20. Epimeric Isopavine *N*-Oxides from *Roemeria refracta*

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Dedicated to Prof. *Maurice Shamma* on the occasion of his 65th birthday

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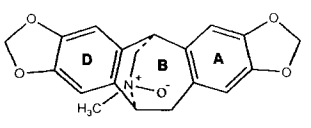
Roemeria refracta DC. (Papaveraceae) of Turkish origin yielded two novel epimeric *N*-oxides, (–)-(5*R*,11*S*,14*R*)-reframidine *N*-oxide (= (–)-(5*R*,11*S*,14*R*)-11,12-dihydro-14-methyl-11,5-(iminomethano)-5*H*-cyclohepta[1,2-*f*:4,5-*f*']bis[1,3]benzodioxole 14-oxide; **1**) and (–)-(5*R*,11*S*,14*S*)-reframidine *N*-oxide (= (–)-(5*R*,11*S*,14*S*)-11,12-dihydro-14-methyl-11,5-(iminomethano)-5*H*-cyclohepta[1,2-*f*:4,5-*f*']bis[1,3]benzodioxole 14-oxide; **2**). The isolated (–)-roelactamine (= (–)-11,12-dihydro-14-methyl-11,5-(iminomethano)-5*H*-cyclohepta[1,2-*f*:4,5-*f*']bis[1,3]benzodioxol-15-one, **4**) is the first natural isopavinoid incorporating a lactam group. The epimeric (–)-15-(2-oxopropyl)reframidines (= (–)-1-[11,12-dihydro-14-methyl-11,5-(iminomethano)-5*H*-cyclohepta[1,2-*f*:4,5-*f*']bis[1,3]benzodioxol-15-yl]propan-2-ones; **5**/**6**) and the epimeric (–)-ethyl (reframidin-15-yl)acetates (= (–)-ethyl [11,12-dihydro-14-methyl-11,5-(iminomethano)-5*H*-cyclohepta[1,2-*f*:4,5-*f*']bis[1,3]benzodioxol-15-yl]acetates; **7**/**8**) are probably artifacts. (±)-Coclaurine (**9**), (±)-*N*-methylcoclaurine (**10**), (–)-roemeridine (**11**), and *N*-feruloyltyramine (**12**) are also isolated from *R. refracta* together with the previously reported bases. Specific ^{13}C-NMR assignments are reported for the first time for the isopavines.

Introduction. – *Roemeria refracta* DC. (Papaveraceae) is known to elaborate isopavines [1] [2] which constitute one of the less populated subgroups of the isoquinoline alkaloids. Thus, previous studies on *R. refracta* of Turkish origin have shown that the major portion of the alkaloidal content are isopavines, (–)-reframidine (**3**) being by far the most abundant [2]. Recently, morphinandienones of the (9*S*)-series [3] and a number of benzyltetrahydroisoquinolines of both (*R*)- and (*S*)-configuration [4] were also reported from *R. refracta*.

A further investigation of *R. refracta* has now allowed the isolation and identification of the two novel epimeric (–)-(5*R*,11*S*,14*R*)- and (–)-(5*R*,11*S*,14*S*)-reframidine *N*-oxides (**1** and **2**, respectively), of (–)-roelactamine (**4**), an interesting isopavine incorporating a lactam rather than the usual tertiary amine moiety, and of two epimeric mixtures, *i.e.* 15-(2-oxopropyl)reframidines [5] (**5**/**6**) and ethyl (reframidin-15-yl)acetates (**7**/**8**), both mixtures being possibly artefacts. Besides **1**, **2**, and **4**–**8**, and in addition to the previously isolated bases from this plant [2–4], the known benzyltetrahydroisoquinolines (±)-coclaurine [6] (**9**), (±)-*N*-methylcoclaurine [6] (**10**), the proaporphine-tryptamine 'dimer', (–)-roemeridine [7] (**11**), and the aliphatic amide feruloyltyramine (**12**) [8] were found as minor components.



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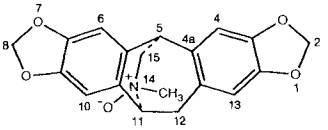

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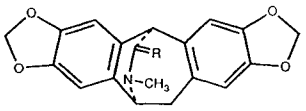
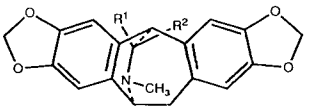
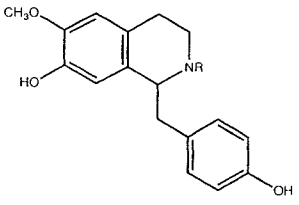


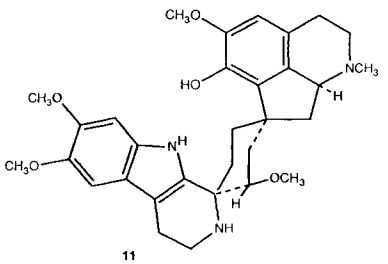
3 R = H_2, (–)-reframidine
4 R = O



5 R¹ = H, R² = CH_2COCH_3
6 R¹ = CH_2COCH_3, R² = H
7 R¹ = H, R² = $CH_2COOCH_2CH_3$
8 R¹ = $CH_2COOCH_2CH_3$, R² = H



9 R = H
10 R = CH_3



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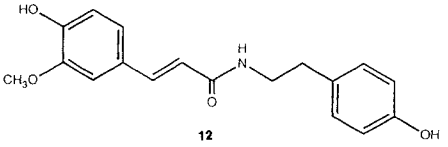

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Results and Discussion. – The polar fractions of *R. refracta* yielded two levorotatory compounds which were shown to be reframidine *N*-oxides **1** and **2** of (5*R*,11*S*,14*R*)- and (5*R*,11*S*,14*S*)-configuration, respectively. Both **1** and **2** display UV spectra characteristic of an isopavine-derived structure (see *Exper. Part*) [1]. Strikingly, the IR spectra of **1** and **2** are almost identical. Their structures are established by spectroscopic means and confirmed by their $NaBH_4$ reduction, both affording reframidine (**3**).

In the ^{1}H-NMR spectra of **1** and **2** (*Table 1*) 4*s* for aromatic H-atoms, 1 MeN group, and 2 methylenedioxy groups, and 2 three-spin systems are in evidence, all of which are reminiscent of (–)-reframidine (**3**). While relatively similar chemical shifts are encountered in the aromatic regions of the spectra of **1**–**3** (*Table 1*), the aliphatic signals display noticeable differences, the most prominent lying with the MeN signal. For **1**, this signal is shifted downfield to δ 3.11 (δ(**1**)–δ(**3**) = 0.64 ppm) due to the deshielding influence of the N–O bond, whereas for **2**, it appears further downfield at δ 3.50 (δ(**1**)–δ(**3**) = 1.03 ppm). The signal of the MeN group of **1** appears at relatively higher field than that of **2** due to the anisotropic effect of the benzene-ring moiety (ring D). The postulated relative configuration at N(4) of **1** and **2** is further supported by the following ^{1}H-NMR data: in **1**, H_α–C(12) (δ 4.75), which is closest to the O-atom, suffers a drastic downfield shift (δ(**1**)–δ(**3**) = 1.9 ppm), whereas in **2**, the corresponding shift is only *ca.* 0.25 ppm. On the other hand, the position of O-atom in **2** causes

Table 1. *^{1}H-NMR Spectra* ($CDCl_3$, 300 MHz) *of Compounds* **1–4**. δ Values in ppm, J in Hz.

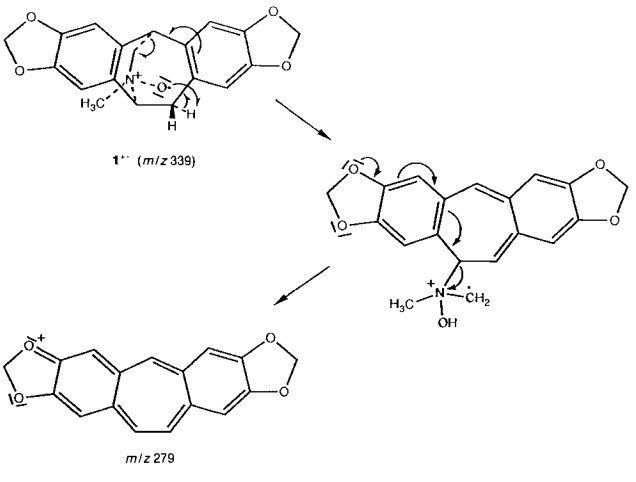
	1	**2**	**3**	**4**
H–C(4)	6.55 (*s*)	6.61 (*s*)	6.62 (*s*)	6.69 (*s*)
H–C(6)	6.72 (*s*)	6.73 (*s*)	6.69 (*s*)	6.73 (*s*)
H–C(10)	6.81 (*s*)	6.90 (*s*)	6.71 (*s*)	6.75 (*s*)
H–C(13)	6.55 (*s*)	6.49 (*s*)	6.50 (*s*)	6.46 (*s*)
CH_2(2)	5.90, 5.85 (2*d*, J = 1.4)	5.92, 5.88 (2*d*, J = 1.2)	5.86, 5.83 (2*d*, J = 1.4)	5.87, 5.85 (2*d*, J = 1.4)
CH_2(8)	5.98, 5.92 (2*d*, J = 1.3)	5.93, 5.92 (2*d*, J = 1.3)	5.92, 5.87 (2*d*, J = 1.4)	5.93, 5.89 (2*d*, J = 1.4)
H–C(5)	3.64 (*d*, J = 6.3)	3.72 (*d*, J = 4.9)	3.60 (*dd*, J = 4.5, 1.5)	4.25 (*s*)
H–C(11)	4.30 (*dd*, J = 2.4, 4.7)	4.62 (*t*, J = 3.5)	3.81 (*t*, J = 3.6)	4.39 (*dd*, J = 2.6, 4.2)
H_α–C(12)	4.75 (*dd*, J = 2.2, 18.4)	3.12 (*dd*, J = 3.0, 19.1)	2.87 (*dd*, J = 3.3, 17.7)	2.95 (*dd*, J = 2.6, 17.3)
H_β–C(12)	2.88 (*dd*, J = 4.9, 18.4)	3.64 (*dd*, J = 4.1, 19.0)	3.49 (*dd*, J = 4.0, 17.5)	3.33 (*dd*, J = 4.2, 17.3)
H_a–C(15)[1]	4.21 (*d*, J = 13.2)	4.22 (*d*, J = 12.6)	3.53 (*dd*, J = 1.4, 10.6)	–
H_d–C(15)[1]	3.98 (*dd*, J = 6.4, 13.2)	4.13 (*dd*, J = 5.3, 12.7)	2.82 (*dd*, J = 4.7, 10.7)	–
MeN	3.11 (*s*)	3.50 (*s*)	2.47 (*s*)	3.10 (*s*)

considerable downfield shifts at H–C(11) (δ 4.62) and H_d–C(15)[1]) (δ 4.13), while the corresponding values for **1** are δ 4.30 and 3.98, respectively.

As indicated by the variations of the coupling constants of the two *ABX* systems, the conformations of **1** and **2** are slightly different. In **1**, the dihedral angle between H–C(5) (δ 3.64) and H_d–C(15)[1]) (δ 3.98) is *ca.* 26°. The H–C(5)/H_a–C(15)[1]) dihedral angle is, therefore, close to 90°, resulting in no noticeable coupling between these protons. The net result is a slightly twisted boat conformation for ring C of **1**. In **2**, the dihedral angle between H–C(5) (δ 3.72) and H_d–C(15) (δ 4.13) is larger (*ca.* 33°); while there is still no coupling between H–C(5) and H_a–C(15), the conformation of ring C is now closer to a perfect boat as compared to **1**.

Differences in the electron-impact (EI) MS of diastereoisomers are normally small; usually only the intensities of some signals differ. In contrast to this, the MS of **1** and **2** are completely different (*Figs. 1* and *2*). The molecular ion $M^{+\cdot}$ 339 is absent in both cases. For **2**, the molecular ion of a dehydrogenation product with m/z 337 ($[M-2]^{+\cdot}$) is found, together with signals of $[M-16]^+$ ions, which are typical for *N*-oxides [9]. In the MS of **1**, none of the typical *N*-oxide signals are present, only the fragment ion at m/z 279 dominates the upper mass range. Under soft ionization conditions like chemical ionization (CI; NH_3), m/z 279 is still the most abundant ion, but in a five signal peak group. The signal of lowest intensity (2 rel.-%) in the CI-MS of **1** can be attributed to $[M+1]^+$ at m/z 340. Therefore, an unambiguous determination of the molecular weight by CI-MS was not possible. Even in the fast-atom-bombardment (FAB) MS (glycerol), the ion m/z 279 is more important than $[M+1]^+$ (96 rel.-%). In

Scheme



[1]) H_a–C(15) is closer to ring A, H_d–C(15) is closer to ring D.

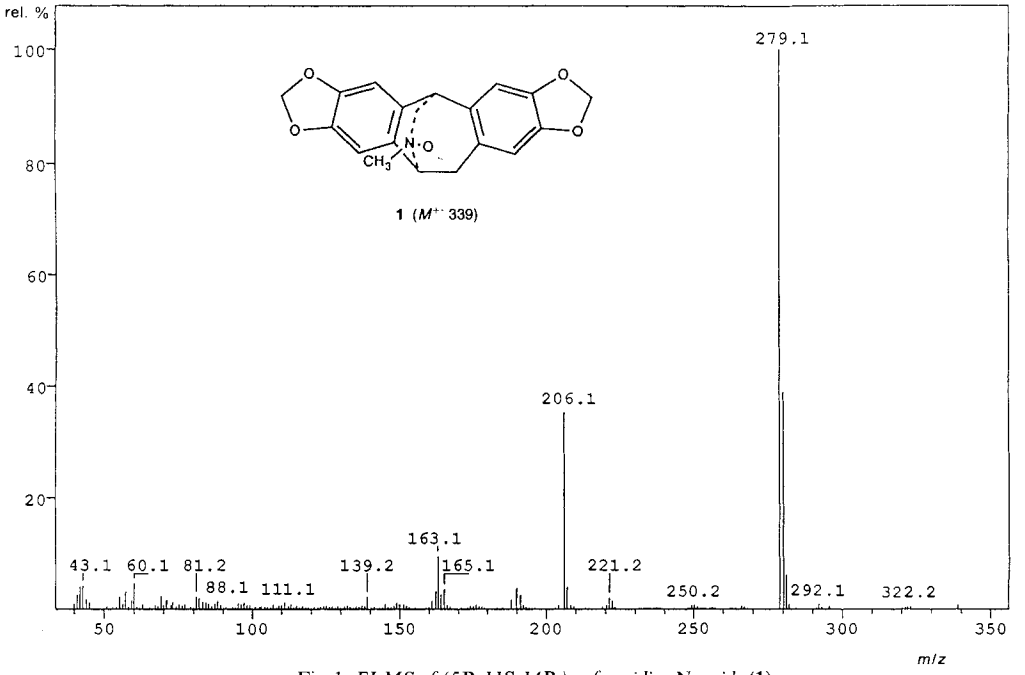


Fig. 1. *EI-MS of (5*R*,11*S*,14*R*)-reframidine* N*-oxide* (**1**)

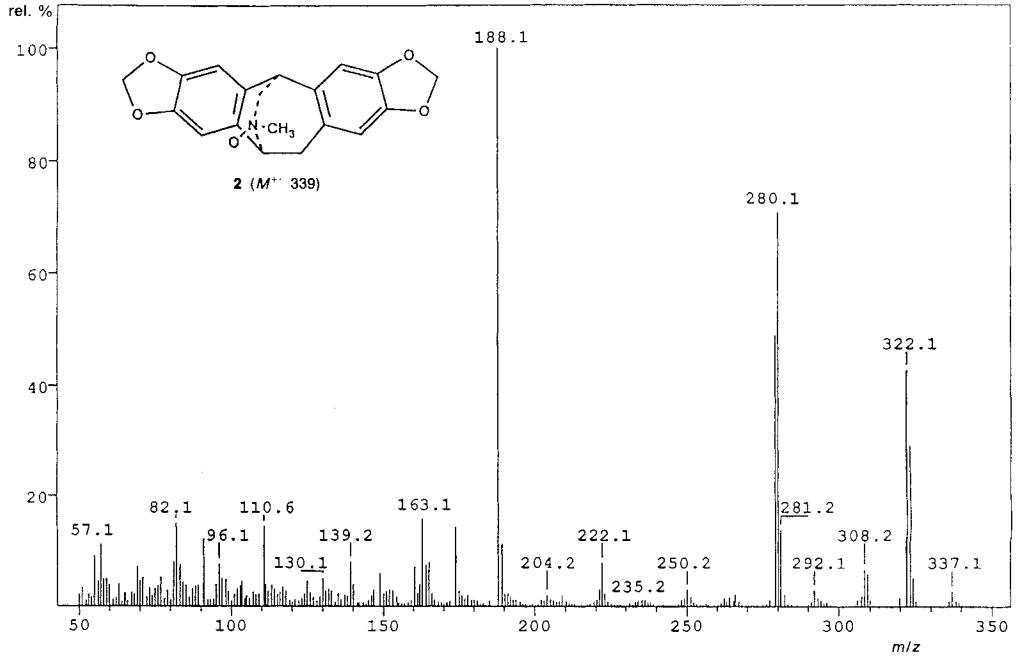


Fig. 2. *EI-MS of (5*R*,11*S*,14*S*)-reframidine* N*-oxide* (**2**)

addition, the characteristic *N*-oxide signals such as $[M+1-16]^+$ and $[M+1-18]^+$ are registered. Finally, in the electrospray-ionization (ESI) MS of both **1** and **2**, measured in H_2O/MeOH, the only signals which are observed are, as expected, those of the single-charged molecular ion. This clearly establishes the ESI-MS method as the softest process for ionizing polar and labile compounds. The formation of the above mentioned ion *m/z* 279 in the MS of **1** once again confirms the spatial neighbourhood of the benzylic H_α–C(12) to the O-atom of the N–O group, which are in *cis*-relation. The explanation of its formation is outlined in the *Scheme*. The most intense fragmentation signals in the MS of **2** are those of the alkaloid reframidine (**3**) itself. Loss of the O-atom in **2** leads to $M^{+\cdot}$ of **3** which exhibits the signals at *m/z* 322, 280, and 188 [2].

The only published ^{13}C-NMR data of isopavinoids are those of the synthetic species (listings of chemical shifts without assignments) [10]. Complete ^{13}C-NMR chemical shift assignments for **1** and **2** were now accomplished by DEPT, ^{13}C,^{1}H INADEQUATE, and COLOC (optimized to ^1J(C,H) 8 = Hz) experiments performed on the parent (–)-reframidine (**3**) (*Table 2*). As expected, considerable downfield shifts are observed for the bridgehead C-atoms and the iminomethano C-atom (C(15)) of **1** and **2**, resulting from the N–O dipole.

Table 2. *^{13}C-NMR Spectra* ($CDCl_3$, 75.5 MHz) *of Compounds* **1**–**4**. δ Values in ppm.

	1	**2**	**3**	**4**
C(2)	100.9	101.2	100.6	100.9
C(3a)	148.4	147.9	146.4	147.1
C(4)	108.1	108.8	107.9	109.1
C(4a)	134.8	133.6	135.5	134.2
C(5)	62.9	60.0	46.4	56.5
C(5a)	132.0	131.0	134.8	129.4
C(6)	106.5	106.4	106.1	105.3
C(6a)	147.0	147.2	145.9	146.4
C(8)	101.4	101.2	100.6	101.3
C(9a)	147.2	147.4	146.3	147.1
C(10)	107.0	107.9	107.1	106.1
C(10a)	126.4	127.3	131.1	129.3
C(11)	78.3	78.4	62.4	60.7
C(12)	31.7	35.3	38.5	33.9
C(12a)	126.2	123.9	127.8	126.0
C(13)	110.7	110.3	110.9	111.2
C(13a)	145.6	146.4	145.2	146.0
C(15)	75.5	78.2	59.6	172.3
MeN	45.3	44.4	45.2	32.4

The IR, ^{1}H-NMR, and MS data of the isolated (–)-roelactamine (**4**) are in good accordance with those reported for an analogous synthetic compound, 6-oxothalidine [11]. Further proof for the structure was obtained from the $LiAlH_4$ reduction of **4** which afforded reframidine (**3**). (–)-Roelactamine is, therefore, 15-oxoreframidine. This unusual alkaloid is the first example of a natural isopavine lactam.

The UV spectrum of **4** displays a maximum at 297 nm, accompanied by a shoulder at 232 nm and an inflection at 240 nm, pointing to an isopavine structure [1]. It has a negative specific rotation, indicating that it probably has a (5*R*,11*S*)-configuration like the aforementioned isopavines **1** and **2**. The IR spectrum has a prominent lactam C=O absorption at 1660 cm^{-1}. The presence of the C=O function is also evidenced by the δ 172.3 resonance in the ^{13}C-NMR ($CDCl_3$) of **4** (*Table 2*).The remaining chemical shifts are assigned from a ^{13}C-NMR DEPT experiment and by comparison with those of the established values of the parent **3**. A selective DEPT experiment provided concise information about the aliphatic C-atoms of **4**.

The MS of **4** furnishes an $M^{+\cdot}$ at *m/z* 337, of high intensity (55%). The most intense signal at *m/z* 280 arises from the retro-*Diels-Alder* reaction in ring C of the isopavine skeleton. This ion can then lose an H-atom to give the aromatic ion with *m/z* 279 (44%).

In the ^{1}H-NMR spectrum of **4**, the resonances of the aromatic protons and of the 2 methylenedioxy protons are very similar to those of **1**–**3** (*Table 1*). However, in the aliphatic region, there is only one *ABX* system in addition to a 1-H *s* and a MeN signal. The downfield shifts of the bridgehead protons and of MeN with respect to the parent **3** can easily be rationalized in terms of the presence of a six-membered lactam ring.

The levorotatory mixture of epimeric 15-(2-oxopropyl)reframidines (**5**/**6**) isolated from *R. refracta* could not be separated. The epimers were characterized and identified by spectroscopic means.

There is a brief report on the isolation of an acetonylreframidine from Egyptian *Argemone mexicana* [5]. However, the location of the acetonyl moiety is indicated as C(11), and the reported spectral data are considerably different from those of **5**/**6**. Therefore, the 15-(2-oxopropyl) derivatives **5**/**6** of reframidine seem to be new compounds.

The mixture **5**/**6** displays a prominent C=O absorption at 1710 cm^{-1} in its IR spectrum, confirming the presence of a nonconjugated keton moiety. In the MS, the M^+ at *m*/*z* 379 corresponds to $C_{22}H_{21}NO_5$. Loss of the acetonyl moiety yields *m*/*z* 322, representing the parent reframidine skeleton minus 1 H-atom. A retro-*Diels-Alder* reaction affords the characteristic stable ion at *m*/*z* 280, which is also the base peak.

Due to the 3:1 ratio of the epimers, two sets of signals in the ^{1}H-NMR spectrum can be evaluated separately, thus making it possible to assign individual chemical shift values to the major and the minor isomer. The decisive factor in assigning the configuration at C(15) center is the coupling mode of H–C(5). It is well established for the isopavines [2] that the dihedral angles between H–C(5) and the vicinal CH_2 are such that H–C(5) displays coupling only with the CH_2 proton proximal to ring D. For **5** (major isomer), H–C(5) (δ 3.67) is a *d* (coupling with H_d–C(15)). Therefore, the acetonyl residue lies on the side of ring A, the configuration being (15*R*). On the other hand, for the minor isomer **6**, H–C(5) (δ 3.45) is a sharp *s*, which is a clear indication of the location of the acetonyl group as being on the side of ring D. Therefore, the configuration of **6** is (15*S*). The remaining chemical shifts for **5** and **6** (see *Exper. Part*) are similar and in accordance with the expected values.

Another reframidine derivative was also isolated as a mixture of epimers and identified as (–)-ethyl (reframidin-15-yl)acetate (**7**/**8**) on the basis of spectral evidence. The IR spectrum of **7**/**8** displays a strong absorption at 1725 cm^{-1}, confirming the presence of the ester function. In the MS, the M^+ is at *m*/*z* 409. The following low-intensity peaks at *m*/*z* 394, 380, 364, and 336 account for $[M-Me]^+$, $[M-Et]^+$, $[M-EtO]^+$, and $[M-COOEt]^+$, respectively. Once again, the base peak at *m*/*z* 280 is attributed to the stable $C_{17}H_{12}O_4^+$ ion, resulting from the retro-*Diels-Alder* reaction of the molecular ion.

In the ^{1}H-NMR spectrum of **7**/**8**, H–C(5) appears as a *d* (δ 3.66) and a *s* (δ 3.54), analogously to the situation in **5**/**6**. Thus, the same arguments can be used safely to define the epimeric relationship at C(15). Although two sets of chemical shifts are recorded for the relevant protons (see *Exper. Part*), differentiation can not be made between the isomers due to their existence in a 1:1 ratio and the overlapping of a number of signals.

It is possible that both epimeric mixtures **5**/**6** and **7**/**8** are artefacts of the isolation process. The original compound may possibly be the corresponding aminoalcohol [12], which, in the presence of acid, is converted into an immonium derivative. The attack of the proper nucleophile would then furnish the various reframidine derivatives substituted at C(15).

In addition to the already reported benzyltetrahydroisoquinolines from *R. refracta* [4], two other known compounds of the same type, (±)-coclaurine (**9**) [6] and (±)-*N*-methylcoclaurine (**10**) [6], were also isolated. Their structures were verified by spectroscopic analyses and by comparison with literature data. Noteworthy is the fact that both **9** and **10** are optically inactive, as evidenced by their zero specific rotations and flat CD curves. In feeding experiments on *Papaver somniferum* seedlings, (±)-[1-^{13}C]coclaurine has been shown to incorporate into thebaine and morphine [13]. However, the isolation of neither **9** nor **10** have been reported so far from the Papaveraceae. The present study is, therefore, the first report of the occurrence of these benzyltetrahydroisoquinolines in this plant family.

A striking result of the present work is the isolation of the proaporphine-tryptamine 'dimer', (−)-roemeridine (**11**) [7] as one of the minor components of the alkaloidal content of *Roemeria refracta*. This unusual compound is the main alkaloid of *Roemeria hybrida*, a species shown to be a rich source for 'dimers' of this type [7]. Compound **11** has also been reported briefly from *Papaver pavoninum* [14]. The present report of its occurrence in another *Roemeria* species, therefore, suggests that this 'dimer' may be a more common element of the Papaveraceae than it was originally considered [7].

The isolation of the aliphatic amide *N*-feruloyltyramine (**12**), identified by its spectroscopic means and comparison with published data for this compound [8], represents the first reported occurrence of this wide-spread amide in the genus *Roemeria*.

The structures of the other known compounds also isolated from *R. refracta* are confirmed by spectral analyses and by comparison with literature data.

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Experimental Part

General. TLC: precoated silica gel *60* F_{254} plates (*Merck*). Prep. column chromatography (CC): silica gel *60H* (*Merck*). CC: silica gel *60* (70–230 mesh, *Merck*). Specific rotations: *Perkin-Elmer-241* polarimeter; in MeOH. UV: *Perkin-Elmer-555* spectrophotometer; in MeOH; λ_{max} in nm (log ε). IR: *Perkin-Elmer-297* instrument; in $CHCl_3$; ν_{max} in cm^{-1}. ^{1}H- and ^{13}C-NMR[2]): *Bruker-AC-300* and *Varian-XL-200* spectrometer, resp.; in $CDCl_3$ at 300 or 50 MHz. ^{13}C-NMR (INADEQUATE, COLOC): *Bruker-AMX-600* spectrometer. EI-MS: *Finnigan-SSQ-700* spectrometer (70 eV), *m/z* (rel. %). FAB-MS: *Finnigan-MAT-90* instrument. ESI-MS: *Finnigan-TSQ-700* spectrometer.

Plant Material. R. refracta was collected from Bayburt in northern Turkey on June 15, 1991. It was identified by one of the authors (*M.A.Ö.*). A voucher sample is deposited in the Herbarium of Pharmacognosy, Faculty of Pharmacy of Ege University.

Extraction and Isolation. The dried powdered aerial and underground parts of *R. refracta* (12.7 kg) were extracted with EtOH at r.t. to furnish crude extracts (1050 g). This was shaken with 5% aq. HCl soln. and filtered. The filtrate was basified with NH_4OH and extracted with $CHCl_3$ to yield the crude alkaloid extract (33 g). The preliminary fractionation was achieved with CC, using $CHCl_3$ gradually enriched with MeOH (1-l fractions). Further separation of *fractions* (*Frs.*) *8–9* (1.3 g; eluted with $CHCl_3$) by prep. CC (benzene/$CHCl_3$/Me_2CO 8:1:1) followed by prep. TLC afforded *(−)-ethyl (reframidin-15-yl)acetate* (**7**/**8**; 20.6 mg), *(−)-15-(2-oxopropyl)reframidine* (**5**/**6**; 26.5 mg), and *(−)-roelactamine* (**4**; 32 mg). *Frs. 17–20* (21.5 g; eluted with 5% MeOH in $CHCl_3$) contained the already known major alkaloids and were investigated on a small scale by prep. TLC to afford *(−)-reframidine* (**3**), (−)-amurine, (−)-reframine, and (−)-noramurine, along with N-*feruloyltyramine* (**12**). *Frs. 23–25* (773 mg; eluted with 5% MeOH in $CHCl_3$) were first subjected to prep. CC (benzene/MeOH/25% NH_4OH 90:10:0.5). Further purification by prep. TLC yielded (−)-norreframidine (84.2 mg), (+)-flavinantine (10.3 mg), (+)-pseudolaudanine (27.9 mg), and (+)-roemecarine (42.8 mg). *Fr. 26* (202 mg; eluted with 10% MeOH in $CHCl_3$) was fractionated by prep. CC (benzene/MeOH/25% NH_4OH 90:10:0.5) and further purified by prep. TLC to furnish (−)-reframoline (32.5 mg), (−)-armepavine (6.2 mg), (−)-refractamine (42.3 mg), and an additional crop of (+)-roemecarine (11.4 mg). Prep. CC of *Frs. 33–35* (500.5 mg; eluted with 15% MeOH in $CHCl_3$) using benzene/$CHCl_3$/MeOH/25% NH_4OH 7:2:1:0.5 followed by prep. TLC yielded *(+)-coclaurine* (**9**; 15.6 mg) and *(±)-N-methylcoclaurine* (**10**; 17.8 mg). *Frs. 36–39* (439.4 mg; eluted with 15% MeOH in $CHCl_3$) were subjected to succesive prep. TLC to purify *(−)-(5*R*,11*S*,14*R*)-reframidine* N-*oxide* (**1**; 86.3 mg). Finally, prep. TLC of the

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[2]) The assignments of the NMR signals are given in accordance with the systematic numbering of reframidines (see *Formula* **2**).

final fractions (997.6 mg; eluted with 20% MeOH in $CHCl_3$) yielded *(−)-(5R,11S,14S)-reframidine* N-*oxide* (**2**; 113 mg) and *(−)-roemeridine* (**11**; 24.5 mg).

(−)-(5R,11S,14R)-Reframidine N-Oxide (= *(−)-(5R,11S,14R)-11,12-Dihydro-14-methyl-11,5-(iminomethano)-5H-cyclohepta[1,2-f:4,5-f′]bis[1,3]benzodioxole 14-Oxide*; **1**). $[\alpha]_D = -146.1$ ($c = 0.167$). UV: 237 (4.01), 299 (3.84), 318 (sh, 3.48). IR: 2990, 2960, 2895, 1505, 1485, 1375, 1260, 1235, 1190, 1090, 1040, 940, 870. ^{1}H-NMR: *Table 1*. ^{13}C-NMR: *Table 2*. EI-MS: *Fig. 1*. CI-MS: 340 (2), 339 (3), 338 (10), 324 (16), 323 (7), 322 (9), 321 (6), 310 (7), 309 (6), 308 (11), 307 (7), 292 (12), 281 (18), 280 (60), 279 (100), 222 (6), 188 (16), 174 (8), 165 (7), 164 (6), 163 (15). FAB-MS: 340 (97, $[M+1]^+$), 279 (100). ESI-MS: 339 ($M^{+\cdot}$).

(−)-(5R,11S,14S)-Reframidine N-Oxide (= *(−)-(5R,11S,14S)-11,12-Dihydro-14-methyl-11,5-(iminomethano)-5H-cyclohepta[1,2-f:4,5-f′]bis[1,3]benzodioxole 14-Oxide*; **2**). $[\alpha]_D = -128.2$ ($c = 0.117$). UV: 234 (sh, 3.86), 244 (infl., 3.69), 296 (3.98). IR: 2960, 2930, 2890, 1505, 1490, 1380, 1265, 1240, 1190, 1090, 1040, 940, 870. ^{1}H-NMR: *Table 1*. ^{13}C-NMR: *Table 2*. EI-MS: *Fig. 2*. ESI-MS: 339 ($M^{+\cdot}$).

Reduction of **1**. To a soln. of 5.1 mg (0.015 mmol) of **1** in 5 ml of MeOH at r.t., excess $NaBH_4$ was added in portions within 30 min under stirring. After 3 h, TLC revealed still the presence of **1**. Stirring was continued overnight. After evaporation of the MeOH, H_2O (7 ml) was added, the soln. acidified with 1N HCl, basified with 5% NH_4OH soln., and extracted with $CHCl_3$ (3 × 6 ml). Evaporation yielded 2.3 mg of reframidine (**3**), 1.7 mg of **1**, and some decomposition products.

Reduction of **2**. As described above with 6.6 mg (0.02 mmol) of **2** (stirring for 1 h instead of overnight): **3** (5.7 mg) and a trace of unreacted **2**.

(−)-Roelactamine (= *(−)-11,12-Dihydro-14-methyl-11,5-(iminomethano)-5H-cyclohepta[1,2-f:4,5-f′]bis-[1,3]benzodioxol-15-one*; **4**). $[\alpha]_D = -22$ ($c = 0.123$). UV: 234 (sh, 3.76), 240 (infl., 3.73), 297 (4.00). IR: 3000, 2895, 1660, 1505, 1485, 1400, 1370, 1345, 1310, 1270, 1245, 1235, 1195, 1170, 1150, 1040, 965, 945, 870. ^{1}H-NMR: *Table 1*. ^{13}C-NMR: *Table 2*. EI-MS: 337 (55, $M^{+\cdot}$), 336 (14), 322 (10), 321 (11), 320 (56), 281 (19), 280 (100), 279 (44), 165 (18), 164 (17), 163 (37), 140 (29), 139 (22), 125 (17).

Reduction of **4**. A soln. of **4** (5.1 mg, 0.015 mmol) in dry THF (3 ml) was added to a soln. of $LiAlH_4$ (5.3 mg, 0.139 mmol) in dry THF (3 ml) while stirring and refluxed under a gentle flow of N_2 for 24 h. After cooling and addition of H_2O/THF 1:4 (10 ml), the mixture was filtered, and the filtrate extracted with $CHCl_3$ (3 × 5 ml), dried (Na_2SO_4), and evaporated: 4.3 mg of crude product. Co-TLC (several solvent systems) with the authentic reference compounds revealed the presence of **3**, **4**, and some minor decomposition products.

(−)-15-(2-Oxopropyl)reframidine (= *(−)-1-[11,12-Dihydro-14-methyl-11,5-(iminomethano)-5H-cyclohepta-[1,2-f:4,5-f′]bis[1,3]benzodioxol-15-yl]propan-2-one*; **5**/**6** *ca.* 3:1). $[\alpha]_D = -100.5$ ($c = 0.19$). UV: 231 (sh, 3.88), 250 (sh, 3.66), 297 (3.90). IR: 3000, 2890, 1710, 1505, 1485, 1370, 1295, 1245, 1190, 1165, 1120, 1040, 940, 845, 835. ^{1}H-NMR (**5**, major isomer): 2.10 (*s*, MeCO); 2.36 (*s*, MeN); 2.43 (*dd*, $J = 17.5, 8.8$, 1H, CH_2CO); 2.70 (*dd*, $J = 17.3, 4.7$, 1H, CH_2CO); 2.91 (*dd*, $J = 17.3, 3.5$, H_α–C(12)); 2.98 (*ddd*, $J = 4.2, 4.2, 8.6$, H–C(15)); 3.31 (*dd*, $J = 17.5, 4.0$, H_β–C(12)); 3.67 (*d*, $J = 4.4$, H–C(5)); 3.70 (*t*, $J = 3.7$, H–C(11)); 5.83, 5.86 (2*d*, $J = 1.4$, CH_2(2)); 5.90, 5.93 (2*d*, $J = 1.4$, CH_2(8)); 6.47 (*s*, H–C(13)); 6.48 (*s*, H–C(4)); 6.70 (2*s*, H–C(10), H–C(6)). ^{1}H-NMR (**6**, minor isomer): 2.12 (*s*, MeCO); 2.38 (*dd*, $J = 16.5, 9.2$, 1H, CH_2CO); 2.54 (*dd*, $J = 16.7, 4.0$, 1H, CH_2CO); 2.59 (*s*, MeN); 2.76 (*dd*, $J = 17.5, 3.2$, H_α–C(12)); 3.45 (*s*, H–C(5)); 3.45 (*dd*, $J = 8.0, 4.0$, H–C(15)); 3.60 (*dd*, $J = 17.7, 3.6$, H_β–C(12)); 3.94 (*t*, $J = 3.3$, H–C(11)); 5.84, 5.85 (2*d*, $J = 1.4$, CH_2(2)); 5.88, 5.92 (2*d*, $J = 1.4$, CH_2(8)); 6.50 (*s*, H–C(13)); 6.62 (*s*, H–C(4)); 6.64 (*s*, H–C(6)); 6.70 (*s*, H–C(10)). EI-MS: 379 (10, $M^{+\cdot}$), 336 (9), 322 (20), 281 (19), 280 (100), 279 (15), 244 (8), 188 (8), 165 (11), 164 (9), 163 (16).

(−)-Ethyl (Reframidin-15-yl)acetate (= *(−)-Ethyl [11,12-Dihydro-14-methyl-11,5-(iminomethano)-5H-cyclohepta[1,2-f:4,5-f′]bis[1,3]benzodioxol-15-yl]acetate*; **7**/**8** *ca.* 1:1). $[\alpha]_D = -104.2$ ($c = 0.19$). UV: 234 (sh, 3.82), 245 (sh, 3.64), 296 (3.93). IR: 2980, 2890, 1725, 1505, 1485, 1375, 1345, 1300, 1245, 1180, 1040, 940, 865. ^{1}H-NMR: 1.25, 1.26 (2*t*, each $J = 7.2$, CH_3CH_2); 2.18 (*dd*, $J = 15.3, 9.5$), 2.23 (*dd*, $J = 15.8$, 8.8, 1H, CH_2CO); 2.36 (*dd*, $J = 15.3, 4.7$), 2.51 (*dd*, $J = 15.7$, 5.0, 1H, CH_2CO); 2.39, 2.59 (2*s*, MeN); 2.73 (*dd*, $J = 17.8, 2.9$), 2.87 (*dd*, $J = 17.1, 3.5$, H_α–C(12)); 2.87 (*m*, H–C(15)); 3.29 (*dd*, $J = 17.3, 4.0$), 3.57 (*dd*, $J = 17.5, 3.6$, H_β–C(12)); 3.39 (*dd*, $J = 9.5, 4.0$, H–C(15)); 3.54 (*s*), 3.66 (*d*, $J = 4.3$, H–C(5)); 3.69 (*t*, $J = 3.7$), 3.91 (*t*, $J = 3.3$, H–C(11)); 4.14 (*q*, $J = 7.2$), 4.15 (*q*, $J = 7.2$, CH_3CH_2); 5.80, 5.81 (2*d*, $J = 1.4$), 5.83, 5.84 (2*d*, $J = 1.4$, CH_2(2)); 5.85, 5.86 (2*d*, $J = 1.4$), 5.88, 5.91 (2*d*, $J = 1.4$, CH_2(8)); 6.44, 6.48 (2*s*, H–C(13)); 6.51, 6.57 (2*s*, H–C(4)); 6.66, 6.67 (2*s*, H–C(6)); 6.68 (2*s*, H–C(10)). EI-MS: 409 (9, $M^{+\cdot}$), 394 (1), 380 (1), 364 (1), 336 (1), 323 (5), 322 (28), 281 (18), 280 (100), 279 (16), 274 (23), 165 (6), 164 (5), 163 (11).

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