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MORPHINANDIENONE ALKALOIDS FROM *ROEMERIA REFRACTA*

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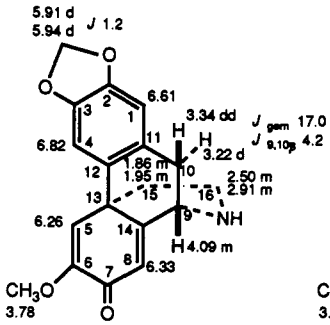
ABSTRACT.—*Roemeria refracta* of Turkish origin has yielded a new morphinandienone, (−)-noramurine [**1**], together with the known (−)-amurine [**2**] and (+)-flavinantine [**3**], all incorporating the *S* configuration at C-9. In the ^{1}H-nmr spectra of 2,3-dioxygenated morphinandienones, the most downfield resonance belongs to the aromatic H-4 on ring A.

In a previous study, we have shown that *Roemeria refracta* DC. (Papaveraceae) is a rich source of isopavine alkaloids (1). We have now found that this plant also contains the new morphinandienone alkaloid (−)-noramurine [**1**], together with the known (−)-amurine [**2**] and (+)-flavinantine [**3**], all possessing the *S* configuration at C-9.



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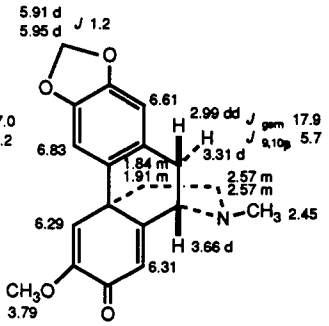

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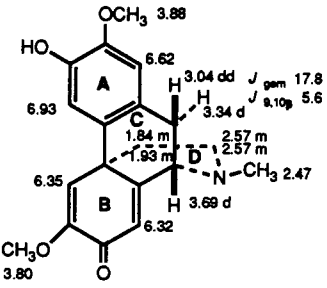

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The ir spectrum of (−)-noramurine [**1**], $C_{18}H_{17}NO_4$, displayed three bands at 1670, 1640, and 1615 cm^{-1}, characteristic of a cross-conjugated dienone system (2). The uv spectrum had two absorption bands at 240 and 290 nm, the latter pointing to C-2, -3 substitution on ring A (2).

The ^{1}H-nmr spectral data, outlined around structure **1**, were consistent with such a substitution pattern, because four aromatic-vinylic proton resonances were clearly in evidence as singlets at δ 6.26, 6.33, 6.61, and 6.82. The spectrum also included a methoxyl singlet at δ 3.78 and a set of methylenedioxy doublets at δ 5.91 and 5.94. No *N*-methyl signal was present, reflecting an *N*-nor structure. This conclusion was supported by the relatively downfield chemical shift of H-9 at δ 4.09 (3).

The mass spectrum furnished molecular ion *m/z* 311, which was also the base peak. Major fragments were *m/z* 296 $[M-Me]^+$, 283 $[M-CO]^+$, 268 $[M-CO-Me]^+$, 252 $[M-CO-OMe]^+$, and 240 $[M-CO-Me-CO]^+$.

The absolute configuration of morphinandienones is reflected in their cd spectra. Compounds with the 9*S* configuration show a maximum between 296 and 307 nm and a minimum near 234 nm, whereas compounds of the *R* configuration have the opposite pattern (4–7). The cd spectrum for our (−)-noramurine exhibited a maximum at 305 nm and a minimum at 235 nm and must, therefore, have the 9*S* configuration as indicated in structure **1**. Indeed, *N*-methylation of **1** furnished a compound identical in all respects with our

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second morphinandienone, (−)-amurine [**2**].

The mass and nmr spectra of (−)-amurine [**2**], $C_{19}H_{19}NO_4$, were in good agreement with those of an authentic sample of (+)-amurine in our possession, as well as with the relevant literature data (8–11). However, our alkaloid displayed negative rotations in both $CHCl_3$ and MeOH solution. Additionally, the cd spectrum was close to that of (−)-noramurine [**1**] but was the mirror image of that of authentic (+)-amurine. It follows that our (−)-amurine [**2**] possesses the 9*S* configuration.

(+)-Amurine with the *R* configuration has been reported from a number of *Papaver* species (12), but only *Meconopsis cambrica* (Papaveraceae) has been shown to contain (−)-amurine (9*S* configuration) (7). Our present finding, therefore, adds a new natural source for (−)-amurine. It should also be pointed out that (−)-amurine is the main morphinandienone in our plant, *R. refracta*.

The third alkaloid we obtained was the known (+)-flavinantine [**3**], $C_{19}H_{21}NO_4$. An nmr nOe study was carried out to ascertain that we had this alkaloid and not its structural isomer, pallidine, in which the substitution pattern on ring A is reversed, with a hydroxyl at C-2 and a methoxyl at C-3. On the one hand, irradiation of the upfield C-6 methoxyl singlet at δ 3.80 effected an enhancement of the vinylic H-5 singlet at δ 6.35. The latter resonance also showed a strong nOe with the aromatic H-4 singlet at δ 6.93. On the other hand, irradiation of the relatively downfield C-2 methoxyl singlet at δ 3.88 resulted in enhancement of the H-1 signal (δ 6.62). Clearly, our alkaloid corresponds to flavinantine and not to pallidine. It also shows in its cd spectrum a maximum at 307 nm and a minimum at 234 nm, so that it belongs to the 9*S* series. Hemingway *et al.* (7) found that flavinantine with the 9*S* configuration, obtained from *M. cambrica*, has the required cd spectrum with a maximum at 301 nm and a minimum at 231 nm, but the specific rotation is reported as negative. Our present results indicate that this alkaloid is dextrorotatory.

It has been reported that the most deshielded proton in 2,3-dioxygenated morphinandienones is the vinylic H-5 (2,13,14), and several assignments have been made accordingly (15–19). In some other studies of 2,3-dioxygenated morphinandienones, however, the most downfield signals are those ascribed to the aromatic protons of ring A (8,20,21). Our nOe results prove that such is indeed the case, with the most downfield resonance due to the aromatic H-4 on ring A.

EXPERIMENTAL

PLANT MATERIAL.—*R. refracta* was collected on June 21, 1988, at Bayburt, in the province of Gümüşhane, in northeastern Turkey. A voucher specimen, No. 1092, was deposted in the Herbarium of the Pharmacognosy Department, Faculty of Pharmacy, Ege University.

EXTRACTION AND FRACTIONATION.—The air-dried and powdered whole plant material (16.7 kg) was extracted with EtOH at room temperature. The crude extract (1 kg) obtained upon removal of the solvent was taken up in 5% HCl and filtered. The filtrate was basified with NH_4OH and extracted with $CHCl_3$. Evaporation of the solvent left an alkaloidal mixture (25 g), which was subjected to cc over Si gel (70–230 mesh, Merck). Elution was with $CHCl_3$ gradually enriched with MeOH. The fractions eluted with 5% MeOH were further separated on another Si gel column (Si gel 60H, Merck). Final purification was by preparative tlc on Si gel glass plates (Merck). Morphinandienones thus obtained were (−)-noramurine [**1**] (4 mg), (−)-amurine (0.5 g), and (+)-flavinantine (13 mg).

(−)-NORAMURINE [**1**].—Amorphous: $[\alpha]_D$ −9° (*c* = 0.09, MeOH), $[\alpha]_D$ −8° (*c* = 0.10, $CHCl_3$); uv λ max (MeOH) 240, 290 nm (log ε 4.08, 3.84); ir ν max ($CHCl_3$) 1670, 1640, 1615 cm^{-1}; eims *m/z* (%) $[M]^+$ 311 (100), 310 (29), 296 (27), 283 (32), 282 (26), 269 (19), 268 (43), 252 (24), 240 (29), 239 (21), 226 (20), 225 (24), 211 (17), 209 (16), 197 (16), 181 (17), 165 (15), 153 (18), 152 (27); cd (MeOH) Δε (nm) 0 (330), +1.39 (305), 0 (290), −0.69 (280), −0.28 (270), −3.12 (252 sh), −8.60 (235), 0 (224), +13.03 (212).

N-METHYLATION OF (−)-NORAMURINE

[1].—Alkaloid **1** (1 mg) was dissolved in MeOH (1 ml), and MeI (0.1 ml) was added. The solution was allowed to stand for 1 h. Evaporation of the solvent at room temperature, followed by tlc to separate the quaternary salts, supplied (−)-amurine [2] (0.6 mg), identical with the natural product.

(−)-AMURINE [2].—Amorphous: $[\alpha]_D$ −14° (c = 0.11, MeOH), $[\alpha]_D$ −10° (c = 0.15, $CHCl_3$); uv λ max (MeOH) 242, 291 nm (log ε 4.18, 3.87); ir ν max ($CHCl_3$) 1660, 1640, 1620 cm^{-1}; eims *m/z* (%) $[M]^+$ 325 (100), 324 (24), 310 (26), 297 (32), 296 (23), 282 (50), 267 (10), 266 (25), 254 (19), 241 (14), 240 (31), 239 (11), 225 (13), 152 (14), 139 (19); cd (MeOH) Δε (nm) 0 (325), +0.82 (306), 0 (296), −1.75 (277 sh), −6.38 (251), −6.18 (249), −12.56 (234), 0 (221), +11.32 (214). Important nmr nOe's are H-1 to H-10α (6%), H-10α to H-1 (9%), H-1 to H-10β (3%), H-10β to H-1 (5%), H-4 to H-5 (35%), H-5 to H-4 (66%), H-5 to 6-MeO (20%), 6-MeO to H-5 (28%), H-15eq (δ 1.84) to H-4 (2%), H-15eq to H-5 (4%), H-8 to H-9 (20%), H-9 to H-8 (55%), H-9 to NMe (4%), NMe to H-9 (19%), NMe to H-10α (9%), H-9 to H-10β (11%). NOe values given here are as percentages of maximum possible nOe effect, so that a full 0.5 enhancement corresponds to 100%.

(+)-FLAVINANTINE [3].—Amorphous: $[\alpha]_D$ +13° (c = 0.13, MeOH), $[\alpha]_D$ +30° (c = 0.1, $CHCl_3$); uv λ max (MeOH) 240, 285 nm (log ε 4.12, 3.81); uv λ max (MeOH-OH^-) 250, 299 nm (log ε 4.20, 3.85); ir ν max ($CHCl_3$) 1665, 1640, 1620 cm^{-1}; eims *m/z* (%) $[M]^+$ 327 (100), 312 (35), 299 (21), 298 (16), 284 (54), 271 (11), 270 (14), 269 (12), 268 (22), 256 (17), 255 (11), 243 (14), 242 (24), 241 (14), 227 (18), 199 (12); cd (MeOH) Δε (nm) 0 (320), +0.36 (307), 0 (300), −2.94 (284), −1.65 (269), −5.61 (248 sh), −14.41 (234), 0 (217), +7.44 (212). Important nmr nOe's are H-1 to 2-MeO (19%), 2-MeO to H-1 (28%), H-1 to H-10α (6%), H-4 to H-5 (15%), H-5 to H-4 (43%), H-5 to 6-MeO (16%), 6-MeO to H-5 (24%), H-8 to H-9 (14%).

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