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PENTASUBSTITUTED APORPHINE ALKALOIDS FROM *PHOEBE MOLICELLA*

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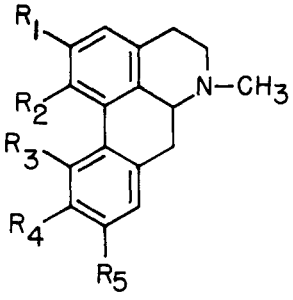
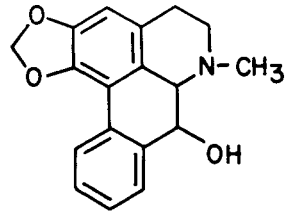
ABSTRACT.—The known aporphine alkaloids norpurpureine,- purpureine, and preocoteine (previously incompletely characterized), as well as the new alkaloid norpreocoteine, have been isolated from *Phoebe molicella* (Lauraceae). The ^{13}C-nmr spectra of three of these pentasubstituted aporphines is presented for the first time, as is a summary of previous work in the genus *Phoebe*.

The genus *Phoebe* of the family Lauraceae is of wide tropical occurrence but has been little studied chemically. The leaf alkaloids of *Phoebe clemensii* (New Guinea) were found to be isocorydine (**1**), 10-hydroxy-1,2-methylenedioxyaporphine (**2**), and *N*-methyllindcarpine (**3**), while the bark consisted largely of laurolitsine (**4**) (1). Nine alkaloids were found in *Phoebe formosana* (Taiwan): the wood yielding roemerine (**5**) and laurolitsine (plus two unknowns), and the bark containing laurolitsine, ushinsunine (**6**), and liriodenine (**7**), as well as three additional unknowns (2). An investigation of bark from *Phoebe porfiria* (Argentina) gave "quaternary and tertiary alkaloides," but only ocoteine (**8**) was identified (3). These three studies represent the only previous investigations we have been able to find.





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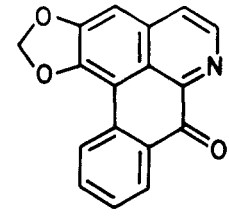

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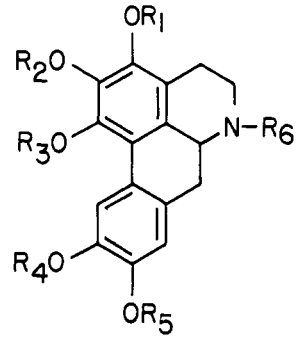
1: $R_1=R_2=R_4=OMe$; $R_3=OH$; $R_5=H$
2: R_1, $R_2=OCH_2O$; $R_4=OH$; $R_3=R_5=H$
3: $R_1=R_3=OH$; $R_2=R_4=OMe$; $R_5=H$
4: $R_1=R_4=OMe$; $R_2=R_5=OH$; $R_3=H$
5: R_1, $R_2=OCH_2O$; $R_3=R_4=OH$; $R_5=H$

A screening program (4) revealed the presence of alkaloids in *Phoebe pittieri* (Costa Rica). Screening by the (Centro de Investigacion en Productos Naturales (CIPRONA) group in Costa Rica identified additional alkaloid-containing species. The present work reports on one new and three known, but previously incompletely characterized, aporphines from *Phoebe molicella*.

RESULTS

Bark of *P. molicella* yielded two alkaloids whose uv, and ^{1}H- and ^{13}C-nmr spectra showed them to be pentamethoxylated aporphines. One had an N-Me group and the other did not; both formed the same methiodide, mp 225-227°. The ^{1}H-nmr methoxy



8: $R_1=R_4=R_5=R_6=CH_3$; R_2, $R_3=CH_2$
9: $R_1=R_2=R_3=R_4=R_5=CH_3$; $R_6=H$
10: $R_1=R_2=R_3=R_4=R_5=R_6=CH_3$
11: $R_1=R_2=R_4=R_5=R_6=CH_3$; $R_3=H$
12: $R_1=R_2=R_4=R_5=CH_3$; $R_3=R_6=H$

and N-Me chemical shifts were identical with those reported for norpurpureine (**9**) and purpureine (**10**) from *Annona purpurea* (Lauraceae) (5). These two alkaloids had also formed the same methiodide, mp 227-229° (5). The ^{13}C-nmr spectral data for norpurpureine were confirmatory (see Experimental section) and, hence, established structures **9** and **10** for our two isolated bark alkaloids. The bark was also found to contain a small amount of preocoteine, described below, as well as traces of minor alkaloids we were unable to obtain in sufficient quantity for identification.

Wood of *P. molicella* contained two main alkaloids as well as a number of minor ones including norpurpureine. The two major alkaloids were tetramethoxylated monophenolic aporphines as evidenced by uv, ^{1}H- and ^{13}C-nmr, and mass spectra. These data also showed one to contain an N-Me group, while the other did not. The ^{1}H-nmr spectra of these two alkaloids, as well as of **9** and **10**, showed only two aromatic proton resonances, both singlets, and the chemical shifts of the two were very similar in all four compounds. One of the wood alkaloids had ^{1}H-nmr chemical shifts and a uv spectrum identical with those reported for preocoteine (**11**) (6). Confirmation of the identity was obtained by comparison of their $CHCl_3$ ir spectra which were identical (7). Our ^{13}C-nmr spectral assignments (table 1) are also in accord with structure **11** for preocoteine.

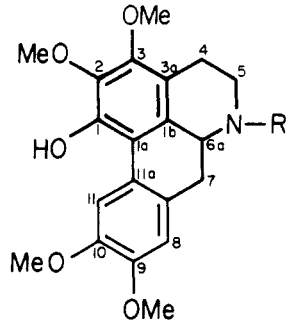
The second wood alkaloid was similar to preocoteine in all respects with the exception of data reflecting its missing N-Me group. In particular, the ^{13}C-nmr spectral assignments (table 1) match those of **9** quite closely. The second alkaloid must, therefore, be norpreocoteine (**12**), reported here for the first time.

The ^{1}H- and ^{13}C-nmr spectra of these alkaloids provide additional examples of the good correlation between chemical shift values and structure in the aporphine series. In the ^{1}H-nmr spectra of **9** and **10**, one methoxy methyl resonance is at high field, typical of that at C-1, while such a resonance is missing in **11** and **12**. This ensures the placement of the free phenolic group. In the ^{13}C-nmr spectra, preocoteine and norpreocoteine each show two low-field methoxy methyl resonances (60-ppm region), typical of hindered methyls, and two nonhindered methoxy methyls (56-ppm region).

Pentasubstituted aporphines are relatively rare in nature, compared with the tetrasubstituted alkaloids. Neither of the Asian *Phoebe* species contained pentasubstituted aporphines, while they are the characteristic of *P. molicella* from Costa Rica and apparently *P. porfiria* from Argentina (3). It will be of interest to see if further American *Phoebe* species continue this trend.

TABLE 1. Carbon-13 assignments for preocoteine and norpreocoteine.

	Preocoteine	Norpreocoteine		Preocoteine	Norpreocoteine
C-1	138.30	138.71	C-8	111.62	111.74
C-1a	118.45	118.22	C-9	147.13[a]	147.18[a]
C-1b	125.15	127.62	C-10	147.12[a]	147.00[a]
C-2	144.26	144.49	C-11	110.92	110.75
C-3	147.30[a]	148.35[a]	C-11a	124.58	124.64
C-3a	115.70	115.48	N-Me	44.01	—
C-4	23.40	23.23	C2-OMe	60.01[b]	60.65[b]
C-5	53.18	42.79	C3-OMe	60.83[b]	59.89[b]
C-6a	62.81	54.00	C9-OMe	56.04	55.80
C-7	34.26	36.36	C10-OMe	56.04	55.80
C-7a	130.48	130.77			



R = Me: preocoteine

R = H: norpreocoteine

[a,b]Assignments in vertical columns can be interchanged. All assignments were substantiated by SFORD spectra.

EXPERIMENTAL

Phoebe molicella Blake was collected near San Jose, Costa Rica, with the assistance of L. Poveda, botanist of the Museo de Historia Natural, San Jose, who identified the species and deposited a voucher sample. Spectral data on isolated alkaloids were obtained as follows: uv, MeOH, Varian Techtron Model 635; ^{1}H- and ^{13}C-nmr, $CDCl_3$, JEOL FX-100, ppm from TMS; ms, Vacuum Generators Model MM16; ir, $CHCl_3$, Beckman 4200.

Dried and ground bark (970 g) was extracted with cold EtOH and the ethanol evaporated to leave 28 g of residue. This residue was purified by differential pH extraction (H_2SO_4, NH_4OH) to yield 2 g of crude alkaloid mixture. Two-thirds of this was chromatographed in two batches on a 2 x 30 cm column of Act I neutral Al_2O_3 using $CHCl_3$-MeOH elution (1% increasing to 20% MeOH). Early fractions in the 5% MeOH elution yielded mostly norpurpureine (**9**), while later fractions of the same polarity yielded mostly purpureine (**10**). Further purification was by a repeated similar chromatography. The content of **9** and **10** in the crude alkaloid mixture (based on actual isolation and tlc of fraction mixtures) was about equal, approximately 200 mg each. One-third of the original crude alkaloid mixture was purified by flash chromatography (Si gel; $CHCl_3$-MeOH). Fractions 17-20 (8:1, $CHCl_3$-MeOH) yielded norpurpureine, while fractions 25-28 (5:1, $CHCl_3$-MeOH) yielded norpreocoteine, described below.

Dried and ground wood (6 kg) was extracted cold with EtOH and evaporated to leave 170 g of residue, which was purified by a differential pH extraction (H_2SO_4, NH_4OH) to leave 4 g of crude alkaloid extract. Of this, 3 g was purified by flash chromatography (Si gel, $CHCl_3$-MeOH, 9:1) and then by plc (same system) to yield pure the two major alkaloids, approximately 200 mg of preocoteine, 300 mg of norpreocoteine, and 20 mg of norpurpureine. Traces of other alkaloids were present, but were not isolated in sufficient quantity for structural characterization.

NORPURPUREINE (**9**).—This was isolated as a colorless oil [Lit. mp. 115-117° (5)] which formed a solid methiodide, mp 225-227° and $[\alpha]^{25}D$ +50° (EtOH), after one recrystallization from MeOH. The re-

ported mp was 227-229° (5). The uv spectrum in MeOH and the ^{1}H-nmr spectrum were essentially identical with those reported (5). The structure was also consistent with the ^{13}C-nmr spectrum: 149.92, 149.16, 147.59, 147.35, 145.31, 130.66, 128.15, 124.41, 122.83, 122.19, 111.33, 110.75, 60.94, 60.59, 60.30, 56.04, 54.05, 36.48, 33.87, 25.77.

PURPUREINE (**10**).—Compound **10** was isolated as a colorless oil (physical properties not given in reference 5), which also formed the same methiodide, mp 225-227°. In addition to the mp, the two methiodides were identical by tlc in two solvent systems. The uv spectrum in MeOH and the ^{1}H-nmr spectrum of purpureine were identical with those reported (5).

PREOCOTEINE (**11**).—Isolated as a brownish oil [Lit. (6) also as an oil], $[\alpha]^{25}D$ +26° (EtOH), preocoteine's uv spectra (MeOH and MeOH plus base) and ^{1}H-nmr spectrum were identical with those reported (6). The ir spectrum was identical with that in a thesis (7). The structure was confirmed by the ^{13}C-nmr spectrum (table 1); ms (*m/e*): 371(100%) M, 370(73), 356(52), 354(23), 340(26), 328(25), 313(13), 311(5), 297(21), 178(5), 149(3).

NORPREOCOTEINE (**12**).—This was isolated as a brownish oil, ms (*m/e*): 357(100%), 356(87), 342(30), 340(22), 326(16), 328(11), 313(7), 311(10), 297(13), 178(14), 149(5); uv spectrum (EtOH 280, 303, 317 and EtOH+OH^- 300 nm); ^{1}H-nmr spectrum 7.99(s, 1H), 6.75(s, 1H), 3.95(s, 3H), 3.90(s, 3H), 3.87(s, 3H), 3.86(s, 3H), 4.1-2.9(br m); ^{13}C-nmr spectrum in table 1.

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LITERATURE CITED

1. S.R. Johns and J.A. Lamberton, *Aust. J. Chem.*, **20**, 1277 (1967).
2. S.T. Lu and T.L. Su, *J. Chinese Chem. Soc.*, **20**, 87 (1973).
3. F. Baralle, A. Busch, M.J. Vernengo, and A.M. Kuck, *Lloydia*, **35**, 300 (1972).
4. J.A. Saenz R. and M. Nassar C., *Rev. Biol. Trop.*, **18**, 129 (1970).
5. P.E. Sonnet and M. Jacobson, *J. Pharm. Sci.*, **60**, 1254 (1971).
6. M. Shamma, R.J. Shine, and B.S. Dudock, *Tetrahedron*, **23**, 2887 (1967).
7. B.S. Dudock, PH.D. Thesis, Pennsylvania State University, 1966.

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