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N-OXIDES OF MORPHINE, CODEINE AND THEBAINE AND THEIR OCCURRENCE IN *PAPAVER* SPECIES

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Key Word Index—*Papaver somniferum*; *P. bracteatum*; Papaveraceae; *N*-oxides; morphine; codeine; thebaine; alkaloids; synthesis.

Abstract—*N*-oxides of morphine, codeine and thebaine have been prepared. Each alkaloid forms two *N*-oxides which have been separated and characterised by PMR, MS and reduction to the parent alkaloid. Both *N*-oxides of morphine and one *N*-oxide of codeine have been isolated from *Papaver somniferum* and both *N*-oxides of thebaine have been isolated from *P. bracteatum*

INTRODUCTION

Biosynthetic studies of morphinane alkaloids have mainly concentrated on the formation of the basic skeleton from amino acid precursors and the subsequent interconversions of these alkaloids [1,2 and refs therein]. In *Papaver somniferum* it is recognised that tyrosine is a precursor of the benzyltetrahydroisoquinoline alkaloid reticuline which undergoes phenolic oxidative coupling to form the morphinandieone, salutaridine, a precursor of thebaine. Thebaine is subsequently converted into codeine which is demethylated to form morphine, the major alkaloid of the mature plant. It has been suggested that the major (if not the only) degradative pathway for morphine in *P. somniferum* involves an initial *N*-demethylation to nor-morphine which is then degraded to non-alkaloidal metabolites [3]. Alkaloidal metabolites, other than nor-morphine, could not be detected when ^{14}C-labelled morphine was fed to plants; however, the high rate of morphine turnover led to the conclusion that the alkaloid plays an active role in metabolism and perhaps acts as a specific methylating agent. The fluctuations of morphinane alkaloid content in *P. somniferum* latex had been noted previously [4] and the periodic disappearance of morphine demonstrated by ^{14}C-labelling techniques [5]. Morphine-[G-^{14}C] fed to capsules was rapidly taken up into the latex and transformed into two non-alkaloidal polar substances, the bulk of which were rapidly translocated out of the latex into the pericarp and developing ovules [6]. In addition to these polar compounds, which are stated not to be amino acids or alkaloids, extracts of *P. somniferum* have shown the presence of several polar unidentified Dragendorff positive spots. The seeds of *P. somniferum* contain "bound" forms of alkaloids which on hydrolysis yield tertiary bases [7,8]. Since *N*-oxides of tertiary bases readily undergo *N*-demethylation the possibility arises that morphinane alkaloid *N*-oxides might be present in *P. somniferum* and account for some of the polar compounds reported previously. The proposal that alkaloid *N*-oxides might be widespread in the plant kingdom [9] has in part been substantiated by finding *N*-oxides of tropane alkaloids [10] and of nicotine [11] as natural products. The present paper describes the preparation, separation and characterisation of *N*-oxides of morphine, codeine and thebaine and the search for these *N*-oxides as natural products.

RESULTS AND DISCUSSION

The *N*-oxides of thebaine, codeine and morphine were prepared. Each alkaloid forms two isomeric *N*-oxides, one being a major and the other a minor product. The separated *N*-oxides were characterised by TLC (Table 1), by their MS and PMR spectra (Experimental, Tables 2 and 3) and by reduction to the corresponding tertiary base. The configuration of the Me group and the oxygen

Table 1. TLC of thebaine, codeine, morphine and their *N*-oxides

Compounds	R_f values in TLC systems* A	B	C	D
Thebaine	0.69	0.87	0.90	0.88
Thebaine *N*-oxide, major isomer	0	0.62	0.57	0.61
Thebaine *N*-oxide, minor isomer	0	0.50	0.42	0.46
Codeine	0.37	0.74	0.81	0.78
Codeine *N*-oxide, major isomer	0	0.40	0.37	0.37
Codeine *N*-oxide, minor isomer	0	0.26	0.28	0.30
Morphine	0.27	0.56	0.75	0.69
Morphine *N*-oxide, major isomer	0	0.23	0.26	0.24
Morphine *N*-oxide, minor isomer	0	0.14	0.17	0.17

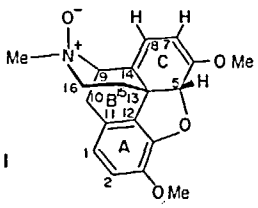
*Adsorbents—A, B, C: Si gel GF_{254}: Kielselguhr (1:1) (Merck); D: Si gel G (Merck). Solvent systems—A: EtOAc–C_6H_6–conc. NH_4OH (80:10:2.5) [29]; B: CCl_4–*n*-BuOH–MeOH–conc. NH_4OH (40:30:30:3); C: Me_2CO–H_2O–conc. NH_4OH (80:15:2); D: Me_2CO–H_2O–conc. NH_4OH (80:15:5).

Table 2. PMR chemical shifts for thebaine, codeine, morphine and their *N*-oxides*

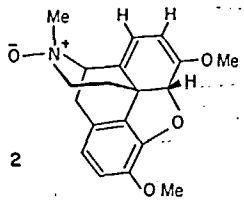
Compound	C-1 and -2Hs	C-7H	C-8H	C-5H	N-Me	MeO
Thebaine†	6.76, 6.63	5.10	5.62	5.30	2.46	3.87, 3.62
1 Thebaine *N*-oxide, major isomer†	6.82, 6.66	5.17	5.95	5.40	3.36	3.87, 3.67
2 Thebaine *N*-oxide, minor isomer†	6.79, 6.64	5.14	5.85	5.40	3.47	3.85, 3.64
Codeine†	6.73, 6.58	5.73	5.30	4.90	2.45	3.86
3a Codeine *N*-oxide, major isomer†	6.80, 6.61	5.80	5.29	5.00	3.39	3.89
4a Codeine *N*-oxide, minor isomer†	6.80, 6.63	5.82	5.30	5.00	3.54	3.87
Morphine‡	6.96, 6.76	5.97	5.43	5.25	2.40	—
3b Morphine *N*-oxide, major isomer‡	7.00, 6.78	6.00	5.45	5.30	3.85	—
4b Morphine *N*-oxide, minor isomer‡	7.00, 6.80	6.00	5.45	5.30	3.98	—

* δ values in ppm from TMS. † $CDCl_3$–CD_3OD. ‡ TFA

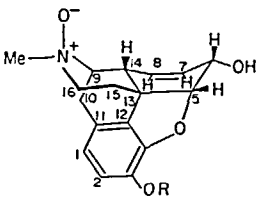
at the nitrogen asymmetric centre was established as follows: thebaine *N*-oxide, major isomer (1), minor isomer (2), codeine *N*-oxide, major isomer (3a) and minor isomer (4a), morphine *N*-oxide, major isomer (3b) and minor isomer (4b). Both *N*-oxides of thebaine were isolated from *P. bracteatum* (thebaine-rich strain) and both *N*-oxides of morphine and the major *N*-oxide of codeine were isolated from *P. somniferum* (Halle strain).



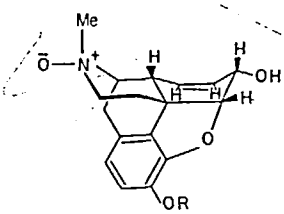
1



2



3a R=Me
3b R=H



4a R=Me
4b R=H

Both morphine and codeine are said to form an *N*-oxide when heated with 30% H_2O_2 and these *N*-oxides can be reduced back to the tertiary base by sulphurous acid [12,13]. On prolonged heating with 3% H_2O_2, codeine forms a bimolecular *N*-oxide which on heating with ethanol and HCl yields codeine *N*-oxide hydrochloride [14]. Several modifications of the H_2O_2 method for the preparation of morphine and codeine *N*-oxides have been described [15,16] and *m*-chloroperbenzoic acid has been recommended as an alternative reagent since high yields of *N*-oxides are obtained with codeine and with morphine (86 and 98% respectively) [17]. *m*-Chloroperbenzoic acid was used initially in the present work for the preparation of thebaine-, codeine- and morphine *N*-oxides and it was noted that whereas thebaine formed two *N*-oxides only one *N*-oxide was obtained from either codeine or morphine. When subsequently the H_2O_2 method was used, each alkaloid yielded two *N*-oxides, a major (corresponding to the *m*-chloroperbenzoic acid product for codeine and morphine) and a minor isomer. Each of the two isomers of thebaine-, codeine- and morphine *N*-oxides were separated by crystallisation of one isomer followed by PLC of the mother liquor. They were characterised by MS, PMR (Table 2) and by reduction to the corresponding tertiary base.

The major MS fragmentation is given in the experimental section. The spectra showed that the two *N*-oxides of thebaine, codeine and morphine were monomeric and that bimolecular *N*-oxides had not been formed. All six compounds gave fragment ions corresponding to M^+, M^+-16, M^+-17, M^+-18 and M^+-HCHO. Each *N*-oxide reduced to the corresponding tertiary alkaloid. The PMR spectrum (Table 2) of the major isomer of thebaine *N*-oxide showed that the signal for the *N*-Me group was shifted downfield to δ3.36 ($\Delta\delta$ N/NO 0.90 ppm, Table 3) due to the oxygen substituent on the nitrogen, but in the spectrum of the minor isomer this signal appeared further downfield at δ3.47 ($\Delta\delta$ N/NO 1.01 ppm, Table 3). Quaternized tropane alkaloids having axial N^+-Me substituents also produce signals in the PMR spectrum which resonate at lower field

Table 3. Differences in chemical shifts ($\Delta\delta$ N/NO) between parent alkaloids and their *N*-oxides*

	C-7H	C-8H	C-5H	N-Me
1 Thebaine *N*-oxide, major isomer†	0.07	0.33	0.10	0.90
2 Thebaine *N*-oxide, minor isomer†	0.04	0.23	0.10	1.01
3a Codeine *N*-oxide, major isomer†	0.07	0.01	0.10	0.94
4a Codeine *N*-oxide, minor isomer†	0.09	0.00	0.10	1.09
3b Morphine *N*-oxide, major isomer‡	0.03	0.02	0.05	1.45
4b Morphine *N*-oxide, minor isomer‡	0.03	0.02	0.05	1.58

* $\Delta\delta$ N/NO = δ amine − δ amine *N*-oxide.
† $CDCl_3$–CD_3OD.
‡ TFA.

than those of the corresponding equatorial isomers, and it has been noted that *N*-oxides exhibit similar behaviour [18,19]. The two thebaine *N*-oxide isomers differ in having either an equatorial N^+-Me substituent (**1**) or an axial one (**2**). It would be anticipated, by analogy with the tropane alkaloid *N*-oxides and to quaternized derivatives of the benzomorphan α-metazocine [20] that the N^+-Me signal for **2** would resonate at lower field than that for **1**. Moreover, the isomer in which the N^+-Me group is equatorial (**1**) would be expected to exhibit a significant downfield shift for the C-8 hydrogen signal due to deshielding by the N^+-O^- group. In the isomer with the axial N^+-Me group (**2**), the oxygen group is further away from the C-8 hydrogen and hence the downfield shift of this signal would not be so great. Conflicting reports appear in the literature for the assignment of the C-7 and C-8 hydrogen signals in the PMR spectrum of thebaine since the signal furthest downfield of the C-7/C-8 AB quartet has been attributed to the C-7 H [21] and to the C-8 H [22]. Clarification was obtained by using europium D-trifluoroacetyl camphorate shift reagent which complexes at the nitrogen in thebaine. The signal at δ5.57 of the AB quartet is shifted to δ5.87 ($\Delta\delta$ 0.30 ppm) whereas the signal at δ 5.04 is shifted to δ 5.20 ($\Delta\delta$ 0.16 ppm) by addition of 0.2 mol of shift reagent (see Experimental). Hence it is concluded that the signal which appears further downfield in the spectrum of thebaine is due to the C-8 hydrogen. Changes in chemical shifts with europium D-trifluoroacetyl camphorate for C-8 H > C-5 H > C-7 H and correlate with the distances between these hydrogens and the tertiary nitrogen (estimated from Dreiding models as 3.9, 4.5 and 5.7 Å respectively). The results expressed in Table 2 show that the major isomer of thebaine *N*-oxide has a signal for the C-8 H which is further downfield ($\Delta\delta$ 0.33, Table 3) than the corresponding signal on the spectrum of the minor isomer ($\Delta\delta$ 0.23, Table 3). These differences are in agreement with assignments made on the basis of the signals for the N^+-Me groups and correlate with the distances between these hydrogens and the oxygen on the nitrogen (estimated from Dreiding models). Hence it is concluded that the major isomer of thebaine *N*-oxide can be represented as **1** and the minor isomer as **2**. Both isomers of thebaine *N*-oxide have identical chemical shifts for the C-5 hydrogen although its distance from the *N*-oxygen is greater for the minor isomer (**2**) than for the major isomer (**1**). The deshielding of the C-5 H signal ($\Delta\delta$ N/NO 0.10 ppm—Table 3) by the proximity of the *N*-oxygen in the major isomer is equalled by the long range deshielding effect of the N^+-O^- bond which is directly in line with the C-5 hydrogen in the minor isomer.

In the PMR spectra of codeine and morphine the signal for the C-7 hydrogen is further downfield than that of the C-8 hydrogen due to the C-6 hydroxyl function [21,22]. Distinct differences between the chemical shifts of the C-7 and C-8 signals were not observed in the spectra of either the two isomers of codeine *N*-oxide (**3a**, **4a**) or of morphine *N*-oxide (**3b**, **4b**). The half boat conformation of ring C in morphine and codeine *N*-oxides results in the C-7 and C-8 hydrogens being orientated below the plane of ring C and hence of the quaternized nitrogen whereas the C ring planar conformation of the thebaine *N*-oxides results in the C-7 and -8 hydrogens being above the plane of the piperidine ring (**1**, **2**). For both the major isomers of codeine- and morphine *N*-oxides the *N*-Me signals appear upfield from the corresponding signals of the minor isomers and this is analogous to the findings for the thebaine *N*-oxides. Since it may be assumed that the stereochemistry of the oxidation process is identical for all three alkaloids, the structures of the major isomers of codeine- and morphine *N*-oxides are **3a** and **3b** respectively, while the minor isomers are **4a** and **4b** respectively.

N-oxides of thebaine, codeine and morphine have not been reported previously as natural products in plants although morphine *N*-oxide has been identified as a metabolite of morphine in man [23] and in animals [24,25]. Codeine *N*-oxide in rats has been reported to yield nor-codeine and codeine [26] and thebaine has been transformed into 14-β-hydroxycodeinone *N*-oxide by fermentation with a strain of *Trametes cinnabarina* [27].

When looking for the natural occurrence of thebaine *N*-oxide, a thebaine-rich strain of *P. bracteatum* was chosen as a likely source. In fact both isomers of thebaine *N*-oxide were detected and isolated by PLC as minor alkaloids, the major isomer in 0.015% yield and the minor isomer in 0.002% yield of fresh capsule. From the more polar basic components of *P. somniferum*, morphine *N*-oxides were isolated, the major isomer in 0.006% yield and the minor isomer in 0.004% yield of fresh capsule. The major isomer of codeine *N*-oxide was also isolated from *P. somniferum* in 0.005% yield of fresh capsule. Although the minor isomer was not detected it is possible that this was a result of the difficulties encountered during the separation and the instability of the compound during chromatography. These findings do indicate that morphine metabolites other than normorphine are produced naturally in contrast to previous findings [3]. The facile conversion of alkaloid *N*-oxides to noralkaloids and the fact that in normal systems codeine *N*-oxide is said to be metabolised into norcodeine [26] suggests that this mechanism may be involved in plants. However, this postulate has not been proved and the evidence of radioactive feeding in *Nicotiana* species indicates that *N*-oxides are probably not involved in *N*-demethylation in the plant [28]. The rapid turnover of morphine and related alkaloids in *P. somniferum* [3–6] indicates that these alkaloids take part in metabolism and hence it is highly probable that the *N*-oxides must also be involved in active metabolism. The low yields of the three alkaloid *N*-oxides suggest that, unlike the corresponding tertiary bases, they do not accumulate but are either transferred into other metabolites or return to the corresponding tertiary bases. In *P. somniferum* latex the alkaloids are almost exclusively located in vesicles [30] and the more polar nature of the *N*-oxides might ensure their exclusion or their retention in these organelles.

Control experiments in which morphine, codeine and thebaine were subjected to the same extraction procedures (see Experimental) indicate that the *N*-oxides were not formed during the isolation procedures and hence it is considered that they are natural products rather than artefacts. *N*-oxides of hyoscyamine and hyoscine [10] and of nicotine [11] have been reported recently as natural products and the present work shows that morphinanes represent yet another group of alkaloids which occur in the more polar *N*-oxide form with tertiary bases. These findings indicate that, as previously proposed [9], many other alkaloids may well occur as

N-oxides. Since the role of *N*-oxides in alkaloid metabolism is likely to be similar for all groups of alkaloids, further study of these compounds may help to answer the intriguing question as to what alkaloids are doing in plants.

EXPERIMENTAL

PMR spectra were determined at 60 MHz in $CDCl_3$–CD_3OD or in DMSO-d6 with TMS as internal reference. High resolution MS were recorded at 70 eV, probe temp. 200–210°. The TLC systems used are given in Table 1, 0.25 mm plates were used for analytical TLC and 0.5 mm plates for PLC; alkaloids and their *N*-oxides were detected with Dragendorff's reagent.

Preparation of N-*oxides. General methods.* (a) Alkaloid (200 mg) was dissolved in $CHCl_3$ or $CHCl_3$–MeOH (5 ml) and *m*-chloroperbenzoic acid (200 mg) in $CHCl_3$ (5 ml) added slowly. The ice-cold mixture was stirred for 6 hr, brought to room temp, dil with $CHCl_3$ and washed with 10% aq $KHCO_3$ to remove excess acid. The $CHCl_3$ soln was washed with a little H_2O, dried, filtered and concentrated under vacuum to an amorphous solid. (b) Alkaloid (200 mg) was dissolved in MeOH (20 ml), 30% aq H_2O_2 (4 ml) added dropwise and the mixture stirred for 16 hr. Excess H_2O_2 was removed by careful addition of MnO_2 to the ice-cold soln. The filtered soln was concentrated under vacuum to yield an amorphous solid.

Thebaine N-*oxides. Method* (*a*). TLC (system B) showed the presence of two *N*-oxides, one major and the other minor, which were separated by PLC. The R_f values (Table 1) and the MS were identical with those obtained by method (b). *Method* (*b*). Yield of total *N*-oxide, 160 mg (76%). TLC (system B) showed the presence of two *N*-oxides and the minor isomer crystallised from Me_2CO–dry Et_2O as colourless needles, mp 135–138° (decomp), yield 32 mg (15%). PLC of the mother liquor (system B) yielded the major isomer as an amorphous solid 128 mg (61%).

Codeine N-*oxides. Method* (*a*). Yield of total *N*-oxide 208 mg (99%). TLC showed the presence of one *N*-oxide which had a MS and R_f values identical to those of the major isomer prepared by method (b). *Method* (*b*). Yield of total *N*-oxide 192 mg (91%). TLC showed the presence of one major and one minor *N*-oxide. The major isomer crystallised as colourless needles from EtOH–Me_2CO, mp 231° (lit. 231–232° [15]), yield 144 mg (68%). PLC of the mother liquor (system B) yielded the minor isomer as an amorphous solid, 48 mg (23%).

Morphine N-*oxides. Method* (*a*). Yield of total *N*-oxides 89 mg (42%). TLC (system B) showed the presence of one *N*-oxide which had a MS and R_f values which were identical with those of the major isomer obtained by method (b). *Method* (*b*). Yield of total *N*-oxides 175 mg (83%). TLC showed the presence of two *N*-oxides (system B), one being major and the other minor. The major isomer crystallised from H_2O as colourless prismatic crystals, mp 270° (decomp) (lit 273°, [13,15]), yield 150 mg (83%). The minor isomer was obtained as an amorphous solid, 25 mg (13%), by PLC (system B) of the mother liquor.

Characterisation of prepared N-*oxides.* (a) *Reduction.* The *N*-oxide (1–2 mg) was dissolved in 5% H_2SO_3 (0.5 ml) and the soln left 18 hr, then made alkaline with conc NH_4OH and extracted into $CHCl_3$ (3 × 10 ml). Combined $CHCl_3$ extracts were washed, dried and evaporated to dryness under red pres. TLC (Table 1) indicated that on reduction, each of the 6 prepared *N*-oxides yielded only one alkaloidal spot which corresponded to the parent tertiary base. (b) *TLC.* R_f values are given in Table 1. (c) *PMR spectra.* All samples were thoroughly dried *in vacuo* to remove solvent; the chemical shifts are recorded in Table 2. (d) *MS.* The six *N*-oxides showed the presence of a M^+ ion together with ion fragments corresponding to M^+-16, M^+-17 and M^+-HCHO.

Thebaine N-*oxide, major isomer. m/e* (%), 327 (27), 311 (18), 310 (9), 309 (27), 297 (9), 268 (91), 255 (27), 254 (100), 253 (27), 239 (71). *Thebaine* N-*oxide, minor isomer, m/e* (%), 327 (38), 311 (35), 310 (25), 309 (12), 297 (10), 268 (35), 255 (41), 254 (100), 253 (81), 239 (72). *Codeine* N-*oxide, major isomer, m/e* (%), 315 (13), 299 (100), 298 (30), 297 (21), 285 (30), 242 (22), 241 (28), 240 (26). *Codeine* N-*oxide, minor isomer, m/e* (%), 315 (15), 299 (100), 298 (46), 297 (8), 285 (69), 242 (39), 241 (85), 240 (92). *Morphine* N-*oxide, major isomer, m/e* (%), 301 (5), 285 (100), 284 (18), 283 (3), 271 (31), 228 (13), 227 (9), 226 (18). *Morphine* N-*oxide, minor isomer, m/e* (%), 301 (5), 285 (100), 284 (16), 283 (4), 271 (26), 228 (11), 227 (11), 226 (16).

Isolation of thebaine, codeine and morphine N-*oxides from plant material. P. bracteatum* Lindl. (*thebaine-rich strain*). Fresh capsules (100 g) were macerated with MeOH containing 2% NH_4OH for 16 hr. The filtered extract was concentrated under red pres to a viscous residue which was extracted with 2% H_2SO_4 (3 × 15 ml). The combined acid extracts were washed with $CHCl_3$ (4 × 50 ml) and then the aq layer adjusted to pH 10 by addition of NH_4OH and extracted successively with (a) $CHCl_3$ (5 × 50 ml) and then (b) $CHCl_3$–MeOH, 9:1 (2 × 40 ml). Extracts (a) and (b) were combined to yield total crude alkaloid 326 mg (0.33%) which was shown by TLC to have thebaine as the major alkaloid. PLC (system B) resulted in the isolation of the major isomer (15 mg, 0.015% fresh capsule) and the minor isomer (2 mg, 0.002% fresh capsule) of thebaine *N*-oxide.

P. somniferum *L.* (*Halle strain*). Fresh capsules (100 g) were extracted by the same procedure as outlined above except that the alkaline aq soln was extracted successively with (a) $CHCl_3$ (5 × 50 ml), (b) $CHCl_3$–*iso*PrOH, 3:1) (5 × 50 ml) and (c) $CHCl_3$–*iso*PrOH–MeOH, 6:2:1 (5 × 50 ml). The combined $CHCl_3$ extract was washed with H_2O, dried and concentrated to dryness under red pres to yield an amorphous solid (75 mg). PLC (system B) of an aliquot (38 mg) yielded the major isomer of codeine *N*-oxide (3.7 mg, 0.007% fresh capsule). Organic extracts (b) and (c) were combined, washed with H_2O, dried and evaporated to dryness under red pres to yield an amorphous solid (80 mg). PLC (system B) of an aliquot (43 mg) resulted in the isolation of the major isomer (3 mg, 0.006% fresh capsule) and the minor isomer (2 mg, 0.004% fresh capsule) of morphine *N*-oxide. To determine whether *N*-oxides were formed as a result of extraction procedures, thebaine, codeine and morphine were allowed to stand for 16 hr in MeOH containing 2% NH_4OH and subsequently subjected to the same extraction methods as outlined above. TLC indicated that *N*-oxides were not formed as a result of the isolation procedure.

Identification of natural N-*oxides.* TLC R_f values (systems A and B) and MS of the natural *N*-oxides were identical with those of the prepared compounds. Reduction of 1 mg quantities with sulphurous acid resulted in one spot on TLC which had identical R_f values to that of the corresponding tertiary base (systems A and B).

PMR Spectra of thebaine and europium D-*trifluoroacetyl camphorate.* The shift reagent europium D-trifluoroacetyl camphorate was added in five separate amounts ranging from 0.04 to 0.2 mol to a $CDCl_3$ soln of thebaine containing TMS as internal reference. A linear relationship was obtained when $\Delta\delta$ was plotted against molar concn of shift reagent for the two doublets (AB system) of the C-7 and -8 hydrogens and for the singlet due to the C-5 hydrogen. Complex formation takes place at the nitrogen and the changes in chemical shift from the observed positions in the spectrum of thebaine are proportional to the distances of the hydrogens from the nitrogen in the order C-8 hydrogen > C-5 hydrogen > C-7 hydrogen. At 0.2 mol concn of shift reagent the following downfield shifts were observed, the doublet at δ 5.62, 0.30 ppm, the C-5 hydrogen singlet at δ 5.30, 0.23 ppm and the doublet at δ 5.10, 0.16 ppm. The doublets at δ 5.62 and 5.10 in the PMR spectrum of thebaine can therefore be attributed to the C-8 and C-7 hydrogens respectively.

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