DETERMINATION OF THE THREE-DIMENSIONAL STRUCTURE OF 1,2-DIMETHYL-7-tert-BUTYLDECAHYDRO-4-QUINOLONE BY PMR SPECTROSCOPY

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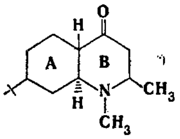
The three-dimensional structure of 1,2-dimethyl-7-tert-butyldecahydro-4-quinolone was analyzed completely by PMR spectroscopy with the aid of the "shift-reagent" technique. The induced shifts are described by a pseudocontact model realized by means of a computer program.

Paramagnetic shift reagents [1,2], which are complexes of the lanthanides with diketones, have recently found broad application in PMR spectroscopy in the analysis of higher-order spectra. The shift-reagent technique seems of particular value in conformational studies when other possibilities of the NMR method prove to be ineffective. 1,2-Dimethyl-7-tert-butyldecahydro-4-quinolone (I), the synthesis of which is presented in [3], serves as an example of this.



I

Because of considerable overlapping of the multiplets, the PMR spectrum of I recorded at 100 MHz does not make it possible to establish its three-dimensional structure. All signals of the 27 protons lie within the limits of a small region of the scale of chemical shifts with a width on the order of 2 ppm. Only two singlets of the N-methyl and tert-butyl groups at 2.26 and 0.90 ppm*, respectively, a doublet ($J_{H,Me}$ 6.0 Hz) of the 2-CH_3 group at 1.18 ppm, and, finally, a complex multiplet of the 2-H proton (which occupies the extreme left-hand position in the spectrum (2.59 ppm) linked by spin–spin coupling (SSC) with the methyl group in the 2 position are isolated from the overall spectral envelope. The presence in the latter multiplet of a vicinal constant of SSC of the 2-H proton with the axial 3-H_a proton on the order of 10 Hz and the superimposition of this multiplet at stronger field than in the case of an equatorially oriented 2-H (3.34 ppm) make it possible to assign an axial orientation to the 2-H proton and an equatorial orientation to the 2-CH_3 group [4]. However, the question regarding the type of ring fusion and orientation of the substituents in the positions [7] remains open without the application of a shift reagent.

We used the europium complex with heptafluorodimethyloctanedione [$Eu(IOD)_3$] as the shift reagent in our study. The reagent was added to a solution of I in the form of an aliquot of a prevously prepared solution. The PMR spectrum was recorded for each concentration, and a series of spin-decoupling experiments were carried out in order to assign the signals.

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*The chemical shifts (δ) are presented for the spectra of a 0.13 M solution of I in CCl_4 at 27° with tetramethylsilane as the internal standard.

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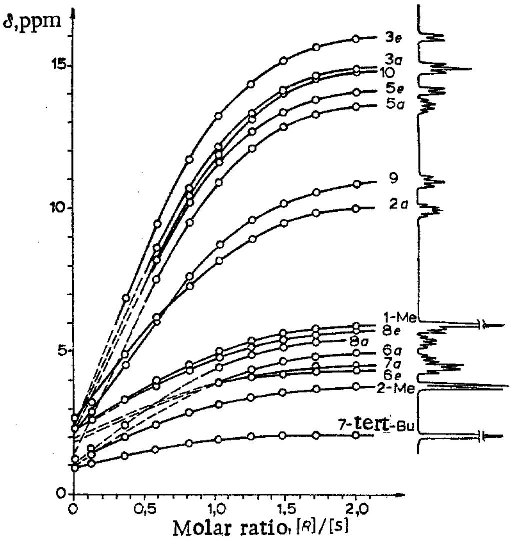

Fig. 1

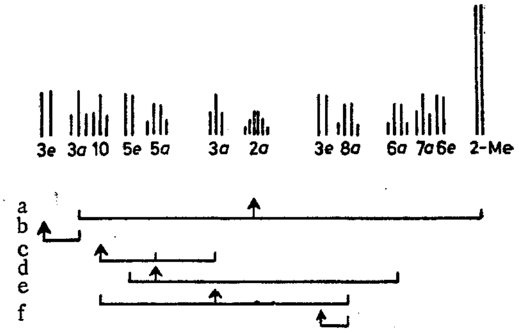

Fig. 2

Fig. 1. Dependence of the chemical shifts of the protons of 1,2-dimethyl-7-tert-butyldecahydro-4-quinolone (I) on the $[Eu(IOD)_3]/[I]$ molar ratio. The final position of the multiplets in the PMR spectrum at the highest reagent concentration is shown in the right-hand portion of the figure.

Fig. 2. Diagram of the spin-decoupling experiment. The vertical line with an arrow indicates the irradiation signal, and the vertical line without an arrow indicates the simplified signal.

The position of the signals of I in the PMR spectrum at the highest reagent concentration is shown in the right-hand portion of Fig. 1. Because of a certain amount of broadening of the signals due to the reagents, only the sufficently large SSC constants (i.e., $J^{gem} \approx J_{aa}^{vic} \approx 10\text{-}12$ Hz), as a rule, show up in the multiplets. In this case, the broadening is greater, the larger the shift experienced by the signal. The necessity for the determination of the multiplicity of the strongly shifted signals does not make it possible to raise the reagent concentration rapidly. The graphs in the left-hand portion of Fig. 1 depict the dependence of the position of the signals in the spectrum as a function of the ratio of the molar concentrations of the reagent and the compound. It is apparent that a linear dependence obtains up to a molar ratio of ∿0.6-0.8, whereas above a molar ratio of ∿1.2-1.4 the induced chemical shifts no longer increase appreciably as the reagent concentration is increased. This sort of trend of the curve indicates the invariability of the site of complexing in the substrate molecule as the molar ratio changes; only the relative number of bonded substrate molecules changes.

A diagram of the spin-coupling experiments corresponding to the spectrum obtained at a molar ratio of ∿1.0 is shown in Fig. 2.

As seen from Fig. 1, above a molar ratio of 1.0 the spectrum is simplified to such an extent that one can isolate the important (from the point of view of the determination of the configuration and conformation) signals of the 9-H, 10-H, and 8-H_a protons. The assignment in this case is made with allowance both for the multiplicity and degree of shifting of the signals. The signals of the 3-H_e protons (doublet, $J^{gem} = -12$ Hz) and the 3-H_a protons (coupled with 2-H_a, see Fig. 2a) experience the greatest paramagnetic shift. This indicates that these protons are closest to the europium atom, and reagent–substrate complexing takes place at the oxygen atom of the carbonyl group. However, the nitrogen atom practically does not participate in complexing, inasmuch as it is blocked by two methyl groups [5]. A second triplet, which also experiences a considerable shift to weak field, must therefore be assigned to the 10-H proton (coupled with 5-H_a and 9-H). A third triplet, assgined to 9-H and shifted considerably more weakly, is coupled with the 8-H_a quartet, which is shifted to an even lesser extent. The assignment of the remaining signals is apparent from Fig. 2 and is not fraught with any difficulties.

As noted above, the 9-H and 10-H protons give signals in the form of triplets with an SSC constant of ∿10-11 Hz; this unambiguously indicates trans fusion of the A/B rings. The signal of the 8-H_a proton is observed as a quartet and thus contains three SSC constants (J_{8a8e}, J_{8a9}, and J_{8a7a}) of 12 Hz each. Hence it follows that the 7-H proton is axially oriented, and the tert-butyl group in the 7 position is therefore equatorially oriented. It should be noted that the signals of the 6-H_a, 7-H_a, and 6-H_e protons are not resolved even in the presence of the shift reagent.

The simplification of the spectrum, as a consequence of which we were able to measure the SSC constants and thereby determine the configuration and conformation of decahydroquinolone I, is due to the fact that the magnitudes of the shifts of the signals under the influence of the shift reagent — the so-called induced shifts — are different, as already noted, for different protons of a given compound. The induced shift for ^1H nuclei has primarily a pseudocontact nature and is determined by the McConnel—Robertson equation [1,6]

$$\Delta_i = B(3\cos^2\varphi_i - 1)/r_i^3, \tag{1}$$

where r_i is the lanthanide—H_i proton distance, and φ_i is the angle formed by the lanthanide—proton direction and the major axis of the complex, which is usually assumed to be collinear with the europium—ligand bond (Fig. 3). Coefficient B is a constant for all of the protons of a given molecule. The Δ_i values are determined as the slope of the linear portions on the graphs of the dependence of the chemical shift (δ_i) on the [reagent]/[substrate] molar ratio (Fig. 1); however, over the range of molar ratios from 0 to ∿0.6, for which graphs of this sort are linear, one often cannot obtain a sufficient number of experimental points because of the complexity of the spectra, and extrapolation leads to considerable error. This difficulty can be overcome in many cases by means of transformation of such graphs to completely linear graphs [7], for which a knowledge of the concentrations is not required and, consequently, the accuracy of the obtained ratios of the Δ_i values becomes higher. To achieve this, instead of graphs of the dependence of the chemical shifts on the

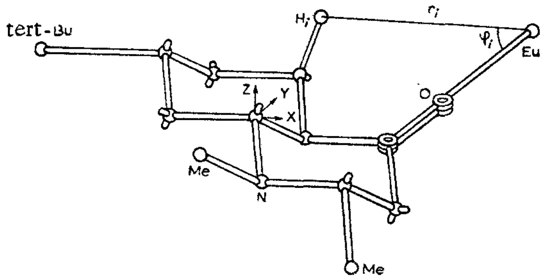

Fig. 3

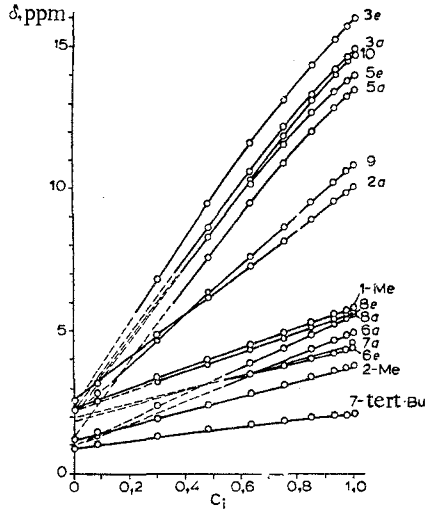

Fig. 4

Fig. 3. Orientation of the trans isomer of I relative to the Cartesian system of coordinates. The C_9 atom is at the origin of the system, C_8 lies on the negative X semiaxis, and C_5 lies on the y axis. The 5a proton was taken as H_i.

Fig. 4. Rectification of the curves (Fig. 1) by means of corrected values C_j, which are proportional to the sum of the shifts in each spectrum.

TABLE 1. Chemical Shifts (δ), ppm) of 1,2-Dimethyl-7-tert-butyl-decahydro-4-quinolone (I) at 0 Reagent Concentration

7-tert-Bu	2-Me	1-Me	2-H_a	9-H	5-H_a	5-H_e	10-H	3-H_a	3-H_e	8-H_a	8-H_e	6-H_e	7-H_a	6-H_a
0,89	1,18	2,26	2,59	2,08*	1,35*	2,19*	2,08*	2,20*	2,30*	1,04*	2,16*	1,98*	1,86*	0,96*

*Obtained by means of extrapolation from graphs (Fig. 4).

experimental molar concentrations, one constructs graphs of these chemical shifts as a function of the corrected values C_j, which are proportional to the sum of the shifts in each spectrum (Fig. 4):

$$C_j = (C_n - C_1)(\Sigma\delta_{ij} - \Sigma\delta_{i1}) / (\Sigma\delta_{in} - \Sigma\delta_{i1}) + C_1,$$

where δ_{ij} is the chemical shift of proton i in spectrum j. By means of such graphs it also becomes much easier to perform extrapolation in order to determine the shifts of the protons at 0 reagent concentration. The extrapolations of the chemical shifts obtained in this manner are denoted by asterisks in Table 1.

On the basis of Eq. (1), one may realize a second approach to the problem of the determination of the configuration and conformation of decahydroquinolone I that makes it possible to answer the question as to which of the 108 (three forms of fusion, three forms of conformations of the carbocycle, three heterorings, two modes of orientation of $N-CH_3$, and two modes of orientation of the tert-butyl group, Fig. 5)* possible three-dimensional structures of I best corresponds to Eq. (I). By excluding unknown parameter B [8] from Eq. (1) and by minimizing the difference between the experimental and calculated ratios of the induced shift by the method of least squares

$$\sum_{i \neq j} \left[\frac{\Delta_i \exp}{\Delta_j \exp} - \frac{\dfrac{3\cos^2\varphi_i - 1}{r_i^3}}{\dfrac{3\cos^2\varphi_j - 1}{r_j^3}} \right]^2, \qquad (2)$$

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*The orientation of the 2-Me group was assumed to be equatorial; in addition, the twist conformation of the ring was disregarded, inasmuch as it does not correlate with the observed SSC constants.

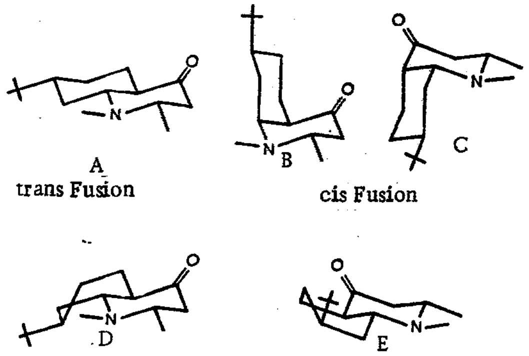

Fig. 5. Three modes of ring fusion (A,B,C); each of the rings (shown only for the carbocycle in the case of trans fusion) can exist in one of three conformations (A,D,E).

one can determine the optimum coordinates of the europium atom. Knowing the latter, one can calculate

$$B=\sqrt{\frac{1}{m}\sum_{1}^{m}\left(\Delta_i\exp\frac{r_i^3}{3\cos^2\varphi_i-1}\right)^2}$$

and one can then detemine the Δ_i^{cal} values by means of expression (I).

The minimum value of expression (2) or of the compatibility factor [9]

$$R=\sqrt{\frac{\Sigma(\Delta_i\,\mathrm{calc}-\Delta_i\,\mathrm{exp})^2\cdot\omega_i}{\Sigma(\Delta_i\mathrm{exp})^2\cdot\omega_i}}, \qquad (3)$$

where ω_i are the weighting coefficients, which are usually assumed to be unity, will serve as the criterion in the selection of the most probable isomer.

We composed two programs using the gradient method [10] (FORTRAN basis) and the Newton method [11] (ALGOL basis) that realize the sorting out of the variants of the structures and optimization in each of the variants of the coordinates of the europium atom. The condition $|\vec{r}_{n+1}-\vec{r}_n|<0.01$ Å for the convergent variant and $|\vec{r}_0-\vec{r}_n|>12$ Å in the case of divergence, where $\vec{r}_0$ is the radius vector of the oxygen atom and $\vec{r}_n$ is the radius vector of the Eu atom after the n-th iteration, was taken as the output condition. The point located 3 Å from the oxygen atom of the carbonyl group along the line of the carbonyl bond [12] was taken as the initial approximation (Fig. 3). The time required for one variant was ∿1 min (with an ES-1020 computer).

Sixteen of the total of 108 variants proved to be convergent, and two of them, with 7e-tert-Bu and 7a-tert-Bu (for trans fusion, a chair – chair conformation of the rings, and an equatorial orientation of $N-CH_3$) lead to a compatibility factor R one order of magnitude lower than in the remaining cases. Thus the result of the calculation, which is in good agreement with the initial determination of the type of fusion and orientation of the substituent in the 7 position (7e-tert-Bu), gives new information: each of the rings has a chair conformation, and the N-methyl group is primarily equatorially oriented.

It must be noted that it does not seem possible to arrive at a preference only on the basis of the calculation of one of the two above-indicated best variants, inasmuch as all of the characteristics for them – compatibility factor R (∿5.2%), the O – Eu distance (∿2.1 Å), and the deviation (∿17°) of the line connecting oxygen and europium from the line of the C = O bond – practically coincide. This is apparently associated, on the one hand, with the limitation of the method (the difference in the effects of the magnetic dipole on the remote ae-oriented tert-butyl group is small) and, on the other hand, the effects of the inaccuracy of the input data – the atomic coordinates obtained by means of dihedral angles under the assumption of idealized geometry of cyclohexane, which should especially affect the coordinates of the protons of the piperidine ring, the form of which is slightly distorted because of the shorter length of the C – N bond as compared with the lengths of the C – C bonds. In addition, coincidence of this sort may be due to the use of the simplified McConnel – Robertson expression, which, in its complete form, includes a term that takes into account deviation from axial symmetry [13]. One also cannot exclude the certain contribution of contact interaction [14]. The latter three factors evidently also make the greatest contribution to the error in the calculation of the induced shifts (Table 2).

It is curious to note that the deviations of the calculated Δ values from the experimental value prove to have different signs for 1e = Me and 1a = Me. Considering this to be result of rapid (on the PMR time scale) inversion of the nitrogen atom [15], one can, from the expression

$$x\cdot\Delta_{1e\text{-}\mathrm{Me}}\mathrm{calc}+(1-x)\cdot\Delta_{1a\text{-}\mathrm{Me}}\mathrm{calc}=\Delta_{1\text{-}\mathrm{Me}}\mathrm{exp}$$

TABLE 2. Induced Chemical Shifts (in parts per million) of the trans Isomer of I in the Double-Chair Conformation

Protons	Δ^{exp}, ppm	Δ^{calc}, ppm[a]	$\Delta^{exp} - \Delta^{calc}$, p	Proton coordinates, Å			K^b	Error, %[c]
				X	Y	Z		
2*a*	7,455	7,453	0,002	2,317	−1,200	0,316	1	0,030
2*e*-Me	2,613	3,070	−0,457	2,592	−2,749	−1,587	1	17,502
3*e*	14,750	14,566	0,184	3,585	0,0	−1,450	1	1,247
3*a*	12,870	12,320	0,550	2,117	0,0	−2,460	1	4,271
9	8,750	8,712	0,038	0,357	0,0	1,009	1	0,440
10	12,920	13,276	−0,356	0,157	1,257	−1,735	1	2,755
5*a*	12,880	11,775	1,105	0,357	2,515	1,009	1	8,578
5*e*	12,840	13,450	−0,610	0,357	3,388	−0,504	1	4,748
7*e*-tertBu	1,400	1,469	−0,069	−4,226	1,257	0,726	1	4,944
7*a*-tertBu	1,400	0,947	0,453	−1,329	1,257	2,774	0	32,351
1*e*-Me	3,420	2,980	0,440	−0,119	−2,692	0,168	1	12,876
1*a*-Me	3,420	5,446	−2,026	−0,119	−1,200	−2,415	0	59,232
2*e*	7,455	4,998	2,457	2,317	−2,074	−1,197	0	32,956
2*a*-Me	2,613	3,676	−1,063	2,592	−1,200	1,095	0	40,700
8*a*	4,522	4,647	−0,125	−1,897	0,0	−1,009	1	2,762
7*a*	2,750	2,708	0,042	−1,697	1,257	1,735	1	1,511
7*e*	2,750	2,283	0,467	−3,123	1,257	0,726	0	16,997
6*e*	2,550	2,473	0,077	−1,897	3,388	0,504	1	3,025
8*e*	3,470	3,304	0,166	−1,897	−0,874	0,504	1	4,778
6*a*	4,000	4,697	−0,697	−1,897	2,515	−1,009	1	17,431

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[a] Calculated from Eq. (1); the coordinates of the Eu, O, and C_4 atoms are, respectively (4.316; 3.129; 0.850), (2.758; 2.119; −0.228), and (2.053; 1.257; −0.726).

[b] The symbol K is an index that indicates that a given proton participates (K = 1) or does not participate (K = 0) in the minimization and calculation of compatibility factor R.

[c] The error is equal to $(\Delta^{exp} - \Delta^{calc}) \cdot (\Delta^{exp})^{-1} \cdot 100\%$.

estimate the predominant equatorial orientation (x) of the N-methyl group, which turns out to be on the order of 83% (± 12% under the condition that the limiting error in the Δ^{calc} value for $N-CH_3$ is 0.3 ppm).

EXPERIMENTAL

The PMR spectra of CCl_4 solutions of the compounds were measured with a JNM-PS-100 spectrometer (JEOL) with an operating frequency of 100 MHz at 27° with tetramethylsilane as the internal standard. Tris(heptafluorodimethyloctanedionato)europium (600 mg per 0.5 ml of CCl_4) was added in ∿0.02-ml portions to a solution of 12 mg of I. The shift reagent was synthesized in the Perm Pharmaceutical Institute by the method in [16] and was purified by repeated crystallization, sublimation, and vacuum drying over P_2O_5. The shifting capacity of the reagent was verified in a 0.2 M solution of morpholine by the method in [17].

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PREPARATION OF 1-AMINOMETHYLENEMERCAPTO DERIVATIVES OF 2,4,6,8-TETRATHIAADAMANTANE AND ADAMANTANE

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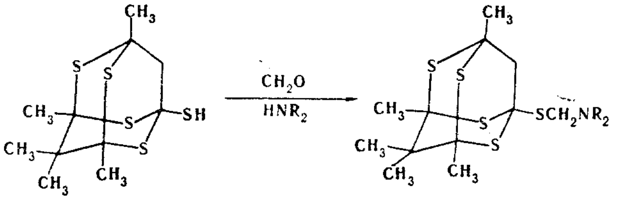
1-Aminomethylenemercapto derivatives of 3,5,7,9,9-pentamethyl-2,4,6,8-tetrathiaadamantane and adamantane were obtained by aminomethylation of 3,5,7,9,9-pentamethyl-2,4,6,8-tetrathiaadamantane-1-thiol and adamantane-1-thiol.

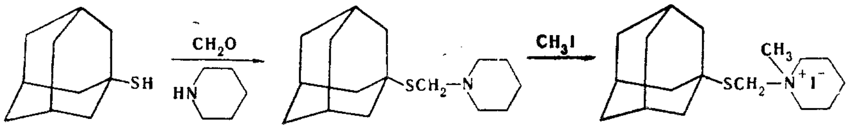
Amino derivatives of adamantane display physiological activity, including antivirus action [1]. In this connection, the amino derivatives of hetero-analogs of adamantane seem of interest.

In the present paper we describe a number of 1-aminomethylenemercapto derivatives obtained by aminomethylation of 3,5,7,9,9-pentamethyl-2,4,6,8-tetrathiaadamantane-1-thiol (I) and adamantane-1-thiol (II). The hydrogen atom in the SH group of these thiols was found to be sufficiently labile to undergo the Mannich reaction with formaldehyde and secondary amines (dimethylamine, diethylamine, piperidine, hexamethyleneimine, morpholine, and piperazine). 1-Aminomethylenemercapto derivatives of 2,4,6,8-tetrathiaadamantane (III-VII) and of adamantane (IX-XII) are formed in good yields, and good yields of bis-(adamantylmethylenemercapto) derivatives of piperazine (VIII and XIII) are also obtained in reaction with piperazine (Table 1).



I

III, IV



II

XII

XII a

III R = CH_3; IV R = C_2H_5

The PMR spectra of 2,4,6,8-tetrathiaadamantane derivatives III-VIII contain a singlet at 4.0-4.55 ppm, which is characteristic for the SCH_2N grouping; signals of protons of CH_3 groups were observed at 1.27-1.49 ppm, and the singlet at 1.97-2.24 ppm corresponded to the

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