Alpinigenine from *Papaver bracteatum* Lindl. Restricted Rotation in an Unusual Oxidation Product

By **David Lavie,* Hana Berger-Josephs, Tamar Yehezkel, Hugo E. Gottlieb,** and **Elie C. Levy,** Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel

Alpinigenine (1) was isolated in relatively large amount from a type of *Papaver bracteatum* Lindl. from Iran. Oxidation of this alkaloid with Jones reagent produced a lactone function and, unexpectedly, converted the NMe into an NCHO, present as a mixture of rotamers. Crystallization afforded one pure component, which equilibrated in solution within 2 h. ^{13}C N.m.r. spectroscopy was used to confirm these results and enabled an insight into the conformation in solution of the seven-membered rings in alpinigenine and its oxidation product. *X*-Ray analysis determined unambiguously the absolute configuration of alpinigenine.

For many years a world-wide attempt, co-ordinated by the United Nations Narcotic Laboratory in Geneva, has been under way in order to develop the poppy *Papaver bracteatum* Lindl. as a source of thebaine.[1] This compound is known to be present in certain populations in up to 98% of the total alkaloid content.[2] Thebaine can easily be converted into codeine, an analgetic which is widely used in medicine. These attempts led to extensive studies, chemical and biosystematic, on this and other species of the genus Oxytona. A number of different varieties and types came under study from plants collected in Iran. In certain of these types of *P. bracteatum*, as well as predominant quantities of thebaine, the alkaloid alpinigenine was isolated in larger amounts (*ca.* 15% of the mixture). However, it was also noted that alpinigenine is present, and could be detected in most varieties, in trace amounts only.[3]

RESULTS AND DISCUSSION

The relative configuration of alpinigenine has been for several years, the subject of controversy; however, its structure is now well established.[4] A number of papers refer to the absolute configuration based on c.d. studies and correlations with known structures.[5] When this study was initiated in our laboratories, an unequivocal assignment of the absolute configuration of alpinigenine was essential, and an *X*-ray diffraction study was performed on a single crystal (Figure). The absolute configuration was determined by anomalous scattering of N and O atoms, by D. Rabinovich and Y. Halfon of this Institute. Full details will be published separately. Thus, the structure shown in (1) is confirmed.

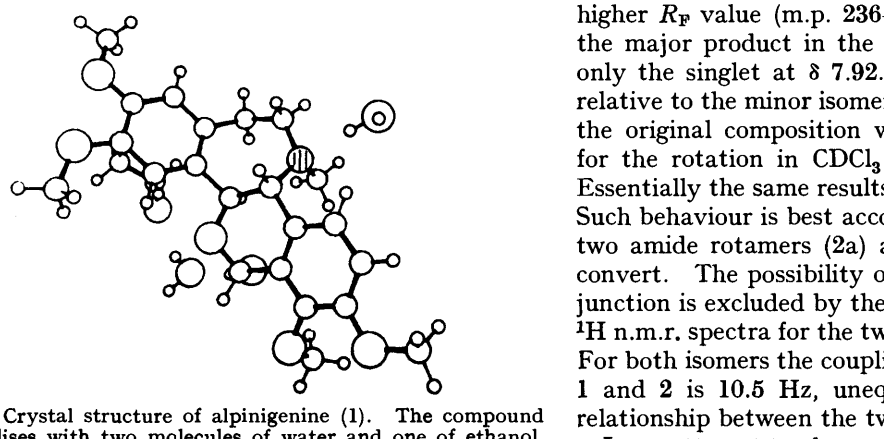
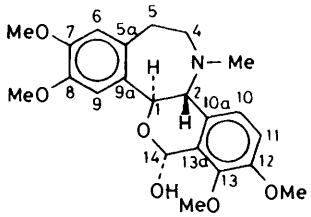
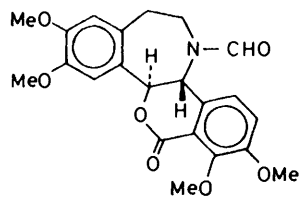


Figure Crystal structure of alpinigenine (1). The compound crystallises with two molecules of water and one of ethanol. Oxygen atoms are drawn as slightly larger circles and the nitrogen atom is hatched



(1)



(2)

During degradation studies on this alkaloid, an unusual product was obtained from the oxidation with Jones reagent. Together with the expected conversion of the lactol into the lactone at C-14 ($\nu_{max.}$ 1 745 cm^{-1}), a formamide group was produced from the NMe function ($\nu_{max.}$ 1 675 cm^{-1}). Careful t.l.c. inspection indicated the presence of two close spots. Indeed, in the ^1H n.m.r. spectrum of the reaction product, two singlets at δ 7.92 and 8.17 for a formamide proton (N–C*H*O) were observed in the ratio 65 : 35. Analysis of the mass spectrum of this mixture showed a molecular-ion peak $M^{+\cdot}$ 413 in accordance with structure (2).

Crystallization of the oxidation product mixture from hot methanol provided one isomer only, the one with higher R_F value (m.p. 236—236.5 °C) corresponding to the major product in the original mixture and having only the singlet at δ 7.92. As time passes, the peaks relative to the minor isomer start to build up, and in 2 h the original composition was re-formed. The half-life for the rotation in $CDCl_3$ solution is *ca.* 15—20 min. Essentially the same results are obtained in [$^2H_6$]DMSO. Such behaviour is best accounted for by the presence of two amide rotamers (2a) and (2b) which slowly interconvert. The possibility of epimerization to a *cis* ring-junction is excluded by the full analysis of the 270-MHz ^1H n.m.r. spectra for the two rotamers shown in Table 1. For both isomers the coupling constant between protons 1 and 2 is 10.5 Hz, unequivocally showing the *trans* relationship between the two hydrogens.

In an attempt to observe signal coalescence, the [$^2H_6$]-DMSO solution of the equilibrated mixture was heated up

TABLE 1

^{1}H N.m.r. data [a]

Proton	(2a) [b]	(2b) [b]	(2a) [c]	(2b) [c]
1	5.51	5.44	5.78	5.79
2	4.56	5.47	4.95	5.19
6	6.68	6.66	6.81	6.84
9	7.28	7.28	7.09	7.06
10	6.92	6.75	6.88	6.79
11	7.18	7.13	7.42	7.38
N–CHO	7.92	8.17	7.95	8.17
Ar–OMe	4.04	4.03	3.87	3.86
	3.95	3.95	3.85	3.85
	3.93	3.91	3.80	3.80
	3.86	3.87	3.73	3.75

[a] $J_{1,2}$ 10.5, $J_{10,11}$ 8.5, and $J_{2,10}$ 1 Hz in every case. [b] $CDCl_3$ solutions, p.p.m. from internal $SiMe_4$. [c] [$^2H_6$]Dimethyl sulphoxide solutions, with the solvent (δ 2.49) taken as an internal standard.

to 120 °C, but no broadening was observed in any signal. This is, however, not unexpected, since the very slow interconversion of the rotamers (with a time-scale of *ca.* 10^3 s, see above) would not be speeded to a rate leading to coalescence (*ca.* 10^{-1}—10^{-2} s) by such a temperature change.

The attribution of structures (2a) and (2b) to the major and minor rotamers, respectively, results from the ^{1}H and the ^{13}C n.m.r. data. Thus, H-2 absorbs at very low field in the minor isomer due to its location in the carbonyl deshielding cone; conversely, in the major isomer H-4β (equatorial) is located in an approximately equivalent position and appears as a multiplet (total width 27 Hz) at δ 4.48 in the $CDCl_3$ solution. No other proton on carbons 4 and 5 in either rotamer absorbs at lower field than the methoxy-groups. Another diagnostic feature is the formamide proton signal, which is *ca.* 0.8 Hz wider in the major than in the minor isomer, a result of *W*-type coupling with H-4α (axial). No proton is in such favourable orientation in structure (2b).

In order to interpret the ^{13}C n.m.r. data of the oxidation products, it is necessary to assign the spectrum of alpinigenine (1), a task which was aided by the analysis of single-frequency off-resonance decoupled (SFORD) spectra, including long-range and second-order couplings, and a correlation to the ^{1}H n.m.r. signals,[6] as well as by comparison with appropriate models.[7]

The ^{13}C chemical shifts (see Table 2) indicate that there are no significant conformational differences between the solid state and the solution. Thus, the axial orientation of the N–Me group is shown by the high-field location of the signals of the three carbons involved in γ-interactions, *i.e.* C-1, C-5, and N–Me itself (δ 33.7 compared to δ 42.2 in laudanosine [7]).

The nitrogen-containing ring of alpinigenine can be compared to that of tetrahydropalmatine,[7] if one takes into account that in the former alkaloid it is seven-membered while in the latter it is six-membered. A comparison of tetralin with benzocycloheptene [8] shows that in the latter hydrocarbon, the benzylic centre is deshielded by *ca.* 7 and the carbon β to the benzene ring by *ca.* 5 p.p.m., relative to the former.

In agreement with the above-mentioned argument, the C-4 signal is situated 4.7 p.p.m. to lower field in alpinigenine than its counterpart in tetrahydropalmatine. However, the benzylic methylene has a similar shift in both compounds (δ 31.1 and 29.0). This indicates that the expected 7 p.p.m. downfield effect of the ring enlargement is counterbalanced by the γ-interactions with C-1 and the *N*-methyl group. C-1 is also shielded by the axial lactol hydroxy-function. This configuration also implies the shielding of the lactol carbon by the C-13 methoxy-group.

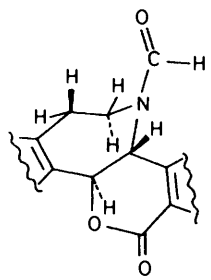
Concerning the ^{13}C spectrum of the oxidation reaction product mixture, two sets of signals in a *ca.* 2 : 1 ratio can be observed. The time necessary to run the ^{13}C n.m.r. spectrum precludes the possibility of observing the pure major component, obtained by crystallization, as in the case of the ^{1}H n.m.r. spectrum. As seen in Table 2, the shifts of all the carbons are quite similar, except for those of C-2 and C-4.

TABLE 2

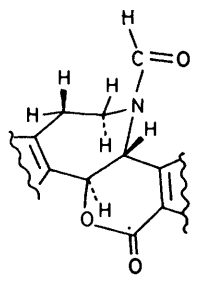
^{13}C N.m.r. data [a]

Carbon	(1) [b]	(2a)	(2b)
1	62.8	77.9	78.2
2	61.8	60.7	54.9
4	56.0	35.3	40.2
5	31.1	31.4	32.4
5a	131.7	131.6	130.7
6	113.2	113.9	113.5
7	146.9 [c]	*d*	*d*
8	147.1 [c]	*d*	*d*
9	108.6	107.3	107.7
9a	135.7	134.9	135.7
10a	128.4	125.5 [c]	126.6 [c]
10	124.6	118.7	118.4
11	113.5	117.5	117.5
12	150.8	154.3	154.0
13	144.8	*d*	*d*
13a	131.0	125.8 [c]	124.5 [c]
14	87.6	160.6	160.4
N–Me	33.7		
N–CHO		163.7	163.9
13-OMe [e]	61.2	61.8	61.8

[a] The chemical shifts are for $CDCl_3$ solutions, in δ from internal $SiMe_4$. [b] A few drops of MeOH were added to improve solubility. [c] Signals in the same column may be interchanged. [d] Signals between δ 148 and 149. [e] Other OMe signals between δ 56.0 and 56.4.



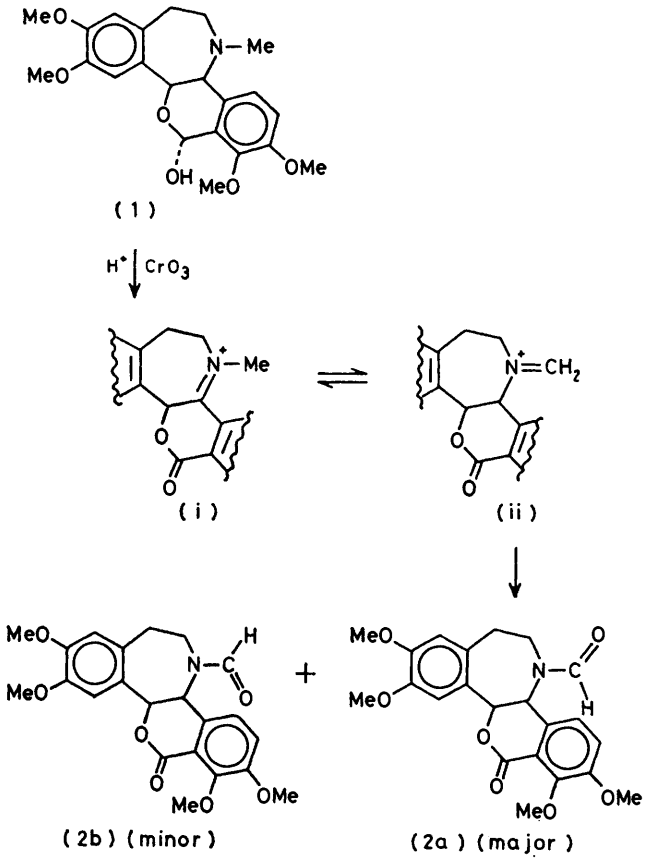
(2a) (major)



(2b) (minor)

In the major component (2a) the signal for C-2 is more deshielded by *ca.* 5 p.p.m., and the signal for C-4 is *ca.* 6 p.p.m. more shielded, than in the minor component (2b). These facts suggest that in (2a) the C=O group of the formamide function is pointing towards C-4, thus causing a γ-effect on this carbon. In the minor component, the C=O is pointing toward C-2 thus inducing the

shielding γ-effect. Since γ-effects are transmitted to sp^3-hybridized carbons through C–H bonds, this implies a proximity of the C=*O* and H-2 atoms that exists only if the conformation of the N-heterocyclic seven-membered ring is a boat, as shown in (2b). However, the C-5 shift



is almost identical to that observed in alpinigenine. For this to occur, the conformation of the seven-membered ring must be such that the C-5 and *N*–CHO group are *gauche*. In this case C-4 is now *gauche* to C-1, having a signal at a very high field. This can be seen also by comparison with the value for C-4 in alpinigenine (this upfield shift may be to a small extent due to formation of the amide). Similarly the C-1 signal was shifted downfield (*ca.* 15 p.p.m. lower than in alpinigenine). Again, only a small part of this deshielding can arise from the electronic influence of the lactone compared to the lactol. It is mostly due to steric reasons; C-1 has lost a γ-effect from the C-14-OH group, as well as from the NMe group, and gained a γ-effect from C-4. Among the aromatic methines, C-11 is deshielded by conjugation with the *para*-lactonic carbonyl group, while C-10 is shielded by a γ-effect from the N atom that was absent in alpinigenine (1).[9]

The formation of such an *N*-formyl derivative from alpinigenine can be best explained as shown in the Scheme, *via* a benzylic oxidation to an immonium salt such as (i) which by tautomerization into (ii) followed by addition of water and further oxidation, would lead to the observed products.

Interestingly other *N*-methylated alkaloids such as thebaine, isothebaine, codeine, and protopine failed to produce a formamide when oxidized in a similar way.

EXPERIMENTAL

M.p.s were recorded on a Fisher–Johns apparatus and are uncorrected. Optical rotations were taken on an automatic Perkin-Elmer 141 polarimeter and refer to chloroform solutions. I.r. spectra were measured on a Perkin-Elmer Infracord 137 spectrophotometer in KBr pellets. ^{1}H and ^{13}C N.m.r. spectra were recorded with Bruker WH 270 (at 270 MHz) and WH 90 (at 22.6 MHz) instruments, respectively. T.l.c. was performed on chromatoplates on alumina (DC-Al_2O_3 F, Merck), and eluted with toluene–acetone–ethanol–6N ammonia (20 : 20 : 4 : 1). Mass spectra were taken on an improved Atlas CH-4 instrument under the direction of Dr. Z. Zaretskii.

Isolation of Alpinigenine (1).—Finely powdered *Papaver bracteatum* capsules (1.5 kg, a batch collected in the Polour region in Iran in 1973 through the help of Prof. I. Lalezari) were soaked in 1.25% ammonia and extracted with benzene (5 l). The residue from the filtrate was treated with light petroleum whereby a solid crystalline mass separated (24 g). The solid was dissolved in hot ethanol, decolourized with charcoal, and reduced to about half its volume. Two crops of thebaine were first collected (13.1 g), m.p. 193—195 °C. The ethanolic mother-liquors, as well as a crystalline material which separated by concentration of the petroleum filtrate, were subjected to fractional crystallizations, which yielded an additional 1.1 g of pure thebaine and a total of 2.6 g of alpinigenine, m.p. 188 °C, $[\alpha]_D$ +228° (*c* 1%). A number of mixture crops, containing appreciable amounts of both alkaloids, were left unresolved. T.l.c. R_F 0.35 (thebaine), R_F 0.55 (alpinigenine). ^{1}H N.m.r. of alpinigenine: δ 7.36 (1 H, d, *J* 8.5 Hz, H-10), 7.25 (1 H, s, H-9), 6.97 (1 H, d, *J* 8.5 Hz, H-11), 6.75 (1 H, s, H-6), 6.47 (1 H, s, H-14), 5.86 (1 H, d, *J* 8.5 Hz, H-1), 4.07 (1 H, d, *J* 8.5 Hz, H-2), 3.93 (3 H, s, OMe), 3.86 (9 H, s, 3 × OMe), 3.4—3.2 (4 H, m, H-4 and H-5), and 2.35 (3 H, s, NMe).

Oxidation of Alpinigenine to (2).—Alpinigenine (1) (900 mg) was dissolved in acetone (70 ml) and Jones reagent (CrO_3–H_2SO_4, *ca.* 3 ml) was added at room temperature while stirring. After the usual work-up, the aqueous solution was extracted with chloroform, dried over sodium sulphate, filtered, and passed through an alumina plug to remove traces of chromium salts. Evaporation of the solvent left a residue (750 mg) which crystallized from hot methanol, m.p. 263—263.5 °C; $[\alpha]_D$ +146.3° (*c* 1%); $\nu_{max.}$ 1 745s and 1675s cm^{-1} (Found: $M^{+\cdot}$, 413.4273. $C_{22}H_{23}O_7N$ requires *M*, 413.4285); ^{1}H n.m.r., see Table 1; *m/e* 413 ($M^{+\cdot}$, 100%), 385 (24%), 384 (50%), 368 (27%), 206 (31%), 193 (43%), 192 (31%), 191 (38%), 178 (21%), 165 (26%), and 164 (23%).

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REFERENCES

[1] U. Nyman and J. G. Bruhn, *Planta Med.*, 1979, **35**, 97.
[2] D. Neubauer and K. Mothes, *Planta Med.*, 1963, **11**, 387.
[3] P. Goldblatt, *Ann. Mo. Bot. Gard.*, 1974, **61**, 264.
[4] M. Maturova, H. Potesilova, F. Santavy, A. D. Cross, V. Hanus, and L. Dolejs, *Coll. Czech. Chem. Commun.*, 1967, **32**, 419; A. Guggisberg, M. Hesse, H. Schmid, H. Böhm, H. Rönsch, and K. Mothes, *Helv. Chim. Acta*, 1976, **50**, 621; I. Lalezari, A. Shafiee, and P. Nasseri-Nouri, *J. Pharm. Sci.*, 1973, **62**, 1718.
[5] A. Guggisberg, M. Hess, and H. Schmid, *Helv. Chim. Acta*, 1977, **60**, 2402.
[6] H. E. Gottlieb, *Isr. J. Chem.*, 1977, **16**, 57.
[7] E. Wenkert, B. L. Buckwalter, I. R. Burfitt, M. J. Gasic, H. E. Gottlieb, E. W. Hagaman, F. M. Schell, and P. M. Wovkulich, in ' Topics in Carbon-13 NMR Spectroscopy,' ed. G. C. Levy, Wiley–Interscience, New York, 1976, Vol. 2.
[8] G. W. Buchanan and R. H. Wightman, *Can. J. Chem.*, 1973, **51**, 2357.
[9] For an early report of a ^{13}C n.m.r. study on the hindered rotation of amides, see G. C. Levy and G. L. Nelson, *J. Am. Chem. Soc.*, 1972, **94**, 4897.