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FOUR NEW CRININE-TYPE ALKALOIDS FROM *STERNBERGIA* SPECIES

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ABSTRACT.—The crinine-type alkaloids (+)-buphanisine [**1**] and (−)-siculine [**2**] have been obtained from *Sternbergia sicula*, while (−)-epimaritinamine [**3**] and (−)-maritinamine [**4**] were found in *Sternbergia lutea*.

Eight *Sternbergia* species are known, belonging to the botanical family Amaryllidaceae. They range from the eastern Mediterranean to the Caucasus. Previous studies on *Sternbergia* species have centered mostly on *Sternbergia lutea* Ker-Gawl. ex Schult. (1,2), which has yielded a variety of lycorine, tazettine, lycorenine, galanthamine, and crinine-type alkaloids (3).

We have now studied the alkaloidal content of *Sternbergia sicula* Tin. ex Guss. and have also reinvestigated *S. lutea*, both of Turkish origin. This paper will describe only the crinine-type alkaloids which we found. Several known analogues of crinine were obtained and are presented in Figure 1. Four new analogues were also isolated, namely (+)-buphanisine [**1**] and (−)-siculine [**2**] from *S. sicula* and (−)-epimaritinamine [**3**] and (−)-maritinamine [**4**] from *S. lutea* (Figure 2).

Because the nmr data that were available in the literature on crinine-type alkaloids were rudimentary and limited mostly to old, low resolution measurements (4–7), we have summarized our 360 MHz ($CDCl_3$/1% C_5D_5N) data for the known alkaloids we found in our two plants around the structures in Figure 1. These complete assignments were supported by spin decoupling and nOe studies. The information summarized in Figure 1 was then of assistance in the structure elucidation of our four new bases.

The mass spectrum of (+)-buphanisine [**1**], $C_{17}H_{19}NO_3$, exhibited a typical crinine-type fragmentation pattern (8,9) with molecular ion *m/z* 285 and base peak *m/z* 215.

The nmr spectrum of (+)-buphanisine ($CDCl_3$/1% C_5D_5N) has been summarized around structure **1**. Noteworthy are the methylenedioxy doublets at δ 5.95 and 5.96, the aliphatic methoxyl singlet at δ 3.37, and the aromatic proton singlets at δ 6.55 and 6.86. The vinylic protons were in evidence at δ 6.05 and 6.50. The equatorial orientation of the methoxyl group was deduced from the coupling constants, $J_{2,3} = 5.2$ Hz and $J_{3,4\alpha} = 4.0$ Hz.

The above data were in full agreement with those reported for (−)-buphanisine obtained from *Boöphone fischeri* (10) and other Amaryllidaceae, except for the positive specific rotation of our product. Indeed, the cd curve of our (+)-buphanisine was the opposite of that described for (−)-buphanisine in the literature (11), and included a minimum at 247 nm. It follows that (+)-buphanisine [**1**] is a new alkaloid, enantiomeric with the known (−)-buphanisine.

The mass spectrum of our second new alkaloid, (−)-siculine [**2**], $C_{16}H_{19}NO_3$, included molecular ion peak *m/z* 273, which was also the base peak. The uv spectrum suffered a strong bathochromic shift in basic solution (see Experimental), suggesting the presence of a phenolic function.

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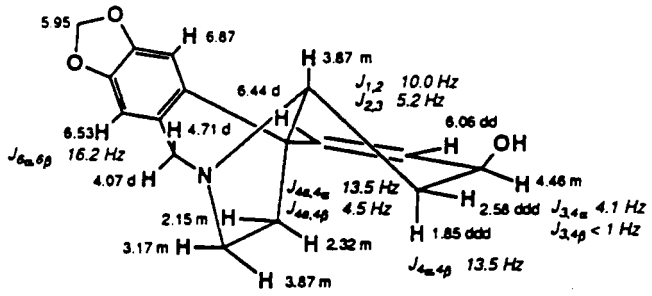
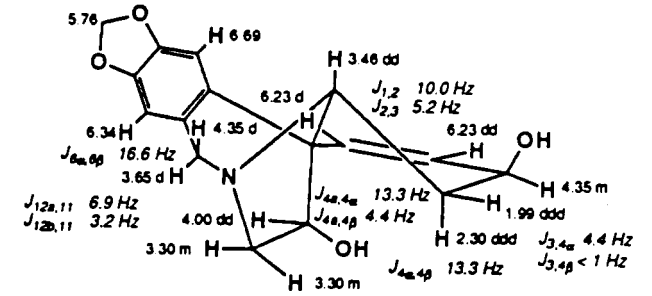
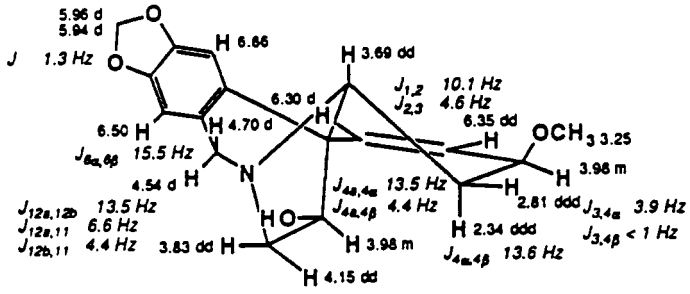


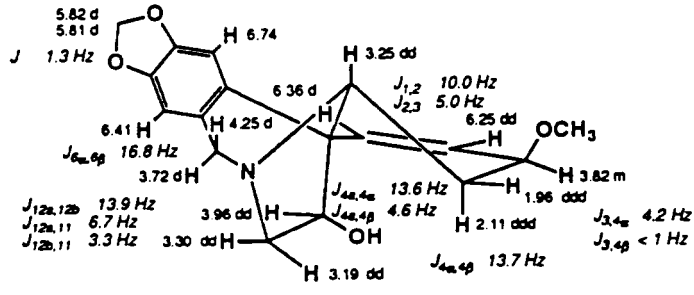
(+)-vittatine



(+)-11-hydroxyvittatine



(−)-11-*epi*-haemanthamine



(+)-haemanthamine

FIGURE 1. Known crinine-type alkaloids.

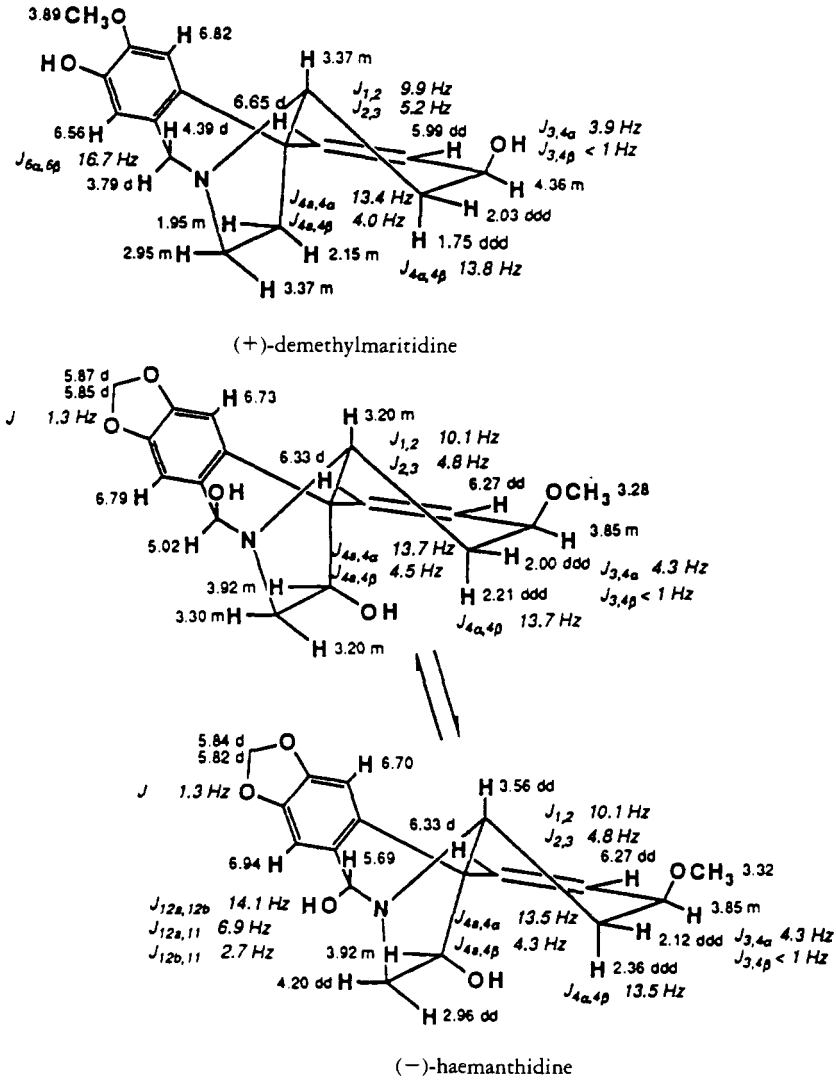
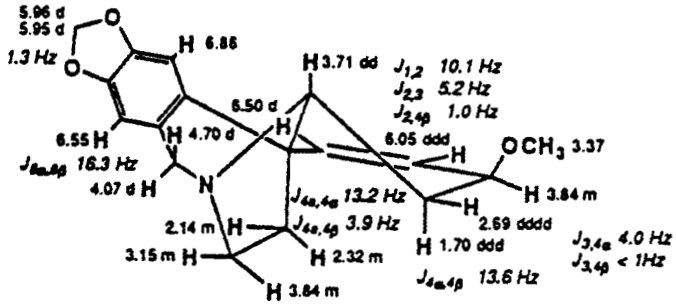


FIGURE 1. Continued.

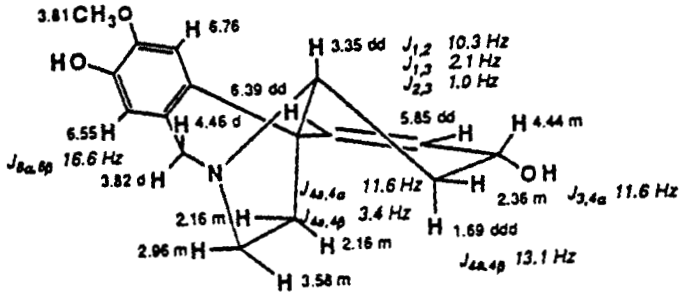
The nmr spectrum of (−)-siculine ($CDCl_3$/1% C_5D_5N) is described around structure **2**. Two aromatic protons were in evidence at δ 6.55 and 6.76, as well as an aromatic methoxyl at δ 3.81 and two vinylic protons at δ 5.85 and 6.39, thus indicating a substitution pattern identical with that of the known (+)-demethylmaritidine (4). Irradiation of H-10 (δ 6.76) resulted in enhancements of the 9-OMe (δ 3.81) and the H-1 (δ 6.39) signals, allowing for a firm assignment of the locations of the aromatic methoxyl and hydroxyl substituents. The C-3 hydroxyl must be pseudo-equatorial because the coupling constant between H-3 and H-4α is large, 11.6 Hz, and an allylic coupling of 2.1 Hz is observed between the vinylic H-1 and the allylic H-3.

The absolute configuration of the alkaloid was determined through the cd spectrum, which was close in shape and sign to that of the known (+)-epimaritidine (12) and included a minimum at 227 nm.

Our last two new alkaloids, namely the diastereomeric (−)-epimaritinamine [**3**] and (−)-maritinamine [**4**], $C_{16}H_{21}NO_3$, are epimeric at C-3 and exhibited closely re-



1



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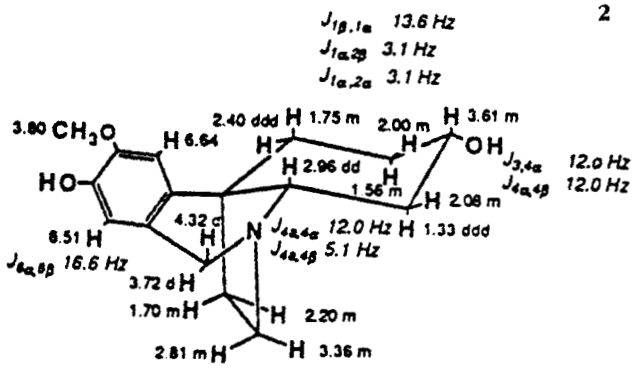

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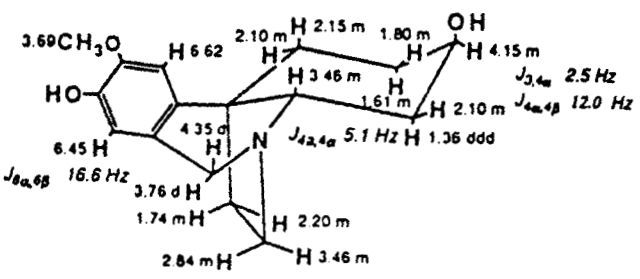

4

lated sets of uv, ir, mass, and cd spectra. In each case, the mass spectral molecular ion, *m/z* 275, was also the base peak.

The nmr spectrum of (−)-epimaritinamine [3] ($CDCl_3$/1% C_5D_5N) displayed singlets at δ 6.51 and 6.64 representing H-7 and H-10, while the 9-OMe group was

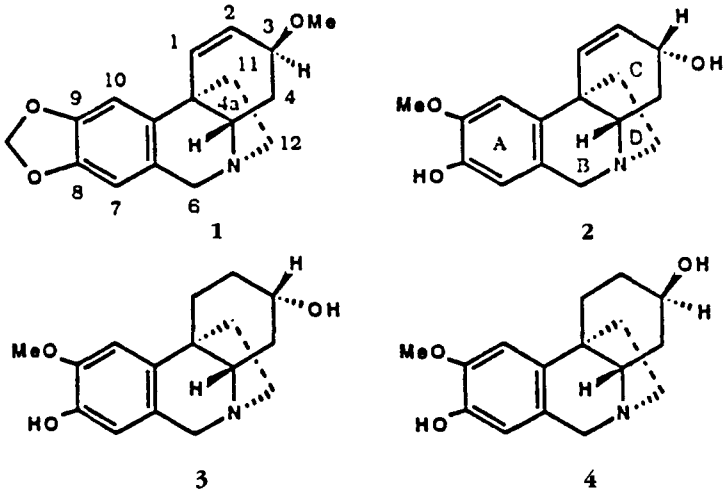

FIGURE 2. New crinine-type alkaloids.

indicated by a singlet at δ 3.80. The assignment of the methoxyl substituent to C-9 was supported by interlocking nOe's connecting 9-OMe, H-10, and H-1eq (see Experimental). The pseudo-equatorial disposition of the C-3 hydroxyl was inferred from the large coupling constant (12 Hz) between H-3 and H-4α.

The ethano bridge has the α configuration, as the cd curve of (−)-epimaritinamine manifests a minimum at 228 nm (12).

Turning now to the diastereomeric (−)-maritinamine [**4**], the exact location of the aromatic methoxyl was arrived at through nmr nOe measurements that interrelated 9-OMe (δ 3.69), H-10 (δ 6.62), and H-1α (δ 2.10).

A significant feature of the nmr spectrum was the long range W coupling between H-1α (δ 2.10) and H-3 (δ 4.15), indicating that they were in the same plane. Additionally, the coupling constant between H-3 and H-4β was small, 2.5 Hz, denoting a dihedral angle of approximately 60°.

The cd spectrum of (−)-maritinamine displayed a minimum at 229 nm, testifying to the absolute configuration shown in expression **4**.

An interesting structural problem becomes evident at this stage. All of our *Sternbergia* alkaloids, new as well as known, possess the identical absolute configuration, with the ethano bridge below the mean plane of the molecule. On the other hand, the stereochemistry at C-3 may vary, as exemplified by the pair (−)-epimaritinamine [**3**] and (−)-maritinamine [**4**]. It has been reported that the plant *Crinum latifolium* produces crinine-type alkaloids of opposite absolute configurations, with the ethano bridge either above or below the mean plane (13). Yet it is evident from perusal of the literature that naturally occurring crinine-type racemic alkaloids are never encountered. The reasons for this apparent paradox are presently unclear.

We also made an effort to correlate specific structural features among the crinines, such as number of aromatic substituents on ring A, oxidation states, and absolute configuration, with botanical origin, especially in terms of genera (*Crinum, Sternbergia, Boöphone,* etc.), but no discernible trend could be noted. This is somewhat surprising, as nature usually proceeds in an orderly fashion.

EXPERIMENTAL

PLANT COLLECTION AND ALKALOID EXTRACTION.—*S. sicula* (11 kg, dry) was collected in November 1985 near the village of Söke in Aydin Province in western Anatolia. *S. lutea* (7 kg, dry) was

gathered in November 1985 near the village of Aydin in Shout Province, also in western Anatolia. Plant specimens were deposited in the Herbarium of Ege University.

The dried plant materials were extracted separately with EtOH at room temperature. Standard acid-base workup using 1% HCl and NH_4OH was followed by chromatography on Si gel columns. Elution was with $CHCl_3$ gradually enriched with MeOH. Monitoring was by tlc, and similar fractions were combined. Final purification was by tlc on Si gel glass plates. Tlc bands were differentiated under short wave-length uv light and by means of Dragendorff's reagent. The bands were desorbed from the Si gel using $CHCl_3$-MeOH (4:1).

Compounds obtained from *S. sicula* were: (+)-vittatine (500 mg), (+)-11-hydroxyvittatine (20 mg), (+)-tazettine (15 mg), (+)-haemanthamine (3 g), (−)-11-*epi*-haemanthamine (20 mg), (−)-haemanthidine (3 g), (+)-demethylmaritidine (5 mg), (+)-buphanisine [**1**] (100 mg) and (−)-siculine [**2**] (5 mg). Compounds isolated from *S. lutea*, with approximate weights in parentheses, include (+)-tazettine (30 mg), (+)-pretazettine (30 mg), (−)-epimaritinamine [**3**] (30 mg), (−)-maritinamine [**4**] (3 mg), (+)-demethylaritidine (10 mg), (+)-haemanthamine (500 mg), (+)-11-hydroxyvittatine (25 mg), (+)-vittatine (50 mg), and (−)-haemanthidine (1 g). All compounds were amorphous except for (−)-haemanthidine, mp 189–190° (MeOH) and (+)-haemanthamine, mp 203–203.5° (MeOH).

(+)-BUPHANISINE [**1**].—$[\alpha]_D$ +18.0° (c = 2.1, $CHCl_3$); cd $\Delta\epsilon$ (nm) (MeOH) +1.82 (288), −1.98 (247); uv λ max (MeOH) 235, 292 nm (log ϵ 3.47, 3.53); eims *m/z* $[M]^+$ 285 (95), 270 (32), 254 (28), 230 (32), 215 (100), 201 (27), 187 (20), 185 (25), 172 (24), 157 (32), 115 (59).

(−)-SICULINE [**2**].—$[\alpha]_D$ −80.0° (c = 1.3, $CHCl_3$); cd $\Delta\epsilon$ (nm) (MeOH) −0.92 (287), +1.17 (257), −2.59 (227); uv λ max (MeOH) 238 sh, 287 nm (log ϵ 3.35, 3.31); λ max (MeOH-OH^-) 247, 294 nm (log ϵ 3.48, 3.39); eims *m/z* $[M]^+$ 273 (100), 256 (12), 255 (4), 254 (8), 230 (23), 218 (16), 201 (68), 189 (58), 175 (28), 174 (18). Significant nmr nOe values were 9-OMe to H-10 (12%), H-10 to 9-OMe (13%), H-1 to H-10 (18%), H-10 to H-1 (17%), H-1 to H-2 (6%), H-2 to H-1 (7%).

(−)-EPIMARITINAMINE [**3**].—$[\alpha]_D$ −4.0° (c = 2.2, MeOH); cd $\Delta\epsilon$ (nm) (MeOH) −0.53 (300), +2.02 (262), −1.67 (228); uv λ max (MeOH) 222 sh, 254, 286 nm (log ϵ 3.45, 2.67, 3.24); eims *m/z* $[M]^+$ 275 (100), 258 (19), 247 (16), 246 (23), 228 (17), 204 (42), 203 (44), 202 (24), 187 (24); hreims calcd for $C_{16}H_{21}NO_3$, 275.1521, found 275.1519. Significant nmr nOe values were H-1α to H-10 (15%), H-2β to H-3β (4%), H-3β to H-2β (5%), H-3β to H-4β (5%), H-3β to H-4a (6%), H-4a to H-3β (4%), H-4β to H-3β (4%), H-7 to H-6β (2%), H-7 to H-6α (4%), H-6β to H-7 (3%), H-6α to H-7 (7%), 9-OMe to H-10 (18%), H-10 to 9-OMe (21%), H-10 to H-1α (8%).

(−)-MARITINAMINE [**4**].—$[\alpha]_D$ −20.3° (c = 1.8, MeOH); cd $\Delta\epsilon$ (nm) (MeOH) −0.48 (291), +0.72 (262), −1.63 (229); uv λ max (MeOH) 228 sh, 257, 286 nm (log ϵ 3.63, 2.67, 3.48); eims *m/z* $[M]^+$ 275 (100), 258 (28), 247 (17), 246 (20), 228 (18), 204 (19), 203 (48), 202 (22), 187 (23). Significant nmr nOe values were H-1α to H-10 (24%), H-2α to H-3α (5%), H-3α to H-2α (3%), H-3α to H-4β (4%), H-3α to H-4α (5%), H-4β to H-3α (6%), H-4α to H-3α (4%), H-7 to H-6β (5%), H-6β to H-7 (21%), H-6α to H-7 (8%), H-7 to H-6α (5%), 9-OMe to H-10 (22%), H-10 to 9-OMe (12%), H-10 to H-1α (14%).

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