Nuclear Magnetic Resonance and *X*-Ray Stereochemical Studies on 1-Benzyltetrahydroisoquinolinium Salts

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The relative stereochemistry at positions 1 and 2 of *N,N*-dialkyl-1-benzyl-1,2,3,4-tetrahydroisoquinolinium salts has been assigned *via* a combination of ^{1}H and ^{13}C n.m.r. studies and confirmed by single-crystal *X*-ray analysis of *trans*-*N*-3-hydroxypropyl-5′-methoxylaudanosinium perchlorate [*trans*-2j)] and *cis*-*N*-3-hydroxypropyl-5′-methoxylaudanosinium iodide [*cis*-(2h)] monohydrate. Quaternization of either laudanosine or 5′-methoxy-laudanosine with an alkyl iodide leads to major isomers which possess a *trans*-relationship between the entering *N*-alkyl group and the 1-benzyl substituent; these isomers characteristically have the less shielded 1-H and *N*-methyl protons in deuteriochloroform. Crystals of *trans*-(2j) and *cis*-(2h) monohydrate both belong to the monoclinic system, Space group *P*2$_1$/*c*, with *a* = 8.123(4), *b* = 20.380(8), *c* = 16.710(6) Å, β = 102.14(5)°, *Z* = 4 for the former, and *a* = 11.475(5), *b* = 17.749(6), *c* = 14.278(5) Å, β = 113.51(5)°, *Z* = 4, for the latter compounds. Full-matrix least-squares refinement of atomic positional and thermal parameters converged at *R* = 0.082 [2 215 reflections] for (*trans*-(2j) and 0.077 [2 987 reflections] for (*cis*-(2h) monohydrate. The stereochemistry of the protonation products arising from these tetrahydroisoquinoline bases is also discussed.

In the course of our development work on a neuromuscular blocking agent containing a *N,N*-dialkyl-1-benzyl-1,2,3,4-tetrahydroisoquinolinium moiety (1), it became necessary to assign the relative stereochemistry at the two chiral centres, C(1) and N(2). For those salts having two different *N*-alkyl substituents, two diastereoisomeric pairs are possible, a *cis* (±)-pair in which the *N*-substituent of higher molecular weight and the benzyl group are *cis*, and a *trans* (±)-pair in which these groups are *trans*.

The stereochemistry of this system was first studied by Radics *et al.*[1-3] who synthesized three quaternary iodides of 1-(3′,4′-dimethoxybenzyl)-6,7-dimethoxy-*N*-methyl-1,2,3,4-tetrahydroisoquinoline (3a) (*i.e.* laudanosine), *viz.* the *N*-methyl (1c), *N*-ethyl (1d), and *N*-benzyl (1e) salts, as well as the hydriodide (1a). These workers, who found a moderate degree of selectivity in the quaternization and protonation reactions, based their assignments of the relative configurations on relative stabilities. Thus, equilibration of the *N*-benzyl-*N*-methyl (±)-pairs (1e) in chloroform showed that the major isomer from the quaternization process was the more stable one. From conformational considerations, these investigators concluded that the substituent (3,4-dimethoxybenzyl) at C(1) and the bulkier (benzyl) group at N(2) were *trans*. Furthermore, they not only extended this conclusion to the *N*-ethyl-laudanosinium iodides (1d), based on the *N*-methyl proton chemical shift, but also concluded that the 1-benzyl group is preferentially pseudo-equatorial in all the salts.

The stereochemistry in laudanosinium ethiodide (1d) was also assigned by Stenlake *et al.*[4] who, like Radics *et al.*, based their conclusion on a conformation in which the benzyl group is pseudo-equatorial in the quaternary salts. However, in this case, the chemical shifts of the methyl protons in the *N*-ethyl group and of 8-H were used to assign the relative stereochemistry at the two
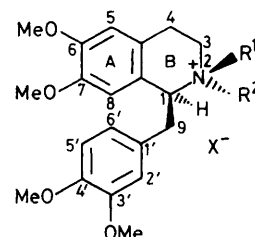
(1)

a; R^1, R^2 = H, Me; X = I
b; R^1, R^2 = H, Me; X = CF$_3$CO$_2$
c; R^1 = R^2 = Me; X = I
d; R^1, R^2 = Me, Et; X = I
e; R^1, R^2 = Me, CH$_2$Ph; X = I
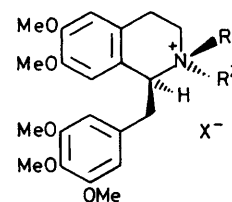
(2)

a; R^1, R^2 = H, Me; X = I
b; R^1 = R^2 = Me; X = I
c; R^1 = R^2 = Me; X = Cl
d; R^1 = R^2 = Me; X = TsO
e; R^1 = R^2 = Me; X = CF$_3$SO$_3$
f; R^1, R^2 = CH$_3$, CD$_3$; X = I
g; R^1, R^2 = Me, Et; X = I
h; R^1, R^2 = Me, CH$_2$[CH$_2$]$_2$OH; X = I
i; R^1, R^2 = Me, CH$_2$[CH$_2$]$_2$OH; X = Cl
j; R^1, R^2 = Me, CH$_2$[CH$_2$]$_2$OH; X = ClO$_4$
k; R^1, R^2 = Me, CH$_2$[CH$_2$]$_2$CH$_3$; X = I

chiral centres. It was assumed that, as a consequence of restricted rotation about the C(1)–C(9) bond, shielding effects resulting from ring c currents would be minimal in both the axial and equatorial *N*-ethyl groups, whereas

the methyl protons of the *N*-ethyl group would be more shielded by ring A when this substituent is axially oriented than when it is equatorial. Therefore, the higher-field triplet was attributed to the diastereoisomer with the axial *N*-ethyl substituent. Similarly, the 8-H signals for the two diastereoisomers appeared as singlets, shifted upfield because of shielding by ring c currents. It was assumed that, owing to greater impedence to free rotation about the C(1)–C(9) and C(9)–C(1′) bonds in the isomer with the equatorial *N*-ethyl group, this shielding would be marginally greater in the diastereoisomer bearing the axial *N*-ethyl group. Therefore, the higher-field singlet was ascribed to the diastereoisomer with the *N*-ethyl group axially disposed (*i.e. cis*), a conclusion which leads to assignments opposite those of Radics *et al.*

RESULTS AND DISCUSSION

Stereochemistry of Alkylation.—In the present work, high resolution ^{1}H and ^{13}C n.m.r. studies were conducted on several 1-benzyl-1,2,3,4-tetrahydroisoquinolinium salts to assign their relative configurations; the results are summarized in Tables 1 and 2.

changes occur at room temperature but that these are slowed down upon cooling, leading to exchange broadening of those signals which are substantially different in
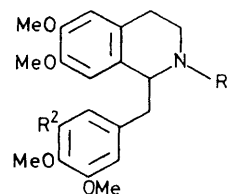
(3)

a; R¹ = Me, R² = H
b; R¹ = Et, R² = H
c; R¹ = Me, R² = OMe
d; R¹ = CH₂[CH₂]₂OH, R² = OMe

the two contributing conformers (Scheme). It is possible that hindered rotation about the C(1)–C(9) or C(9)–C(1′) bonds contribute to the observed broadening; however, the fact that C(4) is broadened leads us to prefer the former argument. *In either case, contrary to previous postulates,*[1–4] *in protonated or N-alkylated laudanosine*

TABLE 1

^{1}H N.m.r. chemical shifts in CDCl₃

Compound	R¹	R²	NMe [a]	7-OMe [b]	8-H	1-H	6-OMe	5-H	NCH₂CH₃
trans-(1a)	H	Me	2.92	3.51	5.85	4.30	3.86	6.65	
trans-(1b)	H	Me	2.99	3.48	5.91	4.40		6.63	
cis-(1b)	H	Me			6.08	4.70			
(1c)	Me	Me	3.91	3.40	5.70	5.24	3.84	6.64	
			3.53						
trans-(1d)	Me	Et	3.72	3.40	5.72	4.98		6.60	1.45
cis-(1d)	Et	Me	3.28	3.41	5.79	4.90		6.66	1.66
trans-(1e)	Me	CH₂Ph	3.64	3.46	5.80		3.89		
cis-(1e)	CH₂Ph	Me	3.19	3.38	5.76		3.87		
trans-(2a)	H	Me	2.91	3.53	5.86	4.25	3.86	6.65	
(2b)	Me	Me	3.90	3.42	5.79	5.24	3.84	6.66	
			3.53						
trans-(2f)	Me	CD₃	3.90	3.42	5.77	5.23	3.84	6.66	
cis-(2f)	CD₃	Me	3.53	3.42	5.77	5.23	3.84	6.65	
trans-(2g)	Me	Et	3.72	3.40	5.72	5.00		6.60	
cis-(2g)	Et	Me	3.28	3.41	5.79	4.90		6.66	
trans-(2h)	Me	[CH₂]₃OH	3.66	3.46	5t86	4.93	3.84	6.68	
cis-(2h)	[CH₂]₃OH	Me	3.23	3.47	5.83	4.70		6.62	
trans-(2k)	Me	Buⁿ	3.80	3.45	5.79	5.15		6.65	
cis-(2k)	Buⁿ	Me	3.32	3.45	5.87	4.70		6.64	

[a] NMe Assignments were verified by selective proton decoupling of ^{13}C spectra (F. W. Wehrli and T. Wirthin, ' Interpretation of Carbon 13 N.M.R. Spectra,' Heyden and Son Ltd., London, 1976, p. 77) in which NMe and OMe are clearly distinguished. [b] 7-OMe assignments were verified by n.O.e. with 8-H.

Before the chemical-shift data were analyzed, consideration had to be given to the question of whether the system under investigation was rigid or conformationally mobile. Conformational mobility was examined by a series of low-temperature ^{13}C n.m.r. studies in deuteriochloroform on laudanosine (3a), its trifluoroacetate salt (1b), its methiodide (1c), *cis*- and *trans*-ethiodides (1d), and *trans*-*N*-3-hydroxypropyl-5′-methoxylaudanosinium iodide (2 h) over a range of temperatures down to −80 °C. For all of the salts studied, considerable broadening of the signals for the four α-carbons on nitrogen, C(4), the benzylic carbon, and C(8) was noted, whereas the other signals remained sharp, as shown in Figure 1, for *cis*- and *trans*-laudanosinium ethiodides (1d). These results imply that fast conformational

(3a) *or* 5′-*methoxylaudanosine* (3c) *the energy difference between a pseudo-axial and a pseudo-equatorial benzyl group is apparently not large enough to lead to a decisive conformational preference even at* −80 °C.

Quaternization of compound (3a) or (3c) with alkyl iodides (such as deuteriomethyl, ethyl, 3-hydroxypropyl, n-butyl, and benzyl) resulted in two diastereoisomeric (±)-pairs with one diastereoisomer predominating in all cases (9 : 1 for the deuteriomethyl, 4 : 1 for the benzyl, and *ca.* 3 : 1 for the remaining alkyl derivatives). *In deuteriochloroform, the minor isomers characteristically had the more shielded* 1-H *and* N-*methyl protons.*

Initial, tentative configurational assignments were obtained from nuclear Overhauser effect (n.O.e.) experiments on *cis*- and *trans*-isomers of *N*-3-hydroxypropyl-

TABLE 2

^{13}C N.m.r. chemical shifts

| Compound	R¹	R²	C(1)	NMe	NCH₂	C(3)	C(4)	ArCH₂	C(4a)	C(5)[a]	C(6)	C(7)	C(8)[a]	C(8a)	C(1')	Solvent
(3a)[b]	Me	H[c]	64.9	42.7		47.1	25.7	40.8	126.2	113.2	147.3	147.3	111.3	132.6	129.4	CDCl₃
			$^1J_{CH}$ 138 Hz	$^1J_{CH}$ 132 Hz		$^1J_{CH}$ 133 Hz	$^1J_{CH}$ 128 Hz	$^1J_{CH}$ 124 Hz								
(3b)	Et	H	62.6	40.4		47.4	25.2	40.8	126.4	113.4	147.4	147.4	111.1	132.9	129.7	CDCl₃
trans-(1b)	H	Me	66.1			45.4	21.3	41.9	120.3	112.1	147.6	149.4	113.3	120.9	127.1	CDCl₃
			$^1J_{CH}$ 146 Hz	$^1J_{CH}$ 144 Hz		$^1J_{CH}$ 140 Hz	$^1J_{CH}$ 131 Hz	$^1J_{CH}$ 129 Hz								
cis-(1b)	Me	H	63.9	39.5		48.3	24.6	35.5								
				$^1J_{CH}$ 144 Hz												
trans-(1d)	Me	Et	70.2	49.0	57.2	53.3	23.6	37.9	120.4	111.9	147.1	149.4	112.3	121.2	127.3	CDCl₃
cis-(1d)	Et	Me	70.6	46.8	59.5	54.0	23.7	37.9	120.8	111.5	147.4	149.5	112.0	121.7	127.3	CDCl₃
trans-(2a)	H	Me	65.4	40.3		44.9	21.4	41.9	120.8	111.3	147.5	149.4	111.5	120.9	131.0	CDCl₃
(2b)	Me	Me	71.9	50.9 / 53.0		55.3	23.7	38.7	119.7	110.7	147.0	149.4	111.8	121.3	130.3	CDCl₃
trans-(2h)	Me	[CH₂]₃OH	70.5	49.8		53.9	23.7	38.5	120.6	111.3	147.1	149.5	112.1	121.3	130.5	CDCl₃
trans-(2g)	Me	Et	69.9	47.6	56.6	52.5	23.0	36.8	121.2	111.5	147.9	148.6	114.4	121.5	128.2	(CD₃)₂SO
cis-(2g)	Et	Me	68.5	45.5	57.9	52.8	22.5	36.4	121.4	111.3	147.9	148.6	114.1	121.8	127.9	(CD₃)₂SO
trans-(2h)	Me	[CH₂]₃OH	69.6	48.2	59.0	52.6	22.8	37.0	121.2	111.3	146.0	148.5	111.8	121.5	131.4	(CD₃)₂SO
cis-(2h)	[CH₂]₃OH	Me	68.6	46.3	60.4	53.4	22.8	36.8	121.4	111.4	146.1	148.6	112.1	121.7	131.2	(CD₃)₂SO
trans-(2h)	Me	[CH₂]₃OH	71.6	49.6	60.7	54.4	24.3	38.8	122.6	112.6	148.1	150.7	113.9	122.6	132.5	CD₃OD
cis-(2h)	[CH₂]₃OH	Me	70.9	47.6	62.6	55.3	24.2	38.6	122.6					122.7	132.3	CD₃OD

[a] C(5) and C(8) were assigned using selective heterodecoupling (see ref. in a, Table 1). [b] The chemical shifts of laudanosine were previously assigned by Levy (G. C. Levy, 'Topics in Carbon 13 N.M.R. Spectroscopy,' Wiley and Sons, New York, 1976, Vol. II, p. 106). [c] The coupling constants are reasonable for such assignments (ref. 7, p. 337).
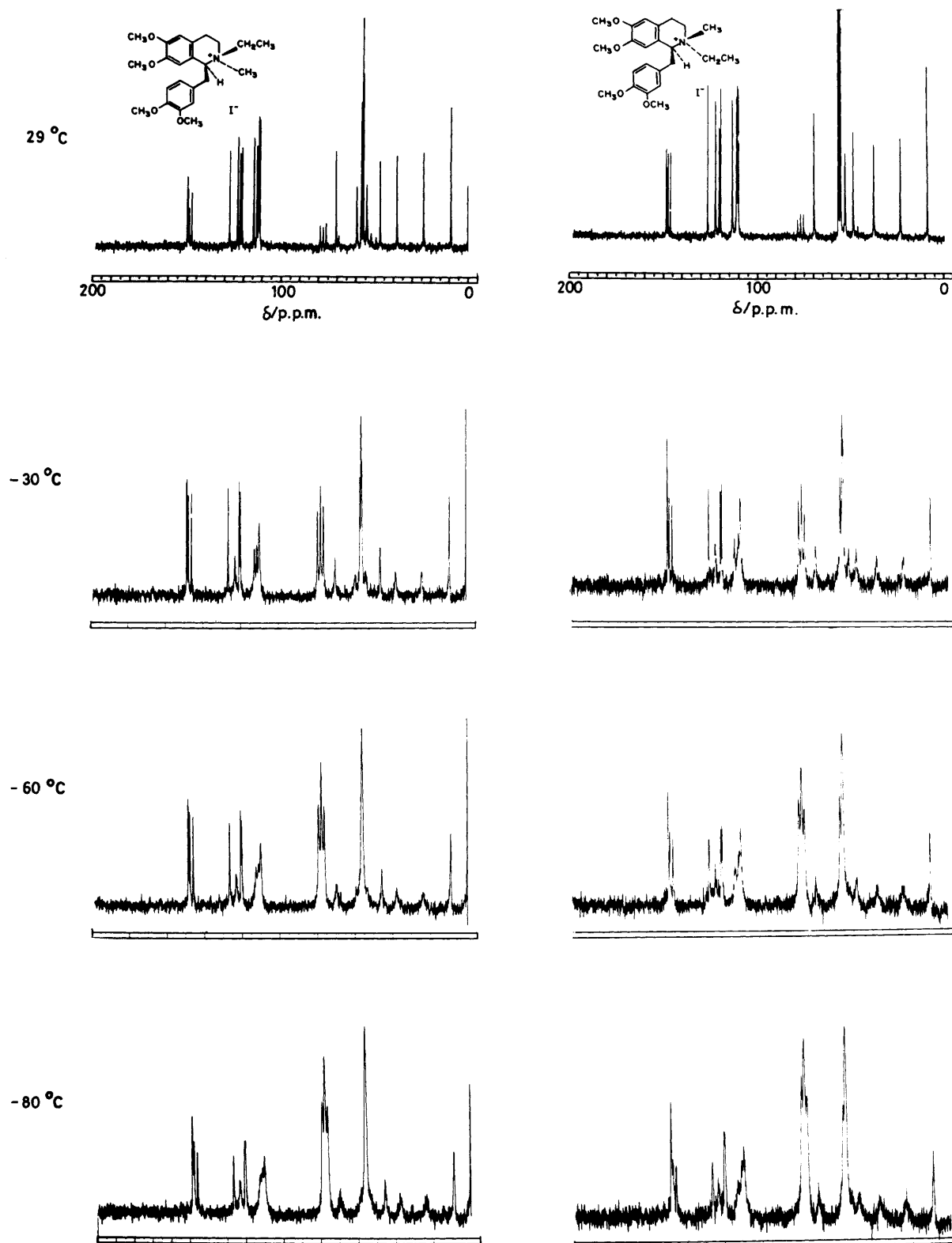
FIGURE 1 ^{13}C N.m.r. spectra of *cis*- and *trans*-(2h) at various temperatures
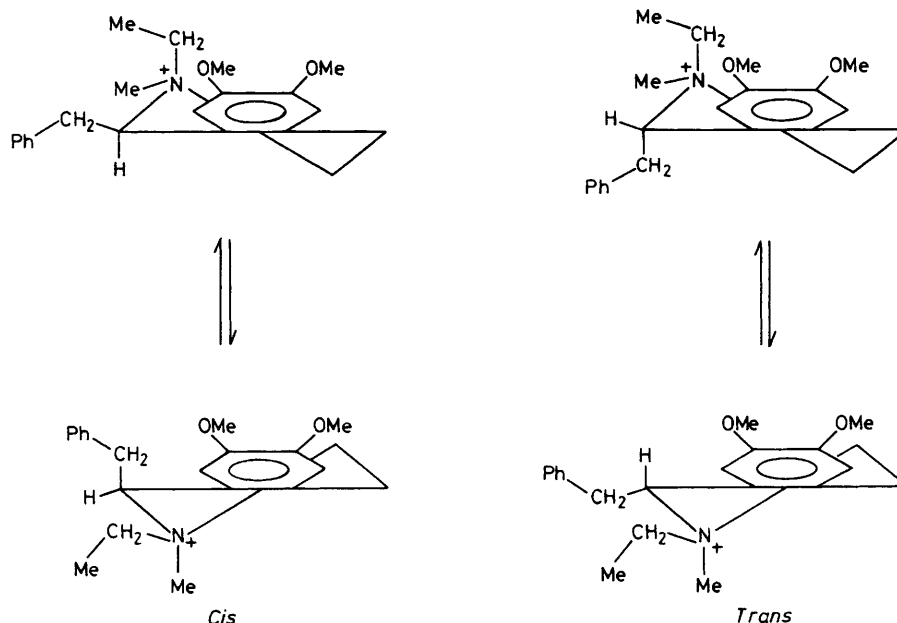
SCHEME

5'-methoxylaudanosinium iodides (2h) and 5'-methoxy-N-methyl-laudanosinium iodide (2b) as summarized in Table 3. The enhancements of the 1-H intensity upon

two N-methyl groups in both conformations that, if fast ring flipping between these two conformations is

TABLE 3

Nuclear Overhauser effect [a]

Compound	Irradiated	Observed	% enhancement
trans-(2h)	NMe (δ 3.29)	1-H	7.2
	7-OMe	8-H	14.0
cis-(2h)	NMe (δ 2.99)	1-H	12.7
	7-OMe	8-H	15.0
(2b)	Low field NMe (δ 3.35)	1-H	9.1
	High field NMe (δ 3.09)	1-H	17.4
	7-OMe	8-H	16.4

[a] 6 mg/0.5 ml $(CD_3)_2SO$ with 1 drop D_2O. Degassed by bubbling with nitrogen gas for 20 min. Data obtained at 80 °C.

irradiation of the N-methyl proton signals reflect the relative orientations of these nuclei. The N-methyl group in cis-(2h) is gauche to 1-H in both conformations and gives rise to a larger enhancement than it does in the trans-isomer where it is gauche in one conformation and nearly anti in the other (Scheme).

Inspection of the n.O.e. results for the N,N-dimethyl salt (2b) reveals a 2 : 1 ratio of enhancement of 1-H upon irradiation, in turn, of each of the two N-methyl protons. This result agrees with that reported by Lindon and Ferrige,[5] and leads to assignment of the higher-field N-methyl group as being trans to benzyl. These workers argued that if one assumes similar energies for the two possible half-chair forms, with a finite barrier to interconversion, then it is only necessary to consider these two individual conformations because the populations of the intermediate states will be low. It follows from consideration of the relative distances between 1-H and the

TABLE 4

Non-hydrogen atom fractional co-ordinates ($\times 10^4$), with standard deviations in parentheses

Atom	x	y	z
(a) trans-(1j)			
C(1)	4 429(7)	1 379(2)	6 654(3)
N(2)	4 114(6)	2 059(2)	6 250(3)
C(3)	2 267(10)	2 121(3)	5 844(4)
C(4)	1 748(10)	1 640(3)	5 146(4)
C(4a)	2 471(8)	963(3)	5 354(4)
C(5)	1 896(8)	442(3)	4 826(4)
C(6)	2 523(7)	−172(3)	4 970(4)
C(7)	3 748(7)	−300(3)	5 661(3)
C(8)	4 391(7)	209(3)	6 179(3)
C(8a)	3 757(7)	848(3)	6 043(3)
C(9)	3 694(7)	1 319(3)	7 426(3)
C(10)	4 527(11)	2 601(4)	6 873(5)
C(11)	5 191(12)	2 109(4)	5 607(5)
C(12)	6 656(17)	2 381(7)	5 830(8)
C(13)	5 415(22)	2 672(7)	5 133(10)
O(14)	6 795(10)	2 689(4)	4 551(6)
O(15)	2 026(6)	−702(2)	4 462(3)
C(16)	923(11)	−581(5)	3 688(5)
O(17)	4 321(6)	−928(2)	5 761(3)
C(18)	5 395(14)	−1 103(4)	6 506(6)
C(1')	4 354(7)	717(3)	7 911(3)
C(2')	6 029(8)	690(3)	8 308(4)
C(3')	6 662(9)	139(3)	8 744(4)
C(4')	5 617(9)	−391(3)	8 779(4)
C(5')	3 921(8)	−362(3)	8 392(4)
C(6')	3 283(8)	192(3)	7 957(4)
O(7')	8 274(7)	77(3)	9 165(4)
C(8')	9 349(11)	638(5)	9 222(8)
O(9')	6 275(6)	−948(2)	9 208(3)
C(10')	6 143(11)	−928(4)	10 048(5)
O(11')	3 034(7)	−918(2)	8 481(4)
C(12')	1 288(12)	−910(4)	8 140(8)
Cl	10 017(2)	2 644(1)	3 101(1)
O(1'')	8 765(8)	2 236(5)	3 258(5)
O(2'')	10 908(11)	2 914(4)	3 840(5)
O(3'')	9 357(16)	3 153(5)	2 611(6)
O(4'')	11 047(10)	2 298(5)	2 748(6)
[C(13')	8 040(16)	2 453(8)	5 115(8)]

TABLE 4 (continued)

Atom	x	y	z
(b) cis-(2h)			
C(1)	4(6)	1 419(4)	3 473(5)
N(2)	1 246(6)	1 570(4)	4 406(4)
C(3)	1 058(7)	2 210(5)	5 021(6)
C(4)	34(7)	2 037(5)	5 419(6)
C(4a)	−1 025(7)	1 549(5)	4 723(5)
C(5)	−2 019(7)	1 346(5)	5 039(6)
C(6)	−2 942(7)	839(5)	4 449(6)
C(7)	−2 916(7)	523(4)	3 582(5)
C(8)	−1 994(7)	716(4)	3 291(5)
C(8a)	−1 003(6)	1 231(5)	3 876(5)
C(9)	−380(8)	2 063(5)	2 697(6)
C(10)	1 661(9)	871(6)	5 047(7)
C(11)	2 323(7)	1 806(5)	4 079(6)
C(12)	2 752(7)	1 197(6)	3 547(6)
C(13)	3 450(9)	1 527(7)	2 955(7)
O(14)	2 615(6)	1 958(5)	2 113(5)
O(15)	−3 905(5)	589(4)	4 719(4)
C(16)	−3 928(9)	865(7)	5 659(7)
O(17)	−3 058(5)	22(3)	3 053(4)
C(18)	−3 806(10)	−280(6)	2 153(6)
C(1')	−1 708(7)	1 997(5)	1 917(5)
C(2')	−2 675(7)	2 355(5)	2 085(6)
C(3')	−3 931(7)	2 253(5)	1 385(6)
C(4')	−4 193(7)	1 815(5)	520(5)
C(5')	−3 217(7)	1 462(5)	367(5)
C(6')	−1 967(7)	1 545(5)	1 058(5)
O(7')	−4 954(5)	2 569(4)	1 483(4)
C(8')	−4 752(9)	2 963(7)	2 392(7)
O(9')	−5 434(5)	1 757(4)	−209(4)
C(10')	−6 148(8)	1 224(7)	49(8)
O(11')	−3 572(5)	1 032(4)	−503(4)
C(12')	−2 604(9)	646(7)	−695(7)
I	−7(1)	−624(1)	1 993(1)
O(W)	894(7)	945(5)	771(5)

TABLE 5

Interatomic distances (Å) and angles (°), with standard deviations in parentheses

(a) Bond lengths

	trans-(2j)	cis-(2h)
C(1)-N(2)	1.540(7)	1.544(9)
C(1)-C(8a)	1.509(7)	1.519(10)
C(1)-C(9)	1.537(8)	1.528(11)
N(2)-C(3)	1.516(9)	1.509(11)
N(2)-C(10)	1.506(9)	1.502(12)
N(2)-C(11)	1.524(11)	1.531(10)
C(3)-C(4)	1.513(10)	1.527(12)
C(4)-C(4a)	1.511(9)	1.500(12)
C(4a)-C(5)	1.398(9)	1.429(11)
C(4a)-C(8a)	1.402(8)	1.344(11)
C(5)-C(6)	1.353(8)	1.396(12)
C(6)-C(7)	1.382(8)	1.375(11)
C(6)-O(15)	1.380(7)	1.369(9)
C(7)-C(8)	1.381(8)	1.380(11)
C(7)-O(17)	1.361(7)	1.370(10)
C(8)-C(8a)	1.401(8)	1.406(11)
C(9)-C(1')	1.507(8)	1.491(11)
C(11)-C(12)	1.30(2) ·	1.511(13)
C(12)-C(13)	1.84(2)	1.496(13)
	[1.49(2)] a	
C(13)-O(14)	1.27(2)	1.426(13)
	[1.64(2)] a	
C(15)-C(16)	1.433(10)	1.441(12)
O(17)-C(18)	1.407(11)	1.415(11)
C(1')-C(2')	1.384(9)	1.379(11)
C(1')-C(6')	1.391(9)	1.394(11)
C(2')-C(3')	1.379(9)	1.400(11)
C(3')-C(4')	1.382(9)	1.388(11)
C(3')-O(7')	1.355(9)	1.356(10)
C(4')-C(5')	1.395(10)	1.374(11)
C(4')-O(9')	1.388(7)	1.392(9)
C(5')-C(6')	1.383(9)	1.387(11)
C(5')-O(11')	1.367(9)	1.375(10)
O(7')-C(8')	1.430(12)	1.411(12)

TABLE 5 (continued)

(a) Bond lengths

	trans-(2j)	cis-(2h)
O(9')-C(10')	1.431(9)	1.422(12)
O(11')-C(12')	1.413(12)	1.422(13)
Cl-O(1'')	1.381(8)	
Cl-O(2'')	1.406(10)	
Cl-O(3'')	1.360(10)	
Cl-O(4'')	1.323(9)	

(b) Bond angles

	trans-(2j)	cis-(2h)
N(2)-C(1)-C(8a)	110.3(4)	107.3(6)
N(2)-C(1)-C(9)	112.4(4)	113.3(6)
C(8a)-C(1)-C(9)	111.2(4)	113.4(6)
C(1)-N(2)-C(3)	109.2(4)	109.2(6)
C(1)-N(2)-C(10)	111.4(5)	109.7(6)
C(1)-N(2)-C(11)	107.5(5)	111.5(5)
C(3)-N(2)-C(10)	107.7(5)	110.4(6)
C(3)-N(2)-C(11)	109.9(5)	107.2(6)
C(10)-N(2)-C(11)	111.2(6)	108.7(6)
N(2)-C(3)-C(4)	112.4(6)	112.4(7)
C(3)-C(4)-C(4a)	112.4(6)	114.2(7)
C(4)-C(4a)-C(5)	119.1(5)	118.2(7)
C(4)-C(4a)-C(8a)	121.9(5)	122.6(7)
C(5)-C(4a)-C(8a)	118.9(5)	118.8(7)
C(4a)-C(5)-C(6)	121.8(6)	119.2(7)
C(5)-C(6)-C(7)	120.1(5)	121.0(7)
C(5)-C(6)-O(15)	124.3(6)	123.1(7)
C(7)-C(6)-O(15)	115.6(5)	115.8(7)
C(6)-C(7)-C(8)	119.6(5)	119.3(7)
C(6)-C(7)-O(17)	116.6(5)	117.5(7)
C(8)-C(7)-O(17)	123.7(5)	123.3(7)
C(7)-C(8)-C(8a)	121.2(5)	120.2(7)
C(1)-C(8a)-C(4a)	122.4(5)	122.6(7)
C(1)-C(8a)-C(8)	119.3(5)	115.9(6)
C(4a)-C(8a)-C(8)	118.3(5)	121.5(7)
C(1)-C(9)-C(1')	111.1(5)	113.3(7)
N(2)-C(11)-C(12)	117.1(9)	114.7(7)
C(11)-C(12)-C(13)	121(1)	111.1(8)
	[123(1)] a	
C(12)-C(13)-C(14)	95(1)	110.9(8)
	[92(1)] a	
C(6)-O(15)-C(16)	117.8(5)	117.7(7)
C(7)-O(17)-C(18)	118.7(5)	115.9(7)
C(9)-C(1')-C(2')	119.5(5)	119.1(7)
C(9)-C(1')-C(6')	120.0(5)	119.9(7)
C(2')-C(1')-C(6')	120.5(5)	120.9(7)
C(1')-C(2')-C(3')	120.3(6)	119.1(7)
C(2')-C(3')-C(4')	119.6(6)	120.2(7)
C(2')-C(3')-O(7')	124.3(6)	124.0(7)
C(4')-C(3')-O(7')	116.1(6)	115.8(7)
C(3')-C(4')-C(5')	120.3(6)	119.8(7)
C(3')-C(4')-O(9')	119.1(6)	120.0(7)
C(5')-C(4')-O(9')	120.6(6)	120.2(7)
C(4')-C(5')-C(6')	120.1(6)	121.0(7)
C(4')-C(5')-O(11')	114.0(6)	115.5(7)
C(6')-C(5')-O(11')	125.9(6)	123.5(7)
C(1')-C(6')-C(5')	119.1(6)	119.0(7)
C(3')-O(7')-C(8')	118.0(6)	117.9(7)
C(4')-O(9')-C(10')	112.6(6)	113.5(7)
C(5')-O(11')-C(12')	116.9(6)	118.0(7)
O(1'')-Cl-O(2'')	109.4(5)	
O(1'')-Cl-O(3'')	111.2(6)	
O(1'')-Cl-O(4'')	108.9(6)	
O(2'')-Cl-O(3'')	107.1(5)	
O(2'')-Cl-O(4'')	110.1(6)	
O(3'')-Cl-O(4'')	110.2(7)	

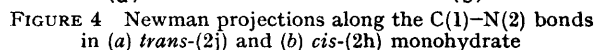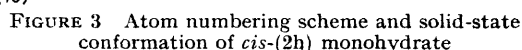a C(13) is disordered over two sites, values in square brackets refer to C(13').

occurring and the relaxation paths are equal, then the N-methyl group cis to 1-H should provide twice as much n.O.e. as does the N-methyl group trans to 1-H. In this respect it should be noted that a relatively high temperature (60—80 °C) was required to obtain consistent n.O.e. results in this system. It is possible that at

ambient temperature the relative rate constants for the internal motion and molecular tumbling are of the same order of magnitude and, as a consequence, the observed n.O.e. is decreased. As the temperature is raised, the molecular correlation time is disproportionately shortened relative to the rate of intermolecular exchange, thus diminishing the effects of internal motion on the observed n.O.e.[6]

The stereochemistry of two representative diastereo-isomeric (±)-pairs of N-3-hydroxypropyl-5'-methoxy-laudanosinium salts, the major (*trans*) isomer as per-chlorate (2j) and the minor (*cis*) isomer as iodide (2h), was established unequivocally by single-crystal X-ray analysis. Non-hydrogen atom fractional co-ordinates, bond lengths, and angles are given in Tables 4 and 5. Views of the solid-state conformations of both salts are shown in Figures 2 and 3, and Newman projections along

FIGURE 3 Atom numbering scheme and solid-state conformation of *cis*-(2h) monohydrate

FIGURE 4 Newman projections along the C(1)–N(2) bonds in (a) *trans*-(2j) and (b) *cis*-(2h) monohydrate

(ΔC_s-E = 18.0, ΔC_2-HC = 62.0°) lies much closer to an envelope form; this serves to decrease non-bonded inter-actions between the gauche benzyl and hydroxypropyl ring substituents by having a larger C(9)–C(1)–N(2)–C(11) torsion angle than that which would occur were ring B to adopt a half-chair form similar to that found in *trans*-(2j).

Based on the correspondence of the chemical shifts in the ^{1}H and [13]C n.m.r. spectra, and the X-ray structural

FIGURE 2 Atom numbering scheme and solid-state conformation of *trans*-(2j)

the C(1)–N(2) bonds in Figure 4. The trimethoxybenzyl group in both isomers has a pseudo-axial orientation, and this form probably also exists in appreciable amounts in solution.

Analysis of deviations of ring B torsion angles (Table 6) from symmetry-related values characterizing ideal en-velope (ΔC_s-E) and half-chair (ΔC_2-HC) conformations indicates that in *trans*-(2j) this ring (ΔC_s-E = 48.4, ΔC_2-HC = 24.3°) lies closer to a half chair than to an envelope form. In *cis*-(2h), on the other hand, ring B

TABLE 6

Endocyclic torsion angles, ω_{ij} (°), for ring B in *trans*-(2j) and *cis*-(2h)

	trans-(2j)	*cis*-(2h)
$\omega_{1,2}$	52.4	−58.8
$\omega_{2,3}$	−64.5	60.6
$\omega_{3,4}$	43.2	−33.0
$\omega_{4,4a}$	−13.0	6.5
$\omega_{4a,8a}$	4.1	−8.4
$\omega_{1,8a}$	−24.0	34.3
ΔC_s-E [a]	48.4	18.0
ΔC_2-HC [a]	24.3	62.0

[a] ΔC_s-E = $|\omega_{4,4a}| + |\omega_{4a,8a}| + |\omega_{3,4} + \omega_{1,8a}| + |\omega_{2,3} + \omega_{1,2}|$, and ΔC_2-HC = $|\omega_{4a,8a}| + |\omega_{1,8a} - \omega_{4,4a}| + |\omega_{1,2} - \omega_{3,4}|$.

TABLE 7

^{1}H N.m.r. chemical shifts for N-3-hydroxypropyl-5'-methoxylaudanosinium iodide (2h)

	cis-(2h)						trans-(2h)					
	NMe	7-OMe	8-H	5-H	1-H	2'-, 6'-H$_2$	NMe	7-OMe	8-H	5-H	1-H	2'-, 6'-H$_2$
CDCl$_3$	3.24	3.47	5.84	6.65	4.75	6.27	3.66	3.46	5.85	6.67	4.99	6.36
(CD$_3$)$_2$CO	3.30	3.42	6.06	6.89	5.21	6.44	3.66	3.41	6.00	6.88	5.22	6.54
CD$_3$CN	2.98	3.36	5.82	6.80	4.65	6.23	3.28	3.37	5.80	6.80	4.61	6.29
CD$_3$OD	3.10	3.40	5.84	6.86	4.75	6.26	3.42	3.39	5.78	6.86	4.71	6.32
(CD$_3$)$_2$SO–D$_2$O ^{a}	2.99	3.31	5.81	6.86	4.80	6.29	3.29	3.29	5.73	6.86	4.70	6.36
Mean	3.12	3.39	5.87	6.81	4.83	6.30	3.46	3.38	5.83	6.81	4.85	6.37
Standard deviation	0.14	0.06	0.10	0.10	0.22	0.08	0.19	0.06	0.10	0.09	0.25	0.10

^{a} D$_2$O was added to move the water peak downfield.

TABLE 8

^{1}H N.m.r. chemical shifts for N-ethyl-laudanosinium iodide (1d)

	cis-(1d)						trans-(1d)					
	NMe	NCH$_2$CH$_3$	7-OMe	8-H	5-H	1-H	NMe	NCH$_2$CH$_3$	7-OMe	8-H	5-H	1-H
CDCl$_3$	3.30	1.66	3.41	5.81	6.66	4.89	3.74	1.45	3.41	5.75	6.64	5.09
(CD$_3$)$_2$CO	3.28	1.70	3.34	5.93	6.88	5.16	3.63	1.48	3.35	5.89	6.87	5.22
CD$_3$CN	2.95	1.53	3.31	5.73	6.80	4.58	3.25	1.31	3.32	5.73	6.79	4.55
CD$_3$OD	3.05	1.62	3.34	5.74	6.84	4.68	3.3	1.39	3.34	5.75	6.85	4.63
(CD$_3$)$_2$SO–D$_2$O ^{a}	2.94	1.48	3.25	5.70	6.85	4.69	3.26	1.29	3.26	5.70	6.84	4.63
Mean	3.10	1.60	3.33	5.78	6.81	4.80	3.44	1.38	3.34	5.76	6.80	4.82
Standard deviation	0.18	0.09	0.06	0.09	0.09	0.23	0.23	0.08	0.05	0.07	0.09	0.31

^{a} D$_2$O was added to move the water peak downfield.

TABLE 9

^{1}H N.m.r. chemical shifts for N-methyl-laudanosinium iodide (1c)

	NMe ^{a}		7-OMe	8-H	5-H	1-H
	trans	cis				
CDCl$_3$	3.53	3.92	3.42	5.79	6.65	5.27
(CD$_3$)$_2$COCD$_3$	3.43	3.74	3.40	5.93	6.88	5.43
CD$_3$CN	3.11	3.38	3.37	5.79	6.80	4.73
CD$_3$OD	3.18	3.48	3.39	5.76	6.86	4.71
(CD$_3$)$_2$SO–D$_2$O	3.09	3.35	3.31	5.76	6.86	4.74
Mean	3.27	3.57	3.38	5.81	6.81	4.98
Standard deviation	0.20	0.25	0.04	0.07	0.09	0.35

^{a} cis and trans Refer to the configuration of the methyl group in relation to the benzyl group.

assignments of the two diastereoisomeric (±)-pairs of salts (2j) and (2h), the trans-configuration can be assigned to all the major alkylation isomers and the cis-configuration to the minor ones. These assignments are contrary to those made by Stenlake et al.,[4] but agree with those of Radics et al.[1-3] for the case which they investigated.

The proton chemical shifts were affected by solvent, especially those for 1-H and the N-methyl protons. In chloroform, a solvent of relatively low polarity, the N-methyl proton signals occurred at lower field than when the n.m.r. spectra were recorded in more polar solvents [(CD$_3$)$_2$SO–D$_2$O, CD$_3$OD, CD$_3$CN], as shown by the values listed in Tables 7—9; the entries in these Tables also indicate that the effect is more profound on the trans- than on the cis-isomers.

The chemical shifts listed in Table 10 show little variation upon change of anion in (CD$_3$)$_2$SO–D$_2$O, whereas, in CDCl$_3$, 1-H and the N-methyl proton signals were greatly affected. These results suggest that the salts exist as ion pairs in CDCl$_3$ and, as a result, the anion affects the charge distribution and, possibly, even the conformational equilibrium of the cation. In polar solvents, the salts are solvated and consequently very little change occurs with change of anion.

Examination of Dreiding models of the two diastereoisomeric pairs of, for example, the N-ethyl-laudanosinium salt (1d) shows that, in the cis-isomer, an unfavourable steric interaction occurs between the benzyl methylene and the methyl protons of the N-ethyl group in either conformation (Scheme). Since this forces the terminal methyl group away from the benzyl methylene and towards the N-methyl group, the N-methyl protons are more shielded. In the trans-isomer, such an unfavourable steric interaction does not exist. This situation means that the difference between the chemical shifts of the N-methyl protons in the two conformations of the cis-isomer should be smaller than the corresponding two conformations of the trans-isomer (vide supra). This is indeed the case since the chemical shift of the N-methyl group in the cis-isomers was found to be less affected by changes in solvent or anion than that in the trans. In addition, the N-methyl protons of the cis-isomer, in

TABLE 10

¹H N.m.r. chemical shifts for N-methyl-laudanosinium salts in CDCl₃ and (CD₃)₂SO–D₂O

| Anion | CDCl₃ | | | | | | (CD₃)₂SO–D₂O [b] | | | | | |
| | NMe [a] | | 7-OMe | 8-H | 5-H | 1-H | NMe | | 7-OMe | 8-H | 5-H | 1-H |
	cis	trans					cis	trans				
I	3.53	3.92	3.43	5.79	6.65	5.27	3.09	3.35	3.31	5.76	6.86	4.74
Cl	3.53	3.98	3.43	5.79	6.62	5.27	3.10	3.36	3.31	5.75	6.86	4.75
CF₃SO₃	3.28	3.58	3.44	5.77	6.63	4.78	3.08	3.32	3.31	5.74	6.86	4.69
TsO	3.43	3.65	3.40	5.74	6.59	4.98	3.08	3.34	3.31	5.74	6.86	4.70
Mean	3.44	3.78	3.43	5.77	6.62	5.08	3.09	3.34	3.31	5.75	6.86	4.72
Standard deviation	0.12	0.20	0.02	0.02	0.03	0.24	0.01	0.02	0.00	0.01	0.00	0.03

[a] cis and trans Refer to the configuration of the methyl group in relation to the benzyl group.   [b] D₂O was added to move the water peak downfield.

contrast to those of the *trans*, show only slight broadening at −80 °C.

Stereochemistry of Protonation.—Protonation of either laudanosine (2a) or 5′-methoxylaudanosine (2c) with strong acids results in two diastereoisomeric (±)-pairs, with one diastereoisomer predominating. The ratio of the two diastereoisomeric (±)-pairs was both solvent and temperature dependent, which strongly suggests thermodynamic control of the composition of the diastereoisomeric mixture [15 : 1 in $CDCl_3$; 4 : 1 in $(CD_3)_2SO$; and 3 : 1 in D_2O for the hydrochloride salt at 29 °C]. The minor isomer always showed the less shielded *N*-methyl proton and the more shielded (*ca.* 7 p.p.m.) benzylic methylene carbon (^{13}C) resonances. We have assigned the *cis*-configuration to all of the minor protonation isomers and, accordingly, the *trans*-configuration to the major protonation products on the basis of the argument given below.

Inspection of the [13]C n.m.r. chemical shift data for *cis*- and *trans*-quaternary salts revealed very little difference (typically <0.4 p.p.m.) between the C(9) (benzylic) signals. This is reasonable since the effect of the two primary alkyl groups should be similar in terms of their steric interaction with C(9) in this mobile ring system. Protonation, on the other hand, can lead to quite different envionments for C(9) depending on the relative orientation of the *N*-methyl group. The higher-field ^{13}C chemical shift observed for C(9) in the minor protonation product indicates that the *N*-methyl group is *cis* to the benzyl group because the steric interaction of C(9) with the *N*-methyl group in this isomer, relative to the less compressed C(9) in the *trans*-isomer, should result in a higher-field signal.[7] The large difference in the chemical shift (*ca.* 7 p.p.m.) observed between the benzylic carbon atoms of the two isomers might be due to the difference in the relative conformational averaging in these isomers (*vide supra*).

Since 1-H is not resolved in both protonation products, n.O.e. cannot be used to assign the relative stereochemistry in the same manner as for the alkylation products. Convincing arguments for the assignment of these protonation products has posed serious experimental problems. Additional work, which, it is hoped, will lead to firmly based assignments for these compounds, has been undertaken and may be the subject of a later publication. The above assignment, that the high-field C(9) is *cis* to *N*-methyl, is preferred since this leads to a consistency in the overall assignments with respect to the *N*-methyl protons. In all cases studied, the *N*-methyl protons *cis* to the benzyl group are less shielded than the *N*-methyl protons *trans* to benzyl. Thus, at least in the case of the alkyl compounds, the usual situation, that lesser shielding of protons in [1]H n.m.r. spectra corresponds to greater shielding of methyl carbons in [13]C n.m.r. spectra, is obeyed.

EXPERIMENTAL

All n.m.r. spectra were recorded on a Varian CFT-20 Fourier transform n.m.r. spectrometer with an 8 192 word data length. [1]H N.m.r. spectra were obtained at 79.54 MHz using 5-mm sample tubes at a probe temperature of 29 °C. [13]C N.m.r. spectra were obtained at 20 MHz using 8-mm sample tubes at 33 °C at a typical sample concentration of 120 mg/0.4 ml solvent.

Laudanosine, 5′-methoxylaudanosine, and all quaternary salts employed in this study were synthesized according to published procedures [2] and all gave satisfactory elemental analyses.

Crystal Data.—(*a*) *trans-N*-3-Hydroxypropyl-5′-methoxy-laudanosinium perchlorate [*trans*-(2j)], $C_{25}H_{36}ClNO_{10}$, $M = 546.0$. Monoclinic, $a = 8.123(4)$, $b = 20.380(8)$, $c = 16,710(6)$ Å, $\beta = 102.14(5)°$, $U = 2 704$ Å^3, $Z = 4$, $D_c = 1.385$ g cm^{-3}, $\mu(Cu-K_\alpha) = 17.4$ cm^{-1}. Space group, $P2_1/c(C_{2h}^5)$ uniquely from systematic absences: $0k0$ when $k \neq 2n$, $h0l \neq 2n$.

(*b*) *cis-N*-3-Hydroxypropyl-5′-methoxylaudanosinium iodide [*cis*-(2h)] monohydrate, $C_{25}H_{38}INO_7$, $M = 591.5$, Monoclinic, $a = 11.475(5)$, $b = 17.749(6)$, $c = 14.278(5)$ Å. $\beta = 113.51(5)°$, $U = 2 666$ Å^3, $Z = 4$, $D_c = 1.473$ g cm^{-3}, $\mu(Cu-K_\alpha) = 100$ cm^{-1}. Space group, $P2_1/c(C_{2h}^5)$ uniquely from systematic absences as for *trans*-(2j).

Crystallographic Measurements.—Crystals of dimensions *ca.* 0.20 × 0.50 × 0.50 mm [*trans*-(2j)] and 0.20 × 0.30 × 0.80 mm [*cis*-(2h) monohydrate] were mounted, respectively, inside a thin-walled glass capillary and on the end of a thin glass fibre. Preliminary unit-cell parameters and space group information were obtained from oscillation and Weissenberg photographs taken with Cu-K_α radiation ($\lambda = 1.5418$ Å) and precession photographs taken with Mo-K_α radiation ($\lambda = 0.7107$ Å). Intensity data to θ = 67° were recorded on an Enraf-Nonius CAD-3 automated diffractometer (Ni-filtered Cu-K_α radiation, θ-2θ scans) as described previously.[8] Totals of 2 215 [*trans*-(2j)] and 2 987 [*cis*-(2h) monohydrate] reflections with $I > 2.0\sigma(I)$ [$\sigma^2(I) =$ scan count + total background count] were judged to be observed and retained for the structure analysis and refinement. In addition to the usual corrections for Lorentz and polarization effects, those for absorption, derived from the φ-dependence of the intensities of the 4 0 8 [*trans*-(2j)] and 0 8 0 [*cis*-(2h) monohydrate] reflections measured at χ = 90°, were also applied. Refined unit-cell parameters were derived from each crystal by least-squares treatment of the diffractometer setting angles for 40 reflections widely separated in reciprocal space.

Structure Analysis.—(*a*) *trans*-(2j). The structure was solved by direct methods by use of the MULTAN [9] series of programmes and the 275 largest *E*-values. 28 Of the 37 non-hydrogen atoms in the asymmetric crystal unit were located in an *E*-map evaluated by use of that set of phase angles which yielded the highest combined figure-of-merit. Approximate positions for the remaining non-hydrogen atoms were then obtained from an F_o Fourier synthesis (R 0.38) phased by this partial structure. Full-matrix least-squares adjustment of positional and isotropic thermal parameters reduced R to 0.180, and when anisotropic thermal parameters were then varied, R decreased to 0.104. During these iterations, however, the thermal parameters for C(13) became extremely large, and so the contributions of this atom were omitted from the later structure-factor calculations and an F_o Fourier synthesis was evaluated. The electron-density distribution indicated that C(13) was disordered over two sites, and, accordingly, it was included with 50% occupancy of each in all further calculations. During the subsequent least-squares iterations, 32 hydrogen

atoms were included at their calculated positions; the refinement converged to R 0.082. Final non-hydrogen atom positional parameters are given in Table 4.

(b) cis-(2h) Monohydrate. Solution of this structure was effected by the heavy-atom method. Iodine co-ordinates, derived from a three-dimensional Patterson map, were used to phase an F_o Fourier synthesis (R 0.41) which yielded approximate positions for all non-hydrogen atoms in the cation. Several cycles of full-matrix least-square refinement of atomic positional and thermal, at first isotropic and subsequently anisotropic, parameters reduced R to 0.124. A difference Fourier synthesis revealed the presence of a significant peak which was ascribed to a water molecule of crystallization, and, with the inclusion of the water oxygen atom contribution into the next round of structure-factor calculations, R decreased to 0.103. Continuation of the least-squares iterations, with all hydrogen atoms in the cation included at their calculated positions, led to convergence at R 0.077. Final non-hydrogen atom positional parameters are given in Table 4.

Calculated hydrogen atom positional and thermal parameters, non-hydrogen atom anisotropic thermal parameters, torsion angles, and lists of observed and calculated structure amplitudes have been deposited as a Supplementary publication (SUP No. 23340, 48 pages).*

In the structure-factor calculations, scattering factors for the non-hydrogen atoms were taken from ref. 10, with those for iodine and chlorine corrected for anomalous dispersion; [11] for hydrogen the values from ref. 12 were used.

* For details of the Supplementary publications scheme, see Notice to Authors No. 7, J. Chem. Soc., Perkin Trans. 1, 1981, Index issue.

The weighting scheme used in the least-squares calculations was of the form: $w^{\frac{1}{2}} = 1$ when $F_o < K$ and $w^{\frac{1}{2}} = K/F_o$ when $F_o > K$ [$K = 13.0$ for trans-(2j) and $K = 30.0$ for cis-(2h) monohydrate], and $\Sigma w \Delta^2$ ($\Delta = F_o - F_c$) was minimized.

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