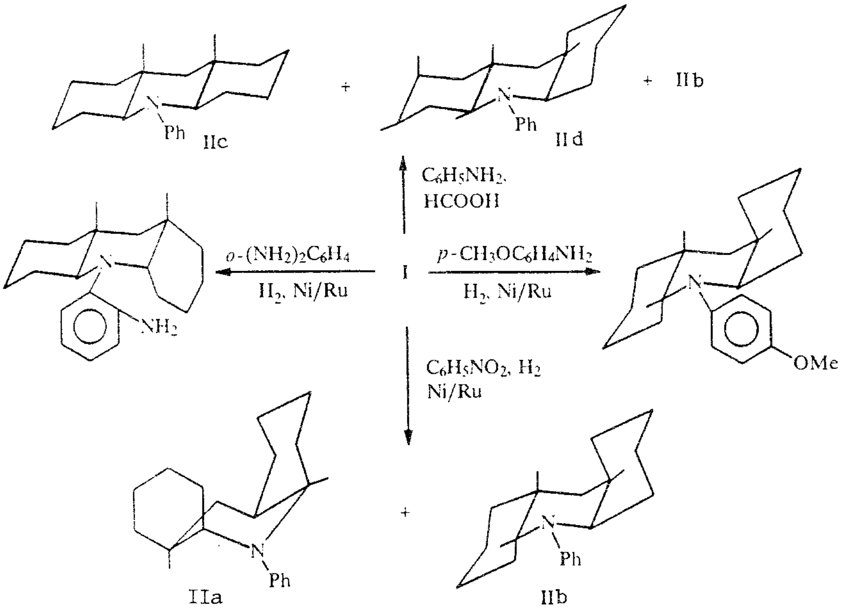
In all cases, the assignment of signals in the ^{13}C NMR spectra was based on the off-resonance spectra and the data of [5-7].

Analysis of the spectra of a mixture of isomers II isolated in the reverse synthesis and described previously [5] showed that in the Leuckart reaction, N-phenylperhydroacridine (II) is formed in the form of a mixture of three isomers with a cis-anti-cis (IIb), trans-syn-trans (IIc), and trans-anti-cis (IId) configuration (Table 3).

The catalytic hydroamination of diketone I with nitrobenzene (and also when aniline is used [5]), cis-syn-cis- (IIa) and cis-anti-cis- (IIb) N-phenylperhydroacridines are formed. N-(p-Methoxyphenyl)perhydroacridine (V) is isolated in the form of the cis-anti-cis isomer, as follows from a comparison of the spectra of the latter and compound IIb (Table 3).

TABLE 4. Valence Angles ω in the IIb Molecule

Angle	ω, deg	Angle	ω, deg
$C_{(4a)}NC_{(10a)}$	113,98(9)	$C_{(8)}C_{(8a)}C_{(9)}$	113,10(1)
$C_{(4a)}NC_{(11)}$	116,50(9)	$C_{(8)}C_{(8a)}C_{(10a)}$	110,70(1)
$C_{(10a)}NC_{(11)}$	110,58(9)	$C_{(9)}C_{(8a)}C_{(10a)}$	110,30(1)
$C_{(2)}C_{(1)}C_{(9a)}$	112,70(1)	$C_{(8a)}C_{(9)}C_{(9a)}$	111,40(1)
$C_{(1)}C_{(2)}C_{(3)}$	110,40(1)	$C_{(1)}C_{(9a)}C_{(4a)}$	112.20(1)
$C_{(2)}C_{(3)}C_{(4)}$	110,90(1)	$C_{(1)}C_{(9a)}C_{(9)}$	112,50(1)
$C_{(3)}C_{(4)}C_{(4a)}$	114,20(1)	$C_{(4a)}C_{(9a)}C_{(9)}$	110,90(1)
$NC_{(4a)}C_{(4)}$	112,60(1)	$NC_{(10a)}C_{(5)}$	114,20(1)
$NC_{(4a)}C_{(9a)}$	109,70(1)	$NC_{(10a)}C_{(8a)}$	110,80(1)
$C_{(4)}C_{(4a)}C_{(9a)}$	108,90(1)	$C_{(5)}C_{(10a)}C_{(8a)}$	111,60(1)
$C_{(6)}C_{(5)}C_{(10a)}$	111,40(1)	$NC_{(11)}C_{(12)}$	124,20(1)
$C_{(5)}C_{(6)}C_{(7)}$	111,80(2)	$NC_{(11)}C_{(16)}$	117,90(1)
$C_{(6)}C_{(7)}C_{(8)}$	110.30(2)	$C_{(12)}C_{(11)}C_{(16)}$	117,90(1)
$C_{(7)}C_{(8)}C_{(8a)}$	113,70(2)		



The introduction of a substituent into the o position of the aromatic ring results in the appearance of an isomer with trans coupling of the rings. Thus, in contrast to the isomers IIa, IIb, IIc, and V N-(o-aminophenyl)perhydroacridine (VIII) has an asymmetric structure (trans-anti-cis or trans-syn-cis), as indicated by the presence in the ^{13}C NMR spectrum of resonance signals belonging to the perhydroacridine skeleton. The presence of a strong-field signal at 18.28 ppm indicates cis coupling of the rings [7], and the substantial difference between the chemical shifts of atoms $C_{(10a)}$ and $C_{(4a)}$ in isomers IId and VIII precludes a trans-anti-cis structure and makes it possible to conclude that the compound VIII has a trans-syn-cis configuration.

Previously, x-ray diffraction analysis was carried out on cis-syn-cis perhydroacridines [5]. To bring out the conformational characteristics of cis-anti-cis-type isomers, an x-ray diffraction analysis was carried out on cis-anti-cis-N-phenylperhydroacridine (IIb) isolated in the pure form. The structure of the IIb molecule with the bond lengths is shown in Fig. 1; the valence and torsion angles are shown in Tables 4 and 5. The carbocyclic and heterocyclic compounds have the chair conformation, the piperidine ring being the most flattened as compared to the carbocyclic compounds, as is evident from the values of the torsion angles (Table 5). The lengths of the endocyclic and exocyclic N−C bonds are customary for piperidine derivatives [8, 9]; the phenyl substituent occupies an equatorial position. The dihedral angle between the planes drawn through the atoms $C_{(4a)}$, $C_{(9a)}$, $C_{(8a)}$, $C_{(10a)}$, and $C_{(11)}$, $C_{(12)}$, $C_{(13)}$, $C_{(14)}$, $C_{(15)}$, $C_{(16)}$, amounts to 52.7°. The $C_{(5)}-C_{(10a)}$, $C_{(1)}-C_{(9a)}$ bonds are axial, and the $C_{(4)}-C_{(4a)}$, $C_{(8)}-C_{(8a)}$ bonds are equatorial with respect to the piperidine ring; this corresponds to the cis-anti-

TABLE 5. Endocyclic Torsion Angles τ in the IIb Molecule

Angle	τ, deg	Angle	τ, deg
$NC_{(4a)}C_{(9a)}C_{(9)}$	55,2(1)	$C_{(2)}C_{(1)}C_{(9a)}C_{(4a)}$	-55,1(1)
$C_{(4a)}C_{(9a)}C_{(9)}C_{(8a)}$	-55,9(1)	$C_{(1)}C_{(9a)}C_{(4a)}C_{(4)}$	52,0(1)
$C_{(9a)}C_{(9)}C_{(8a)}C_{(10a)}$	55,1(1)	$C_{(9a)}C_{(4a)}C_{(4)}C_{(3)}$	-53,6(1)
$C_{(9)}C_{(8a)}C_{(10a)}N$	-54,2(1)	$C_{(10a)}C_{(5)}C_{(6)}C_{(7)}$	-57,3(1)
$C_{(8a)}C_{(10a)}NC_{(4a)}$	56,5(1)	$C_{(5)}C_{(6)}C_{(7)}C_{(8)}$	56,3(1)
$C_{(10a)}NC_{(4a)}C_{(9a)}$	-56,3(1)	$C_{(6)}C_{(7)}C_{(8)}C_{(8a)}$	-54,6(1)
$C_{(4a)}C_{(4)}C_{(3)}C_{(2)}$	56,0(1)	$C_{(7)}C_{(8)}C_{(8a)}C_{(10a)}$	52,4(1)
$C_{(4)}C_{(3)}C_{(2)}C_{(1)}$	-54,9(1)	$C_{(8)}C_{(8a)}C_{(10a)}C_{(5)}$	-51,7(1)
$C_{(3)}C_{(2)}C_{(1)}C_{(9a)}$	-55,1(1)	$C_{(8a)}C_{(10a)}C_{(5)}C_{(6)}$	55,0(1)

TABLE 6. Coordinates of Nonhydrogen Atoms ($\times 10^4$) and Their Equivalent Isotropic Temperature Factors in the Structure of IIb

Atom	x	y	z	B_{iso}^{eq}
N	4394(1)	2230(2)	1144(1)	2,78(2)
$C_{(1)}$	3154(1)	157(3)	490(1)	4,18(4)
$C_{(2)}$	3409(1)	-395(3)	8(1)	4,46(4)
$C_{(3)}$	4139(1)	209(3)	54(1)	4,04(4)
$C_{(4)}$	4266(1)	2796(3)	217(1)	3,48(3)
$C_{(4a)}$	4016(1)	3440(3)	705(1)	2,93(3)
$C_{(5)}$	4280(1)	5309(3)	1814(1)	3,82(4)
$C_{(6)}$	4034(1)	5687(4)	2311(1)	5,20(4)
$C_{(7)}$	3305(1)	5137(4)	2270(1)	5,59(5)
$C_{(8)}$	3166(1)	2598(4)	2080(1)	5,08(4)
$C_{(8a)}$	3418(1)	2077(3)	1586(1)	3,67(3)
$C_{(9)}$	3013(1)	3315(3)	1139(1)	3,86(4)
$C_{(9a)}$	3281(1)	2758(3)	659(1)	3,37(3)
$C_{(10a)}$	4148(1)	2744(3)	1622(1)	3,10(3)
$C_{(11)}$	5102(1)	2460(3)	1205(1)	2,85(3)
$C_{(12)}$	5431(1)	4411(3)	1041(1)	3,44(3)
$C_{(13)}$	6115(1)	4495(3)	1115(1)	4,25(4)
$C_{(14)}$	6482(1)	2679(4)	1360(1)	4,69(4)
$C_{(15)}$	6162(1)	747(3)	1532(1)	4,53(4)
$C_{(16)}$	5481(1)	637(3)	1454(1)	3,67(3)

cis configuration. The low values of the equivalent isotropic temperature factors of the atoms of the heterocyclic and carbocyclic compounds (Table 6) indicate the existence of the IIb isomer in the crystal in the form of a single conformation isomer.

EXPERIMENTAL

The ^{13}C NMR spectra were recorded in $CDCl_3$ with a Varian FT 80A instrument, with TMS as the internal standard; the IR spectra were recorded in Vaseline oil and hexachlorobutadiene (in the form of a suspension) with an IKS-29 spectrometer; TLC was carried out on Silufol UV-254 plates; the eluent was 3:1:1 hexane–ether–acetone, and the developer was iodine vapor.

Crystals of compound IIb were monoclinic; a = 20.468(1), b = 5.580(2), c = 27.107(1) Å; β = 98.8(1)°; V = 3059.6(4) Å^3, Z = 8, d_{calc} = 1.17 g/cm^3; space group C2/c. The cell parameters and intensities of 1768 independent reflections with $F^2 \geq 3\sigma$ were measured with an Enraf-Nonius CAD4 diffractometer (23°C, λMoKα, graphite monochromator, $\theta/2\theta$ scanning). The structure was deciphered by Patterson's method and refined by the full-matrix method of least squares, initially in the isotropic and then anisotropic approximation. All H atoms were objectively revealed in the difference synthesis and were not used in subsequent calculations. The final R factor was 0.035 ($R_W = 0.046$). The calculations were performed with a PDP-11 computer using SDP-PLUS programs [10]. The coordinates of the atoms and their temperature factors are listed in Table 6.

The catalytic hydroarylamination of diketone I was carried out in accordance with the techniques of [11, 12] in the presence of ruthenium-modified Raney nickel. The hydrogenates were separated from the catalyst by hot filtering and were partially evaporated (~1/4 of the volume), and cooled. The compounds II-VIII, which precipitated out, were filtered and recrystallized from alcohol. The IIb isomer was separated from the mixture with IIa by multiple recrystallization from methanol [5]. Resinlike products were removed from compound VIII on a column packed with γ-Al_2O_3, 60 cm high, hexane being used as the eluent. The characteristics of N-arylperhydroacridines III-VIII are listed in Table 2, and the reaction conditions and yields, in Table 1.

The reverse synthesis of N-phenylperhydroacridines IIb, IIc, IId was carried out in accordance with the technique of [3]. The mixture of isomers IIb, IIc, IId was not separated, and they were identified by their ^{13}C NMR spectra.

The data of the ultimate analysis for C, H, N for the newly synthesized compounds III-VIII are consistent with the calculated data.

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