Constituents of West African Medicinal Plants XIX: Funiferine *N*-Oxide, a New Alkaloid from *Tiliacora funifera* (Menispermaceae)

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Abstract ☐ A phytochemical investigation of the roots of *Tiliacora funifera* (Menispermaceae) resulted in the isolation and identification of funiferine *N*-oxide, a new bis(benzylisoquinoline) alkaloid.

Keyphrases ☐ Funiferine *N*-oxide—isolated from extract of roots of *Tiliacora funifera*, structure elucidated ☐ *Tiliacora funifera*—extract of roots, funiferine *N*-oxide isolated and identified ☐ Alkaloids—funiferine *N*-oxide, isolated from extract of roots of *Tiliacora funifera*, structure elucidated

Tiliacora funifera (*T. warneckei*) Engl. ex Diels (Menispermaceae) is a stout spreading undershrub or woody climber found in the grassy regions and thickets along coastal areas of Ghana (1). The plant is used natively as a medicinal for the treatment of gastric fevers, strangulated hernia, and menstrual irregularities (2).

A number of alkaloids have been isolated from several *Tiliacora* species. Tiliacorine, a biphenyldibenzodioxin bis(benzylisoquinoline) alkaloid, was isolated from *T. acuminata* (3), *T. racemosa* (4, 5), and *T. funifera* (6); its diastereoisomer, tiliacorinine, was found in *T. racemosa* (5) and *T. dinklagei* (7). Several secondary amine derivatives of tiliacorine and tiliacorinine were isolated, including nortiliacorinine A from *T. racemosa* (5), *T. funifera* (8), and *T. dinklagei* (7); nortiliacorinine B from *T. racemosa* (5); and nortiliacorine A from *T. funifera* (8). Funiferine (I), a nondibenzodioxin bis(benzylisoquinoline) biphenyl alkaloid, was found in *T. funifera* (6, 9, 10) and *T. dinklagei* (7); tiliageine (II), a closely related base, was isolated from *T. dinklagei* (7, 11). Furthermore, several incompletely characterized alkaloids were isolated from *T. triandra* (12) and *T. racemosa* (13, 14).

This paper reports the isolation and identification of funiferine *N*-oxide (III), a new alkaloid from the roots of *T. funifera*. This base, previously isolated from *T. funifera* (15), was designated TB-2. This study was undertaken to reisolate and subsequently identify this alkaloid to the exclusion of the other known alkaloids (6, 8–10) of this species.

DISCUSSION

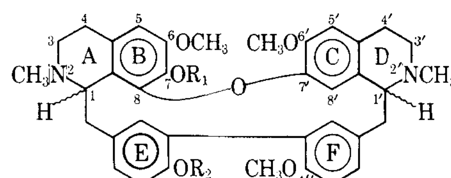
Dried, powdered roots were extracted by percolation with ethanol, and the ethanolic extract was concentrated (40°, *in vacuo*) to a syrupy residue. The residue was partitioned between dilute hydrochloric acid and chloroform, and the acidic fraction was made basic with ammonium hydroxide and extracted with chloroform. The chloroform extract was chromatographed over silicic acid in chloroform and chloroform–methanol mixtures. Elution with chloroform–methanol (95:5) afforded a fraction that was twice rechromatographed over silicic acid in chloroform–methanol mixtures to afford a mixture of I and III. These bases were subsequently separated by preparative TLC.

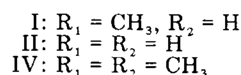
Compound III was obtained as a white powder, mp 207–209° dec.; $[\alpha]_D^{25}$ +44.0° (c 0.1, methanol); λ_{max} (methanol): 216 (log ϵ 4.75) and 288 (3.95) nm; ν_{max} (KBr): 1500 cm^{-1}. The NMR spectrum showed signals at δ 2.62 (s, 3H) and 3.16 (s, 3H) ppm, corresponding to two *N*-methyl groups, the latter at a lower field than expected (16); 3.27 (s, 3H), 3.51 (s, 3H), 3.81 (s, 3H), and 3.91 (s, 3H) ppm, corresponding to four *O*-methyl groups; and 6.30–7.55 (m, 9H) ppm, corresponding to nine aromatic protons. The mass spectrum showed the molecular ion at *m/e* 638 (32) and other significant fragment ions at *m/e* 622 (100), 621 (75), 607 (18), 515 (1), 431 (1), 430 (1), 396 (25), 395 (83), 381 (30), 198 (72), 175 (25), and 174 (32).

These spectral data were indicative of a bis(benzylisoquinoline) alkaloid with a molecular ion 16 mass units higher than that of I and a prominent M − 16 ion characteristic of *N*-oxides (17, 18). Furthermore, the NMR spectrum showed that one *N*-methyl signal was shifted downfield (δ 3.16 ppm), which is also characteristic of *N*-oxides (19, 20). Therefore, it was considered likely that III was an *N*-oxide of I or a closely related base. To prove this assumption, it was decided to reduce III with sulfurous acid (21) to the parent base.

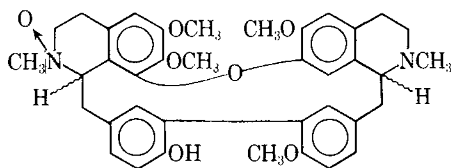
Treatment of III with sulfurous acid overnight afforded I, identical by a direct comparison (UV, IR, NMR, and mass spectra; TLC; and melting point and mixed melting point) with an authentic reference sample (10). Thus, III corresponded to a funiferine *N*-oxide, and it remained to be established with which nitrogen atom in funiferine the oxide was associated. A comparison of the NMR chemical shift values of III and I showed that the methoxy signals (I, δ 3.39, 3.48, 3.79, and 3.87 ppm; and III, δ 3.27, 3.51, 3.80, and 3.89 ppm) and the aromatic signals [I, δ 6.33–7.25 (9H) ppm; and III, δ 6.30–7.55 (9H) ppm] were similar. Furthermore, one of the two *N*-methyl signals of each was quite similar (I, δ 2.36 and 2.64 ppm; and III, δ 2.62 and 3.16 ppm).

The NMR spectral signals for the *N*-methyl groups of I can be postulated as δ 2.36 for N-2 (ring A) and δ 2.64 for N-2′ (ring D). This postulation is valid since a controlled oxidation of bis(benzylisoquinoline) alkaloids with potassium permanganate in acetone is reported to cleave the benzylic bond of the isoquinoline moiety, which is unsubstituted at C-8 (or C-8″), to afford a tertiary lactone and an aromatic aldehyde (22). Oxidation of *O*-methylfuniferine (IV) gave a product (V) with *N*-methyl signals at δ 2.32 and 3.05 ppm, assigned to the N-2 (ring A) and N-2′ (ring

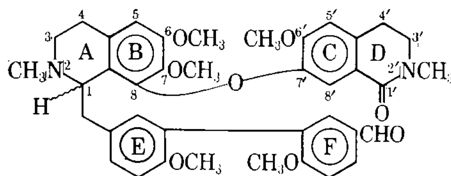




I: $R_1 = CH_3$, $R_2 = H$
II: $R_1 = R_2 = H$
IV: $R_1 = R_2 = CH_3$



III



V

D) positions, respectively. Therefore, the NMR spectral signals for the N-methyl groups of I can be unequivocally established as δ 2.36 ppm for the ring A group and δ 2.64 ppm for the ring D group. Since the signal at δ 2.36 ppm in I is shifted downfield to δ 3.16 ppm in III and the signal at δ 2.64 ppm in I is virtually in the same position (δ 2.62 ppm) in III, the structure of III as a funiferine N-oxide may be assigned as shown.

Finally, III was prepared by oxidation of I according to established procedures (21) for the preparation of N-oxides. Treatment of I in ethanol with hydrogen peroxide (15%) for 30 min at room temperature gave at least four compounds (TLC) in addition to unreacted starting material. Repeated chromatography of this mixture over silica gel G afforded a compound that was identical with III by a direct comparison (UV, IR, NMR, and mass spectra; melting point and mixed melting point; and TLC).

It is unlikely that III is an artifact formed during the isolation procedure, since it can be detected by TLC in fresh extracts of *T. funifera* roots. In addition, I subjected to the same isolation procedure as described earlier does not produce detectable amounts of III.

This paper is the first reported isolation of an N-oxide from a *Tiliacora* species and of an N-oxide of the bis(benzylisoquinoline) group. Alkaloid N-oxides previously were reviewed, and it was suggested that many alkaloids might occur naturally in the form of their N-oxides (23). Numerous plant families contain alkaloid N-oxides, including the Apocynaceae (24), Leguminosae (25), Gramineae (26), Polygonaceae (27), Rubiaceae (28), Solanaceae (20), Monimiaceae (29), Ranunculaceae (30), Boraginaceae (31), Compositae (32), and Orchidaceae (33). N-Oxides have been reported for many differing alkaloidal classes such as monomeric indole (26), dimeric indole (24), pyrrolizidine (32), quinolizidine (25), aporphine (29), tropane (34), pyridine–pyrrolidine (20), and piperidine (33).

EXPERIMENTAL[1]

Plant Material—The plant material[2] was collected in Ghana in 1975. The roots were separated from the aboveground material, dried, and ground to a coarse powder.

Extraction and Fractionation—*T. funifera* roots (6 kg) were extracted with 95% ethanol (40 liters) in a glass percolator to yield a syrupy residue (57 g), which was partitioned between 5% hydrochloric acid (700 ml) and chloroform (700 ml) three times. The aqueous layer was made basic with ammonium hydroxide and extracted with chloroform (700 ml) four times. These chloroform extracts were pooled, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to yield a nonquaternary alkaloid fraction (10 g).

Chromatography and Isolation of III—The nonquaternary alkaloid fraction was dissolved in chloroform (50 ml) and chromatographed over a silicic acid[3] (100 mesh) (600 g) column prepared by slurry in chloroform. Elution was begun with chloroform, and the polarity was increased gradually by the addition of methanol. Fractions, 500 ml, were collected and monitored by TLC. Eventual elution with chloroform–methanol (4:1) afforded a fraction (1.2 g) that was dissolved in chloroform–methanol (95:5) and chromatographed over a column of silica gel G[4] (80 mesh) (180 g) prepared by slurry[5] in chloroform–methanol (95:5).

Elution was begun with chloroform–methanol (95:5), and the polarity was gradually increased by the addition of methanol. Fractions of 50 ml were collected and monitored by TLC. Eventual elution with chloroform–methanol (9:1) gave a fraction (180 mg) (R_f 0.37, 0.42, and 0.60) that was subsequently rechromatographed over a column of silica gel G (80 mesh)[4] (180 g) prepared in the same manner[5] as before. Elution was begun in chloroform–methanol (95:5), and the polarity was increased gradually to chloroform–methanol (9:1). Fractions of 25 ml were collected and monitored by TLC.

Elution with chloroform–methanol (9:1) afforded fractions that were combined on the basis of TLC (R_f 0.37 and 0.42) to yield a residue (36 mg). Finally, this residue was subjected to preparative TLC over silica gel G [chloroform–methanol–concentrated ammonium hydroxide (10:2:0.1)] (four plates) to afford III (26 mg), mp 207–209°, R_f 0.37; $[\alpha]_D^{25}$ +44.0° (c 0.1, methanol); λ_{max} (methanol): 261 (log ϵ 4.75) and 288 (3.95) nm; ν_{max} (KBr): 1500 cm^{-1}; NMR: δ 2.62 (s, 3H, N-2′ NCH_3), 3.16 (s, 3H, N-2 NCH_3), 3.27 (s, 3H, C-7 OCH_3), 3.51 (s, 3H, C-6′ OCH_3), 3.81 (s, 3H, C-6 OCH_3), 3.91 (s, 3H, C-4″ OCH_3), and 6.30–7.55 (m, 9H, ArH) ppm; mass spectrum: M^+ *m/e* 638 (32) for $C_{38}H_{42}N_2O_7$, 622 (100), 621 (75), 607 (18), 515 (1), 431 (1), 430 (1), 396 (25), 395 (83), 381 (30), 364 (3), 349 (2), 198 (72), 175 (24), and 174 (32).

Reduction of III—To III (22 mg) was added sulfurous acid (6%) (5.0 ml), and the solution was allowed to stand overnight. Then the solution was diluted with water (50 ml), made basic with concentrated ammonium hydroxide, and extracted four times with chloroform (50 ml). The chloroform extracts were combined, dried (anhydrous sodium sulfate), filtered, and evaporated *in vacuo* to afford I as a white amorphous powder (20 mg), mp 178–180°; R_f 0.65 in chloroform–methanol–concentrated ammonium hydroxide (10:0.5:0.1); λ_{max} (methanol): 212 (log ϵ 4.63) and 288 (3.80) nm; ν_{max} (KBr): 3400, 2930, 2840, 2790, 1600, 1580, 1500, 1450, 1410, 1350, 1312, 1270, 1235, 1115, 1065, 1020, and 875 cm^{-1}; NMR: δ 2.35 (s, 3H, NCH_3), 2.63 (s, 3H, NCH_3), 3.39 (s, 3H, OCH_3), 3.47 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), and 6.32–7.25 (m, 9H, ArH) ppm; mass spectrum: M^+ *m/e* 622 (65), 515 (1), 396 (20), 395 (67), 381 (23), 364 (6), 349 (4), 198 (100), 175 (32), and 174 (30). The identity of the reduction product as I was established by direct comparison (UV, IR, NMR, and mass spectra and mixed melting point) with an authentic sample.

Preparation of III from I—Compound I (400 mg) was dissolved in ethanol (15 ml) and stirred with 15% hydrogen peroxide[6] (15 ml) at room temperature for 30 min. The reaction mixture was diluted with water (150 ml) and extracted four times with chloroform (150 ml). The combined chloroform extracts were evaporated *in vacuo* and examined by TLC [chloroform–methanol–concentrated ammonium hydroxide (10:1.5:0.1)]. The product was a mixture of at least four compounds (R_f 0.42, 0.37, 0.25, and 0.14), besides some unreacted starting material (R_f 0.85). These compounds were separated by column chromatography on silica gel G. A column (2.0 × 25 cm) was prepared with silica gel G[5] (30 g) by slurry in chloroform–methanol–concentrated ammonium hydroxide solution (10:1:0.1).

The sample was dissolved and eluted with the same solvent system in which the column was packed, with small fractions (6 ml) being collected. Attention was focused on fractions 42 and 43, a mixture of two compounds, one of which (R_f 0.37) showed the same R_f as III. Fractions 42 and 43 subsequently were subjected to column chromatography over silica gel G[5] (20 g) (column 1.5 × 25 cm), using chloroform–methanol–concentrated ammonium hydroxide (10:1:0.1) as the eluent.

Small fractions were collected (4 ml), and the compound at R_f 0.37 was obtained in pure form from fractions 53–59. This compound was a white crystalline substance, mp 206–207° dec.; $[\alpha]_D^{25}$ +40.0° (c 0.1, methanol); λ_{max} (methanol): 216 (log ϵ 4.80) and 288 (3.94) nm; ν_{max} (KBr): 3400 (br), 2930, 2830, 2790, 1600, 1580, 1500, 1450, 1420, 1360, 1320, 1270, 1240, 1125, 1060, 1015, 875, and 815 cm^{-1}; NMR: δ 2.60 (s, 3H, NCH_3), 3.15 (s, 3H, NCH_3), 3.26 (s, 3H, OCH_3), 3.51 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), and 6.30–7.55 (m, 9H, ArH) ppm; mass spectrum: M^+ *m/e* 638 (17), 622 (83), 621 (58), 607 (13), 515 (1), 431 (1), 430 (1), 396 (27), 395 (82), 381 (35), 364 (6), 349 (4), 198 (100), 175 (38), and 174 (37).

Compound III and this synthetic product (R_f 0.37) were shown to be identical by a direct comparison (IR, UV, and NMR spectra; melting point and mixed melting point; and TLC).

Oxidation of IV—To IV (150 mg) [prepared from I by methylation with ethereal diazomethane (35)] dissolved in acetone (150 ml) was added potassium permanganate (75 mg) in acetone (100 ml) dropwise over 1 hr. The reaction was allowed to stand for 6 more hr at room temperature with constant stirring and was then filtered and evaporated. TLC analysis showed two spots [chloroform–methanol (9:1)], the lower one (R_f 0.40) corresponding to the original material and the higher one (R_f 0.65) corresponding to the oxidation product (V). The mixture was separated over a column (1.5 × 25 cm) on silica gel G[5] (25 g) in chloroform–methanol (95:5). Small fractions (8 ml) were collected using the same solvent system in which the column was packed.

[1] Melting points were taken on a Thomas-Hoover apparatus or a Fisher-Johns apparatus and are uncorrected. UV spectra were obtained on a Perkin-Elmer model 202 recording spectrophotometer, and IR spectra were determined on a Perkin-Elmer model 257 recording spectrophotometer in potassium bromide pellets. NMR spectra were recorded in deuterated chloroform on a Hitachi Perkin-Elmer model R-24 high-resolution spectrometer, with tetramethylsilane as the internal standard and chemical shifts reported in δ (parts per million) units. Mass spectra were taken with a LKB-9000 mass spectrometer. The optical rotations were measured on a Perkin-Elmer model 241 polarimeter. TLC was done on silica gel G (Merck) plates coated with 0.25 mm of adsorbent and activated at 110° for 1 hr. The solvent system of chloroform–methanol–concentrated ammonium hydroxide (10:1.5:0.1) was used unless otherwise noted. The alkaloids were visualized by spraying with Dragendorff reagent (Munier). All reagents were analytical grade unless otherwise noted.

[2] The plant material was collected and identified by Mr. K. Obeng-Darko, Faculty of Agriculture, University of Science and Technology, Kumasi, Ghana. Voucher specimens are on deposit at the Faculty of Pharmacy, University of Science and Technology, Kumasi, Ghana.

[3] Mallinckrodt, St. Louis, Mo.

[4] E. Merck, Darmstadt, Germany.

[5] A slurry of silica gel G in distilled water (1:2) was prepared, stirred for 5 min, dried overnight at 110°, and passed through an 80-mesh sieve.

[6] J. T. Baker Co.

Fractions 21–25 afforded a slightly yellowish compound (35 mg), mp 123–125°; $[\alpha]_D^{25}$ +27° (c 0.15, methanol); λ_{max} (methanol): 231 (log ϵ 4.60), 275 (4.14), 285 (4.13), and 295 (sh) (4.10) nm; ν_{max} (KBr): 2940, 2840, 1690, 1650, 1600, 1500, 1450, 1415, 1340, 1280, 1270, 1200, 1190, 1120, 1070, 1025, and 820 cm^{-1}; NMR: δ 2.32 (s, 3H, N-2 NCH_3), 3.05 (s, 3H, N-2′ NCH_3), 3.68 (s, 3H, OCH_3), 3.75 (s, 6H, 2-OCH_3), 3.83 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 7.10–8.00 (m, 9H, ArH), and 10.00 (s, 1H, ArCHO) ppm; mass spectrum: M^+ *m/e* 666 (1), 411 (100), 256 (26), 241 (1), 206 (4), and 204 (3).

REFERENCES

(1) F. R. Irvine, "Woody Plants of Ghana," Oxford University Press, London, England, 1961, p. 36.
(2) A. N. Tackie, D. Dwuma-Badu, J. E. Knapp, and P. L. Schiff, Jr., *Lloydia,* **35,** 474 (1972).
(3) L. VanItallie and A. J. Steenhauer, *Pharm. Weekbl.,* **59,** 1381 (1922).
(4) K. V. J. Rao and L. R. Row, *J. Sci. Ind. Res., Sect. B,* **16,** 156 (1957).
(5) B. Anjaneyulu, T. R. Govindachari, S. S. Sathe, N. Viswanathan, K. W. Gopinath, and B. R. Pai, *Tetrahedron,* **25,** 3091 (1969).
(6) A. N. Tackie and A. Thomas, *Planta Med.,* **16,** 158 (1968).
(7) A. N. Tackie, D. Dwuma-Badu, J. S. K. Ayim, T. T. Dabra, J. E. Knapp, D. J. Slatkin, and P. L. Schiff, Jr., *Lloydia,* **38,** 210 (1975).
(8) A. N. Tackie, D. Dwuma-Badu, J. E. Knapp, and P. L. Schiff, Jr., *Phytochemistry,* **12,** 203 (1973).
(9) A. N. Tackie and A. Thomas, *Ghana J. Sci.,* **5,** 11 (1965).
(10) A. N. Tackie, D. Dwuma-Badu, J. E. Knapp, and P. L. Schiff, Jr., *Lloydia,* **36,** 66 (1973).
(11) A. N. Tackie, D. Dwuma-Badu, T. T. Dabra, J. E. Knapp, D. J. Slatkin, and P. L. Schiff, Jr., *Experientia,* **30,** 847 (1974).
(12) R. R. Paris and S. K. Sasorith, *Ann. Pharm. Fr.,* **25,** 627 (1967).
(13) T. K. Palit and M. P. Khare, *Phytochemistry,* **8,** 1559 (1969).
(14) A. K. Baru, P. Chakrabarti, and A. S. Dutta Gupta, *J. Indian Chem. Soc.,* **47,** 920 (1970).
(15) T. U. Okarter, M. Pharm. thesis, University of Science and Technology, Kumasi, Ghana, 1971.
(16) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Englewood Cliffs, N.J., 1965, p. 84.
(17) N. Bild and M. Hesse, *Helv. Chim. Acta,* **50,** 1887 (1967).
(18) T. A. Bryce and J. R. Maxwell, *J. Chem. Soc., Chem. Commun.,* **1965,** 206.
(19) E. Weiss, K. Bernauer, and A. Girardet, *Helv. Chim. Acta,* **54,** 1342 (1971).
(20) J. D. Phillipson and S. S. Handa, *Phytochemistry,* **14,** 2683 (1975).
(21) E. J. Shellard, J. D. Phillipson, and K. Sarpong, *Xenobiotica,* **1,** 455 (1971).
(22) M. Shamma and J. E. Foy, *Tetrahedron Lett.,* **1975,** 2249.
(23) J. D. Phillipson, *Xenobiotica,* **1,** 419 (1971).
(24) F. Puisieux, J.-P. Devissaguet, C. Miet, and J. Poisson, *Bull. Soc. Chim. Fr.,* **1967,** 251.
(25) A. Kh. Aslanov, A. S. Sadykov, V. N. Zainutdinov, and Yu. K. Kushmaradov, *Nauch. Tr. Goszapov,* **286,** 63 (1966); through *Chem. Abstr.,* **67,** 71108.
(26) S. K. Dutta and S. Ghosal, *Chem. Ind.,* **1967,** 2046.
(27) B. A. Abdusalamov, A. S. Sadykov, and K. A. Aslanov, *Nauch. Tr. Tash. Gas. Univ.,* **263,** 3 (1964); through *Chem. Abstr.,* **63,** 3314.
(28) E. J. Shellard, J. D. Phillipson, and K. Sarpong, *Phytochemistry,* **10,** 2505 (1971).
(29) E. Weiss, K. Bernauer, and A. Giraret, *Helv. Chim. Acta,* **54,** 1342 (1971).
(30) V. G. Khozhdaev, S. K. Maekh, and S. Y. Yunusov, *Khim. Prirodn. Soed.,* **1972,** 631.
(31) Z. Jerzmanowska and Z. Sykulska, *Dissnes. Pharm. Warsz.,* **16,** 71 (1964).
(32) R. Schoental, *J. Chem. Soc.,* **1960,** 2375.
(33) S. Brandänge and B. Lüning, *Acta Chem. Scand.,* **24,** 353 (1970).
(34) J. D. Phillipson and S. S. Handa, *Phytochemistry,* **14,** 999 (1976).
(35) A. I. Vogel, "Practical Organic Chemistry," 3rd ed., Wiley, New York, N.Y., 1956, p. 971.

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Cardiovascular Actions of Three Harmala Alkaloids: Harmine, Harmaline, and Harmalol

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Abstract □ Each of three harmala alkaloids, harmine, harmaline, and harmalol, decreased heart rate and increased pulse pressure, peak aortic flow, and myocardial contractile force in intact normotensive anesthetized dogs. Harmine reduced systemic arterial blood pressure and total peripheral vascular resistance; harmaline-evoked decreases were frequently followed by a secondary increase; and the effects of harmalol on these two parameters were inconsistent. A direct negative chronotropic effect of harmala alkaloids was suggested by observations of bradycardia in the isolated perfused rat heart and in the intact dog; neither vagotomy nor atropinization affected harmala alkaloid-induced bradycardia in the dog. Reduction in femoral vascular resistance by the alkaloids was not apparently due to activation of cholinergic, β-adrenergic, or histaminic (H_1) receptors.

Keyphrases □ Alkaloids, harmala—cardiovascular activity in dogs □ Harmine—cardiovascular activity in dogs □ Harmaline—cardiovascular activity in dogs □ Harmalol—cardiovascular activity in dogs □ Cardiovascular activity—three harmala alkaloids in dogs

Although the seeds of *Peganum harmala* have been used for centuries as a folk medicine, the harmala alkaloids continue to be of interest because of the effects they elicit on the central nervous system (CNS) and the cardiovas-