Base-Catalyzed C-2 Exchange and Epimerization of Cocaine Analogs: Methyl 3β-Substituted 8-Methyl-8-azabicyclo[3.2.1]octane-2-carboxylates

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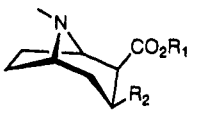
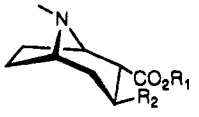
The kinetic and thermodynamic parameters associated with epimeric 2-carbomethoxy-3β-substituted tropanes have been investigated by means of base-catalyzed deuterium incorporation, epimerization, and by molecular modeling. The equilibration results, as well as the molecular mechanics calculations, showed the 2α-epimers to be more stable than the 2β-epimers. However, it was found that the energies of the transitions states for deprotonation at C-2 from the β-face were higher than those for deprotonation from the α-face. These results are contrary to what would have been predicted based on the assumption that the more exothermic reaction pathway would involve a more stabilized transition state.

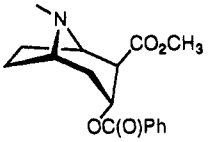
Introduction

The structure of methyl 3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate (1), better known as cocaine, has been well established by various techniques. These include classical organic chemistry by Findlay[1-3] and Hardegger,[4] proton and carbon-13 nuclear magnetic resonance spectroscopy by Sinnema[5] and Carroll,[6] and X-ray diffraction by Gabe.[7] The piperidine ring is in a chair conformation with the carbomethoxy and benzoyloxy groups occupying axial and equatorial positions, respectively. Epimerization of these substituents leads to the isomers pseudococaine (2), allococaine (3), and allopseudococaine (4).





1, $R_1 = CH_3$; $R_2 = OC(O)Ph$ **2**, $R_1 = CH_3$; $R_2 = OC(O)Ph$
5, $R_1 = CH_3$; $R_2 = OH$ **7**, $R_1 = CH_3$; $R_2 = OH$
8, $R_1 = H$; $R_2 = H$ **9**, $R_1 = H$; $R_2 = H$
10, $R_1 = CH_3$; $R_2 = Ph$ **11**, $R_1 = CH_3$; $R_2 = Ph$



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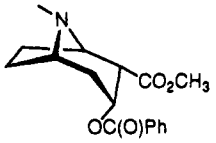

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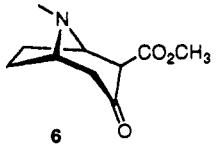

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A recently reported[8] metabolite of cocaine (1), ecgonine methyl ester (5), is an important synthetic precursor, since its benzoylation yields cocaine (1). The preparation of this key synthetic intermediate from 2-carbomethoxy-3-tropinone (6) by sodium amalgam reduction[9] leads to the formation of the C-2 epimer, pseudoecgonine methyl ester (7), as a byproduct. It has been generally accepted that the latter accumulates due to its being the thermodynamically preferred epimer.[10] Holmes[10] has stated that the pseudoform must be more stable since ecgonine (8) and its esters are converted to the pseudoisomers by alkali. Casale,[11] having observed that ecgonine methyl ester (5) was easily and irreversibly epimerized under basic conditions to pseudoecgonine methyl ester (7), suggested that 5 is thermodynamically less stable than the pseudoanalog. These conclusions were also based on literature reports regarding the facile formation of the pseudoconfiguration. Specifically, Findlay[1] and Siegel[12] have shown that the C-2 equatorial epimer is easily formed in the saponification of cocaine (1) by strong base. It has also been shown by Fodor and Kovacs[13,14] that ecgonine (8) was irreversibly

Table I. Reaction Products from Treatment of Ecgonine Methyl Ester (5) with 0.1 M NaOMe/MeOD[a] at 7 °C as a Function of Time

time (h)	composn[b] (%) 5 + 5d	5d	7d	% reaction[c]
0	100	0	0	0
3	100	5	0	5
6	100	9	0	9
12	100	12	0	12
24	100	18	0	18
48	100	40	0	40
72	100	56	0	56
96	100	65	0	65
120	100	69	0	69
156	100	77	0	77
168	100	82	0	82
192	98	88	2	90

[a] 160-fold excess of MeOD. [b] Determined by GC/MS. [c] Obtained as the sum of 5d and 7d.

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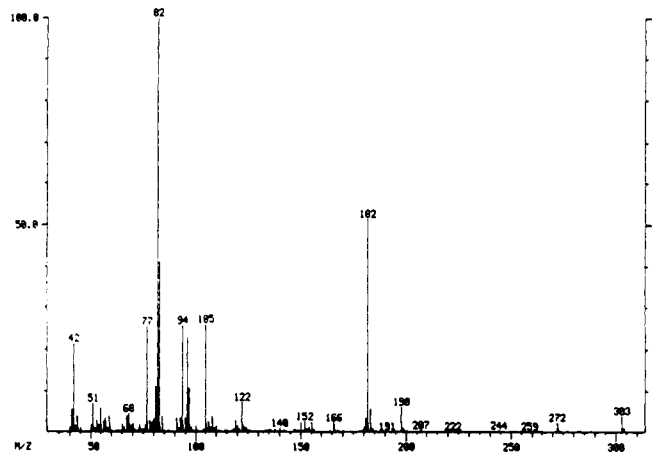

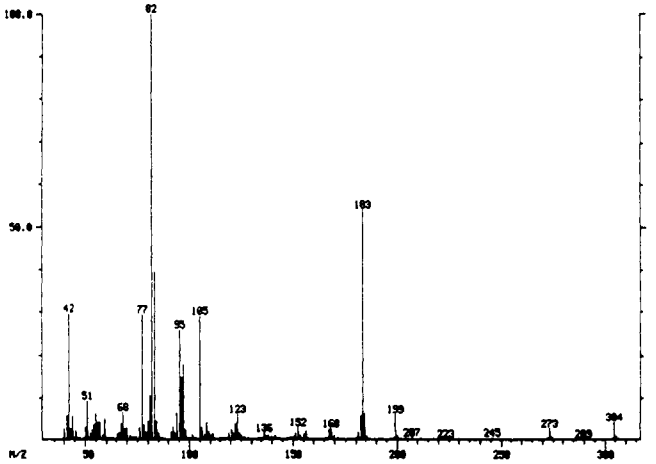

Figure 1. EIMS of cocaine (1) and 2-deuteriococaine (1d).

Table II. Reaction Products from Treatment of Ecgonine Methyl Ester (5) with 0.1 M NaOMe/MeOD[a] at 25 °C as a Function of Time

	composn[b] (%)			
time (h)	5 + 5d	5d	7d	% reaction[c]
0	100	0	0	0
3	95	26	5	31
6	91	40	9	49
12	89	67	11	78
24	86	73	15	88
36	81	78	19	97
48	78	65	22	87
60	75	69	25	94
120	64	ND[d]	36	ND[d]

[a] 160-fold excess of MeOD. [b] Determined by GC/MS. [c] Obtained as the sum of 5d and 7d. [d] Not determined.

converted to pseudoecgonine (9); DeJong[15,16] reported that pseudoecgonine (9) could be obtained from ecgonine (8), ecgonine methyl ester (5) and cocaine (1). On the basis of their attempt to interconvert the C-2 axial/equatorial isomers in the related 3β-phenyltropane-2-carboxylate derivatives 10 and 11, Clarke and co-workers[17] suggested that the C-2 equatorial configuration was more stable. In the course of a research program requiring specifically mass-labeled cocaine derivatives and analogs we have investigated exchange and epimerization at the C-2 position of ecgonine methyl ester (5) and pseudoecgonine methyl ester (7). Our studies relate to the kinetics as well as to the thermodynamics involved in this situation. The experimental results are compared with predictions based on several different molecular modeling methods.

Results

Deuterium incorporation and epimerization of ecgonine methyl ester (5) and pseudoecgonine methyl ester (7) in dilute base in 160-fold molar excess deuteriomethanol as a function of temperature is shown in Tables I–IV. The material remaining at the end of each reaction was analyzed by proton nuclear magnetic resonance spectroscopy and mass spectrometry; it was also benzoylated and the product similarly analyzed (Figures 1 and 2). Deuterium incorporation was determined from the relative abundances of m/z's 198–201 (m/z 199 = molecular ion for unlabeled esters and m/z 200 = molecular ion for deuterated esters). The experimental intensities for M + 1 and M + 2 for all standard compounds were in close agreement with their theoretical values. The extent of

Table III. Reaction Products from Treatment of Ecgonine Methyl Ester (5) with 0.1 M NaOMe/MeOD[a] at 65 °C as a Function of Time

	composn[b] (%)			
time (h)	5 + 5d	5d	7d	% reaction[c]
0	100	0	0	0
1	44	43	56	99
3	21	21	79	100
6	15	15	85	100
12	12	12	88	100
24	9	9	91	100
120	3	3	97	100
156	3	3	97	100

[a] 160-fold excess of MeOD. [b] Determined by GC/MS. [c] Obtained as the sum of 5d and 7d.

Table IV. Reaction Products from Treatment of Pseudoecgonine Methyl Ester (7) with 0.1 M NaOMe/MeOD[a] at 7 °C as a Function of Time

	composn[b] (%)			
time (h)	5d	7 + 7d	7d	% reaction[c]
0	0	100	0	0
6	3	97	8	11
12	3	97	13	16
24	3	97	17	20
48	3	97	19	22
96	3	97	28	31
168	3	97	38	41
240	3	97	47	50

[a] 160-fold excess of MeOD. [b] Determined by GC/MS. [c] Obtained as the sum of 5d and 7d.

Table V. Reaction Products from Treatment of Methyl 3β-Phenyltropane-2α-carboxylate (11)[a] with 0.1 M NaOMe/MeOD[b] at 65 °C as a Function of Time

	composn[c] (%)				
time (h)	10 + 10d	10d	11 + 11d	11d	% reaction[d]
0	1	0	99	0	0
6	1	0.16	99	0	0
24	1	0.43	99	1	1
72	1	0.72	99	2	3
165	1	0.85	99	6	7
357	1	0.85	99	13	14
3500	1	0.85	99	90	90

[a] Contained 1% of the β isomer 10. [b] 160-fold excess of MeOD. [c] Determined by GC/MS. [d] Obtained as the sum of 10d and 11d.

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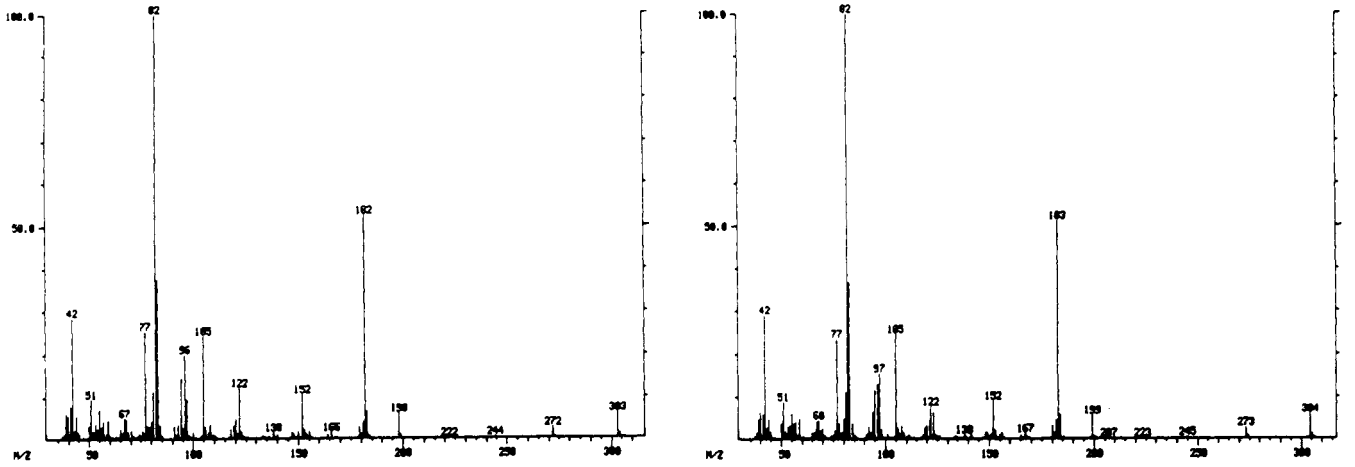


Figure 2. EIMS of pseudococaine (2) and 2-deuteriopseudococaine (2d).

Table VI. Reaction Products from Treatment of Methyl 3β-Phenylpropane-2β-carboxylate (10) with 0.1 M NaOMe/MeOD[a] at 65 °C as a Function of Time

time (h)	composn[b] (%) 10 + 10d	10d	11d	% reaction[c]
0	100	0	0	
6	93	2	7	9
24	65	18	35	53
48	52	19	48	67
144	41	20	59	79

[a] 160-fold excess of MeOD. [b] Determined by GC/MS. [c] Obtained as the sum of 10d and 11d.

epimerization with time and temperature was determined from the normalized FID response of the relative peak areas for ecgonine methyl ester (5) and pseudoecgonine methyl ester (7). The results with the methyl 3β-phenyltropane-2-carboxylates 10 and 11 are shown in Tables V and VI. The initial rates of incorporation and epimerization were determined by the first-order rate expression

$$k = \frac{2.303}{t} \log \frac{[x_0]}{[x_1]}$$

where k = rate constant, $[x_0]$ = initial concentration, $[x_1]$ = concentration of unreacted compound, and t = time in seconds. The enthalpy of activation for incorporation and epimerization was determined by

$$\Delta H^{\ddagger} = \frac{RT_1T_2}{T_1 - T_2} 2.303 \log \frac{k_1T_2}{k_2T_1}$$

where $\Delta H^{\ddagger}$ = enthalpy of activation, R = ideal gas constant, k = rate constant, and T = the absolute temperature.

The entropy of activation for incorporation and epimerization was determined from the relationship

$$k = \frac{k_BT}{h} e^{\Delta S^{\ddagger}/R} e^{-\Delta H^{\ddagger}/RT}$$

where k_B = Boltzman constant and h = Plank constant.

The free energy of activation was calculated from

$$\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$$

Deuterium Incorporation. The results of treatment of 5, 7, 10, and 11 with base in 160-fold excess deuteriomethanol (Tables I–VI) at 7, 25, and 65 °C were used to calculate the initial rates and energies associated with deuterium incorporation and epimerization (Table VII). Clearly, ecgonine methyl ester (5) was the most reactive, with a deuterium incorporation rate 2–3 orders of magnitude greater than those for pseudoecgonine methyl ester (7) and for the 3-phenyl analogs 10 and 11. Thus, at 65 °C complete monodeuteration of 5 was achieved in 3 h while after 240 h 7 was only 47% deuterated, 10 was 48% deuterated after 144 h, and 11 was only 10% deuterated after 357 h. No epimerization was seen for either of the 2α-epimers 7 and 11, and the energy of activation for epimerization was approximately 3-fold greater than for deuteration. In general, the 2β-epimers 5 and 10 were more reactive than the 2α-epimers 7 and 11, and 3-hydroxy compounds 5 and 7 were more reactive than the 3-phenyl analogs 10 and 11.

Molecular Modeling. The energies associated with ecgonine methyl ester (5) and pseudoecgonine methyl ester (7), each with the N-methyl group either anti or syn to the three-carbon bridge, obtained from various modeling

Table VII. Summary of Deuterium Incorporation and Epimerization Rates and Energies in Basic Deuteriomethanol[a]

parameter	temp (°C)	compd 5 D^b	compd 5 E^c	compd 7 D^b	compd 7 E^c	compd 10 D^b	compd 10 E^c	compd 11 D^b	compd 11 E^c
$k_1 \times 10^6$ (s^{-1})	7	4.3	0.029	–	–	–	–	–	–
	25	29	4.5	0.023	–	–	–	–	–
	65	740	230	3.8	–	4.4	3.3	0.10	–
$\Delta H^{\ddagger}$ (kcal/m)	7	17	45	–	–	–	–	–	–
	25	17	45	27	–	–	–	–	–
	65	17	45	27	–	–	–	–	–
$\Delta S^{\ddagger}$ (cal/m/deg)	7	−22	68	–	–	–	–	–	–
	25	−22	73	−3	–	–	–	–	–
	65	−24	58	−4	–	–	–	–	–
$\Delta G^{\ddagger}$ (kcal/m)	7	23	26	–	–	–	–	–	–
	25	24	23	28	–	–	–	–	–
	65	25	25	28	–	–	–	–	–

[a] From Tables I–VI. [b] Deuterium incorporation. [c] Epimerization.

Table VIII. Energies Obtained from Molecular Modeling

run	method	structure	energy (kcal/mol) ecgonine methyl ester (5) 5anti	5syn	pseudoecgonine methyl ester (7) 7anti	7syn
1	MNDO	Tripos file	-121.76			
		optimized **5anti** from run 1		-118.90	-121.65	-120.66
2	MNDO	X-ray	-123.93			
		optimized **5anti** from run 2		-120.59	-122.77	-121.40
3	MAXIMIN2	optimized structures from run 1	13.67	17.71	2.22	1.97
4	AMI	optimized structures from run 1	-133.68	-131.32	-129.46	-128.89
5	MM2	optimized structures from run 1	-132.30	-128.92	-133.20	-132.90

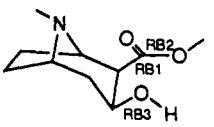
Table IX. Equilibrium Concentration at 65 °C Calculated from Molecular Modeling Energies (Table VIII)

run	method	composition: ecgonine methyl ester (5) 5anti	5syn	pseudoecgonine methyl ester (7) 7anti	7syn	5	7
1	MNDO	99	1	94	6	49	51
2	MNDO/X-ray	99	1	87	13	83	17
3	MAXIMIN2	100	0	36	64	0	100
4	AM1	92	8	72	28	100	0
5	MM2	99	1	24	76	6	94

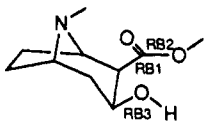
Table X. Equilibrium Concentrations of Ecgonine Methyl Ester (5) and Pseudoecgonine Methyl Ester (7) Calculated from the Conformations within 1 kcal of the Global Energy Minimum

method	composition (%): ecgonine methyl ester (5)	pseudoecgonine methyl ester (7)
MNDO	45	55
MAXIMIN2	3	97
MM2	11	89

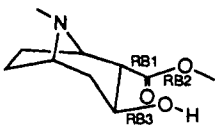
methods, are shown in Table VIII. The equilibrium concentrations of the epimeric ecgonine methyl esters at 65 °C, calculated from the energies obtained by computational chemistry methods, are shown in Table IX. Conformational search of the MNDO optimized structures (defining as rotatable bonds RB1 = C-2 to the carbomethoxy group; RB2 = carbonyl to the methoxy group, and RB3 = C-3 to the hydroxy group) within a 1 kcal window gave 10 conformers for *anti*-ecgonine methyl ester (**5anti**)



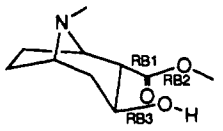
5anti



5syn



7anti



7syn

and six for *syn*-ecgonine methyl ester (**5syn**). For pseudoecgonine methyl ester (**7**), 20 anti conformations (**7anti**) and 19 syn conformations (**7syn**) were found. After MAXIMIN2 the number of conformations within 1 kcal of the global minimum was unchanged for *anti*- and *syn*-ecgonine methyl ester (**5anti** and **5syn**, respectively), but was reduced to 19 for **7anti** and 15 for **7syn**. After MNDO (without optimization about the rotatable bonds) there were three conformers within 2 kcal of the global minimum for **5anti** and **5syn**; there were 12 conformers each for **7anti** and **7syn**. After MM2 optimization of the conformational search results (maintaining the rotatable bond torsion angles) there were two conformers within 2 kcal of the global minimum for **5anti**, one for **5syn**, three for **7anti**, and three for **7syn**. The equilibrium concentrations at 65 °C, calculated from these conformations, are shown in Table X. The same C-2 anion was obtained from MNDO optimization of deprotonated ecgonine methyl ester and deprotonated pseudoecgonine methyl ester, both with the *N*-methyl group anti to the two-carbon bridge; the anion also had the *N*-methyl group in the anti position. Starting from deprotonated ecgonine methyl ester and deprotonated pseudoecgonine methyl ester, both with the *N*-methyl in the syn conformation, gave the same syn C-2 anion.

Table XI. EIMS Fragments of Cocaine (1) and Pseudococaine (2) and for the Deuterated Analogs 1d and 2d

lit. m/z	lit. ref	obsd: 1 and 2 m/z	1 and 2 fragment structure	1d and 2d m/z	1d and 2d fragment structure
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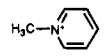
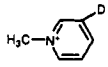
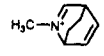
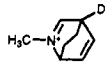
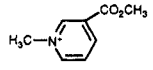
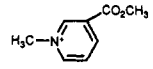
94	18, 20	94		95	
122	20	122		123	
152	19, 20	152		152	

Discussion

It is well-known that ecgonine methyl ester (**5**) is readily epimerized to pseudoecgonine methyl ester (**7**) under basic conditions. Since this epimerization involves inversion of configuration at the position α to the carboxyl function it undoubtedly proceeds by formation of an anion at C-2 followed by reprotonation. In deuterated medium, this reaction is, therefore, expected to lead to the formation of deuterioecgonine methyl ester (**5d**) and deuteriopseudoecgonine methyl ester (**7d**). This was shown to be the case. Specifically, the mass spectra of the esters exhibited an increase of 1 Da for the molecular ion, consistent with incorporation of one deuterium atom. The site of incorporation could not be determined from the mass spectra of either ecgonine methyl ester (**5**) or pseudoecgonine methyl ester (**7**). However, since the major fragmentation pathways for C-3 substituted tropanes and for cocaines have been reported by Blossey,[18] Shapiro,[19]

(18) Blossey, E.; Budzinkiewicz, H.; Ohashi, M.; Fodor, G.; Djerassi, C. *Tetrahedron* 1964, *20*(3), 585–595.

and Cooper,[20] we expected the mass spectra of the benzoylated derivatives to provide this information. Fragments useful in this determination are outlined in Table XI.

It has been shown that carbons 1, 5, 6, 7, and 8 constitute the *N*-methylpyrrolidinium cation m/z 82, representing the base peak for both cocaine and pseudococaine. Since there was no change in the relative intensities of the ions of m/z 82 and 83 for the labeled cocaines as compared to the unlabeled standards, it is clear that none of these positions had become deuterated. Similarly, since no change in the relative intensities of m/z's 152 and 153 for labeled cocaine or labeled pseudococaine was observed, deuterium incorporation at carbons 1, 3, 4, and 5 (associated with the 3-carbomethoxy-*N*-methylpyridinium cation) was unlikely. The deduction that deuterium incorporation had taken place at C-2 was confirmed by the observed increase of 1 Da in m/z for the *N*-methylpyridinium cation (m/z 94). This cation retains the original C-2 proton, and loses the carbomethoxy group, resulting in a m/z 95 ion with a substantial collapse in m/z 94, in the deuterated cocaines.

Conclusive evidence for deuterium incorporation at C-2 was obtained from the proton nuclear magnetic resonance spectra of the labeled cocaines. The resonance assignments for cocaine (1) and pseudococaine (2) have been reported by Sinnema[5] and Carroll.[6] Specifically, the chemical shift of the proton at C-2 is 3.0 ppm for the equatorial position (as in cocaine) and 3.1 ppm for the axial position (pseudococaine). In both compounds the signals are well separated from any others. The proton nuclear magnetic resonance spectra of the deuterated cocaines were essentially indistinguishable from the unlabeled standards, but the signals at 3.0 and 3.1 ppm were absent.

Since the deuterated esters produced in this reaction were in fact labeled at C-2 the initial ratio of the deuterated esters formed represents the relative rates of protonation (by deuterium) of the C-2 anion **A** from either the α- or the β-face to give deuterioecgonine methyl ester (**5d**) and deuteriopseudoecgonine methyl ester (**7d**), respectively. The data in Tables I and II show that protonation from the α-face is 44 and 5.2 times faster than protonation from the β-face, respectively. Similarly, the data in Tables III and IV show that the rate of deprotonation from the α-face exceeds the rate of deprotonation from the β-face by a factor of approximately 36. These observations suggest that the β-face is sterically hindered by the nitrogen bridge.

If pseudoecgonine methyl ester (7) is indeed more stable than ecgonine methyl ester (5), as reported in the literature and determined to be the case in our molecular mechanics calculations, and protonation of the anion **A** is an exothermic process, the Hammond postulate should apply, meaning that the transition state should resemble the protonated enolate. Although the Hammond postulate does not address the relative heights of the transition states it would not be unreasonable to assume that the energy of the transition state might be lower for the more exothermic pathway. In this hypothetical situation (Figure 3) the activation energy for protonation of the anion (**A**) from the β-face, $E_{A\rightarrow 7^*}$, would be lower than the energy of protonation from the α-face, $E_{A\rightarrow 5^*}$ and, therefore, the rate of protonation from the β-face should exceed that of protonation from the α-face. In fact, the opposite situation occurs. In other words, the transition state for protonation of the enolate anion to give ecgonine methyl ester (5^*) is

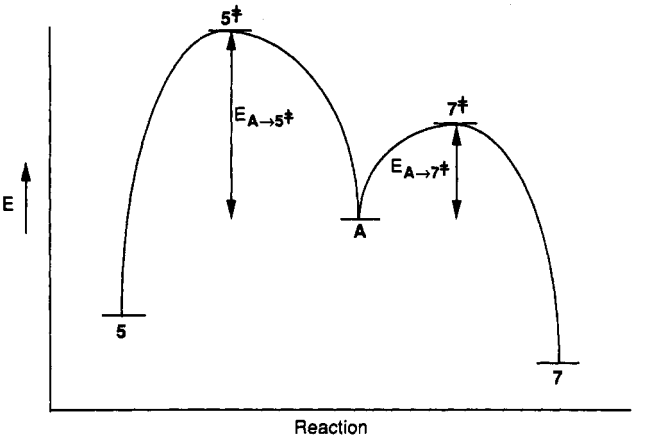


Figure 3. Hypothetical energy diagram assuming $E_5 > E_7$ and $E_{5^*} > E_{7^*}$.

lower lying than the transition state to give pseudoecgonine methyl ester (7^*). If the above assumption concerning the reflection of the more thermally stabilized product in the transition state is valid, one would expect ecgonine methyl ester (5) to be more stable than pseudoecgonine methyl ester (7), which is contrary to previous findings and to the results of our experiments and calculations. To account for the reported[1,10-16] predominance of pseudoecgonine methyl ester (7) it would have to be argued that its rate of deprotonation must be very slow, leading to its accumulation. This possibility is supported by our observations. Specifically, although ecgonine methyl ester (5) underwent both epimerization and exchange at 25 °C, the pseudoester 7 failed to undergo either at temperatures lower than 65 °C, indicating that no ionization of the axial hydrogen at C-2 is taking place under these conditions. This is consistent with the observation that in cyclohexyl ketones enolization is more facile when it involves the equatorial proton.[21] If the following two conditions are met, (a) the energy of activation for protonation of the anion **A** from the β-face, $E_{A\rightarrow 7^*}$, exceeds the energy of activation for protonation from the α-face, $E_{A\rightarrow 5^*}$

$$E_{A\rightarrow 7^*} > E_{A\rightarrow 5^*} \qquad \text{(a)}$$

(b) the energy of activation for deprotonation from the β-face, $E_{7\rightarrow 7^*}$, exceeds the energy of deprotonation from the α-face, $E_{5\rightarrow 5^*}$

$$E_{7\rightarrow 7^*} > E_{5\rightarrow 5^*} \qquad \text{(b)}$$

it would be possible to satisfy both the Hammond postulate and the concept that the transition state leading to the more exothermic product would have some stabilization, *as well as* for pseudoecgonine methyl ester (7) to accumulate (by virtue of its being unable to deprotonate), in spite of its being thermodynamically less stable than ecgonine methyl ester (5) (Figure 4). However, the data at 65 °C refute this interpretation. Thus, treatment of pseudoecgonine methyl ester (7) with excess base in deuterated solvent at 65 °C led to the virtually instantaneous formation of 3% deuterated ecgonine methyl ester (**5d**); this amount was invariant over a period of 240 h, during which time 50% of the starting material had become deuterated. It therefore appears that pseudoecgonine methyl ester (7) predominated even under conditions which allowed it to undergo deprotonation. On the basis of the invariant amount of ecgonine methyl ester (5) over 50% reaction, it appears that the equilibrium concentra-

(19) Shapiro, R. H.; Amenta, D. S.; Kinter, M. T.; Tomer, K. B. *Spectrosc. Int. J.* **1983**, *2*, 227-231.
(20) Cooper, D. *Spectra* **1985**, *10*(3), 14-20.
(21) Zimmermen, H. E. *J. Am. Chem. Soc.* **1957**, *79*(24), 6554-6558.

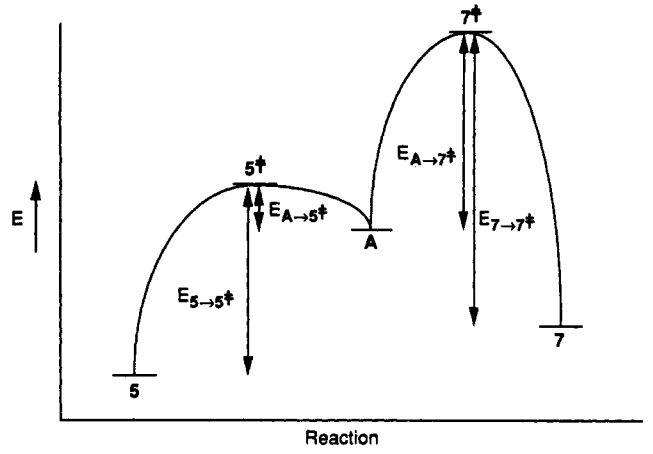


Figure 4. Hypothetical energy diagram assuming $E_5 < E_7$ and $E_{5'} < E_{7'}$.

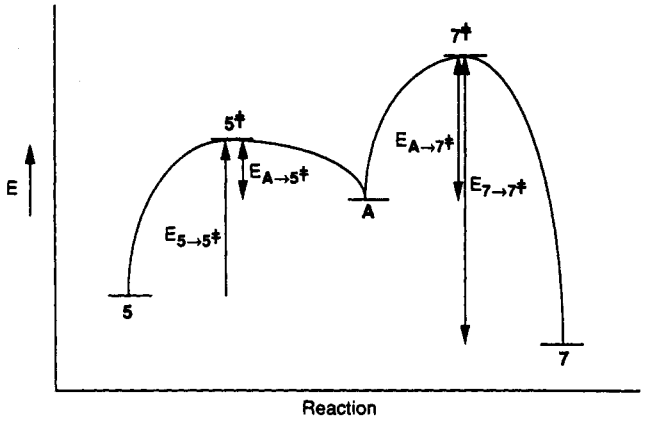


Figure 5. Proposed energy diagram representing the experimentally determined parameters.

tion of ecgonine methyl ester (5) at 65 °C is 3%, meaning that it must be about 2.7 kcal/mol higher in energy than pseudoecgonine methyl ester (7). It follows, therefore, that in this case the Hammond postulate does not apply (Figure 5).

The analogous situation seems to occur in the methyl 3β-phenyltropane-2-carboxylate isomers 10 and 11, although the reactions in this series are much slower. Thus, investigation of the reactions of the isomeric methyl 3β-phenyltropane-2-carboxylates 10 and 11 in deuterated solvent at 65 °C with excess base provided the rates of deprotonation to form the anion, the rates of reprotonation of this anion, as well as the thermodynamic energy difference between the epimers. The results paralleled those observed for the ecgonine methyl esters 5 and 7 in that the rate of deprotonation from the α-face was found to be substantially greater than proton abstraction from the β-face (factor of 50), and the rate of anion protonation from the β-face greatly exceeded the rate of anion protonation from the α-face. It might be noted that all the rates in this system were smaller by 1 order of magnitude compared to those in the ecgonine methyl ester system. Finally, the α-epimer 11 was more stable than the β-epimer 10 by at least 3.0 kcal/mol.

Investigation of ecgonine methyl ester (5) and pseudoecgonine methyl ester (7) using molecular modeling techniques (Table VIII) revealed that the results obtained from various methods differed widely. Thus, MNDO gave nearly identical heats of formation for ecgonine methyl ester (5) and pseudoecgonine methyl ester (7), suggesting equal populations at equilibrium. Using AM1 on the MNDO-optimized structures indicated that ecgonine methyl ester (5) was the preferred isomer by ca. 2.5 kcal/mol; i.e., its equilibrium concentration at 65 °C should be ca. 95%. MAXIMIN2, on the other hand, gave an energy difference of 11–12 kcal/mol in favor of pseudoecgonine methyl ester (7). Carrying out MM2 calculations starting from the MNDO-optimized structure gave an energy difference of 1.58 kcal/mol, predicting an equilibrium concentration of 94% of pseudoecgonine methyl ester (7) at 65 °C, close to the experimental value. Since the results of conformational search indicated that both ecgonine methyl ester (5) and pseudoecgonine methyl ester (7) had several conformations of similar steric energies, it appeared that entropy considerations may help reconcile the theoretical and experimental observations. The results (Table X) show that although the Boltzman distributions of 5 and 7 at 65 °C obtained from the MAXIMIN2 and MM2 conformational energies are predictive of the experimental equilibrium concentrations, the result obtained from the MNDO conformational energies is not even close.

Conclusions

1. The C-2 deprotonation rate of methyl 3-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate from the α-face was at least 3 orders of magnitude greater than from the β-face at 25 °C (Table VII). Similarly, the rate of deuteration of the C-2 anion from the α-face exceeded the rate of deuteration at the β-face by a factor of five (Table II). Under equilibration conditions, the product of protonation from the β-face predominates ($K = 32$) (Tables IV and V). Therefore, (a) the pseudoisomer is thermodynamically and kinetically favored; (b) lowering of the energy of the transition state leading to the thermodynamically favored product is not observed; (c) there is steric hindrance at the β-face; and (d) exchange of the α-proton at C-2, without epimerization, can be accomplished by lowering the temperature.

2. Molecular mechanics calculations in this system are in general agreement with experimental results while MNDO calculations are not.

Experimental Section

Instrumentation. A quadrupole gas chromatograph mass spectrometer (GC/MS) was used to acquire mass spectra by selective ion monitoring (SIM) and full scan mode. A 30-m fused silica DB-5 capillary column (i.d. 0.25 mm) was employed with helium (99.999% UHP) as the carrier gas. The injection port temperature was 250 °C, and the sample was injected in the splitless mode. The initial column temperature was 140 °C and was ramped at 15 °C/min to 260 °C. The quadrupole mass analyzer operated under electron ionization conditions at 70 eV.

A gas chromatograph was used to determine rates of epimerization. A 30-m fused silica, DB-1701 capillary column (i.d. 0.25 mm) was employed with helium (99.999% UHP) as the carrier gas. The injection port temperature was maintained at 230 °C, and samples were injected in the split mode (50:1). The initial column temperature was 180 °C and ramped at 4 °C/min to 200 °C and then ramped at 6 °C/min to 280 °C. Detection was flame ionization operated at 280 °C. The gas chromatograph was also coupled with a Hewlett-Packard Model 5971A mass selective detector (MSD) operated at 70 eV to acquire SIM and full scan spectra.

Proton magnetic resonance spectra were obtained with a 60 MHz spectrometer. The compounds were dissolved (10% w/v) in deuteriochloroform with tetramethylsilane as the internal standard.

Methyl alcohol-*d* was 99.5 + atom % D and deuterium oxide was 99.9 + atom % D. Reactions were run in 3-mL Reacti-vials sealed with Teflon/neoprene septa caps. All extractions were

performed in 3-mL Teflon-capped glass vials.

Molecular mechanics calculations were performed using the SYBYL software package (version 5.32, Tripos Associates, Inc. a subsidiary of Evans & Sutherland) operating on a Digital Equipment Corp. (DEC) microVAX workstation and an Evans & Sutherland PS-330 graphics terminal.

Synthesis of Standards. Ecgonine-2-d_1 methyl ester (**5d**) was prepared as previously described.[22] The 2-deuterioecgonine methyl ester (**5d**) was isolated following the procedure of Casale[11] to give 24.5 mg of the crystalline hydrochloride salt (41% yield). The 2-deuterio analog of cocaine (**1d**) was synthesized from 2-deuterioecgonine methyl ester (**5d**) following the benzoylation procedure of Sinnema.[5]

The 2-deuterio analogs of pseudoecgonine methyl ester (**7d**) and pseudococaine (**2d**) were synthesized following the procedures of Carroll[6] and Sinnema,[5] respectively. Unlabeled ecgonine methyl ester (**5**), pseudoecgonine methyl ester (**7**), cocaine (**1**), and pseudococaine (**2**) were obtained from this laboratory and were part of an authenticated reference collection of the S.B.I. Drug Laboratory.

Deuterium Incorporation and Epimerization. Into three separate 3-mL vials was placed 25 mg of unlabeled ecgonine methyl ester (**5**) (0.126 umol), 1.00 mL of MeOD (40.2 mmol), and 3.0 mg of NaOMe (0.0555 mmol), and the vials were sealed under nitrogen with septa caps. One vial was kept at 7 °C (vial A), one at 25 °C (vial B), and one at 65 °C (vial C). Into the fourth and fifth vials were placed 25 mg of pseudoecgonine methyl ester (**7**) (0.126 mmol), 1.00 mL of MeOD (40.2 mmol), and 3.0 mg of NaOMe (0.0555 mmol), and the vials were sealed under N_2 and kept at 25 °C (vial D) and 65 °C (vial E). Aliquots of 50 μL were removed from vials A–E in intervals as outlined in Tables I–IV. Each aliquot was quenched with 10 μL of D_2O (500 μmol) and extracted once with $CHCl_3$ (1 mL); the extracts were washed with 5% $NaHCO_3$ (0.5 mL), dried over Na_2SO_4, filtered, and subjected to both GC and GC/MS analysis. Reactions involving the methyl 3β-phenyltropane-2-carboxylates were performed in an identical manner at 65 °C (Tables V and VI).

Molecular Modeling. Ecgonine methyl ester (**5anti**) with the *N*-methyl group anti to the three-carbon bridge (i.e., equatorial to the piperidine ring) was constructed using the TRIPOS fragment library. The structure was subjected to MAXIMIN2 followed by MNDO with full geometry optimization. The resulting geometry was used as the starting point for constructing ecgonine methyl ester (**5**) with the *N*-methyl group syn to the three-carbon bridge, as well as anti and syn pseudoecgonine methyl ester. Each structure was then optimized using MNDO, AM1, and MAXIMIN2. The MNDO-optimized structures and the AM1-optimized structures were each optimized using MM2. The MNDO-optimized structures were subjected to conformational search (defining as rotatable the bonds RB1, from C-2 to the carbomethoxy group; RB2, from the carbonyl to the methoxy group; and RB3, from C-3 to the hydroxy group) within a 1-kcal window. Each of the resulting conformers was then subjected to MAXIMIN2, MNDO, and MM2. The rotatable bonds RB1, RB2, and RB3 were not optimized in these calculations. The energies obtained were used in a program called BOLTS, developed in our laboratories (J.P.B.), which allows the analysis of conformational populations based on energy differences according to the Boltzman equation (Table IX). The MNDO-optimized structures were also used to obtain the corresponding C-2 anions; each of these was optimized by MNDO as well. *anti*-Ecgonine methyl ester (**5anti**) was also constructed using the X-ray coordinates for cocaine (**1**), removing the benzoyl group and adding the hydrogen atoms; the MNDO-optimized form of this structure was then modified to *syn*-ecgonine methyl ester (**5syn**), *anti*-pseudoecgonine methyl ester (**7anti**), and *syn*-pseudoecgonine methyl ester (**7syn**). Each of these structures was also optimized using MNDO. The heats of formation (or the energies, in the case of MAXIMIN2) are shown in Table VII. The equilibrium concentrations of ecgonine methyl ester (**5**) and pseudoecgonine methyl ester (**7**) at 65 °C, predicted by the energies obtained from the optimizations, were calcualted using BOLTS and are shown in Table VIII.

(22) Casale, J. F.; Lewin, A. H.; Raney, H. T.; Cooper, D. A. *J. Label. Cmpds Radiopharm.* **1991**, *19*, 327–335.

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Inter- and Intramolecular [4 + 2] Cycloadditions of Nitroalkenes with Olefins. 2-Nitrostyrenes

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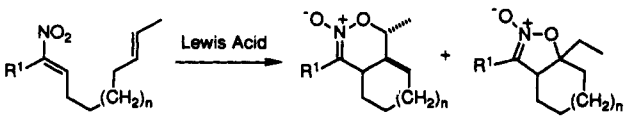
Aromatic nitroalkenes **9–12** underwent Lewis acid catalyzed cycloadditions with various cyclic alkenes to afford high yields of nitronates **25–30** with exclusive anti selectivity. Hammett studies helped to further delineate the role of the Lewis acid. Reaction of nitroalkenes **8** and **10** with various cyclic dienes in the presence of a Lewis acid demonstrated the ability of nitroalkenes to behave as dienes in cycloadditions. The major products were the syn diastereomers which arise from an endo-folded transition structure. Finally, intramolecular cycloaddition of **36–39** allowed a correlation between the stereochemical course of the reaction and positions of sp^2 centers in the tether to be addressed.

Introduction

Within the realm of ring-forming reactions, cycloadditions have secured an immutable and well-deserved stature in the minds and hands of chemists. The introduction of heterodienes[1] has extended the synthetic versatility of cycloaddition reactions by allowing rapid access to various heterocycles. Within these laboratories, we have extensively examined the use of nitroalkenes as dienes in [4 + 2] cycloadditions.

Scheme I



(1) Weinreb, S. M.; Boger, D. B. *Hetero Diels–Alder Methodology in Organic Synthesis*; Academic Press: Orlando, 1987.

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