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Hydroacridines XVIII [1]. Synthesis and NMR Spectroscopic Investigation of (4aα,8aβ,9aα,10aβ)-Tetradecahydroacridine and Some of its Derivatives

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Summary. The reductive amination of (*R**,*R**)-2,2′-methylene-*bis*-cyclohexanone (**1**) with methylamine and potassium borohydride affords a mixture of (4aα,8aβ,9aα,10aβ)- and (4aα,8aα,9aβ,10aα)-tetradecahydro-10-methylacridine (**2**, **3**) in a ratio of approximately 1.3:1 in 57% overall yield. By N-demethylation of **2**, via the N-nitrosamine **4** the first synthesis of (4aα,8aβ,9aα,10aβ)-tetradecahydroacridine (**5**) could be performed. The relative configurations and conformations of compounds **2–5** as well as the barrier of conformational inversion of **5** ($\Delta G^{\#}_{300} = 55.5 \pm 0.4\,\mathrm{kJ \cdot mol^{-1}}$) were determined by NMR spectroscopy.

Keywords. Acridines, tetradecahydro; ^{13}C NMR; Conformational analysis; N-Nitrosamines.

Hydroacridine, 18. Mitt. [1]**. Synthese und NMR-spektroskopische Untersuchung von (4aα,8aβ,9aα,10aβ)-Tetrahydroacridin und einigen seiner Derivate**

Zusammenfassung. Die reduktive Aminierung von (*R**,*R**)-2,2′-Methylen-*bis*-cyclohexanon (**1**) mit Methylamin und Kaliumborhydrid ergibt in einer Gesamtausbeute von 57% ein Gemisch aus (4aα,8aβ,9aα,10aβ)- und (4aα,8aα,9aβ,10aα)-Tetradecahydro-10-methylacridin (**2**, **3**) im Verhältnis von *ca*. 1.3:1. Durch N-Demethylierung von **2** gelang über das Nitrosamin **4** die erste Synthese von (4aα,8aβ,9aα,10aβ)-Tetradecahydroacridin (**5**). Die relativen Konfigurationen und die Konformationen der Verbindungen **2–5** sowie die Aktivierungsenergie der Konformationsumwandlung von **5** ($\Delta G^{\#}_{300} = 55.5 \pm 0.4\,\mathrm{kJ \cdot mol^{-1}}$) wurden NMR-spektroskopisch bestimmt.

Introduction

The reductive amination of (*R**,*R**)-2,2′-methylene-*bis*-cyclohexanone (**1**) with $MeNH_2$ and KBH_4 has been reported to yield an N-methylperhydroacridine by *Vysotskii* [2]; its steric structure could not be specified by the author. As by-products, several stereoisomeric 2,2′-methylene-*bis*-cyclohexanols have been reported.

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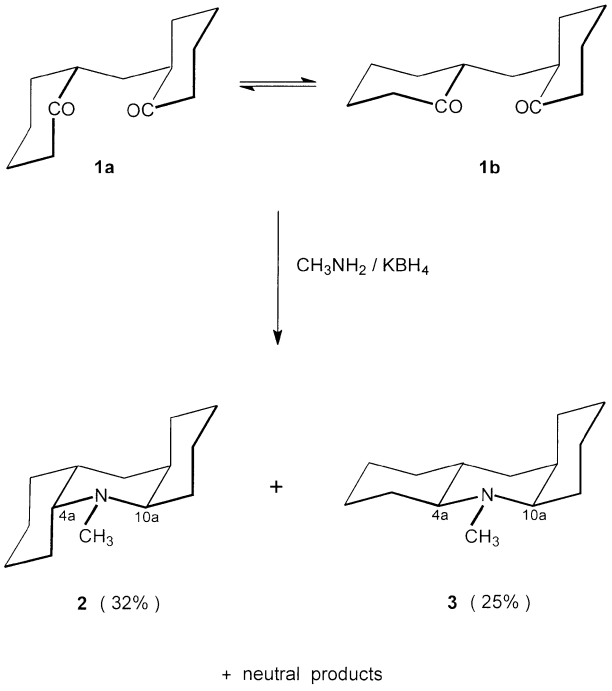
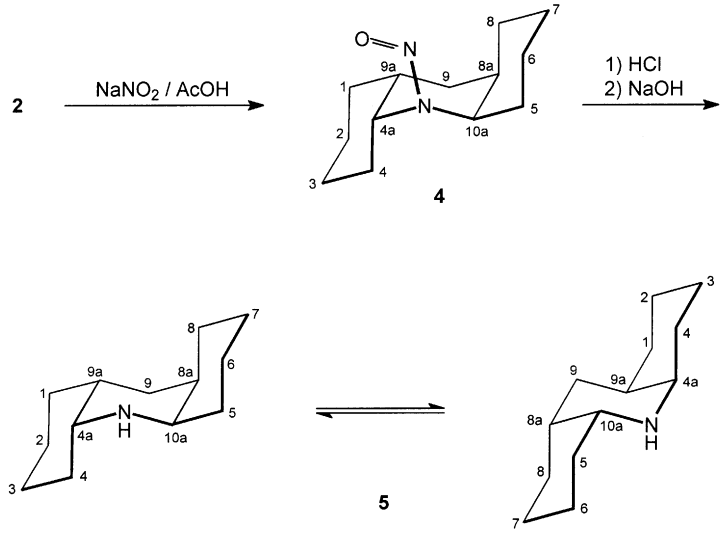


Scheme 1

By repetition of the procedure of *Vysotskii* we were able to demonstrate that the described reaction yields a mixture of two stereoisomeric N-methylperhydroacridines (Scheme 1) which could be identified as (4aα,8aβ,9aα,10aβ)-tetrahydro-10-methylacridine (**2**; the compound referred to in Ref. [2]) and (4aα,8aα,9aβ,10aα)-tetrahydro-10-methylacridine (**3**), respectively. As deduced from ^{13}C NMR spectroscopy, **2** was also present in the product mixture resulting from catalytic hydroamination of **1** with $MeNH_2$ and H_2/Ni-Ru [3]; it could not be isolated in this case, though.

We have now been able to isolate and characterize pure **2**. Our data support the assumption that, prior to *Vysotskii*'s work [2], compound **2** has occured at least twice in the literature as a component of reaction mixtures and without distinct proof of its structure. In the first case, mild hydrogenation of *cis*-1,2,3,4,4a,9,9a,10-octahydro-10-methylacridine at platinum afforded presumably **2** (which was referred to as N-methyl-δ-perhydroacridine by the authors) in a mixture with its *cis-cisoid-trans* isomer [4] from which only a small amount of its hydroiodide could be isolated whose melting point (224–226°C [4]) agrees fairly well with that of the authentic hydroiodide prepared in the present work. The second case deals with reductive amination of **1** with $MeNH_2$ and HCOOH [5, 6] which has been described to yield a mixture of four stereoisomeric N-methylperhydroacridines, three of them being already known to the literature [5–7]. The fourth one, not isolated, was characterized by the proton chemical shift of its N-CH_3 group in the ^{1}H NMR spectrum of the product mixture only [5, 6] which corresponds to that of the authentic compound **2**.



Scheme 2

In addition to the isolation and characterization of **2**, we were able to obtain (4aα,8aβ,9aα,10aβ)-tetradecahydroacridine (**5**) by N-demethylation of **2** *via* (4aα,8aβ,9aα,10aβ)-tetradecahydro-10-nitrosoacridine (**4**, Scheme 2). To our knowledge, this is the first synthesis of compound **5** reported so far.

Results and Discussion

The reductive amination of **1** with $MeNH_2$ and KBH_4 was performed according to Ref. [2], however, using a modified workup procedure (see Experimental). After removal of the 2,2′-methylene-*bis*-cyclohexanols (referred to as ''neutral products'' in Scheme 1), the ^1H NMR spectrum of the crude aminic fraction exhibited two sharp N-CH_3 resonances (CCl_4; $\delta = 2.16$ and 2.07 ppm, respectively) demonstrating the presence of two isomeric N-methylperhydroacridines. After separation, the isomer with the N-CH_3 peak at 2.16 ppm turned out to be the compound described by *Vysotskii*; based on its ^{13}C NMR spectrum it was assigned structure **2**. Due to its conformational mobility originating from the two *cis* junctions, only two sharp signals are present in the room temperature ^{13}C NMR spectrum of **2** (N-CH_3: 39.42 ppm, C-9: 30.86 ppm; Ref. [3]: 39.78 and 31.08 ppm); the remaining signals suffer from considerable line broadening. The second isomer whose ^1H NMR spectrum has been reported repeatedly in the literature (δ(N-CH_3) in CCl_4: 2.07 [5, 6], 2.10 [7] ppm) was identified as compound **3** by comparison of its ^{13}C NMR spectrum with that of an authentic sample [7].

During the reductive amination applied in this investigation, the configurations at the tertiary carbon atoms in α positions to the carbonyl groups remain unaffected. Therefore, the configurations of the resulting amines are related to those of the starting diketone in a defined way. Obviously, conformer **1a** leads to amine **2**, and conformer **1b** gives rise to amine **3** (Scheme 1). Thus, only transoid perhydroacridines are to be expected from diketone **1**. Besides **2** and **3**, the

formation of a *trans-transoid-trans*-N-methylperhydroacridine (so far unknown) cannot be excluded. The formation of this compound is, however, defavoured by the fact that its piperidine ring should have a twisted boat form (like the central ring in *trans-transoid-trans*-perhydroanthracene [8]). Based on the present experience with **1**, it might be predicted that the same reaction applied to (*R**,*S**)-2,2′-methylene-*bis*-cyclohexanone would result in a mixture of *trans-cisoid-trans*, *cis-cisoid-trans*, and, possibly, *cis-cisoid-cis* (sterically less favoured) N-methylperhydroacridines.

The possibility to isolate and purify compound **2** prompted us to strive for its parent heterocycle **5** for which no synthesis has been reported so far. It could finally be obtained in very poor overall yield by demethylation of **2** *via* N-nitrosamine **4** (Scheme 2), a strategy already successfully applied to other stereoisomers of N-methylperhydroacridine [5–7]. To reduce losses, no purification of intermediate **4** was carried out prior to denitrosation. For characterization purposes, a pure sample of **4** was synthesized by nitrosation of **5**. The structures of both **4** and **5** were confirmed by their ^{1}H and ^{13}C NMR spectra.

^{13}C NMR spectroscopy of compounds **4** *and* **5**

The ^{13}C NMR spectrum of compound **5** has been recorded both at room and low temperatures. At room temperature, only C-9 – being the sole carbon atom that, owing to symmetry, preserves its chemical shift during the fast conformational inversion process of **5** (Scheme 2) – gives rise to a sharp resonance ($\delta = 30.48$ ppm). Lowering the temperature causes further broadening of all signals except that of C-9, and at 300 K coalescence is observed. Further temperature decrease results in 13 sharp peaks. The complete assignment, achieved from a 2D INADEQUATE spectrum at 250 K, has been published previously [9]; to facilitate comparison, the shift values are included in Table 1. From the low temperature ^{13}C NMR data, a free energy of activation of $\Delta G^{\#}_{300} = 55.5 \pm 0.4\,\mathrm{kJ \cdot mol^{-1}}$ and a rate constant of $k_{300} \approx 1370\,\mathrm{s^{-1}}$ can be obtained for the chair-chair conformational interchange of **5**. For the carbocyclic analogue of **5** (*cis-transoid-cis*-perhydroanthrancene) in $CHCl_3$, a value of $\Delta G^{\#}_{318} = 60.5 \pm 0.4\,\mathrm{kJ \cdot mol^{-1}}$ has been reported [10].

The ^{13}C NMR spectrum of N-nitrosamine **4** exhibits 13 sharp signals, indicating conformational homogeneity even at room temperature. This fact can be rationalized taking into account two effects: (*i*) a drastic steric interaction between the N-nitroso oxygen atom and the C-4/C-5 methylene groups in the case of an equatorially oriented linkage with respect to the piperidine ring (termed "$A^{(1,3)}$ strain" by *Johnson* and *Malhotra* who have for the first time analyzed its conformational implications with respect to cyclohexane derivatives containing exocyclic double bonds [11]), and (*ii*) the high rotational energy barrier of the N-N bond in aliphatic N-nitrosamines ($\Delta G^{\#} \approx 96\,\mathrm{kJ \cdot mol^{-1}}$, [12] (temperature not given)) which is almost twice as high than that determined above for the ring inversion of **5**. Thus, for the lowest energy conformation of **4** an all-chair conformation with the N-O bond oriented *anti* relative to C-10a (and, at the same time, to the equatorial C-5 methylene group) and *syn* to C-4a is to be expected (cf. Scheme 2). In this arrangement, the axial C-4 methylene group does not interfere with the nitroso oxygen atom. The conformation deduced above is strongly

Table 1. ^{13}C chemical shifts ($CDCl_3$; δ in ppm from internal *TMS*) and selected shift differences (cf. Text; $\Delta\delta = \delta(\mathbf{4}) - \delta(\mathbf{5})$) of compounds **4** and **5**; data for compound **5** are taken from Ref. [9]; values with the same superscript may be interchanged

	4	**5**	$\Delta\delta$
C-1	29.47[1]	30.87	
C-2	19.67[2]	20.07	
C-3	24.91[3]	25.89	
C-4	23.00	25.54	−2.54
C-4a	49.72	55.08	−5.36
C-5	27.80	32.06	−4.26
C-6	20.42[2]	20.02	
C-7	25.88[3]	26.29	
C-8	25.61[3]	25.12	
C-8a	36.91	35.73	1.18
C-9	29.98[1]	30.06	
C-9a	27.83	29.08	−1.25
C-10a	55.63	46.21	9.42

supported by a comparison of the ^{13}C NMR chemical shifts of **4** (Table 1) with those given in Ref. [13] for the *syn* and *anti* conformers of N-nitroso-*cis*-decahydroquinoline (conformers **B–s** and **B–a**, compound **2**) and N-nitroso-2β-methyl-*cis*-decahydroquinoline (conformers **B–s** and **A**, compound **6**).

Most relevant for the conformation of **4** are the ^{13}C NMR signals of the four tertiary carbons C-4a, C-8a, C-9a, and C-10a which were identified by means of an APT spectrum. A discrimination of δ(C-4a) from δ(C-10a) as well as of δ(C-8a) from δ(C-9a) may well be achieved by a comparison of the chemical shift differences of these carbon atoms when going from amine **5** to N-nitrosamine **4** (cf. Table 1) with the appropriate differences in the system *cis*-decahydroquinoline [14]/*syn*- and *anti*-N-nitroso-*cis*-decahydroquinoline [13]. In each of these N-nitrosamine conformers, the α-carbons *syn* to N-O experience an upfield shift of more than 4 ppm, whereas the corresponding *anti* α-carbons are deshielded by about 7 ppm with respect to the parent amine. This striking contrast in the behaviour of the α-*syn* and α-*anti* carbon atoms leaves no doubt that the signal at 49.72 ppm has to be assigned to C-4a, whereas the resonance at 55.63 ppm must be ascribed to C-10a.

The same effect, although to a much lesser extent, is exerted on the *syn* and *anti* carbon atoms in the β positions of the piperidine ring of decahydroquinolines by N-nitrosation. Therefore, the signals at 36.91 and 27.83 ppm could be unambiguously assigned to C-8a and C-9a, respectively. In addition, the resonances of C-4 and C-5 were assigned by direct comparison with the ^{13}C NMR shifts of appropriate conformers of N-nitroso-*cis*-decahydroquinoline [13].

Experimental

General

Melting points were determined using a Boetius hot-plate microscope and are uncorrected. ^{1}H NMR spectra in CCl_4 were aquired with a Varian EM 360/390 NMR spectrometer (60 MHz, CW mode); all other NMR spectra were measured on a Bruker AM 400 WB NMR spectrometer (^{1}H: 400.13 MHz, ^{13}C: 100.62 MHz) equipped with an Aspect 3000 computer as 0.4–1 *M* $CDCl_3$ solutions in 5 mm tubes. All NMR spectra are referenced to internal *TMS*. ^{13}C NMR spectra were recorded in the APT mode (attached proton test, [15, 16]) employing a relaxation delay of 3 s. Data processing was performed on a work station (Bruker X 32) running the UXNMR software.

Syntheses

(R,R*)-2,2′-Methylene-bis-cyclohexanone* (**1**, m.p.: 58°C) was synthesized, separated, and purified as described earlier [17].

(4aα,8aβ,9aα,10aβ)-Tetradecahydro-10-methylacridine (**2**) and
(4aα,8aα,9aβ,10aα)-Tetradecahydro-10-methylacridine (**3**)

10.4 g (50 mmol) of **1** were subjected to reductive amination with 36 ml of 30% aqueous $MeNH_2$ and 5.4 g (100 mmol) of KBH_4 according to Ref. [2].

The reaction mixture was then acidified with concentrated HCl (*pH* = 2). The precipitated inorganic chlorides were removed by filtration and washed with MeOH; the volatile components of the combined filtrates were removed on a steam bath applying vacuum towards the end of the evaporation procedure. To the residue, 200 ml H_2O were added, and the mixture was shaken on a steam bath for 15 min. Then, the aqueous extract was separated from a viscous, water insoluble phase (termed ''neutral products''; cf. Scheme 1). The viscous product was washed with additional 40 ml of H_2O, and the combined aqueous solutions were alkalized with 40% aqueous NaOH to *pH* 12. The resulting oily organic layer which crystallized partly upon cooling was extracted twice with diethyl ether (50+30 ml); the etheral solution was dried over K_2CO_3, and an aliquot was taken for ^{1}H NMR spectroscopy. Two sharp singlets (N-CH_3) at 2.16 and 2.07 ppm, respectively (CCl_4, internal *TMS*) were observed in the spectrum. After removal of the diethyl ether, the remainder of the etheral solution afforded 5.9 g of an oily residue (57% overall yield of N-methylperhydroacridines) which crystallized in part. After filtration, 2.7 g (26%) of crude solid and 3.2 g of oil were obtained. Trituration with acetone resulted in a melting point of 58–64°C for the crude solid, and its ^{13}C NMR spectrum was identical with that of **2** as reported previously [3]. In the ^{13}C NMR spectrum of the oily fraction, the two characteristic signals of **2** (C-9 and N-CH_3) were present in addition to the fourteen signals of an authentic sample of **3** [7]. From the relative intensities of the N-CH_3 signals (39.41 ppm for **2**, 36.45 ppm for **3**; $CDCl_3$), an approximate product distribution of **2**:**3** = 20:80 could be estimated. Thus, the total yield of **2** amounts to about 32% and that of **3** to about 25%.

Compound **2** was purified *via* its hydroiodide. Crude **2** obtained as described above (m.p.: 58–64°C) was dissolved in warm acetone. The solution was acidified with 67% HI until a *pH* value of 3 was reached, and formation of hydroiodide crystals could soon be observed. After 24 h the hydroiodide was filtered, washed with acetone, and recrystallized from EtOH. The purified hydroiodide was mixed with an excess of 40% aqueous NaOH, and the mixture was subjected to steam distillation. Towards the end of the distillation, cooling had to be interrupted to allow melting of **2** which had solidified in the condenser.

M.p.: 65–66°C (Ref. [2]: m.p.: 63–64°C); ^{1}H NMR (298 K, $CDCl_3$): $\delta = 2.25$ ppm (s, N-CH_3), all other signals broadened; ^{13}C NMR (298 K, $CDCl_3$): $\delta = 39.42$ (N-CH_3), 30.86 (C-9) ppm, all other signals broadened; picrate: m.p.: 194–196°C (MeOH; Ref. [2]: m.p.: 191–192°C); hydroiodide: m.p.:

227–229°C (EtOH); methiodide (prepared at room temperature in acetone): m.p.: 278–279°C (not recrystallized).

Compound **3** was not isolated in pure form from the oily fraction. ^{13}C NMR (298 K, $CDCl_3$): $\delta = 70.33$ (C-4a), 63.61 (C-10a), 39.45, 37.72, 37.06, 36.45 (N-CH_3), 33.79, 30.92, 30.67, 27.46, 27.01, 26.15, 25.83, 19.79 ppm; a complete signal assignment will be presented in one of the forthcoming papers of this series.

The neutral products were not worked up further.

(4aα,8aβ,9aα,10aβ)-Tetrahydroacridine (**5**)

To a solution of 5.6 g (27 mmol) of **2** in 70 ml AcOH and 120 ml H_2O, a solution of 40 g (580 mmol) of $NaNO_2$ in 50 ml H_2O was added dropwise during 0.5 h on the steam bath. After the addition was complete, heating was continued for one more hour. Subsequently, another batch of 70 ml AcOH and 120 ml H_2O was added, and a solution of 80 g (1.6 mol) $NaNO_2$ in 100 ml H_2O was dropped to the mixture over 0.5 h, followed by heating for 1 h. After cooling, the oily product formed was extracted three times with 250 ml diethyl ether each. The etheral extracts were washed with 5×150 ml 10% aqueous NaOH and dried over Na_2SO_4. The ether was removed, and the residue (crude **4**) was refluxed for 2 h with 50 ml of 36% HCl. The excess of HCl was then removed under reduced pressure, and the residue was rendered strongly alkaline by addition of 40% aqueous NaOH. Steam distillation afforded pure **5** which crystallized completely in the condenser. It was recovered by dissolution in a small amount of diethyl ether and subsequent evaporation of the solvent.

Yield: 0.35 g (6.7%); long colourless prisms; m.p.: 116–117°C; ^1H NMR (250 K, $CDCl_3$): $\delta = 3.03$ (m, $\nu_{1/2} = 5.2$ Hz, 1H, H-10a), 2.88 (dt, $J = 12.4$, 4.4 Hz, 1H, H-4a) ppm; $C_{13}H_{23}N$ (193.3); calcd.: N 7.24; found: N 7.11; picrate (prepared in MeOH, crystallized after complete evaporation of the solvent): m.p.: 163–165°C.

(4aα,8aβ,9aα,10aβ)-Tetradecahydro-10-nitrosoacridine (**4**)

To a solution of 145 mg (0.75 mmol) of **5** in 1 ml AcOH and 2 ml H_2O, a solution of 150 mg (2 mmol) of $NaNO_2$ in 2 ml H_2O was added dropwise on the steam bath, and heating was continued for 10 min. A yellow oil was formed which quickly crystallized upon cooling, affording an almost white solid. The latter was separated by filtration, washed with H_2O, dissolved in a minimal amount of acetone at room temperature, and reprecipitated by addition of an excess of a diluted aqueous $KHCO_3$ solution ($pH = 8.5$). After filtration and washing to neutral pH with H_2O, pure **4** was obtained.

Yield: 158 mg (94%); m.p.: 100°C; ^1H NMR (298 K, $CDCl_3$): $\delta = 5.10$ (dt, $J = 12.5$, 4.4 Hz, 1H, H-4a), 4.07 (m, $\nu_{1/2} = 8.4$ Hz, 1H, H-10a) ppm; $C_{13}H_{22}N_2O$ (222.3); calcd.: N 12.60; found: N 12.53.

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