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SIX ALKALOIDS FROM *PAPAVER* SPECIES*

GÜNAY SARIYAR and MAURICE SHAMMA†

Department of Pharmacognosy, Faculty of Pharmacy, University of Istanbul, Istanbul, Turkey; †Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802, U.S.A.

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Key Word Index—*Papaver fugax*; *P. pseudo-orientale*; Papaveraceae; phthalideisoquinoline alkaloids; secoberbine alkaloids; papaveroxine; narcotinehemiacetal; macrantaldehyde; narcotinediol; papaveroxinoline; narcotolinol.

Abstract—*Papaver fugax* produced the new alkaloids (−)-narcotinehemiacetal and (−)-papaveroxine. New alkaloids from *P. pseudo-orientale* are (−)-narcotinediol, (+)-macrantaldehyde, (−)-papaveroxinoline, (−)-narcotolinol and (−)-narcotinehemiacetal.

INTRODUCTION

One of the still incompletely understood aspects of isoquinoline alkaloid chemistry concerns the actual steps involved in the *in vivo* transformation of protoberberines into phthalideisoquinolines [1–3]. Both alkaloidal types are of common occurrence, particularly among members of the Papaveraceae and the Fumariaceae. Two papers may have thrown some light into this matter. Firstly, it was determined that the aerial parts of a Turkish sample of *Papaver pseudo-orientale* Fedde. (Medw.) (Papaveraceae) produce the new alkaloids (+)-macrantaline (**3**) and (−)-macrantoridine (**4**) which on purely structural grounds may be considered intermediate between a tetrahydroprotoberberine such as **2** on the one hand, and the corresponding well-known phthalideisoquinoline (−)-α-narcotine (**6**) on the other [4].

Secondly, a study of the aerial parts of *Fumaria vaillantii* Loisel (Fumariaceae), also of Turkish origin, revealed the presence, albeit in small amounts, of the new alkaloid (+)-egenine (**5**). It was, therefore, possible to envisage an *in vivo* process in which a tetrahydroprotoberberine of type **1** could be stereospecifically *N*-methylated, and then oxidized in stages to (+)-egenine (**5**). This hemiacetal could then suffer further oxidation to the known phthalideisoquinoline (+)-bicuculline (**7**) which significantly co-occurs with (+)-egenine (**5**) in *F. vaillantii* [5].

RESULTS AND DISCUSSION

We have presently carried out an investigation of the aerial parts of Turkish *P. fugax* Poir., as well as of the capsules of *P. pseudo-orientale* Fedde. (Medw.), the results of which throw additional light on this problem.

The main alkaloid in *P. fugax* proved to be the new (−)-papaveroxine (**9**), $C_{24}H_{27}NO_8$, which was accompanied by the also new and structurally related (−)-narcotinehemiacetal (**8**), $C_{22}H_{25}NO_7$. As could be expected, the known (−)-α-narcotine (**6**) was also present [6]. The ^{1}H NMR spectra for (−)-narcotinehemiacetal (**8**) and (−)-papaveroxine (**9**) have been summarized around their respective structures. It will be noted that the spectrum for **9** shows an acetyl methyl singlet at δ2.05 and an aldehyde singlet at 10.81, while the spectrum for the corresponding hemiacetal **8** exhibits a one-proton singlet at δ6.33 representing the hemiacetal ring (anomeric) hydrogen.

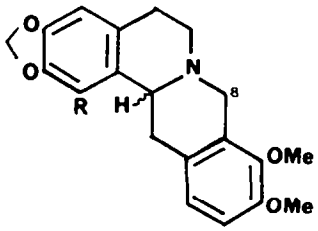
Both (−)-narcotinehemiacetal (**8**) and (−)-papaveroxine (**9**) had mass spectra with base peak *m/z* 220 due to rings A and B of the molecules. The IR spectrum of **9** included an ester carbonyl band at 1735 cm^{-1} and a conjugated aldehyde band at 1685 cm^{-1}.

Manganese dioxide oxidation of (−)-narcotinehemiacetal (**8**) provided (−)-α-narcotine (**6**). Conversely, lithium aluminium hydride reduction of (−)-α-narcotine (**6**), in ether at about 0°, supplied nearly equal amounts of (−)-narcotinehemiacetal (**8**) and (−)-narcotinediol (**10**) [7, 8]. Additionally, acid hydrolysis of (−)-papaveroxine (**9**) generated (−)-narcotinehemiacetal (**8**), while lithium aluminium hydride reduction of **9** gave rise to (−)-narcotinediol (**10**).

Turning now to *P. pseudo-orientale*, the capsules of this plant provided the known (−)-macrantaline (**3**) and the morphinandienone (+)-salutaridine as the main alkaloids [4]. These were accompanied by an appreciable quantity of the new aldehydic alkaloid (+)-macrantaldehyde (**11**), $C_{22}H_{25}NO_6$, $\nu_{max}^{CHCl_3}$ 1685 cm^{-1}, whose ^{1}H NMR spectrum showed an aldehydic proton at δ10.25, besides peaks for one *N*-methyl, three methoxyls and one methylenedioxy groups. The mass spectrum of (+)-macrantaldehyde again showed a base peak at *m/z* 220, representing rings A and B of the molecule, and analogous to the base peak for (−)-narcotinehemiacetal (**8**) and (−)-papaveroxine (**9**). In accord with its structure, sodium borohydride reduction of (+)-macrantaldehyde (**11**) provided (+)-macrantaline (**3**) [4]. Significant amounts of the known [4] amino acid (−)-macrantoridine (**4**) were also detected in the plant, so that aldehyde **11** co-exists with its corresponding alcohol **3** and its acid **4**.

Papaver pseudo-orientale further supplied several minor alkaloids structurally related to those discussed

*This paper is dedicated to Professor Turhan Baytop on the occasion of his 65th birthday.



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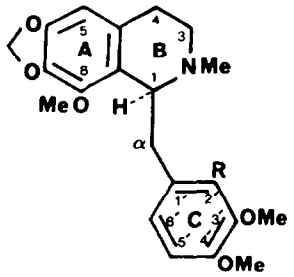

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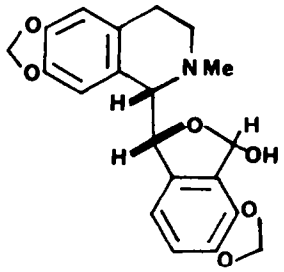

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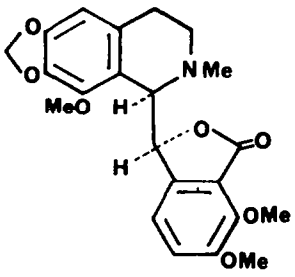

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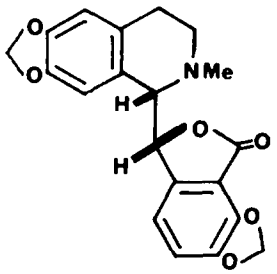

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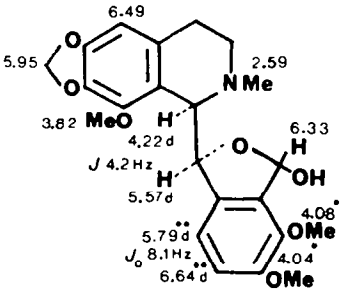

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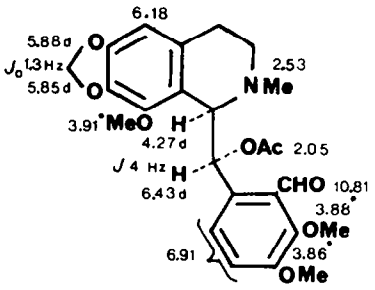

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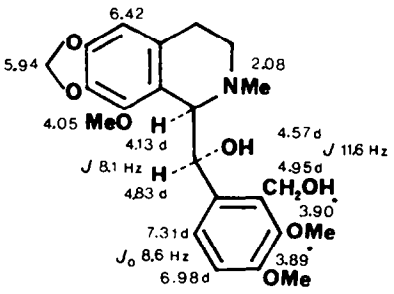

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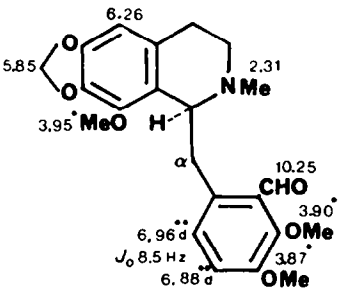

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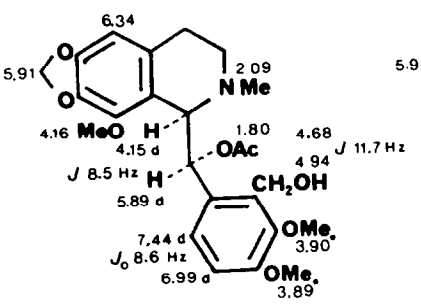
above. The first of these was (−)-α-narcotine (**6**) which is presently reported for the first time in *P. pseudo-orientale* [6]. The second was (−)-narcotinehemiacetal (**8**), identical with material obtained from *P. fugax*. The third was (−)-narcotinediol (**10**), $C_{22}H_{27}NO_7$, here obtained for the first time as a natural product, and identical with material obtained from the *in vitro* lithium aluminium hydride reduction of either (−)-α-narcotine (**6**) or (−)-papaveroxine (**9**), or else from the sodium borohydride reduction of narcotinehemiacetal (**8**).

The fourth was the novel (−)-papaveroxinoline (**12**), $C_{24}H_{29}NO_8$, $\nu_{max}^{CHCl_3}$ 1725 cm^{-1}, whose mass spectrum again showed a base peak at m/z 220 since its A and B rings are identical to those in species **8**, **9**, and **11**. The most significant feature of the ^1H NMR spectrum of (−)-papaveroxinoline (**12**) was the downfield shift of the H-α doublet to δ5.89, as compared to the corresponding proton absorption in narcotinediol (**10**) which is found at δ4.83. Indeed, acid hydrolysis of (−)-papaveroxinoline (**12**) led to (−)-narcotinediol (**10**). Furthermore, sodium borohydride in methanol reduction of (−)-papaveroxine (**9**) at room temperature furnished two products, namely (−)-papaveroxinoline (**12**) and (−)-narcotinediol (**10**). It was also observed that upon standing in wet chloroform



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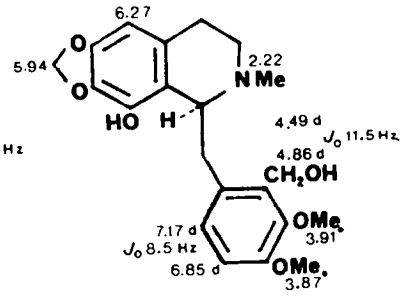

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for several days at room temperature, papaveroxinoline (**12**) tended to hydrolyse to narcotinediol (**10**).

A fifth minor alkaloid from *P. pseudo-orientale* was the new (−)-narcotolinol (**13**), $C_{21}H_{25}NO_6$, which bears a phenolic function in ring A. This was indicated by mass spectral base peak *m/z* 206 instead of the usual *m/z* 220. The ^{1}H NMR spectrum shows methoxyl singlets at δ3.87 and 3.91 for the ring C substituents. Significantly, the downfield methoxyl absorption near δ4.1 assigned to the C-1 methoxyl in the spectra of (−)-macrantaline (**3**) [4], (−)-narcotinediol (**10**) and (−)-papaveroxinoline (**12**), was not present. Finally, diazomethane *O*-methylation of (−)-narcotolinol (**13**) gave rise to (−)-macrantaline (**3**).

Two other alkaloids we found in *P. pseudo-orientale* whose presence should be mentioned, but which do not belong to the secoprotoberberine-phthalideisoquinoline series, are the known (+)-salutaridine [9] and (−)-thebaine.

The characterization of the above new alkaloids, coupled with the already known alkaloids (−)-macrantaline (**3**), (−)-macrantoridine (**4**) [4] and (+)-egenine (**5**) [5], allows for a tentative and hypothetical scheme to explain the *in vivo* conversion of tetrahydroprotoberberines into phthalideisoquinolines. A tetrahydroprotoberberine such as **2** could undergo *N*-methylation and oxidation at C-8 to supply (−)-macrantaldehyde (**11**). This aldehyde could be readily reduced to (−)-macrantaline (**3**) or oxidized to (−)-macrantoridine (**4**). An alternate route for (−)-macrantaldehyde would result in its oxidation at C-α to generate (−)-narcotinehemiacetal (**8**), which could in turn undergo further oxidation to the classical phthalideisoquinoline alkaloid (−)-α-narcotine (**6**). Alternate biogenetic pathways, involving oxidation, reduction or acetylation, would lead to such compounds as (−)-papaveroxine (**9**), (−)-narcotinediol (**10**) and (−)-papaveroxinoline (**12**).

A final remark should be appended here concerning the specific rotations of some of our alkaloids. In general, *N*-methylated tetrahydrobenzylisoquinolines of the *S* configuration (H-1α as drawn in the accompanying diagrams) show a positive specific rotation, and the pendant ring C lies away from the *N*-methyl group and towards ring A. On the other hand, the corresponding *N*-nortetrahydrobenzylisoquinolines with the *S* chirality show a negative specific rotation, and exist mostly in a conformation where ring C is proximate to the secondary nitrogen function. This generalization may even be extended to the tetrahydroprotoberberine alkaloids which show a strong negative rotation for the *S* series, and to the aporphines which exhibit a positive rotation for the identical absolute configuration.

The situation, however, is more ambiguous with C-1 and C-2′-substituted and *N*-methylated tetrahydrobenzylisoquinolines of the type presently encountered. In such instances, ring C may lie nearer to the right side or to the left side, or in between, depending upon the size and nature of the substituents. The result is that specific rotations may vary in sign as well as in magnitude, even though the absolute configuration at C-1 remains unchanged. The signs of rotation used in our discussion above were determined using methanol as solvent. In one case, namely that of (−)-narcotinediol (**10**), a change in the sign of rotation was observed in the less polar solvent chloroform, and this has been noted in the Experimental.

EXPERIMENTAL

General experimental procedures. NMR spectra are at 360 MHz in $CDCl_3$ soln. CD spectra are in MeOH. After each of the chemical transformations detailed below, specific rotations were obtained, in addition to the usual NMR spectral and TLC comparisons with authentic materials.

Plant materials. Papaver fugax was collected by Prof. T. Baytop in June, 1984, at Uludere, near Hakkari, in southeastern Turkey, at an altitude of 1350 m. *Papaver pseudo-orientale* was gathered at Yildizdag, near Sivas in eastern Turkey, in July, 1984, by Profs. N. and E. Özhatay and G. Sariyar, at altitudes of 1750–2000 m. Voucher specimens were retained in the Herbarium of the Faculty of Pharmacy, Istanbul University.

Extraction of alkaloids from P. fugax. The total dried aerial parts (550 g) were extracted with MeOH at room temp. Evaporation of the solvent left a residue which was dissolved in 5% HOAc and extracted first with petrol and then with Et_2O. The aq. fraction was basified with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ layer was washed, dried and concd *in vacuo* to yield 2.8 g of crude alkaloidal fraction.

Extraction of alkaloids from P. pseudo-orientale. The dried powdered capsules (145 g) were extracted with MeOH. The procedure described above was followed, except that 5% HCl was used instead of 5% HOAc, to yield 3.7 g of crude alkaloids.

Separation of the alkaloids. CC on silica gel H (for TLC), and TLC on silica gel 60 F-254 glass plates (0.25 or 0.5 mm thick) were used. The various solvent systems were: I, C_6H_6–Me_2CO–MeOH (7:2:1); II, C_6H_6–$CHCl_3$–EtOAc–MeOH (4:3:3:0.5); III, C_6H_6–$CHCl_3$–EtOAc–MeOH (3:4:3:0.5); IV, C_6H_6–Me_2CO–NH_4OH (9:1:0.1); V, C_6H_6–EtOH–NH_4OH (8:2:0.03); VI, cyclohexane–$CHCl_3$–Et_2NH (5:4:1).

Isolation of the alkaloids. The alkaloidal fraction from *P. fugax* (2.8 g) supplied (−)-papaveroxine (**9**, 900 mg), (−)-α-narcotine (**6**, 250 mg), and (−)-narcotinehemiacetal (**8**, 200 mg). Alternate extraction of the powdered aerial parts of *P. fugax* using 3% HCl in lieu of 5% HOAc, followed by chromatography, still furnished

alkaloids **6**, **8** and **9**. The alkaloidal fraction from *P. pseudo-orientale* (3.7 g) furnished (−)-α-narcotine (**6**, 3 mg), (−)-narcotinehemiacetal (**8**, 5 mg), (−)-papaveroxinoline (**12**, 7 mg), (+)-macrantaline (**3**, 920 mg), (−)-narcotolinol (**13**, 7 mg), (+)-salutaridine (1 g), (+)-macrantaldehyde (**11**, 200 mg), (−)-thebaine (12 mg) and (−)-macrantoridine (**4**, 33 mg).

(−)-*Narcotinehemiacetal* (**8**). Mp 155–158° (MeOH); λ_{max}^{MeOH} nm (log ε): 237 (3.97), 282 (3.55); EIMS *m/z* (rel. int.): 415 $[M]^+$ (0.01), 397 (0.1), 222 (1.6), 221 (14), 220 (100), 205 (10); CIMS *m/z*: 416 $[M+1]^+$; $[\alpha]_D^{25}$ − 220° (*c* 0.092; MeOH) or − 286° (*c* 0.2; $CHCl_3$).

(−)-*Papaveroxine* (**9**). Mp 130–131° (Et_2O); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1615, 1685, 1735, 2930; UV λ_{max}^{MeOH} nm (log ε); 238 (3.95), 282 (3.54); EIMS *m/z* (rel. int.): 397 (0.4), 221 (14), 220 (100), 218 (3), 205 (11), 203 (2), 149 (2); CIMS *m/z*: 458 $[M+1]^+$; $[\alpha]_D^{25}$ − 35° (*c* 0.13; MeOH).

(−)-*Narcotinediol* (**10**). Amorphous; UV λ_{max}^{MeOH} nm (log ε): 236 (4.02), 281 (3.52); EIMS *m/z* (rel. int.): 399 $[M-18]^+$, 221 (14), 220 (100), 218 (2), 205 (11), 203 (1); CIMS *m/z*: 418 $[M+1]^+$; $[\alpha]_D^{25}$ − 14.1° (*c* 0.08; MeOH) or + 53.1° (*c* 0.16; $CHCl_3$); CD Δε (nm): + 0.62 (283), − 4.3 (245), + 4.8 (230). Acetylation of **10** (Ac_2O) furnished the known (−)-narcotinediol diacetate [8], $[\alpha]_D^{25}$ − 43.5° (*c* 0.17; MeOH) or − 47.3° (*c* 0.15; $CHCl_3$).

(+)-*Macrantaldehyde* (**11**). Amorphous; UV λ_{max}^{MeOH} nm (log ε): 241 (3.98), 283 (3.59); EIMS *m/z* (rel. int.); 399 $[M]^+$ (0.1), 220 (100), 218 (4), 205 (12), 203 (2); CIMS *m/z*: 400 $[M+1]^+$; $[\alpha]_D^{25}$ + 4.8° (*c* 0.4; MeOH); CD Δε (nm): − 2.5 (241).

(−)-*Papaveroxinoline* (**12**). Mp 177–180° (MeOH); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1615, 1725, 2990; UV λ_{max}^{MeOH} nm (log ε): 234 (4.18), 281 (3.56); EIMS *m/z* (rel. int.): 399 (0.3), 222 (2), 221 (14), 220 (100), 218 (1.5), 206 (1.4), 205 (7.5); CIMS *m/z*: 460 $[M+1]^+$; $[\alpha]_D^{25}$ − 7.3° (*c* 0.1; MeOH); CD Δε (nm): + 1.0 (283), − 4.5 (246), + 1.0 (236).

(−)-*Narcotolinol* (**13**). Mp 190–191° (Et_2O); UV λ_{max}^{MeOH} nm (log ε): 232 (4.15), 283 (3.56); EIMS *m/z* (rel. int.): 387 $[M]^+$ (0.11), 220 (6), 208 (2), 207 (13), 206 (100), 205 (5), 164 (1), 149 (2), 148 (1); CIMS *m/z*: 388 $[M+1]^+$, 370 $[M+1-18]^+$; $[\alpha]_D^{25}$ − 13° (*c* 0.1; MeOH); CD Δε (nm): − 4.2 (241).

(+)-*Macrantaline* (**3**). $[\alpha]_D^{25}$ + 13.3° (*c* 0.16; MeOH).

(−)-*Macrantoridine* (**4**). $[\alpha]_D^{25}$ − 163.1° (*c* 0.16; MeOH).

Reduction of (−)-*narcotinehemiacetal* (**8**). Hemiacetal **8** (9 mg) was dissolved in MeOH (3 ml) and the soln treated with excess $NaBH_4$. Stirring was continued for 3 hr. Work-up gave (−)-narcotinediol (**10**, 6.6 mg).

Oxidation of (−)-*narcotinehemiacetal* (**8**). The alkaloid (2.5 mg) in C_6H_6 (3 ml) was treated with Aldrich activated MnO_2 (100 mg). The mixture was stirred for 2 hr. Filtration and evaporation of the solvent supplied (−)-α-narcotine (**6**, 1.1 mg).

Reduction of (−)-α-*narcotine* (**6**). Alkaloid **6** (60 mg) in Et_2O was reduced with excess $LiAlH_4$ with stirring for 2 hr at near 0°. Work-up including TLC using system II provided (−)-narcotinehemiacetal (**8**, 15 mg) and (−)-narcotinediol (**10**, 16 mg).

Reduction of (−)-*papaveroxine* (**9**). (a) With $NaBH_4$. The alkaloid (20 mg) in MeOH was treated with excess $NaBH_4$, and the mixture stirred overnight at room temp. Work-up, including TLC using system III, supplied (−)-papaveroxinoline (**12**, 3.1 mg) and (−)-narcotinediol (**10**, 3.7 mg). (b) With $LiAlH_4$. The alkaloid (20 mg) in Et_2O was treated with excess $LiAlH_4$. The mixture was stirred for 6 hr. Work-up, including TLC using system III, furnished (−)-narcotinediol (**10**, 14 mg).

Hydrolysis of (−)-*papaveroxine* (**9**). The alkaloid (7 mg) was treated with 5% HCl at room temp. for 20 hr. Work-up provided (−)-narcotinehemiacetal (**8**, 5 mg).

Hydrolysis of (−)-*papaveroxinoline* (**12**). The alkaloid (1 mg) was dissolved in 5% HCl and the soln left for 48 hr. Work-up furnished (−)-narcotinediol (**10**, 0.7 mg).

O-*Methylation of* (−)-*narcotolinol* (**13**). The alkaloid (0.8 mg) was dissolved in MeOH, and excess ethereal CH_2N_2 added. The soln was left at near 0° overnight. Work-up, including TLC using system III, yielded (+)-macrantaline (**3**, 0.4 mg).

Reduction of (+)-*Macrantaldehyde* (**11**). The alkaloid (3.5 mg) in MeOH was treated with excess $NaBH_4$. The mixture was stirred for 2 hr. Work-up including TLC gave (+)-macrantaline (**3**, 2 mg).

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