

## THE TEN PROAPORPHINE-TRYPTAMINE DIMERS

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**ABSTRACT.**—Turkish *Roemeria hybrida* produces ten proaporphine-tryptamine dimers, two of which, (–)-roehybridine [1] and (–)-roemeridine [8], were previously known. The dimers have been divided into three subgroups based on the stereochemistry at C-9 and at the spiro C-10 center. The first subgroup, syn 9-OMe axial, includes (–)-roehybridine [1], (–)-nor-roehybridine [2], (–)-*O*-methylroehybridine [3], (–)-roehybridine β-*N*-oxide [4], and (–)-roehybramine [5]. The second subgroup, syn 9-OMe equatorial, has only two members, (+)-roehymine [6] and (+)-roehybramine [7]. The third subgroup, anti 9-OMe axial, includes (–)-roemeridine [8], (–)-*O*-methylroemeridine [9], and (–)-roemebramine [10]. In the syn series, **A**, the proaporphine nitrogen atom and the non-basic nitrogen of the indole moiety are on the same side of ring D, whereas they are on opposite sides in the anti series, **B**.

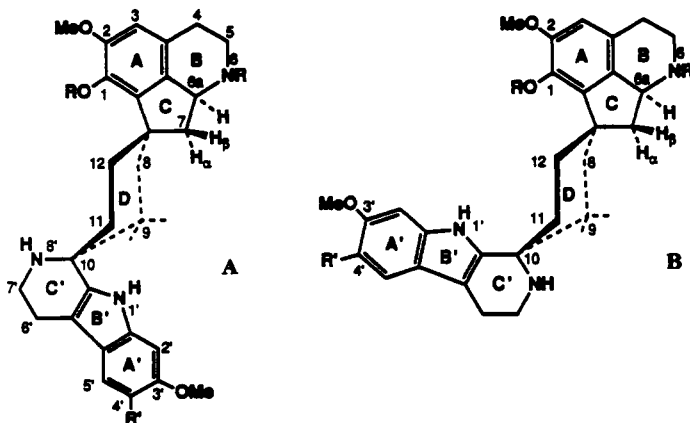
The proaporphine-tryptamine dimers are a recently recognized group of heptacyclic alkaloids most probably formed biogenetically by Mannich-type condensation of a ketonic tetrahydroproaporphine with a tryptamine analogue. Prior to the present work, only two of these dimers had been known, namely (–)-roehybridine [1] and (–)-roemeridine [8] (1,2), and structures had been proposed for them (3,4).

The purpose of the present paper is to describe eight additional proaporphine-tryptamine dimers and to reconsider some of the previously made structural and <sup>1</sup>H-nmr spectral assignments.

We have investigated several Turkish *Roemeria* (Papaveraceae) species and have found that proaporphine-tryptamine dimers occur only in *Roemeria hybrida* DC. (3). The original literature reports on (–)-roehybridine [1] and (–)-roemeridine [8] also indicated that same plant as the source of these alkaloids (1,2). There is a report that *Papaver pavoninum* (Papaveraceae) may possibly produce (–)-roemeridine (5).

The proaporphine-tryptamine dimers may be classified into two broad stereochemical series labeled syn and anti, as exemplified by structures **A** and **B**. In the syn series, **A**, the proaporphine nitrogen atom and the non-basic nitrogen of the indole moiety are on the same side of ring D, whereas in the anti series, **B**, they lie on opposite sides.

We have found that all proaporphine-tryptamine dimers include an aliphatic



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methoxyl substituent on ring D, specifically at C-9. Within the syn series, this methoxyl may be either axial or equatorial, but in the anti series only dimers with an axial C-9 methoxyl are encountered.

A further subdivision of the dimers is possible based upon the fact that some are dimethoxylated on ring A' at at C-3' and C-4', while others are only monomethoxylated, specifically at C-3'. All dimers are oxygenated at C-1 and C-2 on ring A. This is in line with the observation that all naturally occurring proaporphines and aporphines are also oxygenated at these two sites. In the case of the proaporphine-tryptamine dimers, the C-1 substituent may be hydroxyl or methoxyl, but a methoxyl seems to be preferred at C-2, as indicated by nmr nOe's which relate 2-OMe to H-3 which in turn is related to the C-4 methylene protons of ring B (see Experimental).

All *Roemeria* proaporphines incorporate the C-6a *S* configuration (3), and so do the dimers under consideration. All assignments of stereochemistry are thus predicated upon the *S* configuration at C-6a.

The discussion that follows has been subdivided into three main parts, reflecting the stereochemical characteristics of the alkaloids in question.

**SYN SERIES, 9-OMe AXIAL.**—The prototype for this group is (–)-roehybridine [1], C<sub>31</sub>H<sub>39</sub>N<sub>3</sub>O<sub>5</sub>, which was first isolated by a Russian team in the 1950s (1) and whose structure elucidation was reported only in 1989 based upon extensive <sup>1</sup>H-nmr studies, including spin decoupling and nOe measurements as well as <sup>13</sup>C/<sup>1</sup>H correlations and COLOC experiments (3).

We have now reisolated (–)-roehybridine and have also obtained three close analogues, (–)-norroehybridine [2], C<sub>30</sub>H<sub>37</sub>N<sub>3</sub>O<sub>5</sub>, (–)-*O*-methyloehybridine [3], C<sub>32</sub>H<sub>41</sub>N<sub>3</sub>O<sub>5</sub>, and (–)-roehybridine β-*N*-oxide [4], C<sub>31</sub>H<sub>39</sub>N<sub>3</sub>O<sub>6</sub>. A fourth alkaloid obtained is (–)-roehybramine [5], C<sub>30</sub>H<sub>37</sub>N<sub>3</sub>O<sub>4</sub>, whose ring A' is monomethoxylated, while the other dimers of this subgroup are dimethoxylated on that ring.

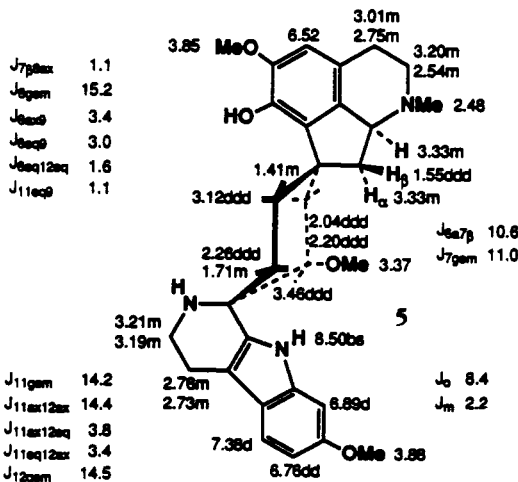
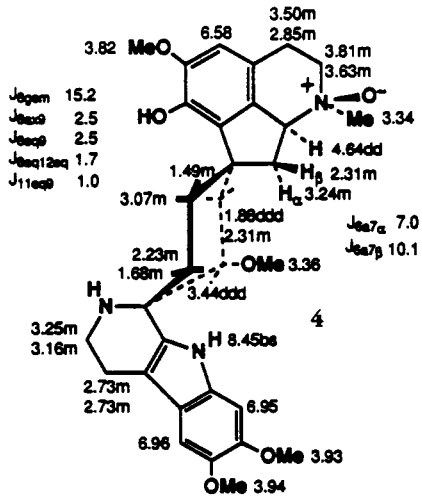
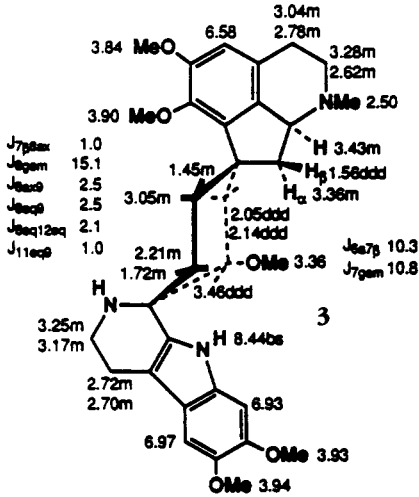
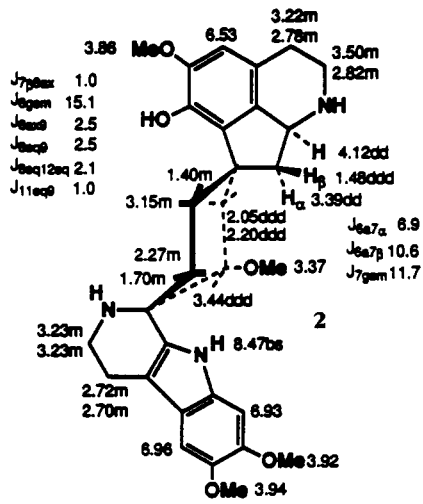
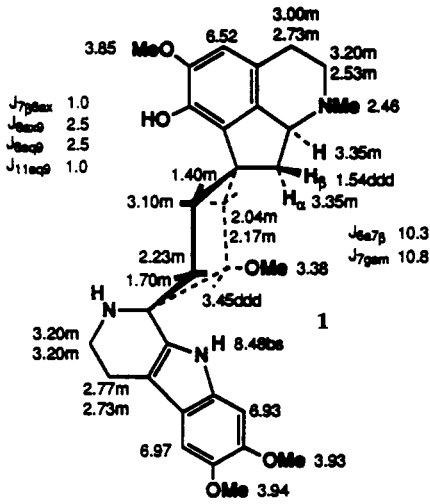
Dimers of the syn 9-OMe axial subgroup may be immediately recognized, as the 9-OMe <sup>1</sup>H-nmr singlet appears in the δ 3.36–3.38 range and H-9 is found between δ 3.44 and 3.46. H-9 actually appears as a narrow ddd, spanning a width of 6 Hz which is typical of equatorial hydrogens in a substituted cyclohexane structure.

As previously reported (3), for (–)-roehybridine [1] the nmr signal for H-6a (δ 3.35) overlaps with that for H-7α. Still, it was possible to observe that irradiation of H-7α caused an nOe of the H-8eq signal (δ 2.04), and irradiation of H-7β (δ 1.54) enhanced H-12eq (δ 1.40). Additionally, nOe's were observed between the broad indolic H-1' signal (δ 8.48) and the axial 9-OMe singlet (δ 3.38) on the one hand, and H-1 lax (δ 2.23) on the other, thus fixing the gross stereochemistry of the molecule.

Very significantly, homodecoupling experiments revealed a long range *W* coupling of ca. 1 Hz between H-9eq (δ 3.45) and H-11eq (δ 1.70), and another *W* coupling of about 2 Hz obtained between H-8eq (δ 2.04) and H-12eq (δ 1.40). There was even a small (1 Hz) *W* coupling between H-7β (δ 1.54) and H-8ax (δ 2.17), indicating that these hydrogens too are nearly in a plane. The above results were in complete agreement with the structure previously advanced for (–)-roehybridine [1] (3).

The nmr chemical shifts for (–)-norroehybridine [2], (–)-*O*-methyloehybridine [3], and (–)-roehybridine β-*N*-oxide [4] resembled those of (–)-roehybridine [1], except for some specific resonances which reflected their structural dissimilarities.

The spectrum of (–)-norroehybridine [2], C<sub>30</sub>H<sub>37</sub>N<sub>3</sub>O<sub>5</sub>, was devoid of the N-6 methyl singlet due to the "nor" nature of the alkaloid. The 9-OMe singlet was at δ 3.37 and H-9eq was at δ 3.44, pointing to a close analogy with (–)-roehybridine [1]. The H-6a signal fell further downfield (δ 4.12) as compared to the corresponding resonance in 1, which was at δ 3.35. Such a downfield shift for a proton attached to a carbon adja-



cent to a basic nitrogen had previously been observed when an *N*-methyl alkaloid is compared to its nor analogue (6). A similar trend was also noted for the (–)-norroehybridine C-5 protons ( $\delta$  2.82 and 3.50), which had moved downfield by about 0.3 ppm.

The nonphenolic (–)-*O*-methyloehybridine [3],  $C_{32}H_{41}N_3O_5$ , was found in the plant and could also be obtained through  $CH_2N_2$  *O*-methylation of (–)-roehybridine [1]. Its 9-OMe singlet was at  $\delta$  3.36, and H-9eq was at  $\delta$  3.46. The main difference in the spectrum, as compared with that of 1, was the presence of an additional methoxyl singlet at  $\delta$  3.90, reflecting *O*-methylation at C-1. The rest of the nmr spectrum of (–)-*O*-methyloehybridine was very similar to that of 1, including W long-range couplings between H-9eq ( $\delta$  3.46) and H-1eq ( $\delta$  1.72), between H-8eq ( $\delta$  2.50) and H-12eq ( $\delta$  1.45), and also between H-7 $\beta$  ( $\delta$  1.56) and H-8ax ( $\delta$  2.14).

The *N*-oxide nature of the highly polar (–)-roehybridine  $\beta$ -*N*-oxide [4],  $C_{31}H_{39}N_3O_6$ , was indicated by the downfield shift of the N-6 methyl singlet which was at  $\delta$  3.34. Likewise, H-6a was downfield, appearing at  $\delta$  4.64, and so were the C-5 methylene protons ( $\delta$  3.63 and 3.81).

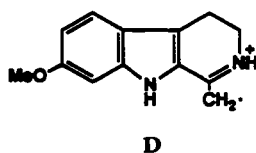
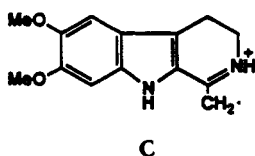
A series of nmr nOe experiments were run in order to settle the stereochemistry at the *N*-oxide center. Irradiation of the *N*-oxide methyl group ( $\delta$  3.34) affected both H-7 $\alpha$  ( $\delta$  3.24) and H-7 $\beta$  ( $\delta$  2.31) in almost equal magnitude, pointing to the alpha and pseudo-equatorial nature of this group. Furthermore, a strong nOe could be observed between the *N*-oxide methyl and H-6a ( $\delta$  4.64), a result of their syn relationship.

An additional point of interest in the nmr spectra of the alkaloids considered so far is that the C-2 methoxyl singlet falls in the  $\delta$  3.82 to 3.86 range. In contrast, the C-1 methoxyl of (–)-*O*-methyloehybridine [3] is further downfield, at  $\delta$  3.90.

Alkaloids 1–3 include, in their mass spectra, molecular ions in the order of 6 to 17% of the base peak which is always  $m/z$  244 and represents the tetrahydro- $\beta$ -carbolinium ion C. In the case of the *N*-oxide 4, however, the molecular ion  $m/z$  549 is very small due to facile loss of oxygen to provide the  $[M - 16]^+$  ion,  $m/z$  533. The base peak is still  $m/z$  244.

The dimer (–)-roehybramine [5],  $C_{30}H_{37}N_3O_4$ , was clearly related to the above alkaloids, as its aliphatic 9-OMe singlet appeared in the nmr spectrum at  $\delta$  3.37 and H-9 was at  $\delta$  3.46. The spectrum also indicated the presence of only two aromatic methoxyls, at  $\delta$  3.85 and 3.88, as well as a 3-proton spin system in ring A'. The methoxyl at  $\delta$  3.85 showed mutual nOe's with H-3 ( $\delta$  6.52), placing it at C-2. The remaining methoxyl ( $\delta$  3.88) displayed reciprocating enhancements with H-4' ( $\delta$  6.76) and H-2' ( $\delta$  6.89), indicating its position at C-3'. Additional interactions between the indolic H-1' ( $\delta$  8.50) and H-2' as well as 9-OMe ( $\delta$  3.37) completed the stereochemical picture.

Interlocking with the above conclusions, the base peak in the mass spectrum of 5 was  $m/z$  214 rather than 244 due to the monomethoxylated ion D.

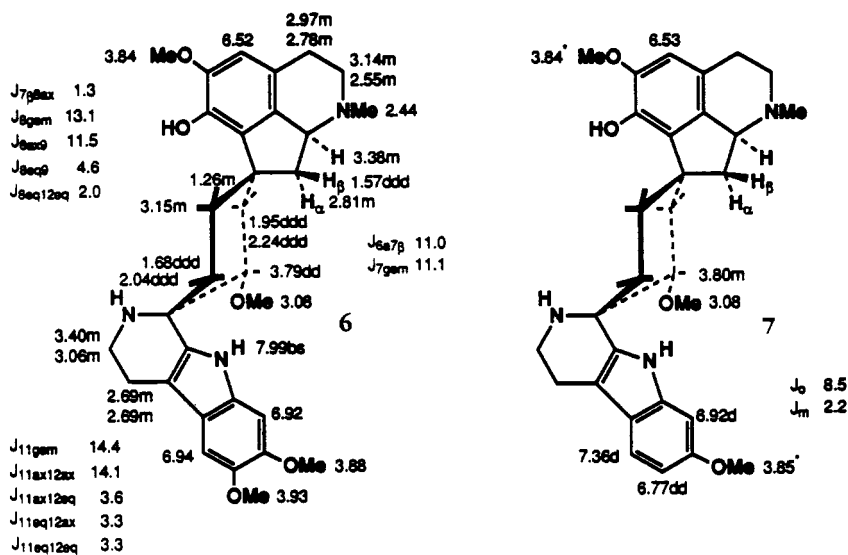


It is also relevant to point out that alkaloids 1–4 have a nearly identical general substitution pattern, and their uv spectra show maxima around 226, 290, 298, and 303 nm, with a shoulder near 308 nm. In contrast, (–)-roehybramine [5], which lacks the 4'-OMe group, exhibits in its uv spectrum a simpler pattern with maxima at 227 and 290 nm and a shoulder at 300 nm.

SYN SERIES, 9-OMe EQUATORIAL.—(+)-Roehymine [6],  $C_{31}H_{39}N_3O_5$ , and its ring A' monomethoxylated analogue (+)-roebramine [7],  $C_{30}H_{37}N_3O_4$ , are the first examples of proaporphine-tryptamine dimers with equatorial 9-OMe groups, and they both belong to the syn series.

In the nmr spectra, the 9-OMe singlet is found at  $\delta$  3.08 for both alkaloids, while the H-9 dd is at  $\delta$  3.79 for (+)-roehymine [6] and at  $\delta$  3.80 for (+)-roebramine [7]. In both instances, the H-9 multiplet spans a width of 17 Hz, reflecting an equatorial and an axial coupling to the H-8 protons in a chair-like ring D.

Because dimer 7 was obtained only in small amount (2 mg), most of our detailed nmr measurements were carried out on its analogue 6. An nmr nOe network was observed for 6 between the indolic H-1' ( $\delta$  7.99) and the axial H-9 ( $\delta$  3.79) and H-11 ( $\delta$  1.68), thus indicating the equatorial character of the 9-OMe substituent. Another set of nOe's connected the axial H-9 ( $\delta$  3.79) with H-7 $\alpha$  ( $\delta$  2.81), which in turn was connected to H-8eq ( $\delta$  1.95). On the other hand, H-7 $\beta$  ( $\delta$  1.57) was related to the neighboring H-12eq ( $\delta$  1.26).



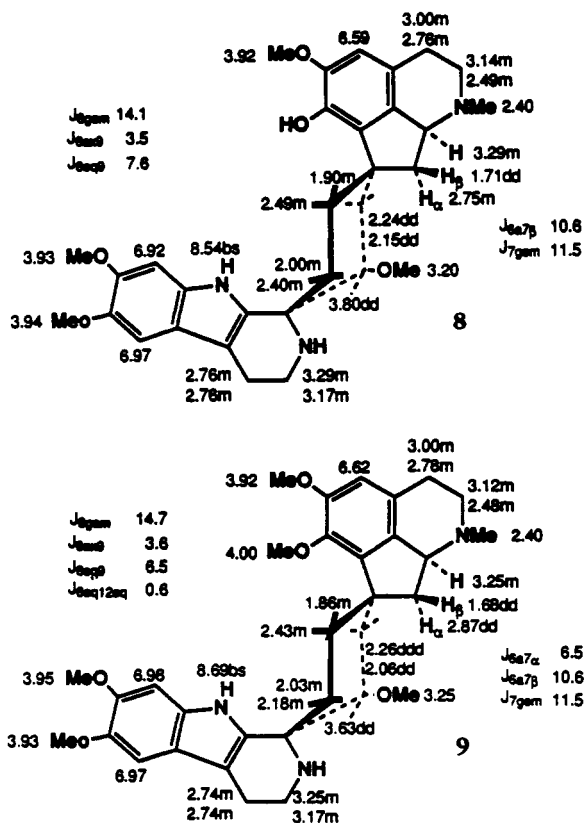
A long-range W coupling (2.0 Hz) appeared between H-8eq ( $\delta$  1.95) and H-12eq ( $\delta$  1.26), and another long-range coupling obtained between H-7 $\beta$  ( $\delta$  1.57) and H-8ax ( $\delta$  2.24). Significantly, however, and in contradistinction to the alkaloids of the roehybridine type, no W coupling was seen between H-9 and H-11eq because of the equatorial character of the C-9 methoxyl.

In the case of (+)-roebramine [7], the C-2 and C-3' methoxyl resonances nearly overlapped at  $\delta$  3.84–3.85. Saturation of this double signal resulted in enhancements of H-3 ( $\delta$  6.53), H-2' ( $\delta$  6.92), and H-4' ( $\delta$  6.77), thus establishing the positions of the methoxyl groups on the proaporphine-tryptamine framework.

As expected, the uv spectrum of (+)-roehymine [6] showed maxima at 226, 291, 297, and 302 nm, with a shoulder at 309 nm, and was thus closely related to the absorption pattern observed for alkaloids 1–4. In contrast, the spectrum of (+)-roebramine [7] exhibited a maximum at 288 nm, with a shoulder at 300 nm, and was thus similar to that of (–)-roehybramine [5]. Likewise, the mass spectrum of (+)-roehymine [6] included molecular ion  $m/z$  533 (7%) and base peak  $m/z$  244 due to ion C. However, the mass spectrum of (+)-roebramine [7] showed molecular ion  $m/z$  503 (6%) and base peak  $m/z$  214, representing ion D.

ANTI SERIES, 9-OMe AXIAL.—Our initial efforts at a structure assignment for (–)-roemeridine [8], an alkaloid first isolated in Russia in the 1950s (1), were handicapped by the low solubility of the compound in  $\text{CDCl}_3$  and by the fact that the nmr spectrum showed some of the ring-D proton resonances as broad and not well-defined signals. The alkaloid was much more soluble in  $\text{CD}_3\text{OD}$ , but then the critical N-1' proton could not be observed. Our structure assignment was then found to be stereochemically at variance with the results of an X-ray study of this dimer carried out in Czechoslovakia (4). We have now reexamined the nmr spectrum of (–)-roemeridine [8],  $\text{C}_{31}\text{H}_{39}\text{N}_3\text{O}_5$ , and have found that somewhat sharper peaks can be obtained in  $\text{CDCl}_3$  at  $50^\circ$ . Furthermore, we now report the isolation and characterization of (–)-*O*-methyloemeridine [9],  $\text{C}_{32}\text{H}_{41}\text{N}_3\text{O}_5$ , which is more soluble than (–)-roemeridine [8] in  $\text{CDCl}_3$  and whose nmr spectrum at  $50^\circ$  is much better delineated. Very significantly, with this new alkaloid we were able to observe nmr nOe interactions between 1-OMe and NH-1'. As a result of our new studies, we find complete agreement with the X-ray conclusions. The nmr results described below for dimers 8 and 9 were obtained at  $50^\circ$  in  $\text{CDCl}_3$  solution.

The spectrum of (–)-*O*-methyloemeridine [9] included an 9-OMe singlet at  $\delta$  3.25 and an H-9 dd at  $\delta$  3.63. The stereochemistry was indicated by a skein of nOe's originating from the indolic H-1' ( $\delta$  8.69) and involving 1-OMe ( $\delta$  4.00), H-9eq ( $\delta$  3.63), H-8ax ( $\delta$  2.06), H-11eq ( $\delta$  2.18), H-12ax ( $\delta$  2.43), and H-2' ( $\delta$  6.98). A smaller network of nOe's was centered around H-7 $\beta$  ( $\delta$  1.68) and was directed towards H-12eq ( $\delta$  1.86) and H-11ax ( $\delta$  2.03). The 1-OMe singlet ( $\delta$  4.00) showed nOe's not only with H-1' ( $\delta$  8.69) but also with H-12ax ( $\delta$  2.43) and H-11eq ( $\delta$  2.18). Signifi-



cantly, no nOe was in evidence between H-7 $\alpha$  ( $\delta$  2.87) and an H-9 signal because of the axial disposition of 9-OMe.

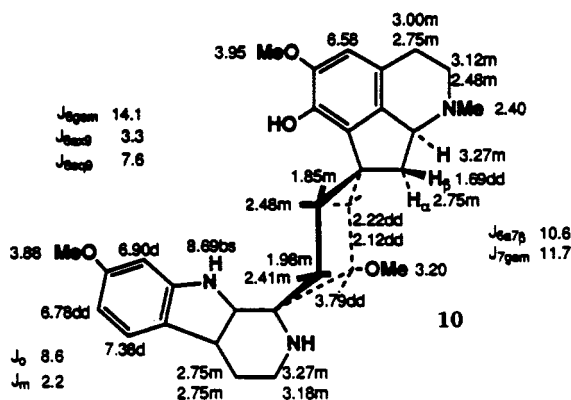
It must be pointed out that ring D in (-)-*O*-methyloemeridine is not a perfect chair as in the (-)-roehybridine series since  $J_{8ax,9} = 3.6$  Hz and  $J_{8eq,9} = 6.5$  Hz. These coupling constants would have been nearly identical if the ring had been a true chair. Also, although a long range W coupling could be observed between H-8eq ( $\delta$  2.26) and H-12eq ( $\delta$  1.86), its value (0.6 Hz) was smaller than in the instance of (-)-roehybridine [1] and its analogues. No W coupling was in evidence between H-9eq ( $\delta$  3.63) and H-11eq ( $\delta$  2.18). Finally, the axially oriented 9-OMe ( $\delta$  3.25) showed nOe's with H-8eq ( $\delta$  2.26).

Turning now to (-)-roemeridine [8], the nOe network emanating from H-1' ( $\delta$  8.54) involved H-2' ( $\delta$  6.92) and H-9eq ( $\delta$  3.80), while H-12ax ( $\delta$  2.49) showed an nOe with H-1'. Another telling nOe was between the axially oriented 9-OMe ( $\delta$  3.20) and H-8eq ( $\delta$  2.24), which in turn was interrelated with H-7 $\alpha$  ( $\delta$  2.75). Finally, saturation of H-7 $\alpha$  ( $\delta$  2.75) affected H-6a ( $\delta$  3.29) as well as H-8eq ( $\delta$  2.24).

The coupling constants between H-9eq ( $\delta$  3.80) and the two protons at C-8 were again unequal,  $J_{8eq,9} = 7.6$  Hz and  $J_{8ax,9} = 3.5$  Hz, reflecting the imperfect chair conformation of ring D.

A significant chemical correlation was carried out at this stage. CH<sub>2</sub>N<sub>2</sub> *O*-methylation of (-)-roemeridine [8] generated (-)-*O*-methyloemeridine [9], so that the two compounds are indeed directly related.

The nmr spectrum of our last alkaloid, (-)-roemebamine [10], C<sub>30</sub>H<sub>37</sub>N<sub>3</sub>O<sub>4</sub>, showed a 9-OMe singlet at  $\delta$  3.20 and an H-9 dd at  $\delta$  3.79. Several features of the spectrum resembled those for (-)-roemeridine [8] and (-)-*O*-methyloemeridine [9], except for the presence of an ABX system,  $\delta$  6.90 d,  $\delta$  6.78 dd, and  $\delta$  7.38 d, representing the aromatic hydrogens of ring A'.



The alkaloid tended to precipitate out of CDCl<sub>3</sub> solution on standing, so that the nmr nOe measurements were obtained in CD<sub>3</sub>OD. The data so collected generally paralleled those for (-)-roemeridine [8], except that the indolic and exchangeable H-1' could not be observed (see Experimental).

The uv spectrum of (-)-roemebamine [10] exhibited a maximum at 290 nm and a shoulder at 299 nm. These values are almost identical with those recorded for (-)-roehybridine [5] and (+)-roebamine [7], which are similarly substituted on rings A and A'.

Because (-)-roemebamine [10] lacks a C-4' methoxyl, its mass spectrum had molecular ion  $m/z$  503 (7%) and base peak  $m/z$  214 corresponding to ion D. These val-

ues are identical with those obtained for (–)-roehybramine [5] and (+)-roebramine [7].

It should be observed that (–)-roemeridine [8] and (–)-roemebramine [10] have almost identical nmr chemical shifts for the axially oriented 9-OMe and for the equatorial H-9. However, the corresponding values for (–)-*O*-methyloemeridine [9],  $\delta$  3.25 and 3.63, are somewhat different. This apparent delinquency is caused by the added steric compression in species 9 due to the presence of the C-1 methoxyl, which affects the conformation of ring D.

GENERAL REMARKS.—The ten proaporphine-tryptamine dimers have been categorized above into three subgroups, syn 9-OMe axial, syn 9-OMe equatorial, and anti 9-OMe axial. There is, a priori, a fourth group which could also be mentioned, namely anti 9-OMe equatorial. We were never able to detect even traces of such an alkaloid, and it may be that this stereochemical arrangement is disfavored because of steric interaction between the equatorial 9-OMe and ring C'. Only further studies of the alkaloids of *R. hybrida* and related plants can answer this point with any degree of finality.

The main dimer in *R. hybrida* is actually (–)-roemeridine [8], which has the anti 9-OMe axial stereochemistry, and the second most prevalent dimer is (–)-roehybridine [1] with the syn 9-OMe axial arrangement. Significantly, these two dimers were the only ones isolated prior to the present work. The third alkaloid in quantitative terms was (+)-roehymine [6], which belongs to the syn 9-OMe equatorial configuration. Dimers with only one methoxyl on ring A' were always present in smaller amounts.

In the initial cc separation of the alkaloids on Si gel, bases belonging to the syn series generally tended to elute prior to anti compounds. Also, syn 9-OMe axial bases 1–5 were readily soluble in CDCl<sub>3</sub>. The two alkaloids with the syn 9-OMe equatorial configuration, 6 and 7, were initially soluble in CDCl<sub>3</sub> but tended to drop out of solution on standing. Bases of the anti series, 8–10 were only marginally soluble in CDCl<sub>3</sub>, so that long-term nmr experiments, such as nOe measurements, had sometimes to be carried out in CD<sub>3</sub>OD as indicated in the Experimental.

A final point concerns the identity of (–)-roemeridine [8]. The original Czech paper on this alkaloid (2) cited an nmr chemical shift of  $\delta$  3.10, which in the light of the present structure for (–)-roemeridine can be assigned to the C-9 methoxyl. However, the sample used in the X-ray determination showed a methoxyl singlet much further downfield at  $\delta$  3.46 (4). Our C-9 methoxyl value for (–)-roemeridine is  $\delta$  3.20. It is possible that, because of the broad nature of some of the nmr peaks of the dimer at room temperature, the resonance for the MeOH of crystallization in the crystals used in the X-ray study was interpreted to represent 9-OMe.

## EXPERIMENTAL

PLANT MATERIAL.—*R. hybrida* was collected on April 22, 1988, in Usak, western Turkey. The plant was identified by Dr. M.A. Önür, Faculty of Pharmacy, Ege University, and a voucher specimen, No. 1091, was deposited in the Herbarium of the Pharmacognosy Department, Faculty of Pharmacy, Ege University.

EXTRACTION AND FRACTIONATION.—The air-dried and powdered plant material (8.8 kg) was extracted with EtOH (180 liters) at room temperature. The crude extract (915 g) was taken up in 5% HCl and filtered. The filtrate was basified with NH<sub>4</sub>OH and extracted with CHCl<sub>3</sub>. Evaporation of the solvent yielded a crude alkaloidal extract (25 g). The preliminary separation of the alkaloids was carried out using a Si gel (70–230 mesh, Merck) column, using CHCl<sub>3</sub> gradually enriched with MeOH as eluent. Fractions displaying similar alkaloidal composition on Si gel tlc glass plates were combined and further fractionated by cc on Si gel 60H (Merck). Final purification of the alkaloids was achieved by preparative tlc on Si gel glass plates. The following compounds were obtained in the order of elution from the initial chromatographic column: (–)-*O*-methyloehybridine (8 mg), (–)-roehybramine (19 mg), (–)-roehybridine (1.7



g), (+)-roehymine (86 mg), (+)-roebramine (2 mg), (-)-*O*-methyloermeridine (7 mg), (-)-nor-roehybridine (2 mg), (-)-roemeridine (3.1 g), (-)-roemebramine (6 mg), and (-)-roehybridine  $\beta$ -*N*-oxide (6 mg). <sup>1</sup>H-nmr spectral values were obtained in CDCl<sub>3</sub> solution except where specified otherwise, and at 500 MHz.

(-)-ROEHYBRIDINE [1].—Amorphous solid,  $[\alpha]_D -16^\circ$  ( $c = 0.075$ , MeOH); uv  $\lambda$  max (MeOH) 225, 281 sh, 290, 298, 303, 307 sh nm (log  $\epsilon$  4.56, 3.95, 4.00, 4.02, 4.00, 3.97); eims  $m/z$  (%)  $[M]^+$  533 (11), 518 (7), 503 (1), 473 (3), 258 (10), 257 (49), 245 (19), 244 (100), 231 (5), 230 (20), 229 (28), 216 (5), 215 (4); hreims  $[M]^+$  calcd for C<sub>31</sub>H<sub>39</sub>N<sub>3</sub>O<sub>5</sub>, 533.2890, found 533.2910; cd (MeOH)  $\Delta\epsilon$  (nm) 0 (347), +0.64 (327), 0 (320), -2.48 (312), -1.41 (303), -4.69 (265 sh), negative tail beyond 240 nm. Important <sup>1</sup>H nmr nOe's are NH-1' to H-2' (10%), H-2' to NH-1' (9%), 9-OMe to NH-1' (2%), H-11ax to NH-1' (2%), H-8eq to 9-OMe (6%), H-9 to H-8eq (4%), H-9 to H-8ax (5%), H-7 $\alpha$  to H-8eq (4%), H-7 $\beta$  to H-12eq (3%), 3'-OMe to H-2' (26%), H-5' to 4'-OMe (30%), 4'-OMe to H-5' (25%), H-5' to H-6' (5%), H-6' to H-5' (10%), H-3 to 2-OMe (11%), 2-OMe to H-3 (24%), H-4 to H-3 (7%).

*O*-METHYLATION OF (-)-ROEHYBRIDINE.—Alkaloid **1** (14 mg) in MeOH (2 ml) was treated with excess ethereal CH<sub>2</sub>N<sub>2</sub> at near 0° for 15 h. Workup followed by tlc furnished amorphous (-)-*O*-methyl-roehybridine [**3**] (9 mg) identical with natural **3** (co-tlc, nmr, ms, uv, optical rotation).

(-)-NORROEHYBRIDINE [2].—Amorphous solid,  $[\alpha]_D -29^\circ$  ( $c = 0.149$ , MeOH); uv  $\lambda$  max (MeOH) 225, 282 sh, 292, 298, 303, 307 sh nm (log  $\epsilon$  4.46, 3.84, 3.88, 3.90, 3.89, 3.87); eims  $m/z$  (%)  $[M]^+$  519 (6), 504 (3), 459 (3), 258 (11), 257 (59), 246 (3), 245 (21), 244 (100), 243 (4), 230 (5), 229 (11), 216 (9), 215 (8); hreims  $[M]^+$  calcd for C<sub>30</sub>H<sub>37</sub>N<sub>3</sub>O<sub>5</sub>, 519.2733, found 519.2721.

(-)-*O*-METHYLROEHYBRIDINE [3].—Amorphous solid,  $[\alpha]_D -17^\circ$  ( $c = 0.187$ , MeOH); uv  $\lambda$  max (MeOH) 229, 281 sh, 292 sh, 299, 303, 308 sh nm (log  $\epsilon$  4.44, 3.85, 3.88, 3.93, 3.93, 3.88); eims  $m/z$  (%)  $[M]^+$  547 (17), 532 (8), 259 (10), 258 (39), 257 (77), 245 (46), 244 (100), 243 (23), 230 (8), 229 (15), 215 (11); hreims  $[M]^+$  calcd for C<sub>32</sub>H<sub>41</sub>N<sub>3</sub>O<sub>5</sub>, 547.3046, found 547.3032.

(-)-ROEHYBRIDINE  $\beta$ -*N*-OXIDE [4].—Amorphous solid,  $[\alpha]_D -36^\circ$  ( $c = 0.056$ , MeOH); uv  $\lambda$  max (MeOH) 224, 282 sh, 291, 299, 303, 308 sh nm (log  $\epsilon$  4.46, 3.86, 3.90, 3.92, 3.92, 3.87); eims  $m/z$  (%)  $[M]^+$  549 (0.3), 533 (3), 518 (2), 258 (7), 257 (35), 245 (19), 244 (100), 230 (13), 229 (26), 216 (4), 215 (4); hreims  $[M]^+$  calcd for C<sub>31</sub>H<sub>39</sub>N<sub>3</sub>O<sub>6</sub>, 549.2839, found 549.2854. Important nmr nOe's are NH-1' to H-2' (7%), H-2' to NH-1' (4%), 9-OMe to NH-1' (3%), H-9 to H-8eq (3%), H-8eq to H-9 (6%), H-9 to H-8ax (4%), H-8ax to H-9 (8%), NMe to H-5 ( $\delta$  3.63) (2%), NMe to H-5 ( $\delta$  3.81) (5%), NMe to H-6a (18%), H-6a to NMe (4%), NMe to H-7 $\alpha$  (4%), NMe to H-7 $\beta$  (3%), H-6a to H-7 $\alpha$  (6%), H-7 $\alpha$  to H-6a (5%), H-7 $\beta$  to H-12eq (4%), H-12eq to H-7 $\beta$  (3%), H-8eq to NMe (5%), H-11ax to NH-1' (4%), H-2' to 3'-OMe (24%), 3'-OMe to H-2' (24%), H-5' to 4'-OMe (29%), 4'-OMe to H-5' (24%), H-6' to H-5' (11%), H-7' ( $\delta$  3.25) to H-6' (4%), H-7' ( $\delta$  3.16) to H-9 (4%), H-3 to 2-OMe (17%), 2-OMe to H-3 (23%), H-4 ( $\delta$  2.85) to H-3 (5%), H-4 ( $\delta$  3.50) to H-3 (3%).

(-)-ROEHYBRAMINE [5].—Amorphous solid,  $[\alpha]_D -13^\circ$  ( $c = 0.185$ , MeOH); uv  $\lambda$  max (MeOH) 227, 280 sh, 290, 300 sh nm (log  $\epsilon$  4.46, 3.74, 3.79, 3.70); eims  $m/z$  (%)  $[M]^+$  503 (7), 488 (3), 244 (3), 231 (6), 230 (20), 229 (8), 228 (9), 227 (46), 215 (16), 214 (100), 213 (4), 201 (4); hreims  $[M]^+$  calcd for C<sub>30</sub>H<sub>37</sub>N<sub>3</sub>O<sub>4</sub>, 503.2784, found 503.2769. Important nmr nOe's are NH-1' to H-2' (14%), H-2' to NH-1' (4%), NH-1' to H-11ax (5%), 9-OMe to NH-1' (2%), 9-OMe to H-9 (7%), H-9 to H-7' ( $\delta$  3.19) (4%), H-9 to H-8ax (3%), H-8ax to H-9 (9%), H-9 to H-8eq (3%), H-8eq to H-9 (5%), H-8eq to 9-OMe (6%), 9-OMe to H-8eq (10%), NMe to H-6a (7%), H-7 $\alpha$  to H-8eq (5%), H-7 $\beta$  to H-12eq (6%), H-12eq to H-11eq (1%), H-12eq to H-11ax (1%), H-11ax to NH-1' (6%), H-12ax to H-11eq (4%), H-12ax to H-8ax (2%), H-8ax to H-12ax (4%), H-2' to 3'-OMe (18%), 3'-OMe to H-2' (27%), 3'-OMe to H-4' (13%), H-4' to 3'-OMe (5%), H-4' to H-5' (23%), H-5' to H-4' (26%), H-6' ( $\delta$  2.73) to H-5' (10%), H-6' ( $\delta$  2.76) to H-5' (5%), H-7' ( $\delta$  3.19) to H-9 (7%), H-7' ( $\delta$  3.21) to H-11eq (4%), 2-OMe to H-3 (30%), H-3 to 2-OMe (17%), H-4 ( $\delta$  2.75) to H-3 (8%), H-4 ( $\delta$  3.01) to H-3 (6%).

(+)-ROEHYMININE [6].—Amorphous solid,  $[\alpha]_D +29^\circ$  ( $c = 0.065$ , MeOH); uv  $\lambda$  max (MeOH) 226, 280 sh, 291, 297, 302, 309 sh nm (log  $\epsilon$  4.55, 3.95, 4.01, 4.02, 4.01, 3.94); eims  $m/z$  (%)  $[M]^+$  533 (7), 518 (4), 473 (3), 258 (11), 257 (54), 245 (18), 244 (100), 230 (20), 229 (28), 216 (5), 215 (4); hreims  $[M]^+$  calcd for C<sub>31</sub>H<sub>39</sub>N<sub>3</sub>O<sub>5</sub>, 533.2890, found 533.2901; cd (MeOH)  $\Delta\epsilon$  (nm) 0 (330), +0.75 (326), 0 (322), -4.60 (305), -3.91 (295), negative tail beyond 240 nm. Important nmr nOe's are NH-1' to H-2' (7%), NH-1' to 9-OMe (2%), NH-1' to H-9 (6%), H-9 to NH-1' (6%), NH-1' to H-11ax (3%), H-11ax to NH-1' (4%), H-9 to H-7 $\alpha$  (6%), H-7 $\alpha$  to H-9 (6%), H-9 to 9-OMe (15%), NMe to H-6a (9%), H-7 $\alpha$  to H-6a (5%), H-7 $\beta$  to H-12eq (5%), H-12eq to H-7 $\beta$  (4%), H-8eq to 9-OMe (6%), H-8eq to H-9 (4%), H-8eq to H-7 $\alpha$  (5%), H-8ax to H-12ax (3%), H-11ax to H-9 (4%), H-11ax to H-12eq (2%), H-12eq to H-11eq (2%), H-2' to 3'-OMe (10%), 3'-OMe to H-2' (24%), H-5' to 4'-OMe (8%), 4'-OMe to H-5'

(35%), H-6' to H-5' (10%), H-6' to H-7' ( $\delta$  3.40) (5%), H-7' ( $\delta$  3.06) to H-11eq (3%), H-3 to 2-OMe (8%), 2-OMe to H-3 (30%), H-4 ( $\delta$  2.78) to H-3 (5%), H-4 ( $\delta$  2.97) to H-3 (5%).

(+)-ROEBRAMINE [7].—Amorphous solid,  $[\alpha]_D + 7^\circ$  ( $c = 0.092$ , MeOH); uv  $\lambda$  max (MeOH) 222 sh, 288, 300 sh nm (log  $\epsilon$  4.17, 3.55, 3.43); eims  $m/z$  (%)  $[M]^+$  503 (6), 488 (4), 257 (7), 244 (14), 231 (7), 230 (32), 229 (24), 228 (15), 227 (62), 216 (6), 215 (23), 214 (100), 213 (9), 212 (9), 199 (12); hreims  $[M]^+$  calcd for  $C_{30}H_{37}N_3O_4$ , 503.2784, found 503.2776. Important nmr nOe's are H-2' to 3'-OMe (5%), 3'-OMe to H-2' (11%), 3'-OMe to H-4' (10%), 2-OMe to H-3 (23%), H-3 to 2-OMe (13%), H-9 to 9-OMe (7%).

(-)-ROEMERIDINE [8].—Amorphous solid,  $[\alpha]_D - 21^\circ$  ( $c = 0.075$ , MeOH); uv  $\lambda$  max (MeOH) 222, 281 sh, 293, 299, 302, 307 sh nm (log  $\epsilon$  4.41, 3.90, 3.93, 3.95, 3.95, 3.89); eims  $m/z$  (%)  $[M]^+$  533 (9), 518 (5), 258 (11), 257 (11), 245 (18), 244 (100), 243 (5), 242 (5), 231 (6), 230 (21), 229 (26), 216 (5), 215 (7); hreims  $[M]^+$  calcd for  $C_{31}H_{39}N_3O_5$ , 533.2890, found 533.2897; cd (MeOH)  $\Delta\epsilon$  (nm) 0 (345), +1.02 (329), 0 (317), -3.33 (309), -2.22 (296), negative tail beyond 240 nm. Important nmr nOe's are NH-1' to H-2' (8%), H-2' to NH-1' (4%), NH-1' to H-9 (8%), H-9 to NH-1' (3%), H-9 to 9-OMe (11%), 9-OMe to H-9 (10%), 9-OMe to H-8eq (3%), H-8eq to 9-OMe (6%), H-8eq to H-9 (7%), H-9 to H-8ax (7%), H-8ax to H-9 (11%), NMe to H-6a (14%), NMe to H-7 $\beta$  (3%), H-7 $\alpha$  to H-6a (9%), H-7 $\alpha$  to H-8eq (5%), H-12ax to NH-1' (9%), H-2' to 3'-OMe (36%), 3'-OMe to H-2' (32%), 4'-OMe to H-5' (32%), H-5' to 4'-OMe (39%), H-6' to H-5' (12%), H-4 ( $\delta$  2.76) to H-3 (8%), H-4 ( $\delta$  3.00) to H-3 (4%), H-3 to 2-OMe (26%), 2-OMe to H-3 (32%).

O-METHYLATION OF (-)-ROEMERIDINE.—Alkaloid **8** (10 mg) in MeOH (2 ml) was treated with excess ethereal  $CH_2N_2$ , and the mixture was kept near  $0^\circ$  for 15 h. Workup and tlc afforded (-)-O-methylroemeridine [**9**] (7 mg), identical with natural **9** (co-tlc, ms, nmr, uv, optical rotation).

(-)-O-METHYLROEMERIDINE [**9**].—Amorphous solid,  $[\alpha]_D - 18^\circ$  ( $c = 0.317$ , MeOH); uv  $\lambda$  max (MeOH) 224, 267 sh, 275, 288, 297, 302, 307 sh nm (log  $\epsilon$  4.41, 3.80, 3.84, 3.86, 3.88, 3.88, 3.83); eims  $m/z$  (%)  $[M]^+$  547 (6), 532 (3), 258 (7), 245 (18), 244 (100), 243 (8), 229 (5), 215 (3); hreims  $[M]^+$  calcd for  $C_{32}H_{41}N_3O_5$ , 547.3046, found 547.3029; cd (MeOH)  $\Delta\epsilon$  (nm) 0 (342), +0.32 (332), 0 (321), -2.20 (302), -1.42 (293), negative tail beyond 240 nm. Important nmr nOe's are NH-1' to H-2' (21%), NH-1' to 1-OMe (11%), 1-OMe to NH-1' (8%), NH-1' to H-9 (10%), H-9 to NH-1' (7%), NH-1' to H-8ax (14%), H-8ax to NH-1' (8%), NH-1' to H-11eq (8%), NH-1' to H-12ax (13%), H-12ax to NH-1' (15%), H-12ax to 1-OMe (19%), 1-OMe to H-12ax (9%), H-9 to 9-OMe (39%), 9-OMe to H-9 (25%), H-9 to H-8eq (6%), H-8eq to H-9 (8%), H-9 to H-8ax (13%), H-8ax to H-9 (12%), H-9 to H-11eq (3%), 9-OMe to H-8eq (11%), H-8eq to 9-OMe (18%), NMe to H-6a (28%), NMe to H-7 $\alpha$  (6%), NMe to H-7 $\beta$  (4%), H-6a to H-7 $\alpha$  (8%), H-7 $\alpha$  to H-8eq (6%), H-8eq to H-7 $\alpha$  (3%), 1-OMe to H-11eq (7%), H-7 $\beta$  to H-11ax (5%), H-7 $\beta$  to H-12eq (8%), H-12eq to H-7 $\beta$  (3%), H-2' to 3-OMe (26%), 3'-OMe to H-2' (51%), H-5' to 4'-OMe (21%), 4'-OMe to H-5' (54%), H-6' to H-5' (21%), H-4 ( $\delta$  3.00) to H-3 (8%), H-4 ( $\delta$  2.78) to H-3 (10%), H-3 to 2-OMe (15%), 2-OMe to H-3 (36%).

(-)-ROEMEBRAMINE [10].—Amorphous solid,  $[\alpha]_D - 21^\circ$  ( $c = 0.193$ , MeOH); uv  $\lambda$  max (MeOH) 225, 262 sh, 268, 290, 299 sh nm (log  $\epsilon$  4.51, 3.85, 3.88, 3.93, 3.82); eims  $m/z$  (%)  $[M]^+$  503 (7), 488 (4), 244 (6), 231 (5), 230 (27), 229 (21), 228 (13), 227 (61), 225 (5), 215 (20), 214 (100), 213 (7); hreims  $[M]^+$  calcd for  $C_{30}H_{37}N_3O_4$ , 503.2784, found 503.2767. Important nmr nOe's (in  $CD_3OD$ ) are NMe to H-6a (18%), H-6a to NMe (6%), H-6a to H-5 ( $\delta$  2.48) (8%), H-5 ( $\delta$  2.48) to H-6a (16%), H-6a to H-7 $\alpha$  (4%), H-7 $\alpha$  to H-6a (10%), H-7 $\alpha$  to H-8eq (6%), H-8eq to H-9 (8%), H-9 to H-8eq (4%), H-8eq to 9-OMe (6%), 9-OMe to H-8eq (4%), 9-OMe to H-9 (24%), H-9 to 9-OMe (13%), H-9 to H-8ax (7%), H-8ax to H-9 (13%), H-12eq to H-7 $\beta$  (2%), H-2' to 3'-OMe (27%), 3'-OMe to H-2' (44%), 3'-OMe to H-4' (12%), H-4' to 3'-OMe (4%), H-4' to H-5' (32%), H-5' to H-4' (42%), H-6' to H-5' (16%), 2-OMe to H-3 (37%), H-3 to 2-OMe (28%), H-4 ( $\delta$  2.75) to H-3 (5%), H-4 ( $\delta$  3.00) to H-3 (6%).

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### ERRATUM

For the paper by A. Ulubelen entitled "A New Alkaloid, Montanine, from *Ruta montana*," *J. Nat. Prod.*, **53**, 207 (1990), the author requests a name change in the title compound due to the earlier use of the name montanine. The new compound is thus re-named monrutanine [1].