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ADDITIONAL ALKALOIDS OF *PACHYGONE OVATA*

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ABSTRACT.—*Pachygone ovata* (Menispermaceae), indigenous to the sandy seashores of southern India, is a woody climber whose fruits have been used as a rodenticide and fish poison. Chromatography of the extract of the roots resulted in the reisolation of the alkaloids liriodenine, coclaurine, trilobine (**1**), and magnoflorine and the isolation of stepholidine, coreximine, isoboldine, norjuziphine, and nortrilobine (**2**). Nortrilobine (**2**) is a new dibenzo-*p*-dioxin bisbenzylisoquinoline alkaloid whose structure was established by a consideration of spectral data and conversion to isotrilobine (**3**).

Pachygone ovata Miers ex Hook. f. & Thoms. (Menispermaceae) is a lofty climber indigenous to the sandy seashores of the Coromandel Coast of India (1-3). The dried fruit of the plant has been used as a rodenticide and fish poison (1-4), and the plant is reputed to have insecticidal or insect-repellent properties (4). In 1979, Dasgupta and Ray reported the isolation of *N*-methylcrotsparine, reticuline, and reticuline-*N*-oxide from extracts of the leaves of *P. ovata* (5). In addition, they also reported the isolation of (+)-quercitol and liriodenine from extracts of the stems and coclaurine and trilobine (**1**) from extracts of the roots of this same plant (5). The isolated reticuline was found to possess central nervous system stimulant, analgesic, and hyperthermic properties (5). Shortly thereafter, Bhat *et al.* reported the isolation and characterization of a new quaternary erythrinane alkaloid, pachygonine, and the isolation of magnoflorine and *O,O*-dimethylmagnoflorine from extracts of *P. ovata* roots (6). This paper reports the reisolation of liriodendine, coclaurine, trilobine (**1**), and magnoflorine from an extract of the roots of *P. ovata* and the isolation of stepholidine, coreximine, isoboldine, norjuziphine, and nortrilobine (**2**) from this same extract. Nortrilobine (**2**) is a new dibenzo-*p*-dioxin bisbenzylisoquinoline alkaloid which has not been isolated previously from a natural source nor described as a synthetic compound.

P. ovata roots were dried, ground, and extracted with EtOH. The EtOH extract was evaporated and the resulting residue stirred with citric acid solution and filtered. The insoluble residue was treated with $CHCl_3$, filtered, and the filtrate partitioned with citric acid solution. The two citric acid solutions were combined, alkalinized to pH 8-10 with NH_4OH, and extracted first with Et_2O (fraction A) and subsequently with $CHCl_3$ (fraction B). The ammoniacal solution was acidified to pH 4 with HCl, and Mayer's Reagent was added until precipitation ceased. The precipitate was filtered by suction, washed with H_2O, dissolved in aqueous MeOH, and passed through a column of anion exchange resin (chloride form). The column was rinsed with aqueous MeOH and the eluent and rinsings were combined and evaporated to afford a residue of crude quaternary alkaloid chlorides (fraction C).

Fraction A (ether-soluble nonquaternary alkaloids) was dissolved in EtOH and subjected to preparative hplc over silica gel with EtOH. Fractions, 200 ml each, were collected and pooled according to their thin-layer chromatographic behavior. Fractions 9-12 were combined, and the phenolic alkaloids were separated from the nonphenolic alkaloids using well-established procedures (7). The phenolic alkaloids were chromatographed over silica gel-Celite (4:1) in $CHCl_3$. Elution with $CHCl_3$-MeOH (98:2) afforded stepholidine, while elution with $CHCl_3$-MeOH (95:5) gave a mixture of

stepholidine and coreximine, the latter of which was ultimately isolated by further column chromatography over the same adsorbent. Stepholidine was first isolated from *Stephania glabra* (Menispermaceae) (8) in 1969 and subsequently from *Papaver somniferum* var. *album* (Papaveraceae) (9) and *Monanthotaxis cauliflora* (Annonaceae) (10). Coreximine was first isolated from *Dicentra eximia* (Papaveraceae) (11) in 1938 and later from *Corydalis pseudoadunca* (Papaveraceae) (12), *Corydalis incisa* (13), *Erythrina orientalis* (Leguminosae) (14), and *Asimina triloba* (Annonaceae) (15). To our knowledge, this is the first reported isolation of any protoberberine-type alkaloid from the genus *Pachygone*.

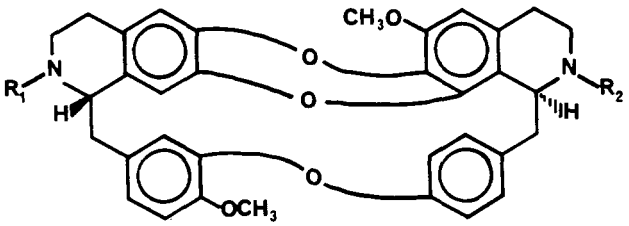
Fractions 15-34 were combined and the phenolic alkaloids separated from the nonphenolic alkaloids as before (7). Repeated column chromatography of the phenolic alkaloids over silicic acid ultimately afforded isoboldine, (+)-norjuziphine, and coclaurine while similar chromatography of the nonphenolic alkaloid fraction gave liriodenine. Isoboldine has been isolated previously from genera of the families Annonaceae, Berberidaceae, Lauraceae, Leguminosae, Monimiaceae, Papaveraceae, Ranunculaceae, Rhamnaceae, and Symplocaceae (16,17) and from *Cocculus trilobus* (Menispermaceae) (18) where it was found to possess insect-feeding-inhibitory properties (18,19). Thus, this appears to be only the second reported isolation of this alkaloid from a menispermaceous species. Norjuziphine was first isolated in 1979 from *Fumaria vaillantii* (Fumariaceae) (20) as its levorotatory isomer $[\alpha]_D$ −18° (c 0.17, MeOH), and this is only the second reported isolation of this 7,8,4′-trioxygenated benzylisoquinoline from nature and the first of its dextrarotatory isomer $[\alpha]^{23}_D$ +12° (c 0.43, MeOH). Coclaurine has been previously isolated from this plant (5) as well as from other menispermaceous species including *Cocculus laurifolius* (21), *Cocculus hirsutus* (21), and *Sarcopetalum harveyanum* (22), and from numerous genera of the family Lauraceae (23). This simple benzylisoquinoline has also been isolated from *Talguenea quniquenervis* (Rhamneae) (24). Liriodenine has been formerly found in various genera of the families Annonaceae, Araceae, Eupomatiaceae, Lauraceae, Magnoliaceae, Menispermaceae, Monimiaceae, Nymphaceae, Papaveraceae, Rhamnaceae, and Rutaceae (25,26) as well as *Pachygone ovata* (5). The alkaloid has been found to exhibit antimicrobial (27) and cytotoxic (28) activities and to possess respiratory-stimulant and short-lasting hypotensive properties (29).

Fractions 35-49 were combined, and the nonphenolic and phenolic alkaloids were separated as before (7). Chromatography of the nonphenolic alkaloids over silica gel yielded trilobine (**1**), which was previously isolated from this plant (5) and which has also been isolated from *Anisocyclea grandidieri* (Menispermaceae) and numerous *Cocculus* species (Menispermaceae) (30).

Finally, combination of fractions 50-59, separation of the nonphenolic and phenolic alkaloids as before (7), and chromatography of the nonphenolic alkaloid fraction over silica gel afforded nortrilobine (**2**), mp 177-180° (MeOH), $[\alpha]^{25}_D$ +216° (c 0.44, $CHCl_3$); uv, λ max (MeOH) 306 nm (sh) (log ε 3.53), 287(3.68), 275(3.66), 237(4.62), and 218(4.60) with no bathochromic shift on the addition of 0.1 N methanolic KOH. The pmr spectrum indicated the presence of two methoxy groups at δ 3.78 (s, 3H) and 3.92 (s, 3H) and a cluster of aromatic protons from δ 6.18-7.7 (m, 10 H) but lacking signals attributable to *N*-methyl groups (31). The mass spectrum showed the molecular ion at *m/z* 548 (6%) (measured 548.2299, and calculated 548.2311 for $C_{34}H_{32}N_2O_5$) and other significant fragment ions at *m/z* 322(15), 321(100), 307(7), 211(5), and 161(53) attributable to a double benzylic cleavage of a bisbenzylisoquinoline alkaloid (32). These spectral data are characteristic of a nonphenolic, secondary dibenzo-*p*-dioxin bisbenzylisoquinoline alkaloid of the isotrilobine (**3**) type, containing one methoxy group in the upper half of the molecule and a second

methoxy group in the lower half of the molecule (31-33). Treatment of nortrilobine with formalin and formic acid afforded isotrilobine (**3**) (pmr, ms, uv, ir), thereby establishing the skeletal structure and *bis*-secondary nature of nortrilobine. A comparison of the specific rotation and the cd spectra of the methylated nortrilobine ($[\alpha]^{31}D$ +230° (c 0.1, $CHCl_3$) and cd, $[\theta]_{293}$ +23,000 and $[\theta]_{232}$ +124,600) with authentic isotrilobine (**3**) ($[\alpha]^{25}D$ +306° (c 0.62, $CHCl_3$) and cd, $[\theta]_{293}$ +21,000 and $[\theta]_{231}$ +82,500), while not identical, suggest that nortrilobine probably possesses the same stereochemistry at its asymmetric centers as isotrilobine (*S,S*). To our knowledge, nortrilobine is the first example of a *bis*-secondary dibenzo-*p*-dioxin bisbenzylisoquinoline alkaloid to have been reported in nature.

The alkaline solution remaining after removal of fractions A and B with Et_2O and $CHCl_3$, respectively, was acidified with HCl and the quaternary alkaloids precipitated with Mayer's Reagent. The resulting precipitate was filtered by suction, washed with H_2O, dissolved in aqueous MeOH, and passed through a column of anion exchange resin (chloride). The column was eluted with aqueous MeOH, and the eluant and rinsings were combined and evaporated. The resulting residue of crude quaternary alkaloid chlorides was adsorbed onto silicic acid and chromatographed over silicic acid in $CHCl_3$. Elution with $CHCl_3$-MeOH (85:15) afforded magnoflorine chloride, which was characterized as its iodide salt after passage over anion exchange resin. Magnoflorine has been isolated from numerous genera of the family Menispermaceae (34,35) and from *Pachygone ovata* (6). Other plant families that have served as a source of magnoflorine include the Annonaceae, Aristolochiaceae, Berberidaceae, Euphorbiaceae, Magnoliaceae, Papaveraceae, Ranunculaceae, Rhamnaceae, and Rutaceae (34,35).



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

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were taken on a Fisher-Johns apparatus anmd are uncorrected. The uv spectra were obtained on a Perkin-Elmer model 552A recording spectrophotometer in MeOH, and the ir spectra were determined on a Perkin-Elmer model 257 recording spectrophotometer in KBr pellets or $CHCl_3$ solutions. The nmr spectra were recorded in $CDCl_3$ on a Hitachi Perkin-Elmer model R-24 high resolution spectrometer with TMS as internal standard or on a Brüker WH-90 (600.6 MHz) spectrometer and chemical shifts recorded in δ (ppm) units. The mass spectra were taken with a Finnigan EI Mass Spectrometer, Spectrel Electronics, interfaced with a Finnigan INCOJ Data System. The optical rotations were measured on a Perkin-Elmer model 241 polarimeter. Cd measurements were taken in methanol solution on a Jasco ORD-UV-5 instrument. Silicic acid (100 mesh) (Mallinckrodt), Celite (acid washed) (Mallinckrodt), and silica gel G (Camag) were used for column chromatography while silica gel G (Camag) was used for tlc. The solvent system C_6H_6-Me_2CO-NH_4OH (4:8:0.1) was used unless otherwise noted. Amberlite IRA-401S(C1) (Mallinckrodt) was used for ion-exchange chromatography. Anhydrous Na_2SO_4 was routinely used for drying organic solvents, and all solvents were evaporated under reduced pressure at 40°.

PLANT MATERIAL.—The plant material used in this study was procured from South India and identified by Dr. Deb, Deputy Director, Indian Botanic Garden, Howrah, West Bengal. A herbarium speci-

men is on deposit in the Department of Medicinal Chemistry, Institute of Medical Sciences, Banaras Hindu University, Varanasi 221005, India.

EXTRACTION AND FRACTIONATION.—Powdered, dried roots (10.64 kg) of *P. ovata* were extracted by percolation with EtOH (95%) (484 liters) and the EtOH evaporated to leave a residue (600 g). The residue was stirred with aqueous citric acid (2%) (10 liters) and filtered. The filtrate (solution A) was extracted five times with $CHCl_3$ (10 liters), and the $CHCl_3$ was evaporated to a solid (35 g). The citric acid insoluble residue from above was dissolved in $CHCl_3$ (500 ml), filtered, and partitioned four times with citric acid solution (2%) (500 ml) (solution B). The acidic layer (solution B) was combined with the original citric acid solution (solution A), alkalinized with NH_4OH to pH 8-10, and extracted, first with Et_2O (97 liters) to afford a light brown oil (35 g) (fraction A), and then with $CHCl_3$ (130 liters) to yield a dark brown oil (16 g) (fraction B).

CHROMATOGRAPHY OF FRACTION A.—Fraction A (35 g) was dissolved in EtOH (50 ml) and subjected to preparative hplc over silica gel (prepacked columns, PAK-500, Waters Associates) with EtOH on a Waters Associates preparative LC/system 500 hplc apparatus. The chamber pressure was 40 atm; the solvent pressure was 15-20 atm; the flow rate was 100 ml/min and 200-ml fractions were collected.

ISOLATION OF STEPHOLIDINE.—Fractions 9-12 were combined, dissolved in Et_2O (100 ml), and partitioned with 100 ml 5% NaOH four times. The alkaline solution was treated with NH_4Cl until pH 8-9 and the resulting turbid solution extracted with 400 ml Et_2O five times. The Et_2O solutions were combined, filtered, and evaporated to afford a residue (680 mg) of phenolic alkaloids which was chromatographed over silica gel-Celite (4:1) (60 g) (column A) in $CHCl_3$. Elution with $CHCl_3$-MeOH (98:2) afforded a colorless residue which, on treatment with $CHCl_3$-MeOH, gave white prismatic crystals of stepholidine (45 mg), Rf 0.55, mp 165° ($CHCl_3$-MeOH); $[\alpha]^{26}D$ −102° (c 0.29, MeOH) and $[\alpha]^{26}D$ −170° (c 0.1, $CHCl_3$), identical by direct comparison (uv, ir, ms, mp) with an authentic reference sample.

ISOLATION OF COREXIMINE.—Elution of column A with $CHCl_3$-MeOH (95:5) afforded a residue (150 mg) that was rechromatographed over silica gel-Celite (4:1) (20 g) with $CHCl_3$-Me_2CO (1:2) as the eluant. Fractions, 10 ml each, were collected, and fractions 21-30 were combined to afford additional stepholidine (30 mg). Fractions 40-80 were combined to afford a residue which was treated with MeOH to afford coreximine (50 mg), Rf 0.49, mp 265° (MeOH); $[\alpha]^{25}D$ −128° (c 0.25, MeOH) and $[\alpha]^{25}D$ −381° (c 0.16, pyr), identical by direct comparison (uv, ir, ms, mp) with an authentic reference sample.

ISOLATION OF COCLAURINE.—Fractions 15-34 from the hplc column were combined (5.96 g) and the phenolic alkaloids (2.76 g) separated from the nonphenolic alkaloids (315 mg), using NaOH solution and NH_4Cl as previously described. Treatment of the phenolic alkaloid fraction (2.76 g) with MeOH gave a colorless residue that was recrystallized from Me_2CO to afford coclaurine (800 mg) as white needles, Rf 0.23, mp 210-212° [$(CH_3)_2CO$], $[\alpha]^{26}D$ +10° (c 0.51, MeOH); cd, $[\theta]_{290}$ −4,960, $[\theta]_{279}$ 0, $[\theta]_{270}$ +1,730, $[\theta]_{249}$ 0 and $[\theta]_{229}$ −9,670 which supports the *R*-stereochemistry for the asymmetric center (36); identical by direct comparison (uv, ir, ms, mp, mmp) with an authentic reference sample (5).

ISOLATION OF ISOBOLDINE.—The MeOH remaining from the crystallization of above coclaurine was evaporated and the resulting residue chromatographed over silicic acid (150 g) (column B). Elution with $CHCl_3$-MeOH (97:3) afforded a residue that was rechromatographed over silicic acid (50 g). Elution of this column with $CHCl_3$-MeOH (99:1) afforded a colorless residue (50 mg) which, on treatment with MeOH, afforded isoboldine (*N*-methyllaurelliptine) (20 mg) as white cubes, Rf 0.20, mp 115-117° (MeOH), $[\alpha]^{25}D$ +35° (c 0.2, MeOH) and $[\alpha]^{13}D$ +54° (c 0.2, EtOH); identical by direct comparison (uv, ir, pmr, ms, mp, mmp) with an authentic reference sample (37).

ISOLATION OF NORJUZIPHINE.—Elution of column B with $CHCl_3$-MeOH (95:5) gave a residue (100 mg) that was rechromatographed over silicic acid (20 g). Elution of this column with $CHCl_3$-MeOH (98:2) afforded a colorless residue (35 mg) which on treatment with MeOH gave norjuziphine (20 mg) as colorless crystals, Rf 0.34, mp 155-157° (MeOH), $[\alpha]^{23}D$ +12° (c 0.43, MeOH); uv, λ max (MeOH) 284 nm (sh) (log 3.22), 280(3.26) and 234(3.52); cd, $[\theta]_{288}$ +2,280, $[\theta]_{280}$ 0, $[\theta]_{274}$ −1,100, $[\theta]_{261}$ 0, $[\theta]_{236}$ −3,800, $[\theta]_{230}$ 0, $[\theta]_{225}$ +1,140 which supports the *S*-stereochemistry for the asymmetric center (36); ir, ν max (KBr) 3260 cm^{-1}, 3010, 2930, 2830, 1612, 1590, 1515, 1490, 1435, 1380, 1340, 1240, 1170, 1160, 1100, 1045, 995, 955, 920, 850, 838, 805, 795, 788, and 750; pmr (MeOH-d_4+TMS), δ 3.82 (s, 3H, OCH_3), 6.53 (d, 2H, J=8Hz, ArH), 6.72 (d, 1H, J=8Hz, ArH), 6.79 (d, 1H, J=8Hz, ArH), and 7.09 (d, 2H, J=8Hz, ArH); ms, *m/z* 285 (<1%) (M^+), 178(100), 163(33) and 107(10). The structure was confirmed via the preparation of the methiodide salt by the treatment of norjuziphine (15 mg) in Me_2CO (10 ml) with methyl iodide (0.5 ml) under reflux for 48 h. Evaporation of the solvent yielded a residue whose ir spectrum was identical with authentic 2-methyl-7-methoxy-8,4′-dihydroxy-1-benzyl-1,2,3,4-tetrahydroisoquinoline methiodide (oblongine methiodide) (38).

Continued elution of the same column with $CHCl_3$-MeOH (98:2) gave additional coclaurine (30 mg).

ISOLATION OF LIRIODENINE.—The nonphenolic alkaloids (315 mg) obtained from combined fractions 15-34 of the hplc column were chromatographed over silica gel-Celite (4:1) (80 g). Elution with $CHCl_3$-MeOH (99:1) afforded a greenish-yellow residue (60 mg) which, on treatment with MeOH, gave liriodenine as yellow needles (32 mg), Rf 0.43, mp 280-284° (MeOH), identical by direct comparison (uv, ir, ms, mp, mmp) with an authentic reference sample (39).

ISOLATION OF TRILOBINE (**1**).—Fractions 35-49 from the hplc column were combined (4.31 g) and the phenolic alkaloids (0.43 g) separated from the nonphenolic alkaloids (3.84 g), using NaOH solution and NH_4Cl as previously described. Chromatography of the nonphenolic alkaloids (3.84 g) over silica gel-Celite (4:1) (100 g) and elution with $CHCl_3$-MeOH (99:1) afforded an amorphous residue (1.2 g). Treatment of this residue with petroleum ether-$CHCl_3$ afforded trilobine (640 mg), Rf 0.43 (double development), mp 203-205° (petroleum ether-$CHCl_3$), $[\alpha]^{24}D$ +282° (c 0.5, MeOH); cd, $[\theta]_{289}$ +55,700 and $[\theta]_{236}$ +119,900; identical by direct comparison (uv, ir, pmr, ms, mp, sp rotn) with an authentic reference sample (5).

ISOLATION OF NORTRILOBINE (**2**).—Fractions 50-59 from the hplc column were combined (460 mg) and the phenolic alkaloids (117 mg) separated from the nonphenolic alkaloids (280 mg), using NaOH solution and NH_4Cl as previously described. Chromatography of the nonphenolic alkaloids (280 mg) over silica gel-Celite (4:1) (50 g) and elution with $CHCl_3$-MeOH (99:1) gave additional trilobine (30 mg), while elution with $CHCl_3$-MeOH (95:5) afforded an amorphous residue (40 mg). Treatment of this residue with MeOH gave nortrilobine (**2**) as a pale white powder, Rf 0.21 (double development), mp 177-180° (MeOH), $[\alpha]^{25}D$ +216° (c 0.44, $CHCl_3$); uv, λ max (MeOH) 300 nm (sh) (log ε 3.53), 287(3.68), 275(3 66), 237(4.62), and 218(4.60); ir, ν max (KBr) 1625 cm^{-1}, 1590, 1505, 1450, 1440, 1365, 1295, 1275, 1230, 1170, 1125, 1025, and 825; pmr, δ 3.78 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 6.21-7.4 (m, 10H, ArH); ms, *m/z* 548 (6%) (M^+) (measured 548.2299 and calcd 548.2311 for $C_{34}H_{32}N_2O_5$, 335(3), 322(15), 321(100), 307(7), 211(5), and 161(53).

PREPARATION OF ISOTRILOBINE (**3**) FROM NORTRILOBINE (**2**).—To nortrilobine (**2**) (15 mg) in MeOH (5 ml) was added formic acid (88%) (1 ml) and formaldehyde (37%) (0.5 ml), and the resulting solution was heated under reflux for 24 h. The solution was cooled, extracted with 10 ml Et_2O four times, alkalinized with NH_4OH to pH 8-9, and extracted five times with 15 ml portions of Et_2O. The alkaline Et_2O extracts were combined and evaporated to afford a residue (13 mg), which was chromatographed over silica gel (10 g). Elution with $CHCl_3$-MeOH (99:1) afforded isotrilobine (**3**) as an amorphous white residue (5 mg), Rf 0.47 (double development); $[\alpha]^{31}D$ +230° (c 0.1, $CHCl_3$); cd, $[\theta]_{293}$ +23,000 and $[\theta]_{232}$ +124,600; identical by direct comparison (uv, ir, pmr, ms) to authentic isotrilobine (**3** .

ISOLATION OF MAGNOFLORINE.—The alkaline solution remaining after removal of fraction A (Et_2O) and fraction B ($CHCl_3$) was acidified to pH 2 with HCl and treated with Mayer's Reagent (40) until precipitation ceased. The resulting precipitate was filtered by suction, washed with H_2O, dissolved in MeOH-H_2O (3:2) (1 liter), and passed over an anion exchange resin (Cl). The column was rinsed with MeOH-H_2O (3:2) (600 ml), and the column eluant and rinsing were combined to leave a dark residue (50 g) of crude quaternary alkaloid chlorides. The residue was dissolved in MeOH (150 ml), adsorbed onto silicic acid (80 g), and chromatographed over silicic acid (400 g) in $CHCl_3$. Elution with $CHCl_3$-MeOH (85:15) afforded a colorless residue (1.4 g) of magnoflorine chloride, which was converted to magnoflorine iodide by passage over anion exchange resin (I) (100 g) in MeOH (200 ml). Magnoflorine iodide crystallized from MeOH as white prisms, mp 248-252°; $[\alpha]^{26}D$ +196° (c 0.45, MeOH), identical to an authentic reference sample (39) by direct comparison (uv, ir, ms, mp, mmp, sp rotn).

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