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NEW APORPHINE ALKALOIDS FROM *PHOEBE VALERIANA*

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ABSTRACT.—From leaves of *Phoebe valeriana* were isolated three new pentasubstituted aporphine alkaloids [1,2,3-trimethoxy-9,10-methylenedioxyaporphine or phoebine (**1**), 1,2-droxynoraporphine or nordelporphine (**5**)], a new phenanthrene alkaloid (**7**), a new dehydroaporphine alkaloid (**8**), and a new oxoaporphine (**9**). In addition, four known aporphine alroaporphine alkaloid (**8**), and a new oxoaporphine (**9**). In addition, four known aporphine alkaloids [nantenine, thaliporphine, 3-hydroxyglaucine or *N*-methylthalbaicaline, and norphoebine (**2**)] and the known oxoaporphine *O*-methylmoschatoline were found. The structures were elucidated principally by spectroscopic methods and chemical transformations.

Our previous reports (1-4) on the chemical investigation of the *Phoebe* genus of Costa Rica showed that those species which produced alkaloids, *P. mollicella* and *P. pittieri*, yielded mainly pentasubstituted aporphine alkaloids, which are relatively rare compared with the tetrasubstituted aporphines. In the present work, we report on alkaloids of the leaves of *Phoebe valeriana* Standl. (Lauraceae), which we have again found to be mainly pentaoxygenated.

Besides the pentaoxygenated aporphines discussed below, the known aporphines nantenine, thaliporphine, 3-hydroxyglaucine (*N*-methylthalbaicaline), and norphoebine as well as the known oxoaporphine *O*-methylmoschatoline were isolated. These alkaloids were characterized by spectral data and comparison with literature references.

The major alkaloid, named phoebine, was assigned structure **1**, based on the following evidence. Mass spectral analysis showed the molecular formula $C_{21}H_{23}NO_5$, and the uv spectrum was indicative of an aporphine. The ^{1}H-nmr spectrum showed three methoxy singlets with the most upfield one (3.72 ppm) assignable to a C-1 methoxy, an N-Me signal at 2.51 ppm, a two proton singlet at 5.95 ppm characteristic of a D-ring methylenedioxy group, and two aromatic singlets at 6.73 and 7.81 ppm, typical of H-8 and H-11 in a pentasubstituted aporphine (5). A synthetic isomer, *N*-methylbaicaline, is known (6) which has the methylenedioxy group at C-2, C-3 in the A ring. This isomer showed a single nine proton singlet for the three methoxy groups (3.84 ppm). Since phoebine must have a C-1 methoxyl and it is clearly different from *N*-methylbaicaline, the only possibility for phoebine is **1**. The proposed structure **1** was also supported by the ^{13}C-nmr spectrum which showed three low field (60 ppm region) methoxy methyl resonances. Structure **1** was established unambiguously by synthesis from the known (2) norphoebine **2** by *N*-methylation with formaldehyde/formic acid. The optical rotation for **1** ($[\alpha]^{24}D$ +49.6) was indicative of the 6a-*S* configuration.

An isolated alkaloid (**3**) of molecular weight 341 was assigned the formula $C_{19}H_{19}NO_5$ based upon the ms and ^{1}H-nmr spectrum which were very similar to those of **1** except for expected discrepancies due to lack of an *N*-methyl and one methoxy methyl signal. Treatment of **3** with Ac_2O/pyridine yielded an *N,O*-diacetyl derivative as evidenced by appearance of a six proton singlet (2.38 ppm) and ir amide and ester car-

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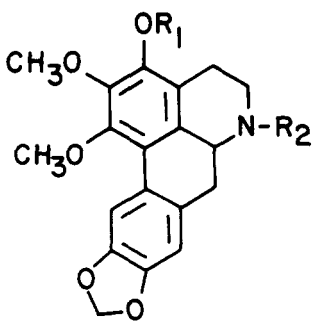
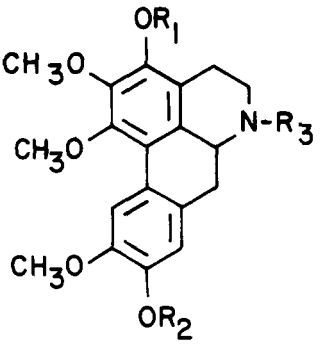
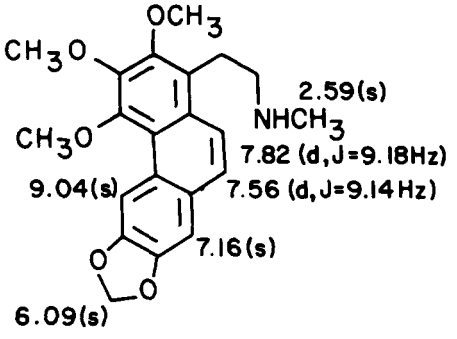


1 $R_1=R_2=CH_3$
2 $R_1=CH_3$, $R_2=H$
3 $R_1=R_2=H$
4 $R_1=H$, $R_2=CH_3$



5 $R_1=R_2=R_3=H$
6 $R_1=H$, $R_2=R_3=CH_3$



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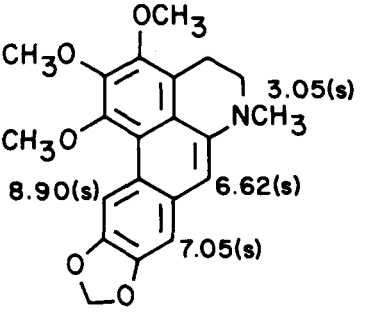

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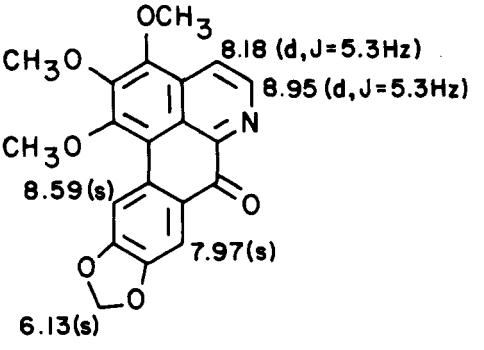

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bonyl bands at 1660 and 1780 cm^{-1}. The uv spectrum showed a bathochromic and hyperchromic shift with base (**7**) and, hence, the phenolic group must be at C-3. Structure **3** was confirmed since the mass spectrum of the diacetyl derivative exhibited characteristic fragment ions at M^+-59 and M^+-101, which again indicated that the phenolic group was at C-3 (8,9).

It is likely that **4**, the *N*-methyl derivative of **3**, is also present in the plant since the proper ^1H- and ^{13}C-nmr signals as well as ms could be detected as minor components of an inseparable mixture with an additional alkaloid (see below).

A third alkaloid, **5**, was comparable to **3** in spectral data except for the lack of the

methylenedioxy group and addition of one methoxy methyl. Acetylation produced a triacetyl derivative (one N-Ac and two OAc groups). The characteristic ms fragments were observed for a 3-OAc substituent (see above). When one of the OMe resonances was irradiated (3.92 ppm) a strong nOe enhancement was noted for the aromatic H-11 proton and, hence, a methoxy group must be at C-10, and the remaining phenolic group must be at C-9. Confirmation evidence for phenolic groups at C-3 and C-9 was obtained by oxidation of **5** with iodine vapor over silica gel to yield a compound whose uv spectrum (λ max 222, 291, 370sh, and 429 nm) was nearly the same as that reported (10) for a 2,7-phenanthrenequinone.

As a further member of the same sequence, we found **6**, which has previously been encountered as *N*-methylthalbaicaline (9) in *Thalictrum baicalense* or 3-hydroxyglaucine (10) in *Ocotea bucherii*. Our isolate was inseparably contaminated with **4**, but could be identified with **6** on the basis of the presence of ^{1}H- and ^{13}C-nmr resonances and ms fragmentation peaks consistent with those reported (9,10). Acetylation of the mixture allowed isolation of 3-acetoxyglaucine whose spectral data also correlated (11).

The three additional new compounds could be assigned as the phenanthrene **7**, dehydroaporphine **8**, and oxoaporphine **9** derivatives of the aporphine **1** by examination of their uv and ^{1}H-nmr spectra and by chemical conversions. The ^{1}H-nmr spectral data of particular importance are given on structures **7-9**. Special features of the phenanthrene **7** spectrum include two aromatic proton singlets, with a very downfield one at 9.04 ppm assignable to H-5, and two doublets at 7.56 and 7.82 (J=9.1 Hz) corresponding to the H-9 and H-10 protons. The ms of **7** showed the characteristic fragmentation which produced an M^{+}-44 ion and the *m/z* 44 base peak for $(CH_2{=}NHCH_3)^{+}$. The uv spectrum of **7** was typical for a phenanthrene. Finally, acetylation of **7** gave an N-Ac derivative identical to that obtained by heating **1** for 2 h in Ac_2O/pyridine (12). Alkaloid **8** had a uv spectrum similar to that of **7**. The nmr spectrum showed three methoxy singlets and three aromatic singlets, with one downfield at 8.90 ppm, assignable to the H-11 proton. A three proton singlet was observed at 3.05 ppm, and such a position is diagnostic of an *N*-methyl in a C-6a, C-7 dehydrophenanthrene (13). Structure **8** was assured by its synthesis from **1** with iodine vapor on silica gel. Finally, alkaloid **9** was found to completely lack the typical nmr resonances for saturated ring protons. This, along with its uv spectrum, suggested the oxoaporphine structure **9**. Indeed, oxidation of **1** with lead tetraacetate (14) produced an oxoaporphine identical with the isolate.

EXPERIMENTAL

PLANT MATERIAL.—*P. valeriana* was collected in Costa Rica, Pavones, Turrialba. A voucher specimen was deposited in the Herbarium of the National Museum of Costa Rica, San Jose, and identified by L. Poveda.

EXTRACTION AND ISOLATION.—Powdered, dry leaves (2.5 kg) were extracted with cold EtOH. The solvent was evaporated to yield a syrupy residue, which was partitioned between 5% HCl and $CHCl_3$. The $CHCl_3$ fraction was concentrated to give a brown residue (2.2 g) of a crude alkaloid salt mixture, and 1.72 g of this was purified as the free base mixture by flash chromatography (Si gel, $CHCl_3$-MeOH, 94:6, 8:2, and 1:1). The several fractions eluted with $CHCl_3$-MeOH (96:4) were combined and subjected to preparative tlc on Si gel using $CHCl_3$-MeOH (95:5). This afforded **1** (730 mg), norphoebine (**2**) (78 mg), nantenine (42 mg), **3** (11 mg), a mixture of **4** and **6** (180 mg), and traces of other minor alkaloids, principally the dehydrophenanthrene **8**. The aqueous acid fraction was made basic to pH 9-10 with NH_3 and extracted with $CHCl_3$ to yield 0.42 g of residue. This contained the above alkaloids (except **1** and nantenine) and in addition afforded the dehydroaporphine **7** (20 mg), the oxoaporphine *O*-methylmoschatoline (3 mg), and the oxoaporphine **9** (10 mg). These alkaloids were isolated by tlc on Si gel using CH_2Cl_2. The more polar aporphines, thaliporphine (6 mg), the noraporphine **5** (12 mg), and the phenanthrene alkaloid **8** (10 mg) were isolated by tlc on Si gel using $CHCl_3$-MeOH (7:3).

IDENTIFICATION OF ALKALOIDS.—We had previously (2) isolated and identified **2** from *P. pittieri*.

Identification of nantenine, thaliporphine, and *O*-methylmoschatoline was by analysis of the high field ^{1}H-nmr spectra and uv spectra and comparison with data from the literature references available (15). Similarly, **6** was identified, but with spectral comparisons to the more recent literature (9,11).

^{1}H-nmr and ^{13}C-nmr spectra for the following data were recorded with TMS as internal standard in $CDCl_3$ at 270 MHz and 67.5 MHz, respectively.

1,2,3-TRIMETHOXY-9,10-METHYLENEDIOXYAPORPHINE (**1**) PHOEBINE.—Recrystallized from Me_2CO, mp 114°; uv λ max (EtOH) 220, 282, 312; ^{1}H nmr 7.81 (s, H-11), 6.73 (s, H-8), 5.95 (s, O-CH_2-O), 3.94 (s, OMe-2), 3.88 (s, OMe-3), 3.72 (s, OMe-1), 2.51 ppm (s, N-Me); ^{13}C nmr 145.13 (C-1), 122.63 (C-1a), 130.07 (C-1b), 149.78 (C-2), 149.47 (C-3), 125.57 (C-3a), 23.61 (C-4), 52.90 (C-5), 62.73 (C-6a), 34.87 (C-7), 130.80 (C-7a), 108.04 (C-8), 146.03 (C-9), 146.50 (C-10), 108.35 (C-11), 122.63 (C-11a), 100.63 (C-9,10 O-CH_2-O), 60.63 (C-1 OMe), 60.09 (C-2 OMe), 60.30 (C-3 OMe), 43.60 ppm (N-Me); eims (*m/z*, %): 369 (1.2) M^+, 368 (1.1), 354 (0.5), 311 (0.6), 309 (0.8), 295 (0.7); NH_3/cims (*m/z*, %): 370 (14) $[M+1]^+$, 369, M^+(60), 367 (13), 339 (3), 337 (4); fabhrms Calcd. for $C_{21}H_{24}O_5N^+$, 370.1654; Found 370.1655; $[\alpha]^{24}D$ +49.6 (c 6.2, $CHCl_3$).

N-*Methylation of* **1**. Compound **1** (15 mg) was prepared by refluxing norphoebine for 18 h with HCHO (37%) and HCOOH (88%) (1:1). Concentrated HCl was added, and the volatiles were removed by evaporation under reduced pressure. The amine salt residue was converted to the free base with NaOH, and the aqueous layer extracted with $CHCl_3$. Purification by preparative tlc ($CHCl_3$-MeOH, 95:5) gave norphoebine (**2**) in 78% yield.

1,2-DIMETHOXY-3-HYDROXY-9,10-METHYLENEDIOXYNORAPORPHINE (**3**).—An amorphous solid; uv λ max (EtOH) 220, 283, 302, 314 sh. nm; uv λ max (EtOH-OH^-) 226, 324; ^{1}H nmr 7.79 (s, H-11), 6.72 (s, H-8), 5.96 (s, O-CH_2-O), 3.97 (s, OMe-2), 3.72 ppm (s, OMe-1); eims (*m/z*, %): 341 (3.5) M^+, 340 (3), 326 (1), 324 (1), 312 (0.5), 297 (1.5), 295 (1), 281 (1.5); NH_3/cims (*m/z*, %): 342 $[M+1]^+$ (2), M^+ 341 (8).

Acetylation of **3**.—Compound **3** (3 mg) was treated with Ac_2O and C_5H_5N (3:1) for 16 h at room temperature. Evaporation of the solvent and purification by preparative tlc ($CHCl_3$-MeOH, 9:1) afforded the diacetate: ir (thin film, cm^{-1}) 1780 (ester), 1660 (amide); ^{1}H nmr 7.91 (s, H-11), 6.76 (s, H-8), 5.99 (s, O-CH_2-O), 3.90 (s, OMe-2), 3.73 (s, OMe-1), 2.38 (s, OAc-3), 2.38 ppm (s, NAc); eims (*m/z*, %) 425 (4) M^+, 383 (1.5), 366 (6), 354 (1.5), 324 (9), 311 (18), 280 (12), 267 (17); NH_3/cims (*m/z*, %) 426 $[M+1]^+$ (2), M^+ 425 (7); fabhrms Calcd. for $C_{23}H_{24}O_7N^+$, 426.1552; Found 426.1541.

1,2,10-TRIMETHOXY-3,9-DIHYDROXYNORAPORPHINE (**5**).—An amorphous solid; uv λ max (EtOH) 220, 282, 303, 312 sh. nm; uv λ max (EtOH-OH^-) 224, 320 nm; ^{1}H nmr 7.89 (s, H-11), 6.79 (s, H-8), 3.99 (s, OMe-2), 3.92 (s, OMe-10), 3.72 ppm (s, OMe-1); NH_3/cims (*m/z*, %) 344 (9) $[M+1]^+$, 343 (3) M^+, 279 (21.5), 237 (24), 223 (35), 217 (15), 205 (16.5), 204 (11), 200 (14), 195 (91), 194 (25), 180 (11), 164 (13.5), 163 (31.5), 125 (16), 124 (27.5), 110 (24), 109 (24).

Acetylation of **5**.—Compound **5** (5 mg) was treated with Ac_2O and C_5H_5N (3:1) for 14 h at room temperature. After evaporation of the solvent and purification by preparative tlc ($CHCl_3$-MeOH, 8:2, on Si gel), the triacetate of **6** was obtained. ^{1}H nmr 8.14 (s, H-11), 6.96 (s, H-8), 3.92 (s, 6H, OMe-2, 10), 3.74 (s, OMe-1), 2.39 (s, 6H, OAc-3,9), 2.34 ppm (s, 3H, NAc); eims (*m/z*, %) 469 (6) M^+, 427 (3.5), 410 (5), 385 (1.5), 368 (9), 367 (5), 355 (14), 338 (2), 326 (13), 314 (6), 313 (12), 210 (19); NH_3/cims (*m/z*, %) 470 (0.2) $[M+1]^+$, 469 (0.6) M^+, 428 (0.3), 391 (5), 386 (0.4), 279 (3.5), 223 (39), 177 (10), 161 (19), 158 (11), 144 (100); fabhrms Calcd. for $C_{25}H_{28}O_8N^+$, 470.1814; Found 470.1827.

1-β-METHYLAMINOETHYL-2,3,4-TRIMETHOXY-6,7-METHYLENEDIOXYPHENANTHRENE (**7**).—An amorphous solid; uv λ max (EtOH) 234 sh, 262, 284, 304, 317, 344, 362 nm; ^{1}H nmr 9.04 (s, H-5), 7.82 (d, J=9.18 Hz, H-9), 7.56 (d, J=9.14 Hz, H-10), 7.16 (s, H-8), 6.09 (s, O-CH_2-O, C6,7), 4.05 (s, OMe), 3.98 (s, OMe), 3.95 (s, OMe), 3.39 (m, 2H, H-2′), 3.00 (m, 2H, H-1′), 2.59 (s, 3H, NMe); eims (*m/z*, %) 369 (1.7) M^+, 326 (38), 325 (10), 311 (10.5), 283 (3.5), 268 (3), 240 (0.6), 209 (2), 179 (4), 163 (5.5), 151 (6.5), 44 (34), 57 (100); NH_3/cims (*m/z*, %) 370 (8) $[M+1]^+$, 369 (34) M^+, 326 (4), 45 (13), 44 (100).

Acetylation of **7**.—Compound **7** (4 mg) was treated with Ac_2O and C_5H_5N (2:1) for 15 h at room temperature. After evaporation of the solvent and purification by preparative tlc (Si gel, $CHCl_3$/MeOH, 7:3), the monoacetate **7** was obtained; ir (thin film, cm^{-1}) 1642 (amide); uv λ max (EtOH) 214 sh, 262, 284, 305, 316, 345, 362 nm; ^{1}H nmr 9.05 (s, H-5), 8.02* (d, J=9.15 Hz, H-9), 7.69* (d, J=9.18 Hz, H-9), 7.60* (d, J=9.14 Hz, H-10), 7.61* (d, J=9.18 Hz, H-10), 6.09 (s, 2H, O-CH_2-O, C6,7), 6.08 (s, 2H, O-CH_2-O, C6,7), 4.06 (s, OMe), 4.05 (s, OMe), 4.01 (s, OMe), 4.00 (S, OMe), 3.96 (S, OMe), 3.95 (s, OMe), 3.55 (m, 4H, H-2′), 3.32 (m, 4H, H-1′), 3.06 (s, N-Me), 2.94 (s, N-Me), 2.10 (s, NAc), 2.03 ppm (s, NAc); eims (*m/z*, %) 411 (3) M^+, 338 (7), 325 (11), 310 (2.5), 157 (5), 149 (16), 85 (19); NH_3/

cims (*m/z*, %) 412 (93) $[M+1]^+$, 382 (7.5), 370 (4.5), 368 (2), 340 (8), 338 (4), 325 (7), 313 (20), 223 (33), 221 (11), 220 (11), 214 (17), 209 (12), 207 (10), 203 (16), 197 (29), 181 (18), 167 (11), 102 (78), 74 (100); fabhrms Calcd. for $C_{23}H_{26}O_6N^+$, 412.1760; Found 412.1756.

Acetylation of **1**.—Compound **1** (30 mg) was treated with Ac_2O and C_5H_5N (1:1) for 2 h at 80°. Evaporation of the solvent gave monoacetate **7** quantitatively.

1,2,3-TRIMETHOXY-9,10-METHYLENEDIOXYDEHYDROAPORPHINE (**8**).—An amorphous solid; uv λ max (EtOH) 218, 240 sh, 256, 266 sh, 328 nm; ^{1}H nmr 8.90 (s, H-11), 7.05 (s, H-8), 6.03 (s, O-CH_2-O, C9,10), 4.06 (s, OMe), 394 (s, OMe), 3.93 (s, OMe), 3.05 ppm (s, N-Me); eims (*m/z*, %) 369 (59), 368 (67), 367 (39) M^+, 352 (23), 336 (8), 323 (1); NH_3/cims (*m/z*, %) 368 (22) [M+1], 367 (100) M^+, 338 (6), 223 (52.5), 194 (3), 177 (9.5); fabhrms Calcd. for $C_{21}H_{22}O_5N^+$, 368.1498; Found 368.1494. The identical compound was obtained by oxidation of **1** by iodine vapor on silica gel (16). A concentrated solution of **1** was streaked on the surface of several tlc plates, and the plates were exposed to iodine vapor in a covered jar for 8 min. The Si gel was removed, extracted with $CHCl_3$-MeOH (4:1), and the solution evaporated to quantitatively yield **8**.

1,2,3-TRIMETHOXY-9,10-METHYLENEDIOXY-OXOAPORPHINE (**9**).—An amorphous solid; uv λ max (EtOH) 210, 228, 272, 311 sh, 324 sh, 438 nm; ^{1}H nmr 8.95 (d, J=5.3 Hz, H-5), 8.59 (s, H-11), 8.18 (d, J=5.3 Hz, H-4), 7.97 (s, H-8), 6.13 (s, O-CH_2-O, C9,10), 4.18 (s, OMe), 4.10 (s, OMe), 4.06 (s, OMe); eims (*m/z*, %) 365 (64) M^+, 350 (47), 335 (18), 322 (20), 321 (33), 307 (26), 306 (19), 292 (18), 264 (18); fabhrms Calcd. for $C_{20}H_{16}O_6N^+$, 366.0978; Found 366.0985. Treatment of compound **1** (15 mg) with lead tetraacetate in glacial HOAc (1:3) at room temperature for 16 h yielded principally the oxoaporphine **9** (~ 90%) and the dehydroaporphine **8** as evidenced tlc and ^{1}H nmr.

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