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Hydroacridines XXI [1]. ^{13}C NMR Spectroscopic Investigation of the Stereoselectivities of Quaternizations of N-Alkyl Derivatives of (4aα,8aβ,9aβ,10aα)- and (4aα,8aα,9aβ,10aα)-Tetradecahydroacridine

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Summary. The stereoselectivities of the quaternization reactions of (4aα,8aβ,9aβ,10aα)- and (4aα,8aα,9aβ,10aα)-tetradecahydro-10-methylacridine with methyl- and ethyl iodide as well as those of (4aα,8aβ,9aβ,10aα)- and (4aα,8aα,9aβ,10aα)-10-ethyl-tetradecahydroacridine with methyl iodide were investigated using ^{13}C NMR spectroscopy including ^{13}C-labelling where appropriate. The methylations of both N-methyl amines occur by predominant (60% and 75%, respectively) equatorial approach, their ethylations occur sterospecifically by equatorial approach, and the methylations of the N-ethyl amines occur by highly stereoselective (>90%) axial approach of the quaternizing reagent.

Keywords. Acridines, tetradecahydro; ^{13}C NMR; ^{13}C-Labelling; Stereoselective reactions.

Introduction

The preferred steric course and the degree of stereoselectivity of quaternizations of N-alkylated saturated nitrogen heterocycles (mainly piperidines and azabicycles containing a fused or bridged piperidine ring) has been the subject of many efforts and discussions (for reviews, see Refs. [2, 3]). Two major causes have led to divergent opinions: (*i*) the lack of a generally accepted, unambiguous method for configurational assignment of the N-epimeric products of quaternization and (*ii*) the lack of an accurate method for the determination of the N-epimeric product ratios.

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(i) Configurational assignment of quaternization products

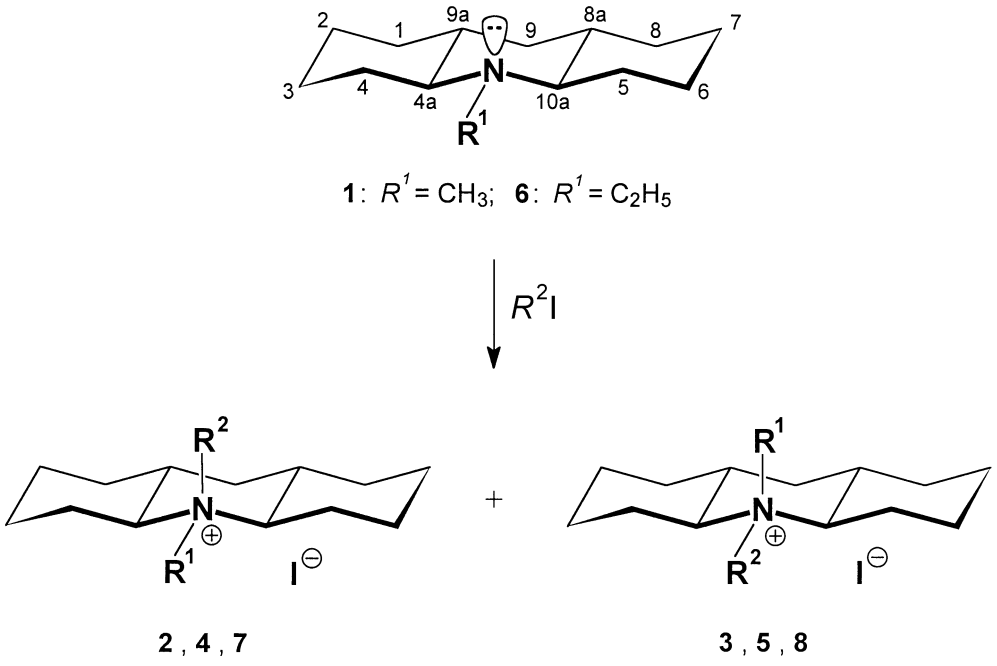
Configurational assignment by X-ray crystallographic analysis has been possible only in a few cases where technically satisfactory crystals of stereochemically homogeneous samples could be obtained [3]. A more convenient and frequently used method is ^{1}H NMR spectroscopy. It relies on the observation that, within members of N-epimeric pairs of quaternary piperidinium salts and in N,N-dimethylpiperidinium salts as well, the signals of axial N^+-methyl groups usually occur at higher field than those of equatorial ones. Unfortunately, quite a number of examples have been noticed [4–10] where this method was either not applicable or give rise to wrong conclusions.

Owing to the much higher sensitivity of the ^{13}C nucleus towards steric factors, configurational assignments should have been greatly facilitated employing ^{13}C NMR. Nevertheless, it seems that so far ^{13}C NMR has only once been used in a such concern [11].

(ii) Determination of quaternization product ratios

In the pioneering studies on the preferred steric courses of quaternizations, the product ratios have been estimated by fractional crystallization. These results must be regarded with caution as has been well documented elsewhere [2]. Since the mid-sixties, the ^{1}H NMR technique was applied almost exclusively; in most of the studies spectrometers operating at 60 MHz in the CW mode were employed. A critical evaluation of the accuracy (or rather inaccuracy) of the results achieved this way was done by *McKenna* and collaborators [3, 9]. However, even with modern instruments ^{1}H NMR can fail in cases when the signals of the relevant N^+-alkyl groups are superimposed on each other [6, 8] or on signals of certain ring protons [4], except when appropriately ring-deuteriated substrates are used [12]. An attempt to determine quaternization product ratios by quantitative ^{2}H NMR spectroscopy [11] was even less successful, as the relevant N^+-CD_3 signals were still worse resolved than the N^+-CH_3 signals in the proton spectrum of the nondeuteriated compounds.

To the best of our knowledge, quantitative ^{13}C NMR spectroscopy has never been used for the determination of quaternization product ratios so far, although ^{13}C NMR in all respects clearly surpasses other methods: (1) the large ^{13}C chemical shift differences between axial N^+-CH_3 (γ-*gauche* effects), equatorial N^+-CH_3, and ring carbons enable unambiguous stereochemical assignments and accurate measurement of signal intensities; (2) using ^{13}C-labelled quaternization reagents, minor quaternization products can be detected and identified even if present in minimal amounts; (3) product ratios can be determined even in the presence of the unreacted amine and/or excess reagent, rendering their removal from the reaction mixture unnecessary; (4) the quaternizations may be run directly in the NMR sample tube, provided that an appropriate NMR solvent is used as reaction medium. These obvious advantages prompted us to employ quantitative ^{13}C NMR spectroscopy and ^{13}C-labelling (where appropriate) in the present investigation of the stereoselectivities of quaternizations of (4aα,8aβ,9aβ,10aα)-tetradecahydro-10-methylacridine (**1**), (4aα,8aβ,9aβ,10aα)-10-ethyltetradecahy-



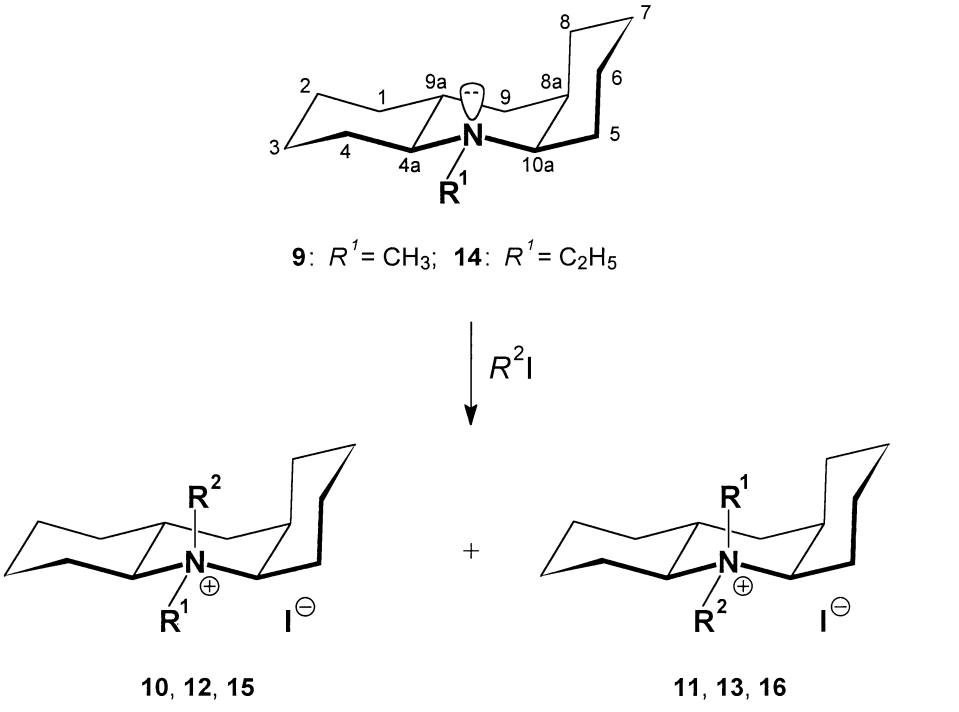
Scheme 1

droacridine (**6**), (4aα,8aα,9aβ,10aα)-tetradecahydro-10-methylacridine (**9**), and (4aα,8aα,9aβ,10aα)-10-ethyl-tetradecahydroacridine (**14**). For the N-methyl amines **1** and **9** both methylations with [^{13}C]methyl iodide and ethylations with ethyl iodide, and for the N-ethyl amines **6** and **14** methylations with [^{13}C]methyl iodide were investigated (Schemes 1 and 2).

Results and Discussion

^{13}C NMR spectra of amines and quaternary salts

To assure unambiguous identification and determination of the quaternization products along with possible unreacted amine in the reaction mixtures prior to the beginning of the study on the stereoselectivities of quaternizations, the natural abundance ^{13}C analogues of the salts **2/3**, **5/7**, **10/11**, and **13/15** were synthesized, isolated in pure state, and their complete ^{13}C NMR signal assignments were achieved *via* 2D INADEQUATE experiments. The signal assignments of the axial and equatorial N^+-CH_3 groups of **2/3** and **10/11** were corroborated by heteronuclear shift correlation with the corresponding ^{1}H NMR signals assigned earlier [13]. For the salts **8** and **16** whose natural abundance ^{13}C analogues could not be isolated, only the signals of the ^{13}C-labelled N^+-CH_3 groups (acquired from



Scheme 2

the reaction mixture) are assigned with certainty (Table 1). The complete ^{13}C signal assignments of the parent amines **1**, **6**, **9**, and **14** (also given in Table 1) has already been performed and discussed in a previous paper of this series [14].

Quaternizations

The quaternizations were performed at room temperature (*ca*. 25°C) directly in the NMR sample tubes, and the subsequent quantitative measurements were run on the entire reaction mixtures. When $^{13}CH_3I$ was used as the quaternizing reagent, the spectra were acquired employing up to 8 scans; this way only the two signals of the ^{13}C labelled N^+-CH_3 groups, but no natural abundance ^{13}C signal could be observed. Because the methiodides **2/3** and **10/11** showed too poor solubility in $CDCl_3$, for the study of the stereoselectivities all quaternizations were run in CD_2Cl_2 as the reaction solvent, and the central line of the CD_2Cl_2 quintet (53.80 ppm [15]) was used as internal reference. The resonances found in this system for the relevant signals of the quaternization products were slightly (however, always less than 0.5 ppm) shifted downfield as compared to the values listed in Table 1.

Table 1. ^{13}C NMR chemical shifts of amines **1**, **6**, **9**, and **14** and the quaternary salts **2/3**, **7/5**, **8**, **10/11**, **13/15** and **16** (±0.1 ppm)[a]

	1[b]	**2** = **3**[c]	**6**[b]	**7** = **5**[b]	**8**[c]	**9**[b]	**10** = **11**[d]	**14**[b]	**15** = **13**[b]	**16**[c]
C-1	33.46	33.05	33.26	33.33	–	33.71	33.71	33.66	33.91	–
C-2	25.83	24.18	25.71	24.10	–	25.71	24.31	25.76	24.05	–
C-3	26.10	25.09	25.98	25.20	–	26.07	25.08	26.09	24.84	–
C-4	31.03	25.69	30.47	24.93	–	30.52	25.86	30.03	25.39	–
C-4a	69.28	77.03	63.98	72.50	–	70.21	76.28	64.38	70.88	–
C-5	31.03	25.69	30.47	24.93	–	30.74	25.08	30.18	24.25	–
C-6	26.10	25.09	25.98	25.20	–	19.74	22.40	20.40	22.76	–
C-7	25.83	24.18	25.71	24.10	–	26.86	22.88	26.77	21.52	–
C-8	33.46	33.05	33.26	33.33	–	27.37	27.75	27.02	28.18	–
C-8a	40.99	34.97	41.37	34.40	–	37.55	33.01	37.47	31.02	–
C-9	40.69	37.46	40.67	37.60	–	39.35	34.15	39.49	32.26	–
C-9a	40.99	34.97	41.37	34.40	–	36.95	31.43	37.09	30.88	–
C-10a	69.28	77.03	63.98	72.50	–	63.67	71.91	57.22	66.69	–
N-CH_3*eq*	36.07	49.05	–	–	44.75	36.54	52.84	–	–	49.85
N-CH_3*ax*	–	39.05	–	40.55	–	–	44.41	–	43.63	–
N-CH_2-	–	–	38.95	53.90	–	–	–	38.44	57.60	–
C-CH_3	–	–	7.22	7.60	–	–	–	5.40	8.83	–

[a] In ppm downfield from internal *TMS* in the solvents specified below; [b] measured in $CDCl_3$; [c] measured in CD_2Cl_2; [d] measured in $CDCl_3$+CD_2Cl_2 (6:1)

In the methylation of **9** with $^{13}CH_3I$, by accident the signal of the equatorial N^+-CH_3 group of **11** (at 53.27 ppm) is superimposed exactly on the highest-field line of the CD_2Cl_2 quintet; fortunately its individual intensity could be quite satisfactorily determined by subtracting the separately measurable intensity of the symmetrical lowest-field line of the quintet.

In the reaction mixture from the ethylation of **1** with EtI all ten signals of **5** were present, and no trace of unreacted **1** or of the salt **4** could be detected. In the mixture from the ethylation of **9**, however, despite of the large excess of EtI and the prolonged reaction time (see Table 2), only about 3% of the salt **13** besides 97% of unreacted **9** were observed. In an early study employing 60 MHz ^1H NMR, in the attempted room temperature ethylation of **9** with EtI in acetone no salt formation could be observed at all [13].

The stereoselectivities, as determined for the investigated quaternizations, are presented in Table 2. With the reagents and under the reaction conditions employed here, alterations of product ratios by equilibration of the N-epimeric pairs of salts may not be expected [5, 9, 16].

The data of Table 2 allow to summarize the factors governing the steric course of quaternizations of (4aα,8aβ,9aβ,10aα)- and (4aα,8aα,9aβ,10aα)-10-alkyl-tetradecahydroacridines as follows:

1) If the incoming quaternizing alkyl group is of smaller size than the exocyclic N-alkyl group already present in the amine, attack on the axial (sterically more hindered) side will predominate.

Table 2. Products and degrees of stereoselectivity of room temperature quaternizations of amines **1**, **6** (Scheme 1), **9**, and **14** (Scheme 2) with alkyl iodides in CD_2Cl_2

Amine	R^2I	Stereoselectivity of products formation (±1.5%)		Reaction time (days)
		Product of axial attack	Product of equatorial attack	
1	$^{13}CH_3I$	**2** (40%)	**3** (60%)	3
	CH_3CH_2I	**4** (not detectable)	**5** (100%)	18
6	$^{13}CH_3I$	**7** (95.5%)	**8** (4.5%)	6
9	$^{13}CH_3I$	**10** (25%)	**11** (75%)	3
	CH_3CH_2I	**12** (not detectable)	**13** (100%)	25
14	$^{13}CH_3I$	**15** (91.5%)	**16** (8.5%)	7

2) If the incoming quaternizing alkyl group and the exocyclic N-alkyl group already present in the amine are the same, attack on the equatorial (sterically less hindered) side will predominate[1].
3) If the incoming quaternizing alkyl group is of larger size than the exocyclic N-alkyl group already present in the amine, exclusive or nearly exclusive equatorial attack should be expected[1].

Although seeming logical and of general validity, these rules do not apply to all systems containing a piperidine ring. For example, it is now well established that methylations and even ethylations of N-methylcamphidine [2, 9] and N-methylpiperidines bearing no substituents in positions 2 and/or 6 [2, 12] rather paradoxically proceed *via* highly predominant axial attack. Introduction of an equatorial alkyl group in position 2 or 6 of the piperidine ring, however, decreases the proportion of axial attack, and for *cis*-1-methyl-2,6-dialkylpiperidines equatorial attack even becomes predominant [17].

As may be seen, the preferred steric course of quaternizations of (4aα,8aβ,9aβ,10aα)- and (4aα,8aα,9aβ,10aα)-10-alkyl-tetradecahydroacridines parallels that of *cis*-1,2,6-trialkylpiperidines, and for amine **1** even the degrees of stereoselectivity compare fairly well to the appropriate values for *cis*-1,2,6-trimethylpiperidine and *cis*-2-ethyl-1,6-dimethylpiperidine.

For the room temperature methylations of *cis*-1,2,6-trimethylpiperidine and *cis*-2-ethyl-1,6-dimethylpiperidine in acetone, 56% and 66% equatorial attack, and for their ethylations 89% and 91% equatorial attack has been reported, respectively [17].

In the methylations of the (4aα,8aα,9aβ,10aα)-stereoisomers **9** and **14**, the preference for equatorial attack is markedly higher (15%), and the preference for axial attack is somewhat lower (4%) than in the corresponding reactions of their

[1] This behaviour can be rationalized by the fact that, with identical alkyl groups, in the transition state the effective steric demands of the partly attached incoming N-alkyl group are higher than that of the fully attached exocyclic N-alkyl group already present in the amine [5]. Hence, if the absolute size of the incoming aklyl group is larger than that of the already fully attached N-alkyl group, equatorial attack will predominate.

(4aα,8aβ,9aβ,10aα)-analogues **1** and **6**, respectively. This difference in stereoselectivity must be related to the fact that in **1** and **6** an incoming axially quaternizing methyl group encounters only four γ-*gauche* steric interactions (with C-4, C-5, C-8a, and C-9a), whereas in **9** and **14** a sum of two γ-*gauche* (C-4 and C-9a) and two *syn*-1,3-diaxial-type steric interactions (with C-6 and C-8) are to overcome. For fully attached N^+-methyl groups, as in the salts **2/3** and **10/11**, these steric strains can be roughly estimated to approximately 13.4 kJ · mol^{-1} for the first and at least 37.7 kJ · mol^{-1} for the latter case[2]; however, the energy barriers to be surpassed in the appropriate transition states of axial quaternization are expected to be higher[1].

In the protonated salts of **9** and **14**, as reported recently [14], in consequence of these *syn*-1,3-diaxial interactions the equilibrium is entirely shifted towards the N-epimers with equatorially oriented N-methyl and N-ethyl groups, respectively.

Experimental

General

The ^{13}C NMR data presented in Table 1 were measured at 296 K on a JEOL GX 400 NMR spectrometer (^{1}H: 399.65 MHz, ^{13}C: 100.4 MHz) equipped with a LSI 11/73 digital computer and a JEOL JEC 32 data processor using solutions ranging from 1.5–2.5 *M* in the solvents indicated (see Table 1) with internal *TMS* in 5 mm sample tubes. For the 2D INADEQUATE experiments, a composite pulse sequence [20] and quadrature detection in f_1 and f_2 were employed. Instrument settings: 1792 scans per increment (64 h measurement time), $\tau = 3/4J = 21.4$ ms (for $J = 35$ Hz), 32 data points in f_1 with zero filling to 64, 16384 data points in f_2 (digital resolution 0.8 Hz). The quantitative ^{13}C NMR spectra were measured with pulse delays of 100 s and without NOE Enhancement.

Materials and quaternizations

[^{13}C]methyl iodide (93 atom% ^{13}C) was purchased from MSD ISOTOPES (a division of Merck Frosst Canada Inc.). The syntheses of amines **1**, **6**, **9**, and **14** [21] and of the natural abundance ^{13}C analogues of the salts **2/3**, **7/5**, **10/11**, and **15/13** [13] have already been described elsewhere.

For all quaternizations with [^{13}C]methyl iodide the following standard procedure was employed: to a solution of 0.1 m*M* of amine in 0.35 cm^3 of CD_2Cl_2 in an NMR sample tube, 0.5 g (3.5 m*M*) of $^{13}CH_3I$ were added, the tube sealed with a stopper, and the mixture was left to react at room temperature for the time specified in Table 2. For the quaternizations with ethyl iodide, 10 m*M* of C_2H_5I were added to 1 m*M* of amine **1** and **9**, respectively, each in 0.75 cm^3 of CD_2Cl_2, in the NMR sample tube and left to react at room temperature for the time specified in Table 2.

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[2] The energy corresponding to one γ-*gauche* interaction is estimated to 3.3–3.8 kJ · mol^{-1} [18], and that corresponding to one *syn*-1,3-diaxial interaction to at least 15.5 kJ · mol^{-1} [19].

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