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QUATERNARY ISOQUINOLINE ALKALOIDS FROM *PAPAVER* SPECIES

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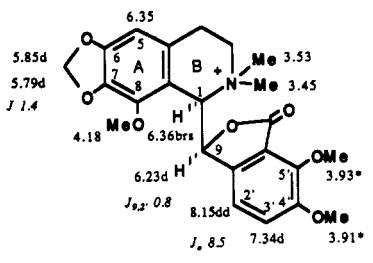
ABSTRACT.—The two main quaternary alkaloids of *Papaver cylindricum* are the new phthalideisoquinoline (+)-*N*-methyl-α-narcotine [**1**] and the known (−)-*N*-methylthebaine. *Papaver pseudo-orientale* provided (−)-α-*N*-methopapaverberbine [**2**], isolated as the iodide, which is the first *N*-methoprotoberberine salt hydroxylated at C-13, as well as the bicyclic cotarnine [**5**] and the quinoidal cotarnoline [**7**].

Although several studies on the alkaloidal content of *Papaver* species (Papaveraceae) have been conducted in the past (1–3), only a limited number have actually focused on the quaternary alkaloids (4). We herewith report on the quaternary alkaloids in the aerial parts of two Turkish Papavers, namely *Papaver cyclindricum* Cullen and *Papaver pseudo-orientale* Fedde (Medw.).

We have found that *P. cylindricum* has two main quaternary alkaloids. The first of these proved to be (+)-*N*-methyl-α-narcotine [**1**], which had never previously been isolated from a natural source. The existence of this salt had been conjectured, however, to explain the biogenesis of such secophthalideisoquinolines as narceine and nornarceine (5).

(+)-*N*-Methyl-α-narcotine [**1**] was isolated as the iodide salt, $C_{23}H_{26}NO_7I$. The ^{1}H-nmr spectrum in $CDCl_3$ has been summarized around structure **1**. Two aromatic doublets sharing an 8.5 Hz coupling constant are readily assigned to H-2′ (δ 8.15) and H-3′ (δ 7.34). The H-5 aromatic singlet appears relatively upfield at δ 6.35. Three methoxyl singlets are in evidence at δ 3.91, 3.93, and 4.18 ppm, the last of which is due to the substituent at C-8. Finally, two *N*-methyl singlets are present, one at δ 3.45 and the other at δ 3.53 ppm. Of particular assistance in the spectral assignments was the presence of a long range benzylic coupling (0.8 Hz) between H-9 (δ 6.23) and H-2′(δ 8.15), Because H-9 shows no other coupling, it is apparent that the dihedral angle it shares with H-1 (δ 6.36) approximates 90°. The present chemical shift assignments for (+)-*N*-methyl-α-narcotine differ somewhat from those given more than ten years ago using a less sensitive nmr spectrometer (6).

The mass spectrum of (+)-*N*-methyl-α-narcotine iodide indicated that Hofmann elimination followed by additional cleavages had occurred during the analytical process, because the base peak, *m/z* 58, is characteristic of the *N*,*N*-dimethyliminium cat-



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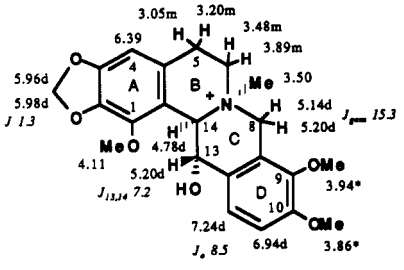

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ion, $[CH_2=N(CH_3)_2]^+$, and is typical of secophthalideisoquinolines such as narceine. Other significant peaks were *m/z* 428 $[M-I]^+$, 427 $[M-HI]^+$, 413 $[M-MeI]^+$, and 220, which are derived from rings A and B of the alkaloid.

The uv spectrum displayed maxima at 224, 291 sh, and 312 nm and was generally similar to that of (−)-α-narcotine (7). Significantly, it showed a drastic change upon the addition of aqueous NaOH, developing maxima at 227 and 271 nm. These values correspond exactly to those reported for the tertiary base narceine (7), so that Hofmann elimination of the quaternary salt must have readily taken place. This facile ring cleavage may also explain why (+)-*N*-methyl-α-narcotine had gone undetected as an alkaloid up to the present time.

Final proof of structure, including absolute configuration, was forthcoming from a semisynthesis using authentic (−)-α-narcotine. *N*-Methylation of this free base with MeI provided (+)-*N*-methyl-α-narcotine iodide, spectrally, chromatographically, and optically identical with the natural product.

We conclude that (+)-*N*-methyl-α-narcotine can now be considered a true alkaloid.

Quaternary phthalideisoquinolines analogous to **1** previously isolated include (−)-*N*-methyladlumine (8) and (−)-*N*-methyl-β-hydrastine (9), both obtained from *Fumaria* species (Fumariaceae).

The second principal quaternary alkaloid of *P. cylindricum* was found to be (−)-*N*-methylthebaine, which had previously been obtained from *Papaver bracteatum* (10). It should be noted at this stage that the free bases (−)-α-narcotine and (−)-thebaine are known to be present in *P. cylindricum* (11).

Turning now to the quaternary alkaloids of *P. pseudo-orientale*, several compounds were isolated. (−)-α-*N*-Methopapaverberbine [**2**] was obtained as its iodide, $C_{22}H_{26}NO_6I$. The $CDCl_3$ ^{1}H-nmr spectrum has been outlined around structure **2**. The *N*-methyl singlet of cis-fused quinolizidine *N*-metho salts is known to fall around δ 3.5, while trans fusion gives a peak near δ 3.3 (12). The fact that the nmr spectrum of (−)-α-*N*-methopapaverberbine [**2**] incorporated an *N*-methyl singlet at δ 3.50 immediately suggested a cis-B/C-fused protoberberine system. Three methoxyl singlets were present, at δ 3.86, 3.94, and 4.11; the last one could be assigned to the C-1 methoxyl which characteristically appears downfield (13–15). The diagnostic H-13 and H-14 doublets were located at δ 5.20 and 4.78. The large 7.2 Hz coupling constant between them indicated a trans relationship (12). The δ 6.39 aromatic singlet clearly represented H-4, and the doublets at δ 6.94 and 7.24, with an 8.5 Hz coupling constant, were due to H-11 and H-12, respectively.

The assignment of a cis B/C fusion to our alkaloid was buttressed by the results of a ^{13}C-nmr study, with the salient results appearing around structure **3**. Significantly, the *N*-methyl carbon is found at δ 52.43 and C-6 at δ 53.10. Such chemical shifts are typical of cis-fused protoberberine *N*-metho salts, whereas the corresponding values for the trans salts are around δ 41 and 64 (12,16).

The uv spectrum of (−)-α-*N*-methopapaverberbine [**2**] showed the expected maxima at 233 and 280 nm. The mass spectrum displayed ion *m/z* 385 $[M-MeI]^+$ and base peak *m/z* 206 for $C_{11}H_{12}NO_3$, representing rings A and B.

The absolute configuration of the alkaloid was indicated by a strong levorotation due to the C-14 *R* configuration (H-14 in α configuration). Because the B/C fusion is cis it follows that the *N*-methyl is α, i.e., below the mean plane of the molecule as drawn, meaning that we are here dealing with an α-*N*-metho salt.

As further confirmation of the structure assignment, the alkaloidal salt was acetylated using Ac_2O in pyridine. The resulting (−)-13-*O*-acetyl-α-*N*-methopapaverberbine [**4**], obtained as the iodide $C_{24}H_{28}NO_7I$, presented a ^{1}H-nmr spectrum with an H-13 doublet significantly downfield at δ 6.02 and an acetate methyl singlet at δ 2.12.

Thus, (−)-α-*N*-methopapaverberbine [**2**] is the first fully characterized, cis-B/C-fused protoberberine salt also hydroxylated at C-13.

In this context, it should be noted that a few simple tetrahydroprotoberberine *N*-metho salts have been isolated from natural sources, including those of (−)-canadine (17), (−)-escholidine (17), (−)-scoulerine (18), (−)-mecambridine (19), (−)-stylopine (20), (+)-stylopine (21), and (−)-sinactine (22).

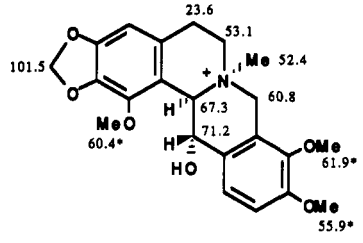
Radiolabeled feeding experiments using 13-hydroxylated protoberberine *N*-metho salts and callus cultures of *Corydalis* species (Fumariaceae) have shown that 13-hydroxylated α-*N*-metho salts play an important role in the biogenetic sequence leading from protoberberines to protopines and then on to indenobenzazepines, spirobenzylisoquinolines, and benzophenanthridines (23–25).

Previous work on *P. pseudo-orientale* of Turkish origin indicated that the following alkaloids are also present: (+)-macrantaline (25), (−)-macrantoridine (25), (+)-salutaridine (25), (+)-macrantaldehyde (26), (−)-α-narcotine (26), (−)-narcotinediol (26), (−)-narcotinehemiacetal (26), (−)-narcotolinol, (26), (+)-norsalutaridine (13), (−)-thebaine (13), (−)-papaveroxine (26), (−)-papaveroxinoline (26), (−)-papaveroxidine (26), (+)-isothebaine (24), (−)-mecambridine (24), (−)-orientalidine (24). Interestingly, all of the previously known benzylisoquinolines, protoberberines, and phthalideisoquinolines of *P. pseudo-orientale* possess both a methylenedioxy and a methoxyl substituent on ring A and two methoxyls on the bottom ring, and indeed (−)-α-*N*-methopapaverberbine [**2**] does not deviate from this norm (13–15, 26).

The main quaternary alkaloid in *P. pseudo-orientale* was the well-known bicyclic isoquinoline cotarnine [**5**], here obtained as the iodide, $C_{12}H_{14}NO_3I$ (27).

Cotarnine, whose ^{1}H-nmr spectral values are outlined around structure **5**, had been prepared by acid treatment of (−)-α-narcotine (5). Because (−)-α-narcotine is sensitive to acid and is usually present in all *Papaver* species, it is difficult to furnish absolute proof of the existence of cotarnine as a true alkaloid.

For the purpose of structure confirmation, cotarnine was reduced with $NaBH_4$ in MeOH to hydrocotarnine [**6**], whose ^{1}H-nmr spectral data are quoted around structure **6** (28).



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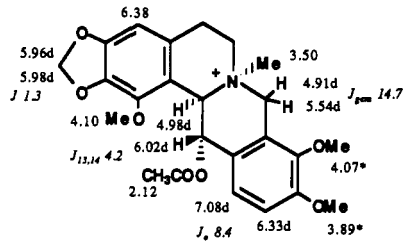

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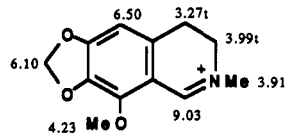

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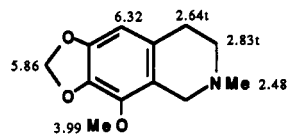

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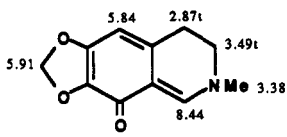

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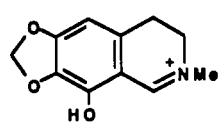

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A minor component of *P. pseudo-orientale* was the orange quinone cotarnoline [**7**], $C_{11}H_{12}NO_3$, whose ^{1}H-nmr spectral characteristics are given around structure **7**. The uv spectrum, with maxima at 232, 256, 350, and 426 nm, suffered a drastic change upon acidification to show maxima at only 251 and 339 nm. An accompanying phenomenon was loss of the orange color. This change may be explained by the formation of iminium salt **8** in acid, with loss of the quinoidal character (29).

It is, of course, possible that cotarnoline is derived from the known phthalideisoquinoline alkaloid (−)-narcotoline, whose rings A and B correspond to those of cotarnoline (30).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Optical rotations are at 25°. ^{1}H-nmr spectra were recorded at 360 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 in July 1988 at Şebinkarahisar, near Giresun, in northeastern Turkey, at an altitude of about 1650 m. *P. cylindricum* was collected in June 1987, at Solhan, near Bingöl, in eastern Turkey, at an altitude of approximately 1800 m. Voucher specimens were retained in the Herbarium of the Faculty of Pharmacy, Istanbul University.

The total aerial parts (*P. cylindricum* 0.7 kg, *P. pseudo-orientale* 2.7 kg) were extracted with MeOH at room temperature. Evaporation of the solvent left a residue which was taken up in 3% HCl. The solution was extracted first with petroleum ether and then with Et_2O. The aqueous layer was basified with NH_4OH and extracted with $CHCl_3$. Solvent evaporation supplied the crude tertiary alkaloids. The remaining aqueous layer was adjusted to pH 6–7 with dilute HCl. Excess aqueous KI solution was added. The solution was extracted with $CHCl_3$, and the organic layer was washed, dried, and concentrated in vacuo to furnish the total quaternary alkaloids (*P. cyclindricum* 1 g, *P. pseudo-orientale* 1 g). Preliminary separation of the alkaloids was achieved by cc, eluting with $CHCl_3$-MeOH (7:3). Further purification was by tlc using the system $CHCl_3$-MeOH (8:2).

ALKALOIDS OF *P. CYLINDRICUM*.—(−)-*N*-Methylthebaine (400 mg) and (+)-*N*-methyl-α-narcotine [**1**] (100 mg) were obtained, both as amorphous iodides.

ALKALOIDS OF *P. PSEUDO-ORIENTALE*.—Amorphous (−)-α-*N*-methopapaverberbine [**2**] (22 mg), cotarnine [**5**] (150 mg), and cotarnoline [**7**] (3 mg) were isolated.

(+)-*N*-METHYL-α-NARCOTINE IODIDE.—Amorphous; uv λ max (MeOH) 224, 291 sh, 312 nm (log ε 4.32, 3.25, 3.46); $[\alpha]_D$ +42° (c = 0.16, MeOH); eims *m/z* (%) 428 (5), 427 (15), 413 (1), 220 (15), 58 (100); ir ν max ($CHCl_3$) 1780, 1720, 1600, 1480, 1460 cm^{-1}. Elemental analysis, $C_{23}H_{26}NO_7I$, calcd for I^- 22.85%, found 22.70%.

N-METHYLATION OF (−)-α-NARCOTINE.—(−)-α-Narcotine (0.5 g) was dissolved in 12 ml MeOH. MeI (3 ml) was added, and the mixture was refluxed gently for 4 h. Solvent evaporation supplied **1** (0.4 g).

(−)-α-*N*-METHOPAPAVERBERBINE IODIDE.—Amorphous; uv λ max (MeOH) 233, 280 nm (log ε 4.22, 3.70); eims *m/z* (%) 385 (1), 368 (1), 367 (2), 206 (100), 204 (3), 164 (3), 142 (17), 127 (6); $[\alpha]_D$ −133° (c = 0.09, MeOH). Elemental analysis, $C_{22}H_{26}NO_6I$, calcd for I^- 24.06%, found 24.26%.

(−)-13-*O*-ACETYL-α-*N*-METHOPAPAVERBERBINE IODIDE.—Salt **2** (8 mg) was treated with pyridine (0.2 ml) and Ac_2O (0.5 ml) overnight. Workup afforded **4** (4.5 mg): eims *m/z* (%) 427 (11), 385 (23), 384 (100), 206 (36), 180 (79), 179 (63), 142 (62), 127 (20); $[\alpha]_D$ −83° (c = 0.015, MeOH).

COTARNINE IODIDE.—Amorphous; uv λ max (MeOH) 228, 253, 339 nm (log ε 4.03, 3.93, 3.98); λ max (MeOH/0.1 N NaOH) 229, 264 nm (log ε 4.02, 3.35); λ max (MeOH/0.1 N HCl) 227, 253, 341 nm (log ε 4.03, 3.90, 3.94); eims *m/z* (%) $[M-I]^+$ 221 (27), 147 (33), 142 (62), 127 (19). Elemental analysis, $C_{12}H_{14}NO_3I$, calcd for I^- 36.56%, found 36.25%.

REDUCTION OF COTARNINE IODIDE.—Treatment of **5** (6 mg) in MeOH (10 ml) with excess $NaBH_4$ furnished hydrocotarnine [**6**] (4 mg): eims *m/z* (%) $[M]^+$ 221 (47), 220 (100), 205 (22), 178 (65), 163 (22), 148 (4).

COTARNOLINE [**7**].—Amorphous; uv λ max (MeOH) 232, 256, 350, 426 nm (log ε 3.92, 3.70,

3.92, 3.35); λ max (MeOH/0.1 N HCl) 251, 339 nm (log ε 3.79, 3.92); eims *m/z* (%) $[M]^+$ 205 (100), 204 (7), 176 (9), 148 (16), 147 (29).

ACKNOWLEDGMENTS

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