Registry No.—**5**, 60526-38-7; **5** *endo*-carbonate precursor, 60526-39-8; **5** *exo*-carbonate precursor, 60562-31-4; **6**, 60526-40-1; **6** *exo*-carbonate precursor, 60526-41-2; **6** *endo*-carbonate precursor, 60562-32-5; **7**, 0526-42-3; **7** *endo*-carbonate precursor, 60526-43-4; **8**, 60526-44-5; **8** carbonate precursor, 60526-45-6; **9**, 60526-46-7; **9** *exo*-carbonate precursor, 60526-47-8; **9** *endo*-carbonate precursor, 60562-33-6; **10**, 60526-48-9; **10** *exo*-carbonate precursor, 60526-49-0; **10** *endo*-carbonate precursor, 60562-34-7; dichlorovinylene carbonate, 17994-23-9; dimethylfulvene, 2175-91-9; spiro[4.2]hepta-2,4-diene, 765-46-8; 5,5-dimethyl-1,3-cyclopentadiene, 4125-18-2; spiro[4.4]-nona-2,4-diene, 766-29-0; methylcyclopentadiene dimer, 26472-00-4.

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Determination of the Configuration and Conformation of α-, β-, and Isotripiperideine by Carbon-13 Nuclear Magnetic Resonance Spectroscopy[1]

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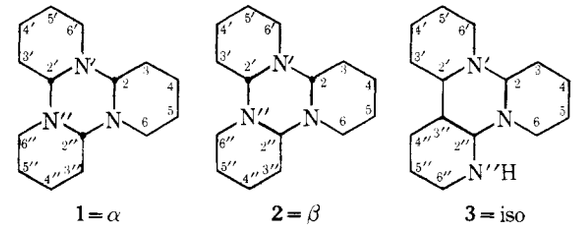
The constitution, configuration, and conformation of the three isomeric tripiperideines (α-, β-, and iso-) have been established by ^{13}C NMR spectroscopy. α-Tripiperideine (**1**) exhibits a five-line spectrum at room temperature which changes to a 15-line spectrum at low temperatures. This is due to a slowing down of the equilibration between three asymmetric topomers of conformation B, which, at room temperature, average to apparent C_3 symmetry. The conformation F of β-tripiperideine (**2**) is established by comparison of the observed ^{13}C chemical shifts with calculated ones using the approach of empirical increments. The same procedure enables one to prove the dominant configuration and conformation I of isotripiperideine (**3**). By comparison of the most stable conformations of **1**, **2**, and **3** it was possible to estimate the energetic limits of the syn-axial lone pair interaction (generalized anomeric effect) between two nitrogen atoms.

NMR spectroscopic investigations of the conformation and dynamic behavior of heterocyclic six-membered ring systems have attracted considerable interest.[3] During the last few years ^{13}C NMR investigations have provided new information about the constitution of natural products[4] and the ground state conformation[5] of a number of saturated heterocycles. In connection with our interest in dynamic ^{13}C NMR studies[6] we report here our investigation of tripiperideines. The temperature dependence of their ^{13}C NMR spectra gives information about constitution, configuration, and conformation as well as about the mechanism and the kinetics of intramolecular rate processes, in contrast to the ^1H NMR spectra of these compounds, which are complex and less informative. In this paper we present our results regarding the ground state conformation of the tripiperideines.

Constitution and Configuration. By dehydrohalogenation of *N*-chloropiperidine three isomeric trimers have been obtained.[7] The α (**1**) and β isomers (**2**) result from the normal trimerization reaction of the azomethine and differ only in the relative configuration of the three asymmetric methine carbons, whereas the iso compound is constitutionally isomeric to the α and β compounds.[8]

α- and β-tripiperideine each contain three asymmetric carbon atoms. The configurational isomers differ in their overall symmetry: one of the compounds is dissymetric (C_3 symmetry, racemic mixture of *RRR* and *SSS* chirality), the other is asymmetric (C_1 point group, also a racemic mixture in this case of *RRS* and *SSR* chirality). The assignment of the configuration of **1** and **2** is easy by ^{13}C NMR spectroscopy: at room temperature the α isomer shows five sharp signals (C_3 symmetry), the β isomer 15 (C_1 symmetry) (Figure 1).

Isotripiperideine (**3**) has only two tertiary carbon atoms (C-2 and C-2″) attached to two nitrogen atoms (signals at 80.9 and 81.8 ppm, Table I) but one tertiary carbon (C-2′) which is attached to only one nitrogen atom (64.2 ppm) and another one (C-3″) which has only carbon neighbor atoms (47.7 ppm).[9] Altogether 15 carbon signals are seen in the spectrum of **3** at room temperature. The constitution of all three isomers and



1 = α **2** = β **3** = iso

the configuration of **1** and **2** are thus directly evident from ^{13}C NMR spectroscopy.

Conformation[10] of 1. The C_3 symmetric conformation of α-tripiperideine requires axial orientation of all three lone pairs of the nitrogen atoms. In conformation A all rings are trans fused.[11] The resulting electron pair repulsion (generalized anomeric effect or "rabbit ear effect")[5a,12] destabilizes

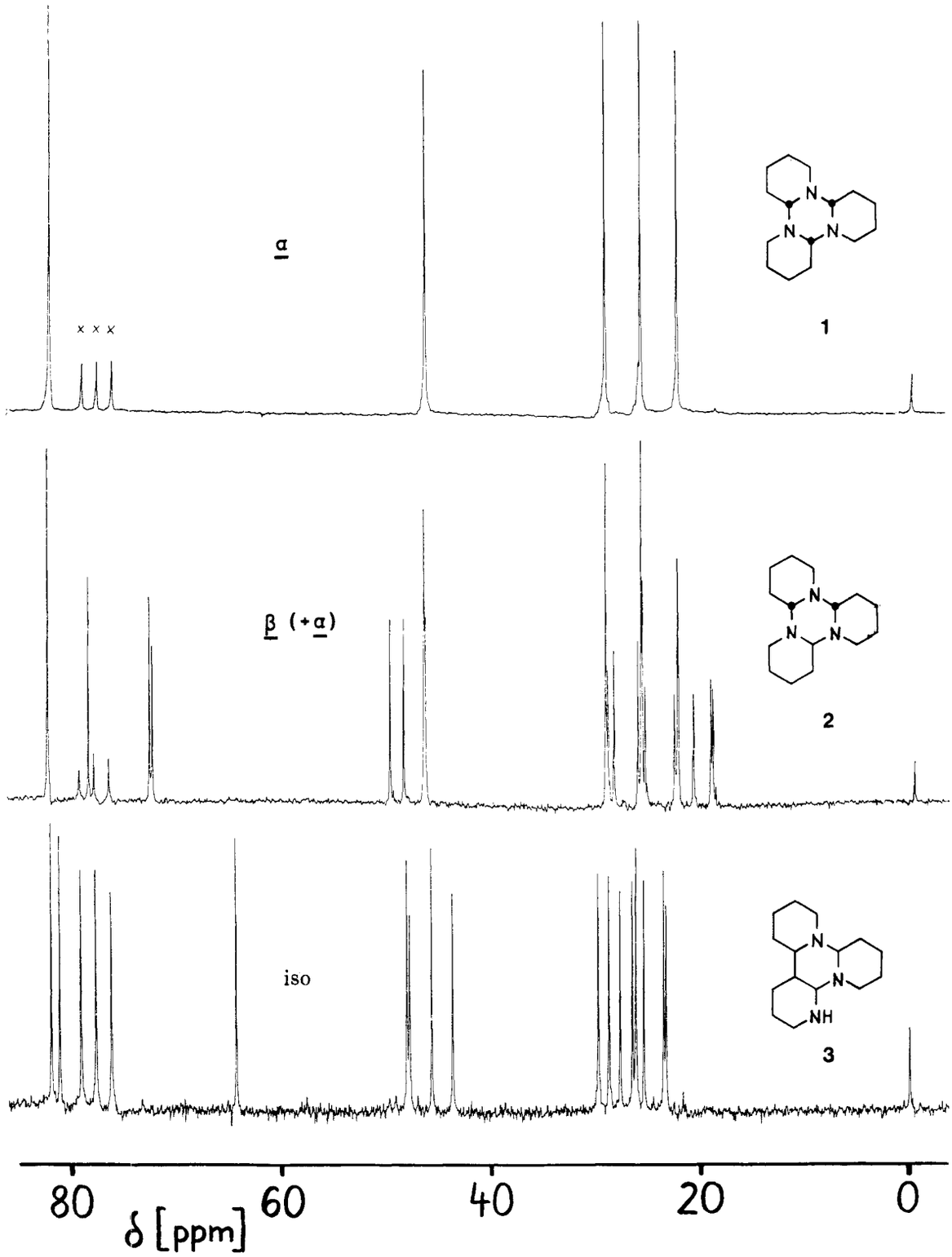


Figure 1. ^{13}C NMR spectra of tripiperideines at room temperature in $CDCl_3$ (X = solvent peaks; **2** contains about 40% of 1).

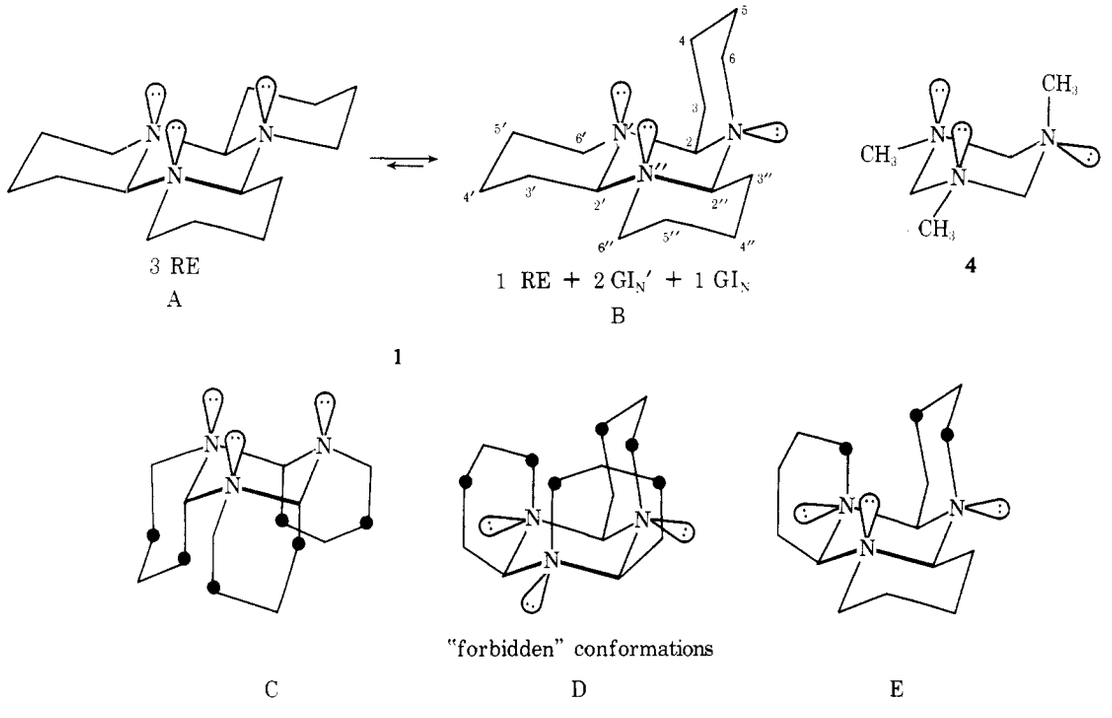
this conformation. The repulsion may be diminished through inversion of one, two, or three nitrogen atoms (conformations B, E, and D),[13] but the inversion of more than one nitrogen atom would lead to strong 1,3-diaxial interactions between the nitrogen-bound CH_2 groups. Thus the only reasonable possibility to reduce the "rabbit ear effect" RE[14] involves the conformation with one nitrogen atom having the lone pair in the equatorial position (conformation B). The number of gauche interactions[14] in B is larger than in A, but in going from A to B the 1,3 interaction of three axial lone pairs is replaced by the interaction of two lone pairs and one axially oriented piperidine ring. E has two syn-axial interactions and C and D have six; C also suffers from three rabbit ear effects. It is evident that the order of stability is A,B > E > D > C but the question remains if the energy of 2 RE is larger than 2 GI_N' + 1 GI_N[14] (i.e., B is more stable than A) or vice versa. The preference of conformation 4 for *N,N',N''*-trimethyl-1,3,5-triazane has recently been observed.[15] Considering this result one would expect B to be more stable than A.

Although conformation B is asymmetric, a rapid inter-

Table I. ^{13}C NMR Spectra of α-, β-, and Isotripiperideine

α-Tripiperideine (1)					β-Tripiperideine (2)			Isotripiperideine (3)			
		δ, ppm[a]			δ, ppm[a]			δ, ppm[a]			
δ, ppm[a,b]	m[c]	Exp[d]	Calcd[e,f]	Position	Exp[g]	Calcd[f,h]	Position	Exp[g]	m[c]	Calcd[f,i]	Position
		85.9	82.9	2′	78.1	81.0	2″	81.8	d	82.9	2 } j
82.2	d	81.8	80.2	2″	72.3	74.0	2′	80.9	d	82.9	2″ } j
		78.0	77.5	2	72.0	71.8	2	64.2	d	63.7	2′
		49.7	48.0	6′ } j	49.6	48.0	6′	48.0	t	49.6	6′
46.6	t	48.4	48.0	6″ } j	48.3	45.4	6″	47.7	d	46.6	3″
		40.6	39.3	6	46.2	44.9	6	45.6	t	48.0	6
		30.2	28.2	3′ } j	29.0	28.2	3′	43.6	t	47.1	6″
29.5	t	28.6	28.2	3″ } j	28.4	26.1	5 } j	29.6		28.6	3′
		28.2	25.6	3	26.1	26.1	5′ } j	28.6		28.2	3
		26.2	26.1	5 } j	25.7	25.6	3	27.6		26.1	5 } j
26.2	t	25.7	26.1	5′ } j	25.4	25.2	3″	26.4		26.1	5′ } j
		25.4	26.1	5″ } j	22.7	23.3	4′ } j	26.1		26.1	5″ } j
		24.5	23.3	4′ } j	20.8	23.3	4″ } j	25.3		25.0	4′
22.7	t	23.8	23.3	4″ } j	19.2	20.8	5″	23.4		24.1	4″
		18.7	17.9	4	19.0	17.9	4	23.2		23.3	4

[a] From internal Me_4Si. [b] In CD_2Cl_2 at 32 °C. [c] Multiplicity in proton off-resonance decoupled spectra: d = doublet, t = triplet. [d] In CD_2Cl_2 at −90 °C. [e] Conformation B. [f] The procedure of calculation is described in the text. [g] In $CDCl_3$ at 32 °C. [h] Conformation F. [i] Conformation I. [j] Relative assignments uncertain.



conversion between the three topomers,[16] each of them with another nitrogen atom inverted, will account for the averaged five-line spectrum of 1 at room temperature. The change of the spectrum on lowering the temperature proves that this is the case: each signal splits into three at temperatures below about −50 °C (Figure 2, details about the kinetics will be given elsewhere[31]). No signals of a molecule of C_3 symmetry remain at low temperature. Conformation A is therefore at least 1.1 kcal/mol higher in free energy than B.[17] However, because of the threefold degeneracy of conformation B we have to correct the value $\Delta G°$ for the entropy term ($T\Delta S° = RT \ln 3 = 0.49$ kcal/mol). Thus the enthalpy difference between A and B is larger than 1.1 − 0.5 = 0.6 kcal/mol. B is destabilized by three gauche interactions: two C–N–C–N segments (GI_N') and one C–C–C–N segment (GI_N). Thus it follows that

$$2\ RE > 2\ GI_N' + 1\ GI_N + 0.6\ kcal/mol \quad (1)$$

The assignment of the signals in the high-temperature spectrum of 1 which is based on literature data makes possible the grouping of corresponding resonances at low temperature. The chemical shift values in the low-temperature spectrum (Table I) in turn provide convincing proof of the proposed conformation B. Assignment of signals in this spectrum rests on comparison of the experimental chemical shifts with the values of calculated data from replacement of three CH groups by nitrogen atoms in perhydrotriphenylene (PHT) of equal configuration.[18]

Since the ^{13}C chemical shift data of the appropriate configuration of perhydrotriphenylene were not available in the literature we calculated these values by eq 2 using the parameters of Dalling and Grant, which were derived from perhydroanthracenes and perhydrophenanthrenes.[19,20c]

$$\delta_{PHT} = \delta_{const} + \delta_{vic} + \delta_{HH} \quad (2)$$

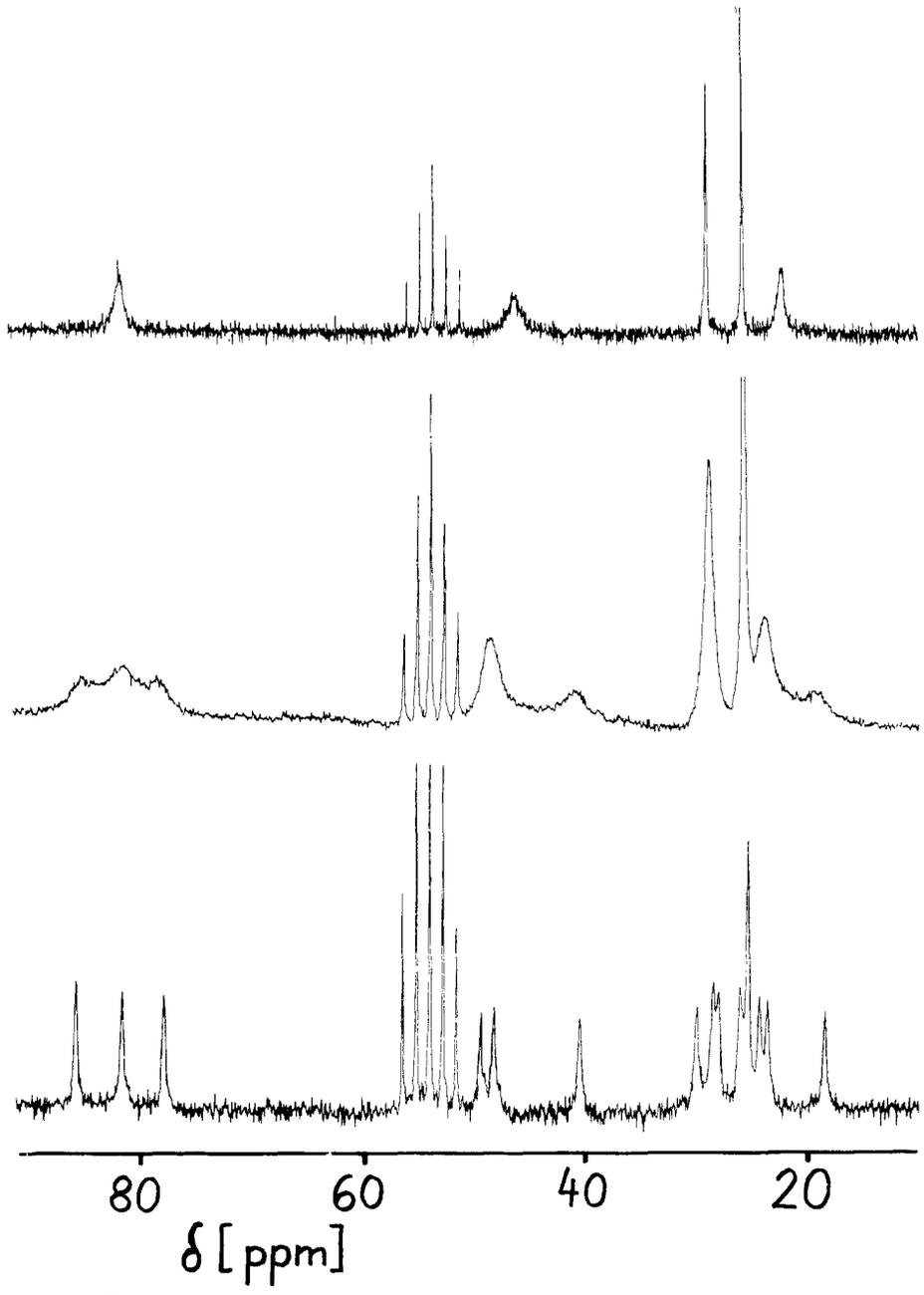


Figure 2. Temperature dependent ^{13}C NMR spectrum of 1 in CD_2Cl_2: top, −20.6 °C, middle, −49.0 °C; bottom, −67.5 °C.

where δ_{PHT} = resulting chemical shift of a carbon in perhydrotriphenylene, δ_{const} = the sum of the constitutional parameters, δ_{vic} = the sum of vicinal gauche and trans parameters, and δ_{HH} = the sum of 1,6 hydrogen–hydrogen interactions.

Replacement of the CH groups by N was then simulated by

$$\delta_{Tripip} = A\,\delta_{PHT} + B \qquad (3)$$

The parameters A and B originate from the comparison of the ^{13}C chemical shifts of *trans*-decalin and quinolizidine, a molecule which contains only one nitrogen atom.[22]

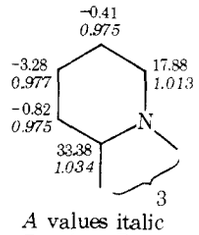
The following example illustrates the procedure for the signal of C-6″. In the analogous perhydrotriphenylene there are two carbons in α and three carbons in β position; C-6″ is involved in two V_g and one V_t interactions; one of its protons is interacting with one of the C-3′ protons. Hence the predicted chemical shift of the hydrocarbon is given by

$$\delta_{PHT}^{6''} = \underbrace{-2.49 + 2\alpha + 3\beta}_{\delta_{const}} + \underbrace{2V_g + V_t}_{\delta_{vic}} + \gamma_{HH} = 29.72 \text{ ppm}$$

The CH → N replacement for this nonbridged carbon involves one α-nitrogen effect and two γ-nitrogen effects:

$$\delta_{Tripip}^{6''} = 1.013 \cdot 29.72 + \alpha_N + 2\gamma_N = 47.99 \text{ ppm}$$

In this fashion the correction terms for CH → N substitution in our system are calculated to be as follows.[23]



A values italic
B values Roman

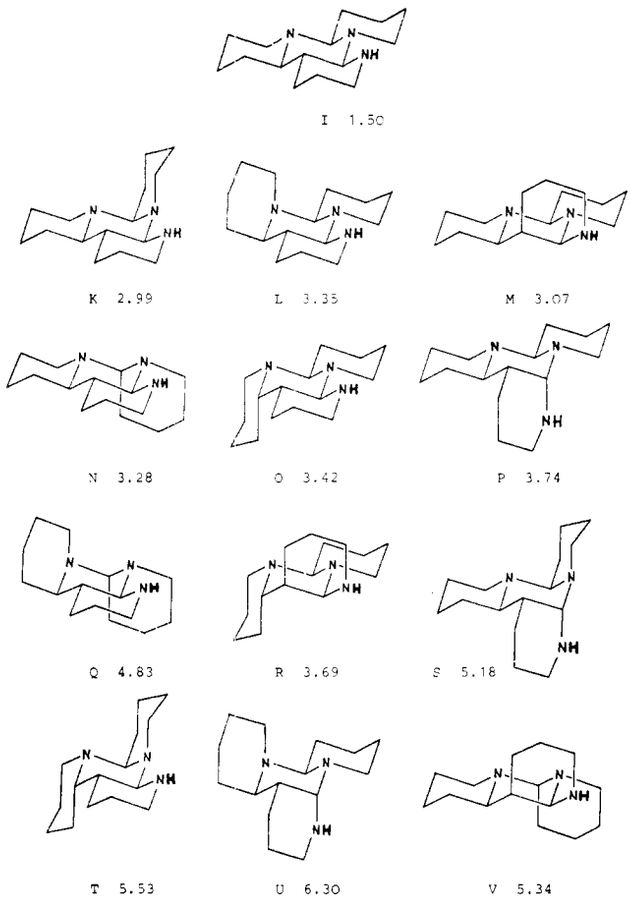


Figure 3. Standard deviations from calculated and observed ^{13}C NMR chemical shifts of some isotripiperideine structures.

The agreement of calculated and observed chemical shifts is satisfying (Table I; standard deviation 1.48 ppm).

Conformation of 2. Definite conclusions about the conformation of **2** may also be drawn from the carbon-13 chemical shifts. The three low-energy conformations (i.e., the conformations without skew pentane interactions), F, G, and H, will be considered in which the C-2″, C-3″ bond is axially oriented.

In these conformations the nitrogen atom N″ has to have an axial lone pair. From the differing steric interactions indicated below the formula[14] it can be seen that the energy difference between G and H is the same as between A and B in **1**, but because of the absence of an entropy term (0.5 kcal/mol in B) the difference in $\Delta G°$ (>1.1 kcal/mol between A and B) is smaller (>1.1 − 0.5 ≥ 0.6 kcal/mol between G and H). F is favored energetically by one gauche interaction, GI′ compared with H. The order of stability therefore should be F > H > G. The energy difference between F and H might lead to a measurable participation of H in the equilibrium. Unfortunately, because of the low stability of **2** we did not succeed in recording a low-temperature spectrum.

Table II. Observed and Calculated[a] Signals (ppm) of the Carbons in 2 Position of 2

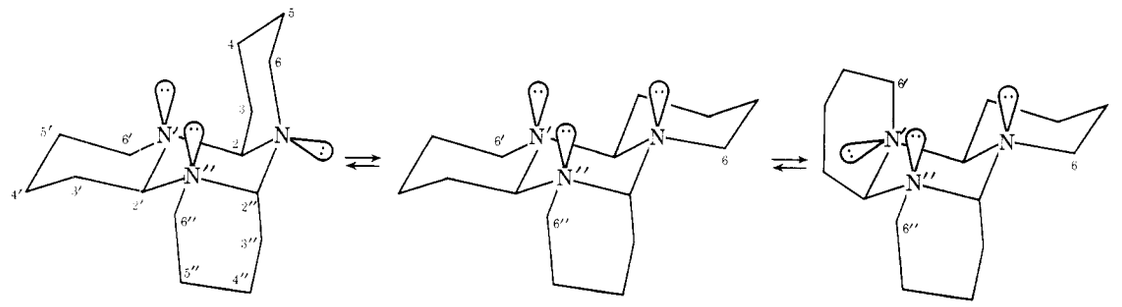
		Conformation		
Position	Obsd	F	G	H
C-2″	78.1	81.0	77.5	77.8
C-2′	72.3	74.0	74.1	68.7
C-2	72.0	71.8	77.2	74.5

[a] The procedure of calculation is described in the text.

The agreement between observed and calculated ^{13}C chemical shifts (Table I; for method of calculation see above) supports the assumption that F is the most stable conformation. A least-squares calculation yields a standard deviation of 1.70 ppm for F, 1.83 ppm for G, but 2.48 ppm for H. Hence H could be excluded. A further experimental criterion for distinguishing conformations F, G, and H is the shift of the carbon at position 6. Whereas C-6′ in H would suffer a strong upfield shift compared to C-6 and C-6″ (calculated for H: C-6 = 48.0, C-6′ = 39.3, C-6″ = 45.4 ppm; compare C-6 in B), the experimental values for all three signals are in the range of 46–50 ppm, in agreement with the calculated values for F (44.9 − 48.0 ppm). The absence of a high-field shift for C-6 (in contrast to B) results from the lack of a γ_{HH} interaction (−5.53 ppm[20c]), between the C-3″ and the C-6 hydrogen atoms in conformation F. The most clear-cut distinction between F and G is based on the carbon signals of position 2. Whereas in F the experimental data (two high-field signals, one low-field signal) are well simulated by empirical calculations, this would not be true for G (Table II). Thus F is the predominant isomer in the equilibrium.

The calculated values of Table I were obtained without consideration of any special lone pair effect.[24]

Conformation of 3. The four asymmetric carbon atoms of isotripiperideine a priori lead to 16 configurational isomers (eight enantiomeric pairs). Inversion of one or both hexahydropyrimidine nitrogen atoms increases the number of possible structures even more. Some conformations are excluded by steric restraint. In addition, we took into consideration only those structures which do not involve 1,3-diaxial interactions of CH_2 groups. The carbon chemical shift values of the remaining 13 conformations (seven configurational isomers) were estimated by calculation of the corresponding configurational isomers of perhydrotriphenylene (carbon analogues) and application of the CH → N replacement shifts in the manner described above.

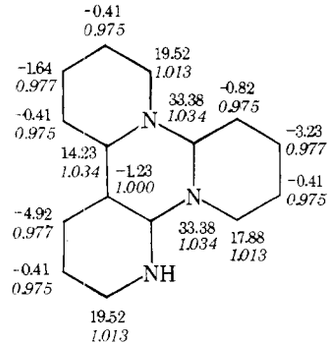


1 RE + 2 GI_N' + 1 GI_N F

3 RE + 1 GI′ G

1 RE + 1 GI′ + 2 GI_N' + 1 GI_N H

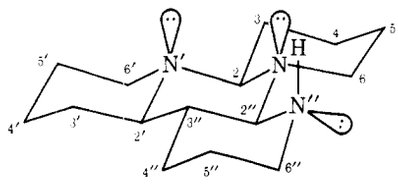
The following replacement parameters were used in eq 2:



A values italic

B values Roman

The resulting shift values were compared to the experimental data. The standard deviations for all 13 structures are exhibited in Figure 3. The least-squares method unequivocally favors conformation I, in which all rings are trans fused and no additional gauche interaction is present.



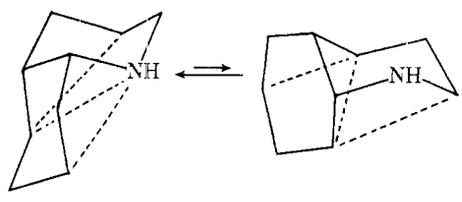
I

It is reasonable to assume that the hydrogen on N″ in the piperidine ring is axially oriented[26] both for steric grounds and to avoid additional rabbit ear effects. Thus, in I at least one generalized anomeric effect of two lone pairs (N and N′) is present. Inversion of the nitrogen atom N′ (leading to conformation L in Figure 3) involves an increase of energy by 1 GI_N' plus 1 GI plus 1 GI′,[14] while inversion of the atom N (K, Figure 3) increases the energy by 1 GI_N plus 1 GI_N' plus 1 GI′.[32] Thus (because $GI_N < GI$) it follows that

$$1\ RE < 1\ GI_N + 1\ GI_N' + 1\ GI' \qquad (4)$$

Conclusion

Carbon-13 NMR spectroscopy provides a simple method for assigning the configuration of α- and β-tripiperideine by symmetry arguments. Furthermore, the dynamic behavior of the α compound (1) indicates its conformation to be B whereas the conformation of β-tripiperideine (2) was deduced from the chemical shift data in conjunction with empirical increment calculations to be very largely F. The same procedure was applied to select the dominant structure I from the 13 possible stereoisomers of isotripiperideine (3). Determination of numeric values for the generalized anomeric effect of two nitrogen lone pairs requires knowledge of the energies of the different types[14] of gauche interactions. The gauche interaction of butane GI is known to be 0.85 kcal/mol;[27] the value of GI_N can be estimated from *N*-methylcyclohexylamine[28] to 0.5 kcal/mol. From the equilibrium of *cis*-decahydroquinolines[5c,k] eq 5 is derived.



$$1\ GI + 2\ GI_N = 2\ GI + GI' - 1.05\ kcal/mol \qquad (5)$$

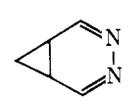
Thus a value of 1.2 kcal/mol results for the gauche interaction GI′ in an 2-azabutane moiety. The increment of GI_N' is not known; thus we assume the values of GI_N and GI_N' to be the same. (This assumption probably results in a too low value of GI_N'.)

The application of these values to eq 1 and 4 yields the limits of the rabbit ear effect in our system:

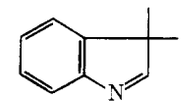
$$1.05\ kcal/mol < 1\ RE < 2.2\ kcal/mol^{32}$$

This energy given here for the generalized anomeric effect is higher than normally assumed,[5a,33] but it is only approximate since it is based on the gauche interaction of a C–N–C–N segment, GI_N' which is not precisely known.

It is interesting to compare our results with those of similar hexahydrotriazine structures. NMR results of *N*,*N*′,*N*″-trimethylhexahydrotriazine (4)[15] are in accord with the findings concerning the conformation of 1. The piperideine structure is also inherent in 3,4-diazanorcaradiene (5).[29] This species



5



6

forms three different trimeric compounds one of which (compound C in ref 29) apparently shows C_3 symmetry in the ^1H NMR spectrum and should thus correspond to 1.

On the other hand, the trimer of β,β-dimethylindolenine (6) has C_1 symmetry.[30] We think that this compound corresponds to 2, since in our opinion there is no strong evidence for the postulated boat conformation of the hexahydrotriazine system.

Experimental Section

α-Tripiperideine (1) and β-tripiperideine (2) (*RRR/SSS*, respectively *RRS/SSR* racemic mixture of dodecahydro-1*H*,6*H*,11*H*-tripyrido[1,2-*a*:1′,2′-*c*:1″,2″-*e*]-*s*-triazine) and isotripiperideine (3) (tetradecahydro-2*H*,11*H*-tripyrido[1,2-*a*:1′,2′-*c*:3″,2″-*e*]pyrimidine) have been prepared as described previously.[7] The ^{13}C FT NMR spectra were recorded at 22.63 MHz using a Bruker HX 90 spectrometer equipped with a Nicolet 1083 computer and a Bruker temperature control unit; 8K data points were used resulting in a resolution of 0.03 ppm for the 2500-Hz spectra in Table I. Usually 3000–8000 FID's were accumulated; the low-temperature spectra in the exchange region required 30 000 FID's. The chemical shifts relative to internal Me_4Si were determined with an accuracy of ±0.2 ppm.

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References and Notes

(1) Supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.
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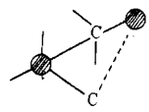
(13) Followed by ring inversion of the adjacent piperidine ring.
(14) RE = generalized anomeric effect, "rabbit ear effect". For gauche interactions the following notations are used:



Gl = butane segment (C–C–C–C)
Gl′ = 2-azabutane segment (C–N–C–C)
Gl_N = propylamine segment (C–C–C–N)
Gl_N' = 2-azapropylamine segment (C–N–C–N)

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(17) I.e., at −90 °C the contribution of A is less than 5%.[31]
(18) Whereas in smaller cyclic systems distinct ^{13}C chemical shift increments caused by alkyl substitution were successfully applied for calculation of nonbridgehead carbons in methylcyclohexanes,[20a] methyldecalines,[20b] methylpiperidines,[5b-d,21] alkyldecahydroquinolines,[5c,f] and methylquinolizidines,[22] this method may lead to wrong values of bridgehead or bridgehead neighbored carbon atoms in polycyclic systems such as methyldecalines[20b] and perhydrophenanthrenes and -anthracenes.[20c] For recent results see ref 5k.
(19) It is also possible to build up the data for PHT using the *experimental* values from corresponding segments of perhydroanthracenes and perhydrophenanthrenes. This results in a slightly better agreement with the observed data. As a consequence also assignments of some carbon signals in the less significant high-field region may have to be interchanged.
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(23) The *A* parameter only considers the nearest nitrogen position. The *B* parameter is the sum of the literature values for the three nitrogen positions. We neglected δ and ϵ effects, which are expected to be small.
(24) C-3″ and C-5″ in F, G, and H suffer the effect of an antiperiplanar lone pair of N-1″. One expects an upfield shift of about −3.5 ppm[25] compared to the calculated values. In our case such an effect could be present in an amount of maximally 2–4 ppm if we change the assignments in the high-field region, but when one does this the standard deviation between observed and calculated values increases.
(25) (a) The observed effect in the pairs **2, 2m,** and **19, 19m** in ref 5f amounts to about −9.5 ppm. It contains also the upfield shifting "γ_g" and "buttressing" effects[5f] (about −6 ppm). (b) E. L. Eliel, V. S. Rao, F. W. Vierhapper, and Z. Juaristi, *Tetrahedron Lett.*, 4339 (1975).
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(32) **Note Added in Proof.** A low temperature investigation of **3** gives evidence for conformational heterogenity of isotripiperideine (65% I, 23% K, and 12% L at −110 °C). This ratio leads to

$$1\ RE = 1\ Gl_N + 1\ Gl_N' + 1\ Gl' - 0.35\ kcal/mol \quad (5)$$

With the assumptions made above ($Gl_N' \approx Gl_N$) it follows that 1 RE = 1.85 kcal/mol.[33]
(33) The relative high value of RE could origin from the rigidity of the polycyclic ring system, whereas the literature values are derived from monocyclic compounds in which ring deformation is facilitated.

Syntheses and Chemistry of *N*-Acyl Substituted Dihydroimidazo[2,1-*b*]thiazolium Salts

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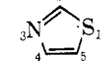
The syntheses of both *N*-acetyl- (**5**) and *N*-carbomethoxy-5,6-dihydroimidazo[2,1-*b*]thiazolium fluoroborate (**6**) from the corresponding *N*-acyl substituted thioimidazolines (**7** and **8**) are described. The reactivity of each of these salts with bases has been evaluated. Treatment of both **5** and **6** with methoxide yielded the known deacylated 3-phenyl-5,6-dihydroimidazo[2,1-*b*]thiazole (**14**). Addition, however, of triethylamine to nitromethane solutions containing **5** and **6** gave yellow, crystalline solids, **15** and **17**, respectively. Spectral analysis indicated that the products obtained were 1:1 adducts of the salts and the solvent. Substitution of nitroethane for nitromethane in each of these reactions yielded the expected homologous adducts (**16** ad **18**). The structure of one of these adducts, **15**, was determined by x-ray crystallography. Formation of **15–18** is believed to occur by the initial nucleophilic addition of the conjugate base of the solvent to the thiazolium ring of the salt to generate a tetrahedral intermediate. Fragmentation of this intermediate in the subsequent step leads to the observed adducts.

Although thiazoles (**1**) and thiazolium salts (**2**) are stable, isolable aromatic compounds, they readily undergo a variety of interesting reactions with nucleophiles.[1,2] The alkylated salts (**2**) are substantially more reactive toward nucleophilic agents than are their neutral precursors (**1**).[1,2]



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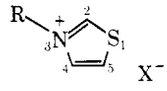

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