PLANT ANTICANCER AGENTS. XXIV. ALKALOID CONSTITUENTS OF *SIMABA MULTIFLORA*[1,2]

MUNEHISA ARISAWA, A. DOUGLAS KINGHORN, GEOFFREY A. CORDELL, and NORMAN R. FARNSWORTH

Department of Pharmacognosy and Pharmacology, College of Pharmacy, University of Illinois at the Medical Center, Chicago, IL 60612

ABSTRACT.—Two new cytotoxic canthin-6-ones, 10-methoxycanthin-6-one (**1**) and 10-hydroxycanthin-6-one (**2**) were isolated from the wood of *Simaba multiflora* (Simaroubaceae). Three canthin-2,6-diones, 10-hydroxy-3-methoxycanthin-2,6-dione (**3**), 3-methoxycanthin-2,6-dione (**4**) and canthin-2,6-dione (**5**), as well as scopoletin (**7**) and the novel coumarino-lignan cleomiscosin A (**6**) were also obtained.

In a continuing search for anticancer and cytotoxic agents from the wood of *Simaba multiflora* A. Juss (Simaroubaceae) (1, 2), further bioactivity-directed fractionation resulted in the isolation of two novel cytotoxic canthin-6-ones, 10-methoxycanthin-6-one (**1**) and 10-hydroxycanthin-6-one (**2**). Three canthin-2,6-diones, 10-hydroxy-3-methoxycanthin-2,6-dione (**3**), 3-methoxycanthin-2,6-dione (**4**), and canthin-2,6-dione (**5**), the novel coumarino-lignan, cleomiscosin A (**6**) (2), and the widely distributed coumarin, scopoletin (**7**), were also isolated. In this paper we present evidence for the structures of compounds **1**, **2**, **3** and **4** and identify the known compounds **5** and **7**. The structure determination of **6** will be discussed elsewhere (2).

EXPERIMENTAL[4]

INITIAL FRACTIONATION.—The initial fractionation of an ethanol extract of the wood (318 kg) of *S. multiflora*[5] has been described previously (1).

SEPARATION AND ISOLATION.—A portion (76.3 g) of the chloroform-soluble, petroleum ether-insoluble residue was treated with methanol and the methanol filtrate evaporated *in vacuo*, redissolved in chloroform and chromatographed on silica gel[6] (700 g) packed in chloroform. The column was eluted successively with mixtures of chloroform and methanol of increasing polarity. A total of 21 fractions (2 liters each) was collected. The eluate from a chloroform-1% methanol mixture afforded scopoletin (**7**, 105 mg, 0.00016%) from fraction 6, 10-methoxycanthin-6-one (**1**, 43 mg, 0.000066%) from fraction 7 and 3-methoxycanthin-2,6-dione (**4**, 256 mg, 0.00040%) from fraction 10. Mixtures containing 2% methanol afforded 10-hydroxycanthin-6-one (**2**, 107 mg, 0.00016%) from fraction 12 and cleomiscosin A (**6**, 24 mg, 0.000037%) from fraction 14. Fraction 15, eluted with chloroform-4% methanol, afforded 10-hydroxy-3-methoxycanthin-2,6-dione (**3**, 32 mg, 0.000049%); and fraction 16 afforded canthin-2,6-dione (**5**, 34 mg, 0.000052%).

IDENTIFICATION OF SCOPOLETIN (**7**).—Yellowish green needles, mp 198–199°; ir, νmax (KBr) 3340, 3020, 2990, 2950, 1705, 1630, 1610, 1565, 1510, 1450, 1435, 1375, 1290, 1260, 1215, 1190, 1135, 1100, 1015, 920, 860, 820, 740 and 660 cm^{-1}; uv, λmax (MeOH) (log ϵ) 344 (4.13), 297 (3.98), 260 (sh) (3.94), 252 (3.96) and 229 nm (4.14); pmr, (60 MHz, DMSO-d_6) δ 3.84 (3H, s, OCH_3), 6.21 (1H, d, J=9.5 Hz, 3-H), 6.79 (1H, s, 8-H), 7.21 (1H, s, 5-H) and 8.06 ppm (1H, d, J=9.5 Hz, 4-H); ms, m/z 192 (M^+, 100%), 177 (51), 164 (17), 149 (33) and 121 (15). Identification was established by comparison with an authentic sample of scopoletin (**7**) isolated from *Zanthoxylum belizense* (3).

---

[1]For Paper XXIII in this series see reference 1.

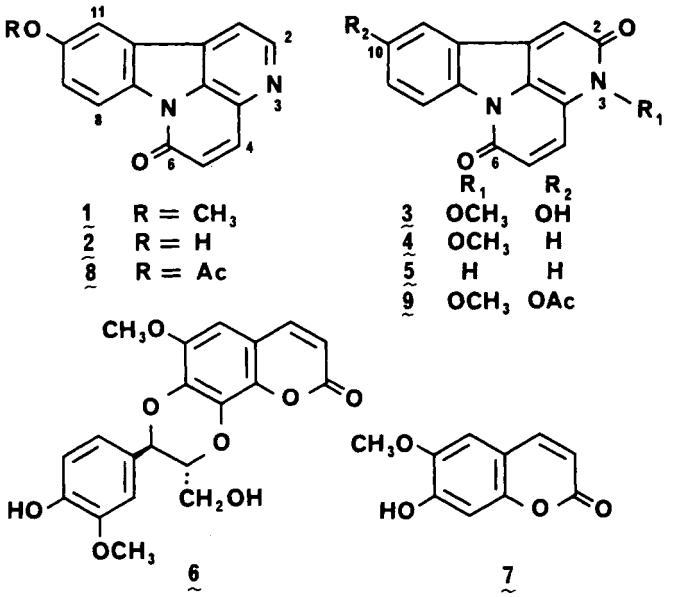
[2]These data were first presented at the Joint Meeting of the American Society of Pharmacognosy and the Society for Economic Botany, Boston, Mass., July 1981.

Present address: Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-01, Japan.

[4]Melting points were determined using a Kofler hot-stage instrument and are uncorrected. Uv spectra were measured on a Beckman model DB-G grating spectrophotometer, and the ir spectra were obtained on Beckman model 18-A spectrophotometer, with polystyrene calibration at 1601 cm^{-1}. Pmr spectra were recorded on a Varian model T-60A instrument, equipped with a Nicolet model TT-7 Fourier Transform attachment. Tetramethylsilane was used as an internal standard, and chemical shifts are reported on the δ (ppm) scale. Low resolution mass spectra were obtained with a Varian MAT 112S double-focusing spectrometer operating at 70 ev. High resolution mass spectra were obtained with a Varian 731 double-focusing spectrometer operating at 70 eV.

[5]The extract was supplied by Polysciences, Inc. through a contract with the Natural Products Branch, Division of Cancer Treatment, National Cancer Institute, Bethesda, MD.

[6]E. Merck, Darmstadt, W. Germany.



CHARACTERIZATION OF 10-METHOXYCANTHIN-6-ONE (**1**).—Pale yellow needles, mp 175–178°; ir, νmax (KBr) 3020, 1670, 1635, 1610, 1495, 1465, 1455, 1440, 1425, 1395, 1350, 1335, 1310, 1275, 1250, 1225, 1155, 1060, 1030, 915, 845, 835 and 815 cm^{-1}; uv, λmax (MeOH) (log ε) 352 (3.83), 310 (3.69), 274 (4.06), 266 (sh) (3.95), 232 (sh) (3.81) and 212 nm (4.20); pmr, (60 MHz, $CDCl_3$) δ 3.91 (3H, s, OCH_3), 6.83 (1H, d, J=9.8 Hz, 5–H), 6.91 (1H, dd, J=2.4, 8.5 Hz, 9–H), 7.65 (1H, d, J=5.0 Hz, 1–H), 7.74 (1H, d, J=8.5 Hz, 8–H), 7.89 (1H, d, J=9.8 Hz, 4–H), 7.97 (1H, d, J=2.4 Hz, 11–H) and 8.65 ppm (1H, d, J=5.0 Hz, 2–H); ms, m/z 250 (M^+, 100%), 249 (14), 222 (10), 221 (20), 220 (15), 207 (8), 192 (14), 179 (19), 153 (11), 125 (11), 111 (12) and 97 (19); mass measurement, m/z 250.0750 ($C_{15}H_{10}N_2O_2$ requires 250.0742).

IDENTIFICATION OF 3-METHOXYCANTHIN-2,6-DIONE (**4**).—Reddish-brown needles, decomposed at 237–240° and above 280°, did not melt; ir, νmax (KBr) 3025, 2950, 1645, 1625, 1605, 1490, 1460, 1415, 1360, 1330, 1245, 1180, 1155, 1140, 1080, 975, 955, 900, 885, 835, 775, 755, 745 and 645 cm^{-1}; uv, λmax (MeOH) (log ε) 420 (4.13), 403 (sh) (3.97), 325 (3.81), 302 (4.01), 292 (4.01), 253 (sh) (4.21), 248 (4.22), 232 (sh) (4.24) and 227 nm (4.24); pmr, (60 MHz, $CDCl_3$) δ 4.20 (3H, s, 3–OCH_3), 6.90 (1H, d, J=9.8 Hz, 5–H), 7.26 (1H, s, 1–H), 7.44 (1H, m, J=1.9, 7.2 Hz, 10–H), 7.57 (1H, m, J=1.9, 7.2 Hz, 9–H), 7.73 (1H, d, J=9.8 Hz, 4–H), 7.99 (1H, dd, J=1.9, 7.2 Hz, 11–H) and 8.62 ppm (1H, dd, J=1.9, 7.2 Hz, 8–H); ms, m/z 266 (M^+, 75%), 225 (48), 234 (100), 208 (22), 207 (93), 180 (11), 179 (40), 152 (16), 151 (20), 133 (9), 128 (21), 127 (16), 101 (41), 100 (11), 90 (15) and 89 (17); mass measurement, m/z 266.0690 ($C_{15}H_{10}N_2O_3$ requires 266.0691).

CONVERSION OF 3-METHOXYCANTHIN-2,6-DIONE (**4**) TO CANTHIN-2,6-DIONE (**5**).—To 3-methoxycanthin-2,6-dione (**4**, 30 mg) in 10% potassium hydroxide solution (50 ml) was added a solution (10%) of sodium hydrogen sulfite at room temperature until there was no more color change. The reaction mixture was neutralized with dilute hydrochloric acid, and the solid which separated was collected and washed wito water. Recrystallization from methanol afforded yellow microneedles of canthin-2,6-dione (**5**, 25 mg), mp 295–305° (dec.) identified by comparison with an authentic sample.

CHARACTERIZATION OF 10-HYDROXYCANTHIN-6-ONE (**2**).—Yellow micro needles, decomposes at 288–293°; did not melt; ir, νmax (KBr) 3070, 2640, 1695, 1645, 1610, 1510, 1475, 1450, 1400, 1355, 1320, 1285, 1250, 1170, 1155, 1065, 985, 930, 850, 835, 815, 801, 790, 720 and 620 cm^{-1}; uv, λmax (MeOH) (log ε) 352 (4.17), 312 (4.07), 304 (sh) (4.04), 275 (4.25), 269 (sh) (4.22) and 288 nm (sh) (4.19), λmax (MeOH+NaOMe) (log ε) 428 (3.93), 356 (4.04), 320 (sh) (4.11), 297 (4.19), 283 (sh) (4.14) and 238 nm (sh) (4.20); pmr, (60 MHz, DMSO-d_6) δ 6.94 (1H, d, J=9.9 Hz, 5–H), 6.99 (1H, dd, J=2.3, 8.5 Hz, 9–H), 7.99 (1H, d, J=2.3 Hz, 11–H), 8.10 (1H, d, J=9.9 Hz, 4–H), 8.11 (1H, d, J=4.9 Hz, 1–H), 8.14 (1H, d, J=8.5 Hz, 8–H) and 8.74 ppm (1H, d, J=4.9 Hz, 2–H); ms, m/z 236 (M^+, 100%), 209 (14), 208 (99), 179 (26), 153 (15), 127 (13), 126 (13), 118 (7), 104 (20), 77 (12), 76 (24), 75 (20), 74 (12), 62 (25), and 52 (18); mass measurement, m/z 236.0581 ($C_{14}H_8N_2O_2$ requires 236.0586).

ACETYLATION OF 10-HYDROXYCANTHIN-6-ONE (**2**).—10-Hydroxycanthin-6-one (**2**, 30 mg) was treated with acetic anhydride-pyridine (1:1, 1 ml) on a steam bath for 1 hr. Work-up in the usual way afforded a monoacetate **8** (28 mg) as colorless needles, mp 240°; pmr, (60 MHz, $CDCl_3$) δ 2.39 (3H, s, 10–OAc), 6.95 (1H, d, J=9.8 Hz, 5–H), 7.27 (1H, dd, J=2.0, 8.4 Hz, 9–H), 7.91 (1H, d, J=5.0 Hz, 1–H), 8.01 (1H, d, J=9.8 Hz, 4–H), 8.08 (1H, d, J=8.4 Hz, 8–H), 8.42 (1H, d, J=2.0 Hz, 11–H) and 8.81 ppm (1H, d, J=5.0 Hz, 2–H); ms, m/z 278 (M^+, 8%), 236 (17), 225 (100), 208 (35), 179 (14), 153 (3), 161 (7), 126 (6), 104 (4), 75 (6), 62 (6), 51 (5) and 43 (37).

METHYLATION OF 10-HYDROXYCANTHIN-6-ONE (**2**).—A methanolic solution of **2** (20 mg) was treated with ethereal methanolic diazomethane[7] at room temperature overnight. Evaporation

[7]Prepared from Diazald, Aldrich Chemical Co., Milwaukee, WI.

afforded a crude solid; which crystallized from methanol as pale yellow needles, 18 mg, mp 177°; the compound was identified as 10-methoxycanthin-6-one (**1**) by direct comparison with natural **1**.

CHARACTERIZATION OF CLEOMISCOSIN A (**6**).—Colorless needles, mp 250–252°; the structure determination of cleomiscosin A (**6**) will be described elsewhere (2).

CHARACTERIZATION OF 10-HYDROXY-3-METHOXYCANTHIN-2,6-DIONE (**3**).—Yellow microneedles, decomposed at 280–290°; ir, νmax (KBr) 3440, 3050, 2950, 1650, 1620, 1575, 1490, 1450, 1415, 1360, 1305, 1290, 1270, 1230, 1155, 1130, 1090, 950, 845, 820, 815, 785, 760, 735 and 650 cm^{-1}; uv, λmax (MeOH) (log ε) 448 (4.24), 423 (4.25), 400 (4.18), 382 (4.17), 365 (4.15), 288 (4.05), 272 (4.09), 248 (sh) (4.25) and 220 nm (4.32); pmr, (60 MHz, pyridine-d_5) δ 4.20 (3H, s, 3-OCH_3), 6.92 (1H, d, J=9.9 Hz, 5-H), 7.25 (1H, s, 1-H), 7.69 (1H, d, J=9.9 Hz, 4-H), 7.72 (1H, s, OH, exchanged with D_2O), and 8.31 ppm (1H, d, J=7.6 Hz, 8-H); ms, m/z 282 (M^+, 67%), 252 (100), 251 (72), 239 (19), 223 (66), 195 (29), 167 (11), 140 (22), 126 (11), 115 (11), 114 (15), 113 (10) and 98 (14); mass measurement, m/z 282.0640 ($C_{15}H_{10}N_2O_4$ requires 282.0641).

ACETYLATION OF 10-HYDROXY-3-METHOXYCANTHIN-2,6-DIONE (**3**).—10-Hydroxy-3-methoxycanthin-2,6-dione (**3**, 25 mg) was reacted with acetic anhydride-pyridine (1:1, 0.5 ml) on a steam bath for 1 hr. Work-up in the usual way gave colorless needles of a monoacetate **9** (17 mg), mp 222°; pmr, (60 MHz, $CDCl_3$) δ 2.37 (3H, s, 10-OAc), 4.19 (3H, s, 3-OCH_3), 6.89 (1H, d, J=9.6 Hz, 4-H), 7.22 (1H, s, 1-H), 7.23 (1H, dd, J=1.1, 8.6 Hz, 9-H), 7.74 (1H, d, J=9.6 Hz, 5-H), 7.92 (1H, d, J=8.6 Hz, 8-H) and 8.34 ppm (1H, d, J=1.1 Hz, 11-H), ms, m/z 324 (M^+, 81%), 293 (15), 282 (43), 253 (16), 252 (96), 251 (100), 224 (22), 223 (63), 222 (8), 196 (8), 195 (24), 195 (13), 169 (7), 168 (6), 167 (5), 166 (8), 144 (6), 141 (5), 140 (16), 114 (9), 113 (7), 89 (10), 87 (8), 80 (9), 62 (13), 61 (11), 52 (10) and 43 (59).

IDENTIFICATION OF CANTHIN-2,6-DIONE (**5**).—Yellow microneedles, mp 290–305° (dec.); ir, νmax (KBr) 3080, 2980, 2860, 1640, 1610, 1580, 1490, 1460, 1420, 1355, 1325, 1240, 1185, 1150, 1120, 1025, 975, 945, 835, 775, 750, 705, 655 and 630 cm^{-1}; uv, λmax (MeOH) (log ε) 445 (4.14), 421 (4.11), 400 (sh) 3.91), 300 (4.01), 291 (3.99), 253 (4.31), 247 (4.34) and 227 nm (4.44); pmr, (60 MHz, CF_3COOD) δ 7.41 (1H, d, J=9.7 Hz, 5-H), 7.72 (1H, m, J=1.0, 7.5 Hz, 10-H), 7.85 (1H, br s, 3-H), 7.96 (1H, d, 1-H), 7.96 (1H, m, J=1.0, 7.5 Hz, 9-H), 8.16 (1H, d, J=9.7 Hz, 4-H), 8.30 (1H, dd, J=1.0, 7.5 Hz, 11-H) and 8.69 ppm (1H, dd, J=1.0, 7.5 Hz, 8-H); ms, m/z 236 (M^+, 100%), 208 (20), 180 (11), 179 (13), 154 (4), 153 (6), 152 (4), 128 (4), 127 (8), 126 (4), 118 (9), 101 (6), 90 (10), 77 (4), 76 (8), 75 (7), 74 (4) and 62 (6); mass measurement, m/z 236.0583 ($C_{14}H_8N_2O_2$ requires 236.0586).

STRUCTURE DETERMINATION OF THE CANTHIN-6-ONE DERIVATIVES.—The molecular formula of **2** was determined to be $C_{14}H_8N_2O_2$ by high-resolution mass spectrometry; the fragmentation pattern was similar to that of 8-hydroxycanthin-6-one (4). Both the ir and uv spectra also displayed similarity with those of canthin-6-one derivatives (5). Acetylation afforded a monoacetate, and methylation produced a monomethyl ether. From this information the isolate was considered to be a monohydroxycanthin-6-one derivative. The location of the hydroxyl group on the nucleus was established to be at the 10-position from its ^1H nmr chemical shifts; a large bathochromic shift occurred in the uv spectrum on the addition of alkali. Doublets were observed for H-1 and H-2 at 8.11 and 8.74 ppm, respectively, and for H-5 and H-4 at 6.94 and 8.10 ppm, respectively (5). Substitution is, therefore, limited to the benzenoid nucleus; and from the alkali-induced bathochromic shift of 76 nm, C-8 (*ortho*) or C-10 (*para*) were considered as possible sites of substitution by a phenolic group. Direct comparison with 8-hydroxycanthin-6-one (4) indicated the two compounds were not identical. The chemical shifts and coupling constants of the three remaining aromatic protons indicated a 1,2,4-substituted nucleus, placing the functional group at C-9 or C-10. This interlocking evidence indicates the isolate to have the structure 10-hydroxycanthin-6-one (**2**).

A second canthin-6-one possessing a uv spectrum similar to **2** was isolated. From the observation of a molecular ion at m/z 250, it was thought to be a methyl ether of **2**. Confirmation of this hypothesis came from the ^1H nmr spectrum, which showed a three-proton singlet at 3.91 ppm for an aromatic methoxy group and an aromatic proton region, very similar to that of **2**. With doublets for H-1 and H-2 at 7.65 and 8.65 ppm and for H-5 and H-4 at 6.83 and 7.89 ppm, respectively, substitution could again be limited to the aromatic nucleus. Methylation of **2** with diazomethane produced a methyl ether identical with the isolate which could, therefore, be assigned the structure 10-methoxycanthin-6-one (**1**). Compound **2** also yielded a monoacetate derivative **8** in which the acetyl singlet appeared at 2.32 ppm, and the three aromatic protons were shifted downfield 0.34–0.45 ppm in comparison with **1**. Comparison with the published data for 9-methoxycanthin-6-one, also isolated from *S. multiflora* (6), indicated that our isolate possessed a different substituent pattern.

The uv spectra of **3**, **4** and **5** were found to be similar with that of indacanthinone (5-methoxycanthin-2,6-dione) (7), and their mass spectra showed molecular ions at m/z 282, m/z 266 and m/z 236, respectively. In the ^1H nmr spectrum of **4**, a pair of doublets at 6.90 and 7.73 ppm were assigned to H-5 and H-4, a one-proton singlet at 7.26 ppm was attributed to H-1, and a three proton singlet at 4.20 ppm to a methoxy group attached to nitrogen (8). Four aromatic protons were observed at 7.44, 7.57, 7.99 and 8.62 ppm for H-10, H-9, H-11 and H-8, respectively, indicating the aromatic nucleus to be unsubstituted. Reaction of **4** with alkaline sodium hydrogen sulfite solution afforded **5**, identified by direct comparison with the natural material (*vide supra*). On this basis **4** was identified as 3-methoxycanthin-2,6-dione.

The molecular formula of **3** was determined to be $C_{15}H_{10}N_2O_4$ by high resolution mass spectrometry. Acetylation afforded a monoacetate **9**, which in the ^1H nmr spectrum displayed two three-proton singlets at 2.37 and 4.19 ppm, attributed to *O*-acetyl and *N*-methoxy groups, respectively. Doublets at 6.89 and 7.74 ppm were attributed to H-5 and H-4, and a one-proton singlet at 7.22 ppm was attributed to H-1. A doublet of doublets at 7.23 ppm and two doublets

at 7.92 and 8.34 ppm were attributed to H-9, H-8 and H-11, respectively, by comparison with **8**. The parent compound was, therefore, identified as 10-hydroxy-3-methoxycanthin-6-one (**3**).

The molecular formula of **5** was deduced to be $C_{14}H_8N_2O_2$ by high resolution mass spectrometry. In the ^1H nmr spectrum doublets for H-5 and H-4 were observed at 7.41 and 8.16 ppm, together with a singlet at 7.96 ppm assigned to H-1 and a broadened singlet at 7.85 ppm assignable to H-3. Four aromatic protons at 7.72, 7.96, 8.30 and 8.69 ppm for H-10, H-9, H-11 and H-8 on the A-ring, indicated the nucleus to be unsubstituted; consequently, the structure is suggested to be canthin-2,6-dione (**5**).

BIOLOGICAL ACTIVITY OF THE ISOLATES.—Of the canthinone derivatives tested for cytotoxic activity (9), only 10-methoxycanthin-6-one (**1**, NSC-341584) and 10-hydroxycanthin-6-one (**2**, NSC-341583) displayed activity (KB system, ED_{50} 2.1 and 2.2 μg/ml, respectively). The *in vitro* cytotoxicity of cleomiscosin A (**6**) will be reported elsewhere (2).

DISCUSSION

Canthin-6-ones are now well established as occurring in the family Simaroubaceae having been previously isolated from the genera *Picrasma* (10–14), *Samadera* (7), *Ailanthus* (4, 15–17), *Simarouba* (18–20), *Soulamea* (10, 21–23) and *Simaba* (6). Canthin-2,6-diones are more rare, and previously only the 5-methoxy- (7) and 3-methoxy- (19, 20) derivatives had been reported.

We report here the isolation and structure elucidation of four new canthinone derivatives, namely **1**, **2**, **3** and **5**, including two canthin-2,6-diones. Compounds **1** and **2** were interrelated through O-methylation and **4** could be correlated with **5** by reduction with sodium hydrogen sulfite. Interpretation of proton nmr spectral data permitted the unequivocal assignment of structures. Recent work by Polonsky *et al.* (6) on the stem bark of *S. multiflora* afforded 9-methoxy canthin-6-one, but the proton nmr spectral data clearly establish the difference between our isolate and that obtained by the French group.

This work also extends the biological activity of canthin-6-ones which hitherto have not displayed cytotoxic activity.

ACKNOWLEDGMENTS

This work was supported in part by Contract CM-97295 from the Natural Products Branch, Division of Cancer Treatment, National Cancer Institute, U.S. Department of Health and Human Services, Bethesda, Maryland. The authors thank Dr. F. Boettner, Polysciences, Inc., Warrington, Pennsylvania, for the plant extract.

Received 7 June 1982

LITERATURE CITED

1. M. Arisawa, A. D. Kinghorn, G. A. Cordell and N. R. Farnsworth, *J. Nat. Prod.*, **46**, 218 (1983).
2. M. Arisawa, S. S. Handa, D. D. McPherson, D. C. Lankin, G. A. Cordell, H. H. S. Fong and N. R. Farnsworth, *J. Nat. Prod.*, submitted for publication.
3. S. Najjar, G. A. Cordell and N. R. Farnsworth, *Phytochemistry*, **14**, 2309 (1975).
4. G. A. Cordell, M. Ogura and N. R. Farnsworth, *Lloydia*, **41**, 166 (1978).
5. G. A. Cordell, *Introduction to Alkaloids—A Biogenetic Approach*, J. Wiley and Sons, New York, N.Y., pp. 619–622, 1981.
6. J. Polonsky, J. Gallas, J. Varenne, T. Prangé, C. Pascard, H. Jacquemin and C. Moretti, *Tetrahedron Letts.*, **23**, 869 (1982).
7. V. S. Iyer and S. Rangaswami, *Curr. Sci. (India)*, **41**, 140 (1972).
8. L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemist", Pergamon Press, Oxford, England, 1969, pp 456.
9. R. I. Geran, N. H. Greenburg, M. M. MacDonald, A. M. Schumacher and B. J. Abbott, *Cancer Chemother. Rep. Pt. 3*, **3**(2), 1 (1972).
10. N. Inamoto, S. Masuda, O. Shimamura and T. Tsuyuki, *Bull. Chem. Soc. Japan*, **34**, 888 (1961).
11. Y. Kimura, M. Takido and S. Koizumi, *Yakugaku Zasshi*, **87**, 1371 (1967).
12. H. Wagner, T. Nestler and A. Neszmelyi, *Tetrahedron Letts.*, 2777 (1978).
13. H. Wagner, T. Nestler and A. Neszmelyi, *Planta Med.*, **36**, 113 (1979).
14. J.-S. Yang, S.-R. Luo, X.-L. Shen and Y.-X. Li, *Yao Hsueh Hsueh Pao*, **14**, 167 (1979); *Chem. Abstr.*, **92**: 72679a (1980).
15. T. Ohmoto, R. Tanaka and T. Nikaido, *Chem. Pharm. Bull.*, **24**, 1532 (1976).
16. K. Szendrei, T. Korbely, H. Krenzein, J. Reisch and I. Novak, *Herba Hung.*, **16**, 15 (1977).
17. T. Ohmoto, K. Koike and Y. Sakamoto, *Chem. Pharm. Bull.*, **29**, 390 (1981).
18. E. V. Lassak, J. Polonsky and H. Jacquemin, *Phytochemistry*, **16**, 1126 (1977).
19. A. M. Giesbrecht, H. E. Gottlieb, O. R. Gottleib, M. O. F. Boulart, R. A. De Lima and A. E. G. Santana, *Suppl. Simp. Plant. Med. Bras.*, **5***th*, 117 (1978).
20. S. M. Giesbrecht, H. E. Gottlieb, O. R. Gottlieb, M. O. F. Goulart, R. A. De Lima and A. E. G. Santana, *Phytochemistry*, **19**, 313 (1980).
21. B. Viala, Thesis, Université de Paris-Sud, Centre d'Orsay, France, 1971; quoted in ref. 18.
22. P. J. Clarke, K. Jewers and H. F. Jones, *J. Chem. Soc., Perkin Trans. I*, 1614 (1980).
23. S. S. Handa, A. D. Kinghorn, G. A. Cordell and N. R. Farnsworth, *J. Nat. Prod.*, in press.