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THE CONFIGURATION AND CONFORMATION OF THE ISOMERIC 3-AMINOPINANES

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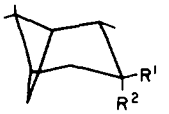
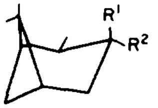
Abstract Tris(dipivaloylmethanato)europium has been successfully used in the analysis of the NMR spectra of the isomeric 3-aminopinanes. The previously assigned configurations of the 2-methyl and 3-amino groups have been confirmed and the preferred conformations have been shown to be those in which the 2-Me group is quasi-equatorial.

IN AN earlier publication,[2] in which we described the synthesis and deamination of the isomeric 3-aminopinanes (I–IV), the configurations of the 2-methyl and 3-amino groups relative to the isopropylidene bridge were assigned on the basis of the stereospecific syntheses employed in the preparation of the compounds and upon their GLC retention data. The preferred conformations of the compounds were assumed to be similar to those of the corresponding hydroxy compounds[3] in which the 2-Me group always adopts the equatorial position. Evidence is now presented in confirmation of these assignments.



I : $R^1 = NH_2$; $R^2 = H$
II . $R^1 = H$; $R^2 = NH_2$



III : $R^1 = H$; $R^2 = NH_2$
IV : $R^1 = NH_2$; $R^2 = H$

The NMR spectra of the amines (I-IV) are complex with only the signals due to the 6,6-*gem*-dimethyl group and the 2-Me group being well defined. The remaining signals between 7·0 and 9·0 τ appear as overlapping multiplets which cannot be resolved at 100 MHz. Consequently, no information concerning the stereochemistry of the compounds can be obtained directly from coupling constants. It has been established,[4] however, that, in the absence of other ring substituents, the 2-Me signal of 2β*H*-pinane* derivatives resonate at *ca* 0·14 to 0·18 ppm higher than those of the corresponding 2α*H*-isomers, whereas the resonance signal of the equatorial 6-Me group always appears at *ca* 0·4 ppm below that of the axial 6-Me group for both series of compounds, due to the magnetic anisotropy of the cyclobutane ring. Electronegative substituents in the 3-position of the 2α*H*-pinane systems do not

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* The αβ-notation has been used throughout and the isopropylidene bridge has been designated the β-configuration.

produce any appreciable change in the positions of resonance of either the equatorial 6-Me group or the 2-Me group, but axial 6-Me signals are shifted by + 0·11 and − 0·04 ppm respectively by 3α- and 3β-OH groups.[4] The Me signals of the 3-aminopinanes follow this pattern fairly closely (Table 1) but it is obvious that an *ab initio* analysis of the spectra does not distinguish between 3α-amino-2β*H*-pinane (II) and 3β-amino-2α*H*-pinane (IV).

TABLE 1. CHEMICAL SHIFTS (τ) OF THE METHYL GROUPS OF THE 3-AMINOPINANES

	2-Me*	eq 6-Me	ax 6-Me
3β-Amino-2β*H*-pinane (I)	9·12	8·85	9·19
3α-Amino-2β*H*-pinane (II)	9·05	8·82	9·16
3α-Amino-2α*H*-pinane (III)	8·93	8·78	9·03
3β-Amino-2α*H*-pinane (IV)	9·06	8·80	9·19

* doublet, $J = 7$Hz.

Use of the recently described NMR shift reagents[5] now allows for an unambiguous assignment of both the configurations and conformations of the aminopinanes. Amines complex strongly with tris(dipivaloylmethanato) europium[Eu(dpm)$_3$][5] and NMR studies using the ytterbium complex indicate that the induced shifts are dependent both on the geometry of the complexed amine and upon its basicity.[6] Steric factors also influence the magnitude of the induced shifts.[7]

The effect of Eu(dpm)$_3$ upon the proton chemical shifts of the isomeric 3-aminopinanes is shown in Fig 1a-d. Unambiguous assignment of almost all the ring protons was made possible by spin decoupling the signals shifted by the europium complex, and the relatively greater induced shifts of the axial 6-Me protons distinguished them

TABLE 2. APPROXIMATE SPIN–SPIN COUPLING CONSTANTS AND DIHEDRAL ANGLES (φ) FOR THE ISOMERIC 3-AMINOPINANES

		ϕ			ϕ			ϕ	
	$J_{2\text{-}3}$	Obs.[a]	Calc.[b]	$J_{3\text{-}4ax}$	Obs.	Calc.	$J_{3\text{-}4eq}$	Obs.	Calc.
1. 3β-Amino-2β*H*-pinane	6	135	126	10	140	148	10	20	18
2. 3α-Amino-2β*H*-pinane[c]	8	25	34	8	25	34	4	95	60
3. 3α-Amino-2α*H*-pinane	6	130	126	6	130	126	10	10	18
4. 3β-Amino-2α*H*-pinane	8	20	34	10	15	18	7	105	131

		ϕ			ϕ			ϕ			
	$J_{2\text{-}1}$	Obs.	Calc.	$J_{4ax\text{-}5}$	Obs.	Calc.	$J_{4eq\text{-}5}$	Obs.	Calc.	$J_{2\text{-}Me}$	$J_{4ax\text{-}4eq}$
1.	2	80	90	2	75	90	6	45	47	7	13
2.	2	80	90	2	75	90	*c*	45	*c*	7	12
3.	2	75	90	4	65	60	4	55	60	7	14
4.	2	75	90	2	70	90	4	50	60	7	14

[a] As measured from Dreiding models (Fig. 2).

[b] As calculated by the Karplus equation.

[c] Poor resolution of the signals of the 4-CH$_2$ protons prevented the accurate measurement of coupling constants.

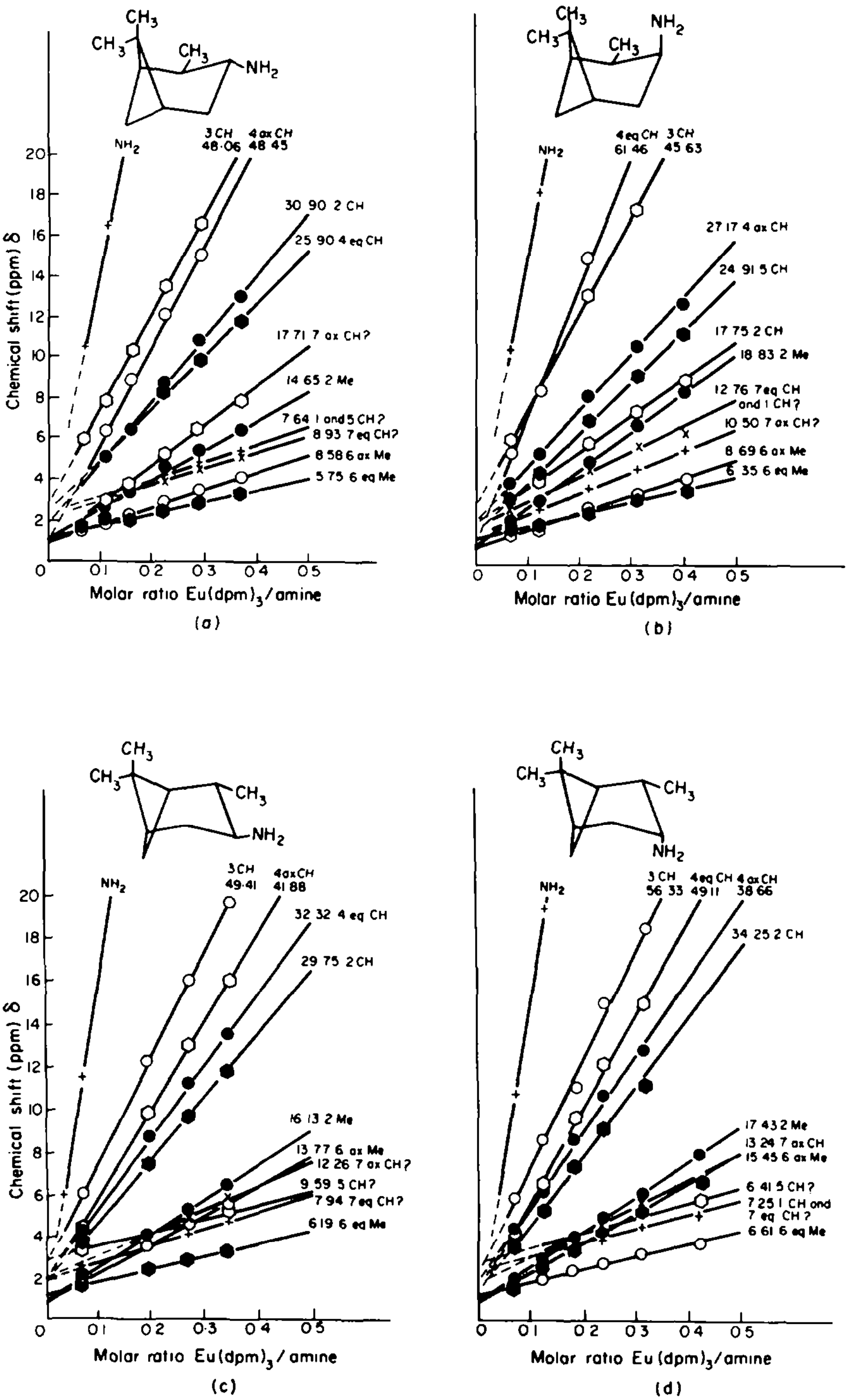


FIG 1. Variations in chemical shifts induced by $Eu(dpm)_3$ for (a) 3α-amino-2α*H*-pinane (b) 3β-amino-2α*H*-pinane (c) 3β-amino-2β*H*-pinane (d) 3α-amino-2β*H*- pinane

from the equatorial 6-Me protons. At a relative concentration of Eu(dpm)$_3$ to amine of *ca* 0·25 : 1·00 the more strongly shifted signals were well separated and line broadening was such that it was possible to measure the coupling constants (Table 2). The dihedral angles as calculated from the observed coupling constants using the Karplus equation[8] corresponds closely to the angles measured from Dreiding models in which the C2-C3-C4 plane deviates from the Cl-C2-C4-C5 plane by an angle of *ca* 20° (Fig 2). These observations not only provide evidence for the assigned configurations and conformations of the aminopinanes but also confirm the postulate that the cyclohexane ring is flattened.[3] Separation of the signals for the 4-CH$_2$ protons enabled measurement of the geminal coupling constant to be made. The value of 14 Hz corresponds closely to geminal coupling of 12·6 Hz quoted for cyclohexane.[9] The geminal coupling for the 7-methylene group appeared to be considerably smaller (*cf* ref 10).

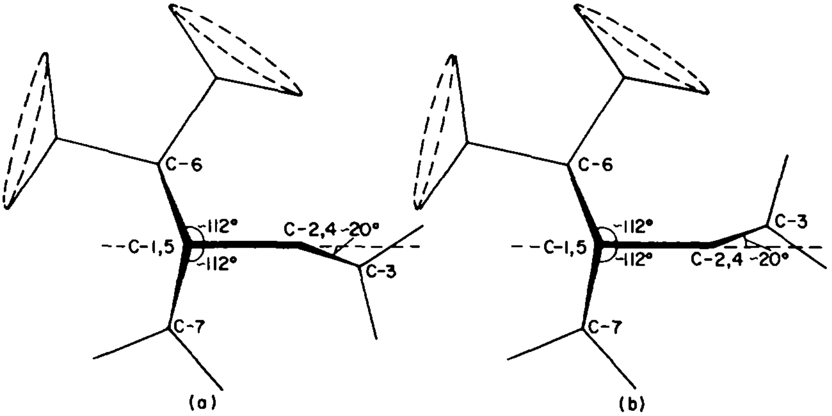


FIG 2. Approximate geometries of (a) 3-amino-2β*H*-pinanes and (b) 3-amino-2α*H*-pinanes.

As the identities of the Me signals could be determined with the greatest ease, the gradients of the induced shifts for these groups with the increasing molar ratio of Eu(dpm)$_3$ to amine were initially used to confirm the configurational and conformational assignments for the isomeric aminopinanes. According to Hinckley's approximation the magnitude of an induced paramagnetic shift, S, of a proton signal as a result of the addition of an equimolar amount of Eu(dpm)$_3$ to substrate is inversely proportional to the cube of the linear distance of the proton from the europium nucleus, r.[11] A logarithmic plot of S for the Me signals of the isomeric aminopinanes against averaged values of r for the protons of the three Me groups as measured from Dreiding models shows a close correlation with the line of gradient − 3·00; the calculated gradient is − 3·10 ± 0·53 with a correlation coefficient of 0·891.* As the variations in the basicities of the isomeric amines are negligible (Table 3) the observed correlation indicated that steric factors are also negligible and that the assigned configurations and conformations with quasi-equatorial 2-Me groups are correct. The correlation with the inverse cube of r, however, is contrary to the findings of Cockerill and Rackham[12] and of Wiewiorowski *et al.*[13] who have suggested that the induced shift is

* In this calculation data for the axial 6-Me group of 3β-amino-2α*H*-pinane was considered invalid as it is highly probable that, due to steric interaction with the β-amino group, the Me group is distorted from the position measured on the Dreiding model.

TABLE 3. BASICITIES OF THE ISOMERIC 3-AMINOPINANES

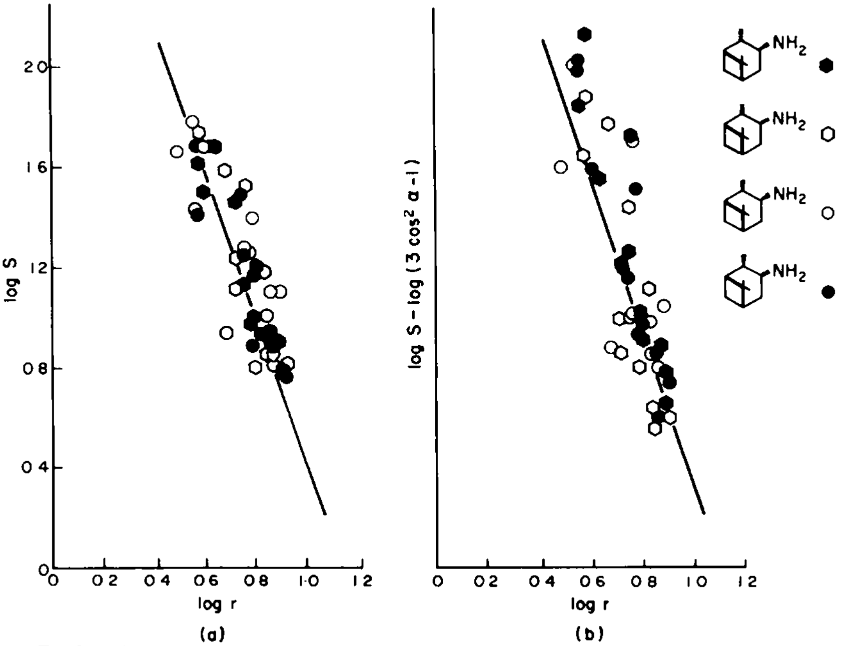
	3β-NH_2	3β-NH_2
2β-Me (equatorial)	10·49±0·06 (axial)	10·44±0·04 (equatorial)
2α-Me (equatorial)	10·47±0·07 (equatorial)	10·31±0·05 (axial)

inversely proportional to the square of the Eu-H distance. A more rigorous treatment of the data using the pseudocontact shift equation of McConnell and Robertson[14] requires that the induced shift be a function not only of the distance r but also of the angle α between the H-Eu axis and the Eu–N axis:

$$S\,(\text{p.p.m.}) = \frac{k(3\cos^2\alpha - 1)}{r^3}$$

The gradient of a logarithmic plot of the data for the Me groups modified to include the angular dependence of the induced shift was found to be − 2·30 ± 0·59 with a correlation coefficient of 0·85. The wider scatter of the points reflected the error in fixing the precise position of the europium nucleus and in the calculation of the angular function which is more sensitive to slight variations in the geometry of the molecules than is r.

Subsequent to the unambiguous assignments of the signals a correlation of the gradients of the induced shifts, S, with the Eu–H internuclear distances for all protons, with and without correction for the angular function, was made (Fig 3). The necessity



(a) (b)

FIG 3. Relationship of log S with log r for compounds I–IV (a) without and (b) with dependence of angular function. (Full line corresponds to a slope of − 3·00).

to consider both the angular function and the internuclear distance has been amply shown by several workers,[15–17] who have observed upfield shifts in the NMR spectra of 'bulky molecules' induced by the presence of europium. These apparently anomolous diamagnetic shifts occurred when the angle α was greater than 54·7° causing the angular function to be negative. However, inspection of the Dreiding models of the 3-aminopinanes showed no angle to be greater than *ca* 47° and no diamagnetically induced shifts were observed and a better correlation between the magnitude of the shifts and the inverse cube of the Eu–H internuclear distance was observed when the angular function was neglected (Fig 3a).

EXPERIMENTAL

The amines (I–IV), prepared by the previously described methods,[2] were purified by recrystallization of the hydrochloride salts immediately prior to the NMR measurements. Eu(dpm)$_3$ was prepared by the method of Eisentraut and Sievers.[18]

The paramagnetic chemical shifts (δ) relative to TMS were measured at 60 MHz on a Perkin-Elmer R12 spectrometer for *ca* 40% solutions in CCl_4 with a molar ratio range of Eu(dpm)$_3$ to amine of 0 to 0·4. Spin decoupling experiments on *ca* 20% solutions of the amines and molar ratio of Eu(dpm)$_3$ to amine of *ca* 0·25 were carried out at 100 MHz on a Varian HA 100 spectrometer.

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