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(+)-SALUTADIMERINE: A DIMERIC MORPHINANDIENONE ALKALOID

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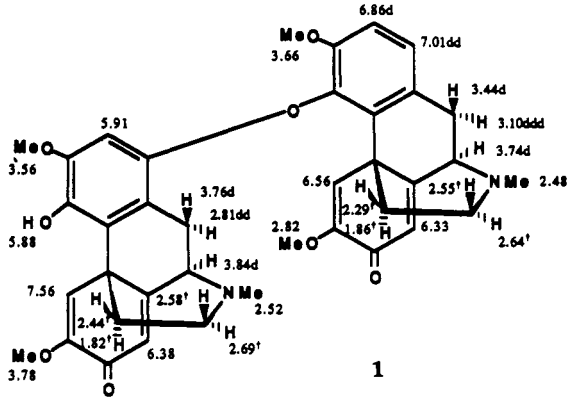
ABSTRACT.—(+)-Salutadimerine [**1**], the first reported dimeric morphinandienone alkaloid, has been found in Turkish *Papaver pseudo-orientale* and *Papaver lasiothrix*.

A hitherto notable feature of the morphinandienone alkaloids has been that they were always obtained as strictly monomeric species (1,2). We now describe the alkaloid (+)-salutadimerine [**1**], which is the first dimeric morphinandienone and is most probably formed biogenetically by oxidative coupling of two (+)-salutaridine entities.

Amorphous (+)-salutadimerine [**1**], $C_{38}H_{40}N_2O_8$, was found in *Papaver pseudo-orientale* Fedde (Medw.) and *Papaver lasiothrix* Fedde (Papaveraceae), both of Turkish origin.

The mass spectrum showed molecular ion *m/z* 652, which was also the base peak. This large molecular ion was accompanied by an $[M]^{++}$ *m/z* 326 peak, testifying to the dimeric nature of this alkaloid. The uv spectrum was that of an isoquinoline alkaloid, with λ max 284 nm (log ε 3.70). The ir spectrum displayed an absorption pattern typical of morphinandienones, with cross-conjugated carbonyl peaks at 1670, 1640, and 1620 cm^{-1} (1,2).

The ^{1}H-nmr spectrum obtained in $CDCl_3$ solution (500 MHz) was clearly indicative of a dimeric species related to (+)-salutaridine [**2**]. The two singlets at δ 2.48 and 2.52 in **1** represent the *N*-methyl group of each moiety. The proton signals of the aliphatic region in the monomeric (+)-salutaridine [**2**] spectrum can be divided into two groups, a CH-CH_2 system due to the protons at C-9 and C-10 and a CH_2-CH_2 combination for the protons at C-15 and C-16. The first of these systems is clearly char-



1

†H-15, H-16, H-15′ and H-16′ signals are ddd.

$J_{9,10\alpha} = 5.8$ Hz, $J_{10gem} = 17.8$ Hz, $J_{15gem} = 12.7$ Hz, $J_{16gem} = 12.7$ Hz, $J_{15ax,16ax} = 12.5$ Hz, $J_{15ax,16eq} = 3.0$ Hz, $J_{15eq,16ax} = 3.0$ Hz, $J_{15eq,16eq} = 3.0$ Hz, $J_{9',10'\alpha} = 6.0$ Hz, $J_{10'gem} = 17.6$ Hz, $J_{1',10'\alpha} = 1.0$ Hz, $J_{15'gem} = 12.7$ Hz, $J_{16'gem} = 12.7$ Hz, $J_{15'ax,16'ax} = 12.5$ Hz, $J_{15'ax,16'eq} = 3.0$ Hz, $J_{15'eq,16'ax} = 3.0$ Hz, $J_{15'eq,16'eq} = 3.0$ Hz.

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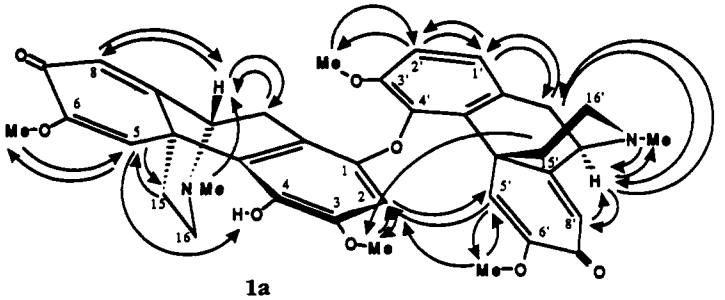
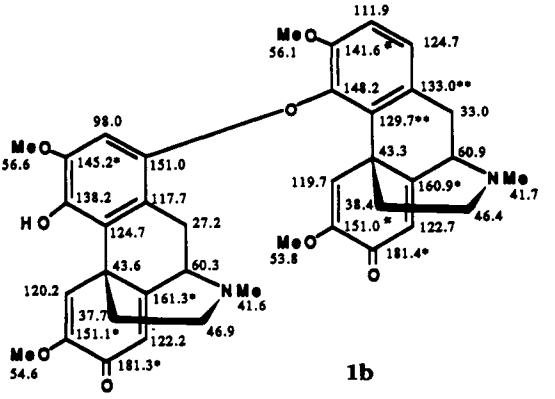


1a

acterized by a doublet for H-9 near δ 3.7 and by a doublet and a doublet of doublets of doublets (ddd) near δ 3.3 and 3.0, respectively, for the two C-10 protons. The ddd is actually due to the splitting of H-10α by H-10β (J_{gem} = 17.6 Hz), by H-9 (J = 5.6 Hz), and by H-1 (J = 1.0 Hz). As for the C-15 and C-16 protons, they are readily recognized because the pattern for each proton takes the form of a ddd. While three of these protons resonate near δ 2.5, H-15α axial appears characteristically upfield near δ 1.7.

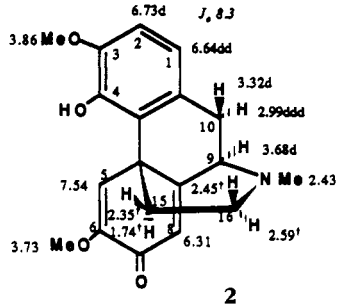
Significantly, these sets of aliphatic signals were mostly duplicated in the spectrum of (+)-salutadimerine [**1**]. But a significant difference was that H-10β axial had moved appreciably downfield to δ 3.76, whereas H-10α equatorial was now slightly upfield at δ 2.81. The signal for H-5 in salutaridine-type compounds is found typically downfield around δ 7.5, while H-8 is close to δ 6.3. For our dimer, two singlets for H-8 and H-8′ could be observed around δ 6.3, but only one singlet for H-5 was seen at δ 7.56. The H-5′ singlet was located significantly upfield at δ 6.56.

Whereas in (+)-salutaridine [**2**] the H-1 and H-2 signals appear at δ 6.64 and 6.73, in the dimer only one such set was present, at δ 7.01 and 6.86. The downfield shift of the H-1′ signal in the dimer is related to the fact that the oxygen at C-4 is now part of a diaryl ether bridge. The observation that only one aromatic AB system was in evidence in the spectrum of the dimer strongly suggested that the terminus of the diaryl ether bridge connecting the two units of the dimer was at C-1. This site, incidentally, is in a para relationship to the C-4 phenolic function and would be a logical position for phenolic oxidative coupling. In line with these observations,

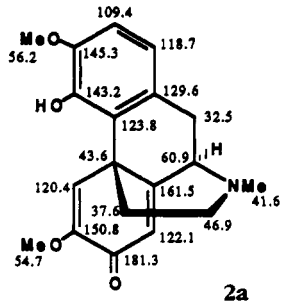


1b

*Values in one moiety are interchangeable with the corresponding values in the other moiety.
**Values are interchangeable.



2



2a

†H-15 and H-16 signals are ddd.

$J_{1,10\alpha}$ = 1.0 Hz, J_{10gem} = 17.6 Hz, $J_{9,10\alpha}$ = 5.6 Hz, J_{15gem} = 12.7 Hz, J_{16gem} = 12.7 Hz, $J_{15ax,16ax}$ = 12.7 Hz, $J_{15ax,16eq}$ = 1.9 Hz, $J_{15eq,16ax}$ = 3.2 Hz, $J_{15eq,16eq}$ = 4.6 Hz.

H-2 appeared as a singlet upfield at δ 5.91. Another point of interest was the upfield shift of the C-6′ methoxyl singlet (δ 2.82) due to shielding by ring A.

A series of nOe measurements provided not only further proof of structure for dimer **1**, but also an insight into its conformation. Some of the nOe results are indicated in diagram **1a** which also shows the approximate conformation of the dimer. Of particular importance are the reciprocating nOe's between H-2 (δ 5.91) and H-5′ (δ 6.56). Also, irradiation of the C-6′ methoxyl (δ 2.82) led to enhancement of the H-2 singlet (δ 5.91). An interesting enhancement of the C-3 methoxyl (δ 3.56) occurred upon irradiation of the H-15′ axial multiplet (δ 1.86), and indeed a molecular model indicated that the protons involved are sufficiently proximate for enhancement to take place.

The results of a ^{13}C-nmr study carried out in $CDCl_3$ have been summarized around structure **1b**. The chemical shift assignments were reinforced by an XH correlation experiment. These shifts are closely related to those for (+)-salutaridine itself (see **2a**) (2), except for those of C-1, C-4′, and neighboring carbons. This difference is, of course, due to the fact that C-1 and C-4′ are directly involved in the diaryl ether bridge.

Because morphinandienones are normally found in nature as optically active species and the major alkaloid in the two plants is (+)-salutaridine, we have indicated the corresponding stereochemistry for the dimer, as represented in structure **1**. It should be noted, however, that this assignment of absolute configuration remains to be proven. Paucity of material precluded further study of the alkaloid.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Optical rotations are at 25°. ^{1}H-nmr spectra were recorded at 500 MHz in $CDCl_3$. Cc was on Merck Kieselgel 60, particle size less than 63 μ. Tlc was on Merck Si gel glass plates, 0.25 mm thick.

PLANT COLLECTION AND EXTRACTION AND ISOLATION OF ALKALOIDS.—*P. pseudo-orientale* was collected and extracted as previously described (3). From 2.7 kg of the plant, 7 mg of amorphous (+)-salutadimerine was obtained. *P. lasiothrix* (1 kg) was collected near Gümushane and gave 6 mg of the dimer. Plant specimens were deposited in the herbarium of the Faculty of Pharmacy, Istanbul University.

(+)-SALUTADIMERINE [**1**].—Uv λ max (MeOH) 284 nm (log ε 3.70); eims *m/z* (%) $[M]^+$ 652 (100), 637 (80), 621 (50), 326 (6), 310 (14); hreims 652.2748 for $C_{38}H_{40}N_2O_8$ (calcd 652.2774), 637.2501 for $C_{37}H_{37}N_2O_8$ (calcd 637.2552); ir ν max ($CHCl_3$) 1670, 1640, 1620 cm^{-1}; $[\alpha]_D$ +36° (*c* = 0.1, MeOH).

Principal nOe's.—H-5 to 6-OMe (19%), 6-OMe to H-5 (31%), H-5 to H-15ax (3%), H-15ax to H-5 (7%), H-5 to H-15eq (4%), H-15eq to H-5 (10%), H-8 to H-9 (14%), H-9 to H-8 (42%), H-9 to 18-NMe (13%), H-10α to H-9 (14%), H-2 to 3-OMe (26%), 3-OMe to H-2 (32%), H-2 to H-5′ (5%), H-5′ to H-2 (8%), H-5′ to 6′-OMe (21%), 6′-OMe to H-5′ (29%), 6′-

OMe to H-2 (3%), H-8′ to H-9′ (10%), H-9′ to H-8′ (36%), H-9′ to 18′-NMe (15%), H-9′ to H-10′α (6%), H-10′α to H-9′ (6%), H-10′α to H-1′ (3%), H-1′ to H-10′α (2%), H-1′ to H-10′β (3%), H-1′ to H-2′ (13%), H-2′ to H-1′ (16%), H-2′ to 3′-OMe (24%), 3′-OMe to H-2′ (26%), 4-OH to H-5 (5%), H-15′ax to 3-OMe (3%), H-15′eq to H-5′ (8%).

ACKNOWLEDGMENTS

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