drogenolysis of $Ak^1CO_2Ak^2$ over rhodium. As this presumably again involved some degree of intermolecular interaction between the rhodium surface and the ester and steric effects and, once more, as only alkyl groups were varied, we carried out correlations with a modification of eq 21 (eq 23). The data used are given in Table I, and results of the correlations are in Table VII.

$$Q_{X^1X^2} = a_{11}n_{11} + a_{12}n_{12} + a_{21}n_{21} + a_{22}n_{22} + a_{23}n_{23} + a_cn_c + a_0 \quad (23)$$

A significant correlation was obtained, accounting for 93.49% of the variance of the data. Unfortunately, n_{22} and n_{12} were both highly linear in n_c, as was n_{12} in n_{22}. We cannot determine with certainty, therefore, the extent to which steric effects are important in this reaction. Clearly, however, polarizability is a major factor. Thus, correlation with eq 24 gave very good results, accounting for 86.10%

$$Q_{X^1X^2} = a_cn_c + a_0 \quad (24)$$

of the variance of the data (set 121C, Table IV). Inclusion of a term for branching at C^{11} gave improved results (set 121B, Table IV), accounting for 90.07% of the variance of the data (see eq 25). Thus, steric effects do make small

$$Q_{X^1X^2} = a_cn_c + a_{11}n_{11} + a_0 \quad (25)$$

but significant contributions. Values of P_c and P_{11} are reported in Table VI. They are uncertain due to the collinearity of n_c with n_{12} and n_{22} noted above.

Conclusion

A long-held tenet in the philosophy of science is the use of the simplest explanation which will account for the observations. This is the essence of Occam's razor. In terms of correlation analysis, this may be interpreted as the use of the smallest possible number of parameters which will account for the data. We believe that we can account for most, if not all, chemical reactivities and physical properties in terms of localized (field and/or inductive) and delocalized (resonance) electrical effects, steric effects, and group polarizabilities. It is not necessary to invoke hyperconjugation parameters to account for physical or chemical phenomena, and therefore it is undesirable to do so.

Syntheses and Conformational Analyses of Isomeric Cocaines: A Proton and Carbon-13 Nuclear Magnetic Resonance Study

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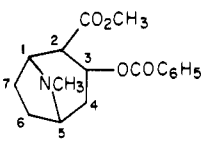
The ^1H and ^{13}C NMR spectra of cocaine (1), pseudococaine (2), allococaine (3), allopseudococaine (4), and the hydrochloride salts of 1, 2, and 4 have been recorded. The conformation of the piperidine ring in all four isomers, including the orientation of the *N*-methyl substituent, was determined from analysis of the data. Vicinal, geminal, and long-range coupling constants strongly suggest a chair conformation for the piperidine ring of all the compounds studied. Comparison of the ^1H and ^{13}C chemical shift data suggests that 2 and 4 have a larger population of axial *N*-methyl substituents than 1 and 3, respectively. Improved procedures for the synthesis of 2, 3, and 4 are reported. In particular, a stereoselective route to 4 is presented.

Cocaine (1), a natural component of coca leaves (*Erythroxylum coca*), is a potent central nervous system stimulant and is a major drug of abuse.[1] As one isomer of 3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester, cocaine (1) has three diastereoisomers known as pseudococaine (2), allococaine (3), and allopseudococaine (4). The structure and stereochemistry of these isomers are well characterized and are as depicted. They can be viewed as *N*-methylpiperidines with an ethano bridge across the 2,6 positions, *N*-methylpyrrolidines with a propano group bridging the 2,5 positions, or as cycloheptanes containing a methylamino bridge. For the purposes of this paper we have viewed 1-4 as *N*-methylpiperidine derivatives.



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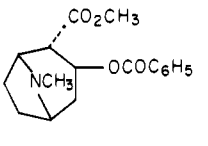

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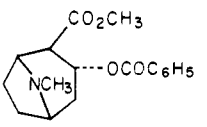

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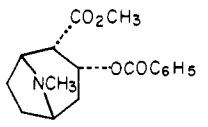
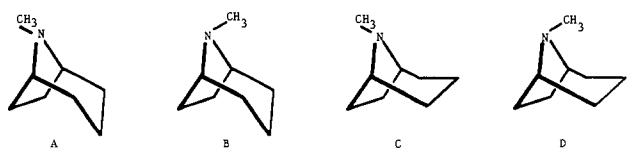


4

In principle, the tropane system can exist in four conformations. The *N*-methyl group can be either syn (A, C) or anti (B, D) to the ethano bridge, and in addition, the piperidine ring can adopt either chair (A, B) or boat (C, D) conformation. Single-crystal X-ray structure determination of cocaine (1) hydrochloride has shown a chair conformation for the piperidine ring with the *N*-methyl group syn to the ethano bridge (A).[2] Examination of the ^1H NMR spectra of 1-4 has led Beyerman and co-workers[3]



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to conclude that the chair form was the preferred conformation of the piperidine ring in all four isomers. In this report we present the ^1H and ^{13}C NMR spectra of all four diastereomeric cocaine isomers, as well as the hydrochloride salts of 1, 2, and 4. A conformational analysis of the piperidine ring including the orientation of the *N*-methyl group is presented for all four isomers.

Results

Synthesis. Certified (−)-cocaine (1) hydrochloride was obtained from Merck & Co., Inc. The synthesis of pseudococaine (2), allococaine (3), and [2-^2H]pseudococaine ([2-^2H]-2) was accomplished by slight modifications of published procedures. An improved reduction–benzoylation sequence led to allopseudococaine (4). Thus, 2 was prepared in 61% yield by the base-promoted epimerization of 1 to give pseudoecgonine methyl ester[4] followed by benzoylation. Epimerization of 1 in O-deuterated methanol gave [2-^2H]-2. The synthesis of 4 was accomplished by the reduction of 2-(carbomethoxy)-3-tropinone, prepared by carbomethoxylation of 3-tropinone with dimethyl carbonate, with sodium borohydride in methanol at −30 °C, which yielded allopseudoecgonine methyl ester uncontaminated by isomeric ecgonine methyl esters. Analogous reduction with sodium borodeuteride gave [3-^2H]-allopseudoecgonine methyl ester. Benzoylation with benzoic anhydride in the presence of excess 4-(dimethylamino)pyridine yielded 4 and [3-^2H]-4, respectively. Hydrolysis of allopseudoecgonine methyl ester, followed by separation of the resulting mixture of allo- and allopseudoecgonine and methylation, provided alloecgonine methyl ester, which was benzoylated.[3] Although the hydrochloride salts of 1, 2, and 4 could be prepared, all attempts to prepare the hydrochloride salt of 3 led to almost instantaneous decomposition.

NMR Spectra. Proton and ^{13}C NMR spectra of 1–4 and of the hydrochloride salts of 1, 2, and 4 were recorded on chloroform, chloroform/methanol (6:1), and dimethyl sulfoxide solutions (Tables I and II). Proton resonance assignments rest largely on decoupling experiments. Assignments of the ^{13}C signals were made on the basis of ^{13}C NMR chemical shift theory, signal multiplicity found in the off-resonance decoupled spectra, specific ^1H decoupling experiments, and the known effects of deuterium substitution on ^{13}C chemical shifts.[5-7]

^1H NMR Spectra. The ^1H NMR spectra of 1–4 (Figure 1) have several distinct common features. The aromatic multiplet due to the benzoyl phenyl appears at 7.2–7.9 ppm, as expected; the *O*-methyl and *N*-methyl group resonances are in the 3.6- and 2.3-ppm regions, respectively. In the 5.5-ppm region appears the proton at C-3; its multiplicity is distinctive for each isomer, and it provides a ready diagnositic for isomer identification. The protons at C-2, C-1, and C-5 have resonances in the region 3.6–2.5 ppm, and the remaining protons (at C-4, C-6, and C-7) resonate between 2.4 and 1.8 ppm.

Selected resonance assignments and coupling constants for 1–4 have been reported by Beyerman and co-workers.[3] With the aid of high-field spectra, decoupling experiments, and computer simulations, we have made chemical shift assignments of all aliphatic protons except those on carbons 6 and 7. Furthermore, in addition to the vicinal

Table I. ^1H NMR Chemical Shifts and Coupling Constants for Compounds 1–4 and Their Hydrochloride Salts

compd	chemical shifts[a]							coupling constants							
	1	2	3	4_{ax}	4_{eq}	5	CH_3N	CH_3O	$J_{1,2}$	$J_{1,3}$	$J_{1,5}$	$J_{2,3}$	$J_{2,4}$	$J_{3,ax}$	$J_{3,4eq}$	$J_{3,5}$	$J_{4,4}$	$J_{4ax,5}$	$J_{4eq,5}$
cocaine (1)																			
$CHCl_3$	3.5	3.0	5.3	2.5	1.8	3.3	2.2	3.7	3.3		~1.0	6.0	0.8	12.0	6.0		12.9	1.8	3.0
$CHCl_3/CH_3OH$[b]	3.6	3.0	5.2	2.4	1.9	3.3	2.2	3.7				6.0		12.0	6.0		11.8		3.1
1·HCl																			
$CHCl_3/CH_3OH$[b]	4.3	3.5	5.5	2.7	2.3	4.2	3.0	3.7	2.4			6.8		11.8	6.8		12.5		2.7
Δ[c]	+0.7	+0.5	+0.3	+0.3	+0.4	+0.9	+0.8	0.0											
pseudococaine (2)																			
$CHCl_3$	3.5	3.1	5.5	1.8	2.1	3.3	2.4	3.6	2.9			10.9		10.5	6.6		12.5		3.0
$CHCl_3/CH_3OH$[b]	3.5	3.1	5.5	1.8	2.1	3.3	2.4	3.7	3.1			10.7		10.7	6.6		12.7		3.1
2·HCl																			
$CHCl_3/CH_3OH$[b]	4.2	4.0[d]	5.6	2.6	2.4	4.0[d]	2.8	3.6				10.7		10.7	6.6		12.8		
Δ[c]	+0.7	+0.9	+0.1	+0.8	+0.3	+0.7	+0.4	−0.1											
allococaine (3)	3.7	2.8	5.6	2.4	1.8	3.2	2.2	3.8	2.2			1.0	2.2	5.2	1.1	~1.0	15.0	3.8	2.2
allopseudococaine (4)																			
$CHCl_3$	3.5[e]	3.2	5.6	2.2	1.9	3.3	2.3	3.5[e]	3.1			4.8		4.8	1.1	~1.0	15.8	4.8	2.2
$CHCl_3/CH_3OH$[b]	3.5	3.2[d]	5.7	2.2	1.9	3.2[d]	2.4	3.6				4.1		4.1			15.5		
4·HCl																			
$CHCl_3/CH_3OH$[b]	4.2[f]	4.2[f]	5.8	3.0	2.3	3.9	2.9	3.6				4.0		4.0			16.5		
Δ[c]	+0.7	+1.0	+0.1	+0.8	+0.4	+0.7	+0.5	0.0											

[a] In parts per million downfield from tetramethylsilane (Me_4Si). [b] $CHCl_3/CH_3OH$ = 6:1. [c] Chemical shift difference between hydrochloride salt and free amine in $CHCl_3/CH_3OH$. [d] H-2 and H-5 overlap. [e] H-1 and H-2 overlap. [f] H-1 and H-2 overlap.

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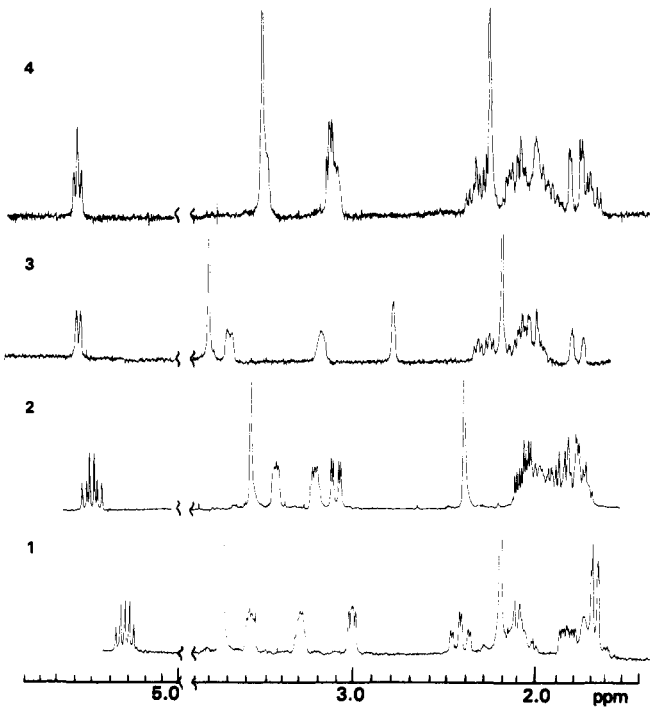


Figure 1. NMR spectra of the aliphatic protons of cocaine (1), pseudococaine (2), allococaine (3), and allopseudococaine (4) at 250 MHz in $CDCl_3$. The chemical shift assignments are in Table I.

coupling constants reported,[3] we have determined a geminal coupling constant for the C-4 methylene and several long-range coupling constants not previously reported. The chemical shifts and coupling constants determined from decoupling experiments are listed in Table I.

Specifically, irradiation at the resonance frequency of the proton at C-3 identified the signals due to the protons at C-2 and C-4. Irradiation at the highest frequency signal of these three resonances invariably led to collapse of the middle frequency signal, suggesting that these signals were due to the geminal methylene protons at C-4.

It followed then that the signal at the lowest frequency of the three resonances decoupled by irradiation at H-3 was due to the proton at C-2. Irradiation at the frequency of H-2 then allowed identification of the proton at C-1. That the remaining signal was due to the bridgehead proton at C-5 was verified by irradiating this proton and observing effects at the C-4 protons. Assignment of the signals associated with the methylene group at C-4 to the axial and equatorial protons was based on the magnitude of their coupling to the H-3 proton, on the observed long-range coupling between the protons at C-2 and C-4 found in 1 and 3, and on observed protonation shifts (vide infra).

Due to the high operating frequency of the spectrometer (250 MHz), no second-order patterns were observed, simplifying the determination of the spin–spin coupling constants. Further simplification resulted from decoupling experiments which essentially allowed the coupling constants to be read directly from the spectra. These values were then used to carry out a partial simulation of the spectrum (without the protons at C-6 and C-7), using the Bruker PANIC program. The coupling constants were then adjusted until good agreement between the calculated and observed patterns for the signals of the protons at C-2, C-3, and C-4 was obtained.

The ^1H NMR parameters of the hydrochloride salts of 1, 2, and 4 were obtained in similar fashion (Table I). Because the hydrochloride salts were extremely insoluble

Table II. Carbon-13 Chemical Shifts of 1-4 and Their Hydrochloride Salts

		carbon position[a]												
compd	solvent	1	2	3	4	5	6	7	NCH_3	OCH_3	C=O	C=O	1′	2′ and 6′	3′ and 5	4′
cocaine (1)	$CDCl_3$	64.76	50.14	66.82	35.46	61.45	25.32[b]	25.17[b]	41.02	51.26	170.63	166.04	130.20	129.57	128.16	132.74
	Me_2SO-d_6	64.47	49.56	67.02	35.03	60.92	24.93[b]	24.93[b]	40.73	51.06	169.95	165.13	129.92	129.09	128.70	133.29
cocaine HCl	Me_2SO-d_6	63.01	45.95	64.14	32.44	62.58	23.96	22.27	40.39	52.53	171.36	164.59	128.99[d]	128.99[d]	128.99[d]	132.82
salt - amine[c]		−1.46	−3.61	−2.88	−2.59	+1.66	−1.07	−2.68	−0.34	+1.47	+1.41	−0.54	−0.93	−0.10	+0.29	−0.47
pseudococaine (2)	$CDCl_3$	62.38	48.38	67.64	33.56	59.50	26.63	23.86	37.36	51.55	171.95	165.22	129.96	129.18	127.91	132.49
	Me_2SO-d_6	62.09	47.95	67.89	33.32	59.07	26.74	23.81	37.13	51.70	171.96	164.84	129.77	129.09	128.65	133.23
pseudococaine HCl	Me_2SO-d_6	62.81	47.41	65.64	33.22	62.08	24.34	21.76	37.80	52.48	169.31	164.87	*e*	129.18	128.89	133.71
salt -amine[c]		+0.72	−0.54	−2.25	−0.1	+3.01	−2.30	−2.05	+0.67	+0.78	−2.65	+0.03		+0.09	+0.24	+0.47
allopseudococaine (4)	$CDCl_3$	61.01	49.41	68.18	36.63	59.60	25.32	24.05	40.38	51.40	171.31	165.41	130.06	129.23	128.40	132.89
	Me_2SO-d_6	60.38	48.23	68.23	35.66	58.77	25.37	24.05	39.71	51.21	170.97	164.70	129.76	128.84[b]	128.75[b]	133.28
allopseudococaine HCl	Me_2SO-d_6	61.50	46.43	65.89	33.41	61.02	23.81	22.25	38.09	52.04	168.63	164.44		129.03[b]	128.94[b]	133.67
salt - amine[c]		+1.12	−1.80	−2.33	−2.25	+2.25	−1.56	−1.80	−1.62	+0.83	−2.34	−0.26		+0.19	+0.19	+0.39
allococaine (3)	$CDCl_3$	62.87	51.80	67.69	36.15	60.48	24.97	24.44	41.51	51.65	171.80	165.26	130.15	129.18	128.26	132.74
	Me_2SO-d_6	62.77	51.02	67.45	35.81	60.04	24.88	24.20	41.37	51.75	171.61	164.88	129.97	129.04	128.85	133.33

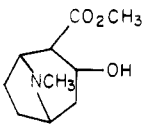
[a] Chemical shifts are given in parts per million downfield from Me_4Si. [b] The assignment for these resonances may be reversed. [c] Chemical shift difference between hydrochloride salt and free amine in Me_2SO-d_6. [d] These resonances appear as one line approximately three times as intense as other protonated carbons. [e] This resonance is overlapped with the 2′,6′ carbons.

in chloroform, the spectra were recorded in a solution of 6:1 deuteriochloroform/deuteriomethanol. For comparison, the spectra of the free bases were also recorded in this medium.

^{13}C NMR Spectra. The ^{13}C NMR spectra of 1–4 were recorded in deuteriochloroform and deuteriodimethyl sulfoxide; the spectra of the hydrochloride salts of 1, 2 and 4 were recorded in deuteriodimethyl sulfoxide. The signal assignments are shown in Table II; the assignments for 1 are in accord with the previously made assignments[8] as corrected by Baker.[9]

The high-field region of the SFORD spectra of 1–4 showed two quartets (CH_3O, CH_3N), three triplets (C-4, C-6, and C-7) and four doublets (C-1, C-2, C-3, and C-5). The CH_3O and CH_3N resonances were most easily distinguished by their expected chemical shift difference. The C-4 resonance was assigned to the lowest field triplet in accordance with other tropane alkaloids.[10] The signals for C-6 and C-7 were usually quite similar; assignments shown were deduced from expected substituent effects. However, in some cases the chemical shift difference was too small to allow definitive assignment. The assignments for C-1, C-3, and C-5 were achieved by specific proton irradiation of the protons on C-1, C-3, and C-5. These assignments were further substantiated by the spectra observed for [2-^{2}H]-pseudococaine ([2-^{2}H]-**2**) and [3-^{2}H]allopseudococaine ([3-^{2}H]-**4**). These spectra showed the absence of the C-2 and C-3 resonance, respectively, presumably due to increased T_1 values, decreased Overhauser effects, and dissipation of the singlets into triplets. In addition, the expected β deuterium effects were observed.[6]

The chemical shift assignment of the carbons in the aromatic region was straightforward. Carbon-1′ was the only singlet in the aromatic region of the SFORD spectra, C-4′ was one-half the intensity of either the ortho (C-2′, C-6′) or meta (C-3′, 3-5′) carbons. The latter resonances were assigned on the basis that the ortho carbons are usually more deshielded than the meta carbon in benzoate esters.[11] The benzoyl and 2-carbomethoxy carbonyl resonances were distinguished by a comparison of cocaine and ecgonine methyl ester (**5**).[12]



5

Discussion

Synthesis. Our attempted preparation of allopseudoecgonine methyl ester from 2-(carbomethoxy)tropinone by hydrogenation over Adams catalyst following the literature procedure[3] gave low yields and was, in general, unsatisfactory. Consequently, the use of other reducing agents was investigated, and it was found that use of sodium borohydride in methanol at −30 °C gave allopseudoecgonine methyl ester cleanly and in relatively good yield. It should be noted that when the reaction is carried out at higher temperature (~0 °C), a mixture of pseudo- and allopseudoecgonine methyl ester is produced.

NMR Spectra and Conformational Analysis. It had been concluded by Beyerman and co-workers[3] that the chair was the preferred conformation of the piperidine ring in all four isomers of cocaine. Our data confirm this conclusion. Specifically, the magnitude of the coupling constants between the protons on C-2, C-3, and C-4, the long-range coupling constant between the protons on C-2 and C-4, and the geminal coupling constant of the protons on C-4 are inconsistent with any other conformation. Thus, the H-3 signals for 1 and 2 (cocaine and pseudococaine, respectively) are much wider than the analogous signals for 3 and 4 (allo- and allopseudococaine). The pattern for 1 is a five-line 1:2:2:2:1 multiplet arising from the overlap of the upfield wing of a low-field triplet with the downfield wing of an upfield triplet. The pattern for 2 is that of a doubled triplet, while the patterns for 3 and 4 are a doublet and a triplet, respectively. These patterns are uniquely consistent with a chair conformation for the piperidine ring, as has been proposed.[3] Thus, the H-3 signal for 1 exhibits one large coupling due to J_{aa} ($J_{3,4a}$) and two smaller, nearly equivalent couplings, J_{ae} ($J_{3,4e}$ and $J_{3,2}$). If the piperidine ring were in a boat conformation, H-3 would be equatorial, and $J_{3,4a}$ would be similar in magnitude to $J_{2,3}$, and $J_{3,4e}$ would be the smallest. Similarly, in 2 the observed multiplicity is due to two nearly equivalent large couplings of H-3 to its axial neighbors at C-2 and C-4, giving rise to a triplet; the doubling is due to coupling to the equatorial proton at C-4.

The narrowness of the signals due to the proton at C-3 in 3 and 4 speaks for its equatorial nature. The doublet observed for 3 is due to the coupling $J_{3,4a}$, and the triplet for 4 arises from the nearly equivalent coupling of H-3 with its axial neighbors at C-2 and C-4. If the piperidine ring were in a boat conformation, the proton at C-3 would be axial, leading to a wide triplet due to the two large couplings, J_{aa} ($J_{2,3}$ and $J_{3,4a}$) for 3 and to a wide doublet due to $J_{3,4a}$ in 4. Therefore, the observed coupling constants support the chair conformation proposed[3] for the piperidine ring in 1–4.

Cocaine (1) exhibits coupling between H-2 and the equatorial proton at C-4. The only other cocaine isomer to possess an equatorial proton at C-2, allococaine (3), also exhibits such coupling, while pseudo- and allopseudococaine (2 and 4, respectively) do not. Therefore, it appears that this is a "*W*"-type coupling[13] between two equatorial protons, H-2 and H-4$_e$. The magnitude of this coupling, 0.8 and 2.2 Hz in 1 and 3, respectively, requires H-2 and H-4$_e$ to be in an exact *W* conformation, further substantiating the chair conformation of the piperidine ring portion of cocaine (1) and allococaine (3). Finally, the magnitudes of J_{gem} for the protons at C-4 support the chair conformation for all four isomers 1–4. According to Pople and Bothner-By's molecular orbital theory of geminal coupling,[14,15] methylene protons which are a gauche-trans pair relative to a vicinal electronegative substituent should show a more negative (larger absolute value) J_{gem} than those in a methylene group which has both protons in a gauche relationship to the substituents. In the first case the substituent must be axial and in the latter equatorial. Thus, the smaller (more negative) J_{gem} for the C-4 methylene group of allococaine and allopseudococaine (axial benzoyloxy) relative to cocaine and pseudococaine (equa-

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Table III. Carbon-13 Chemical Shifts for the NCH_3 Equatorial and Axial Conformers of Tropine (6) and Pseudotropine (7)[a]

compd	1	2	3	4	5	6	7	NCH_3
e-6	60.74	39.50	63.41	39.50	60.74	25.34	25.34	41.13
a-6	56.36	29.87	63.41	29.87	56.36	28.54	28.54	32.64
e-7	61.85	41.58	63.08	41.58	61.85	26.25	26.25	40.80
a-7	58.15	32.61	63.08	32.61	58.16	29.17	29.17	32.82

[a] The data in this table were taken from ref 18.

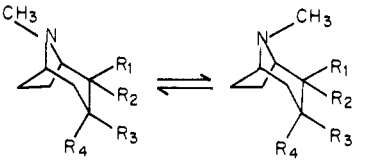
torial benzoyloxy) is consistent with all four diastereoisomers having the chair conformation.

It has also been shown that the magnitude of the geminal coupling is influenced by the C-CH_2-C angle.[16,17] Specifically, the magnitude of J_{gem} becomes more positive as the angle becomes smaller. Because J_{gem} is the same for 1 and 2 and does not vary between 3 and 4, the ring conformations must be almost identical.

Inspection of the proton chemical shifts of 1–4 (Table I) reveals that the protons on C-1, C-5, and the CH_3O and CH_3N group have very similar values (±0.2 ppm) for all four compounds. The chemical shifts of H-3 show the expected downfield shift of the equatorial (3 and 4) relative to the axial (1 and 2) protons. By contrast, the chemical shift of H-2 is downfield when the proton is axial (2 and 4) relative to the chemical shift of the equatorial analogue (1 and 3). The most striking difference in the chemical shifts is found in a comparison of the C-4 methylene protons. The relative positions, as well as the magnitude of the chemical shift difference, of the 4_{ax} and 4_{eq} protons in 1, 3, and 4 are rather similar. In contrast, the relative position of the 4_{ax} and 4_{eq} are reversed in 2. In fact, it is tempting to question the resonance assignments for these signals. However, the assignments are unambiguous. It is quite clear that the axial proton at C-4 must be involved in the two large spin–spin couplings, i.e., to H-3 (axial in 2) and to its geminal partner. It would therefore appear as a triplet, with additional small coupling to H-5 possible. The equatorial proton would be involved in only one large coupling (J_{gem}), a medium coupling ($J_{ea} = J_{4,3}$) and a possible small coupling to H-5. It would therefore appear as a doubled doublet. The spectrum of pseudococaine clearly shows the doubled doublet at 2.5 ppm ($H\text{-}4_e$); the triplet for $H\text{-}4_a$ is somewhat obscured by H-6 and H-7. However, there are no other signals downfield of $H\text{-}4_e$ which are not otherwise accounted for. Therefore, even if the absolute chemical shift of $H\text{-}4_a$ could be in error by ±0.1 ppm, there is no doubt but that it is *upfield* of $H\text{-}4_e$.

With regard to the assignment of $H\text{-}4_a$ and $H\text{-}4_e$ in 3 and 4, the situation is not quite as clear-cut. Because H-3 is equatorial in 3 and 4, it was expected that $J_{3,4a}$ would be larger than $J_{3,4e}$, and the assignments were made on this basis. The assignment for 3 was also supported by the long-range coupling between the protons at C-2 and C-4 found in 1 and 3. Since the assignment of $H\text{-}4_{ax}$ in 1 is unambiguous, it was clear that the long-range coupling $J_{2,4}$ was associated with $H\text{-}4_e$. Since $J_{2,4}$ represents coupling of the "*W*" type,[13] the C-4 proton involved in this coupling in 3 must be equatorial, confirming the assignment based on $J_{3,4}$. The assignment for $H\text{-}4_{ax}$ in 4 is also supported by the observed protonation shifts (vide infra).

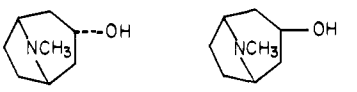
It therefore follows that there must be a factor associated with pseudococaine (2) which leads to an upfield shift for the axial proton at C-4 and to a downfield shift for its equatorial portion relative to their positions in 1, 3 and 4. In fact, the analogous situation obtains with regard to H-2. The H-2 resonance in allococaine (3), equatorial H-2, is 0.4 ppm upfield of the H-2 resonance in allopseudococaine (4, axial H-2), i.e., the equatorial position in the case is shielded relative to the axial position as is the case with the protons at C-4. By contrast, the proton at C-2 in pseudococaine (2, axial H-2) is only 0.1 ppm downfield of H-2 in cocaine (1, equatorial H-2), suggesting shielding of ca. 0.3 ppm in pseudococaine (2). It therefore appears that there must be conformational differences between the isomers. Since analysis of the vicinal, geminal, and long-range coupling constants seems to strongly support chair conformations for all four isomers, the difference would appear most likely to be due to the orientation of the *N*-methyl group. Thus, nitrogen inversion can lead to equilibration between the conformers A and B in each of the isomeric cocaines, and differences in the population of A and B might account for the observed differences in chemical shifts between isomers.



A B

cocaine (1), $R_1 = CO_2CH_3$; $R_2 = H$; $R_3 = OCOPh$; $R_4 = H$
pseudococaine (2), $R_1 = H$; $R_2 = CO_2CH_3$; $R_3 = OCOPh$; $R_4 = H$
allococaine (3), $R_1 = CO_2CH_3$; $R_2 = H$; $R_3 = H$; $R_4 = OCOPh$
allopseudococaine (4), $R_1 = H$; $R_2 = CO_2CH_3$; $R_3 = H$; $R_4 = OCOPh$

Differentiation of axial and equatorial *N*-methyl group in piperidine and its derivatives has been carried out successfully by use of ^{13}C NMR.[10] In particular, Schneider and Sturm have studied the low-temperature ^{13}C NMR of tropine (6) and pseudotropine (7) in $CFCl_3/CH_3OH$ (2:1).[18] They found that the nitrogen inversion could be "frozen" on the NMR time scale at −70 °C. The chemical shift reported for the equatorial and axial *N*-methyl isomers of 6 and 7 are listed in Table III.



6 7

Comparison of the chemical shifts in Table III to those of 1–4 in Table II, particularly those for C-4, C-5, C-6, C-7, and NCH_3, suggests that pseudococaine (2) has a larger population of axial *N*-methyl than cocaine (1). Similarly, the comparison suggests that allopseudococaine (4) has a larger population of axial *N*-methyl conformers than allococaine (3). The comparison also indicates that the

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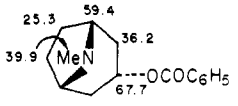
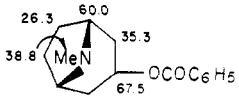
conformational preference for an axial *N*-methyl group in pseudococaine relative to cocaine is greater than that in allopseudococaine relative to allococaine. In regard to these preferences, it is interesting that tropine (**6**), which has an endo 3-substituent compared to an exo 3-substituent in pseudotropine (**7**), has a greater preference for an equatorial *N*-methyl (1.20 kcal mol) than pseudotropine (**7**; 0.72 kcal/mol).[18]

Further support for this interpretation was derived from a comparison of the observed ^{13}C chemical shifts with the values expected when one considers the effect of introducing an axial or an equatorial carbomethoxy group onto tropine benzoate (**8**) and pseudotropine benzoate (**9**). The



8



9

^{13}C NMR chemical shift for pseudotropine benzoate (**9**) and tropine benzoate (**8**) have been determined and are as depicted on the formulas.[19] The introduction of an axial or equatorial carbomethoxy group to **9** yields cocaine (**1**) and pseudococaine (**2**), respectively. Similarly, introduction of an axial carbomethoxy group to **8** yields allococaine (**3**), and an equatorial group gives allopseudococaine (**4**). It would be expected that C-1, C-2, and C-3 of both cocaine (**1**) and pseudococaine (**2**) would be deshielded by the introduction of the carbomethoxy group. This effect should be larger in pseudococaine (**2**) due to the equatorial conformation of the carbomethoxy group than in **1** in which the group is axial. The introduction of the carbomethoxy group should have no effect on C-5, C-6, and C-7; however, in the case of cocaine (**1**) an upfield shift, due to the γ effect, is expected for C-4. Inspection of the data in Table II shows that, in fact, larger downfield shifts are observed for **1** than for **2**. These observations are readily explained by the previously made suggestion that the population of axial *N*-methyl conformers in pseudococaine is larger than in cocaine. If this is the case, then the observed shift differences can be explained since an axial *N*-methyl appears at higher field than an equatorial *N*-methyl, the axial β effect is less deshielding than the equatorial β effect, and the axial γ effect is more shielding than the equatorial γ effect.[10] A similar comparison of allococaine (**3**) to allopseudococaine (**4**) indicates that the conformational population with axial *N*-methyl in **4** exceeds that in **3**. However, the difference is not as great as between **1** and **2**.

The carbon-13 protonation shifts obtained by comparison of the spectra of the free bases **1**, **2**, and **4** with those of their hydrochloride salts are also consistent with the suggestion that **2**, as the free base, has a larger percentage of axial *N*-methyl when compared to its salt as well as compared to allopseudococaine (**4**) and its salt. In general, protonation of amines leads to shielding of both β and γ carbons. The effect at the α carbon can be shielding or deshielding, depending on the structure of the amine.[10,20] An inspection of the protonation shifts of **1**, **2**, and **4** (Table II) reveals that protonation of allopseudococaine (**4**) gives upfield shifts at C-2, C-4, C-6, and C-7 that might be expected. In contrast, pseudococaine (**2**), which differs from allopseudococaine (**4**) only in the stereochemistry at C-3, shows much smaller upfield shifts at C-2 and C-4, and slightly larger upfield shifts at C-6 and C-7. The *N*-methyl is shifted upfield in **4** and downfield in **2**. Carbon-1 and C-5 are shifted downfield in both compounds. It follows that in the case of allopseudococaine (**4**) both the free base and salt possess largely equatorial *N*-methyl. In the case of pseudococaine (**2**) the small protonation shifts for C-2 and C-4 combined with the relatively larger shifts for C-6 and C-7 suggest a smaller axial *N*-methyl population for the hydrochloride than for the free base of **2**. These conclusions are summarized in Table IV.

Table IV. Relative Population of Conformer A (Equatorial *N*-Methyl) in Cocaines

larger	smaller
2	1
4	3
2	2·HCl
2	4
2	4·HCl

Examination of the effect of protonation on the ^{13}C chemical shifts also reveals that the effects for cocaine (**1**) are quite different from those for **2** and **4**. Carbon-2 of cocaine shows the largest β upfield shift, and C-1 shows a 1.5-ppm upfield shift compared to +0.7 and +1.0 downfield shift for **2** and **4**, respectively. In addition, the 2-carbomethoxy carbonyl is shifted downfield 1.4 ppm compared to upfield shifts of −2.7 and −2.4 in **2** and **4**. This cannot be due to conformational change in the piperidine ring since the geminal and vicinal coupling constants of **1**, **2**, and **4** are almost identical with those of their hydrochloride salts. We believe these results strongly suggest that at least part of the cocaine hydrochloride conformation population is made up of a conformer possessing a hydrogen bond between the $-^{+}NH$ and the 2-carbomethoxy group.

Some support for both these suggestions can be found in the protonation effects on the ^{1}H chemical shifts (Table I). These shifts were obtained by comparing the spectra of the hydrochloride salts in 6:1 chloroform/methanol solution with those of the free amines in the same medium. Significantly, no major changes in the uncoupling constants were observed precluding substantial changes in the conformation of the piperidine ring. In general, the observed protonation shifts are unremarkable. Typical downfield shifts of 0.7 ppm are observed for most of the protons α to nitrogen in **1**, **2**, and **4**. The largest protonation shifts are manifested at the axial 2 and 4 protons in **2** and **4**. Exceptions are the low protonation shifts of the *N*-methyl group in **2** and of H-4_{ax} in **1**. The former is probably due to the change in the conformation of the *N*-methyl group upon protonation, proposed to account for the observed ^{13}C protonation shifts. The latter supports the proposed formation of a proton bridge between the nitrogen and the axial carbomethoxy group in **1**. Such a species would keep the anisotropy of protonated group well away from C-4, leaving only inductive deshielding, which is equivalent for H-4_{ax} and H-4_{eq}, as observed.

Since the hydrochloride salt of allococaine was unstable, we were unable to make the comparison in this case.

Experimental Section

^{1}H NMR spectra were determined in $CDCl_3$ or $CDCl_3/CD_3OD$ (6:1), using a Bruker WM-250 spectrometer operating at 250.70 MHz; ^{13}C NMR spectra were recorded in $CDCl_3$ or Me_2SO-d_6, using a JEOL JNM-PS-100 FT spectrometer operating at 25.034 MHz. The ^{1}H and ^{13}C NMR spectra were recorded in 5-mm tubes, using approximately 10 mg/0.6 mL and 40 mg/0.4 mL solution, respectively. An internal deuterium lock was used for both ^{1}H and ^{13}C NMR spectra. Chemical shifts of all compounds are reported in parts per million (δ) relative to Me_4Si.

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(+)-Pseudococaine (2) Hydrochloride. To a stirred solution of 1.8 g (9 mmol) of pseudoecgonine methyl ester [prepared from (-)-cocaine (1) by the literature procedure[4]] and 1.51 g (10 mmol) of DBU in dry C_6H_6 (100 mL) was added 3.07 g (13 mmol) of recrystallized benzoic anhydride. The solution was refluxed 21.5 h, at which point the reaction was >95% complete (GC). After cooling to ambient temperature, the mixture was washed with 10% Na_2CO_3 solution (3 × 100 mL) and with H_2O (6 × 100 mL), dried (Na_2SO_4), and evaporated. Treatment of the residual yellow, oily solid (3.1 g) with methanolic HCl followed by evaporation of the solvent and recrystallization from MeOH/Et_2O gave 2.24 g (73%) of (+)-pseudococaine (2) hydrochloride: mp 208–209 °C (lit.[21] mp 210 °C); $[\alpha]^{24}_D$ +41.3° (c 1, MeOH) [lit.[21] $[\alpha]^{20}_D$ +41° (c 5, H_2O)].

The 2-deuterio analogue [2-^{2}H]-2 was analogously prepared from 2-deuterioecgonine methyl ester which had been prepared from (-)-cocaine in O-deuterated methanol.

(±)-2-(Carbomethoxy)-3-tropinone. The procedure described below avoids the use of benzene and was found to be superior to that reported.[22]

In an oven-dried, 500-mL, round-bottomed, three-neck flask, under N_2, were placed 60 mL of freshly distilled (from P_2O_5) cyclohexane and 7.1 g (0.296 mol) of NaH (from a 50% mineral oil dispersion, washed with dry cyclohexane) and 27.4 mL (29.33 g, 0.325 mol) of freshly distilled dimethyl carbonate (Eastman). This mixture was heated to a very gentle reflux, with stirring, and a solution of 20.59 g (0.148 mol) of 3-tropinone (Hooker) in 125 mL of dry cyclohexane was added dropwise to the refluxing mixture over a 20-min period. No significant H_2 evolution was noted, so 0.5 mL MeOH was added. After a few minutes, the reaction mixture started foaming and darkening. After 1.75 h, the foaming had subsided, so the reaction mixture was allowed to cool to 30 °C; water (250 mL) was added carefully at first until no further fizzing was observed then rapidly. The layers were separated, and the cyclohexane layer was extracted with additional H_2O (2 × 100 mL). The combined aqueous extract was saturated with NH_4Cl (~120 g) and extracted with $CHCl_3$ (8 × 100 mL). The combined $CHCl_3$ extract was washed with saturated aqueous NaCl (2 × 50 mL) and dried over Na_2SO_4 overnight. The solvent was evaporated after removal of the drying agent, leaving a yellowish oil which crystallized upon standing. TLC (SiO_2, EtOAc/MeOH/NH_4OH = 1:1:0.04) and GC (3% Se-30, 165 °C, 25 mL/min) showed a pure product. This material (23.4 g, 80% yield) corresponded in every way to a sample which had been prepared by the literature procedure[22] and characterized fully.

(±)-Allopseudoecgonine Methyl Ester. To a solution of 9.32 g (47 mmol) of 2-(carbomethoxy)-3-tropinone in 900 mL of dry MeOH at -30 °C was added 9.32 g (245 mmol) of $NaBH_4$, the mixture was stirred until H_2 evolution ceased (ca. 4 h), and concentrated HCl (24 mL) was added, and then the solution was evaporated to dryness. The residual oil was dissolved in H_2O (500 mL), and the solution was acidified to pH 3 and extracted twice with Et_2O. The aqueous phase was then basified to pH 11 with NH_4OH and extracted with CH_2Cl_2 (4×). The combined CH_2Cl_2 extract was dried (Na_2SO_4) and concentrated to give 6.63 g (71%) of (±)-allopseudoecgonine methyl ester. Purification was best accomplished via the HBr salt. A solution of 0.72 g (3.6 mmol) of the product in MeOH was treated with 0.61 g of 48% HBr. Evaporation of the solvent gave 0.92 g of a solid. Recrystallization from MeOH/Et_2O afforded 0.65 g of (±)-allopseudoecgonine methyl ester hydrobromide as a white solid, mp 183–185 °C. This salt is sensitive to light, heat, and moisture.

Anal. Calcd for $C_{10}H_{18}BrNO_3$: C, 42.87; H, 6.47; N, 5.00; Br, 28.52. Found: C, 42.84; H, 6.55; N, 4.91; Br, 28.24.

The 3-deuterio analogue required for the preparation of [3-^{2}H]-4 was prepared by carrying out the reduction with $NaBD_4$ in MeOD.

Allococaine (3). A sample of 5.9 g (30 mmol) of (±)-allopseudoecgonine methyl ester was refluxed overnight in H_2O (65 mL). The water was removed by evaporation and freeze-drying, leaving 5 g (85%) of a tan semisolid. This material was slurried in ice-cold $CHCl_3$ and allowed to warm to ambient temperature. The insoluble material was removed by filtration and recrystallized from absolute EtOH to give 2.0 g (44%) of (±)-alloecgonine. Heating of this material in 8% HCl/MeOH (75 mL) at 50 °C over 16 h, evaporation of the solvent, and crystallization of the residue from MeOH/Et_2O gave 2.1 g (82%) of (±)-alloecgonine methyl ester hydrochloride. Neutralization of 0.57 g (24 mmol) with saturated K_2CO_3, extraction with CH_2Cl_2, and evaporation of the solvent (after Na_2SO_4 drying) afforded 0.40 g (83%) of the free base. This material was benzoylated, following the literature,[3] to give 0.39 g (64%) of crude (±)-allococaine; 0.17 g (40%) of alloecgonine methyl ester hydrochloride was also recovered. Allococaine was purified by chromatography on 9 g of 100/200A Florisil, eluting with 2% → 50% Me_2CO in CH_2Cl_2 followed by 5% MeOH in CH_2Cl_2. The product was obtained as an off-white solid, mp 93–95 °C (lit.[3] mp 95–97 °C), which by NMR and elemental analysis was shown to contain 0.33 mol of H_2O.

Anal. Calcd for $C_{17}H_{21}NO_4 \cdot {}^1/_3H_2O$: C, 66.20; H, 6.95; N, 4.55. Found: C, 66.24; H, 6.98; N, 4.35.

(±)-Allopseudococaine (4) Hydrochloride. A solution of 0.23 g (11.6 mmol) of (±)-allopseudoecgonine methyl ester in CH_2Cl_2 (15 mL) was allowed to react overnight with 1.2 g (53.1 mmol) benzoic anhydride in the presence of 0.65 g (53.3 mmol) of DMAP. The reaction mixture was then diluted with Et_2O, washed with H_2O, and dried over K_2CO_3. Treatment with NH_4OH gave 0.36 g of crude (±)-allopseudococaine. Attempted purification by chromatography on Florisil led to decomposition. Consequently, the oil was dissolved in methanolic HCl, and the resulting salt was recrystallized from EtOH/hexanes to give 0.12 g of (±)-allopseudococaine (4) hydrochloride as a white solid, mp 209–210 °C (lit.[3] mp 209–210 °C).

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Registry No. (-)-1, 50-36-2; (-)-1·HCl, 53-21-4; (+)-2, 478-73-9; (+)-2·HCl, 6363-57-1; (±)-3, 21030-42-2; (±)-4, 21030-43-3; (±)-4·HCl, 21030-50-2; (+)-pseudoecgonine methyl ester, 65913-90-8; (±)-2-(carbomethoxy-3-tropinone, 36127-17-0; 3-tropinone, 532-24-1; (±)-allopseudoecgonine methyl ester, 46255-79-2; (±)-allopseudoecgonine methyl ester hydrobromide, 79735-01-6; (±)-alloecgonine, 79735-02-7; (±)-alloecgonine methyl ester hydrochlorid, 79735-03-8; (±)-alloecgonine methyl ester, 46255-78-1.

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