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NMR STUDIES ON 2,3-DISUBSTITUTED BICYCLO(2,2,2)OCTANES

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Abstract– Derivatives of the two diastereoisomers of 3-aminobicyclo-(2,2,2) octan-2-ol in which the 2 and 3 substituents were held rigidly in a *cis* or *trans* relationship by the symmetrical bicyclo(2,2,2)octane ring system were prepared and their NMR discussed.

THERE are two possible diastereoisomers (III and IX) of 3-aminobicyclo-(2,2,2)-octan-2-ol. Sicher *et al.*,[1] prepared the *trans* isomer (IX) by the nucleophilic attack of NH_4OH on 2,3-epoxybicyclo(2,2,2)octane[2] at 160°; conversion of the *trans* isomer to the *cis* isomer (III) was achieved by heating its N-benzoyl-O-methanesulfonyl derivative with anhydrous CH_3COOK in ethanol. This involves the nucleophilic attack by the amide carbonyl oxygen on the carbon carrying the methane sulphoxy group and leads to the corresponding Δ^2-oxazoline[3,4] with inversion of configuration. Hydrolysis of the Δ^2-oxazoline ring with aq. HCl afforded the required *cis*-3-aminobicyclo(2,2,2)octan-2-ol (III). Nelson[5] also prepared an oxazolidine as an intermediate to the *cis*-aminoalcohol (III) from bicyclo(2,2,2)oct-2-ene.[6] Addition of iodoisocyanate to bicyclo(2,2,2)oct-2-ene gave the corresponding intermediate which was methanolized without previous isolation to yield *trans*-3-iodo-2-carbomethoxy-aminobicyclo(2,2,2)octane. Pyrolysis of this compound gave the *cis*-bicyclo(2,2,2)-octyl(3,2-*d*)oxazolidin-2-one. Base catalysed hydrolysis of this oxazolidine gave the *cis*-aminoalcohol (III).

In the present work, *cis* and *trans*-3-aminobicyclo(2,2,2)octan-2-ol were prepared following the conditions described by Sicher.[1] *cis*-3-Aminobicyclo(2,2,2)octan-2-ol (III) was also prepared by the LAH reduction of 3-hydroxyiminobicyclo(2,2,2)octan-2-one (II).[7]

trans-3-Dimethylaminobicyclo(2,2,2)octan-2-ol (X) was prepared from IX by the Eschweiler–Clarke modification of the Wallach reaction.[8] The *cis*-primary amine (III), when subjected to the same procedure gave the N-methyl-*cis*-bicyclo(2,2,2)octyl-(3,2-*d*) oxazolidine which upon LAH reduction gave the *cis*-dimethylaminoalcohol (IV).[5] Compound IV was also prepared from the HCl salt of X by oxidation to the ketone (XIV) followed by LAH reduction. This procedure afforded a 4:1 mixture of *cis* and *trans*-dimethylaminoalcohols (as measured by NMR) from which IV was obtained pure by fractional crystallization of the HCl salts..

The monomethylaminoalcohols (VIII and XVII) were prepared by refluxing the appropriate aminoalcohol in anhydrous benzene with aqueous formaldehyde and anhydrous Na_2SO_4[9] followed by LAH reduction of the intermediate. The NMR spectra of the crude intermediates from the *cis* and *trans* aminoalcohols showed interesting differences which will be reported at a future date.[10] Fractional crystalliza-

tion of the hydrochloride salts of the LAH reduction products gave the appropriate monomethylaminoalcohols (VIII and XVII).

The dimethylaminoalcohols (IV and X) and the dimethylaminoketone (XIV) were quaternized in quantitative yield by refluxing with methylbromide in alcohol.

Esterification of the diastereosomers (IV and X) of 3-dimethylaminobicyclo-(2,2,2)octan-2-ol and their methobromides (V and XI) proceeded readily in a 50% v/v solution of acetic anhydride in acetic acid; the *trans* isomer (X) was completely esterified in a 25% v/v solution of acetic anhydride in acetic acid, whereas the *cis* isomer (IV) was incompletely esterified; similar results were reported for the *cis* and *trans* isomers of 2,3-disubstituted bornanes.[11]

The bicyclo(2,2,2)octane molecule is symmetrical about three axes (Fig 3) which intersect on the C(1)–C(4) axis.

There are present six 1,2 and six 1,3 nonbonded interactions. This arrangement represents the energy maximum of nonbonded interactions and theoretically there should be some method of avoiding the strain. Turner, Meader and Winkler[12] claimed that this can be attained by rotation on the C(1)–C(4) axis and is possible without distortion of the bond angles if the twist around the axis does not exceed 10°. Schleyer and Nicholas[13] showed that rotation increases rather than decreases the energy of the molecule. IR and Raman spectra[14] confirmed the non-twisted structure for bicyclo(2,2,2)octane.

Substituents in the 2 and 3 positions are subject to the same nonbonded interaction with the ring irrespective of whether the substituents are *cis* or *trans*. There are no *axial* or *equatorial* bonds in the molecule because of the three trigonal axes (Fig 3). Any change in the physical and chemical properties of the 2 and 3 substituents should be due to interaction with the ring structure (which is the same for both substituents whether *cis* or *trans*) and mutual interaction (which will vary between *cis* and *trans* isomers).

The NMR spectra of 2,3-disubstituted bicyclo(2,2,2)octane derivatives (Table 1) are now used to elucidate configuration and to identify reaction products; elucidation of configuration is based on comparison of the coupling constants between H(1), H(2), H(3) and H(4) (Fig 3) with the values predicted by Karplus for ethane derivatives.[15, 16]

In the case of substitution in the 2 and 3 position, the molecule will tend to rotate on the C(1)–C(4) axis to relieve the interaction of the substituents with the 5 and 6 or 7 and 8 methylene groups. Assuming a 10° rotation without distortion of the bond angles,[12] the 2,3 dihedral angle would vary within a 20° angle depending on substituents. The coupling constants ($J_{2,3}$) of the *cis* derivatives vary between 6·7 and 8·7 Hz corresponding to an angle of 25° and 0° respectively. The *trans* derivatives have coupling constants (3·1–6·6 Hz) indicating an angle change of 127° to 149°. The *cis*-aminoalcohol (III) has a $J_{2,3}$ (8·7 Hz) in accordance with a dihedral angle of 0° as expected for *cis* protons. The *trans*-aminoalcohol (IX) has a $J_{2,3}$ (3·9 Hz) corresponding to a dihedral angle of 127°; 7° more than the expected 120° dihedral angle for *trans* protons. This can be interpreted by examination of models (Fig 4).

A rotation about the C(1)–C(4) axis in the *trans* disubstituted compound (Fig 4a) will tend to relieve interaction of both substituents with the C(5), C(6), C(7) and C(8) methylene groups. The same rotation of the *cis* compound (Fig 4b) will relieve interaction with one substituent (A) but at the same time will move the other substituent

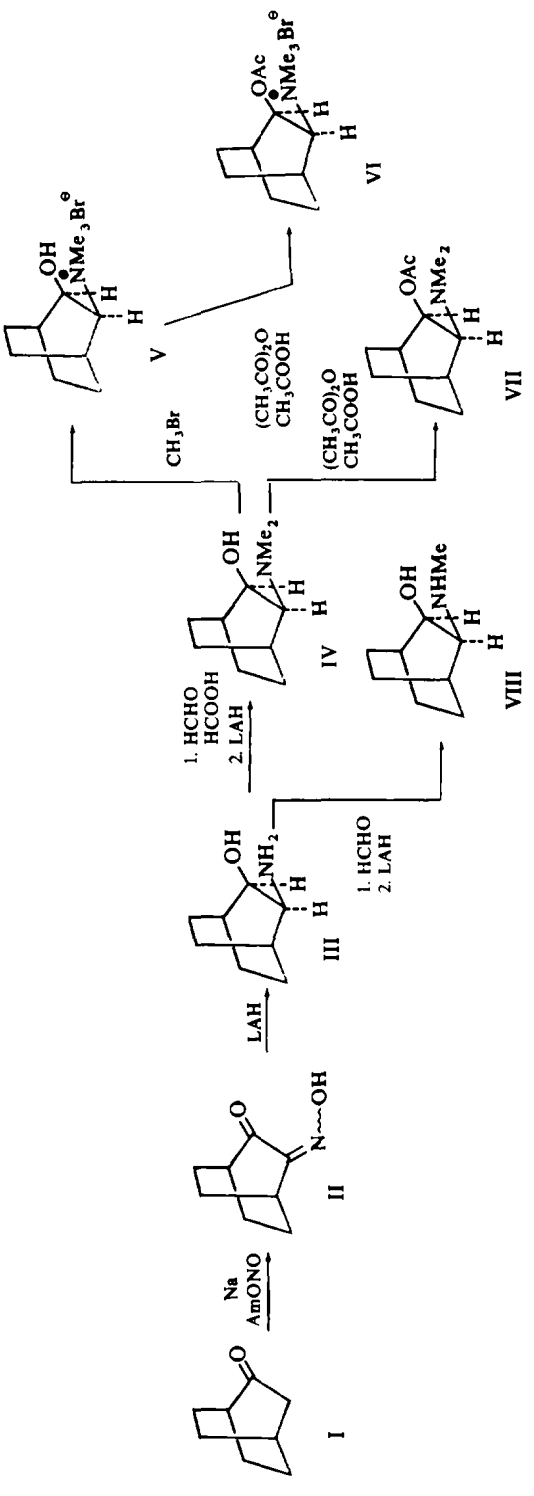


FIG 1. Preparation of *cis*-2.3-disubstituted bicyclo(2.2.2)octanes

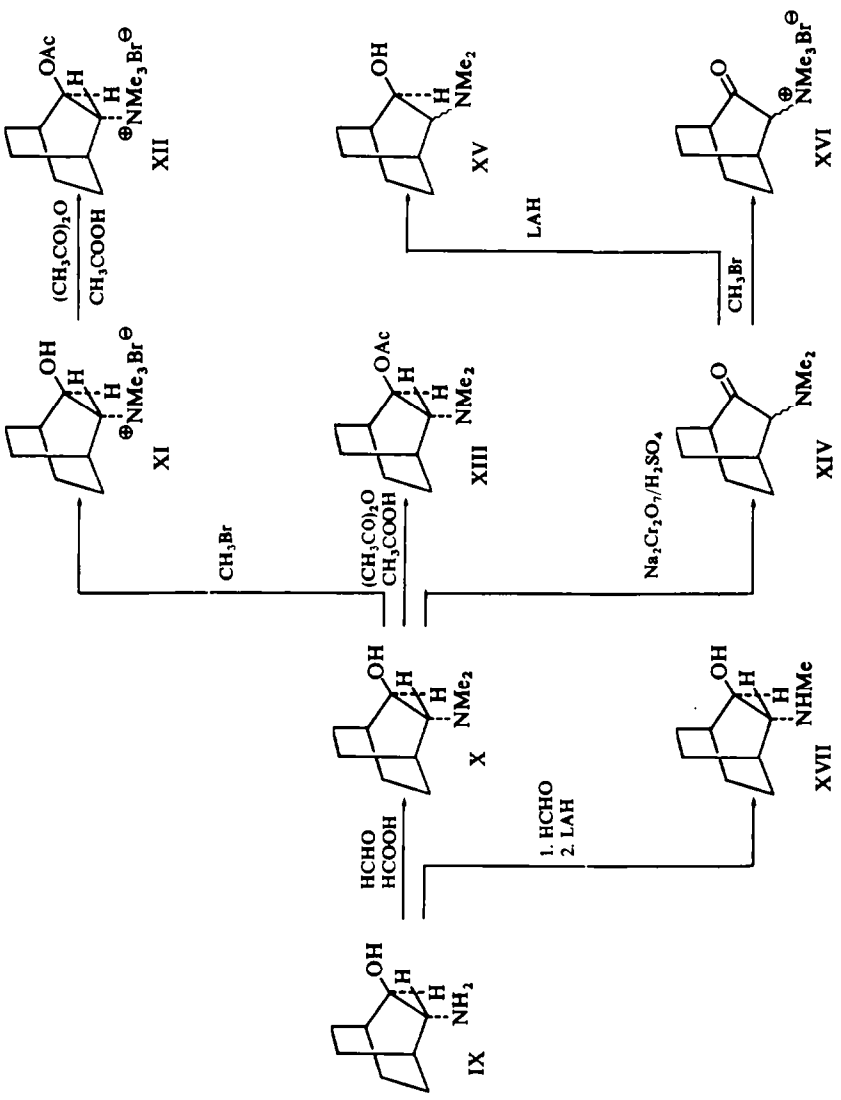


FIG 2. Preparation of *trans*-2,3-disubstituted bicyclo(2,2,2)octanes and bicyclo(2.2.2)-octan-2-ones.

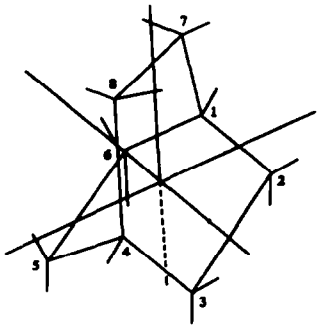
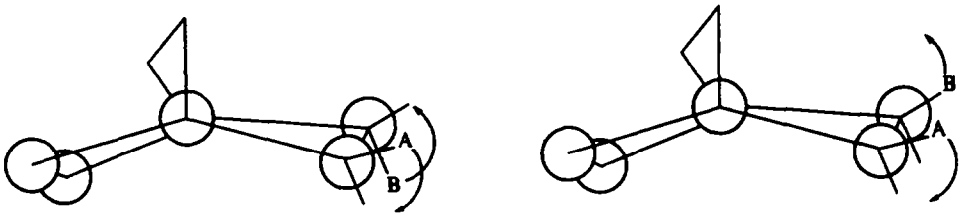


FIG 3.



a FIG 4. b

(B) into closer contact with the ethylene bridge. As a result, the *trans*-aminoalcohol rotates to a large extent to relieve steric interaction, and it remains the same (Table 2) as one or two Me groups are introduced onto the amino function; however, quaternization of the *trans*-dimethylaminoalcohol ($J_{2,3} = 3{\cdot}8$ Hz) forces the nitrogen away from the nearest ethylene bridge to increase the dihedral angle to $> 135°$ ($J_{2,3} > 4$ Hz). The primary *cis*-aminoalcohol does not rotate to relieve steric interaction initially. Proceeding from the primary amino group to the secondary and tertiary amino group, moves the nitrogen away from the nearest ethylene bridge to relieve steric interaction (Table 2). Quaternization of the *cis*-dimethylaminoalcohol forces the nitrogen further away from the nearest ethylene bridge resulting in a smaller coupling constant (larger dihedral angle). The dihedral angle H(2)–H(3) does not change in either the *cis* or *trans* compounds when proceeding from the monomethyl to the dimethylaminoalcohols.

The coupling constants $J_{1,2}$ and $J_{3,4}$ are also consistent with the above rotations about the C(1)–C(4) axis with the introduction of various groups onto the amino function (Table 2). $J_{1,2}$ and $J_{3,4}$ vary only slightly in the different derivatives of the *trans*-amino alcohol, indicating that the initial rotation of the primary amino alcohol is sufficient to relieve steric interaction in the secondary and tertiary aminoalcohols. An increase in $J_{1,2}$ from 2·1 Hz in the *cis*-aminoalcohol to 4·02 Hz in the dimethylaminoalcohol corresponds to a decrease in the dihedral angle H(1)–H(2) consistent with a movement of the nitrogen away from the nearest ethylene bridge. Quaternization of the *cis*-dimethyl derivative results in a further increase in $J_{1,2}$ from 3·42 Hz (IV-salt) to 5·04 Hz corresponding to an even further decrease in the H(1)–H(2)

dihedral angle in accordance with the nitrogen group moving away from the nearest ethylene bridge.

Acetylation of the *cis*-dimethylaminoalcohol has little effect on $J_{2,3}$; however, quaternization of the acetylated product increases the H(2)–H(3) dihedral angle by approximately 12° with a corresponding decrease in $\theta_{1,2}$ which indicates a movement of the quaternary nitrogen away from the nearest ethylene bridge.

Quaternization of the dimethylaminoketone (XIV) has little effect on $J_{3,4}$ which may indicate that the carbonyl function reduces the flexibility of this ring system and thus reduces the rotation about the C(1)–C(4) axis.

Long range proton-proton couplings across four single bonds have been recognized for some time and it is well known that the maximum coupling occurs through a "W" arrangement.[17, 18] The resonance lines of H(2) and H(3) in the *cis* and *trans* compounds are broadened slightly by a long range coupling of approximately 1 Hz with one proton on C-6 or C-7 and C-5 or C-8 respectively. The H(2) and H(3) protons are capable of forming a perfect "W" configuration with one of the above protons (Fig 5).

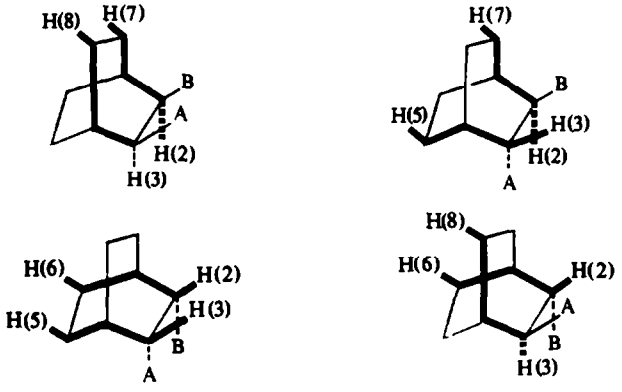


FIG 5.

In the absence of any other subsitituents in the bicyclic system, it is impossible to make further configurational assignments of A and B (Fig 5) based on long range coupling. Substitution in the 5, 6, 7 or 8 position would make long range coupling a useful correlation in the assignment of the configuration of A and B.[19]

Alkylation of the 3-primary amino group introduced an upfield shift of the signal for H(3) in the diastereoisomers studied due to the increased electron density of the N atom upon progressive introduction of alkyl groups: this can be shown by the fact that the corresponding salts of the amines as well as the trimethylammonium bromide derivatives, which would have almost identical electron density on the N atom, showed only a slight change in τ values for H(3) (Table 3).

Acetylation of the alcohol group produced a downfield shift of both H(2) and H(3) presumably due to the negative inductive effect of the acetate group.

Recently, Nelson and Wilson[20] prepared the methiodides of VII and XIII and tested them for cholinergic and cholinesterase activity. The aminoalcohols and ketones are now being studied for muscarinic effects and interaction with acetylcholinesterase.

TABLE 1. NMR DATA OF SOME 2.3-DISUBSTITUTED BICYCLO(2,2,2)OCTANES

Compounds	Solvent	Chemical shift (τ)							J(Hz)
		5,6,7, 8-CH_2	H(4)	H(1)	H(3)	H(2)	—NMe	—OAc	
II *Syn*- and *anti*-3-hydroxyimino-bicyclo(2,2,2)octan-2-one	$CDCl_3$	7·9–8·5 m†	6·36 anti bm 7·45 syn bm						
IX *trans*-3-aminobicyclo(2,2,2)-octan-2-ol	B-$CDCl_3$	8·11–8·91 m*			7·26 b.d	6·57 b.d			$J_{2,3}$ = 3·9
	S-D_2O	8·05–8·80 m*			6·84 d.d	6·21 b.d.d			$J_{2,3}$ = 4·3 $J_{3,4}$ = 1·4 $J_{1,2}$ c.a. 1·8
XVII *trans*-3-methylaminobicyclo-(2,2,2)octan-2-ol	B-$CDCl_3$	8·1–8·9 m*			‡	6·55 b.d.d	7·85 s		$J_{2,3}$ = 3·1
	S-D_2O	7·96–8·81 m*			7·01 d.d	6·17 b.d.d	7·22 s		$J_{2,3}$ = 4·3 $J_{3,4}$ = 1·8 $J_{1,2}$ c.a. 2·0
X *trans*-3-dimethylaminobicyclo(2,2,2)octan-2-ol	B-$CDCl_3$	8·09–8·89 m*			‡	6·38 m	7·72 s		$J_{2,3}$ c.a. 3·0
	S-D_2O	8·01–8·76 m†	7·83 m§		‡	6·12 b.d.d	7·06 d		$J_{2,3}$ = 3·8 $J_{1,2}$ c.a. 2·1
XIII *trans*-2-acetoxy-3-dimethylamino-bicyclo(2,2,2)octane hydrochloride	D_2O	8·20–8·65 m	7·75 m§	8·03 m §	6·64 d.d	5·04 b.d.d	7·11 s	7·86 s	$J_{2,3}$ = 3·84 $J_{3,4}$ = 2·0 $J_{1,2}$ c.a. 2·4
XI *trans*-3-dimethylaminobicyclo-(2,2,2)octan-2-ol methobromide	D_2O	8·0–8·5 m†	7·71 m§		‡	5·82 m	6·85 s		$J_{3,4}$ = 1·7 $J_{2,3}$ > 4
XII *trans*-2-acetoxy-3-dimethylamino-bicyclo(2,2,2)octane methobromide	D_2O	7·92–8·62 m†	7·61 m		6·29 d.d	4·78 m	6·87 s	7·86 s	$J_{2,3}$ = 6·6 $J_{3,4}$ = 1·0
XIV 3-dimethylaminobicyclo-(2,2,2)octan-2-one hydrochloride	D_2O	7·7–8·5 m	7·3 m §	7·53 m §	5·97 b.d		7·02 s		$J_{3,4}$ = 1·6
XVI 3-dimethylaminobicyclo-(2,2,2)octan-2-one methobromide	D_2O	7·78–8·48 m	7·12 b.m§	7·49 b.m§	5·71 b.d		6·68 s		$J_{3,4}$ = 1·26

TABLE 1— *continued*

Compounds	Solvent	Chemical shift (τ)							*J*(Hz)
		5,6,7, 8-CH_2	H(4)	H(1)	H(3)	H(2)	—NMe	—OAc	
III *cis*-3-aminobicyclo(2,2,2)octan-2-ol	B-$CDCl_3$	7·9–8·9 m*			6·95 b.d.d	6·33 b.d.d			$J_{2,3}$ = 8·7 $J_{1,2}$ = 2·1 $J_{3,4}$ < 2
	S-D_2O	8·02–8·72 m*			6·55 b.d	5·91 b.d.d			$J_{2,3}$ = 8·7 $J_{2,1}$ = 2·5 $J_{3,4}$ = 2·0
VIII *cis*-3-methylaminobicyclo-(2,2,2)octan-2-ol	B-$CDCl_3$	7·93–9·34 m*			~7·43‡ partially obscured	6.32 b.d	7·58 b.s		$J_{2,3}$ = 7·8 $J_{1,2}$ c.a. 3·9
	S-D_2O	8·1–8·7 m*			6·7 b.d	5·9 b.d	7·28 s		$J_{2,3}$ = 8·4
IV *cis*-3-dimethylaminobicyclo-(2,2,2)octan-2-ol	B-$CDCl_3$	7·85–8·95 m*			‡	6·32 d.d	7·73 s		$J_{2,3}$ = 7·8 $J_{1,2}$ = 4·02
	S-D_2O	7·8–8·8 m*			6·8 b.d	5·81 d.d	7·09 d		$J_{2,3}$ = 7·44 $J_{1,2}$ = 3·42 $J_{3,4}$ < 2
VII *cis*-2-acetoxy-3-dimethylaminocyclo-(2,2,2)octane hydrochloride	D_2O	8·3–8·9 m*			6·54 b.d	4·79 d.d	7·1 s	7·78 s	$J_{2,3}$ = 7·9 $J_{1,2}$ = 4·54
V *cis*-3-dimethylaminobicyclo-(2,2,2)octan-2-ol methobromide	D_2O	7·63–8·88 m†	7·75 m§		‡	5·55 b.d.d	6.7 5b.s		$J_{2,3}$ = 6·93 $J_{1,2}$ c.a. 5·04
VI *cis*-2-acetoxy-3-dimethylaminobicyclo-(2,2,2)octane methobromide	D_2O	7·46–8·62 m*			6·37 d	4·68 t	6·74 s	7·75 s	$J_{2,3}$ = 6·7 $J_{2,1}$ = 5·1

Code: S = hydrochloride salt; B = free base; b.d = broad doublet; b.d.d. = broad doublet of doublets; d.d = doublet of doublets; m = multiplet; s = singlet; b.s. = broad singlet; t = triplet; * = H(1) and H(4) inclusive; † = H(1) inclusive; ‡ = obscured by —NMe resonance; § = assigned by spin decoupling.

TABLE 2. DIHEDRAL ANGLES ($\theta_{2,3}$ $\theta_{3,4}$ AND $\theta_{1,2}$) OF SOME 2,3-DISUBSTITUTED BICYCLO(2,2,2)OCTANES CALCULATED FROM KARPLUS' EQUATIONS[15] USING COUPLING CONSTANTS ($J_{2,3}$, $J_{3,4}$ AND $J_{1,2}$) FROM TABLE 1.

Compound No.	$J_{2,3}$	$\theta_{2,3}$	$J_{1,2}$	$\theta_{1,2}$	$J_{3,4}$	$\theta_{3,4}$
IX B	3·9	132°				
IX S	4·3	134°	c.a. 1·8	c.a. 60°	1·4	63°
XVII B	3·1	127°				
XVII S	4·3	134°	c.a. 2·0	c.a. 58°	1·8	60°
X B	c.a. 3·0	c.a. 127°				
X S	3·8	131°	c.a. 2·1	c.a. 58°		
XIII S	3·84	48°	c.a. 2·4	c.a. 55°	2·0	58°
XI M					1·7	61°
XII M	6·6	149°			1·0	67°
XIV S					1·6	62°
XVI M					1·26	64°
III B	8·7	0°	2·1	58°		
III S	8·7	0°	2·5	55°	2·0	58°
VIII B	7·8	12°	c.a. 3·9	c.a. 45°	1·26	64°
VIII S	8·4	0°				
IV B	7·8	12°	4·02	44°		
IV S	7·44	17°	3·42	48°		
VII S	7·9	11°	4·54	41°		
V M	6·93	23°	c.a. 5·04	c.a. 37°		
VI M	6·7	25°	5·1	37°		

Code: B = free base; S = hydrochloride salt; M = methobromide salt.

TABLE 3. EFFECT OF ALKYLATION OF THE 3-AMINO GROUP OF *cis* AND *trans*-3-AMINOBICYCLO(2.2.2)OCTAN-2-OL ON THE CHEMICAL SHIFT* OF H(3)

Stereo config. of substituents	Solvent	Primary	Secondary	Tertiary	Quaternary
		IX	XVII	X	XI
trans	B-$CDCl_3$	7·26	c.a. 7·58	c.a. 7·72	
	S-D_2O	6·84	7·01	c.a. 7·06	c.a. 6·85
		III	VIII	IV	V
cis	B-$CDCl_3$	6·95	c.a. 7·43	c.a. 7·73	
	S-D_2O	6·55	6·7	6·8	c.a. 6·75

Code: *The chemical shift in τ: B = base: S = salt.

EXPERIMENTAL

The NMR spectra were obtained on a 60 MHz Perkin–Elmer R-10 instrument in various solvents with TMS as internal standard (see Table 1). The IR spectra were measured on a Unicam S.P. 200 spectrophotometer as Nujol mulls. M.ps were uncorrected. Microanalysis by Dr. F. B. Strauss, Oxford and Mr. C. S. Crouch, Brunswick Square, London.

(a) 3-*Hydroxyiminobicyclo*(2,2,2)*octan*-2-*one* (II)[7, 21]

Bicyclo(2,2,2)octan-2-one (5·0 g, 0·04 mole) was added portionwise to Na wire (1·0 g, 0·04 mole) in dry ether (75 ml). Freshly distilled amylnitrite (4·68 g, 0·04 mole) was added slowly, the temp being maintained at 5°. After stirring the mixture for 3 hr at room temp ice water was added and the ethereal layer was separated and washed with water. The aqueous layer and washings were combined and acidified with 20% AcOH (250 ml) and extracted with ether. The ethereal extracts, dried over $MgSO_4$, were evaporated *in vacuo* to yield an orange coloured oil which solidified on standing. The solid was recrystallized from light petroleum (40°–60°) to yield II (600 mg; 10%), m.p. 130–134°, lit.[7] 131–134°. (Found: C, 62·6; H, 7·3; N, 9·1. Calc. for $C_8H_{11}NO_2$: C, 62·7; H, 7·3; N, 9·1%).

(b) 3-*Dimethylaminobicyclo*(2,2,2)*octan*-2-*one* (XIV)

Aqueous chromic acid soln (25 ml) [from $K_2Cr_2O_7 \cdot 2H_2O$ (5 g), conc H_2SO_4 (3 ml) and water] was added dropwise with stirring and ice-cooling to an aq. soln (50 ml) of *trans*-3-dimethylaminobicyclo(2,2,2)octan-2-ol HCl (4·4 g; 0·21 mole). The mixture was stirred for 5 hr at room temp, then made alkaline ($NaHCO_3$) and extracted with ether. After washing the ethereal extracts with $NaHCO_3$ soln and drying over K_2CO_3, the solvent was evaporated *in vacuo* to yield a yellowish oil (3 g; 84%) from which the hydrochloride was prepared in ether with 20% ethanolic HCl: m.p. 165–169°, dec. (Found: C, 59·0; H, 8·9; N, 6·9; Cl, 17·2: Calc. for $C_{10}H_{18}NOCl$: C, 59·0; H, 8·9; N, 6·9; Cl, 17·4%).

(c) cis-3-*Aminobicyclo*(2,2,2)*octan*-2-*ol* (III)

3-Hydroxyiminobicyclo(2,2,2)octan-2-one (0·9 g, 0·006 mole) in dry ether (50 ml) was added dropwise with stirring to a suspension of LAH (2 g; 0·05 mole) in dry ether (100 ml). Stirring was continued overnight and the excess LAH was destroyed with water (2 ml) followed by 5 N NaOH (2 ml). The mixture was filtered, dried ($MgSO_4$), and evaporated *in vacuo* to yield *cis*-3-aminobicyclo(2,2,2)octan-2-ol (0·42 g; 50%). The hydrochloride salt was prepared by acidifying an ethereal soln of the base with 20% ethanolic HCl and recrystallized from EtOH/ether, m.p. 264–275° (dec), lit.[1] 269–274°. (Found: C, 53·9; H, 9·2; N, 7·8: Calc. for $C_8H_{16}NOCl$; C, 54·0; H, 9·1; N, 7·9%).

(d) cis-3-*Methylaminobicyclo*(2,2,2)*octan*-2-*ol* (VIII)

A mixture of *cis*-3-aminobicyclo(2,2,2)octan-2-ol (400 mg; 0·003 mole), anhydrous Na_2SO_4 (1 g) and aqueous formaldehyde (40% w/v, 4·5 ml, 0·06 mole) in benzene (30 ml) was heated under reflux for 4·5 hr. The mixture was cooled, filtered and evaporated *in vacuo* to yield an oily solid. An ethereal soln (30 ml) of this solid was added to a suspension of LAH (1 g) in dry ether (50 ml) and refluxed overnight. The mixture was poured into ice, filtered and made alkaline with NaOH aq (33% w/v). The alkaline soln was extracted with ether and the ethereal liquors were dried (K_2CO_3) and evaporated *in vacuo* to yield an oily solid. The HCl salt was prepared in ether as described for (c) (354 mg; 61%) m.p. 249–256° dec. (Found: C, 56·5; H, 9·4; N, 7·4; Cl, 18·8. Calc. for $C_9H_{18}NOCl$; C, 56·4; H, 9·4; N, 7·3; Cl, 18·6%).

(e) trans-3-*Methylaminobicyclo*(2,2,2)*octan*-2-*ol* (XVII)

trans-3-Aminobicyclo(2,2,2)octan-2-ol (2 gm, 0·14 mole) was treated with aqueous formaldehyde under the conditions described above (d). The resulting white solid was reduced with LAH as in (d). The HCl salt of the LAH reduction product was recrystallized several times from EtOH/ether to yield *trans*-3-methylaminobicyclo(2,2,2)octan-2-ol, m.p. 193–194°. (Found: C, 56·5; H, 9·2; N, 7·4; Cl, 18·9. Calc. for $C_9H_{18}NOCl$: C, 56·4; H, 9·4; N, 7·3; Cl, 18·6%).

(f) cis-3-*Dimethylaminobicyclo*(2,2,2)*octan*-2-*ol* (IV)[5]

(i) A mixture of III[1] (260 mg; 0·0018 mole) formic acid (5 ml) and aqueous formaldehyde (40% w/v, 5 ml, 0·066 mole) was heated on a boiling water bath for 12 hr. The mixture was evaporated to dryness *in vacuo* and the resulting oil was dissolved in water, washed with ether, basified with K_2CO_3 and extracted with ether. The ethereal liquors were dried (K_2CO_3) and evaporated *in vacuo* to yield crude N-methyl-*cis*-*bicyclo*(2,2,2)octyl(3,2-d)-oxazolidine (285 mg, 95%) HCl salt (EtOH/ether) m.p. 211–215° dec. Lit.[5] 240–242°. (Found: C, 59·2; H, 8·7; N, 6·8; Cl, 17·4. Calc. for $C_{10}H_{18}NOCl$; C, 59·0; H, 8·9; N, 6·9; Cl, 17·4.

The above isolated oxazolidine (144 mg, 0·00086 mole) in dry ether (30 ml) was added to a suspension of LAH (1 g) in dry ether (50 ml). The mixture was stirred and heated under reflux for 4 hr, stirring being continued for a further 12 hr at room temp. The excess LAH was destroyed with water. The ether layer was decanted and the salts washed with ether. The combined ethereal soln and ether washings were washed

with water and dried (K_2CO_3). The soln was filtered and the solvent removed *in vacuo* to yield a yellowish oil (140 mg, 92%) which was transformed into the HCl salt as described above m.p. 243–246° dec; lit.[5] 239–240°. (Found: C, 58·6; H, 9·9; N, 6·8; Cl, 17·1. Calc. for $C_{10}H_{20}NOCl$; C, 58·4; H, 9·7; N, 6·8; Cl, 17·2%).

(ii) 3-*Dimethylaminobicyclo*(2,2,2)*octan*-2-*one* (1·8 g) was reduced with LAH (1·5 g) as in (i) to yield an oil. The NMR of the HCl salt showed a quartet 5·8 τ (J = 7·4 Hz and J = 3·4 Hz) and a broad doublet at 6·12 τ (J = 3·8 Hz) with a 4:1 ration of the integrals (assuming 1 proton for each signal). Fractional crystallization of the HCl salt from EtOH/ether gave a pure compound with the quartet at 5·81 τ in the NMR spectrum and IR and m.p. identical to the *cis*-dimethylaminoalcohol in (i).

(g) trans-3-*Dimethylaminobicyclo*(2,2,2)*octan*-2-*ol* (X)

trans-3-Aminobicyclo(2,2,2)octan-2-ol[1] (20 g, 0·14 mole) was reductively alkylated as in (i) to yield X (14 g, 57%). The HCl salt was prepared from ethereal soln of the base by acidifying with 20% ethanolic HCl, m.p. 246–248° de. (Found: C, 58·5: H, 9·8: N, 6·9: Cl, 17·6. Calc. for $C_{10}H_{20}NOCl$: C, 58·4; H, 9·7; N, 6·8; Cl, 17·2%. Base, m.p. 72–75°. Found: C, 70·9; H, 11·3; N, 8·2. Calc. for $C_{10}H_{19}NO$: C, 71·0; H, 11·2; N, 8·3%).

General method for quaternization of the tertiary amines

The tertiary amines IV, X and XIV were quarternized with MeBr as follows: A cold solution of MeBr (33% v/v in MeOH, 1·5 ml, 0·609 mole) was added to the tertiary base (0·004 mole) in MeOH (30 ml) and the mixture was stirred at room temp in a stoppered flask for 24 hr followed by heating under reflux for 3–4 hr. The solvent was removed *in vacuo* and the residue washed with ether to remove unreacted amine. The residue was recrystallized from EtOH/ether.

(a) *cis*-3-Dimethylaminobicyclo(2,2,2)octan-2-ol methobromide (V), m.p. 280–282° dec. (Found: C, 50·2; H, 8·5; N, 5·4; Br, 30·5; Calc. for $C_{11}H_{22}NOBr$; C, 50·0; H, 8·3; N, 5·3; Br, 30·2%).

(b) *trans*-3-Dimethylaminobicyclo(2,2,2)octan-2-ol methobromide (XI), m.p. 284–287° dec. (Found: C, 49·9; H, 8·5; N, 5·3; Br, 30·0. Calc. for $C_{11}H_{22}NOBr$; C, 50·0; H, 8·3; N, 5·4; Br, 30·2%).

(c) 3-Dimethylaminobicyclo(2,2,2)octan-2-one methobromide (XVI), m.p. 222–228° dec. (Found: C, 50·2; H, 7·6; N, 5·1; Br, 30·8; Calc. for $C_{11}H_{20}NOBr$; C, 50·4; H, 7·6; N, 5·3; Br, 30·5%).

General method for esterification with acetic anhydride

A mixture of 2 g of the hydroxybicyclo(2,2,2)octane (hydrochloride salts of the tertiary bases IV and X of their methobromides V and XI) in 100 ml of a 50% v/v Ac_2O in AcOH was refluxed for 24 hr. The excess acid and anhydride were removed *in vacuo* to yield a solid residue which was shaken with 20 ml dry ether to remove any remaining acid anhydride. The crude product was recrystallized from ethanol/ether.

(a) *cis*-2-Acetoxy-3-dimethylaminobicyclo(2,2,2)octane hydrochloride (VII), m.p. 260–264°. (Found: C, 58·4; H, 8·7; N, 5·7; Cl, 14·1. Calc. for $C_{12}H_{22}NO_2Cl$; C, 58·2; H, 8·9; N, 5·7; Cl, 14·3%).

(b) *cis*-2-Acetoxy-3-dimethylaminobicyclo(2,2,2)octane methobromide (VI)—too hygroscopic for analysis.

(c) *trans*-2-Acetoxy-3-dimethylaminobicyclo(2,2,2)octane methobromide (XII). m.p. 220–224°. (Found: C, 50·9; H, 7·8; N, 4·6; Br, 26·0. Calc. for $C_{13}H_{24}NO_2Br$; C, 51·0; H, 7·8; N, 4·6; Br, 26·1%).

(d) *trans*-2-Acetoxy-3-dimethylaminobicyclo(2,2,2)octane hydrochloride (XIII) m.p. 239–241°. (Found: C, 58·0; H, 8·9; N, 5·6; Cl, 14·2. Calc. for $C_{12}H_{22}NO_2Cl$; C, 58·2; H, 8·9; N, 5·7; Cl, 14·3%).

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