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STEREOSPECIFICITY OF THE $^3J_{CH}$ SPIN–SPIN COUPLING CONSTANTS IN BICYCLIC cis-DIAZIRIDINES.

STEREOCHEMISTRY OF 2,4,6-TRIALKYL-1,3,5-TRIAZABICYCLO[3.1.0]-HEXANES*

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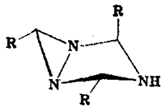
I. I. Chervin, and R. G. Kostyanovskii

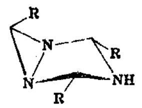
UDC 543.422.25:541.63:547.717

Stereospecificity of the $^3J_{C,N,C,H}$ spin–spin coupling constants ($^3J^{trans} > J^{gauche}$) in the ^{13}C NMR spectra of 1,5-diaza- and 1,3,5-triazabicyclo[3.1.0]hexanes was observed. Proceeding from this, the preferred conformations of the d,*l* and meso isomers of 2,4,6-trialkyl-1,3,5-triazabicyclo[3.1.0]hexanes were established, and a mechanism for the interconversion of these isomers via openings of the five-membered ring and an imino-enamine equilibrium was proposed. It is also shown that the stereochemical result of the Schmitz reaction is determined in the step involving cyclization of the iminium intermediate.

2,4,6-Trialkyl-substituted 1,3,5-triazabicycle[3.1.0]hexanes (TABH), which are formed by the action of NH_3 and chloramine on aldehydes (the Schmitz reaction [2, 3]) or in the chlorination of 2,4,6-trialkyl-1,3,5-triazans [3], exist in the form of one d,*l* isomer (a) and two meso isomers (b, c). The preferred "chair" conformation and an endo orientation of the methyl group in the 6 position in the least populated isomer (b) are proposed for all three isomers [3]. We have previously proposed an alternative boatlike conformation for the d,*l* and two meso isomers (Ia-c) of 2,4,6-trimethyl-1,3,5-triazabicyclo[3.1.0]hexane proceeding from the assumption of the common character of the mechanism of the formation of 1,5-diazabicyclo-[3.1.0]hexanes (DABH) and TABH and the common character of the factors that stabilize the boat form and on the basis of the results of the x-ray diffraction analysis of Ia [4].



a



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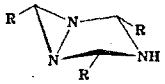
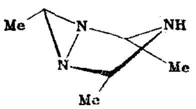
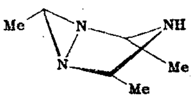


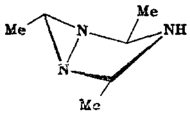
c



Ia



Ib



Ic

$R = CH_3$; C_2H_5; C_3H_7; $(CH_3)_2CH$; C_4H_9; $C_2H_5(CH_3)CH$; C_5H_{11}; C_6H_{13}

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*Communication 42 from the series "Asymmetric unbridged nitrogen." See [1] for communication 41.

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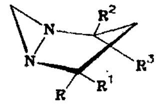
TABLE 1. ^{13}C Chemical Shifts (δ, ppm) and $^{1}J_{CH}$ Spin–Spin Coupling Constants (SSCC, Hz) of 2,4,6-Trimethyl-TABH Ia-c and VIa, b

Compound	$C_{(2)}$	$C_{(4)}$	$C_{(6)}$	2-Me	4-Me	6-Me
Ia	72,57 (157,5)	75,43 (146,5)	46,29 (164,2)	15,33 (127,0)	21,55 (126,3)	17,16 (127,0)
Ib	75,83 (144,6)	75,83 (144,6)	53,22 (164,2)	25,11 (126,3)	25,11 (126,3)	23,00 (127,0)
Ic	75,07 (156,9)	75,07 (156,9)	41,11 (163,0)	15,45 (127,0)	15,45 (127,0)	17,29 (127,0)
VIa	71,79 (154,4)	71,28 (144,7)	57,60 —	14,20 (127,0)	22,00 (126,3)	14,18, 28,32 (127,0)
VIb	71,23 (146,5)	71,23 (146,5)	58,75 —	24,06 (126,3)	24,06 (126,3)	12,87, 26,65 (127,0)

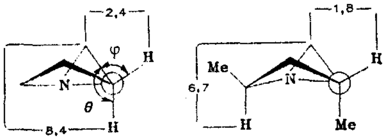
An exo orientation of the methyl group in the 6 position and a dipseudoaxial orientation in the 2 and 4 position of TABH Ib were confirmed by a comparison of the ^{13}C spectra [analysis of the chemical shifts (CS)] of this compound and the corresponding meso-2,4,6-trimethyl-DABH (Table 1).

In the present research, on the basis of the stereospecificity of the $^{3}J_{CH}$ spin–spin coupling constants (SSCC) we obtained more rigorous proof for the conformation and orientation of the methyl groups of TABH Ia-c, and, proceeding from this, we examined the stereochemistry of the Schmitz reaction and the equilibrium transformation of TABH.

The $^{3}J_{CNCH}$ constants are widely used for conformational analysis [5]. In the case of 1,5-diazabicyclo[3,1,0]hexane (II) and the d,*l* and meso isomers (IIIa, b) of 2,4-dimethyl-1,5-diazabicyclo[3.1.0]hexane, respectively, we observed stereospecific ^{3}J constants of the $C_{(6)}$ atom of the diaziridine ring with the protons attached to the $C_{(2)}$ and $C_{(4)}$ atoms [1]. Small ^{3}J constants (1.8-2.4 Hz) with the pseudoequatorial protons ($^{3}J_{CH}^{gauche}$) and significant ^{3}J constants (6.7-8.4 Hz) with the pseudoaxial protons ($^{3}J_{CH}^{trans}$) are observed in the case of boatlike DABH II and IIIa, b.

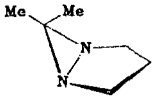


II,IIIa,b

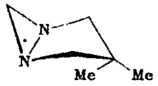


II R=R¹=R²=R³=H; IIIa R=R³=Me, R¹=R²=H; b R=R²=H, R¹=R³=Me

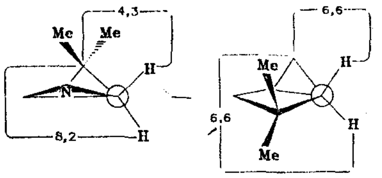
Flattening* of the five-membered ring (a decrease in dihedral angle φ and an increase in θ) in 6,6-dimethyl-DABH (IV) particularly affects the $^{3}J_{CH}^{gauche}$ constant but changes the $^{3}J_{CH}^{trans}$ value only slightly. Population of the "chair" conformation in the case of 3,3-dimethyl-DABH (V) leads to equalization of the two constants.



IV



V



Thus an angular dependence of the $^{3}J_{CNCH}$ SSCC in the case of bicyclic cis-diaziridines (DABH) is clearly observed. One may also assume the existance of the same dependence or at least retention of the relationship $^{3}J_{CH}^{trans} > {}^{3}J_{CH}^{gauche}$ also for the structurally similar TABH.

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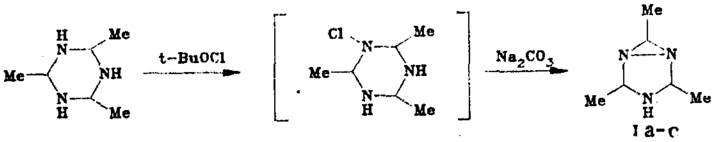
*Population of the "chair" conformation when an endo substituent is introduced into the 6 position is assumed in [1]; however, one should evidently speak only of flattening of the five-membered ring.

TABLE 2. $^{2}J_{CH}$ and $^{3}J_{CH}$ Spin–Spin Coupling Constants (SSCC) of 2,4,6-Trimethyl-TABH Ia-c and VIa, b

SSCC, Hz	Compound				
	Ia	Ib	Ic	VIa	VIb
^{2}J CH_3—$C_{(6)}$—H	5,5	—*	6,7	—	—
^{2}J CH_3—$C_{(2)}$—H	1,2	0,0	1,2	1,2	0,0
^{2}J CH_3—$C_{(4)}$—H	0,0	0,0	1,2	0,0	0,0
^{3}J $C_{(6)}$—$N_{(1,5)}$—$C_{(2)}$—H	5,5	1,8	5,5	—*	3,7
^{3}J $C_{(6)}$—$N_{(1,5)}$—$C_{(4)}$—H	1,8	1,8	5,5	—*	3,7
^{3}J $C_{(2)}$—$N_{(3)}$—$C_{(4)}$—H	4,9	4,9	0,0	4,9	3,7
^{3}J $C_{(4)}$—$N_{(3)}$—$C_{(2)}$—H	0,0	4,9	0,0	0,0	3,7
^{3}J $C_{(2,4)}$—$N_{(1,5)}$—$C_{(6)}$—H	3,7	3,7	3,7	—	—

*Not determined because of the low concentration of the isomer.

We studied the ^{13}C spectra of the mixture of 2,4,6-trimethyl-TABH isomers Ia-c obtained by the method in [3].

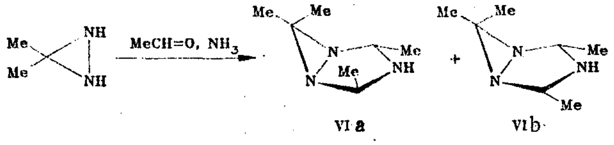


The ratio of TABH isomers Ia:Ib:Ic is 89:5:6; as in [3], a decrease in the amount of isomer Ib is observed.

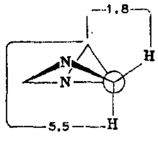
The assignment of the signals in the ^{13}C spectra is in agreement with the assignment presented in [3] except for the methyl groups in the 2 and 6 positions in Ia, the more accurate assignment of which was made on the basis of the $^{2}J_{CH}$ values (Table 2).

As assumed in the case of TABH Ia, the "boat" conformation of which was established by x-ray diffraction analysis [4], two different ^{3}J constants of the $C_{(6)}$ atom with the protons attached to the $C_{(2)}$ and $C_{(4)}$ atoms are observed. In analogy with DABH II and IIIa, b, the lower $^{3}J_{CH}$ value (1.8 Hz) can be ascribed to coupling of the $C_{(6)}$ atom with the pseudoequatorial proton (i.e., to $^{3}J_{CH}^{gauche}$), and the larger $^{3}J_{CH}$ value (5.5 Hz) can be ascribed to coupling with the pseudoaxial proton ($^{3}J_{CH}^{trans}$). The $^{3}J_{C_{(6)}H}$ constant of 5.5 Hz for Ic then constitutes evidence for a pseudoaxial orientation of H in the 2 and 4 positions, and the $^{3}J_{C_{(6)}H}$ constant of 1.8 Hz for Ib constitutes evidence for a pseudoequatorial orientation. A "boat" conformation for TABH meso isomers Ib and Ic with dipseudoequatorial methyl gorups in the 2 and 4 positions for Ic and dipseudoaxial methyl groups in the 2 and 4 positions for Ib hence follows from this.

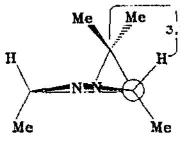
meso-2,4,6,6-Tetramethyl-TABH (VIb), which models TABH Ib in the chair form with an endo methyl group in the 6 position (as assumed in [3]), was obtained in a mixture with d,*l* isomer VIa (VIa:VIb = 91:9) via the scheme



As in the case of DABH IV, the presence of an endo methyl group in VIb leads to flattening of the five-membered ring and, correspondingly, to an increase in $^{3}J_{C_{(6)}H}^{gauche}$. This makes it possible to exclude the endo orientation of the methyl group in the 6 position of Ib that was proposed in [3].

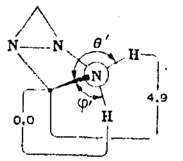


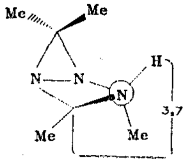
Ia-c



VIb

The orientation of the methyl groups in the 2 and 4 positions of TABH Ib and Ic is also confirmed by the ${}^3J_{C(4)NC(2)H}$ or ${}^3J_{C(2)NC(4)}$ SSCC which are clearly observed from the ${}^{13}C$ spectra of TABH Ia, b and VIa, b, in contrast to DABH [1]. It follows from the ${}^{13}C$ spectrum of Ia that the $C_{(2)}$ atom couples with the pseudoequatorial proton in the 4 position with ${}^3J$ = 4.9 Hz (${}^3J_{CH}{}^{trans}$), whereas the $C_{(4)}$ atom couples with the pseudoaxial proton in the pseudoaxial proton in the 2 position with ${}^3J$ = 0 Hz (${}^3J_{CH}{}^{gauche}$). The latter is evidently due to the fact that the dihedral angle (φ') between the C–H and C–N bonds is close to 90°. In 6,6-dimetyl derivative VIb with flattening of the five-membered ring dihedral angle θ' decreases, and ${}^3J_{C(2)H}{}^{trans}$ decreases correspondingly.





The conformation of TABH Ia-c also follows from an analysis of the CS of the ${}^{13}C$ nuclei and the ${}^1J_{CH}$ constants. In 6,6-dimethyl-TABH VIb the endo methyl group in the 6 position is shielded substantially as compared with the exo methyl group (Table 1) due to the effect of steric compression and the effect of the trans-orientated unshared pairs of the N atoms of the diaziridine ring [1]. It may therefore be assumed that the methyl group in the 6 position of Ib, the CS of which is close to that of the exo methyl group in the 6 position of VIb (Table 1), also has an exo orientation.

The close ${}^1J_{C(6)H}$ constants of all three TABH isomers Ia-c (Table 1) indicate an identical endo orientation of the hydrogen atom in the 6 position. Moreover, the values of these constants (163-164.2 Hz) virtually coincide with those found for the endo protons in the 6 position in DABH (164-166.4 Hz) [1]; the $C_{(6)}$ constant with the exo proton in the 6 position in DABH is 180-183.1 Hz [1].

The substantial difference in the ${}^1J_{C(2,4)H}$ values for the pseudoaxial (154-157.5 Hz) and pseudoequatorial (144.6-146.5 Hz) protons of TABH Ia-c must be noted.

As in the case of DABH [1], the degree of deviation of the five-membered ring of TABH Ia-c can be observed from the CS of the $C_{(6)}$ atom, which is affected by the steric compression of the $C_{(6)}$–H bond by the $N_{(3)}H$ group in the "boat" conformation. According to this test, the greatest deviation of the five-membered ring is observed for Ic [$\delta C_{(6)}$ 41.11 ppm]; this can be explained by repulsion of the dipseudoequatorial methyl groups from the three-membered ring. Minimization of the steric interaction of the syn-dipseudoaxial methyl groups of Ib, on the other hand, leads to flattening of the five-membered ring [$\delta C_{(6)}$ 53.22 ppm].

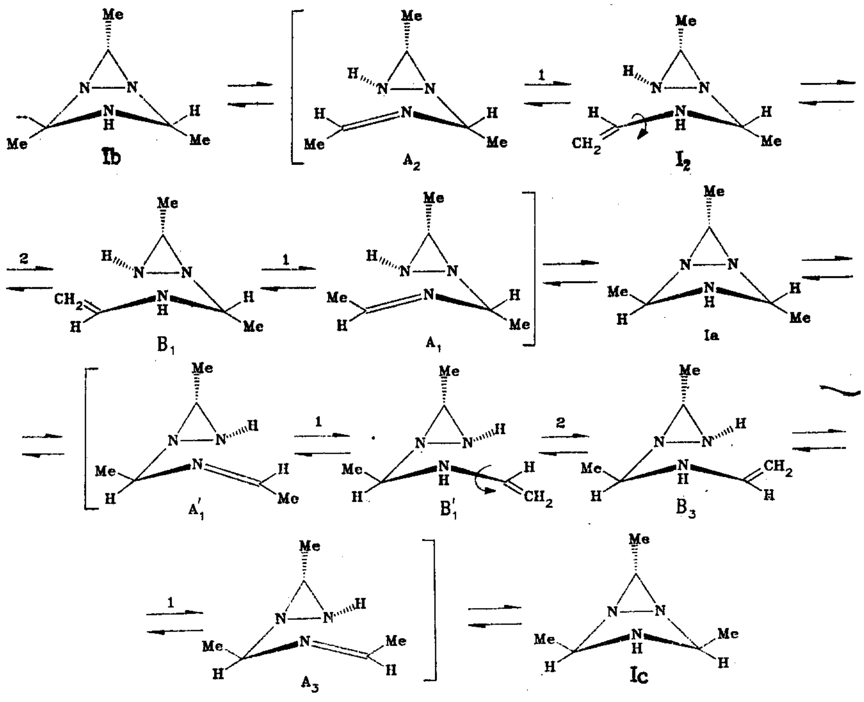
In the examined TABH Ia-c and VIa, b the latter two compounds with an endo methyl group in the 6 position have the most flattened ring. This can be observed not only from the values of the ${}^3J_{CH}$ constants but also, in the case of VIa, from the decrease in the effect of steric compression of $C_{(2)}$ by the pseudoaxial (or, more precisely, exo) methyl group in the 4 position, as a consequence of which the $C_{(2)}$ and $C_{(4)}$ atoms have almost the same CS (Table 1). In Ia (with a bent five-membered ring), however, the differences in the CS of the $C_{(2)}$ and $C_{(4)}$ atoms is evidently due primarily to the shielding syn γ effect of the pseudoaxial methyl group in the 4 position.

The high-field shift of the $C_{(2)}$ and $C_{(4)}$ nuclei of TABH VIa, b as compared with Ia and Ib (Table 1) is a consequence of steric compression of the C–H bonds by the endo methyl group in the 6 position.

Thus 2,4,6-trimethyl-TABH and, correspondingly, 2,4,6-trialkyl-TABH exist in solution primarily in the "boat" conformation with an exo orientation of the substituent in the 6 position. The meso isomers Ib and Ic differ with respect to the orientation of the substituents in the 2 and 4 positions — in the first case these substituents are dipseudoequatorial, whereas in the second case they are dipseudoaxial.

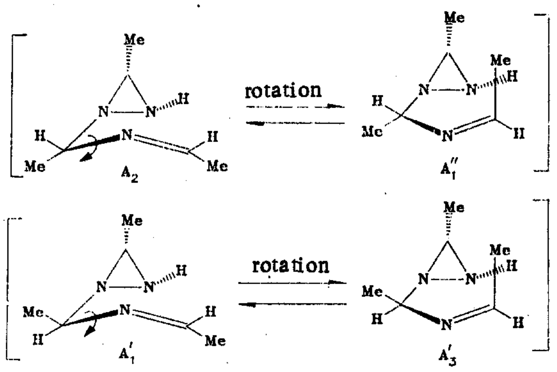
Steric interaction of the dipseudoaxial substituents in the 2 and 4 positions thermodynamically destabilizes Ib as compared with Ia and Ic, and isomer Ib is therefore virtually absent in the equilibrium mixture [3]. This isomer is converted only to Ia, since the simultaneous cleavage of two bonds, viz., the $N_{(1)}$–$C_{(2)}$ and $N_{(5)}$–$C_{(4)}$ bonds, is required for direct isomerization to Ic.

It might be assumed that the key intermediate in the Ib Ia Ic equilibrium transformation is imine A (or the corresponding iminium salt under the conditions of acidic catalysis by NH_4Cl/HCl in MeOH [3]), which exists in tautomeric equilibrium with enamines B (the enammonium salt). This is confirmed by exhaustive deuteration of the methyl groups in the 2 and 4 positions of VIa and VIb when they are maintained in EtOD. The more rapid establishment of the Ia ⇄ Ib equilibrium as compared with the Ia ⇄ Ic equilibrium [3] constitutes evidence that the rate-determining step in the process is cleavage of the $N_{(1)}$—$C_{(2)}$ or $N_{(5)}$—$C_{(4)}$ bond.



1 — 1,3H shift; 2 — rotation

An alternative mechanism of isomerization via rotation about the $C_{(2)}$—$N_{(3)}$ or $N_{(3)}$—$C_{(4)}$ bond in intermediate A can be excluded on the basis of the fact that sterically unfavorable drawing together of the three-membered ring and the methyl groups in the 2 and 4 positions occurs in the transition state. In addition, the geometry of the cyclization transition state is close to that of the less stable chair form.



Imine A is also a key intermediate in the Schmitz reaction [2, 3]. As in the case of the Ib ⇄ Ia ⇄ Ic isomerization, the cyclization of this imine is evidently realized through a transition state with a geometry that is close to that of the final TABH in the boat form. The relationship of the yields of the isomeric TABH (Ia > Ic > Ib) is hence readily explained, since it is completely apparent that the precursor of Ia, viz., A_1 or A'_1, undergoes cyclization through the sterically least hindered transition state, whereas the precursor of Ib, viz., A_2, undergoes cyclization through the most hindered transition state, in which the methyl groups in the 2 and 4 positions are syn-dipseudoaxial. In conformity with this, the amount of 2,4,6-trialkyl-TABH isomer b in the kinetic mixture decreases as the volume of alkyl substituents in the 2 and 4 positions increases, as previously observed in [3].

Thus, proceeding from the established conformation of 2,4,6-trimethyl-TABH we propose a mechanism for the equlibrium transformation of the d,*l* and meso isomers that include imino-enamine tautomerism, the possibility of which was demonstrated independently. The previously discussed mechanism [3] should be excluded, since it is based on an erroneous assignment of the conformation of the TABH isomers and assumes a step involving rapid inversion of the nitrogen atoms of the diaziridine ring.

On the basis of the correct assignment of the conformation of TABH isomers Ia-c it was also shown that the stereochemical result of the Schmitz reaction is determined in the step involving cyclization of the iminium intermediate by steric interactions in the transition state, the geometry of which is close to the geometry of the reaction products.

EXPERIMENTAL

The NMR spectra of solutions of the compounds in $CDCl_3$ were measured with a WM-400 spectrometer (^1H 400.13 MHz; ^{13}C 100.62 MHz) with tetramethylsilane as the internal standard.

2,4,6-Trimethyl-1,3,5-triazabicyclo[3.1.0]hexanes Ia-c. A 1.43-g (13.2 mmole) sample of tert-BuOCl was added dropwise with stirring and cooling (—35°C) to a solution of 1.70 g (13.2 mmole) of 2,4,6-trimethyl-1,3,5-triazacyclohexane [3] in 75 ml of methanol and 0.74 g (7 mmole) of Na_2CO_3, after which stirring was continued at —35°C for 1 h and at 20°C for 1 h. The solvent was evaporated in vacuo, and the products were extracted from the residue with hot hexane (two 50-ml portions). Evaporation of the hexane in vacuo gave 0.98 g (59%) of acicular crystals of a mixture of Ia-c with mp 92-97°C (with sublimation), which, according to the ^1H and ^{13}C NMR spectra, were identical to the compounds described in [3].

2,4,6,6-Tetramethyl-1,3,5-triazabicyclo[3.1.0]hexanes VIa, b. A 0.88-g (20 mmole) sample of acetaldehyde was added dropwise with stirring and cooling (—35°C) to a solution of 0.72 g (10 mmole) of 3,3-dimethyldiaziridine and 0.40 g (23 mmole) of ammonia in 30 ml of methanol, and the mixture was maintained at —10°C for 7 h. The solvent was evaporated in vacuo, and the residue was sublimed at 30°C (1 mm) to give 0.90 g (64%) of hydroscopic crystals of a mixture of VIa, b with mp ~20-30°C. PMR spectrum ($CDCl_3$): VIb: 1.21 (3H, s, 6-CH_3), 1.30 (3H, s, 6-CH_3), 1.37 (6H, d, ^3J = 6.10 Hz, 2,4-CH_3), 1.98 (1H, broad s, NH), 3.88 (2H, q, 2,4-H); VIa: 1.50 (3H, s, 6-CH_3), 4.12 (1H, q, ^3J = 6.35 Jz, 4-H), 4.44 (1H, q, ^3J = 6.35 Hz, 2-H); the signals of the 2,4,6-CH_3 groups are overlapped with the corresponding signals of preponderant isomer VIb. Found: C 57.3; H 10.9%. Calculated [for the crystal hydrate $(C_7H_{15}N_3)_3 \cdot H_2O$]: C 57.1; H 10.7%.

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