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NEW PROAPORPHINE ALKALOIDS FROM *ROEMERIA HYBRIDA*

Belkis Gözler,[1] Tekant Gözler,[1] I. Ergün Mete,[1] Alan J. Freyer,
Hélène Guinaudeau[2] and Maurice Shamma

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

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Abstract: Roemeria hybrida (L.) DC. (Papaveraceae) of Turkish origin has yielded the new proaporphine alkaloids (-)-roemerialinone (3), (-)-isoorientalinone (4), (-)-isoroemerialinone (5), (-)-11,12-dihydroorientalinone (6), (+)-8,9-dihydroisoroemerialinone (9) and (-)-α-roemehybrine (11). Catalytic reduction of (-)-isoorientalinone (4) led to (+)-8,9-dihydroisoorientalinone (8) which corresponds to the partly characterized "(+)-dihydroorientalinone" originally obtained from Papaver orientale. The previously known (-)-roehybrine (10) of undetermined structure was also reisolated, and its structure was elucidated. Known proaporphines present are (-)-mecambrine (1) and (-)-orientalinone (2). The isolation of such pairs of diastereomeric proaporphines as 2 and 4, and 3 and 5, points to the fact that enzyme catalyzed intramolecular oxidative coupling of a specific tetraoxygenated tetrahydrobenzylisoquinoline may occur in either of two modes, depending upon the folding of the pendant benzylic ring.

The genus Roemeria, belonging to the botanical family Papaveraceae, is known to be rich in proaporphine and aporphine alkaloids.[3] Since Roemeria hybrida (L.) DC. grows naturally in certain areas of western Turkey, it was collected in April 1985, and its ethanolic extracts were studied for their alkaloidal content. The present paper will be concerned solely with the proaporphines found in the plant.

The first proaporphine isolated was the known (-)-mecambrine (1), whose detailed ^{1}H NMR spectrum is now given for the first time around expression 1. Acid catalyzed rearrangement of this dienone supplied the aporphine (+)-mecambroline [≡ (+)-1,2-methylenedioxy-10-hydroxyaporphine].[3]

The second proaporphine proved to be the somewhat uncommon (-)-orientalinone (2) which had previously been found among a few Papaver species (Papaveraceae).[4] In our hands, acid catalyzed rearrangement of this alkaloid gave rise to (+)-isocorytuberine [≡ (+)-1,10-dihydroxy-2,11-dimethoxyaporphine].[3] The characterization of this dextrorotatory rearrangement product confirmed the C-6a S configuration of our (-)-orientalinone (2).

Since it is known that the dienone-phenol rearrangement proceeds with migration of ring A to that terminus of the dienone which lies syn to H-6a, the methoxyl group in ring D of (-)-orientalinone (2) is located at C-9.[5] An independent proof of the relative stereochemistry of (-)-orientalinone is provided by the NMR spectrum where the chemical shift difference (Δδ) between the two adjacent olefinic protons of the bottom ring is relatively small, 0.46 ppm.[6]

The next two proaporphines we considered were the diastereomeric (-)-roemerialinone (3) and (-)-isoroemerialinone (5). Besides (-)-orientalinone (2), these are the first monomeric proaporphine dienones known bearing an extra oxygenated function in ring D.

The mass spectra of (-)-roemerialinone (3) and (-)-isoroemerialinone (5) are quite similar to that for (-)-orientalinone (2), and present molecular ion m/z 341 which is 14 a.m.u. higher than the corresponding peak in the spectrum of 2. Significantly, the base peak for 3 and 5, m/z 326, is formed by facile loss of a methyl group from the molecular ion. An exactly similar

cleavage pattern is observed with (-)-orientalinone (2) where the base peak m/z 312 corresponds to loss of a methyl from the molecular ion.

The NMR spectrum of (-)-roemerialinone has been summarized around expression 3. It is related to that for (-)-orientalinone (2), especially in regard to the vinylic protons of ring D.[5] The two compounds must thus incorporate the identical relative stereochemistry. Since they also show comparable CD curves with maxima between 235 and 241 nm, they must possess the same C-6a S configuration. This conclusion was further confirmed by acid catalyzed rearrangement of (-)-roemerialinone (3) to the aporphine (+)-N-methylhernagine [≡ (+)-1,2,11-trimethoxy-10-hydroxyaporphine] of known absolute configuration.[3]

The NMR spectrum of (-)-isoroemerialinone (5) differs significantly from that of (-)-roemerialinone (3) in the olefinic region. The Δδ for the adjacent vinylic protons is 0.71 ppm, which indicates that (-)-isoroemerialinone (5) incorporates the opposite configuration at the C-13 spiro center, so that the 11-methoxyl substituent on ring D is on the side opposite H-6a.[6]

Two new dihydroproaporphines containing enone systems, namely (-)-11,12-dihydroorientalinone (6) and (+)-8,9-dihydroisoroemerialinone (9), were also isolated in the present study.

The mass spectrum of (-)-11,12-dihydroorientalinone (6) presents molecular peak m/z 329, and base peak m/z 315. Both ions are larger by two a.m.u. from the corresponding ones in the spectrum of (-)-orientalinone (2).

The NMR spectrum of (-)-11,12-dihydroorientalinone (6) presented a complex aliphatic absorption pattern which could be interpreted through spin decoupling and NOE studies. Reciprocal NOE's could be detected between H-8 (δ 5.82) and H-6a (δ 3.34), pointing to a syn relationship between these hydrogens. The negative specific rotation in such a syn dihydroproaporphine is diagnostic of a C-6a S configuration.[6]

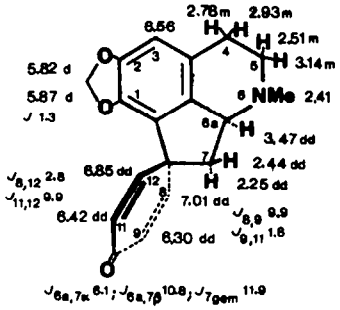
(+)-8,9-Dihydroisoroemerialinone (9), the second dihydroproaporphine obtained, showed an NMR spectrum somewhat close to that for (-)-11,12-dihydroorientalinone (6). Chemical shifts assignments were again confirmed through spin decoupling and NOE experiments. The vinylic H-12 signal (δ 5.72) is enhanced through irradiation of H-7β (δ 1.87), while H-7β shows no NOE with H-6a (δ 3.27). It follows that the double bond of ring D is situated anti to H-6a. The S absolute configuration at H-6a for 9 is readily derived from the positive specific rotation.[6]

In order to further confirm the stereochemical assignments for our two natural dihydroproaporphines 6 and 9, a series of controlled catalytic hydrogenations were carried out. Reduction of (-)-roemerialinone (3) using palladium on carbon supplied (-)-11,12-dihydroroemerialinone (7). Analysis of the NMR spectrum of this material immediately indicated a syn relationship between H-6a and the double bond of ring D which bears the methoxyl substituent. With the exception of the C-1 methoxyl absorption (δ 3.74), this spectrum was extremely close to that of natural (-)-11,12-dihydroorientalinone (6).

When a crude sample of (-)-orientalinone was subjected to similar catalytic reduction, two dihydro derivatives were obtained. The major product was (-)-11,12-dihydroorientalinone (6) identical in all respects with the natural product. A minor component, however, was (+)-8,9-dihydroisoorientalinone (8). The NMR spectrum, as well as the specific rotation and the CD curve, of this minor compound were very close to those for (+)-8,9-dihydroisoroemerialinone (9). The characterization of 8 testifies to the presence of a small amount of (-)-isoorientalinone (4) in our sample of crude (-)-orientalinone (2).

A useful NMR generalization at this stage is that the vinylic proton absorptions for a pair of diastereomeric dihydroproaporphines bearing an extra oxygenated function on ring D will appear at different chemical shifts. In the syn series, this proton will be found around δ 5.82, as in (-)-11,12-dihydroorientalinone (6) and (-)-11,12-dihydroroemerialinone (7), while the absorption falls near δ 5.72 in the anti series as exemplified by (+)-8,9-dihydroisoroemerialinone (9) and (+)-8,9-dihydroisoorientalinone (8).

Comparison of the NMR data and optical measurements of our (+)-8,9-dihydroisoorientalinone (8) with Battersby's "(+)-dihydroorientalinone" obtained from *Papaver orientale* some twenty years



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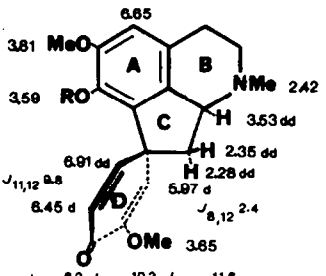

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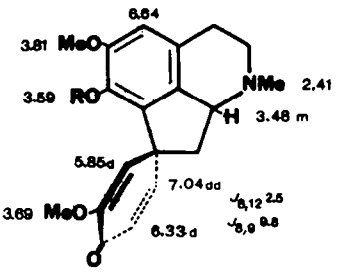

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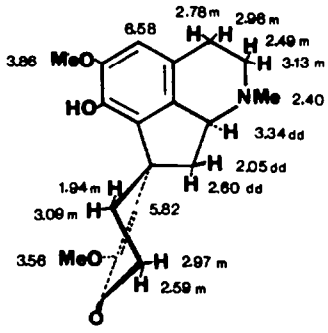

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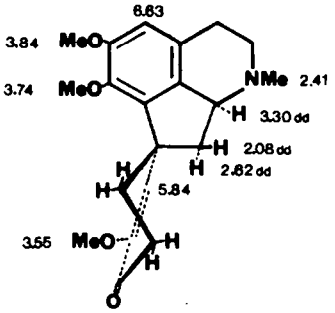

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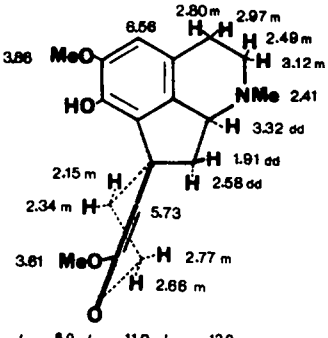

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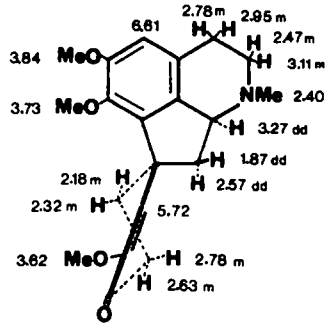

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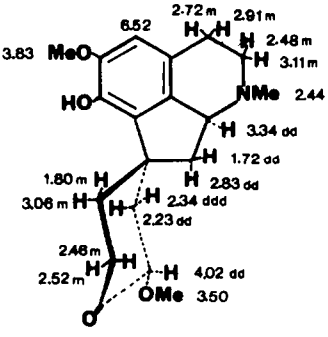

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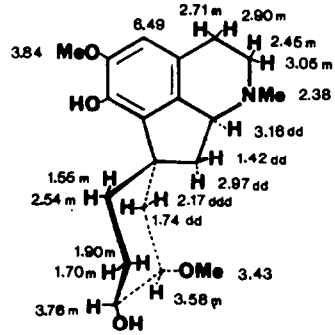

11

ago,[7] and for which no stereochemical assignments had been advanced, makes it evident that Battersby's compound corresponds to (+)-8,9-dihydroisoorientalinone (8).

Turning now to the tetrahydroproaporphine ketones, the alkaloid (-)-roehybrine (10) was first isolated from R. hybrida which had been grown in a private garden in Czechoslovakia.[8] The compound had been partially characterized at that time. It was recognized to possess an aromatic methoxyl group and a phenolic function, an N-methyl, a ketone, and an aliphatic methoxyl, based mainly upon an analysis of the mass spectral cleavage pattern. No firm conclusions could be reached concerning the exact structure and stereochemistry. Presently, we were fortunate enough in reisolating this alkaloid, whose NMR spectrum is now detailed around expression 10.

NMR spin decoupling and NOE studies on (-)-roehybrine (10) showed that H-9 (δ 4.02), which is gem to the aliphatic methoxyl, is syn to H-7α (δ 2.83), which is itself syn to H-6a (δ 3.34). The equatorial orientation of the C-9 methoxyl was first indicated by the magnitude of the coupling constants between H-9 (δ 4.02), and $H\text{-}8_{eq}$ (δ 2.34) and $H\text{-}8_{ax}$ (δ 2.23). The 12.5 Hz coupling between H-9 (δ 4.02) and $H\text{-}8_{ax}$ (δ 2.23) is indicative of an axial-axial relationship, while the 6.4 coupling between H-9 (δ 4.02) and $H\text{-}8_{eq}$ (δ 2.34) reflects an axial-equatorial arrangement. The equatorial assignment for the C-9 methoxyl substituent was then further buttressed by the finding of large reciprocating NOE's between H-9 (δ 4.02) and H-7α (δ 2.83). A further observation in support of the steric assignment in ring D is the long range W coupling between $H\text{-}8_{eq}$ (δ 2.34) and $H\text{-}12_{eq}$ (δ 1.80).

The S absolute configuration at C-6a for base 10 may be deduced from the levorotatory nature of the compound, as well as from the CD curve which shows a maximum at 232 nm.[6]

We have also found that (-)-roehybrine (10) is accompanied in the plant by its hitherto unreported dihydro relative (-)-α-roemehybrine (11). Species 11 shows mass spectral molecular ion m/z 333 (21%) and base peak m/z 332. This fission pattern parallels that for (-)-roehybrine (10) where the base peak again corresponds to $(M - 1)^+$. A generalization may be drawn at this point. When a ring D vinylic methoxyl substituent is present, as in species 2-9, the base peak corresponds to $(M - 15)^+$ due to facile loss of the methoxyl methyl group. In alkaloids 10 and 11 on the other hand, where the ring D methoxyl is aliphatic, this loss of a methyl group is not as prominent and the base peak corresponds to $(M - 1)^+$.

Just like roehybrine (10), α-roemehybrine (11) is levorotatory, and incorporates the C-6a S configuration.

We had recourse to extensive NMR decoupling and NOE studies in order to map out the stereochemical topography of ring D in (-)-α-roemehybrine (11). H-9 (δ 3.58), which is geminal to the aliphatic methoxyl (δ 3.43), must occupy an equatorial site since its coupling constants with the C-8 methylene protons are small ($J_{8ax,9}$ = 4.2 Hz; $J_{8eq,9}$ = 4.0 Hz) and almost equal in magnitude. The aliphatic C-9 methoxyl is therefore axial. These conclusions were then confirmed by the detection of reciprocating NOE's of almost equal amplitude between H-9 (δ 3.58), and $H\text{-}8_{ax}$ (δ 1.74) and $H\text{-}8_{eq}$ (δ 2.17). Furthermore, $H\text{-}8_{eq}$ (δ 2.17) shows reciprocating NOE's with H-6a (δ 3.16) and H-7α (δ 2.97). Significantly, irradiation of the aliphatic methoxyl signal (δ 3.43) also resulted in enhancement of $H\text{-}8_{eq}$ (δ 2.17) and H-7α (δ 2.97). It follows that the spiro C-13 center has the same configuration as in (-)-orientalinone (2) and (-)-roehybrine (10).

NMR NOE measurements on (-)-α-roemehybrine (11) additionally attested to the chair conformation of ring D. Specifically, reciprocating NOE's were observed between H-10 (δ 3.76), $H\text{-}8_{ax}$ (δ 1.74) and $H\text{-}12_{ax}$ (δ 2.54), all of which are axial. A significant coupling was also noted between $H\text{-}8_{eq}$ (δ 2.17) and $H\text{-}12_{eq}$ (δ 1.55). Such a W long range interaction occurs when the cyclohexane ring is in a chair conformation.

The presence in R. hybrida of diastereomeric pairs such as (-)-orientalinone (2) and (-)-isoorientalinone (4), and (-)-roemerialinone (3) and (-)-isoroemerialinone (5), points to the fact that enzyme catalyzed intramolecular oxidative coupling of a specific tetraoxygenated tetrahydrobenzylisoquinoline may occur in either of two modes, depending upon the folding of the pendant benzylic ring.

If one were to apply the aryl migration rule referred to above, acid catalyzed rearrangement of (-)-isoorientalinone (4) should lead to the aporphine (+)-bracteoline [≡ (+)-1,10-dihydroxy-2,9-dimethoxyaporphine]. Significantly, this tetraoxygenated alkaloid has been found among the Papaveraceae.[3]

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EXPERIMENTAL

NMR spectra are at 360 MHz in $CDCl_3$. CD spectra are in MeOH. All alkaloids are amorphous. Plant Collection and Extraction, and Alkaloid Isolation: R. hybrida was collected in Turkey, along the Izmir-Uşak highway, on April 26, 1985. A sample, No. 924, was deposited in the herbarium of the Faculty of Pharmacy, Ege University. The dried powdered plant (9.4 kg) was extracted with cold EtOH to furnish crude extracts (845 g). This was shaken briefly with 5% aq HCl. The acid soln was basified with NH_4OH, and extracted with $CHCl_3$ to give the crude alkaloids (50 g). The separation of the alkaloids was accomplished on a silica gel chromatographic column (Merck 70-230 mesh ASTM). Elution was with $CHCl_3$ gradually enriched with MeOH. Final purification was by TLC on silica gel glass plates. The following proaporphines were obtained: (-)-mecambrine (1), 7 mg; (-)-orientalinone (2), 25 mg; (-)-roemerialinone (3), 22 mg; (-)-isoroemerialinone (5), 2 mg; (+)-8,9-dihydroisoroemerialinone (9), 7 mg; (-)-11,12-dihydroorientalinone (6), 10 mg; (-)-roehybrine (10), 5 mg; and (-)-α-roemehybrine (11), 10 mg.

(-)-Mecambrine (1): $C_{18}H_{17}NO_3$; m/z 295 (M^+, 100), 294 (47), 266 (49), 252 (31); CD Δε (nm) 0 (312), -0.64 (298 sh), -8.5 (265), 0 (248), +6.3 (238).

(-)-Orientalinone (2): $C_{19}H_{21}NO_4$; m/z 327 (M^+, 72), 326 (29), 313 (21), 312 (100), 298 (12), 284 (20); CD Δε (nm) 0 (328), -7.6 (290), 0 (261), +11 (235).

(-)-Roemerialinone (3): $C_{20}H_{23}NO_4$; λ max (MeOH) 228 sh, 249 sh, 289 nm (log ε 4.18, 4.00, 3.73); ν max ($CHCl_3$) 1660, 1630, 1605 cm^{-1}; m/z 341 (M^+, 67), 340 (33), 339 (21), 326 (100), 324 (16), 312 (13), 310 (16), 298 (17), 283 (13); CD Δε (nm) 0 (328), -3.7 (282), 0 (264), +5.2 (241), negative tail below 230 nm.

(-)-Isoroemerialinone (5): $C_{20}H_{23}NO_4$; m/z 341 (M^+, 65), 340 (28), 326 (100), 312 (15); $[\alpha]_D$ -47° (c 0.08, $CHCl_3$).

(-)-11,12-Dihydroorientalinone (6): $C_{19}H_{23}NO_4$; λ max (MeOH) 230 sh, 269 nm (log ε 3.82, 3.81); ν max ($CHCl_3$) 1680, 1610 cm^{-1}; m/z 329 (M^+, 62), 314 (100), 300 (4), 299 (5), 298 (7), 286 (31), 230 (30), 229 (24); CD Δε (nm) 0 (310), -4.4 (262), 0 (223), positive tail below 220 nm; $[\alpha]_D$ -81° (c 0.08, MeOH). Important NMR NOE's are H-6a to H-8 (9%), H-8 to H-6a (7%), H-8 to MeO-9 (12%), MeO-9 to H-8 (24%), H-6a to H-7α (5%), H-7α to H-6a (8%), MeO-2 to H-3 (24%).

(-)-11,12-Dihydroroemerialinone (7): $C_{20}H_{25}NO_4$; m/z 343 (M^+, 69), 342 (48), 328 (100), 312 (17), 300 (25), 285 (15), 270 (25); CD Δε (nm) 0 (295), -2.1 (267), 0 (245), positive tail below 215 nm.

(+)-8,9-Dihydroisoorientalinone (8): $C_{19}H_{23}NO_4$; CD Δε (nm) 0 (310), +2.1 (275), + 3.7 (253), -2.2 (225 sh), negative tail below 215 nm; $[\alpha]_D$ +37° (c 0.15, $CHCl_3$).

(+)-8,9-Dihydroisoroemerialinone (9): $C_{20}H_{25}NO_4$; λ max (MeOH) 226 sh, 266 nm (log ε 3.92, 3.90); ν max ($CHCl_3$) 1680, 1620, 1595, 1480, 1455 cm^{-1}; m/z 343 (M^+, 38), 342 (68), 329 (22), 328 (100), 312 (7), 300 (79), 285 (10), 270 (5), 269 (5), 257 (6), 256 (6), 244 (15), 243 (10), 242 (7); $[\alpha]_D$ +23° (c 0.07, MeOH); CD Δε (nm) 0 (305), +5.6 (257), 0 (237), negative tail below 217 nm. Important NMR NOE's are H-7β to H-12 (4%), H-12 to H-7β (3%), H-12 to MeO-11 (8%), H-6a to H-7α (2%).

(-)-Roehybrine (10): $C_{19}H_{25}NO_4$; λ max (MeOH) 226 sh, 282, 319 nm (log ε 4.06, 3.55, 3.23); ν max ($CHCl_3$) 2940, 2910, 2820, 2790, 1720, 1480 cm^{-1}; m/z 331 (M^+, 60), 330 (100), 316 (44), 288 (56), 274 (3), 272 (3), 256 (17), 230 (16), 216 (12), 188 (20); CD Δε (nm) 0 (315), -0.3 (285 sh), -0.7 (272), 0 (249), +1.2 (232), negative tail below 230 nm; $[\alpha]_D$ -55° (c 0.16, MeOH).

Important NMR NOE's are H-3 to MeO-2 (15%), MeO-2 to H-3 (23%), NMe to H-6a (21%), H-6a to H-7α (2%), H-7α to H-6a (4%), H-9 to H-7α (14%), H-7α to H-9 (4%), H-9 to $H\text{-}8_{eq}$ (4%), H-9 to MeO-9 (17%), MeO-9 to H-9 (5%).

(-)-α-Roemehybrine (11): $C_{19}H_{27}NO_4$; λ max (MeOH) 227 sh, 280 sh, 286 nm (log ε 4.12, 3.72, 3.53); m/z 333 (M^+, 21), 332 (100), 318 (8), 316 (5), 302 (5), 290 (25), 274 (3), 272 (7), 258 (10), 230 (19); $[\alpha]_D$ -49° (c 0.15, MeOH). Important NMR NOE's are MeO-2 to H-3 (20%), H-3 to MeO-2 (14%), H-3 to H-4a (6%), NMe to H-6a (6%), H-6a to NMe (5%), H-6a to $H\text{-}8_{eq}$ (5%), $H\text{-}8_{eq}$ to H-6a (4%), H-6a to H-7α (2%), H-7α to $H\text{-}8_{eq}$ (2%), $H\text{-}8_{eq}$ to H-7α (1%), $H\text{-}8_{eq}$ to H-9 (6%), H-9 to $H\text{-}8_{eq}$ (6%), MeO-9 to $H\text{-}8_{eq}$ (5%), MeO-9 to H-7α (1%), H-9 to $H\text{-}8_{ax}$ (6%), $H\text{-}8_{ax}$ to H-9 (9%), $H\text{-}8_{ax}$ to $H\text{-}10_{ax}$ (3%), $H\text{-}10_{ax}$ to $H\text{-}8_{ax}$ (7%), $H\text{-}10_{ax}$ to $H\text{-}12_{ax}$ (4%), $H\text{-}12_{ax}$ to $H\text{-}10_{ax}$ (5%), $H\text{-}8_{ax}$ to $H\text{-}12_{ax}$ (1%).

Acid Rearrangement of Proaporphines: Proaporphines 1, 2 and 3 (4 mg of each) were dissolved separately in HOAc (3 mL) and conc HCl (2 drops) was added. After standing for 48 h, the solutions were basified with $NaHCO_3$ and extracted with $CHCl_3$. The residues obtained after evaporation of the solvent were purified by TLC. The yield of aporphine in each case was around 75%.

Controlled Catalytic Hydrogenation: Proaporphines 2 (crude, 10 mg) was dissolved in MeOH (3 mL) and 5% Pd/C (5 mg) added. The mixture was stirred in a hydrogen atmosphere for 13 min. Work-up including TLC, provided 6 (4.5 mg) and 8 (1 mg). Similar reduction of pure 3 (5 mg) provided enone 7 (3 mg).

References and Footnotes

1. Permanent address: Faculty of Pharmacy, Ege University, Izmir, Turkey.
2. Permanent address: Faculté de Médecine et de Pharmacie, Université de Limoges, 87025 Limoges Cedex, France; or CNRS, UA 496, Centre d'Etudes Pharmaceutiques, 92290 Chatenay-Malabry, France.
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