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FOUR β-CARBOLINE ALKALOIDS FROM *ROEMERIA HYBRIDA*

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ABSTRACT.—Turkish *Roemeria hybrida* has furnished the new 1-benzyltetrahydro-β-carbolines (−)-roecarboline [**1**] and (+)-norroecarboline [**2**], together with the new simple β-carbolines roeharmine [**3**] and (−)-1,2,3,4-tetrahydroroeharmine [**4**].

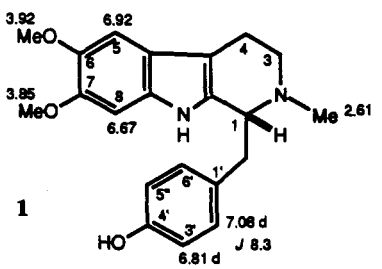
Although a large number of 1-benzyltetrahydroisoquinoline alkaloids that are derived biogenetically from two tyrosine units are known, the corresponding 1-benzyltetrahydro-β-carbolines or 1-benzyl-β-carbolines are very rare. In fact, only one such alkaloid was known prior to the present study, namely the optically inactive ceciline found in Brazilian *Aniba santalodora* (Lauraceae) (1). Such a species would be formed in vivo from one tyrosine- and one tryptamine-derived moieties.

As part of an ongoing study of the alkaloids of Turkish *Roemeria hybrida* (L.) DC. (Papaveraceae), we have obtained two optically active 1-benzyltetrahydro-β-carbolines, (−)-roecarboline [**1**] and (+)-norroecarboline [**2**], together with two simple β-carbolines, roeharmine [**3**] and (−)-1,2,3,4-tetrahydroroeharmine [**4**].

(−)-Roecarboline [**1**], $C_{21}H_{24}N_2O_3$, had a uv spectrum that displayed maxima at 227, 278, 298 sh, 303, and 307 sh nm, characteristic of an indole chromophore (2). A bathochromic shift upon addition of alkali indicated the probable presence of a phenolic function.

The ^{1}H-nmr spectrum has been summarized around structure **1**. Salient features are the AA′BB′ system at δ 6.81 and 7.08, pointing to a para substituted phenyl moiety, two methoxyl singlets at δ 3.85 and 3.92, an *N*-methyl singlet at δ 2.61, and two aromatic singlets at δ 6.67 and 6.92.

The low resolution electron impact mass spectrum lacked a molecular ion



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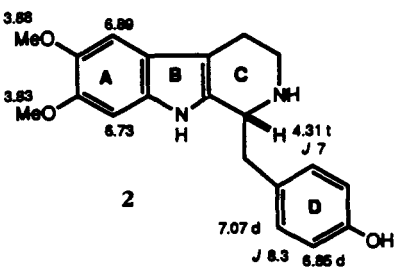

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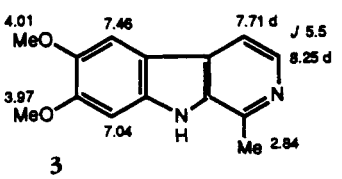

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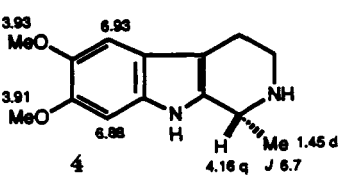

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due to facile cleavage of the C-1 to C-α doubly benzylic bond. Rather, the base peak, *m/z* 245, was also the peak of high-

est mass and represented rings A, B, and C of the molecule. On the other hand, the chemical ionization mass spectrum using isobutane afforded molecular ion *m/z* 352, thus confirming the molecular composition of the alkaloid.

The cd spectrum showed a small maximum at 327 nm and a negative tail beyond 240 nm. Such a pattern is characteristic of the C-1 *R* configuration for substituted tetrahydro-β-carboline systems (3).

(+)-Norroecarboline [**2**], $C_{20}H_{22}N_2O_3$, was present in the plant in an amount nearly equal to that of (−)-roecarboline [**1**]. The uv spectrum was almost identical to that of **1**. The ^{1}H-nmr spectrum, outlined around structure **2**, was also very similar to that of **1**. Conspicuous differences in the spectrum of **2** as compared to that of **1** were the absence of the *N*-methyl signal and the presence of a one-proton triplet at δ 4.31. This signal is due to H-1. The corresponding signal in the ^{1}H-nmr spectrum of (−)-roecarboline [**1**] comes further upfield and is not readily observed because it overlaps with other aliphatic resonances. An exact analogy for such a phenomenon is provided by the 1-benzyltetrahydroisoquinolines where the H-1 signal for a nor compound is again shifted downfield vis-à-vis the corresponding signal for the *N*-methyl analogue (4).

Also because of facile benzylic cleavage, the mass spectrum of (+)-norroecarboline [**2**] included no molecular ion peak. Rather, an *m/z* 231 base peak testified to the nor nature of the alkaloid and represented rings A, B, and C. A chemical ionization mass spectrum did indeed furnish an *m/z* 338 molecular ion peak, in accord with the proposed structure **2**.

The cd spectrum of (+)-norroecarboline [**2**] closely resembled that of **1**, indicating again the C-1 *R* configuration. The fact that alkaloids **1** and **2** possess the identical absolute configuration but opposite signs of rotation can be explained by the spatial disposition of the pendent ring D depending upon the presence or absence of the *N*-methyl group. In the nor compound **2**, ring D lies preferentially on the less hindered N-2 side, while in the *N*-methyl analogue **1** it is located toward the indole side. A parallel trend has been amply documented in the 1-benzyltetrahydroisoquinoline series (5).

As final proof of structure, *N*-methylation of (+)-norroecarboline [**2**] afforded (−)-roecarboline [**1**], identical in all respects with the natural product.

The fully aromatic nature of our third alkaloid, the optically inactive roeharmine [**3**], $C_{14}H_{14}N_2O_2$, was deduced from the relatively simple ^{1}H-nmr spectrum which has been summarized around structure **3**. The two aromatic doublets at δ 7.71 and 8.25, with the characteristic 5.5 Hz coupling constant, point to an aromatic ring C. The presence of methoxyl singlets at δ 3.97 and 4.01 and aromatic singlets at δ 7.04 and 7.46 established the substitution pattern in ring A. Finally, the δ 2.84 three-proton singlet could be assigned to the C-1 methyl group (6,7).

The aromaticity of the compound was also reflected in the simplicity of the mass spectrum. Molecular ion peak *m/z* 242 was also the base peak. A methyl radical could easily be expelled to give the *m/z* 227 (73%) peak. Also, a prominent *m/z* 199 (46%) peak was formed by loss of CO from the *m/z* 227 ion. Such a fragmentation pattern is typical of β-carbolines (8).

The complex uv spectrum of roeharmine [**3**] is also characteristic of β-carbolines (see Experimental). A distinct bathochromic shift was obtained upon addition of acid; this resulted from protonation of the imine nitrogen of ring C.

Our fourth and last alkaloid is simply the reduced form of roeharmine and corresponds to (−)-1,2,3,4-tetrahydroroeharmine [**4**], $C_{14}H_{18}N_2O_2$. In the ^{1}H-nmr spectrum, the C-1 methyl now resonates as a doublet at δ 1.45, while H-1 is found as a quartet at δ 4.16. Molecular

ion peak *m/z* 246 (35%) is present in the mass spectrum, and the base peak *m/z* 231 is formed by easy loss of a methyl radical from that ion.

The cd curve of (−)-1,2,3,4-tetrahydroroeharmine [**4**] has a low maximum at 329 nm and a negative tail around 240 nm, thus designating the C-1 *R* configuration (3).

Because *R. hybrida* has been shown to produce proaporphine-β-carboline dimers in large quantities (9), as well as a variety of proaporphine monomers (10), it is not surprising to find that 1-benzyltetrahydro-β-carbolines as well as simple β-carbolines also occur in the plant. Finally, it should also be pointed out that a 6,7-dioxygenation pattern, as in the present case, was previously unknown among naturally occurring simple β-carbolines (11–13).

EXPERIMENTAL

PLANT MATERIAL.—*R. hybrida* was collected on April 22, 1988, in the province of Uşak, in western Turkey. A voucher specimen, No. 1091, was deposited in the Herbarium of the Department of Pharmacognosy, Faculty of Pharmacy, Ege University.

EXTRACTION AND FRACTIONATION.—The air-dried and powdered plant material (8.8 kg) was extracted with EtOH at room temperature. Evaporation of the solvent yielded a dark syrupy residue (915 g), which was dissolved in 5% HCl and filtered. The acidic filtrate was basified with NH_4OH and extracted with $CHCl_3$. The organic solvent was distilled in vacuo to furnish a residue of crude alkaloids (25 g). Preliminary fractionation was achieved on a column of Kieselgel 60 (70–230 mesh, Merck), using $CHCl_3$ gradually enriched with MeOH. Further fractionation was carried out by preparative cc using Si gel 60H (Merck). Final purification was by preparative tlc on Si gel glass plates (Merck). The compounds were obtained from the column in this order: roeharmine (7 mg), (−)-roecarboline (7 mg), (+)-norroecarboline (6 mg), and (−)-1,2,3,4-tetrahydroroeharmine (3 mg). All ^{1}H-nmr spectra were obtained at 360 MHz in $CDCl_3$. All compounds are amorphous.

(−)-ROECARBOLINE [**1**].—$[\alpha]_D$ −5° (*c* = 0.13, MeOH), $[\alpha]_D$ −27° (*c* = 0.14, $CHCl_3$); uv λ max (MeOH) 227, 278, 298 sh, 303, 307 sh nm (log ε 4.44, 3.85, 3.91, 3.93, 3.88); uv λ max (MeOH − OH^-) 232, 299, 303 sh, 309 sh nm (log ε 4.55, 4.27, 4.26, 4.20); eims *m/z* (%) 245 (100), 230 (6), 229 (10), 201 (8); cims (isobutane) *m/z* $[M]^+$ 352; cd (MeOH) Δε (nm) +0.40 (327), 0 (319), −1.81 (308), −1.30 (296), −3.11 (256), −2.91 (242), negative tail beyond 240 nm. Important nmr nOe's are H-5 to 6-OMe (20%), 6-OMe to H-5 (10%), H-8 to 7-OMe (14%), 7-OMe to H-8 (9%).

(+)-NORROECARBOLINE [**2**].—$[\alpha]_D$ +4° (*c* = 0.21, MeOH), $[\alpha]_D$ +35° (*c* = 0.07, $CHCl_3$); uv λ max (MeOH) 227, 274, 297, 302, 307 sh nm (log ε 4.49, 3.92, 3.97, 3.97, 3.92); uv λ max (MeOH − OH^-) 213, 228, 299, 309 sh nm (log ε 4.49, 4.45, 4.05, 3.95); eims *m/z* (%), 231 (100); cims *m/z* $[M]^+$ 338; cd (MeOH) Δε (nm) +0.45 (330), 0 (318), −0.99 (311), −0.63 (300), negative tail beyond 240 nm.

N-METHYLATION OF **2**.—Alkaloid **2** (1.5 mg) in MeOH (2 ml) was treated with 37% aqueous HCHO (5 drops). The solution was allowed to stand for 3 h. Portions of $NaBH_4$ were added while stirring and cooling. Workup afforded **1** (0.8 mg).

ROEHARMINE [**3**].—Uv λ max (MeOH) 237, 253 sh, 294 sh, 304, 342 nm (log ε 4.40, 4.18, 4.06, 4.18, 3.72); uv λ max (MeOH − H^+) 239, 264 sh, 270, 323, 383 nm (log ε 4.27, 4.13, 4.15, 4.18, 3.80); eims *m/z* (%) $[M]^+$ 242 (100), 241 (6), 228 (12), 227 (73), 200 (7), 199 (46), 198 (7), 197 (8), 184 (23), 181 (9), 171 (12), 170 (5), 169 (10), 156 (7); hreims $[M]^+$ calcd for $C_{14}H_{14}N_2O_2$, 242.1055, found 242.1068.

(−)-1,2,3,4-TETRAHYDROROEHARMINE [**4**].—$[\alpha]_D$ −4° (*c* = 0.12, MeOH), $[\alpha]_D$ −4° (*c* = 0.10, $CHCl_3$); uv λ max (MeOH) 223, 268 sh, 273, 297, 301, 307 sh nm (log ε 4.19, 3.58, 3.60, 3.76, 3.76, 3.71); eims *m/z* (%) $[M]^+$ 246 (35), 245 (19), 232 (16), 231 (100), 217 (11), 216 (10), 215 (10), 202 (9), 187 (13); cd (MeOH) Δε (nm) +0.33 (329), 0 (319), −0.99 (313), −0.28 (298), negative tail beyond 240 nm; hreims $[M]^+$ calcd. for $C_{14}H_{18}N_2O_2$, 246.1368, found 246.1349.

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