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STERIC INFLUENCE ON THE CHEMICAL REACTIONS AND NMR SPECTRA OF 2,3-DISUBSTITUTED BORNANES

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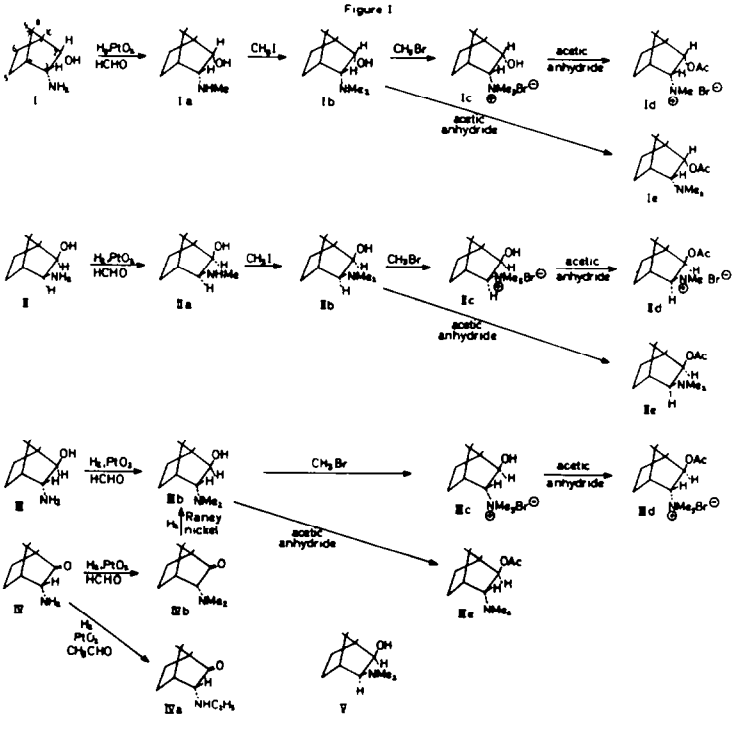
Abstract—Steric influence on the alkylation and esterification of three diastereoisomers of 2-hydroxy-3-aminobornane was studied and the NMR spectra of the various stereoisomers discussed. Acetylcholine analogues with the onium and acetyl functions held rigidly in *cis* and *trans* relationship were synthesized.

THE amino and hydroxyl functions of the diastereoisomers of 2-hydroxy-3-aminobornane are situated in different steric environments and would be expected to exhibit differences in their chemical reactions. The alkylation of the amino function and acetylation of the hydroxyl function of the three known diastereoisomers[1-3] of 2-hydroxyl-3-aminobornane (I, II, III) were therefore studied.

Figure 1



Alkyl groups may be introduced into primary and secondary amines by reductive alkylation.[4] The tendency for an amine and a carbonyl compound to interact initially and for the product to undergo hydrogenation would be influenced by the steric environment of the amino group.

Reductive alkylation was carried out in ethanol at atmospheric pressure with platinum oxide, and hydrochloric acid was added to act as a strong alkylating catalyst. Using formaldehyde as the alkylating compound, reductive alkylation of both 2-*endo*-hydroxy-3-*endo*-aminobornane (I) and 2-*exo*-hydroxy-3-*exo*-aminobornane (II) stopped at the secondary amine stage giving Ia and IIa respectively. This is not surprising as the amino function of each has an α-*cis* oriented OH group whose steric influence would discourage alkylation beyond the secondary amine stage. In addition, the C-8 Me group of II introduces further steric hindrance to the amino function which accounts for the observed slower rate of reaction of II than I. Nevertheless reductive alkylation is a good method for the syntheses of Ia and IIa free from primary or tertiary amines. It is also a one step synthesis of Ia which was previously synthesized[5] in a two-stage reaction.

In contrast, under the same conditions, the reductive alkylation of 2-*exo*-hydroxy-3-*endo*-aminobornane (III) whose hydroxyl and amino functions are *trans* to each other, preceeded to the tertiary amine stage without difficulty, producing exclusively 2-*exo*-hydroxy-3-*endo*-dimethylaminobornane (IIIb).

Reductive alkylation of 3-*endo*-aminobornan-2-one (IV) having the keto function α- to the *endo* group also proceeded as expected to the tertiary amine stage, producing 3-*endo*-dimethylaminobornan-2-one (IVb) which is a novel method for the synthesis[6] of this compound.

The size of the alkylating agent is also an important factor. When acetyldehyde was used as the alkylating agent instead of formaldehyde, reductive alkylation of IV stopped at the secondary amine stage giving 3-*endo*-ethylaminobornan-2-one (IVa).

Direct alkylation of a primary amine with an alkyl halide may result in the formation of secondary, tertiary and quaternary amines in varying amounts. Methylation of the 2-hydroxy-3-aminobornane isomers (I, II, III) with methyl iodide in ether proceeded readily to the tertiary amine Ib, IIb, and IIIb, while quaternization was found to be negligible. This knowledge made it possible to devise a method by which tertiary bases (Ib, IIb) were synthesized by direct alkylation, with methyl iodide, of the primary amines (I, II) or the secondary amines (Ia, IIa) in ether in the presence of two or one mole of potassium carbonate respectively, which neutralized the hydrogen iodide as it was formed.

Quaternization of the three tertiary amines (Ib, IIb, and IIIb) though negligible in ether proceeded readily in methanol, probably *via* a S_N1 mechanism.

Steck and Ross[7] reported the synthesis of dl-2-*exo*-hydroxy-3-*exo*-dimethylaminobornane (V) by catalytic reduction of 3-dimethylaminobornan-2-one in ethanol at ca. 40 Kg/cm^2 of hydrogen with Raney nickel as catalyst, but there are now doubts about their configurational assignment. Recent evidence[8] indicates that the 3-dimethylaminobornan-2-one used by Steck and Ross has an *endo*-dimethylamino group. To find out if there was an inversion of configuration during hydrogenation, 3-*endo*-dimethylaminobornan-2-one (IVb) was hydrogenated at atmospheric pressure in ethanol using Raney nickel as catalyst. The isolated product, m.p. 106° has $J_{2,3}$ of 3·5 Hz indicating that H(2) and H(3) are *trans* to each other.[9] The IR spectrum

was identical to that of IIIb of established *endo*- amino and *exo*-hydroxy configuration. Thus the compound reported by Steck and Ross[7] must be *endo*-dimethylamino and *exo*-hydroxy, i.e. IIIb.

Steric factors were also found to be important in the esterification of the hydroxyl function of the diastereoisomers (Ib, IIb, IIIb) of 2-hydroxy-3-dimethylaminobornane and their methobromides (Ic, IIc, IIIc). Acetic anhydride was used so that the reaction would go to completion. The methobromides, but not the methoiodides, were stable under the experimental conditions. The esterification of IIIb and its methobromide (IIIc) whose hydroxyl functions are *trans* to the nitrogen group, proceeded readily by refluxing in a 25% v/v solution of acetic anhydride in acetic acid for 24 hr to give IIIe and IIId respectively. Esterification of IIb and IIc under the same condition was unsuccessful; the difficulty was not surprising as the OH functions of IIb and IIc were flanked on one side by the bulky alkylamino group and on another side by the 8-Me group. Complete esterification of IIb and IIc to produce IIe and IId respectively were effected by refluxing in 80% v/v acetic anhydride in acetic acid; 50% v/v acetic anhydride in acetic acid gave incomplete esterification, whereas acetic anhydride alone produced compound decomposition. Esterification of Ib and Ic proceeded readily in a 80% v/v solution of acetic anhydride in acetic acid to yield Ie and Id respectively.

NMR data of the compounds synthesized are recorded in Table 1, and they are used both to elucidate configuration and to identify reaction products.

Elucidation of the configurations of the diastereoisomers of 2,3-substituted bornane was based on comparing the coupling constant between H(2), H(3) and H(4) with values predicted by Karplus for ethane derivatives.[9, 10] In general the *cis* (0° dihedral angle) coupling constants are much larger than the *trans* (122° dihedral angle) coupling constants. Subtle differences between the observed coupling constants and the calculated value have been observed.

The coupling constants (9–9·5 Hz) between H(2-*exo*) and H(3-*exo*) of the 2,3-*endo* substituted bornane series (Ia, Ib, Ic, Id, Ie) are consistantly higher by 1·2–2 Hz than that of H(2,-*endo*), H(3-*endo*) of the corresponding 2,3-*exo*-substituted bornanes (IIa, IIb, IIc, IId, IIe) which have coupling constants of 7–7·8 Hz. The calculated coupling constant for two *cis* vicinal protons (0° dihedral angle) from Karplus's equation is 8·2 Hz. That H(2-*endo*), H(3-*endo*) have lower coupling constants in the present series can be explained by the steric interference between the 8-Me and the substituted *exo* functions. Calculations[11] of distance of approach (based on Wilcox's model[12]) between the *exo*-OH and the 8-Me group indicated that it is less than the sum of the van der Waals radii of the two groups. In the case of more bulky substituents such as trimethylammonium bromide, it is expected that steric interference would be even larger. It is thus reasonable to assume that the dihedral angles between H(2-*endo*) and H(3-*endo*) of 2,3-*exo*-substituted bornanes would be distorted so that their values would be greater than 0°, and the corresponding observed coupling constants would be lower than 8·2 Hz. The same argument can be applied to the coupling constants of H(2-*endo*-) H(3-*exo*) of the 2-*exo*, 2-*endo*-substituted bornanes; the dihedral angles of H(2) and H(3) would be greater than 120°, and the observed coupling constants (3·2–4·4 Hz) are thus larger than the calculated value (2·1 Hz) based on 120°. With norbornene derivatives, some workers reported that $J_{H(endo)H(endo)}$ is smaller than $J_{H(exo)H(exo)}$ though recent evidence[13] had shown this is

TABLE 1. NMR SPECTRA OF 2,3-SUBSTITUTED BORNANES AND 3-SUBSTITUTED-BORNAN-2-ONE

	Compounds	Solvent	Chemical shift (τ)								J (Hz)
			10-CH_3	9-CH_3	8-CH_3	H (4)	H (3)	H (2)	—NMe	—OAc	
I	2-*endo*-Hydroxy-3-*endo*-aminobornane[14]	B-$CDCl_3$	9·14	9·10	9·10		6·52 m	6·41 m			$J_{2x,3x} \sim 9$
Ia	2-*endo*-Hydroxy-3-*endo*-methylaminobornane[14]	S-D_2O	9·19	9·11	9·06		6·42 q	5·88 b.d.	7·34		$J_{2x,3x} = 9$ $J_{3x,4} \sim 4$
		B-$CDCl_3$	9·14	9·10	9·10		7·00 q.d.	6·30 d.d.	7·65		$J_{2x,3x} = 9·2$ $J_{2x,6x} = 1·4$ $J_{3x,4} = 4$ $J_{3x,5x} = 1·0$
Ib	2-*endo*-Hydroxy-3-*endo* dimethylaminobornane	S-D_2O	9·14 s	9·10	9·06		6·43 m	5·90 b.d.	7·05 7·21 (1)		$J_{2x,3x} = 9$ $J_{3x,5x} = 1·5$ $J_{3x,4} \sim 4·2$
		B*-$CDCl_3$	9·11	9·11	9·11		~7·60 m	6·37 b.d.	7·80		$J_{2x,3x} = 9·4$ $J_{3x,4} \sim 4·2$
Ic	2-*endo*-Hydroxybornan-3-*endo*-yltrimethyl-ammonium bromide	DMSO	9·18	9·05	9·05		~ 6·1 m		6·67	4·00 (OH)	$J_{OH,2x} \sim 5·6$
		DMSO + D_2O	9·19	9·06	9·06		~6·25 m	5·86 b.d.	6·73		$J_{2x,3x} = 9·4$ $J_{3x,4} = 3·4$ $J_{2x,6x} \sim 1$
Id	2-*endo*-Acetoxy-bornan-3-*endo*-yltrimethyl-ammonium bromide	$CDCl_3$	9·16 s	9·02	8·83		5·50 m	4·45 d	6·34	7·78	$J_{2x,3x} = 9·5$ $J_{3x,4} = 3·8$

Ie	2-*endo*-Acetoxy-3-*endo*-dimethylaminobornane hydrochloride	$CDCl_3$	9·15 s	9·02	8·98	6·3 t.m.	4·68 d.d.	7·2 q[1]	7·64	$J_{2x,3x} = 9·5$ $J_{2x,6x} = 1$
II	2-*exo*-Hydroxy-3-*exo*-aminobornane	B, $CDCl_3$	9·06 s	9·22	8·93	6·96 b.d.	6·62 b.d.			$J_{2N,3N} = 7·8$
IIa	2-*exo*-Hydroxy-3-*exo*-methylaminobornane	S-D_2O	9·07 s	9·15	8·96	6·83 d	6·09 d	7·26		$J_{2N,3N} = 7·7$
		B*-$CDCl_3$	9·06 s	9·23	8·98	7·43 d	6·57 d	7·58		$J_{2N,3N} = 7·3$
IIb	2-*exo*-Hydroxy-3-*exo*-dimethylaminobornane	S-D_2O	9·07 s	9·16	8·97	6·74 d	6·06 d	7·12		$J_{2N,3N} = 7·6$
		B*-$CDCl_3$	9·04 s	9·23	8·96	7·78	6·58	7·72		$J_{2N,3N} = 7$
IIc	2-*exo*-Hydroxybornan-3-*exo*-yltrimethylammonium bromide	DMSO	9·12 s	9·16	8·77	6·37 b.d.	6·09 q	6·76	3·95 d (OH)	$J_{OH,2N} = 6$
		DMSO + D_2O	9·12 s	9·16	8·77	6·51 b.d.	6·06 d	6·78		$J_{2N,3N} = 7·7$
IId	2-*exo*-Acetoxybornan-3-*exo*-yltrimethylammonium bromide	$CDCl_3$	9·16 s	9·08	8·74	5·58 b.d.	4·55 d	6·45	7·83	$J_{2N,3N} = 7·5$
IIe	2-*exo*-Acetoxy-3-*exo*-dimethylaminobornane hydrochloride	$CDCl_3$	9·13	9·13	8·67	6·67 t.m.	4·79 d	7·1 q[1]	7·58	$J_{2N,3N} = 7·7$
III	2-*exo*-Hydroxy-3-*endo*-aminobornane[14]	B-$CDCl_3$	9·15	9·15	8·94	6·54 m	6·94 d			$J_{2N,3X} = 3·4$
IIIa	2-*exo*-Hydroxy-3-*endo*-methylaminobornane[14]	B-$CDCl_3$	9·15	9·15	8·93	6·95 t	6·91 d	7·65		$J_{2N,3X} = 3·2$ $J_{3X,5X} \sim 1$

	Compounds	Solvent	Chemical shift (τ)								J (Hz)
			10-CH_3	9-CH_3	8-CH_3	H (4)	H (3)	H (2)	—NMe	—OAc	
IIIb	2-*exo*-Hydroxy-3-*endo*-dimethylaminobornane	S-D_2O	9·13 s	9·10	9·00		~ 6·45 m		7·05, 7·13 (1)		
		B-$CDCl_3$	9·14	9·14	8·94		7·67 m	6·73 d	7·8		$J_{2N,3X}$ = 3·5
IIIc	2-*exo*-Hydroxybornan-3-*endo*-yltrimethylammonium bromide	DMSO	9·15	9·15	8·91		~6·1 m		6·78		
IIId	2-*exo*-Acetoxybornan-3-*endo*-yltrimethylammonium bromide	$CDCl_3$	9·17[a]	9·06	8·77		5·45 m	4·78 d	6·43	7·86	$J_{2N,3X}$ = 4·3 $J_{3X,4}$ ~ 4·2
IIIe	2-*exo*-Acetoxy-3-*endo*-dimethylaminobornane hydrochloride	DMSO	9·27 s	9·11	8·95		6·2 b.t.	5·0 d	7·3, 7·36 (1)	7·91	$J_{2N,3X}$ = 4·4
IV	3-*endo*-Amino-bornan-2-one	S-D_2O	9·04 s	8·94	9·05	7·5 m	5·94 d				$J_{3X,4}$ = 4·7
		B-$CDCl_3$	9·08 s	8·99	9·12	7·85 m	6·56 d				$J_{3X,4}$ = 4·5
IVa	3-*endo*-Ethylamino-bornan-2-one	S-D_2O	9·06 s	8·96	9·07	7·45 m	5·99 d		8·7 t 6·76 g[(2)]		$J_{3X,4}$ = 4·7
		B*-$CDCl_3$	9·10	9·00	9·12	7·90 m	6·75 d		8·88 t 7·4 q[(2)]		$J_{3X,4}$ = 4·3
IVb	3-*endo*-Dimethyl-amino-bornan-2-one	S-D_2O	9·05	8·94	9·06	7·35 m	5·97 d		6·93		$J_{3X,4}$ = 4·7

S = hydrochloride salt, B = free base, B* = base extracted from solution of salt in D_2O by reaction with NaOD, b = broad, s = sharp, m = multiplet, d = doublet, t = triplet, q = quadruplet, X = exo, N = endo

(1) Splitting of N-Me signal, due to hindered rotation

(2) N-Et signals

incorrect. The absence of 8-Me to interact sterically with the *exo*-substituent may explain the near equal coupling constants of $J_{H(endo)H(endo)}$ and $J_{H(exo)H(exo)}$ in norbornene.

Long range couplings between H(2-*exo*), H(3-*exo*) and the protons of C-6 amd C-5 of magnitude between 1–1·5 Hz are observed, similar to those reported by Anet.[9] No such long range couplings are observed with H(2-*endo*), H(3-*endo*) of the 2,3-*exo*-substituted bornanes (Table 1).

In their study of monosubstituted bornanes, Flautt and Erman[11] found that the α-methyne peak of the *exo*-substituted isomer (proton *endo*) is located at higher field than the peak of the corresponding *endo* isomer (proton *exo*). With bornane-2,3-diols, the only disubstituted bornanes cited, there did not appear to be a clear correlation, due most probably to the anisotropic effect of the pyridine-diol complex. In the present study on 2,3-disubstituted bornanes, Flautt and Erman's rule on the chemical shift difference of *endo* and *exo* protons was found to be true in all cases. The values of $\Delta_{endo-exo}$ varied between 0·08–0·61 ppm, even when comparing *endo*, *exo* protons of different steric environment e.g. comparing similar 2,3-*exo*-substituted bornanes or 2,3-*endo*-substituted bornanes with 2-*exo*-3-*endo*-substituted bornanes (see Table 1, e.g. comparing H(3) of II and III, $\Delta_{endo-exo}$ = (6·96–6·54) ppm = 0·42 ppm, and so on).

Alkylation of the 3-primary amino group introduced an up-field shift of the signal for H(3) in the three diastereoisomers of 2-hydroxy-3-aminobornane studied (Table 2). The magnitude of the shift was approximately the same in the three cases with the

TABLE 2. EFFECT OF ALKYLATION OF THE 3-AMINO GROUP OF 2-HYDROXY-3-AMINOBORNANE DIASTEREOISOMERS ON THE CHEMICAL SHIFT* OF H(3)

Stereo config. of substituents / R	NH_2	$NHCH_3$	$N(CH_3)_2$
	I	Ia	Ib
2-*endo*-OH-3-*endo*-R	6·52	7·00 (6·42)†	7·6 (6·43)†
		0·48	0·6
	II	IIa	IIb
2-*exo*-OH-3-*exo*-R	6·96	7·43 (6·83)†	7·78 (6·74)†
		0·47	0·35
	III	IIIa	IIIb
2-*exo*-OH-3-*endo*-R	6·54	6·95	7·67
		0·41	0·72

* The chemical shifts in τ.

† The chemical shift of the hydrochloride salt in D_2O.

introduction of the first Me group into the amino function. Differences are shown on the introduction of the second Me group, depending on the steric environment of the basic group. With 2-*exo*-hydroxy-3-*endo*-dimethylaminobornane (IIIb) whose dimethylamino function is least hindered, a 0·72 ppm upfield shift from its secondary amine analogue was recorded, which is double that of the corresponding shift of 2-*exo*-hydroxy-3-*exo*-dimethylaminobornane (IIb) whose dimethylamino function is most sterically hindered. The dimethylamino function of 2-*endo*-hydroxy-3-*endo*-dimethylaminobornane, whose degree of steric hindrance is intermediate between that of IIb and IIIb, has a upfield shift of 0·6 ppm, intermediate between that of IIb and IIIb. That the observed upfield shift was due to the increased electronegativity of the N atom with increased alkylation can be shown by the fact that the corresponding salts of the amines did not show any such effect (Table 2), nor did the trimethylammonium bromide derivatives (Table 1).

The Me peaks of the bornane derivatives (Table 1) were tentatively assigned as 8,9 or 10-Me according to the empirical rules postulated by previous workers.[14-17]

It is noted that the esters Id, IId and IIId are analogues of acetylcholine in which the ester function and onium head are held in rigid relationship to each other, in the *cis*-geometry in Id and IId, and *trans*-geometry in IIId. Enzyme and pharmacological studies will be reported separately.

EXPERIMENTAL

Natural (+)-camphor, supplier: BDH, was used as the starting material for the syntheses of the diastereoisomers of 2-hydroxy-3-aminobornane.[1, 3] The NMR spectra were obtained on a 60 MHz Perkin–Elmer R-10 instrument with TMS as internal standard. The IR spectra were measured on a Unicum SP 200 spectrophotometer as Nujol mulls or KCl discs. M. pts were uncorrected. Micro-analysis by Dr. F. B. Strauss, Oxford, and Mr. G. S. Crouch, Brunswick Square, London. The hydrochloride salts of the amines were used for analysis as the free bases were found to be unstable in some cases.

General procedure of reductive alkylation

A mixture containing 0·1 mole of the appropriate primary amine (I, II, III and IV), 15 ml of 40% formalin soln (0·2 mole) and 5 ml conc HCl in 100 ml 95% EtOH was hydrogenated under atm press with 400 mg Adam's catalyst. The reaction was generally completed after 24 to 36 hr when the calculated volume of H_2 was used. The catalyst was filtered off, the EtOH solution made slightly acidic with ethanolic HCl and the solvent was then removed under reduced press. The crude solid residue was recrystalized from EtOH and ether.

(a) 2-endo-*Hydroxy*-3-endo-*methylaminobornane* (Ia). 10 g 2-*endo*-hydroxy-3-*endo*-aminobornane[3] yielded 10·5 of Ia (HCl salt), 80%, m.p. 315° (char.). The base, m.p. 86·5° was recrystalized from EtOH-water. (Found for HCl salt: C, 60·3; H, 10·0; N, 6·5; Cl, 16·1: Calc. for $C_{11}H_{22}$ONCl: C, 60·1; H, 10·1; N, 6·4; Cl, 16·1%).

(b) 2-exo-*Hydroxy*-3-exo-*methylaminobornane* (IIa). 12 g. 2-*exo*-hydroxy-3-*exo*-aminobornane[1] yielded 11·9 g of IIa (HCl salt), m.p. 324–327° (char.), yield: 76·4% (Found for HCl salt: C, 60·45; H, 10·15; N, 6·7; $C_{11}H_{22}$ONCl requires: C, 60·1; H, 10·1; N, 6·4%).

(c) 2-exo-*Hydroxy*-3-endo-*dimethylaminobornane* (IIIb). (i) 7·3 g. 2-*exo*-hydroxy-3-*endo*-aminobornane[1, 3] yield 8·5 g of IIIb (HCl salt), 84·3%, m.p. 360–365° (char.). The base, m.p. 106° was crystalized from light petroleum (40–60°). Found for HCl salt: C, 61·7; H, 10·3; N, 6·2; Cl, 15·4; Calc. for $C_{12}H_{24}$ONCl: C, 61·65; H, 10·35; N, 6·0; Cl, 15·2%).

(ii) 3·5 g freshly prepared IVb dissolved in 15 ml EtOH was hydrogenated at atm pressure with 1·5 g Raney Ni (W5) as catalyst. The reduction was complete after 24 hr. The isolated base had m.p. 106°, with IR spectrum identical to that of IIIb; yield, 3·07 g (80%).

(d) 3-endo-*Dimethylaminobornan*-2-*one* (IVb). 13·7 g freshly prepared IV[6] yielded 16·8 g of IVb (HCl salt), 88·4%, m.p. 251°, the IR spectrum of which was identical to that of an authentic sample of IVb.[6]

(e) 3-endo-*Ethylaminobornan*-2-*one* (IVa). 2 g freshly prepared IV was alkylated with acetaldehyde to yield 1·5 g of IVa (HCl salt) 64%, m.p. 293° (HCl salt). (Found for HCl salt: C, 62·4; H, 9·7; N, 5·8; C, 15·5; Calc. for $C_{12}H_{22}ONCl$: C, 62·2; H, 9·6; N, 6·0; Cl, 15·3%).

General method for alkylation to tertiary amines of the primary or secondary amines with methyl iodide

The primary amines (I, II) and secondary amines (Ia, IIa) were alkylated to tertiary amines (Ib, IIb) with MeI by the following general method.

0·1 mole of the primary amine and 0·4 mole MeI (half this quantity was used for secondary amine) were dissolved in 200 ml ether in a 500 ml flask, and the soln stirred with a magnetic stirrer for 12 hr. during which time the hydrogen iodide salt of the secondary or tertiary amine precipitated as fine crystals. 0·1 mole K_2CO_3 dissolved in 50 ml water was added, and the flask gently shaken for a few min to dissolve the salt into the aqueous layer and the base thus released was extracted by the ether layer. If primary amine was the starting material, additional K_2CO_3 (0·1 mole) was added in small portions during the next 24 hr. The reaction was complete on the third or fourth day. The ether layer was separated off, dried over Na_2SO_4 and the base precipitated as the hydrochloride salt with ethanolic HCl. The yields varied between 70–80%.

(a) 2-endo-*Hydroxy*-3-3ndo-*dimethylaminobornane* (Ib). Hydrochloride salt crystalized from EtOH and ether, m.p. 336° (sealed). (Found for: HCl salt: C, 61·5; H, 10·2; N, 6·1; Calc. for $C_{12}H_{24}ONCl$: C, 61·65; H, 10·35; N, 6·0%).

(b) 2-exo-*Hydroxy*-3-exo-*dimethylaminobornane* (IIb). Hydrochloride salt, m.p. 310–315° (char. sealed). (Found for HCl salt: C, 61·3; H, 10·4; N, 6·2%).

General method for the quaternization of the tertiary amines

The tertiary amines Ib, IIb and IIIb were quaternized with MeBr as follows:

A soln of 33% w/v of MeBr in MeOH was prepared, taking the usual precautions, and kept below 0°. 0·05 mole of the tertiary base dissolved in 5 ml MeOH in a 100 ml flask was cooled to 0° and 52·5 ml of MeBr soln (0·1 mole) was added. The flask was securely stoppered and left at room temp for 24 hr after which the soln was refluxed for several hr. The solvent was removed *in vacuo* and the creamy residue was shaken with 20 ml ether to remove any unreacted amine. The solid was recrystallized from EtOH and ether giving crops of flake-like crystals. The unreacted amine was quaternized again so that a quantitative yield was obtained; this was necessary for Ib and IIb, but not IIIb.

(a) 2-endo-*Hydroxybornan*-3-endo-*yltrimethylammonium bromide* (Ic), m.p. 316·5° (sealed), (lit.[18] ~ 270°). (Found: C, 53·6; H, 8·7; N, 4·8; Br, 27·9; Calc. for $C_{13}H_{26}ONBr$: C, 53·4; H, 9·0; N, 4·7; Br, 27·5%).

(b) 2-exo-*Hydroxybornan*-3-exo-*yltrimethylammonium bromide* (IIc). m.p. 323·5° (sealed). (Found: C, 53·3; H, 8·95; N, 4·9; Br, 27·2%).

(c) 2-exo-*Hydroxybornan*-3-endo-*yltrimethylammonium bromide* (IIIc), m.p. 305–310° (char.). (Found: C, 53·5; H, 8·65; N, 4·7%).

General method of esterification with acetic anhydride

A mixture of 2 g of the hydroxybornane (hydrochloride salt of the tertiary bases, Ib, IIb, IIIb, or their methobromides Ic, IIc, IIIc) in 100 ml of a suitable concentration of Ac_2O in AcOH was refluxed gently for 24 hr, and the acid and anhydride were removed *in vacuo*. The solid residue was shaken with 20 ml dry ether to remove any remaining acid and anhydride, and was recrystalized from EtOH and dry ether. To acetylate IIIb and its methobromide (IIIc), it was sufficient to use a concentration of 25% v/v Ac_2O in AcOH, while 80% v/v of Ac_2O in AcOH was required to effect the complete esterification of Ib, IIb and their methobromides (Ic and IIc).

(a) 2-endo-*Acetoxy*-3-endo-*dimethylaminobornane hydrochloride* (Ie). m.p. 263°, (Found: C, 61·1; H, 9·3; N, 5·2; Cl, 12·5; $C_{14}H_{26}NO_2Cl$ requires: C, 61·0; H, 9·5; N, 5·1; Cl, 12·85%).

(b) 2-exo-*Acetoxy*-3-exo-*dimethylaminobornane hydrochloride* (IIe). m.p. 259–60° (sealed). (Found: C, 60·9; H, 9·2; N, 5·1; Cl, 12·7%).

(c) 2-exo-*Acetoxy*-3-endo-*dimethylaminobornane hydrochloride* (IIIe). m.p. 271·5° (Found: C, 61·05; H, 9·5; N, 5·3%).

(d) 2-endo-*Acetoxybornan*-3-endo-*yltrimethylammonium bromide* (Id). m.p. 236·5° (sealed), (Found: C, 54·0; H, 8·1; N, 4·2; Br, 23·6. $C_{15}H_{28}NO_2Br$ requires: C, 53·9; H, 8·4; N, 4·2; Br, 23·9%).

(e) 2-exo-*Acetoxybornan*-3-exo-*yltrimethylammonium bromide* (IId). m.p. 268° (sealed), (Found: C, 53·65; H, 8·45; N, 4·4; Br, 23·9%).

(f) 2-exo-*Acetoxybornan*-3-endo-*yltrimethylammonium bromide* (IIId). m.p. 224°, (Found: C, 53·70; H, 8·7; N, 4·3; Br, 24·0%).

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