Chem. Pharm. Bull.
29(6)1501—1509(1981)

Nuclear Magnetic Resonance Studies of 2-Amino- and 2-Substituted Amino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenols

MICHIO MOTOHASHI,* EIJI MIZUTA, and MASAO NISHIKAWA

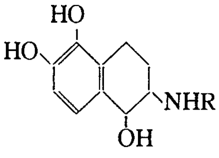
Central Research Division, Takeda Chemical Industries, Ltd.,
Jusohonmachi, Yodogawa-ku, Osaka 532, Japan

(Received October 3, 1980)

Carbon-13 and proton nuclear magnetic resonance studies were conducted on 2-amino- and 2-substituted amino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenols, which have a very potent β_2-adrenoceptor-stimulating activity, especially in the *trans* isomer. The results suggested that in the *trans* isomer, the saturated part of the tetralin skeleton takes a half-chair conformation having both hydroxy and alkylamino groups in di-equatorial orientation. The structure coincides with the crystal structure of *trans*-2-cyclobutylamino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenol hydrobromide. The measurement of proton relaxation times of the *trans*-2-isopropyl derivative in solution indicated the existence of two equilibrium conformers related to the isopropylamino group, one having a conformation very similar to that of the cyclobutylamino analog in its solid state with respect to the C(2)-N$^+$ bond.

Keywords——aminotetralinol; catecholamine; β_2-adrenergic stimulant; spin-lattice relaxation time; CMR; PMR

Two of the present authors (M.M. and M.N.) and their coworkers have reported the synthesis of potent β-adrenoceptor-stimulating 2-amino- and 2-substituted amino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenols (**1**).[1–3] The O,N-*cis* and *trans* isomers of **1** have both been stereoselectively prepared, and the latter isomer was found to be 10 to 100 times more potent than the former. The very potent β_2-adrenergic-stimulating activity of **1** indicates that the steric arrangement of the functional groups of these compounds is favorable for interaction with the β_2-adrenoceptor, and very important information about the structure of the receptor can be obtained by analyzing the orientation of the functional groups in these molecules. Structure analysis by X-ray diffraction techniques[4] of *trans*-2-cyclobutylamino-5,6-dihydroxy-1,2,3,4-tetrahydro-1-naphthalenol (**1d**, *trans* isomer), which has the most potent β_2-adrenergic activity in *in vitro* assay among the compounds **1** prepared, indicated that the cyclohexene moiety of the compound is in a half-chair conformation with both the benzylic hydroxy and the cyclobutylamino groups occupying di-equatorial positions. Comparison of the crystal structure with that of *dl*-isoproterenol sulfate[5] showed that both compounds have a similar conformation of the aliphatic side chain including the alkylamino group, providing additional support for the hypothesis that this orientation of the aliphatic part of both compounds is the one actually required for the elicitation of β_2-activity.



1

Chart 1

The analysis of the conformation of potent β-adrenoceptor-stimulating agents in solution may provide further information about the interaction between β-agonists and the receptor. For this purpose, nuclear magnetic resonance (NMR) studies of **1** and some related compounds were done.

Carbon Magnetic Resonance (CMR) Spectra

Natural abundance CMR spectra were obtained by ^{1}H-noise decoupling, ^{1}H off-resonance decoupling and ^{1}H selective decoupling techniques. The results are shown in Table I. Careful

Table I. ^{13}C-Chemical Shifts of Aminotetralinols[a,b]

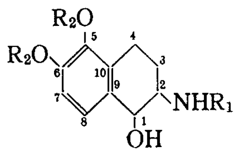
Compound	**1a**	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**	**1h**	**1i**	**2a**	**2b**[16]
R_1	-H	$-CH_3$	-isoPr	-cBu	-tBu	-H	$-CH_3$	-isoPr	-tBu	-isoPr	-tBu
R_2	-H	-H	-H	-H	-H	-H	-H	-H	-H	$-CH_3$	$-CH_3$
Configuration at C(1)-C(2)	*trans*	*trans*	*trans*	*trans*	*trans*	*cis*	*cis*	*cis*	*cis*	*trans*	*trans*
Salt	HBr	HBr	HBr	HBr	1/2F[c]	HBr	HBr	1/2F	HBr	HCl	HCl
C (1)	70.4	69.3	70.0	69.2	70.4	66.5	64.8	65.1	67.4	70.0	70.3
C (2)	54.5	61.8	58.6	59.5	57.5	52.1	59.8	55.6	55.3	58.7	57.5
C (3)	24.8	22.1	(23.4)[d]	(22.8)	26.4	(21.1)	(20.0)	(20.3)	(22.6)	(23.6)	26.7
C (4)	22.1	22.1	(22.3)	(21.8)	22.5	(22.3)	(22.5)	(22.5)	(22.2)	(22.2)	22.5
C (5)	141.4	141.4	141.3	141.4	141.4	141.7	141.7	141.7	141.7	(145.4)	(145.4)
C (6)	144.0	144.1	144.0	144.1	144.0	144.7	144.8	144.8	144.8	(152.1)	(152.1)
C (7)	115.1	115.1	115.1	115.2	115.1	115.1	115.2	115.3	115.2	112.5	112.5
C (8)	119.9	120.0	120.0	120.4	120.0	123.3	123.4	123.5	123.3	124.2	124.2
C (9)	129.4	129.3	129.5	129.0	129.6	128.3	128.1	128.3	128.5	(130.4)	130.5
C (10)	124.7	124.5	124.7	124.6	124.7	124.5	124.6	124.9	124.5	(130.5)	130.5
C (11)		31.0	49.8	51.0	60.0		31.2	48.4	59.6	49.9	60.0
C (12)			20.1	27.6	26.4			19.8	26.4	20.0	26.3
C (13)			18.8	27.9	26.4			19.0	26.4	18.8	26.3
C (14)				15.5	26.4				26.4		26.3
C (15)										(56.7)	(56.7)
C (16)										(61.0)	(61.1)

[a] $c=0.16$ M in D_2O, at 40°, δ from TMS, ppm.

[b] See references 2—4 for all compounds except **2b**.

[c] Hemi fumarate.

[d] Values in parentheses may be interchanged.



R_1 -Me: $-CH_3$ [11]
-isoPr: $-CH(CH_3)_2$ [11(12,13)]
-cBu: $-CHCH_2CH_2CH_2$ [11,12,14,13]
-tBu: $-C(CH_3)_3$ [11(12,13,14)]
R_2 $-CH_3$ [15,16]

examination of the data in Table I and also the proton magnetic resonance (PMR) spectral data in Table III clearly show that all *trans* isomers have similar conformations. The same seems to be true for the *cis* isomers.

The chemical shift of C(1) is scarcely influenced by the difference between H and CH_3 in R_2 or by the kind of alkyl substituents, R_1, on the amino group. It is largely determined by the configuration around the C(1)—C(2) bond, and is 69.2—70.4 ppm in the *trans* isomer and 64.8—67.4 ppm in the *cis* one. As will be mentioned in the following section, from the coupling constant of the methine proton H(1) attached to C(1), the *trans* isomer (J=8—10 Hz) was assumed to have di-equatorial orientation of the benzylic hydroxy and the alkylamino groups and the *cis* isomer (J=3—4 Hz) to have axial-equatorial or equatorial-axial orientation. Senda *et al.*[6] have reported that the C(1) chemical shift of 1-tetralinol derivatives, having a pseudo-axial hydroxy group at C(1), appears at somewhat higher field than that of the derivatives having a pseudo-equatorial group. They also showed that the C(1) chemical shift in 1-tetralinol (3) itself was 67.7 ppm. On the other hand, Iwamura *et al.*[7] assumed from their study of the infrared spectrum that the hydroxy group in **3** is predominantly axial because of the allylic strain exerted between the hydroxy group and the proton, H(8), attached at C(8). In view of these reports, di-equatorial orientation of the two substituents on C(1) and C(2) in the *trans* isomer of **1** is supported by the chemical shift of C(1). The obvious difference of the C(1) chemical shifts between the *cis* and *trans* isomers shown in Table I suggests that the orientation of the hydroxy group on C(1) is different between these two isomers. Thus, in the *cis* isomer with a C(1) chemical shift resembling that of **3** the hydroxy group will take the axial conformation, the alkylamino group being equatorial. The C(2) peak of **1** was easily assigned by the ^{1}H off-resonance technique and by the change due to the substituents, R_1.

Table II. SCS Calculation for Aromatic Carbons (ppm from TMS)

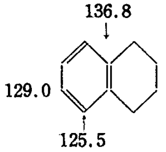
Carbon	δ_{calc}	1c		1h	
		δ_{obs}	$\Delta\delta^{a)}$	δ_{obs}	$\Delta\delta^{a)}$
C (5)	139.8	141.3	−1.5	141.7	−1.9
C (6)	143.3	144.0	−0.7	144.8	−1.9
C (7)	118.2	115.1	+3.1	115.3	+2.9
C (8)	119.4	120.0	−0.6	123.5	−4.1
C (9)	130.7	129.5	+1.2	128.3	+2.4
C (10)	126.0	124.7	+1.3	124.9	+1.1

a) $\Delta\delta=\delta_{calc}-\delta_{obs}$

SCS parameters (plus value indicates a downfield shift)[8]

	C(*a*)	*ortho*	*meta*	*para*
-OH	+26.9	−12.6	+1.8	−7.9

1,2,3,4-tetrahydronaphthalene[9]



The chemical shift also shows some dependency on the orientation of the substituents around the C(1)—C(2) bond, but the substituent (R_1) on the amino group exerts a much larger influence. In the region from 22 to 27 ppm, C(3) and C(4) signals were observed. For some of the compounds which show two well separated peaks, the ^1H selective decoupling technique was applied to determine the assignment. The results are shown in Table I.

The chemical shifts of the aromatic carbons in **1** are hardly affected by R_1. In ^1H off-resonance spectra, four singlets and two doublets were observed. Two of the former at low field (141—145 ppm) were assigned to C(5) and C(6). Further assignment was made by the calculation of the substituent chemical shift (SCS). Observed and calculated chemical shifts are listed for **1c** and **1h** in Table II. There are some small discrepancies in the table which may be due to the difference of the solvent used, *i.e.*, the spectra of **1** were obtained with D_2O solution whereas the parameters used for the calculation of the chemical shift were taken from data obtained with cyclohexane solution. However, such discrepancies did not result in any ambiguity in the CMR assignment.

The difference of chemical shifts between the *trans* and *cis* isomers of **1** was largest at C(8), the former resonating at about 3 ppm higher field than the latter. The higher shift of the *trans* isomer can be explained by the allylic strain brought about between the equatorial hydroxyl at C(1) and the proton attached to C(8). A definite chemical shift difference was also observed for C(9), though it was smaller. Orientational difference of the hydroxy group on C(1) may cause this difference. These considerations concerning the chemical shift of the aromatic carbons consistently support the preceding assumption of the axial-equatorial orientation of the benzylic hydroxy and the alkylamino groups in the *cis* isomer.

PMR Spectra

Table III shows the PMR spectral data of the aminotetralinol, **1** and **2**, measured in various solvents. A PMR spectrum of **1c** in D_2O is shown in Fig. 1 as a typical example. In the region of the aromatic protons, two doublets were observed for the *trans* isomer with a coupling constant of 8—9 Hz. Measurements of the nuclear Overhauser effect (NOE) between these two aromatic protons and H(1) were used to determine the assignment. In the *cis* isomer, these signals were fused into one peak.

The signal of H(1) appeared at 4—5 ppm. The *trans* isomer resonated at slightly higher field than the *cis* isomer and exhibited a coupling constant of 8—10 Hz, indicating the axial orientation of both H(1) and H(2). The coupling constants of the *cis* isomer were 3—4 Hz, which shows that the two protons were *gauche* to each other. The signal of H(2) in the *trans* isomer was a double-double-doublet as shown in Fig. 1. The coupling constant, $J_{H(1)-H(2)}$ was determined to be 8.7 Hz from the splitting of the H(1) signal and the remaining coupling constants 11.7 and 3.4 Hz were inevitably assigned to $J_{H(2)-H(3)}$. The existence of a large coupling constant, 11.7 Hz, means that H(2) must be in axial orientation, and this result is consistent with the assumption of the equatorial orientation of the alkylamino group mentioned in the previous section.

TABLE III. ^{1}H-Chemical Shifts of Aminotetralinols[a]

Compd.	Salt	Solv.[b]	H(8) (d, s)	H(7) (d, s)	H(1) (d)	H(2) (d, d, d)	OCH_3 (s)	OCH_3 (s)	
1a	HBr	A	6.99 (8.5)	6.83 (8.5)	— (8.9)	3.37 (3.5, 8.9, 11.3)			
1b	HBr	A	6.98 (8.4)	6.85 (8.4)	4.73 (8.8)	3.26 (3.1, 8.8, 11.0)			$-CH_3$ 2.85 (s)
1c	HBr	A	7.00 (8.5)	6.87 (8.5)	4.78 (8.7)	3.40 (3.4, 8.7, 11.7)			$-CH(CH_3)_2$ 3.73 (sept, $J=6.4$) $-CH_3$ 1.38 (d, $J=6.4$) $-CH_3$ 1.49 (d, $J=6.4$)
1d	HBr	B	6.94 (8)	6.70 (8)	4.61 (8)	3.05 (3, 8, 11)			$-CH(CH_2)(CH_2)=$ 3.00 (sept, $J=8$)
1e	F[c]	A	6.99 (8.7)	6.85 (8.7)	4.72 (9.4)	3.42 (3.5, 9.4, 11.9)			$-C(CH_3)_3$ 1.48 (s)
1f	HBr	A	6.89 (s)	6.89 (s)	— (3.3)	3.56 (3.3, 6.0, 9.0)			
1g	HBr	A	6.86 (s)	6.86 (s)	4.85 (3.5)	3.34 (3.5, 4.2, 11.9)			$-CH_3$ 2.85 (s)
1i	HBr	A	6.86 (s)	6.86 (s)	4.84 (3.4)	3.69 (3.4, 6.6, 9.7)			$-C(CH_3)_3$ 1.50 (s)
2a	HCl	A	7.30 (8.6)	7.04 (8.6)	4.81 (8.2)	3.41 (3.0, 8.2, 11.6)	3.88 (s)	3.78 (s)	$-CH(CH_3)_2$ 3.70 (sept, $J=6.0$) $-CH_3$ 1.45 (d, $J=6.0$) $-CH_3$ 1.40 (d, $J=6.0$)
2a	Base	C	7.26 (8.4)	6.82 (8.4)	4.29 (8.4)	2.70 (3.0, 8.4, 10.9)	3.86 (s)	3.80 (s)	$-CH(CH_3)_2$ 3.05 (sept, $J=6.2$) $-CH_3$ 1.13 (d, $J=6.2$) $-CH_3$ 1.06 (d, $J=6.2$)
2a	HCl	B	7.23 (9)	6.94 (9)	4.72 (9)	3.23 (3, 9, 12)	3.77 (s)	3.69 (s)	$-CH(CH_3)_2$ — $-CH_3$ 1.30 (d, $J=6$) $-CH_3$ 1.36 (d, $J=6$)
2b	HCl	A	7.33 (8.7)	7.09 (8.7)	4.77 (8.6)	3.47 (3.2, 8.6, 11.8)	3.90 (s)	3.80 (s)	$-C(CH_3)_3$ 1.50 (s)
2b	Base	C	7.29 (8.6)	6.82 (8.6)	4.18 (8.8)	2.67 (3.2, 8.8, 11.2)	3.84 (s)	3.79 (s)	$-C(CH_3)_3$ 1.17 (s)
2b	HCl	B	7.24 (9)	6.93 (9)	4.61 (9)	3.30 (3, 9, 12)	3.76 (s)	3.68 (s)	$-C(CH_3)_3$ 1.39 (s)
2c[d]	HCl	B	7.21 (9)	6.95 (9)	4.62 (9)	3.09 (3, 9, 12)	3.79 (s)	3.66 (s)	$-CH(CH_2)(CH_2)=$ 3.96 (sept, $J=6$)

a) δ ppm, T=36—40°, $c=0.2-0.25$ M.

b) A: D_2O, B: d_6-DMSO+D_2O, C: $CDCl_3$+D_2O.

c) Hemi fumarate.

d) R_1=cBu, R_2=$-CH_3$.

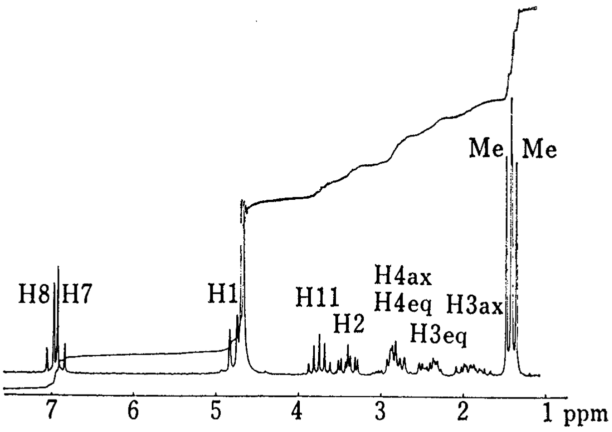


Fig. 1. ^{1}H-NMR Spectrum of **1c** (c=0.2 M in D_2O at 40°)

The signals due to H(3) appear at 2.0—2.5 ppm in **1c**. By the decoupling technique, the multiplet near 2.5 ppm was assigned to H(3eq) and that near 2.0 ppm to H(3ax). H(4ax) and H(4eq) were in the unresolved multiplet near 2.85 ppm. To determine the coupling constants between H(3) and H(4), the resolution of the spectrum was improved by measurement at high temperature. The spectrum of **1c** obtained at 90° showed no essential change in the whole spectral profile, including the coupling constants, from the spectrum obtained at room temperature, but the peaks were sharp enough for analysis of the coupling constants, as is clear from the spectrum of H(3ax) in Fig. 2. Of the sixteen peaks which theoretically exist, fifteen were separately observed (Fig. 2) and, assuming ABX-type coupling for H(4ax), H(4eq)

Table IV. Observed and Calculated Coupling Constants

Protons	**1c**[a]	**1d**[b]	**1d**[c]	Half-boat[d] conformation
H(1)-H(2)	8.5(Hz)	162(°C)	8.8(Hz)	11.7(Hz)
H(2)-H(3ax)	11.3	180	12.1	9.1
H(2)-H(3eq)	3.5	77	1.1	6.2
H(3ax)-H(4eq)	6.3	46	6.1	7.4
H(3ax)-H(4ax)	9.9	180	12.1	9.5
H(3eq)-H(4eq)	4.1	59	2.7	8.4
H(3eq)-H(4ax)	5.6	75	0.5	3.4
H(3ax)-H(3eq)	13.4			
H(4ax)-H(4eq)	17.4			

[a] Coupling constant in D_2O at 90°.
[b] Tortional angle in the crystalline state.[4]
[c] Calculated coupling constant in the crystalline state.
[d] Coupling constant.

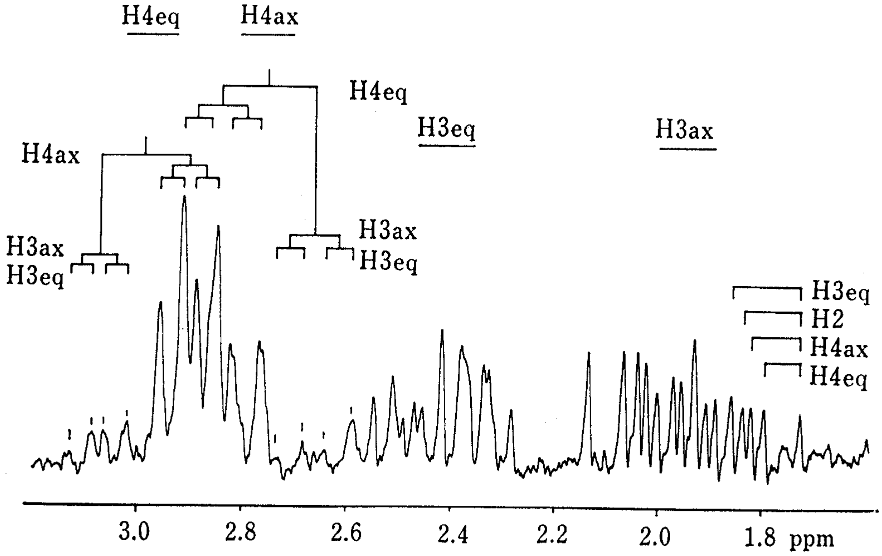


Fig. 2. ^{1}H-NMR Spectrum of H(3) and H(4) of **1c** at 90° in D_2O

and H(3ax), $J_{H(3ax)-H(4ax)}$ and $J_{H(3ax)-H(4eq)}$ were estimated to be 9.9 and 6.3 Hz, respectively. Similarly, for H(4ax), H(4eq) and H(3eq), $J_{H(3eq)-H(4ax)}$ and $J_{H(3eq)-H(4eq)}$ were estimated to be 5.6 and 4.1 Hz, respectively. Several methods have been proposed to calculate the coupling constant of the vicinal protons from their dihedral angle and *vice versa*.[10-12] From the dihedral angles obtained by the X-ray analysis of **1d**,[4] coupling constants of proton signals due to the saturated part of the tetralin ring in **1d** were calculated by the equation derived by Wohl.[12] The values obtained are listed in Table IV together with the coupling constants of **1c** estimated from its high temperature spectrum. The table also shows the coupling constants calculated from the dihedral angles in a typical half-boat conformation of the tetralin ring constructed with Büchi's Dreiding stereomodel. The values estimated for **1c** were intermediate between those calculated for **1d** and those for the Dreiding model, suggesting that the conformation of **1c** in aqueous solution is a kind of half-chair. The conformation was retained at high temperature (90°) and in DMSO or even nonpolar chloroform solutions (Table III), as well as in the crystalline state. Moreover, the substituent, R_1, did not produce any noticeable change in it. This evidence strongly suggests that the conformation elucidated in this and the previous reports is energetically preferable for the alkylamino tetralinols, **1**.

Conformation of the Alkylamino Group

To determine the preferred orientation of the alkyl group on the nitrogen atom of **1c**, the proton spin-lattice relaxation time and the NOE were used. According to Akasaka,[13] the correlation between the spin-lattice relaxation time of a proton i, $(T_1)_i$, and the internuclear distance of protons i and j, r_{ij}, is expressed by the following equation, under the condition $\omega_H^2\tau_c^2 \ll 1$:

$$(T_1)_i^{-1} = 3/2 \cdot \gamma_H^4 \hbar^2 \Sigma(r_{ij}^{-6})\tau_c \qquad (1)$$

where ω_H and γ_H are the NMR frequency and the proton gyromagnetic ratio, respectively. The symbol $\hbar$ is the Planck constant divided by 2π. These three are all known constants. The correlation time represented by τ_c is a function of the molecular size, the nature of the solvent, the concentration and the solution temperature. In the case of a small molecule, however, τ_c is usually smaller than 10^{-10} sec and the conditional formula holds.

Using the method developed by Chachaty and his collaborators,[14] we examined the conformation of **1c**. The method is based on the premise that τ_c for every proton is the same. Since the molecule **1c** is semi-rigid, the premise should be correct at least for the protons attached directly to the tetralin skeleton. As for the alkylamino side chain, it is necessary in order to apply this method to show that the movement of the side chain is not faster than the overall isotropic reorientation of the molecule. The correlation times of ^{13}C except methyl and quaternary carbons, were determined from T_1 values of the carbons in the molecule, they were $(0.26 \pm 0.03) \times 10^{-10}$ sec ($c = 0.1$ M, T$=40°$), indicating no extra rapid movement. Thus, by assuming one conformation, r_{ij} values can be determined geometrically and substituted in equation 1, together with $(T_1)^{-1}$ obtained experimentally as described later, to calculate τ_c for each proton i on the skeleton. Then the mean value of τ_c, $\bar{\tau}_c$, and the standard deviation, τ_{SD}, are computed and a factor, R, used as a measure of invariability of τ_c, is defined by the equation, $R = \tau_{SD}/\bar{\tau}_c$. Repeating the calculation for various possible conformations lead to the selection of the one which yielded the smallest R. Proceeding with this calculation, we estimated the possible conformation. The tetralin group was assumed to be in a half-chair form. The coordinates of the carbons forming this ring and three oxygens and a nitrogen attached directly to this ring were taken from the crystallographic data of **1d**.[4] The protons on this skeleton were reasonably situated but those which could be deuterated in D_2O were neglected since they caused little interaction with the relaxation time of the protons in question. For the methyl protons which are not fixed in the staggered position, but which rotate rapidly around the axis in the NMR time scale, it is assumed that the probability of existence of protons in the staggered position is higher than in other positions. The orientation of the two methyls in the isopropyl group was assumed to be fixed in the staggered position. The bond lengths of C–C and C–H were also assumed to be 1.54 and 1.09 Å, respectively, and the bond angle to be 109.5°. To calculate T_1, the C(2)–N$^+$ and N$^+$–C(11) bonds were rotated independently at an interval of 5°. Conformations in which the Van der Waals radius of a proton overlaps with that of another were rejected.

The $(T_1)_i^{-1}$ values were estimated by least-squares fit against the semilogarithmic plot of initial recovery of the proton longitudinal magnetization as a function of the time separation between the 180° and 90° pulses (Fig. 3),[14] and are listed in the second column of Table VI. The protons, H(4ax) and H(4eq), were unresolved in the spectrum. However, since they were located far from the isopropyl group, the same (T_1) value was assigned to them.

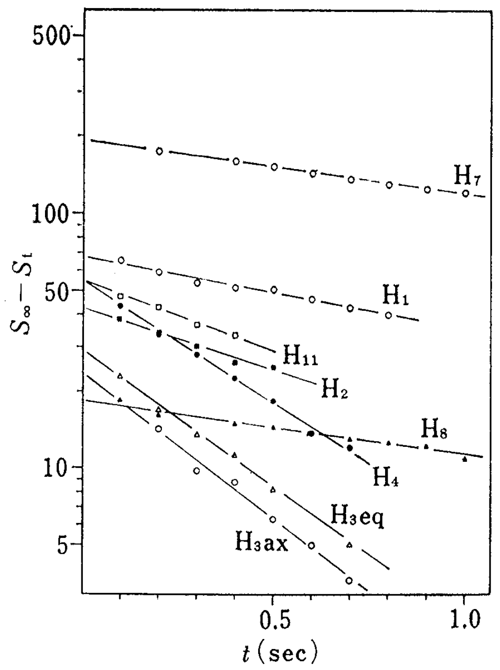


Fig. 3. Semilogarithmic Plot of the Recovery of the Proton Longitudinal Magnetization as a Function of the Time Separation between the 90° and 180° Pulses

The vertical scale is arbitrary.

The factor R calculated for each conformation is illustrated on the contour map in Fig. 4, with dihedral angles of C(2)–N$^+$, θ_4, and N$^+$–C(11), θ_5, defined in accordance with the preceding paper.[4] Two minima, A and B, were detected on the map. The conformers corresponding to these two minima are shown in Table V with their R values. Their Newman projections are shown in Chart 2, which clearly shows that both conformers are stereochemically favor-

Table V. Minima of the R Value

Conformer	θ_4	θ_5	$R^{a)}$
A	160$^{(\circ)}$	10$^{(\circ)}$	0.15
B	70	350	0.12

a) $R=\tau_{\mathrm{SD}}/\tau_{\mathrm{c}}$ $\left(\tau_{\mathrm{SD}}=\sqrt{\sum_i(\tau_i-\bar{\tau}_{\mathrm{c}})^2/n}\right)$

Table VI. Calculated and Observed Proton Spin-Lattice Relaxation Times and Correlation Times

Proton	$(T_1)^{-1}_{\mathrm{obs}}$	$(T_1)^{-1}_{\mathrm{calcd}}$	
		Conformer A	Conformer B
H(1)	0.64(sec)	0.55	0.71
H(2)	1.13	1.34	1.23
H(3eq)	2.51	2.91	2.81
H(3ax)	2.64	3.37	2.84
H(4eq)	2.15	1.97	1.92
H(4ax)	2.15	2.00	1.95
H(7)	0.49	0.40	0.40
H(8)	0.50	0.52	0.53
H(11)	1.27		
$\tau_c(\times 10^{-10}$ sec)		0.77	0.76

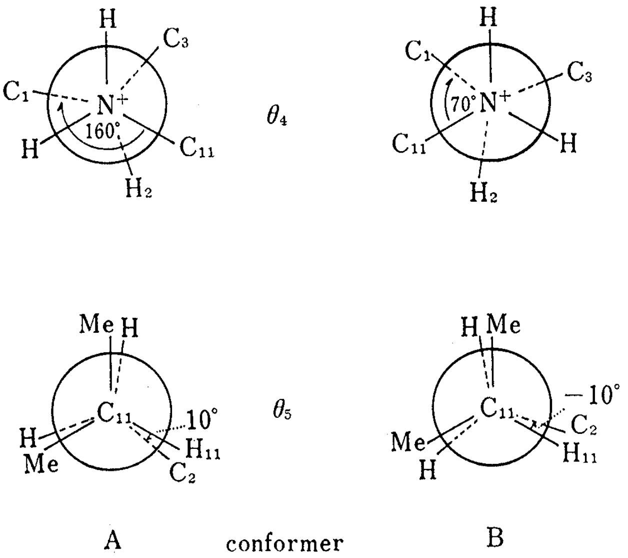


Chart 2

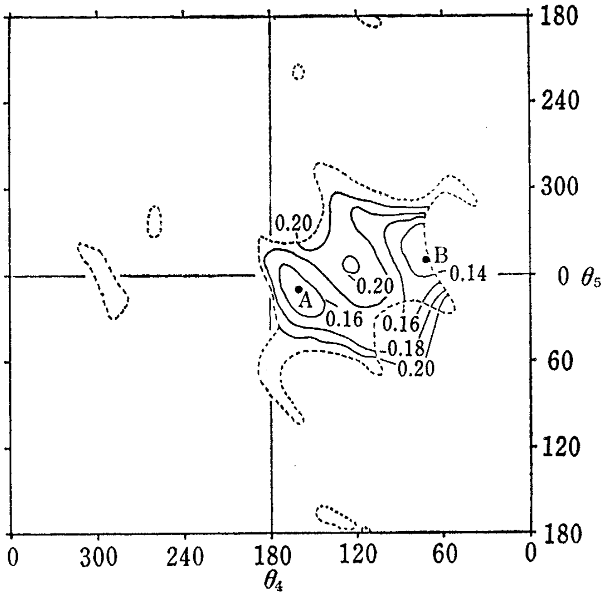


Fig. 4. *R*-Value Contour Map with respect to θ_4 and θ_5

Dashed lines are the borders of the possible areas. Contour lines of *R* larger than 0.2 were omitted.

able. $\bar{\tau}_c$ values for conformers A and B were 0.77×10^{-10} and 0.76×10^{-10} sec, respectively. With these $\bar{\tau}_c$ and r_{ij} values of the conformers, $(T_1)^{-1}$ for each skeletal proton was calculated and the results are listed in Table VI for comparison with the observed $(T_1)^{-1}$ values. The agreement between the observed and the calculated $(T_1)^{-1}$ was similar for both conformers. To determine which conformer is the real one, NOE between H(2) and the methyl protons was measured. Increments of the H(2) peak were 4.3 and 6.9% on irradiating to 1.49 and 1.38 ppm methyl, respectively. Using these values, the ratio of average internuclear distances between H(2) and the two methyls was calculated by use of the well-known equation[13] to be 1.08. The ratios estimated from conformers A and B were 3.58 and 0.28, respectively. Since these values were inconsistent with 1.08, we assumed that the molecule was in equilibrium between conformers A and B.

By using the equation derived by Navon *et al.*,[15] the contribution of staggered methyl groups in the isopropyl group to the relaxation of H(11) was estimated from the angle between the rotation axis and the radius vector, Δ, and the correlation times of H(11) were calculated to be 0.67 and 0.87×10^{-10} sec for conformers A and B, respectively, in reasonable agreement with the times of skeletal protons.

The stereostructure of conformer A was consistent with that of **1d** in its crystalline state with respect to the conformation of the aminotetralinol moiety as well as the torsional angle θ_4. The results indicate that this conformation is markedly preferred for **1** and has an important role in the β_2-adrenoceptor-stimulating activity.

Experimental

The ^{13}C-Fourier transform NMR spectra were obtained with a Varian XL-100-12 spectrometer, and the PMR spectra were measured with Varian XL-100-12 (100 MHz) and EM-390 (90 MHz) spectrometers. Proton relaxation time and NOE were measured with the XL-100-12 spectrometer. The sample for NOE and relaxation time measurements was dissolved in D_2O after lyophilization twice with D_2O, and the solution was degassed to eliminate the effect of dissolved oxygen, then the measurement tube was sealed ($c = 0.2$ M). An adequate amount of EDTA-2Na ([EDTA]/[**1c**] $\simeq 1/50$) was added to the sample solution. The pD value of the sample solution was 6.7. The initial sample temperature for Fourier transform measurement was

40°. Carbon relaxation times were measured with a JNM-FX-200 spectrometer (JEOL Ltd.) in D_2O (c=0.1 M, T=40 °).

Computation in the present study was carried out with IBM 370/48 and JEC-6 (JEOL Ltd.) computers using programs that we prepared.

***trans*-5,6-Dimethoxy-2-isopropylamino-1,2,3,4-tetrahydro-1-naphthalenol Hydrochloride** (2a)——5,6-Dimethoxy-2-isopropylamino-3,4-dihydro-1(2H)-naphthalenone hydrochloride[2] (396 mg) was hydrogenated with $NaBH_4$ (100 mg) in EtOH (20 ml) at 5—7°, and the solution was stirred for 40 min. Water was added to the reaction mixture, and EtOH was evaporated. The residue was treated with EtOAc and 10% NaCl solution. The organic layer was dried over Na_2SO_4 and the solvent was evaporated. The residue was converted into the hydrochloride by EtOH–HCl, and the resulting product was recrystallized from EtOH–Et_2O. Yield, 310 mg (68%). mp 193° (dec.). *Anal.* Calcd for $C_{15}H_{23}NO_3 \cdot HCl$: C, 59.54; H, 7.92; N, 4.74. Found: C, 59.70; H, 8.01; N, 4.64.

Acknowledgement The authors are grateful to JEOL Ltd. for ^{13}C relaxation time measurement, and to Drs. E. Ohmura, K. Morita and Y. Sanno for encouragement and helpful advice throughout this work.

References

1) M. Nishikawa, M. Kanno, H. Kuriki, H. Sugihara, M. Motohashi, K. Itoh, O. Miyashita, Y. Oka, and Y. Sanno, *Life Sci.*, **16**, 305 (1975).
2) Y. Oka, M. Motohashi, H. Sugihara, O. Miyashita, K. Itoh, M. Nishikawa, and S. Yurugi, *Chem. Pharm. Bull.*, **25**, 632 (1977).
3) K. Itoh, M. Motohashi, H. Kuriki, H. Sugihara, N. Inatomi, M. Nishikawa, and Y. Oka, *Chem. Pharm. Bull.*, **25**, 2917 (1977).
4) M. Motohashi, Y. Wada, K. Kamiya, and M. Nishikawa, *Chem. Pharm. Bull.*, **28**, 3656 (1980).
5) M. Mathew and G.J. Palenik, *J. Am. Chem. Soc.*, **93**, 497 (1971).
6) Y. Senda, J. Ishiyama, S. Imaizumi, and K. Hanaya, *J. Chem. Soc.*, *Perkin Trans* I, **1977**, 217.
7) H. Iwamura and K. Hanaya, *Bull. Chem. Soc. Japan*, **43**, 3901 (1970).
8) J.B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York, 1972, p. 90, 97, 197.
9) L.F. Johnson and W.C. Jankowski, "Carbon-13 NMR Spectra," John Wiley and Sons, New York, 1972.
10) R.U. Lemieux and J.W. Lown, *Can. J. Chem.*, **42**, 893 (1964).
11) R.J. Abraham, *Mol. Phys.*, **5**, 513 (1962).
12) R.A. Wohl, *Chimica*, **18**, 213 (1964).
13) K. Akasaka, *Kagaku* (*Kyoto*), Zokan, **67**, 25 (1976).
14) C. Chachaty, T. Zemb, G. Langlet, T.D. Son, H. Buc, and M. Morange, *Eur. J. Biochem.*, **62**, 45 (1976).
15) G. Navon and A. Lanir, *J. Magn. Reson.*, **8**, 144 (1972).
16) H. Sugihara, K. Ukawa, A. Miyake, and Y. Sanno, *Chem. Pharm. Bull.*, **26**, 411 (1978).