Carbon-13 Magnetic Resonance: Evidence for Non-chair Conformations in Tropane Derivatives

By **Peter Hanisch** and **Alan J. Jones,*** The National NMR Centre, Australian National University, Canberra A.C.T. 2600, Australia, and Department of Chemistry, University of Alberta, Canada
Alan F. Casey, Norfolk and Norwich Hospital, St. Stephen's Road, Norwich, Norfolk NR1 3SR
John E. Coates, Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton T6G 2G2, Alberta, Canada

The assignments of the methylene carbon resonances, C-2 and -4 and C-6 and -7, in the tropanes are clarified. Carbonyl and hydroxy additivity parameters in the tropane series (carbonyl α effect, −17.2 p.p.m.; equatorial hydroxy: α, +46.8; γ, −1.1 p.p.m.; axial hydroxy: α, +47.9; γ, −0.9 p.p.m.) differ from those in the analogous piperidines, carbonyl (−14.7 p.p.m.), equatorial hydroxy: α, +42.6 and γ, −2.7 p.p.m., and axial hydroxy: α, +28.1 and γ, −4.7 p.p.m., respectively. These and related data are interpreted in terms of evidence for boat contributions to the conformation of tropine. The intramolecular bonding present in the three tropanes, ecgonine methyl ester (14), 3α-hydroxydiphenylmethyltropan-3β-ol (18), and tropanyl phenyl ketone (19) have been verified by comparing the effects of protonation observed in the carbon-13 spectra. The conformational change from boat to chair conformers is exemplified in (19). It is suggested that (16) has some preference for a non-chair conformation but the nitrogen–carbonyl interaction found in (19) is not observed in this case. The hydrochloride (19a) dissolved in methanol is a ketone–alcohol equilibrium mixture as shown by the carbon-13 spectra. The hydrochloride derivatives of (14) and (18) are also in boat conformations for solutions in methanol but an equilibrating mixture is observed in less polar media with the chair conformation contributing. Evidence is presented for a zwitterionic structure for 3α-phenyltropane-3β-carboxylic acid (17).

THERE has been much interest in the ^{1}H n.m.r. spectroscopy of tropane due to the relationship of this bicyclic tertiary base to the muscarinic antagonist, atropine. Many of these studies have been directed towards determining the preference for the boat or chair conformation in tropine. A detailed review is available.[1] Most recently Casy *et al.*[2] have suggested a preference for the boat conformation in several tropane derivatives in which strong cross-ring intramolecular interactions of the type N · · · C···O and N · · · H–O were indicated by the broadening of the proton signal due to the coupling between the 1(5)-H and 2(4)-H protons in the boat conformer compared with the chair. This broadening arises as a consequence of eclipsing of these protons in the boat conformer and the results corroborate previous u.v. studies[3] in some cases.

Carbon-13 n.m.r. studies on tropane derivatives have thus far been limited.[4-6] A minor controversy has existed concerning the assignment of the C-2 and -4 and C-6 and -7 methylene carbons. The present study resolves this ambiguity and shows that the highest field resonance of the pair attributable to C-2 and -4 and C-6 and -7 must be assigned to C-6 and -7. Further, the reliability of carbon-13 chemical shifts as an index of preferred conformation especially in non-chair hydrogen bonded structures is tested by application of the method to appropriate tropane derivatives.

RESULTS

For the purpose of clarity we have summarized carbon-13 n.m.r. data on the tropanes according to their structural similarity in Table 1. Table 1 contains data for tropane (2) and the derivatives (1), (4), (6), (7), (8a), and (9a), previously reported by Wenkert[4] and Maciel *et al.*[5] Data determined in the present work is given for the two solvent systems [^{2}H]chloroform, and D_2O or [$^2H_4$]methanol. The conventional labelling system for the tropane ring is employed. Phenyl ring carbon atoms are labelled C_q, C_o, C_m, C_p, corresponding to the quaternary, *ortho*-, *meta*-, and *para*-carbon sites. Assignment of the carbon resonances was by

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[2] A. F. Casy and J. E. Coates, *Org. Magnetic Resonance*, 1974, **5**, 441.
[3] M. R. Bell and S. Archer, *J. Amer. Chem. Soc.*, 1960, **82**, 151.
[4] E. Wenkert, *Accounts Chem. Res.*, 1974, **7**, 46.
[5] L. Simeral and G. E. Maciel, *Org. Magnetic Resonance*, 1974, **6**, 226.
[6] S. J. Daum, C. M. Martini, R. K. Kullnig, and R. L. Clark, *J. Medicin. Chem.*, 1975, **18**, 496.

TABLE 1

Carbon-13 chemical shifts of tropane derivatives

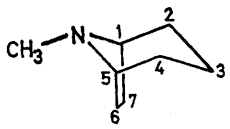
Compound	Solvent	NMe	C-1, -5	C-2, -4	C-6, -7	C-3	C_{-q}	C_{-o}	C_{-m}	C_{-p}	C=O	Ester CH_2/ CH_3
Nortropane (1) [a]	$CDCl_3$		54.7	32.9	29.0	17.2						
Tropane (2) [a]	$CDCl_3$	40.4	61.2	29.9	25.6	15.9						
Tropan-3-one (3)	$CDCl_3$	38.4_6	60.9_6	47.6_9	27.9_4	208.2_3						
Tropan-3-one hydrochloride (3a)	D_2O	39.0_7	63.2_9	46.5_1	24.9_6	206.9_5						
Tropan-3-one methiodide (3b)	D_2O	51.4_7 (eq)	69.2_2	26.3_9	26.3_3	208.2_3						
		45.1_1 (ax)										
Tropine ethylene glycol acetal [a]	$CDCl_3$	38.6	59.8	39.7	25.3	106.9						C-3′
Didehydro-3α-hydroxy-diphenylmethyltropan-3β-ol (5)	$CDCl_3$	40.1_4	60.9_6	38.8_4	25.5_7	64.5_2	139.9_9	128.0_7	126.8_8	126.8_8		(6.60_3)
Pseudotropine (6) [a]	$CDCl_3$	39.2	60.1	38.3	26.7	62.7						
Pseudotropine (6) [b]	H_2O	39.2_4	64.3_3	25.5_7	39.9_3	59.9_8						
Tropine (7)	$CDCl_3$	40.3_0	60.2_6	39.4_3	26.0	63.8_2						
Tropine hydrochloride (7a)	D_2O	39.1_1	62.0_4	37.4_4	24.8_7	62.0_4						
Atropine (8) [c]	$CDCl_3$	40.2_4	59.6_6	36.2_5	25.2_8	64.0_9	136.1_6	128.8_2	128.2_3	127.6_3	172.2_6	
Atropine hydrochloride (8a) [c]	D_2O	39.2_2	62.3_1	34.4_6	23.7_3	63.5_0	135.7_3	128.9_9	128.1_2	128.1_2	171.6_6	
Atropine hydrochloride (8a) [b]	H_2O	39.5_7	63.0_3	24.0_3	35.2_6	66.4_3	136.1_7	129.9_7	128.0_7	128.9_6	137.7_7	
			62.9_2	23.7_6	35.0_9							
Atropine methiodide (8b) [b]	D_2O	51.5_4 (ax)		25.2_7								
			68.1_0		32.3_9	64.5_4	136.1_3	129.8_7	128.9_5	128.9_5	173.6_8	
		44.8_5 (eq)		25.0_5								
					58.2_6	64.4_2	136.4_7	130.0_2	129.1_7	128.9_5	173.1_6	
Hyoscine (9) [b]	H_2O	53.4_2	53.7_5	25.2_0	58.0_5							
3α-Tropane benzoate (10)	$CDCl_3$	40.5_1	59.8_8	36.7_9	25.8_9	68.1_3	132.8_1	130.9_8	129.4_7	129.9_0	165.8_3	
3α-Tropane benzoate hydrochloride (10a)	D_2O	39.4_3	62.3_6	34.7_9	24.7_1	65.3_2	133.5_2	129.3_6	128.7_9	129.3_6	165.3_5	
3β-Tropane benzoate (11)	$CDCl_3$	38.7_3	60.3_7	35.8_7	26.7_0	67.8_6	132.7_1	129.5_3	128.2_8	129.9_6	165.3_5	
3β-Tropane benzoate hydrochloride (11a)	D_2O	38.9_1	63.8_3	35.4_5	24.4_5	65.6_6	134.4_5	130.0_2	129.6_4	129.6_4	167.4_0	
3β-Phenyltropane hydrochloride (12)	$CDCl_3$	39.4_3	64.2_5	37.1_2	24.9_2	33.6_1	142.5_3	128.8_8	127.8_0	127.1_0		
3α-Phenyltropane hydrochloride (12)	D_2O	38.9_0	64.5_8	37.2_3	24.0_2	32.1_6	143.2_3	129.1_6	127.3_8	127.3_8		
3α-Phenyltropane hydrochloride (13)	$CDCl_3$	39.1_1	62.9_0	32.5_8	24.2_2	29.6_1	*d*	128.6_6	126.3_4	126.3_4		
3α-Phenyltropane hydrochloride (13)	D_2O	38.4_2	63.1_3	33.0_7	23.4_8	29.5_2	*d*	128.6_7	126.7_8	126.5_1		
Ecgonine methyl ester (14)	$CDCl_3$	39.2_7	58.8_0	41.4_8	27.1_9	71.6_9					174.7_9	52.3_3
Ecgonine methyl ester (14)	$[^2H_4]$MeOH	38.5_7	60.8_0	39.7_6	25.6_8	71.5_9					175.6_0	52.7_6
Ecgonine methyl ester hydrochloride (14a)	$CDCl_3$	37.7_6	62.0_4	38.2_5	24.0_6	69.7_0					173.4_4	53.0_8
Ecgonine methyl ester hydrochloride (14a)	$[^2H_4]$MeOH	38.2_5	63.6_0	39.2_7	24.0_6	69.9_1					174.5_7	53.3_5
3β-Phenyltropine (15)	$CDCl_3$	40.3_0	60.9_1	45.4_8	25.6_8	72.6_7	150.5_6	128.0_7	124.6_7	126.5_6		
3β-Phenyltropine (15)	$[^2H_4]$MeOH	40.5_7	62.2_0	46.0_2	25.9_4	72.9_9	151.8_1	128.7_2	125.6_4	127.0_4		
3β-Phenyltropine hydrochloride (15a)	$[^2H_4]$MeOH	39.6_5	64.2_0	44.7_8	25.1_9	71.9_6	150.0_8	129.0_9	125.8_0	127.8_0		
3β-Phenyltropine hydrochloride (15a)	D_2O	38.8_5	63.6_7	43.0_0	23.4_7	70.9_5	147.4_4	128.8_9	124.5_7	127.7_5		60.3_7 [e]
Ethyl 3α-phenyltropane-3-carboxylate (16)	$CDCl_3$	39.8_1	59.0_2	41.4_8	28.2_1	46.0_7	142.5_8	128.1_2	126.7_2	126.6_1	175.3_8	14.2_4
												61.5_0 [e]
Ethyl 3α-phenyltropane-3-carboxylate (16)	$[^2H_4]$MeOH	39.7_0	60.5_3	40.1_4	27.2_4	46.9_3	142.7_4	128.9_3	127.6_9	127.6_9	176.9_4	14.2_4
Ethyl 3α-phenyltropane-3-carboxylate hydrochloride (16a)	$CDCl_3$	38.7_3	62.9_0	33.9_3	22.9_8	44.7_8	138.5_9	128.5_5	126.7_7	127.7_4	173.3_8	61.3_3 [e]
												13.7_0
Ethyl 3α-phenyltropane-3-carboxylate hydrochloride (16a)	$[^2H_4]$MeOH	38.7_9	64.2_5	35.2_8	23.3_0	45.8_0	139.6_1	129.4_2	127.9_6	128.6_6	175.0_9	62.3_1 [e]
												13.9_7
3α-Phenyltropane-3β-carboxylic acid (17)	$[^2H_4]$MeOH	38.6_0	64.4_4	36.4_4	23.0_6	47.5_0	141.4_0	129.1_2	127.5_5	127.8_2	168.4_5	
3α-Phenyltropane-3β-carboxylic acid hydrochloride (17a)	$[^2H_4]$MeOH	38.9_7	64.0_6	35.0_4	22.9_0	46.9_6	138.8_2	129.2_8	127.6_1	128.5_8	177.8_1	

TABLE 1 (*Continued*)

Compound	Solvent	NMe	C-1, -5	C-2, -4	C-6, -7	C-3	C_{-q}	C_{-o}	C_{-m}	C_{-p}	C=O	Ester CH_2/ CH_3
3α-Phenyltropane-3β-carboxylic acid hydrochloride (17a)	D_2O	38.2_1	63.1_8	34.5_3	22.2_3	44.8_4	138.3_8	128.9_4	127.1_6	128.1_8	177.8_7	
3α-Hydroxydiphenylmethyltropan-3β-ol (18)	$CDCl_3$	40.0_3	58.9_1	41.9_7	28.9_7	(75.6_9)	145.0_6	128.2_8	127.2_6	127.2_6		C-3′ (80.1_1)
3α-Hydroxydiphenylmethyltropan-3β-ol (18)	$[^2H_4]$MeOH	40.4_0	60.0_4	42.5_6	29.4_5	(77.1_4)	146.6_3	129.5_2	127.7_4	126.9_9		C-3′ (80.3_7)
3α-Hydroxydiphenylmethyltropan-3β-ol hydrochloride (18a)	$[^2H_4$MeOH]	39.2_6	62.6_8	40.4_6	28.3_8	(76.1_7)	145.0_1	129.3_6	128.6_6	128.0_7		C-3′ (80.9_2)
3α-Hydroxydiphenylmethyltropan-3β-ol hydrochloride (18a)	D_2O	38.7_4	61.1_8	39.1_7	27.2_0	(74.8_8)	142.8_6	128.1_8	128.1_8	128.1_8		C-3′ (80.8_2)
3α-Phenyltropan-3β-yl phenyl ketone (19)	$CDCl_3$	39.4_9	58.1_0	44.8_3	29.2_9	50.3_9	(141.8_8) (141.6_8)	(128.9_8) (128.4_5)	(127.4_7) (127.1_5)	(126.6_1) (127.1_5)	202.6_2	
3α-Phenyltropan-3β-yl phenyl ketone (19)	CD_2Cl_2	39.7_0	58.4_2	45.2_6	29.6_7	50.5_1	(142.4_2) (142.2_0)	(129.2_0) (128.7_2)	(127.7_4) (127.4_8)	(126.8_8) (127.4_8)	202.6_7	
3α-Phenyltropan-3β-yl phenyl ketone (19)	$[^2H_4]$MeOH	39.1_6	60.7_4	44.5_6	29.2_9	51.9_0	(142.4_2) (141.8_3)	(130.6_6) (129.5_2)	(128.7_2) (128.5_0)	(128.5_0) (127.9_6)	195.7_7	
3α-Phenyltropan-3β-yl phenyl ketone hydrochloride (19a)	$CDCl_3$	38.7_3	63.4_4	35.9_3	22.9_8	50.0_1	(138.1_6) (138.1_6)	(128.1_8) (127.8_5)	d d	(127.5_8) (129.0_9)	202.4_1	
3α-Phenyltropan-3β-yl phenyl ketone hydrochloride (19a)	$[^2H_4]$MeOH	37.0_0	64.5_7	37.0_6	23.5_2	d					d	
3α-Phenyltropan-3β-yl phenyl ketone hydrochloride (19b)	$[^2H_4]$MeOH	37.0_6	(C-1) 67.3_8 (C-5) 74.8_2	(C-2) 40.3_0 (C-4) 44.4_0	C-6 30.5_9 C-7 26.5_4	C-3 52.6_0					C-8 109.4_1	

[a] Data from ref. 4. [b] Data from ref. 5. [c] Broad resonances observed at C-1 and -5, C-2 and -4, and C-6 and -7. Resonances at 54.6_8 and 67.9_7 and 54.3_8 and 64.8_4 p.p.m. are assigned to the remaining tropic acid methine and methylene carbons in atropine and its hydrochloride, respectively. [d] Not observable due to low concention. [e] High field resonance (CH_3); low field resonance (CH_2); resonance C-3′ 66.0_3 p.p.m.

conventional techniques. The distinction between the methylene carbons, C-2 and -4 and C-6 and -7, is based on comparison of the data for the protonated *N*-methylated derivatives. For example, the chemical shift of the C-2 and -4 and C-6 and -7 are 46.5_1 and 24.9_9 p.p.m., repectively, in the protonated tropinone (3a) and 26.3_7 and 26.3_2 p.p.m., respectively, in the *N*-methylated derivative (3b). That is, a larger γ-interaction is apparent at C-2 and -4 in the *N*-methyl derivative due to the steric compression between



the protons at this site and the axial *N*-methyl group. Conversely, the resonances at 24.9_9 and 26.3_3 p.p.m. are assigned to C-6 and -7. In all the tropanes studied the lower field methylene shift is assigned by analogy to C-2 and -4. Ambiguities remain in the assignment of the quaternary carbon resonances in (5) and (18) and the aromatic carbon resonances in (19) and its hydrochlorides (19a and b).

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DISCUSSION

(1) *Additivity Effects.*—The preferred conformation of the tropane ring is established as a chair.[4] Introduction of a carbonyl group at C-3, as in (3), results in an α-carbonyl substituent effect at C-2 and -4 of −17.2 p.p.m. which is larger than that observed in the piperidines (−14.7 p.p.m.)[7] and cyclohexanes (−13.4 p.p.m.).[8] This may be due, in part, to the rigidity of the tropane ring system. Axial and equatorial hydroxy substituent parameters may be derived by comparing the carbon-13 chemical shifts in (2), (6), and (7). The values are: equatorial α, +46.8; β, +8.4; γ, −1.1, and $\delta_{C-6,7}$, +1.1 p.p.m.; axial α, +47.9; β, +9.5; γ, −0.9, and $\delta_{C-6,7}$, +0.4 p.p.m. Of greatest significance is the similarity between α- and γ-effects for the different hydroxy configurations. The analogous effects differ widely in the cyclohexanes (equatorial α, +43.2 and γ, −1.1 p.p.m.; axial α, +37.8 and γ, −6.8 p.p.m.) as well as in the piperidines (equatorial α, +42.6 and γ, −2.7 p.p.m.; axial α, +28.1 and γ, −4.7 p.p.m.).[9,10] It is possible that there exists a contribution of the boat form in (7) due to severe 1,3-diaxial inter-

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actions in the chair conformer. Further, comparison of the C-6 and -7 carbon resonances in (6) and (7) indicates an hydroxy δ shielding of 0.7 p.p.m. for (7) in contrast to the deshielding effect expected (2.6 p.p.m.).[11] These data suggest contributions from the boat conformer of (7). Equatorial phenyl substituent parameters are obtained from comparison of (7) and (15), α, +9.1; β, +6.4; and γ, +1.1 p.p.m. Compared with the analogous parameters obtained in 4-phenylpiperidines, α, +17.7; β, +6.7; and γ, −0.3 p.p.m.,[10] a large decrease in the α-effect is observed. The contributions

TABLE 2

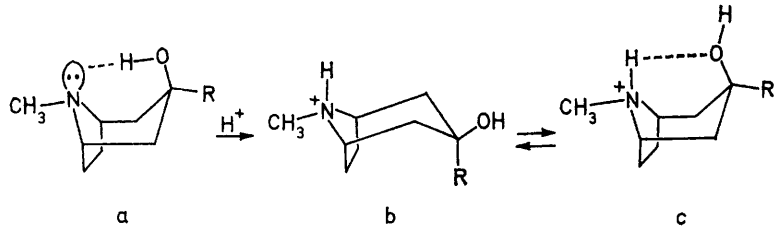
Additivity effects induced on the introduction of the 6,7-ethano bridge to the corresponding piperidine ring system

	Structure			
Effect	Piperidine	*N*-Methyl-piperidine	*N*-Methyl-4-piperidone	1-Methyl-4-phenyl-piperidin-4-ol
α	+7.0	+4.5	+4.9	+9.2
β	+5.4	+3.8	+6.2	+7.1
γ_{C-3}	−8.3	−8.0	+0.2	+2.6
γ_{N-Me}		−6.5	−7.5	−6.0

from the boat conformer in (7) may again account for these parameters differing. Introduction of the ethano bridge to the piperidine ring induces the carbon-13 chemical shifts given in Table 2. The α-effect of +7.0 p.p.m. in piperidine can be taken as the representative value for the introduction of the ethano bridge with the attenuation to +4.5 and +4.9 p.p.m. in *N*-methylpiperidine and *N*-methyl-4-piperidone, respectively, resulting from the γ-effect of the *N*-methyl group with the ethano bridge. The γ-effect on C-3 (−8.0 p.p.m.) can be taken as a representative value, this shielding being attenuated (+0.2 p.p.m.) as expected [7] in *N*-methyl-4-piperidone. The deshielding γ-effect of 2.6 p.p.m. in *N*-methyl-4-phenylpiperidin-4-ol is unusual but has also been observed in 1,2,2,6,6-pentamethyl-4-phenylpiperidin-4-ol. The γ-effect at the *N*-methyl group is on average −6.5 p.p.m.

(2) *Tropane Conformations and Protonation Effects.*— In order to determine the preferred conformations of the tropanes both the free base and protonated derivatives were studied. The induced protonation effects for some representative cases are summarized in Table 3.

It is well established [12-14] that 3-phenyltropin-3-ol (15) and its corresponding hydrochloride (15a) exist preferentially in the chair conformation. Consequently, ' chair ' protonation effects in the tropane system for solutions in methanol can be determined using this compound as a model, *i.e.*, β_{N-Me} −0.9; $\beta_{C-1,5'}$ 2.0; $\gamma_{C-2,4'}$ −1.2; $\gamma_{C-6,7'}$ −0.8 and $\delta_{C-3'}$ −1.0 p.p.m. However, if the tropane ring exists in a boat conformation in the free base and protonation induces a conformational change different protonation effects would be expected. The major effect upon protonation in this situation will be to produce a γ-shielding effect at C-2 and -4 in the protonated chair conformation as indicated in Figure b. Any deviations from this γ-effect are expected to reflect a change from preferred chair (Figure b) to preferred boat conformer (Figure c) in the protonated tropane molecule. In the case of 3α-phenyl substituted derivatives it is expected that a shielding effect will be observed at C-6 and -7, the consequence of the restricted rotation of the anisotropic phenyl group in the chair conformer. Further, a shielding effect at C-1 and -5 is also expected in the boat conformer, the consequence of eclipsing between the 1(5) and 2(4) hydrogen atoms. Therefore, referring to the Figure, if the chair conformation (Figure b) predominated in the protonated form a relief of the hydrogen interactions will produce an increased deshielding at C-1 and -5 compared to those in the protonated boat conformation (Figure c). Utilizing these protonation aspects, the tropane conformations can be discussed.



Suggested conformation aspects on protonation of a tropane molecule existing in a preferred boat conformation in a (free base) and c (hydrochloride) due to the intramolecular hydrogen bonding nature of the hydroxy-group

(i) *3α-Phenyltropan-3β-yl phenyl ketone* (19). Large protonation effects (C-1,5, +4.1; C-2,4, −7.5 and C-6,7, −5.8 p.p.m.) are observed in (19) for the solution in methanol (see Table 3 for chloroform values), indicating a change in conformation in this compound. Evidence has been presented suggesting that the free base (19) exists in a boat conformation, the consequence of an N · · · C=O interaction.[2] However, Daum *et al.*[6] very recently suggested that a flattened piperidine ring structure preponderates. Their principal evidence lay in the observation that no nitrogen–carbonyl interaction was indicated by the absence of a shift in the benzoyl carbon atom ^{13}C signal. In the present work, after repeated

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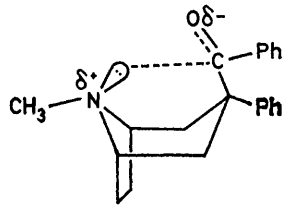
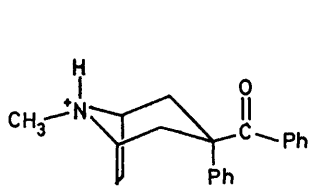
studies of this compound under variable temperature and concentration conditions, we observed that the carbonyl resonance for the solution of (19) in methanol is upfield (6.8 p.p.m.) relative to that found for the solution in chloroform. This upfield shift must arise from an N · · · C⋯O interaction, since hydrogen bonding with solvent would be expected to deshield the carbonyl resonance. The *N*-methyl resonance also shifts to lower field on cooling, a further indication of the stabilized intramolecularly bonded structure in methanol. With these observations in mind we suggest that the behaviour of the base (19) in methanol is a result of a greater degree of nitrogen–carbonyl interaction in this solvent than in chloroform, the methanol being better able to stabilize, by an appropriate solvation mechanism, the partial charge separation which is produced by this interaction. A similar argument has been used to explain the u.v. absorption of (19).[3] The carbon-13 data indicate that the structure of the base (19) in chloroform is similar to that in methanol since similar protonation effects are observed in the two solvent systems. However, the absence of the carbonyl carbon shift for the chloroform solution supports the suggestion [6] of a flattened piperidine ring structure in this solvent. The change in the conformation of (19) (boat), as illustrated in Figure b, is



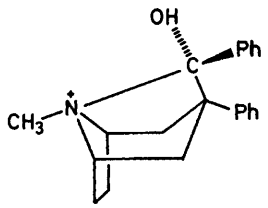
(19)

thus indicated for the hydrochloride (19a) (chair) for the solution in methanol, while the change in chloroform is less marked (flattened chair–chair). Subtraction of the protonation effects in (15) (chair–chair) from those in (19) (boat–chair) give values for the proposed conformational change for solutions in methanol. That is, N-Me, +0.7; C-1,5, +2.1; C-2,4, −6.3; and C-6,7, −5.0 p.p.m. in going from a boat conformer to a chair conformer. The major effects are as expected. C-1,5 is deshielded (2.1 p.p.m.) as a consequence of removal of the eclipsing hydrogen, C-6,7 is shielded (5.0 p.p.m.) due to the result of the orientation of the axial 3-phenyl substituent (parallel to the C-6,7 bond) and C-2,4 is shielded (6.3 p.p.m.) due to the introduction of a γ-gauche interaction at these carbon atoms with the $\overset{+}{N}$–H proton. These values clearly add support for contributions of the boat conformation in the base.

The solvent effects ($CDCl_3$–CD_3OD) occurring for the hydrochloride of (19) are of additional interest. As noted earlier, smaller chemical shift differences arise for the solution in methanol. Bell and Archer have suggested [3] that the hydrochloride in methanol is a mixture which consists mainly of the form with the ' formally bonded ' nitrogen and carbonyl function (19b) in equilibrium with the form possessing the normal ketone (19a). The occurrence of the two species is verified in the carbon-13 spectra by the observation of a ^{13}C resonance at 109.4$_1$ p.p.m. due to C-8, now a hydroxy carbon, and also by the i.r. spectrum which exhibits absorption bands at 3 400 and 1 675 cm^{-1} attributable to hydroxy and carbonyl functions, respectively. The assignment of the carbon resonances in (19a and b) was facilitated by a change in the concentration of (19b) between separate spectral determinations. The chemical shifts of (19a) in methanol are similar to those obtained for the solution in [^{2}H]chloroform (<1 p.p.m. difference) and enable assignment of the shifts due to the chair conformation in the mixture. The formation of the N–C-8 bond



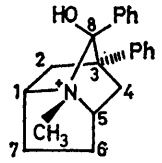
(19a)



(19b)

generates an asymmetric centre at C-8. Hence each carbon in the molecule (19b) gives rise to an individual resonance. Structure (19b) can be represented as a norbornyl derivative. Unfortunately the carbon chemical shifts of the analogous norbornyl system without the ethano bridge have not been reported. Therefore, the distinction between the methine and methylene carbons is based only on the assumption that the hydroxy group will exert a larger γ-shielding effect at C-1 and -2 compared with C-5 and -4.

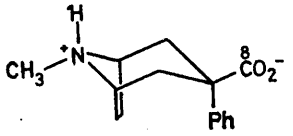
(ii) *Ethyl* 3α-*phenyltropane*-3β-*carboxylate* (16). The hydrochloride of (16) studied in solution in chloroform or methanol shows large protonation effects at C-1,5 (+3.9 and +3.7 p.p.m.), C-2,4 (−7.6 and −4.9 p.p.m.), and C-6,7 (−5.3 and −3.9 p.p.m.), respectively. Earlier ^{1}H n.m.r. studies [2] did not indicate boat contributions to the structure of this molecule. However, comparison of the ^{13}C data for the base and hydrochloride of (16) with that for (19) indicates contributions from at least a



flattened chair conformer in the free base (16). The large increase in protonation effects compared with those in (15) should be noted and compared with those in (19). No nitrogen–carbonyl interaction in (16) is indicated for solutions in either chloroform or methanol. Thus the conformational change induced by protonation must be similar to that for (19) in chloroform. That is, a flattened chair to a chair conformation.

(iii) 3α-*Phenyltropane*-3β-*carboxylic acid* (17). The

protonation effects observed in the carbon-13 spectra of (17) and (17a) suggest a zwitterionic structure for the base (17). This proposal is based on the small chemical shift differences observed upon protonation at all the carbon positions except at C-8 (+9.3 p.p.m.) and C-2,4 (−1.4 p.p.m.). The large deshielding at C-8 is due to a change from the carboxylate anion in the zwitterion (17)



(17)

to the protonated form in the acid (18a). The shielding at C-2 and -4 is attributed to the different γ-effects of the carboxylate anion and carboxylic acid group.

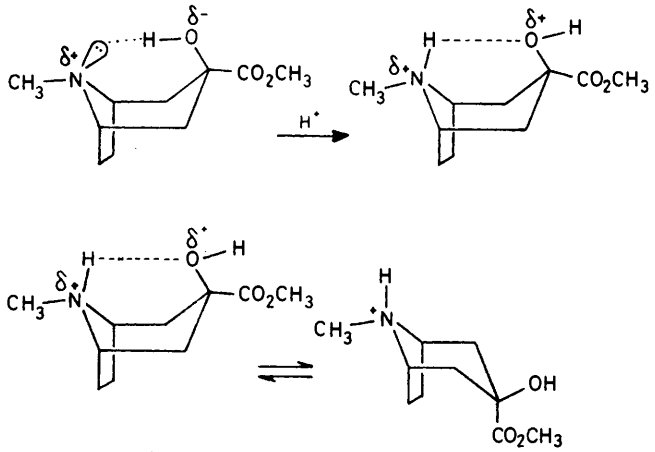
(iv) *Ecgonine methyl ester* (14). Both ^{1}H n.m.r. and i.r. spectral data provide evidence [2] that in solution the boat conformation of (14) is significantly populated. The change in chemical shifts between the base and hydrochloride are similar to those observed in (15) but are small (see Table 3) compared with those observed in (16) and (19), in particular, at C-2, and -4 and C-6 and -7. The protonation effects observed in (14) are thus boat–boat effects. It is noteworthy that the protonated boat form of (14) may be stabilized by intramolecular hydrogen bonding. Differences in the effects of protonation of (14) for solutions in [^{2}H]chloroform and [$^2H_4$]methanol, in particular the shielding effect at C-2 and -4 (−3.3 and −0.5 p.p.m., respectively) suggest contributions from the chair conformer (14a) in chloroform. That is, the boat conformer is favoured in the more polar methanol (solvation of charged centres) and the chair conformer in chloroform. The chemical shifts observed in the hydrochloride (14a) are average values for the above equilibrium. The protonation effects observed for the solution of (14) in chloroform are explained as follows. The deshielding (+3.2 p.p.m.) at C-1 and -5 is attributed to a greater amount of ' formal charge ' on the nitrogen when in the chair conformer than the boat conformer where the charge is expected to be delocalized over both the nitrogen and oxygen atoms. In addition, the interaction between the eclipsed hydrogens is relieved. The shielding effect (−3.3 p.p.m.) at C-2 and -4 is a result of the introduction of the more pronounced γ-effect of the N–H proton in the chair conformation.

TABLE 3

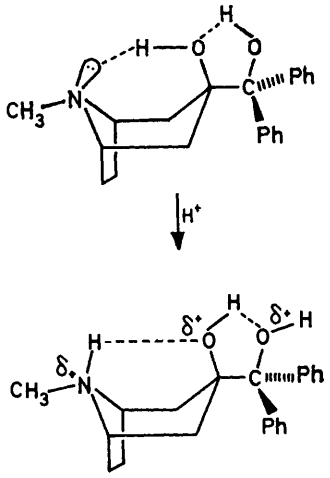
Protonation effects on the carbon-13 chemical shifts in various tropanes

Compound	Solvent	Carbon position and effect β (NMe)	β (C-1, -5)	γ (C-2, -4)	γ (C-6, -7)	δ (C-3)
(14)	$CDCl_3$	−1.5	+3.2	−3.3	−3.1	−2.0
(16)	$CDCl_3$	−0.1	+3.9	−7.6	−5.3	−1.3
(19)	$CDCl_3$	−0.8	+5.3	−8.9	−6.3	−0.4
(14)	[$^2H_4$]MeOH	−0.3	+2.8	−0.5	−1.6	−1.7
(15)	[$^2H_4$]MeOH	−0.9	+2.0	−1.2	−0.8	−1.0
(16)	[$^2H_4$]MeOH	−0.9	+3.7	−4.9	−3.9	
(17)	[$^2H_4$]MeOH	+0.4	−0.4	−1.4	−0.2	−0.5
(18)	[$^2H_4$]MeOH	−1.1	+2.6	−2.1	−1.1	−1.0
(19)	[$^2H_4$]MeOH	−0.2	+4.1	−7.5	−5.8	
	Average	−0.6	+3.0	−4.2	−3.1	−1.1

(v) 3α-*Hydroxydiphenylmethyltropan*-3β-*ol* (18). The effects of protonation in (18) can be explained in a similar manner to that above with intramolecular hydrogen bonding possible in the hydrochloride (18a) with the boat form predominating. However, the larger protonation effect for the solution in methanol (−2.1 p.p.m.) at C-2 and -4, compared with that in (14) (−0.5 p.p.m.), demands a difference in the equilibria for the hydrochlorides (18a) and (14a). That is, we suggest the chair form of the hydrochloride (18a) is more dominant.



Conclusions.—The importance of studying *both* protonation and solvent effects on the carbon-13 chemical shifts of nitrogen heterocycles in which intermolecular interactions are possible is clear from the above conformational analyses. Carbon-13 n.m.r. clearly provides information which is an invaluable adjunct to ^{1}H n.m.r. data in this area.



EXPERIMENTAL

Carbon-13 n.m.r. spectra were determined on a Bruker HFX-90 spectrometer operating at 22.63 MHz. All samples

were contained in precision ground 10 mm o.d. tubes. The spectrometer was used in the cross-coil configuration. On average an 8 μs pulse, corresponding to an approximate tilt angle of 45°, was employed. The delay between pulses was 0.8 s, for an average spectral width of 5 000 Hz. Accumulation time averaged 20 min, over 8 K data points for concentrations of the order of 0.2M. For off-resonance coupled spectra this time was approximately doubled. To observe some of the intramolecularly bonded carbonyl carbon resonances it proved necessary to use a 90° pulse with a 20 s delay between pulses.

Compounds (5) and (12)—(19) and their derivatives were obtained by methods described previously.[2] Typically hydrochlorides were made by bubbling anhydrous HCl into an ether solution of the free base and the precipitate obtained was purified by recrystallization to constant m.p. Free bases were generated from the corresponding hydrochloride by treatment with 5% sodium hydroxide solution, extraction with chloroform, drying ($MgSO_4$) followed by evaporation to dryness, and finally be recrystallization from the appropriate solvent.

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