A New Rearrangement Product of Thebaine, isolated from *Papaver bracteatum* Lindl. Structural Assignment of Thebaine *N*-Oxides

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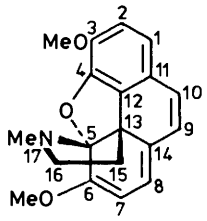
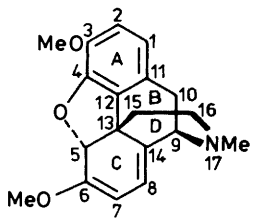
From *Papaver bracteatum* an unusual alkaloid is isolated: 6,7,8,9,10,14-hexadehydro-4,5-epoxy-3,6-dimethoxy-17-methylthebinan (**1**). This alkaloid is also obtained from the mixture of rearrangement products of one of the thebaine *N*-oxides. The structure of another constituent of the latter mixture is deduced to be 6,7,8,9,10,14-hexadehydro-3,6-dimethoxythebinan-4-ol (**15**). The presence of both thebaine *N*-oxides in *Papaver bracteatum* is confirmed, and their structures are revised on chemical and spectroscopic grounds.

The plant species *Papaver bracteatum* is regarded as a promising substitute for *P. somniferum*, in that it is a rich source of the morphinan alkaloid thebaine (**2**).[1] It is known to contain several minor alkaloids belonging to the class of morphinans and biogenetically derived from the major alkaloid thebaine: codeine,[2] neopine,[2] oripavine,[3] 14β-hydroxycodeinone,[4] 14β-hydroxycodeine,[2b,4] thebaine methochloride,[5] and the isomeric thebaine *N*-oxides.[6] Recently, we reported the presence of two other thebaine-derived alkaloids, having a rearranged skeleton: neodihydrothebaine and bractazonine,[7] both members of the rare class of dibenz[*d,f*]azonine alkaloids.

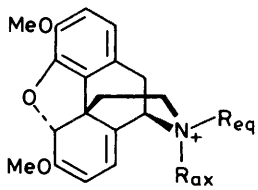
In this paper we report the isolation of another alkaloid, which has unusual features. In accordance with a nomenclature system for compounds of this class of thebaine-derived products, newly proposed here, the compound is identified as 6,7,8,9,10,14-hexadehydro-4,5-epoxy-3,6-dimethoxy-17-methylthebinan (**1**). This compound is also found as a rearrangement product of one of the thebaine *N*-oxides. The presence of those thebaine *N*-oxides is confirmed, and their structures are revised on chemical and spectroscopic grounds.



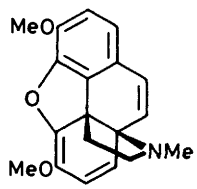
(**1**)



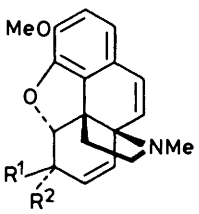
(**2**)



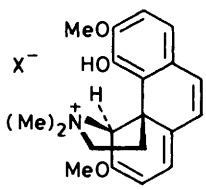
(**3**) $R_{eq} = O^-$, $R_{ax} = Me$
(**4**) $R_{eq} = Me$, $R_{ax} = O^-$



(**5**)



(**6**) $R^1R^2 = O$
(**7**) $R^1 = R^2 = OMe$



(**8**)

Results and Discussion

From counter-current extracts [2a] of capsules of *P. bracteatum*, cv. 'Arya I', a small quantity of a yellow alkaloid was isolated, which forms orange-red spots in silica gel t.l.c. if neutral solvents are used, but yellow spots if basic solvent mixtures are employed. On evaporation of the solvent the latter spots become brownish red. In acidic solution the compound has a strong red colour, but the alkaloid is recovered unchanged from such solutions.

The presence of both thebaine *N*-oxides in *P. bracteatum*, cv. 'Arya II' is confirmed. In column chromatography of synthetic reference samples of the *N*-oxides mentioned, the faster running so-called 'major isomer' decomposed, giving a series of spots in t.l.c. One of the decomposition products proved to be identical with the alkaloid above mentioned, and this made the structural elucidation much easier. It is impossible, however, to decide whether this alkaloid represents an actual natural substance, or an artefact. In view of the ease of decomposition of the thebaine *N*-oxide mentioned, it is highly probable that within the plant the same type of decomposition will occur, rendering such artefacts 'natural substances'.

This *P. bracteatum* alkaloid represents a new class of rearrangement products of morphinans. In order to facilitate discussions, the numbering system of the morphinan/thebinan alkaloids is used for this new class of alkaloids.

The molecular weight of the natural compound, isolated from *P. bracteatum*, was determined as 309.1365 ($C_{19}H_{19}NO_3$) by high-resolution mass spectrometry. This corresponds to loss of 18 mass units from a thebaine *N*-oxide. The ^{1}H n.m.r. analysis indicates some profound structural changes in comparison with thebaine (**2**) or the thebaine *N*-oxides (**3**) and (**4**), while at the same time many original features are retained. The presence of an additional double bond, bearing two hydrogen atoms in a *cis*-relation, is noted in particular (δ 6.19 and 6.34, *J* 10 Hz), while the pattern typical for 7-H and 8-H is still present (δ 5.13 and 5.65, *J* 7 Hz). The 5-H resonance is missing. The *N*-methyl resonance is observed at low field, compared with thebaine, but at high field when compared with the thebaine *N*-oxides. This position (δ 2.98) is consistent with the presence of an electron-withdrawing function near the nitrogen atom, *e.g.* a double bond (as in an enamine) or an α-oxygen substituent. The

possibility of an α-hydroxy group was ruled out by examination of the i.r. spectrum which displayed no hydroxyl absorption band (though the ^{1}H n.m.r. analysis showed the presence of 0.5 molecules of water included in the crystals of the compound). The product lacks enamine character as well, because the ^{1}H n.m.r. analysis showed no changes in the resonances of unsaturated protons upon addition of D_2O.[8] The additional double bond therefore most likely is located between C-9 and C-10, as in some indolinocodeine derivatives.

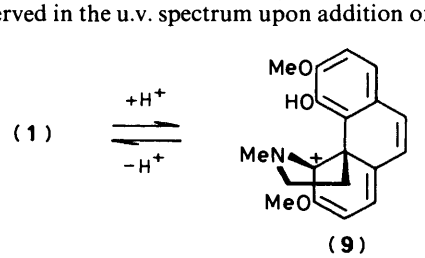
The rest of the aliphatic part of the ^{1}H n.m.r. spectrum displays the presence of four protons only mutually coupled, as was proven by computer simulation of their resonance pattern (see Experimental section). The geminal coupling constants ($^2J_{AB}$ 8.7 and $^2J_{CD}$ 12.0 Hz) indicate that an electronegative function is present in the α-position with respect to H_A/H_B. The vicinal coupling constants ($^3J_{AC}$ 0, $^3J_{AD}$ 7.2, $^3J_{BC}$ 4.9, and $^3J_{BD}$ 12.0 Hz) indicate that H_A, H_B, H_C, and H_D possess fixed steric orientations. Therefore the ethanamine unit is intact, though the nitrogen atom must have shifted from C-9 to another position.

Assuming that the C-13–C-15 bond is intact as well, only two positions for the new attachment of the nitrogen atom are to be considered in view of the results obtained thus far: C-5 [structure (**1**)] and C-14 [structure (**5**)]. The latter proposal, however, is not compatible with the ^{1}H n.m.r. position of the *N*-methyl resonance, because in compounds structurally related to (**5**), the *N*-methyl resonance is found at normal values [*e.g.* at δ 2.50 for (**6**), and at δ 2.44 for (**7**)].[9] The only feasible explanation for the low field position of the *N*-methyl resonance—when adhering to structure (**5**)—would have to be found in anisotropic or steric effects. Models, however, fail to indicate why such effects would be operating more drastically for (**5**) than for (**6**) or (**7**).

Experiments performed in order to hydrolyse the enol ether function of the natural compound were completely unsuccessful, pure starting compound being recovered. The enol ether function has an unusual stability, which is not to be expected for structure (**5**).

The u.v. spectrum of the compound is very similar to the one of thebaicyclomethine (**8**),[10] and thus indicates the presence of three double bonds in conjugation with the aromatic moiety. Moreover, a very drastic bathochromic effect is observed upon addition of acid, indicating that the conjugation in the polyene system of the compound is strongly increased. Such behaviour would be conceivable for structure (**5**) only if the C-14–N bond were to be opened. This process is unlikely, because it must be a reversible one, for the compound is recovered unchanged from a CF_3CO_2H solution. For these reasons structure (**5**) must be rejected as a structural proposal for the natural compound.

Turning now to structure (**1**), the effects observed in the u.v. spectrum may be explained by the proposition that the C-5–O bond is broken reversibly in the presence of acid (Scheme 1). The resulting carbocation (**9**) is stabilized by delocalization of the electron deficiency throughout the polyene and aromatic moiety, and by the contribution of the nitrogen atom, which now is capable of participation through its unshared electron pair. This nitrogen participation explains the bathochromic effect observed in the u.v. spectrum upon addition of acid.



Scheme 1.

Table 1. ^{13}C N.m.r. chemical shifts (δ_C/p.p.m.) of compounds (**1**), (**2**), (**9**), and (**15**) in $CDCl_3$

	(1)	(2)	(9)[a]	(15)
C-1	117.5[b]	119.0	119.3	118.6[b]
C-2	111.9	112.9	109.7	108.9
C-3	141.3	142.6	141.8	146.2
C-4	146.1	144.6	146.2	149.6
C-5	107.9	88.9	177.6	61.6
C-6	156.6	152.3	143.3[b]	152.8
C-7	95.2	95.7	122.7[c]	95.0
C-8	116.9[b]	111.3	118.2	118.0[b]
C-9	124.3[c]	60.6	122.0[c]	124.9[c]
C-10	124.9[c]	29.4	129.6	126.3[c]
C-11	124.5	127.5	126.2	126.7
C-12	129.8	133.2	118.7	124.4
C-13	58.7	45.8	60.8	50.3
C-14	134.7	132.2	145.6[b]	133.9
C-15	40.5	36.8	45.4	42.1
C-16	48.7	45.8	58.2	46.1
NMe	36.1	42.2	40.2	
3-OMe	55.9	56.3	56.1[d]	55.8
6-OMe	55.0	54.6	56.3[d]	55.3

[a] In $CDCl_3$ containing approximately 3 equiv. of CF_3CO_2H. [b,c] and [d] Assignments may be reversed.

It is clear that in acidic solution compound (**9**) is not very susceptible to enol ether hydrolysis. This accounts for the unusual stability of the enol ether function.

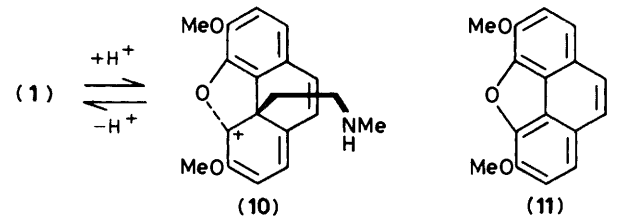
The ^{1}H n.m.r. spectrum of the natural compound in CF_3CO_2H shows major changes for the resonances of the C-7, C-8, C-15, and C-16 hydrogens, and for the *N*-methyl resonance. An electron deficiency which is delocalized over the skeleton of the compound will especially affect the resonances of protons attached to a carbon bearing a partial positive charge. Therefore it is expected that the 7-H resonance will be influenced the most, while the 10-H, 8-H, and 9-H resonances must be affected to a lesser extent. The ^{1}H n.m.r. resonances of the protons of the double-bond system in CF_3CO_2H indeed may be interpreted in terms of the effect mentioned above. The line widths of the resonances mentioned decrease in the order 7-H > 10-H ≃ 8-H > 9-H. These data indicate that the electron deficiency will be largely located at C-5. Further support for structure (**1**) is derived from the ^{13}C n.m.r. spectrum in $CDCl_3$ (Table 1). With respect to thebaine (**2**) the following multiplicity changes have taken place: 1 t (C-10), and 2 d (C-9 and C-5) in the spectrum of thebaine (**2**) correspond with 2 d (C-9 and C-10, δ_C 124.3 and 124.9 p.p.m., respectively) and 1 s (C-5, δ_C 107.9 p.p.m.) in the spectrum of compound (**1**). Other major differences with the data on thebaine are observed for the C-13 resonance (δ_C 58.7 p.p.m.), and the unusual chemical shift of the *N*-methyl resonance (δ_C 36.1 p.p.m.). In structure (**1**) the latter resonance will be influenced by an extra γ-oxygen effect. The very low field-position of the C-5 resonance is explained by a multisubstitution effect. In all other respects the ^{13}C n.m.r. spectrum is in agreement with expectations for structure (**1**).

Transformations, which are somewhat related to the (**1**) ⇌ (**9**) equilibrium (Scheme 1), were observed earlier for the carbinolamine-lactone group in the indole alkaloid haplophytine,[11] as well as for the carbinolamine ether group in the modified protoberberine alkaloid solidaline.[12] There are several natural carbinolamine derivatives, *e.g.* shihunine,[13] haplocine,[14] ribasine,[15] *etc.* With these results therefore the structure of the natural alkaloid is established to be (**1**).

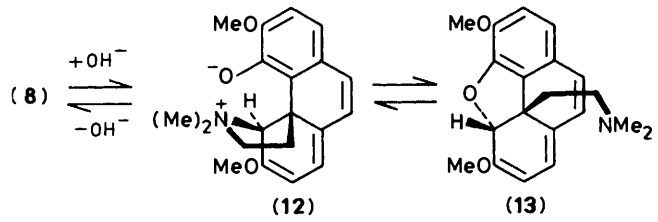
In view of the interesting behaviour of compound (**1**) in acidic solution, and the proposed transformation (**1**) ⇌ (**9**), it was intriguing to verify this aspect by recording the ^{13}C n.m.r. spectrum of (**1**) in acidic solution as well. That experiment might

Table 2. Interatomic distances for certain non-bonded atoms in thebaine *N*-oxide isomers, estimated from Dreiding models.

			Interatomic distances (nm)					
	$N-R_{ax}$	$N-R_{eq}$	8-H....N	8-H....O	C-8....N	C-8....O	C-14....N	C-14....O
(3)	Me	O	0.38	0.48	0.35	0.47	0.24	0.37
(4)	O	Me	0.38	0.37	0.35	0.36	0.24	0.29



Scheme 2.



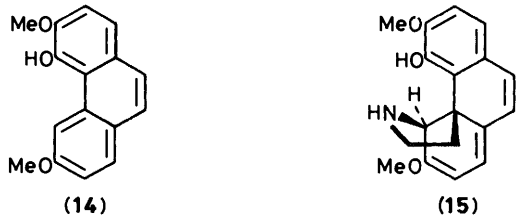
Scheme 3.

add further support to the proposed transformation (Scheme 1), and might eliminate an alternative C-5–N ring-opening mechanism (Scheme 2). The latter mechanism bears some resemblance to the mechanism operating for the photo- and thermo-labile compound thebaicyclomethine (**8**) in the presence of alkali (Scheme 3). In view of the stability of (**1**) in acidic solution a mechanism involving an intermediate like (**10**), which undoubtedly is liable to decompose, giving the phenanthrenofuran (**11**), is considered less probable.

Addition of trifluoroacetic acid to the $CDCl_3$ solution indeed resulted in profound changes of the ^{13}C n.m.r. analysis (Table 1). In the presence of acid the signal multiplicities were not changed. The carbocation nature of C-5 in acidic solution is strongly supported by its chemical shift, observed at δ_C 177.6 p.p.m. Significant downfield shifts are expected for the carbons which contribute to the delocalization of the electron deficiency. As derived from the ^1H n.m.r. analysis, the contributions of the C-7, (C-14), and C-10 carbons will be of decreasing order. Upfield shifts, resulting from polarization of C=C bonds, generally are expected for the interjacent carbons. The downfield shift observed for the *N*-methyl resonance is in agreement with a partial charge delocalization involving the nitrogen atom.

The observation of an upfield shift of the C-12 resonance strongly supports the proposed transformation (**1**) $\rightleftharpoons$ (**9**). In the alternative proposal (**1**) $\rightleftharpoons$ (**10**) such an upfield shift on C-12 will be less important, because then the C-4 substituent cannot contribute at all to an electron surplus at C-12. All results therefore are in accord with structure (**1**), as well as the transformation (**1**) $\rightleftharpoons$ (**9**).

The formation of compound (**1**) from the 'major isomer' of the thebaine *N*-oxides, according to the literature having structure (**4**),[6] is incomprehensible. This shed doubt as to the structural assignments of these *N*-oxides. The structural features of another product, isolated from the mixture resulting from decomposition of the 'major isomer' of the thebaine *N*-oxides, strengthened this doubt. This product shows close structural similarities with both thebaine (**2**) and compound (**1**). The most striking difference with the latter compound is the absence of a *N*-methyl resonance in the spectra of this decomposition product. The presence of the additional double bond bearing two *cis* hydrogens (J 9 Hz), corresponding to 9-H and 10-H of (**1**), is noted again in its ^1H n.m.r. spectrum. Corresponding with the 7-H and 8-H assignments for thebaine,[6] the signals at δ 5.30 and 5.79 are ascribed to 7-H and 8-H, respectively, in the decomposition product, which also retains the 5-H resonance. The latter shows some broadening, while a fine splitting is observed on the 7-H resonance. This coupling must be ascribed to an allylic coupling $^4J \simeq 1$ Hz. The C-5 hydrogen obviously occupies a position which is somewhat more perpendicular to the C-6–C-7–7-H system than in thebaine itself. The ^1H n.m.r. similarities of this decomposition product with compound (**1**) indicate that it is a substituted 4b,5-dihydrophenanthrene derivative as well. The ethanamine unit has been preserved, and its four hydrogens are only mutually coupled and in a fixed steric conformation. The aromatic proton resonance pattern shows a pronounced difference in chemical shift, which might indicate that the C-4–C-5 epoxy bridge may have been opened. The mass spectrum, obtained by g.c.m.s., is virtually identical with that of α-thebaol (**14**). For this reason, elimination of the ethanamine unit must be a highly favoured process. Such behaviour indeed can be expected if the epoxy bridge is missing in a compound very similar to (**1**). The mass spectrum of the compound, recorded using a direct inlet system (probe), gave in addition to the spectrum of α-thebaol a molecular ion of low abundancy at m/z 297, in agreement with the formula $C_{18}H_{19}NO_3$. These results indicate (**15**) as a likely structure for the compound.



The ^{13}C n.m.r. spectrum of this compound is in good agreement with the structural proposal (**15**) (Table 1). The stability of compound (**15**) is low. During purification attempts further decomposition was always observed.

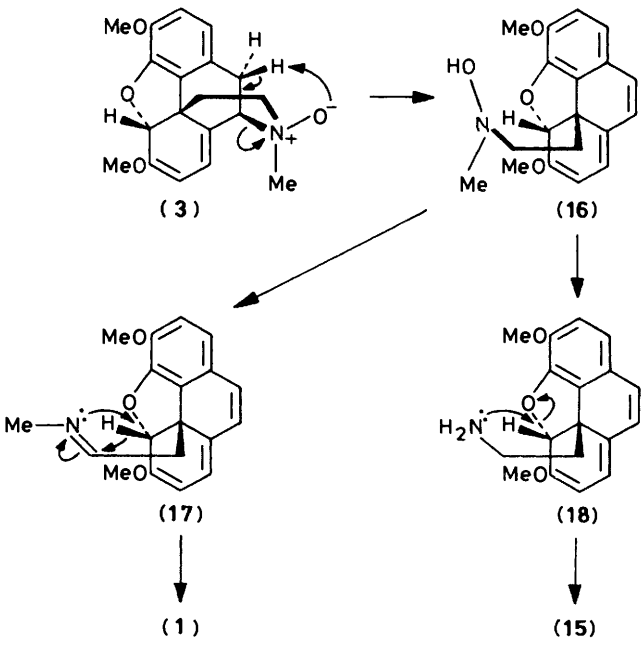
In order to discuss the possible mechanisms of formation of compounds (**1**) and (**15**), the steric orientation of the *N*-methyl group and N–O dipole in the 'major isomer' of the thebaine *N*-oxides must be determined first. Ring D of the thebaine *N*-oxides will preferentially assume the chair conformation, because of interference of the N-17 substituent (regardless of whether it is methyl or oxygen) with 10-H_β in the boat conformation. The interatomic distances, estimated from Dreiding models (Table 2), are given for the compounds having ring D in the chair conformation.

The estimated interatomic distances in the thebaine *N*-oxides indicate that the C-8–C-14 double bond must be polarized to a

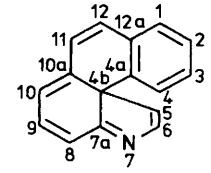
larger extent in the thebaine *N*-oxide isomer (**3**) than in isomer (**4**). Hence, the C-8 hydrogen resonance of (**3**) will appear downfield from the corresponding resonance of (**4**). Accordingly, structure (**3**) is the structure of the isomer designated in the literature as the 'major isomer'.[6] The structural assignments of these compounds in the literature (ref. 6) therefore are erroneous. The *N*-methyl group in morphinan *N*-oxide isomers, found mostly downfield in ^{1}H n.m.r. spectra, will be the *N*-methyl group of the isomer having the highest degree of steric interference with 10-H_β. Such an *N*-methyl group will be in the N-17_{eq} position with ring D in the chair form, and in the N-17_{ax} position when the boat form would be preferred. For quaternary morphinans the chair form generally will be the conformation preferred, because of reduced steric interference of the nitrogen substituents with 10-H_β. The assignments of the structures of the codeine and morphine *N*-oxide pairs[6] were based on the assignments of the structures of the thebaine *N*-oxides. Consequently, the new assignments for the latter compounds compel a reversal of the assignments of the former.

The explanation for the striking difference in stability of the two *N*-oxides of thebaine (see Experimental section) is most likely to be found in the steric orientation of the oxygen atom attached to nitrogen. In the thebaine *N*-oxide 'major isomer' (**3**), the oxygen atom is very near to 10-H_β. The interatomic 10-H_β–N-17_{eq}–oxygen distance is estimated from Dreiding models at 0.24 nm. The Van der Waals radii being 0.12 nm (H) and 0.14 nm (O), this spatial arrangement makes the 10-H_β hydrogen atom available for a *cis* amine oxide elimination. The electron deficiency at the nitrogen atom increases the acidity of protons in a β-position with respect to nitrogen. The *cis* amine oxide elimination (Cope reaction) is known to be a both photochemically and thermally catalysed process. A similar reaction for the other isomer, (**4**), is sterically unfavourable, because inversion at a quaternary nitrogen atom is not a normally occurring process. The first product of the decomposition of (**3**) therefore will be the hydroxylamine (**16**). This intermediate will eliminate water, resulting in compound (**17**). In the latter compound a hydride transfer from C-5 is facilitated by the high stability of the resulting carbocation. So, a hydride transfer to the C-16–N double bond, with nucleophilic attack of the nitrogen lone pair on the C-5 carbon atom, may yield compound (**1**). This series of reactions effectively is the abstraction of water from the *N*-oxide (**3**) (Scheme 4). The other product, (**15**), is presumably formed from the hydroxylamine intermediate (**16**) by conversion of the latter into the *N*-nor compound (**18**), followed by nucleophilic attack of the secondary amine on the C-5 carbon, with concomitant opening of the C-5–oxygen bond. The latter process must involve an inversion of the configuration at C-5 (see Scheme 4).

The existing systematic nomenclature prescribes for compounds (**1**) and (**15**) names which are derived from naphth[1,2-*d*]indole. The latter compound unfortunately has a numbering system which is completely different from the one used in the morphinan alkaloid field. Existing trivial names in this class being not easily adaptable for the description of both new compounds (**1**) and (**15**), it is considered useful to propose a new systematic nomenclature for compounds belonging to the class of the compounds (**1**) and (**15**), and thebaicyclomethine (**8**). Because all compounds hitherto known are derived from thebaine, the name for the basic skeleton of this class is also derived from that compound: thebinan (Figure). Using thebinan as a basis, the carbons of the original morphinan nucleus retain their numbering, and the suffixes adhering to the numbering of the naphth[1,2-*d*]indole system are avoided. Rings A, B, C, and D retain their names in the thebinan nomenclature. In the new nomenclature, compounds (**1**) and (**15**) will have the names 6,7,8,9,10,14-hexadehydro-4,5-epoxy-3,6-dimethoxy-17-methylthebinan (**1**) and 6,7,8,9,10,14-hexadehydro-3,6-dimethoxythebinan-4-ol (**15**). For the hitherto unknown pentacyclic ring system of compound (**1**) the name is analogous to those usual for the pentacyclic morphinan derivatives.



Scheme 4.



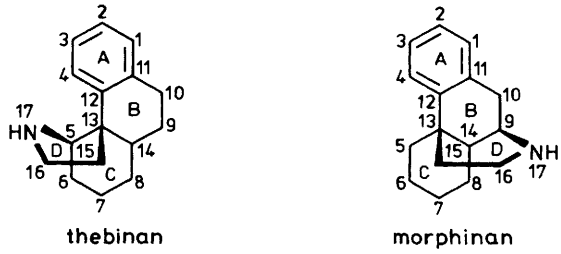


Figure.

Experimental

G.c.–m.s. was carried out using a Carlo Erba GLC–Kratos MS 80 combination of gas chromatograph–mass spectrometer, connected to a Kratos DS 55 data system. Electron-impact spectra were recorded at 70 eV. ^{1}H N.m.r. spectra were recorded at 90 MHz with a Varian EM 390 spectrometer (unless stated otherwise). Tetramethylsilane was internal standard (δ 0). The ^{1}H n.m.r. spectra of compounds (**1**) and (**15**) were recorded at 200 MHz using a Bruker WP 200 spectrometer. ^{13}C N.m.r. spectra were recorded at 20 MHz in deuteriochloroform solution (unless stated otherwise) on a Varian CFT-20 spectrometer. The spectra of compounds (**1**) and (**15**) were recorded at 50 MHz using a Bruker WP 200 instrument. Chemical shifts are

given with respect to deuteriochloroform (δ 76.9 p.p.m.). U.v. spectra were recorded in dichloromethane solution with a Perkin-Elmer 555 u.v.–vis. spectrophotometer. I.r. spectra were recorded in KBr disks on a Perkin-Elmer 297 infrared spectrophotometer. G.l.c. was carried out using a Pye Series 104 gas chromatograph, equipped with a flame ionization detector, using on-column injection and glass columns, packed with 3% OV-17 on Chrompack SA (80—100 mesh), operating at 270 °C. For g.l.c. retention times thebaine was chosen as a reference (RR_t 1.00). T.l.c. was performed on silica gel GF_{254} plates, using ethyl acetate–diethylamine (19:1) (system a), benzene–acetone–methanol (7:2:1) (system b), and chloroform–methanol (7:3) (system c). Alkaloid detection was accomplished using u.v. light (254 nm) and iodoplatinate spray reagent. M.p.s were determined on a Kofler hot-stage, and have been corrected.

Isolation of Compound (**1**) *from* P. bracteatum, *cv.* '*Arya I*' *Capsules.*—Counter-current fractions 97—127 (2.55 g)[2a] were repeatedly crystallized from methanol–diethyl ether, yielding alpinigenine (1.31 g). The mother liquors were separated on an alumina column (W 200 neutral, activity III, 50 g), eluted with n-heptane–chloroform (5:2; saturated with water). In the fractions first eluted an alkaloid was detected, having an orange-red colour in t.l.c. Preparative t.l.c., first using alumina plates (type E) with chloroform–n-heptane–diethyl ether (5:4:1), and then using silica gel plates with solvent system b, afforded the pure product (**1**) (4.3 mg).

Isolation of both Thebaine N-*Oxides from* P. bracteatum, *cv.* '*Arya II*' *Capsules.*—Pulverized capsules of *P. bracteatum*, cv. 'Arya II', grown in the gardens of the Agricultural University at Wageningen, The Netherlands, were extracted by agitation with benzene–butan-1-ol (1:1), after wetting with 10% aqueous K_2CO_3. The solvents were removed under reduced pressure below 40 °C, and the residue was dissolved in 0.1 M aqueous HCl. Extraction of this solution with n-hexane removed apolar neutral materials (1.1% of dry weight of capsule tissue). The pH of the acidic solution was then adjusted to 11—12 using 1M aqueous NaOH, after addition of ice, and the mixture was extracted using chloroform. Evaporation of the solvent afforded the non-phenolic alkaloid fraction (2.2% of dry weight of capsule tissue). A phenolic fraction (0.3% of dry weight) was obtained by chloroform–propan-2-ol (3:5) extraction after adjustment of the pH of the aqueous solution to 8.9. The latter fraction, however, consisted mainly of thebaine. Chromatography on alumina (W 200 neutral, activity III) with benzene–acetic acid (39:1) first yielded thebaine, followed by thebaine *N*-oxide 'major isomer' (0.004% of dry weight), and finally the 'minor isomer' (0.013% of dry weight). The non-phenolic alkaloid fraction was submitted to column chromatography on silica gel, eluted with chloroform–methanol (7:3). First thebaine was eluted, and then successively the two thebaine *N*-oxides: the 'major isomer' (0.011% of dry weight), and the 'minor isomer' (0.025% of dry weight). Both compounds were identified by ^{1}H n.m.r. spectroscopy and t.l.c. The so-called 'major isomer' proved to be highly unstable, which may account for the low yields mentioned above. A t.l.c. analysis of the fractions had shown that the quantities of the two isomeric *N*-oxides contained in those fractions were comparable.

Synthesis of both Thebaine N-*Oxide Isomers.*—This synthesis was performed as outlined in the literature.[6] In t.l.c. analysis of the reaction mixture no decomposition was observed. When the spot of the 'major isomer' was removed from the t.l.c. plate, and eluted with methanol, t.l.c. analysis of the product, immediately following evaporation of the solvent at low temperature, showed no decomposition either. Upon simultaneous immediate ^{1}H n.m.r. analysis, however, the samples always showed considerable decomposition. T.l.c. analysis of the contents of the n.m.r. tubes after the recording of the ^{1}H n.m.r. spectrum confirmed this observation. The so-called 'major isomer' was detected in minor amounts in these mixtures. Its ^{1}H n.m.r. data were in agreement with literature data.[6] The so-called 'minor isomer' was stable under these conditions. Its ^{1}H n.m.r. analysis was in full agreement with literature data.[6]

Thebaine *N*-oxide 'minor isomer' (**4**). G.c.–m.s. *m/z* 327 (M^+, 0.5%), 312 (22), 311 (100), 297 (11), 296 (53), 254 (11), 239 (12), and 139 (11); M.s. (probe) *m/z* 327 (M^+, 7%), 312 (17), 311 (66), 309 (47), 296 (15), 294 (13), 268 (12), 255 (42), 254 (100), 240 (15), 239 (57), 225 (13), 211 (16), 152 (12), 139 (15), and 127 (12).

Preparation of the two Decomposition Products (**1**) *and* (**15**).—Thebaine (2 g) was treated for 18 h with hydrogen peroxide, according to the literature method.[6] The crude products were analysed by t.l.c. (system c). Only a trace of thebaine was detected, next to the two *N*-oxides. The *N*-oxide with the higher R_F value, (**3**), was somewhat more intense than the other one [(**4**)]. The product mixture was submitted to rapid column chromatography on silica gel using chloroform–methanol (7:3). First a trace of thebaine was eluted, and the *N*-oxide with the higher R_F value, (**3**), was eluted within 2 h. The fractions containing the latter compound were evaporated at low temperature, and stored for 18 h at 5 °C T.l.c. analysis then already showed some decomposition. The latter compound, on being refluxed in chloroform, gave the desired product (**1**). Next to this compound several other products were observed, including the other major decomposition product (**15**). The *N*-oxide with the lower R_F value, (**4**), proved to be resistent to heat in chloroform or methanol. The decomposition products were chromatographed on a silica gel column, eluted with chloroform, followed by chloroform–methanol mixtures (1—2%). The first fractions contained some materials with high R_F values, which were discarded. Next compound (**15**) was eluted, followed by mixtures of the latter compound with compound (**1**). The weight of these fractions was 0.663 g. Fractions, containing mainly (**1**), were best purified by crystallization from methanol, in which (**1**) proved to be practically insoluble, while (**15**), and minor contaminants, were very soluble. The yield of 6,7,8,9,10,14-*hexadehydro*-4,5-*epoxy*-3,6-*dimethoxy*-17-*methylthebinan* (**1**) was 0.286 g, m.p. 174—175 °C; $\lambda_{max.}$(CH_2Cl_2) 272, 306, and 376 nm (ε 8 800, 3 800, and 4 200 $dm^3\ mol^{-1}\ cm^{-1}$); $\lambda_{max.}$(CH_2Cl_2 + CF_3CO_2H) 326 and 496 nm (ε 7 700 and 1 500 $dm^3\ mol^{-1}\ cm^{-1}$); $\nu_{max.}$ 1 570 and 1 219 cm^{-1}; δ_H (200 MHz; $CDCl_3$) 2.10 (1 H, m), 2.44 (1 H, m), 2.66 (1 H, m), 2.80 (1 H, m), 2.8 (1 H, br s, ½ H_2O), 2.98 (3 H, s, NCH_3), 3.70 and 3.86 (each 3 H, s, OCH_3), 5.13 (1 H, d, *J* 7 Hz, 7-H), 5.65 (1 H, d, *J* 7 Hz, 8-H), 6.19 (1 H, d, *J* 10 Hz, part of AB-pattern, 9-H), 6.34 (1 H, d, *J* 10 Hz, part of AB-pattern, 10-H), and 6.58 (2 H, 2 d, *J* 8 Hz, AB-pattern for 1-H and 2-H). Upon computer simulation of the pattern of the ethanamine protons, excellent matching was obtained using the parameters δ 2.10 (H^D), 2.44 (H^C), 2.66 (H^B), and 2.80 (H^A), having J_{AB} 8.7, J_{AD} 7.2, J_{BC} 4.9, J_{BD} 12.0, and J_{CD} 12.0 Hz; δ_H (90 MHz; CF_3CO_2H) 2.90 (2 H, m), 3.87 (3 H, s, NCH_3) 3.95 (6 H, s, 2 OCH_3), 3.5—4.4 (2 H, m), 6.09 (1 H, d, $w_{\frac{1}{2}}$ 1.8 Hz, *J* 7.2 Hz, 8-H), 6.31 (1 H, d, $w_{\frac{1}{2}}$ 2.1 Hz, *J* 9.9 Hz, 10-H), 6.47 (1 H, d, $w_{\frac{1}{2}}$ 1.1 Hz, *J* 9.9 Hz, 9-H), 6.52 (1 H, d, $w_{\frac{1}{2}}$ 2.3 Hz, *J* 7.2 Hz, 7-H), and 6.81 (2 H, s, 1-H and 2-H); *m/z* 309.1365 (M^+; $C_{19}H_{19}NO_3$ requires *M*, 309.1365); m.s. (probe) *m/z* 310 (22%), 309 (M^+, 100), 295 (13), 294 (60), 279 (31), 266 (30), 251 (19), 250 (12), 235 (13), 234 (11), and 222 (14); g.c.–m.s. *m/z* 310 (17%), 309 (M^+, 100), 294 (15), 293 (13), 292 (82), 266 (12), 251 (23), 250 (17), 236 (20), 207 (12), and 139 (11).

In preparative t.l.c. of the mother liquors on silica gel with ethyl acetate–triethylamine (19:1), 6,7,8,9,10,14-*hexadehydro*-3,6-*dimethoxythebinan*-4-*ol* (**15**) was isolated as a brownish oil (0.134 g), δ_H (200 MHz; $CDCl_3$) 2.06 (1 H, m), 2.23

(1 H, m), 2.92 (1 H, m), 3.16 (1 H, m), 3.71 and 3.88 (each 3 H, s, OCH_3), 4.89 (1 H, s, $w_{\frac{1}{2}}$ 3 Hz, 5-H), 5.30 (1 H, dd, *J* 1, 7 Hz, 7-H), 5.79 (1 H, d, *J* 7 Hz, 8-H), 6.20 and 6.31 (each 1 H, d, AB-pattern, *J* 9 Hz, together 9- and 10-H), and 6.58 and 6.72 (each 1 H, d, AB-pattern, *J* 8 Hz, together 1- and 2-H). Upon computer simulation of the pattern of the ethanamine hydrogens excellent matching was obtained using the parameters δ 2.06 (H^D), 2.23 (H^C), 2.92 (H^B), and 3.16 (H^A), having J_{AB} 9.2, J_{AC} 8.1, J_{AD} 7.2, J_{BC} 5.3, J_{BD} 10.0, and J_{CD} 12.8 Hz; g.c.–m.s. *m/z* 255 (17%), 254 (*M* −43, 100), 240 (11), 239 (66), 211 (14), 196 (7), 168 (11), 152 (9), 140 (8), 139 (17), and 127 (12) (this spectrum is identical with that of α-thebaol); m.s. (probe): in addition to the mass spectrum obtained by g.c.–m.s., an ion was observed at *m/z* 297 (M^+, 9%).

Synthesis of the Methiodide of Compound (**1**).—Compound (**1**) was converted into its methiodide salt by dissolution in excess of methyl iodide, and gently warming the mixture at 30 °C for a few minutes, whereupon the precipitated methiodide (needles) was collected, m.p. 172—173 °C; δ_H (90 MHz; $CDCl_3$) 2.6—3.8 (3 H, m), 3.46 and 3.83 (each 3 H, s, NCH_3), 3.85 and 3.89 (each 3 H, s, OCH_3), 4.8 (1 H, m), 5.81 (2 H, s, 7- and 8-H), 6.25 and 6.45 (each 1 H, d, AB-pattern, *J* 10 Hz, together 9- and 10-H), and 6.75 (2 H, A_2-pattern, *J* 9 Hz, 1-and 2-H).

Attempted Hydrolysis of the Enol Ether Function of Compound (**1**).—(*a*) A solution of compound (**1**) (24 mg) in 2M aqueous hydrochloric acid (1 ml) was stirred for 1 h at room temperature, and then heated at 96 °C for 135 min. The still cherry-red solution was treated with conc. aqueous ammonia, and extracted with chloroform. The extract was dried over sodium sulphate, and concentrated under reduced pressure. ^1H N.m.r. and t.l.c. analysis showed that the yellow compound (**1**) was recovered completely unchanged.

(*b*) A solution of compound (**1**) (23 mg) and toluene-*p*-sulphonic acid (29 mg) in water (1 ml) and dioxane (1 ml) was refluxed for 24 h. After work-up as given above, t.l.c. analysis of the product showed the presence of only pure (**1**).

Chromatographic Data.—G.l.c. data. (**1**) RR_t 1.14; (**2**) RR_t 1.00; (**15**) RR_t 0.93. *T.l.c. data*: R_F values. (**1**) a, 0.47; b, 0.50; c, 0.49; (**2**) a, 0.32; b, 0.23; c, 0.46; (**3**) a, 0.03; b, 0.12; c, 0.25; (**4**) a, 0.01; b, 0.04; c, 0.15; (**15**) a, 0.77; b, 0.08; c, 0.63.

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