

(-)-PAPAVEROXIDINE, A MODIFIED PHTHALIDEISOQUINOLINE  
ALKALOID FROM PAPAVER PSEUDO-ORIENTALE

GÜNAY SARIYAR<sup>1</sup> and MAURICE SHAMMA\*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

Our initial studies on the contents of Turkish *Papaver pseudo-orientale* (Medw.) Fedde (Papaveraceae) have yielded a variety of alkaloids that proved to be modified phthalideisoquinolines (1,2). Among these should be mentioned the alcohol acetate, (-)-papaveroxinoline [1] (1), and the aldehyde acetate, (-)-papaveroxine [2] (1). We have now obtained from the same plant, which however was collected at a different site, the new alkaloid (-)-papaveroxidine [3], which is the carboxylic acid acetate that completes the triad alcohol-aldehyde-carboxylic acid.

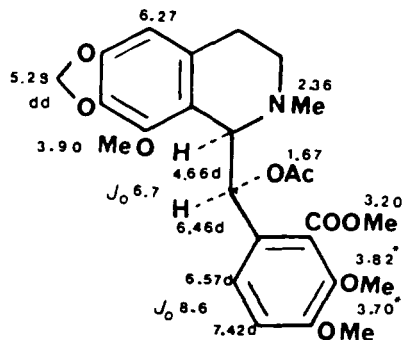
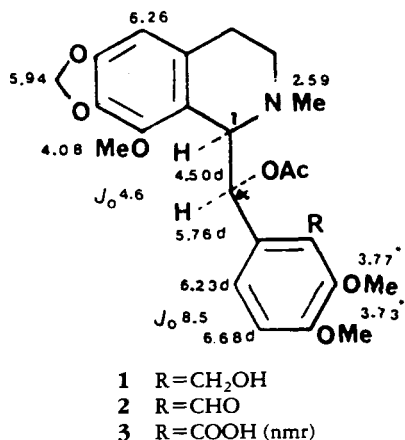
(-)-Papaveroxidine [3], C<sub>24</sub>H<sub>27</sub>NO<sub>9</sub>, λ<sub>max</sub> (MeOH) 237 sh, 283 nm (log ε 4.09, 3.44), has an ir spectrum (CHCl<sub>3</sub>) with carbonyl bands at 1615 and 1735 cm<sup>-1</sup>. The eims displayed a base peak at m/z 220, representing rings A and B of the molecule, while no molecular ion could be observed due to cleavage of the scissible C-1 to C-α bond. However, the cims exhibited an ion at m/z 474 [M + 1]<sup>+</sup>.

A better-defined high resolution <sup>1</sup>H

nmr spectrum of (-)-papaveroxidine could be obtained in CD<sub>3</sub>CN than in CDCl<sub>3</sub>, and this has been summarized around the structure for 3. Besides the N-methyl absorption at δ 2.59, three O-methyl peaks were present at δ 3.73, 3.77, and 4.08, the last of which could be assigned to the C-8 methoxyl. The acetate methyl group was represented by a singlet at δ 2.02. The important diagnostic H-1 and H-α doublets were located at δ 4.50 and 5.76. The methylenedioxy substituent appeared as a singlet at δ 5.94. Three aromatic protons were in evidence, including a singlet at δ 6.26 assignable to H-5.

In order to support further our structure assignment, the material was first esterified with ethereal CH<sub>2</sub>N<sub>2</sub> to supply (-)-papaveroxidine methyl ester [4], C<sub>25</sub>H<sub>29</sub>NO<sub>9</sub>, whose nmr spectrum, best obtained in C<sub>6</sub>H<sub>6</sub>-d<sub>6</sub>, is quoted around the structure for 4. The critical H-1 and H-α absorptions appear as doublets at δ 4.66 and 6.46, with J<sub>1,α</sub> = 6.7 Hz. The methyl group of the methyl ester appeared at δ 3.20, significantly more upfield than the three remaining methoxyls that were found at δ 3.70, 3.82, and 3.90.

LiAlH<sub>4</sub> reduction of ester 4 then pro-



<sup>1</sup>Permanent address: Faculty of Pharmacy, Istanbul University, Istanbul, Turkey.

vided the known diol (–)-narcotinediol, identical both with material obtained from the  $\text{LiAlH}_4$  reduction of (–)- $\alpha$ -narcotine and with the natural product of the same name (1).

Our *P. pseudo-orientale* extracts contained two major alkaloids, (+)-salutaridine (1) and (–)-papaveroxine [2] (1). The minor alkaloids were (–)-narcotine-hemiacetal (1), (–)-papaveroxinoline [1] (1), (–)-narcotinediol (1), (–)-thebaine (1), (+)-norsalutaridine, and the aforementioned (–)-papaveroxidine [3].

### EXPERIMENTAL

**PLANT MATERIAL.**—*P. pseudo-orientale* was collected at Sebinkarahisar (Giresun) in northeastern Turkey, at an altitude of 1450 to 1600 m in July 1986. Voucher specimens were retained in the Herbarium of the Faculty of Pharmacy, Istanbul University.

**PLANT EXTRACTION.**—The dried stems and leaves (1.2 kg) and the capsules (107 g) were each extracted separately with MeOH at room temperature. Evaporation of the solvent left a residue that was dissolved in 5% HCl and extracted first with petroleum ether and then with  $\text{Et}_2\text{O}$ . The aqueous acidic fraction was basified with  $\text{NH}_4\text{OH}$  and extracted with  $\text{CHCl}_3$ . The organic layer was washed with  $\text{H}_2\text{O}$ , dried, and concentrated in vacuo to yield 5 g and 1 g of crude alkaloids, respectively.

**SEPARATION OF THE ALKALOIDS.**—Column chromatography was on Si gel H (for tlc), and elution was with  $\text{C}_6\text{H}_6$ - $\text{Me}_2\text{CO}$ -MeOH (7:2:1). Tlc was on Si gel 60 F-254 glass plates. The tlc solvent systems were  $\text{C}_6\text{H}_6$ - $\text{Me}_2\text{CO}$  (9:1),  $\text{C}_6\text{H}_6$ -

$\text{Me}_2\text{CO}$ -MeOH (7:2:1),  $\text{EtOAc}$ -MeOH- $\text{C}_6\text{H}_6$  (1:1:1),  $\text{CHCl}_3$ - $\text{EtOAc}$ -MeOH (60:35:5), and  $\text{CHCl}_3$ -MeOH- $\text{NH}_4\text{OH}$  (90:10:1).

**ALKALOID ISOLATION.**—The capsule extracts (1 g) supplied (–)-papaveroxine [2] (250 mg), (–)-narcotine-hemiacetal (25 mg), (–)-papaveroxinoline [1] (70 mg), (–)-narcotinediol (15 mg), (+)-salutaridine (600 mg), (+)-norsalutaridine (3 mg), and (–)-papaveroxidine [3] (7 mg). The stems and leaves extracts (5 g) furnished 2 (700 mg), 1 (120 mg), narcotine-hemiacetal (150 mg), narcotinediol (210 mg), (+)-salutaridine (1.3 g), (+)-norsalutaridine (10 mg), (–)-thebaine (3 mg), and 3 (90 mg).

(–)-PAPAVEROXIDINE [3].—Mp  $164^\circ$  ( $\text{Et}_2\text{O}$ ); eims  $m/z$  (rel. int.) 220 (100), 204 (14); cims  $m/z$   $[\text{M} + 1]^+$  474;  $[\alpha]_{\text{D}} - 139.5^\circ$  ( $c = 0.13$ , MeOH).

(–)-PAPAVEROXIDINE METHYL ESTER [4].—Treatment of 3 with ethereal  $\text{CH}_2\text{N}_2$  for 3 h furnished 4. Ester 4 showed cims  $m/z$   $[\text{M} + 1]^+$  488,  $[\alpha]_{\text{D}} - 19.2^\circ$  ( $c = 0.16$ , MeOH).

**REDUCTION OF 4.**—Treatment of 4 (4 mg) in  $\text{Et}_2\text{O}$  (20 ml) with  $\text{LiAlH}_4$  provided (–)-narcotinediol (2.5 mg) following work-up.

### ACKNOWLEDGMENTS

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