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CONSTITUENTS OF *PAPAVER BRACTEATUM*: *O*-METHYL-α-THEBAOL AND 10-*n*-NONACOSANOL. LANTHANIDE-INDUCED CHEMICAL SHIFTS IN ^{1}H NMR AND ^{13}C NMR*

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Key Word Index—*Papaver bracteatum*; Papaveraceae; phenanthrenes; *O*-methyl-α-thebaol; plant waxes; 10-*n*-nonacosanol; alkaloids, isothebaine, ^{13}C NMR chemical shifts, lanthanide-induced chemical shifts in ^{1}H NMR and ^{13}C NMR.

Abstract—Two non-alkaloidal constituents were identified in *Papaver bracteatum*: *O*-methyl-α-thebaol and 10-*n*-nonacosanol. *O*-Methyl-α-thebaol is a new natural compound. The presence of isothebaine is confirmed. Lanthanide-induced chemical shifts can be used for the assignments of the ^{13}C NMR chemical shifts of isothebaine and phenanthrenes The use of lanthanide-induced chemical shifts in the identification of methoxyl resonances in ^{1}H NMR is discussed.

INTRODUCTION

Natural phenanthrenes have so far been reported from the Dioscoreaceae, Combretaceae, Orchidaceae, Euphorbiaceae, Gramineae and Papaveraceae. α-Thebaol (**1**) was found in the Papaveraceae as a constituent of the dried latex of *Papaver somniferum* (opium) [3], as well as of *P. bracteatum* capsule tissue [4]. Another phenanthrene derivative (**2**) was claimed earlier for opium [5], but its characteristics are identical to those of α-thebaol, mentioned in a later report by the same authors [3].

The finding of α-thebaol (**1**) in *P. bracteatum* prompted us to look into the possible presence of other phenanthrenes in this species. In organic solvent extracts of *P. bracteatum* a neutral constituent was detected. Its concentration often exceeded the thebaine concentration for extracts prepared from complete plants in the presence of ammonia or alkaline solutions. This compound was isolated and its structure elucidated.

RESULTS AND DISCUSSION

O-*Methyl-α-thebaol*

GC/MS screening of counter-current fractions of *P. bracteatum* capsule tissue revealed the presence, in trace amounts, of a compound having mass spectral fragmentations resembling those of α-thebaol, but higher by 14 mass units. For this compound *O*-methyl-α-thebaol (**3**) was considered a possible structure in view of the known natural occurrence of α-thebaol in the plant material used [4]. Therefore *O*-methyl-α-thebaol was synthesized from thebaine (**4**) through *O*-acetyl-α-thebaol (**5**) [6]. The synthetic material proved to be identical to the natural product in GC/MS.

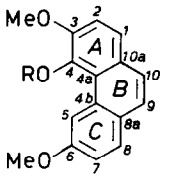
The presence of α-thebaol in *Papaver bracteatum* and *P. somniferum* is most likely due to its formation as a biodegradation product of the morphinan alkaloid thebaine (**4**). Both species contain this compound, the former as a major constituent, the latter as a minor one. The detection of *O*-methyl-α-thebaol next to α-thebaol in *P. bracteatum* adds a further metabolite to the pathway: **4** → **1** → **3**. This is the first report on the natural occurrence of *O*-methyl-α-thebaol.

10-n-*Nonacosanol*

In methanol–ammonia (98 : 2) extracts of the leaves of *P. bracteatum* plants, cv Arya I, grown in a phytotron [7, 8], a non-alkaloidal compound attracted attention because of its prominence. It was also observed in chloroform extracts of the leaves of *P. bracteatum* cv Arya II, grown in The Netherlands. Its relative concentration in the methanol–ammonia extracts mentioned above was 1–1.5 times the thebaine concentration. Later research confirmed the presence of this neutral constituent in *P. bracteatum* extracts prepared by procedures involving direct contact of organic solvents with the plant material. The compound in question is absent from aqueous acetic acid extracts.

The IR spectrum of the isolated compound indicates an aliphatic alcohol (see Experimental). In carbon tetrachloride solution the hydroxyl stretching vibration is found at 3630 ± 1 cm^{-1}, having $\Delta\nu_{1/2} = 26 \pm 1$ cm^{-1} and $\alpha/\beta = 0.7$, characteristic of the hydroxyl stretching vibration of a secondary alcohol [9]. The mass spectrum of the natural compound is identical to that of the aliphatic secondary alcohol 10-*n*-nonacosanol (**6**). The ^{1}H NMR spectrum is in agreement with this structural assignment. The mass spectrum of the silylated compound is in one respect different from that reported in ref. [10]. An ion is

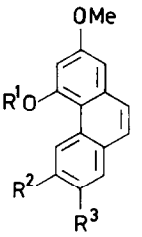
*Part 9 in the series. For Parts 7 and 8 see refs. [1] and [2].



1 R=H

3 R=Me

5 R=Ac



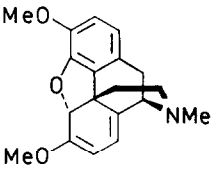
2 R^1=H, R^2=OMe, R^3=H

15 R^1=Me; R^2=OMe, R^3=OH

16 R^1=Me, R^2=OH, R^3=OMe

17 R^1=Me, R^2=R^3=H

18 R^1=Me, R^2=OMe, R^3=H



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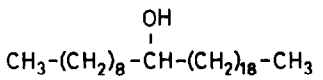

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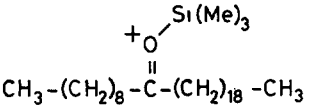
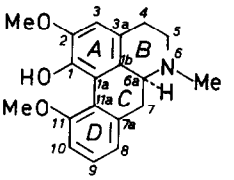
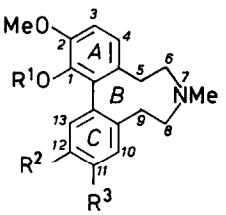


7 ·m/z 495



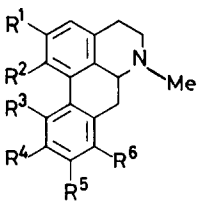
8



9 R^1=R^3=H; R^2=OMe

10 R^1=R^2=H; R^3=OMe

13 R^1=Me; R^2=OMe; R^3=H



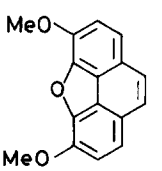
11 R^1=R^2=R^5=R^6=H; R^3=R^4=OMe

12 R^1=R^2=R^5=H; R^3=R^4=OMe; R^6=D

21 R^1=R^4=R^5=OMe; R^2=OH; R^3=R^6=H

22 R^1=OMe; R^2=OH; R^3=R^6=H; R^4,R^5=OCH_2O

23 R^1=R^2=OMe; R^3=R^4=R^5=R^6=H



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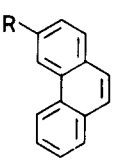

19 R=OMe

20 R=H

observed at *m/z* 495 ($[M-H]^+$), having an abundance of about three times that of the molecular ion. This fragment ion may be formulated as structure **7**.

Leaves of *P. somniferum* plants have been reported to contain a water-repellent wax layer [11], and 10-*n*-nonacosanol (**6**) was demonstrated as the major lipid from the epicuticular wax of *P. somniferum* [10]. Within the genus *Papaver*, 10-*n*-nonacosanol has been found earlier in *P. rhoeas* [12, 13], in opium [14, 15], in *P. fugax*, *P. orientale*, *P. macrostomum*, *P. commutatum* and *P. dubium* [16]. The finding of this compound in *P. bracteatum* adds further confirmation to the general occurrence of 10-*n*-nonacosanol within this genus.

Isothebaine

The presence of the aporphine alkaloid isothebaine (**8**) was reported earlier for the species *P. bracteatum*, either as a major constituent [17, 18], or as a minor one [19, 20]. In the latter case, the plant material was correctly identified, judged from its alkaloid profile, while in the former cases plant identification is highly doubtful. GC/MS screening of our counter-current fractions showed the presence of a trace of this alkaloid. Its identification was confirmed by comparison with a sample isolated from *P. pseudo-orientale* plant material.

In a ^{1}H NMR ASIS experiment on isothebaine, the methoxyl resonance at δ3.95 underwent the largest upfield

shift, and according to ref. [21] this resonance should therefore be assigned to the C-2 methoxyl group. Such assignment, however, is incorrect, as was concluded from a $Pr(fod)_3$-induced shift experiment in ^1H NMR.

In the structural identification of the dibenz[d,f]-azonine alkaloids neodihydrothebaine (**9**) and bractazonine (**10**) from *P. bracteatum* [22], the lanthanide shift reagent $Pr(fod)_3$ was employed to discriminate between methoxyl resonances. A similar experiment, performed on isothebaine, showed that the methoxyl resonance at δ3.95 in the ^1H NMR spectrum is virtually unaffected by the presence of the shift reagent, while the methoxyl resonance at δ3.89 shifts to higher field, with considerable line-broadening. In a $Pr(fod)_3$-induced shift experiment in ^{13}C NMR it was found that this bidentate shift reagent coordinates mainly with the C-1 hydroxyl and C-2 methoxyl groups of **8**, and exhibits virtually no interaction with the C-11 methoxyl group (see below). Consequently, the methoxyl resonance at δ3.95 must be assigned to the C-11 methoxyl group, while that at δ3.89 is ascribed to the C-2 methoxyl group [22].

The lanthanide shift reagent $Eu(fod)_3$ was employed for the identification of methoxyl resonances in the ^1H NMR spectra of the aporphine alkaloids **11** and **12** [23]. According to ref. [23], the methoxyl group located at δ3.90 showed the largest induced shifts, and that at δ3.72 showed much smaller shifts. Close examination of the results presented [23], however, indicates that this interpretation is erroneous. Linear regression with best fit for the experimental data shows that upon addition of $Eu(fod)_3$ the methoxyl resonance originally found at δ3.72 passes by the methoxyl resonance originally found at δ3.90. The normalized shielding gradients dδ (calculated induced shifts in ppm for equimolar complexes) [22] are hence δ3.72 dδ −13.7 and δ3.90 dδ −1.5. The shift reagent forces the C-11 methoxyl group into a position near ring A, which results in strong deshielding. This observation enables definitive assignments: the C-11 methoxyl group of compounds **11** and **12**, found at δ3.72, is strongly influenced by the presence of the shift reagent, while the C-10 methoxyl group, found at δ3.90, is influenced to a lesser extent.

Treatment of the dibenz[d,f]azonine alkaloid *O*-methylneodihydrothebaine (**13**) [22] with $Pr(fod)_3$ results in largest upfield shifts for the C-1 methoxyl resonance, because the effects of the shift reagent and of the anisotropy exerted by the aromatic ring C are working in the same direction. Consequently, there is an apparent difference with the above analysis on **11** and **12**. For the latter compounds, the effects of the shift reagent and the anisotropy exerted by ring A are both downfield. This apparent difference results from different orientations of the methoxyl groups with respect to the neighbouring aromatic moieties. In *O*-methylneodihydrothebaine (**13**), the aromatic rings are perpendicular. The C-1 methoxyl group is forced into the diamagnetic area of the neighbouring aromatic ring and experiences an additional upfield shift. In aporphine alkaloids, the aromatic rings have an angle of twist of the biphenyl system of *ca* 30° [24]. The C-11 methoxyl group of **11** and **12** is consequently forced by the shift reagent into a position within the paramagnetic area of ring A, resulting in an additional downfield shift.

^{13}C NMR chemical shifts of some phenanthrenes

In Table 1 ^{13}C NMR chemical shift assignments are given for the phenanthrene derivatives **1**, **3**, **5** and **14**

Table 1 ^{13}C NMR chemical shifts of some phenanthrenes

Identification of carbon	**1**	**3**	**5**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
1	119 6	124.6*	126 7	119.7	102.2	102.3	101.5	101.5	129.9	128.5
2	115.8	116 8	116 0	117.0	160.3	159.9	159.9	160.0	116 6	126.5
3	143.6*	151.1	149.1	141.0	99.6	99 5	99.2	99.0	158.4	126.5
4	143.7*	147 1	136 7	141.3	158 6	158 3	158.1	158 1*	104.1	122.6
4a	118.6	124 3	123 5	125.5	115 9	116 4	115.6	115.4	131.6	130.3
4b	131.3	130.8	129 5	125.5	127 6	125 2	130 5	131.7	129.8	130.3
5	110.4	109.1	108 5	141.3	109 1	109.7	127 7	109.7	122.6	122.6
6	157.9	158.1	157 7	141.0	147 4*	146.2	126 4*	158.2*	126.5	126.5
7	111 1	113.3	112.4	117.0	147.1*	148 5	124.8*	114.6	126.5	126 5
8	129.0	129.3	129.5	119.7	113.4	112.4	128.3†	129.3	128.5	128 5
8a	127 2	127.6	127.6	122.0	126.4	128.4	131.8	126 6	132.4	132.0
9	125.3	125.2	125 0	123.2	128.5	127.9	128 2†	128.0	126.0	126 9
10	124.6	124.8*	124.2	123 2	125.2	125.6	126.8*	124 5	124.5	126.9
10a	129 0	128 8	128.2	122 0	135.8	135 4	135.5	136 0	126.8	132.0
2-OMe	—	—	—	—	55.6	55 5	55 0	55 1	—	—
3-OMe	56 9	56.6	56 2	58 2	—	—	—	—	55.3	—
4-OMe	—	60.0	—	—	56 0	55.9*	55.3	55.5	—	—
6-OMe	55.3	55 3	54.9	58 2	56 0	—	—	55 1	—	—
7-OMe	—	—	—	—	—	56.1*	—	—	—	—
C=O	—	—	168.2	—	—	—	—	—	—	—
MeC=O	—	—	20.8	—	—	—	—	—	—	—

*,†These assignments may be interchanged.

The data for compounds **15** and **16** [in $(CD_3)_2CO$] are taken from ref. [25], the data on **17**, **18** and **19** from ref [26], and the assignments for phenanthrene (**20**) from ref. [27]. Apart from **15** and **16**, all compounds were dissolved in $CDCl_3$.

(available from this research), and the natural phenanthrenes **15** and **16**, for which unassigned ^{13}C NMR data were reported in ref. [25]. The literature data [26] on model compounds **17**, **18** and **19** are assigned as well. For comparison, the literature data [27] on phenanthrene itself, **20**, are included. Most assignments are based on increment calculations and mutual comparison of the spectra of the compounds. The assignments for C-3, C-4, C-5 and C-6 of compound **14** are made on account of relative signal intensities. C-4a, C-4b, C-8a and C-10a were assigned on similar grounds.

Assignments for C-9 and C-10 in the models **19** and **20** are based on comparison with styrene and 4-methoxystyrene. This indicates that the C-10 resonance in **15**–**18** must be found *ca* 2 ppm upfield from the C-9 resonance. The C-9 resonance of α-thebaol (**1**) is expected at a δ value similar to that of the C-10 resonance in **15** and **16**, whereas the C-10 resonance of **1** will be comparable with the C-9 resonance of **19**. The assignments for C-9 and C-10 of compounds **3** and **5** fit into this pattern. The assignments for C-4b and C-8a in **15** and **16** are based on the data of 2-methoxyphenol (see Table 2). Comparison of the data for α-thebaol (**1**) with those for *O*-methyl-α-thebaol (**3**) shows that methylation of the C-4 phenolic function of the former compound leads to shifts of the carbon atoms in *ortho* and *para* positions with respect to that substituent, which strongly deviate from the well-known incremental values. The newly introduced methoxyl group will be forced into an out-of-plane position, because of the crowded nature of the compound. In this position the C-4 methoxyl group of **3** is not suitable for conjugation with the aromatic moiety. The latter conjugation, however, is incorporated in incremental values of standard chemical shift theory. Acetylation of the phenolic function of α-thebaol leads to less-pronounced deviations from the usual incremental values, because of the much smaller conjugation effect of an acetoxy function.

$Pr(fod)_3$-induced shift experiments were performed in ^{13}C NMR of phenanthrenes **1**, **3** and **14**. Such experiments result in induced chemical shifts (expressed as normalized shielding gradients dδ) as well as in effects on the line widths of the carbon resonances involved. The latter effects are expressed conveniently as comparative peak heights for 1:10 complexes (see Experimental). For compound **14** the dδ values were negligible (0–1 ppm). The line-broadening showed that bidentate coordination of the shift reagent with the oxygen atoms of **14** did not occur. The O/O distance, estimated from Dreiding models at 0.35 nm, obviously is not suitable at all for such coordination. As no specific coordination site was present in this molecule, the effects were randomized.

Table 2 ^{13}C NMR chemical shifts and $Pr(fod)_3$-induced effects for 2-methoxyphenol in $CDCl_3$

Identification of carbon	δ	dδ	h'*
1	145.5	34 5	69
2	146.4	27.9	100
3	110.6	9.8	63
4	121.3	5.1	83
5	120.0	5.7	71
6	114.4	5.9	48
OMe	55.6	30.1	30

*See Experimental

For α-thebaol (**1**) the dδ values were negligible too (1–2 ppm). The effects on line widths showed coordination of the shift reagent with the C-4 hydroxyl and C-3 methoxyl groups. Therefore this experiment allowed definite identification of the methoxyl resonances of **1**. For *O*-methyl-α-thebaol (**3**) induced chemical shifts as well as comparative peak heights showed strong coordination of the shift reagent with the C-3 and C-4 methoxyl groups, and negligible coordination with the C-6 methoxyl group. The C-4 methoxyl group, being in a hindered position, is most influenced in both respects. Consequently, this experiment allowed definitive assignment of the methoxyl resonances of compound **3** (see Table 1).

^{13}C *NMR chemical shift assignments for isothebaine*

The ^{13}C NMR chemical shift assignments for the aporphine alkaloid isothebaine (**8**) are based on comparison with literature assignments for related alkaloids, as well as on the results of an experiment using $Pr(fod)_3$-induced chemical shifts in ^{13}C NMR.

The data reported for thaliporphine (**21**) and domesticine (**22**) [28, 29] were helpful in the assignments of ring A and ring B carbons. Assignments for ring D carbons are based on the literature spectrum of nuciferine (**23**) [29, 30], using incremental calculations. The assignments for C-1a, C-1b and C-11a were difficult. C-1a and C-11a are expected to give resonances at similar δ values, and will therefore be found at δ119.1 and 121.5, respectively. The discrimination between these two resonances was based on comparison of the C-1a chemical shift with the corresponding chemical shift in thaliporphine (**21**), whereas the C-11a chemical shift was calculated from the C-11a chemical shift in nuciferine (**23**) using the *ortho* effect of a methoxyl substituent in similar situations. The *ortho* effect mentioned amounts to −11.2 ppm, as is indicated by comparison of the C-2 chemical shifts of *o*-xylene (δ136.4) and 1,2-dimethyl-3-methoxybenzene (δ125.2). Having assigned the C-1a and C-11a resonances, we found the C-1b resonance of isothebaine to be at δ127.6. The assignments for ring A carbons of **8** are in agreement with those of corresponding carbons in similar situations [29].

A $Pr(fod)_3$-induced shift experiment in ^{13}C NMR provided the assignments of the methoxyl resonances and enabled discrimination between the C-3 and C-10 carbons, the latter being hardly influenced. The bidentate shift reagent $Pr(fod)_3$ coordinates mainly with the C-1 hydroxyl and C-2 methoxyl groups. The induced chemical shifts (see Table 3) show that the shift reagent—in agreement with expectations—is more strongly coordinated to the C-1 hydroxyl group. These effects extend to carbons in a γ-position with respect to the affected oxygen-bearing carbon. Such a γ-effect is operating on C-7a, and on C-11 as well, whereas the C-11 methoxyl resonance is virtually not influenced. The relatively small induced shifts observed for the aliphatic part of the alkaloid show that in this case coordination with the unshared electron pair on nitrogen is very weak compared with the C-1 hydroxyl/C-2 methoxyl coordination. The loss of height of the C-1 and C-2 resonances in this experiment is quite extraordinary; the resonances were hardly detectable. In Table 3 the comparative peak heights of the resonances are given as percentages of the

Table 3. ^{13}C NMR chemical shifts and $Pr(fod)_3$-induced effects for isothebaine (**8**) in $CDCl_3$

Identification of carbon	δ	dδ	h'*
1	141.4	79	2
1a	119.1	14	13
1b	127.6	14	19
2	148.4	70	2
3	110.5	20	45
3a	123 6	12	30
4	28 4	8	82
5	52.4	4	73
6a	62.0	5	72
7	35.6	4	81
7a	139.2	5	45
8	121.8	−1	65
9	127.8	−1	100
10	111.2	0	79
11	153.3	9	35
11a	121.5	12	18
NMe	43.4	4	61
2-OMe	55.5	57	7
11-OMe	56 4	1	66

*See Experimental.

original peak heights. For this purpose, the relative height of the C-9 resonance, being least influenced in this experiment, was assigned 100%. The preferential coordination of the lanthanide shift reagent with especially the C-1 hydroxyl within the pair C-1/C-2 oxygens is reflected in the induced chemical shifts as well as in the losses of height of the neighbouring carbon resonances. A significant coordination with the C-11 methoxyl group, or between the C-1 and C-11 oxygens, is not indicated. This observation may be explained from the O/O distances, which amount to *ca* 0.28 nm for C-1 OH/C-2 OMe, and to *ca* 0.16 nm for C-1 OH/C-11 OMe, according to Dreiding models. The latter distance is not suitable for optimal coordination of the bidentate shift reagent with those oxygens. This result is in full agreement with the observations in ^1H NMR mentioned above.

When induced chemical shifts and comparative peak heights for isothebaine are compared, C-1a seems to behave anomalously, in decreasing its relative peak height to a larger extent than its neighbouring carbons C-1b and C-11a, while simultaneously the induced chemical shift of C-1a is less than may be expected on account of the above-mentioned preferential coordination of the shift reagent with the C-1 hydroxyl group (compare the dδ value for C-3). Therefore, a similar experiment was performed using 2-methoxyphenol as a model substance (see Table 2). Also for this compound a strong loss of height and a relatively small induced shift of the C-6 resonance was noted.

The C-2 resonance of 2-methoxyphenol, though strongly influenced with respect to its chemical shift, is aberrant, however, in being least influenced in peak height. The exact geometry of the coordination of the shift reagent with the model compound 2-methoxyphenol on the one hand, and with the alkaloid isothebaine on the other, presumably is responsible for the different behaviour of the methoxyl group bearing carbons in these compounds.

EXPERIMENTAL

Extraction of capsules of *P. bracteatum* cv Arya I, cultivated by Franco-Pavot Industries, France, and counter-current separation of the extracts were performed as reported earlier [4].

GC/MS was carried out using a JEOL 1100 GLC/JEOL JMS 07 or a Hewlett–Packard 5710A/JEOL JMS D-300 combination of gas chromatograph/mass spectrometer. The latter combination was connected to a JMA 2000 data system. Spectra were recorded at 70 eV. ^1H NMR spectra (in $CDCl_3$) were recorded at 90 MHz with TMS as internal standard ($\delta = 0$ ppm). ASIS effects were studied by gradual addition of C_6D_6 to a $CDCl_3$ soln of the compound.

^{13}C NMR spectra (in $CDCl_3$) were recorded at 20 MHz with a Varian CFT-20 spectrometer, or at 50 MHz using a Bruker WP 200 instrument, with $CDCl_3$ as internal reference ($\delta = 77.0$). Shift experiments in ^{13}C NMR were performed by addition of 0.1 equiv. of tris (1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)praseodymium [$Pr(fod)_3$] to a soln of the compound in $CDCl_3$. The resulting induced chemical shifts are expressed as normalized shielding gradients dδ (calculated induced shifts in ppm for equimolar complexes). Comparative relative peak heights h' are given for the 1:10 complexes of the shift reagent and compound. The signal for $C-y$, showing the least decrease of peak height, arbitrarily was assigned 100%. In formula: $h'(C-x) = [h_1(C-x)/h_0(C-x)] \times [h_0(C-y)/h_1(C-y)] \times 100\%$, where h_0 is the relative peak height in the spectrum without shift reagent, and h_1 is the relative peak height in the spectrum with $Pr(fod)_3$. GC was carried out on a Pye Series 104 gas chromatograph, equipped with a FID, using on-column injection and glass columns, packed with 3% OV-17 on Chrompack SA (80–100 mesh), operating at 270° (system a), or with 3% SE-30 on Chromosorb W-HP (80–100 mesh), operating at 270° (system b). For GC retention times thebaine was chosen as a reference ($RR_t \equiv 1.00$). TLC was performed on silica gel GF 254 plates with EtOAc–Et_2NH (19:1) (system a), or C_6H_6–Me_2CO–MeOH (7:2:1) (system b). Detection was accomplished in UV light (254 nm) and with iodoplatinate spray reagent. Melting points are corr.

Detection of O-*methyl-α-thebaol* (**3**) *in* P. bracteatum. GC/MS screening of counter-current fractions [4, 31] showed in fractions 9–28 the presence of a trace of a compound having mass spectral fragmentations strongly resembling those of α-thebaol (**1**) [4], but higher by 14 mass units. Synthetic *O*-methyl-α-thebaol (**3**) was compared in GC/MS with the natural compound, thus establishing its identity.

Synthesis of O-*methyl-α-thebaol* (**3**). *O*-Methyl-α-thebaol was prepared from thebaine (**4**) through *O*-acetyl-α-thebaol (**5**).

O-*Acetyl-α-thebaol* (**5**). A mixture of thebaine (3 g), NaOAc (0.3 g) and Ac_2O (9 ml) was stirred and refluxed for 18 hr [6]. The brown soln was concd, diluted with H_2O (20 ml), acidified (HOAc) and extracted with $CHCl_3$ (3 × 70 ml). The extract was dried ($MgSO_4$) and the solvent was evapd *in vacuo*, yielding a brown oil (3.87 g). Chromatography on silica gel, using $CHCl_3$ as eluant, afforded first 3,6-dimethoxyphenanthreno[4,5-bcd]furan (**14**) (0.3 g, yield 12%) and then *O*-acetyl-α-thebaol (**5**) (1.14 g, yield 40%).

3,6-*Dimethoxyphenanthreno*[4,5-*bcd*]*furan* (= 6-*methoxy*-O-*methylmorphenol*) (**14**). ^1H NMR: δ4.32 (6H, *s*, 2 × OMe), 7.33 and 7.63 (4H, AB pattern, $J = 8.4$ Hz, H-2 + H-7 and H-1 + H-8, respectively), 7.68 (2H, *s*, H-9 + H-10). GC/MS *m/z* (rel. int.): 253 (15), 252 (78), 238 (16), 237 (100), 194 (19), 138 (15), 126 (17), 75 (13). $Pr(fod)_3$-induced effects in ^{13}C NMR (see Table 1): Identification of carbon (dδ, h'): C-1, C-8 (0, 56); C-2, C-7 (1, 68); C-3, C-5 (1, 95); C-4, C-5 (1, 83); C-4a, C-4b (1, 100), C-8a, C-10a (0, 82); C-9, C-10 (1, 90); C-3 OMe, C-6 OMe (1, 79).

O-Acetyl-α-thebaol (**5**). ^{1}H NMR: δ 2.47 (3H, *s*, MeCO), 3.86 and 3.89 (6H, 2 × *s*, 2 × OMe), 7.27 (1H, *dd*, $J_{5,7}$ = 2.4 Hz, $J_{7,8}$ = 8.8 Hz, H-7), 7.35 (1H, *d*, $J_{1,2}$ = 8.8 Hz, H-2), 7.56 (2H, *s*, H-9 and H-10), 7.77 (1H, *d*, $J_{7,8}$ = 8.8 Hz, H-8), 7.80 (1H, *d*, $J_{1,2}$ = 8.8 Hz, H-1), 8.63 (1H, *d*, $J_{5,7}$ = 2.4 Hz, H-5). GC/MS *m/z* (rel. int.): 296 (28), 255 (18), 254 (100), 240 (12), 239 (70), 211 (14), 210 (10), 152 (11), 139 (15), 43 (10).

α-Thebaol (**1**). *O*-Acetyl-α-thebaol (1 g) in 50% aq. KOH (50 ml) was heated for 1 hr under reflux [32]. The chilled reaction mixture was acidified using conc. HCl and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and evapd, giving a 100% yield of crude **1**. The ^{1}H NMR spectrum of this material showed the methoxyl resonances at δ 3.62 and 3.85, as such different from the ^{1}H NMR spectrum (60 MHz) of **1** isolated from opium [3], in which these resonances coincided at *ca* 4.02 ppm. For this reason an analytical sample was prepared by silica gel TLC (*n*-hexane–EtOAc, 17:3, 1 or 2 developments). Mp 96° (lit. [6] mp 94°). The IR spectrum was superimposable on that of authentic α-thebaol. ^{1}H NMR: δ 3.99 and 4.06 (6H, 2 × *s*, 2 × OMe), 6.91 (1H, *s*, OH), 7.23 (1H, *dd*, *J* = 2.4 Hz, *J* = 8.4 Hz, H-7), 7.24 and 7.42 (2H, 2 × *d*, *J* = 8.4 Hz, H-1 and H-2), 7.51 (2H, AB pattern, *J* = 9.5 Hz, H-9 and H-10), 7.76 (1H, *d*, *J* = 8.4 Hz, H-8), 9.28 (1H, *d*, *J* = 2.4 Hz, H-5). The assignment of the *dd* at δ 7.23 was verified by irradiation at δ 9.28. GC/MS *m/z* (rel. int.): 255 (17), 254 (100), 240 (10), 239 (63), 211 (29), 196 (11), 183 (8), 168 (9), 152 (8), 140 (8), 139 (13). Pr(fod)$_3$-induced effects in ^{13}C NMR (see Table 1): Identification of carbon (dδ, *h'*): C-1 (2, 70); C-2 (1, 69); C-3 (2, 63); C-4 (2, 59); C-4a (2, 51); C-4b (1, 68); C-5 (1, 68); C-6 (2, 78); C-7 (1, 59); C-8 (2, —); C-8a (2, 49); C-9 (1, 81); C-10 (1, 77); C-10a (2, —); C-3 OMe (2, 56); C-6 OMe (1, 100). The resonances for C-8 and C-10a coincided in the shifted spectrum.

O-Methyl-α-thebaol (**3**). α-Thebaol (272 mg) was treated with excess dimethyl sulphate (1 ml) in MeOH–H_2O (1:1, 20 ml), containing KOH (3 g), and refluxed for 3 hr. The product was purified by silica gel TLC (*n*-hexane–Et_2NH, 19:1, 3 developments). Yield 35%. Yellowish oil [33]. ^{1}H NMR: δ 3.99 (6H, *s*, 2 × OMe), 4.02 (3H, *s*, OMe), 7.25 (1H, *dd*, *J* = 2.7, *J* = 8.7 Hz, H-7), 7.32 (1H, *d*, *J* = 8.7 Hz, H-2), 7.52 (2H, *s*, H-9 + H-10), 7.63 and 7.72 (2H, 2 × *d*, *J* = 8.7 Hz, H-1 and H-8), 9.25 (1H, *d*, *J* = 2.7 Hz, H-5). GC/MS *m/z* (rel. int.): 269 (18), 268 (100), 253 (29), 225 (19), 210 (31), 167 (10), 139 (12). Pr(fod)$_3$-induced effects in ^{13}C NMR (see Table 1): Identification of carbon (dδ, *h'*): C-1 (4, —); C-2 (2, 35); C-3 (45, 34); C-4 (53, 35); C-4a (14, 79); C-4b (10, 100); C-5 (10, 34); C-6 (4, 84); C-7 (12, 32); C-8 (2, 38); C-8a (3, 83); C-9 (2, 33); C-10 (6, —); C-10a (6, 77); C-3 OMe (26, 17); C-4 OMe (35, 13); C-6 OMe (3, 42). The C-1 and C-10 resonances coincided in the shifted spectrum.

^{13}C NMR chemical shifts of vinyl carbons in styrene and 4-methoxystyrene. Styrene C_6H_5–C^1H=C^2H_2: C-1 δ 137.0 and C-2 δ 113.5; *p*-methoxystyrene C-1 δ 136.5 and C-2 δ 111.3 (solvent $CDCl_3$).

Isolation of 10-n-*nonacosanol* (**6**) *from the leaves of* P. bracteatum. Freeze-dried leaves of *P. bracteatum* cv Arya I (96 g) were briefly immersed in $CHCl_3$. The $CHCl_3$ soln was washed with 5% aq. HOAc and concd *in vacuo*, yielding a solid residue (781 mg) which was submitted to chromatography on a silica gel column eluted with toluene–$CHCl_3$ (1:1). Fractions containing **6** were combined and concd *in vacuo*, yielding a yellow solid (130 mg). Recrystallization from MeOH (2 ×) and Me_2CO (1 ×) yielded a colourless crystalline substance (87.1 mg), pure by GC, but having $[\alpha]_D^{20}$ +0.3° (*c* = 2.4; $CHCl_3$). This material was submitted to TLC (alumina, eluant C_6H_6–$CHCl_3$, 10:1). The isolated material had mp 81° (lit. [14] mp 81–82°) and $[\alpha]_D^{20}$ ± 0.000° (*c* = 1.1; $CHCl_3$) (reported [14] ±0° (*c* = 2.5); cf. ref. [34]). ^{1}H NMR: δ 0.86 (6H, *t*, *J* = 6 Hz), 1.26 (52H, broadened signal, 26 × CH_2), 3 56 (1H, *br* signal, CHOH). IR (molten film) ν_{max} cm^{-1}: 720 (CH_2 rocking), 1132 (C–OH stretching), 1470 (CH_2 deformation), 2854 (CH_2 symmetric stretching), 2868 (Me symmetric stretching), 2920 (CH_2 asymmetric stretching) and 2960 (Me asymmetric stretching). The OH stretching vibration was observed as two broad bands, centred at 3200 and 3300 cm^{-1}. MS *m/z* (rel. int.): 407 (9), 406 (30), 298 (10), 297 (45), 157 (47), 156 (7), 139 (7), 125 (13), 111 (26), 98 (7), 97 (67), 96 (13), 95 (11), 85 (25), 84 (13), 83 (100). High-resolution MS: *m/z* 406.452 ($C_{29}H_{58}$; $[M-H_2O]^{+\cdot}$), *m/z* 297.316 ($C_{20}H_{41}O$; $[M-C_9H_{19}]^+$) and *m/z* 157.158 ($C_{10}H_{21}O$; $[M-C_{19}H_{39}]^+$).

*O-TMSi-*10-n-*nonacosanol.* Nonacosanol was silylated almost quantitatively by Regisil in pyridine in 1 hr at room temp. GC/MS *m/z* (rel. int.): 496 (0.15), 495 (0.45), 483 (0.3), 482 (1.1), 481 (2.8), 371 (4.4), 370 (18), 369 (59), 231 (5.4), 230 (20), 229 (100).

*O-Acetyl-*10-n-*nonacosanol.* Acetylation of **6** was performed in Ac_2O–pyridine–EtOAc (1:1:1) by heating at 60° for 2 hr. GC/MS *m/z* (rel. int.): 407 (2.8), 406 (8.4), 279 (2.4), 111 (25), 97 (45), 83 (50), 71 (30), 69 (32), 57 (60), 55 (35), 43 (100).

Detection of isothebaine (**8**) *in* P. bracteatum. Upon GC/MS screening a trace of isothebaine was detected in counter-current fractions 1–8 [4, 31]. Identification of this alkaloid was attained in GC/MS by comparison with an authentic sample isolated from *P. pseudo-orientale* plant material.

Isolation of isothebaine (**8**) *from* P. pseudo-orientale. Powdered *P. pseudo-orientale* plant material (0.9 kg, mainly stems, some capsules), collected in Turkey [35], was extracted with 5% aq. HOAc. The pH of the extract was adjusted to 9–10 using conc. aq. NH_3, and $CHCl_3$–*i*-PrOH (4:1) extraction was performed. Concn *in vacuo* yielded a dark-brown residue. GC analysis showed the thebaine content to be *ca* 6% of the isothebaine content. This residue was submitted to CC on silica gel G, using *n*-hexane–EtOAc–Et_2NH (first 50:50:1, and then 25:75:1) as eluant. Fractions containing **8** were combined and evapd, yielding a dark-green residue (500 mg) containing mainly **8** (> 80% by GC). For analytical purposes, pure **8** was obtained by silica gel TLC (system b). ^{1}H NMR: Identical to the spectrum reported in ref. [36]. The pattern obtained for the aromatic protons was difficult to interpret because of higher order effects. GC/MS *m/z* (rel. int.): 312 (19), 311 (100), 310 (54), 309 (16), 296 (28), 295 (11), 294 (47), 293 (11), 281 (12), 280 (38), 279 (10), 268 (19).

ASIS experiment in ^{1}H NMR of isothebaine (**8**). On gradual addition of C_6D_6 to a $CDCl_3$ soln of **8**, the methoxyl resonance at δ 3.95 in $CDCl_3$ shifted to δ 3.50 in $CDCl_3$–C_6D_6 (1:1). The other methoxyl resonance at δ 3.89 shifted to δ 3.68, while the *N*-methyl resonance shifted from δ 2.53 to 2.36. These shifts were proportional to the amount of C_6D_6 added during the experiment. The upfield shifts observed for the methylene and methine protons were negligible (< −0.05 ppm). The aromatic protons experienced upfield shifts (H-3: −0.11 ppm; H-8 and H-10: *ca* −0.16 and *ca* −0.31 ppm; H-9: −0.17 ppm). In $CDCl_3$–C_6D_6 (1:1), these resonances were well resolved: δ 6.57 (1H, *s*, H-3), 6.70 and 6.89 (2H, 2 × *dd*, *J* = 1.2, *J* = 7.8 Hz, H-8 and H-10), 7.11 (1H, *dd*, *J* = 7.8, *J* = 7.8 Hz, H-9). A similar effect on the aromatic proton resonances was observed when Pr(fod)$_3$ (0.1 eqiv.) was added to a $CDCl_3$ soln of **8**. In the ^{1}H NMR spectrum (200 MHz) these resonances were observed at δ 7.05 ('*t*'), 6.79 (*d*), and 6.56 (*d*). The resonance of H-3, however, could not be assigned due to excessive peak broadening. For better resolution of the resonances of the aromatic protons, ASIS is here to be preferred over lanthanide-induced shifts, whereas for identification of methoxyl resonances the latter method is clearly superior to ASIS. The dδ (OMe) values observed were δ 3.89 dδ 19 and δ 3.95 dδ 3.

GC data. Relative retention times: **1**, a 0.80, b 1.02; **3**, a 0.67, b 0.80; **4**, a 1.00, b 1.00; **5**, a 0.99, b 1.04; **6**, a 1.24, b 2.84; OTMSi-**6**,

a 0.88, b 2.65; OAc-**6**, a 1.27, b 3.0; **8**, a 1.60, b 1.33; **14**, a 0.55, b 0.77.

TLC data. R_f values: **1**, a 0.80, b 0.88; **3**, a 0.88, b 0.89; **4**, a 0.48, b 0.20; **5**, a 0.86, b 0.86; **6**, a 0.93, b 0.92; **8**, a 0.54, b 0.43; **14**, a 0.84, b 0.87.

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