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Hydroacridines XXV [1]. First Synthesis of (4aα,8aα,9aβ,10aβ)-Tetradecahydroacridine and New Syntheses of (4aα,8aα,9aα,10aβ)- and (4aα,8aβ,9aα,10aβ)-Tetradecahydroacridine

Francisc Potmischil[1,*], **Joachim Buddrus**[2], and **Jörg Lambert**[2]

[1] Department of Organic Chemistry, University of Bucharest, Bucureşti-1, Romania
[2] Institut für Spektrochemie und Angewandte Spektroskopie, Dortmund, Germany

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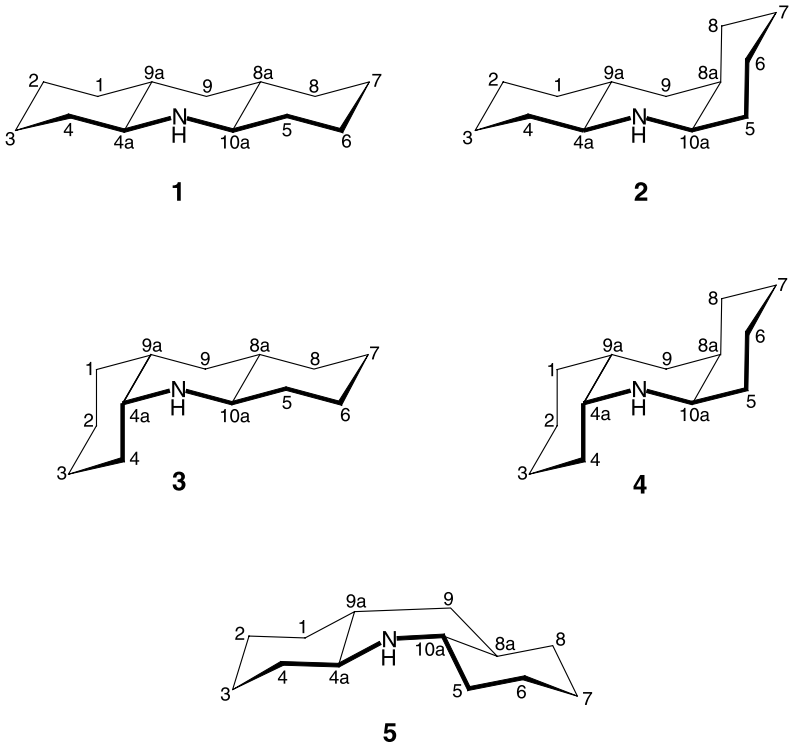
Summary. On heating in dry *DMSO*, in the presence of potassium *t*-butoxide, the *N*-nitrosamine of (4aα,8aβ,9aβ,10aα)-tetradecahydroacridine is completely converted into the *N*-nitrosamine of (4aα,8aα,9aα,10aβ)-tetradecahydroacridine. Under similar conditions, the *N*-nitrosamine of (4aα,8aα,9aβ,10aα)-tetradecahydroacridine yields a ternary equilibrium mixture containing itself (19%), and the *N*-nitrosamines of (4aα,8aβ,9aα,10aβ)-tetradecahydroacridine (46%) and the so far unknown (4aα,8aα,9aβ,10aβ)-tetradecahydroacridine (35%). The resulting *N*-nitrosamines can be smoothly denitrosated to the corresponding secondary amines.

Keywords. Acridines, tetradecahydro; Isomerizations; Nitrogen heterocycles; *N*-Nitrosamines; Strained molecules.

Introduction

Aliphatic *N*-nitrosamines exhibit a high energy barrier of the restricted rotation around the N–NO bond (80–100 $kJ \cdot mol^{-1}$) [2–6]. Therefore, in cycloaliphatic *N*-nitrosamines with sterically hindered N–NO groups, to relieve steric strain, the cyclic frameworks often assume conformations that cannot appear in the parent secondary amines [7–9]. Thus, base-catalyzed equilibration of sterically hindered *N*-nitrosamines, followed by *N*-denitrozation, can become a valuable synthesis route leading to otherwise inaccessible or hardly accessible stereoisomers of saturated azaheterocycles [8]. In the present paper we report new, very convenient syntheses of the otherwise hardly accessible (4aα,8aα,9aα,10aβ)- (**3**) and (4aα,8aβ,9aα,10aβ)-tetradecahydroacridine (**4**), and the first synthesis of (4aα,8aα,9aβ,10aβ)-tetradecahydroacridine (**5**), by equilibration of the *N*-nitrosamines of

* Corresponding author. E-mail: potmisch@yahoo.com

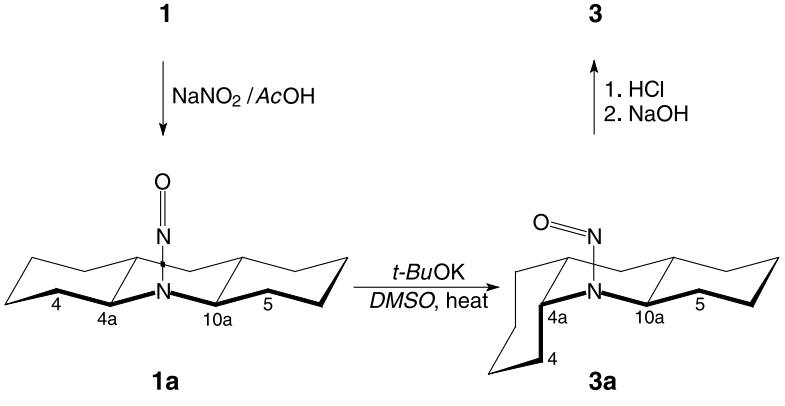


Scheme 1

the most easily available (4aα,8aβ,9aβ,10aα)- (**1**) and (4aα,8aα,9aβ,10aα)-tetradecahydroacridine (**2**) (Scheme 1).

Results and Discussion

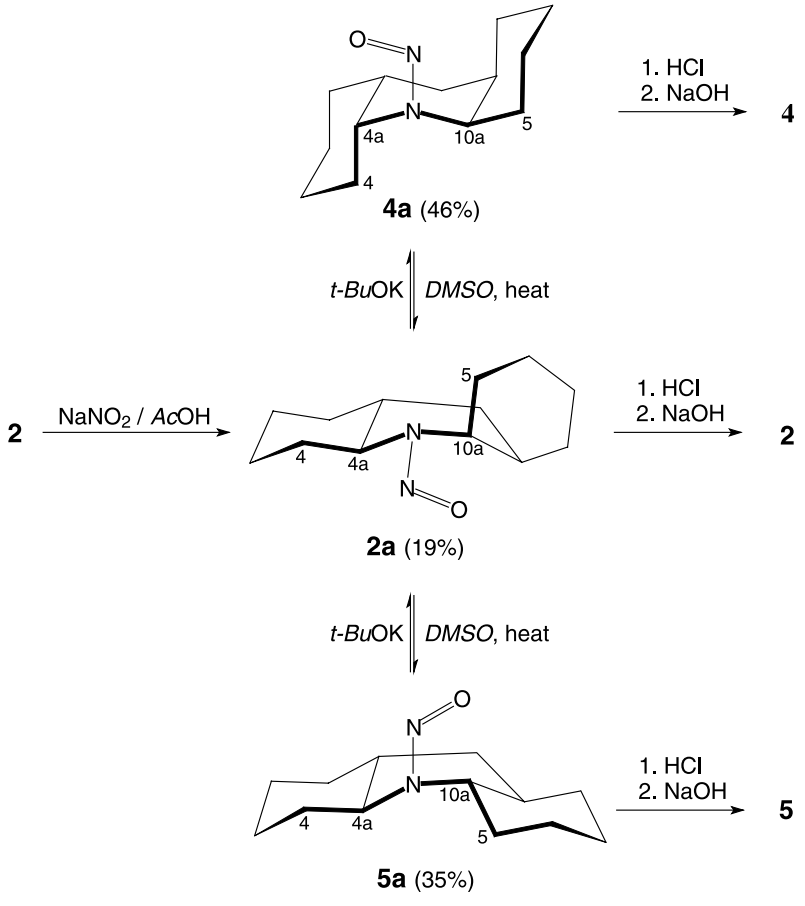
In (4aα,8aβ,9aβ,10aα)-tetradecahydro-10-nitrosoacridine (**1a**), there is a severe steric hindrance between the −N=O oxygen atom and the C-4 (or C-5) methylene group, and, due to the rigidity of the *trans-cisoid-trans*-fused tricyclic system, the (C-4a)(C-10a)N–N=O group is forced to assume a strained conformation, with the



Scheme 2

−N=O oxygen atom twisted out of the plane containing the (C-4a)(C-10a)N–N atoms [7, 9, 10] (see Scheme 2). The steric strain of **1a** is eliminated by *t-Bu*OK-catalyzed inversion of the configuration of carbon C-4a (or C-10a), when (4aα,8aα,9aα,10aβ)-tetradecahydro-10-nitrosoacridine (**3a**) is formed, in which the (C-4a)(C-10a)N–N=O group can assume a normal, strainless planar conformation, with the −N=O oxygen oriented *syn* to C-4a (or C-10a). Although the tricyclic framework of **3a** may be estimated to be less stable by approx. 10.5 kJ · mol^{-1} than that of **1a** [11, 12], the difference between the energies of the >N–N=O groups in **1a** and **3a** is still large enough ($\geq$80 kJ · mol^{-1}) [2–6] to shift the equilibrium entirely towards **3a**.

Similar to **1a**, in (4aα,8aα,9aβ,10aα)-tetradecahydro-10-nitrosoacridine (**2a**) there is also a steric hindrance between the −N=O oxygen and the C-4 and C-5 methylene groups. However, in **2a** the steric interaction with the C-5 methylene group can be largely relieved owing to the flexible *cis* junction, that allows the piperidine ring to adopt a twisted boat conformation with the C-5 carbon in a boat-axial position. Thus, the (C-4a)(C-10a)N–N=O group can preserve a coplanar structure, provided the −N=O oxygen is oriented *syn* to C-10a [10]. Due to its asymmetric structure, **2a** may be expected to yield, under the equilibration con-



Scheme 3

ditions, two different products, in dependence on whether the configuration of C-4a or that of C-10a is inverted (Scheme 3). Inversion of the configuration of C-4a should afford (4aα,8aβ,9aα,10aβ)-tetradecahydro-10-nitrosoacridine (**4a**), in which the (C-4a)(C-10a)N–N=O group can assume an unstrained coplanar conformation with the oxygen atom oriented *syn* to C-4a, and so the piperidine ring can also regain the normal chair conformation. On the other hand, inversion of the configuration of C-10a should afford (4aα,8aα,9aβ,10aβ)-tetradecahydro-10-nitrosoacridine (**5a**), having a *trans-transoid-trans*-fused framework, with the piperidine ring locked in a stable boat form; one may expect that in **5a** there is no more steric hindrance between the −N=O oxygen atom and the C-5 methylene group, and thus the (C-4a)(C-10a)N–N=O group could assume a coplanar conformation, provided the oxygen atom is oriented *syn* to C-10a, as shown in Scheme 3.

Indeed, in the ^{13}C NMR spectrum of the mixture of amines obtained after *N*-denitrosation of the equilibration products appeared, besides all characteristic signals of **2** and **4** [13], 7 more intense additional signals belonging to none of the other known stereoisomers [13, 14]. Their number, their relative intensities, and their chemical shifts leave no doubt that these 7 signals belong to the so far unknown stereoisomer **5**. The ratio of the three stereoisomers in the reaction mixture could be evaluated, by aid of a quantitative ^{13}C NMR spectrum, as approx. 19% unchanged **2**: 46% **4**: 35% **5**. Owing to its relative high melting point, **4** crystallized and could be largely removed. A sample of the remaining oily mixture, containing 32% **2**, 7% **4**, and 61% **5**, allowed an unambiguous carbon framework- and ^{13}C chemical shift assignment of **5** by a 2D-INADEQUATE experiment. The assigned experimental ^{13}C chemical shifts of **5** compare very well with the predicted ones, as follows: C-1,8: found 33.67 (pred. 33.59), C-2,7: 25.99 (26.06), C-3,6: 25.09 (25.21), C-4,5: 35.16 (35.04), C-4a,10a: 54.47 (55.45), C-8a,9a: 37.29 (35.95), and C-9: 35.88 (36.47) ppm. The predicted chemical shifts (in parentheses) were calculated by a procedure of linear correlations [15] with the chemical shifts of its carbocyclic analogue, *trans-transoid-trans*-tetradecahydroanthracene [16]. The new stereoisomer **5** could not yet be separated in pure state for further characterization.

Experimental

General

Melting points were determined using a *Boetius* hot-plate microscope. ^{13}C NMR spectra (100.4 MHz) were measured on a JEOL GX 400 spectrometer equipped with an LSI 11/73 computer and a JEOL JEC 32 data processor; the 2D INADEQUATE experiment was performed on the same instrument, using a composite pulse sequence and instrumental settings as described in an earlier paper [17].

(4aα,8aα,9aα,10aβ)-Tetradecahydroacridine (**3**, $C_{13}H_{23}N$)

The transformation of **1** into its *N*-nitrosamine **1a** is accomplished with a yield of 89%, as reported earlier [18]. In a round-bottom flask fitted with a reflux condenser was prepared a solution of **1a** (18 g, 81 mmol) and *t-Bu*OK (12.5 g, 111 mmol) in dry *DMSO* (400 cm^3). The air was evacuated with a water-jet aspirator pump, and the mixture was heated under vacuum for 12 h to 90–95°C, with occasional shaking by hand. After cooling, H_2O (660 cm^3) was added, the *pH* adjusted with *Ac*OH to value 5, the raw *N*-nitrosamine **3a** extracted with ether (200 + 150 + 150 + 150 cm^3), and the ether removed. The ^{13}C NMR spectrum of the residue was identical with that of an authentic sample of **3a** (mp 44–45°C), prepared by *N*-nitrosation of pure **3** [19]. The residue was dissolved in *Et*OH (40 cm^3), HCl 36% (120 cm^3, 1.2 mol) was added, the mixture heated for 1 h under reflux, and then the *Et*OH and

excess HCl were removed under reduced pressure. The residue was alkalized with conc. aqueous NaOH to $pH = 12$, and the resulting dark oily product was subjected to steam-distillation. The resulting colorless oil solidified soon on standing, yielding 13.3 g (85%) of crystals, melting at 56–68°C. The ^{13}C NMR spectrum of a sample of this product was identical with that of an authentic sample of **3** [13]. After purification through its picrate [19], its mp raised to 72–73.5°C (Ref. [21] 72–74.5°C; Ref. [19] 72–73°C).

(4aα,8aβ,9aα,10aβ)- (**4**, $C_{13}H_{23}N$) *and (4aα,8aα,9aβ,10aβ)-Tetradecahydroacridine* (**5**, $C_{13}H_{23}N$) The transformation of **2** into its *N*-nitrosamine **2a** is accomplished with nearly quantitative yield, as reported earlier [18]. The reaction, with **2a** (15.2 g, 68 mmol) and *t-Bu*OK (10.7 g, 95 mmol) in *DMSO* (340 cm^3), and working up of the reaction mixture, including *N*-denitrosation and removal of the *Et*OH and excess HCl, was conducted as described above for **1a**. On alkalization of the residue with conc. aqueous NaOH, a mixture of solid and oily bases was obtained, which was extracted with ether. After removal of the ether, the residue was filtered off, yielding 4.43 g (33.5%) of raw solid and 6.85 g (52%) of a dark oil. The solid base was identified as to be **4**, by its mp 116–117°C after crystallisation from hot acetone (Ref. [20] 116–117°C), and its ^{13}C NMR spectrum, identical with that of an authentic sample of **4** [13]. The oil, purified by steam-distillation and analysed by quantitative ^{13}C NMR spectroscopy, proved to be a mixture of approx. 32% unchanged **2**: 7% **4**: 61% **5**. Taking into account the amount of previously separated solid **4**, the equilibrium ratio of the three *N*-nitrosamines in the reaction mixture may be estimated as approx. 19% **2a**: 46% **4a**: 35% **5a**.

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