A SPECTRAL METHOD FOR THE DETERMINATION OF THE POSITION OF A PHENOLIC GROUP ON RING A OF AN APORPHINE. FOUR NEW APORPHINES FROM *POLYALTHIA ACUMINATA*

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ABSTRACT.—*Polyalthia acuminata* Thw. (Annonaceae) has furnished the new aporphines (−)-norliridinine (**1**), (−)-3-hydroxynornuciferine (**2**), (−)-norannuradhapurine (**9**), and (−)-noroliveroline (**11**). Monophenolic aporphines bearing the phenol group at C-3 exhibit both a bathochromic shift as well as hyperchromic effect in their uv spectra in basic solution. *N*-Methylation of **1** yields (−)-liridinine, which is thus firmly represented by expression **7**. Similar treatment of **2** leads to (−)-3-hydroxynuciferine (**8**) which is identical with the alkaloid (−)-lirinine. This last transformation establishes with certainty the position of the phenol in (−)-lirinine.

Since it is well known that the plant family Annonaceae is rich in isoquinoline alkaloids, a systematic study of *Polyalthia acuminata* Thw. (syn. *Enicosanthum acuminatum* Thw.) was undertaken. Seventeen kilograms of the dried bark and leaves of this tree, a member of the Annonaceae, were collected on the island of Sri Lanka and were found to yield four new aporphine alkaloids, (−)-norliridinine (**1**), (−)-3-hydroxynornuciferine (**2**), (−)-norannuradhapurine (**9**), and (−)-noroliveroline (**11**). Known alkaloids also present, which were characterized either spectrally or by comparison with authentic samples, were the oxoaporphines *O*-methylmoschatoline (≡liridine) and liriodenine; the aporphines (−)-3-methoxynuciferine, (−)-*O*-methylisopiline (≡(−)-*O*-methylnorlirinine), (−)-anonaine, (−)-nornuciferine, (+)-isoboldine, (−)-isopiline, (−)-asimilobine, (−)-caaverine, (−)-tuduranine, (−)-norushinsunine and (−)-anolobine; the proaporphine (+)-stepharine; the tetrahydrobenzylisoquinolines (±)-juziphine, (+)-reticuline, (±)-*N*-methylcoclaurine, (±)-norjuziphine, and (±)-coclaurine; the berbines (−)-kikemanine and (−)-stepholidine; the phenethylamine hordenine; and the indoles 2-methyltetrahydro-β-carboline, *N*,*N*-dimethyltryptamine and (±)-tetrahydroharman (eleagnine). A lignan also found is (±)-syringaresinol.

The mass spectra for both (−)-norliridinine (**1**) and (−)-3-hydroxynornuciferine (**2**) show molecular ion peaks *m*/*z* 297 ($C_{18}H_{19}O_3N$) and base peak *m*/*z* 196. The nmr spectra reveal two methoxyl singlets at δ3.63 and 3.93 for **1**, and at δ3.72 and 3.98 for **2**. The H–11 absorption for (−)-norliridinine appears as a doublet at δ8.24 (J_A=8.2 Hz), and the corresponding doublet is found at δ8.21 (J_A=7.5 Hz) in the case of (−)-3-hydroxynornuciferine. A multiplet between δ7.21 and 7.33 represents H–8, H–9, and H–10 in the spectrum of **1**, and the corresponding multiplet for **2** is between δ7.15 and 7.29.

Acetylation of (−)-norliridinine (**1**) and (−)-3-hydroxynornuciferine (**2**) leads to the corresponding *O*,*N*-diacetyl derivatives **3** and **4**, respectively. Significantly, diazomethane *O*-methylation of **1** and **2** furnished the known aporphine (−)-*O*-methylisopiline (**5**) (1). Compounds **1** and **2** were also found to be different from the previously characterized alkaloid (−)-isopiline (**6**) (1), which we also found to be present in *P. acuminata*.

The location of the phenolic group in (−)-norliridinine (**1**) and (−)-3-hydroxynornuciferine (**2**) was established by comparison of their uv spectra. Both compounds exhibit a bathochromic shift in their spectra in basic solution due to the presence of the phenolic functions. But compound **2** also shows a hyperchromic effect at 315 nm, while **1** furnishes no such phenomenon. It is known that mono-

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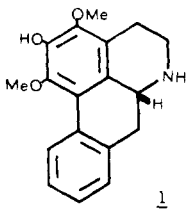
phenolic aporphines possessing the hydroxyl function at C–9 display a bathochromic, as well as hyperchromic, effect in their uv spectra upon addition of base (2). It was, therefore, not surprising to find that an aporphine with a phenolic group at the corresponding position in ring A, *i.e.*, at C–3, exhibits a similar effect. Thus, the phenolic function in **2** must be located at C–3, while the hydroxyl is at C–2 in species **1**.



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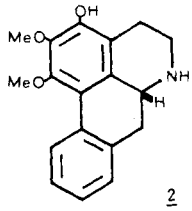

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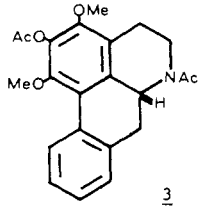

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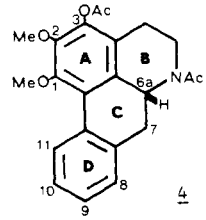

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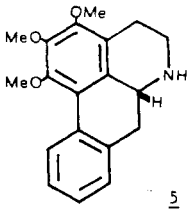

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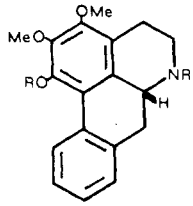
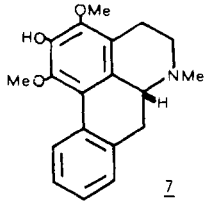


6, R = H

6A, R = Ac



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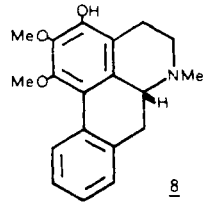

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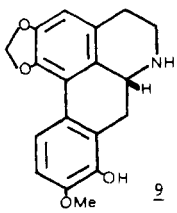

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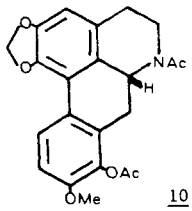

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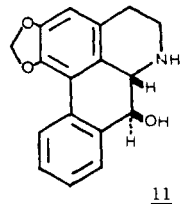

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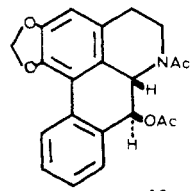

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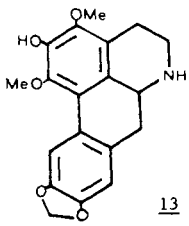

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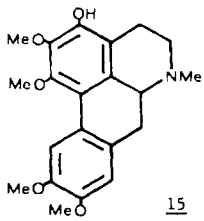

15

14, as in 13 but 2-methoxy-3-hydroxy

16, as in 15 but 2-hydroxy-3-methoxy

To complete the characterization of alkaloids **1** and **2**, formaldehyde and formic acid were used to *N*-methylate the two compounds to give the known natural product (−)-liridinine (**7**) (3) and the semi-synthetically known (−)-3-hydroxynuciferine (**8**), (4) respectively. An important point to be made here is that the structure of (−)-liridinine (**7**) was uncertain previous to the present correlation, since it was not known if the phenol was located at C–1 or C–2. The

chemical interrelation of (−)-norliridinine with (−)-liridinine achieved here firmly establishes the latter to be represented by expression **7**. Additionally, the alkaloid (−)-lirinine, which is a dimethoxymonohydroxyaporphine known to be present in a *Liriodendron* species and previously of uncertain structure concerning the exact location of its substituents, (5) corresponds in its nmr spectrum with semi-synthetic (−)-3-hydroxynuciferine (**8**), and these materials are indeed identical.

Turning now to the third new alkaloid, the phenol (−)-norannuradhapurine (**9**), $C_{18}H_{17}O_4N$, it was established that the circular dichroism (cd) curve exhibits a positive tail near 216 nm, so that the compound possesses the R configuration, as indicated. (6).

The nmr spectrum of (−)-norannuradhapurine (**9**) includes a methoxyl singlet at δ3.93, and a methylenedioxy absorption appearing as a doublet of doublets at δ5.94 and 6.08 ($J=1.5$ Hz). The aromatic region of the spectrum shows a singlet at δ6.55 representing H–3, and a doublet of doublets at δ6.82 and 7.64 ($J=8.5$ Hz) for H–10 and H–11, respectively. The uv spectrum of **9** with a maximum at 281 nm undergoes a bathochromic shift in base due to the presence of the phenolic group. However, no hyperchromic effect is observed, indicating that the phenol is at C–8 rather than C–9. Acetylation of (−)-norannuradhapurine (**9**) afforded the diacetyl derivative (**10**).

The fourth new aporphine from *P. acuminatum* is (+)-noroliveroline (**11**), $C_{17}H_{15}O_3N$. The mass spectral molecular ion is m/z 281, and the base peak is m/z 280. The nmr spectrum includes a broad doublet at δ4.74 ($J=9.2$ Hz) representing H–7. The large coupling constant points to the fact that H–7 and H–6a must be in a trans relationship to each other. Other features of the spectrum are a doublet of doublets at δ5.94 and 6.00 ($J=0.6$ Hz) for the methylenedioxy protons, a singlet at δ6.57 (H–3), a multiplet centered at δ7.35 (H–9 and H–10), another multiplet at δ7.70 (H–8), and a downfield multiplet at δ8.02 (H–11). The cd curve has a positive tail near 210 nm, indicating the R configuration. Finally, (−)-noroliveroline (**11**) affords N,O-diacetylnoroliveroline (**12**) upon acetylation with acetic anhydride in pyridine.

With the above establishment of the position of the phenolic function in (−)-norliridinine (**1**) and (−)-3-hydroxynornuciferine (**2**), and the clarification of the structures of (−)-liridinine (**7**) and (−)-lirinine (**8**), it becomes possible to locate with certainly the position of a phenolic group on ring A of an aporphine, provided the nmr spectrum as well as the uv spectra in neutral and basic solution are recorded. A case in point concerns the recently isolated aporphine xyloguyelline for which structures **13** and **14** were considered, but for which a preference for **13** was enunciated (7). A related instance is that of O-demethylpurpureine, for which alternate structures **15** and **16** were presented (8).

EXPERIMENTAL

STANDARD EXPERIMENTAL CONDITIONS.—Nmr spectra are in $CDCl_3$ solution. Uv spectra and cd curves were collected in methanol solution. Tlc was on Merck Silica Gel F–254 glass plates. All compounds obtained are amorphous.

PRELIMINARY FRACTIONATION.—The dried bark and leaves of *P. acuminata* (17 kg) were extracted with ethanol at room temperature. The solvent was evaporated, and the residue dissolved in 5% hydrochloric acid. The solution was filtered and extracted with chloroform. The organic layer was separated, dried, and evaporated to an oil (12 g). Preliminary fractionation was carried out on a column of neutral alumina, elution being with methylene chloride-methanol. Four groups were thus obtained. Group I was composed of non-alkaloidal material, groups II and III included non-phenolic alkaloids, and group IV contained the phenolic alkaloids.

FRACTIONATION OF GROUP II.—Fractionation of group II was on a silica gel column, using methylene chloride-methanol. Further purification was by tlc. The alkaloids thus obtained were *O*-methylmoschatoline (≡liridine) (5 mg), liriodenine (4 mg), (−)-3-methoxynuciferine (8 mg), (−)-*O*-methylisopiline (7 mg), and (+)-stepharine (4 mg).

FRACTIONATION OF GROUP III.—The same procedure was used as for group II above, and the following alkaloids were obtained: (−)-*O*-methylisopiline (4 mg), (−)-nornuciferine (6 mg), 2-methyltetrahydro-β-carboline (9 mg), (+)-stepharine (3 mg), and *N*,*N*-dimethyltryptamine (6 mg).

FRACTIONATION OF GROUP IV.—The same procedure was used as for group II to provide: (±)-syringaresinol (19 mg), (−)-kikemanine (4 mg), (−)-stepholidine (4 mg), (+)-isoboldine (2 mg), (−)-isopiline (2 mg), (−)-asimilobine (21 mg), (−)-norannuradhapurine (2 mg), (−)-norliridinine (14 mg), (−)-3-hydroxynornuciferine (27 mg), (−)-caaverine (1 mg), (−)-noroliveroline (18 mg), (±)-juziphine (6 mg), (+)-reticuline (5 mg), (−)-tuduranine (2 mg), (−)-norushinsunine (2 mg), (±)-*N*-methylcoclaurine (2 mg), (±)-norjuzipine (2 mg), (±)-coclaurine (4 mg), hordenine (5 mg), (±)-tetrahydroharman (1 mg), and (−)-anolobine (2 mg).

(−)-NORLIRIDININE (**1**).—$C_{12}H_{19}O_3N$; λ max 230 sh, 274, 282 sh, 304 sh nm (log ε 4.05, 3.95, 3.89, 3.38); λ min 248 nm (log ε 3.57); λ max MeOH–OH^- 218 sh, 231 sh, 252, 276, 290 sh, 326 nm (log ε 4.10, 3.98, 4.00, 3.84, 3.76, 3.28); λ min MeOH–OH^- 240, 272, 308 nm (log ε 3.95, 3.83, 3.24); ms *m/z* 297 (M^+, 54), 296 (100), 282 (17), 280 (21), 266 (19), 250 (13), 236 (7), 165 (9), 152 (4), 149 (7); cd Δε(nm), 0(318), +3.9(273), 0(254), −38(238), 0(224), +16(215); R_f 0.54 diethylamine-chloroform (1:9 v/v).

(−)-*N*,*O*-DIACETYLNORLIRIDINE (**3**).—Acetylation of **1**, as all others in this work, was with acetic anhydride in pyridine at room temperature overnight; $C_{22}H_{23}O_5N$; nmr (360 MHz) δ2.16 and 2.33 (2s, 3H, $NCOCH_3$), 2.42 (s, 3H, $OCOCH_3$), 3.58 and 3.80 (2s, 6H, 2 x OCH_3), 7.21–7.36 (m, 3H, H-8,9,10), 8.28–8.36 (m, 1H, H-11); ms *m/z* 381 (M^+, 0.3), 349 (20), 309 (33), 308 (26), 307 (100), 280 (18), 268 (32), 267 (81), 265 (49), 251 (17); R_f 0.42 methanol-chloroform 2:98.

O-METHYLATION OF **1** AND **2**.—Solutions of **1** and **2**, in methanol, were treated with ethereal diazomethane for three days near 5° (standard conditions), to give (−)-*O*-methylisopiline (**5**) in about 80% yield; $C_{19}H_{21}O_3N$; nmr (200 MHz) δ3.74 (1s, 3H, C-1 OCH_3), 3.92 and 3.96 (2s, 6H, 2 OCH_3), 7.20–7.30 (3H, m, H-8,9,10), 8.28 (d, 1H, J_A=8.5 HI, H-11); ms *m/z* 311 (M^+, 57), 310 (100), 309 (66), 296 (26), 294 (29), 280 (41), 279 (26), 251 (22), 236 (21), 169 (25), 149 (52); R_f 0.29 methanol-chloroform 1:9.

N-METHYLATION OF **1**.—This was achieved by refluxing 15 h with formaldehyde and formic acid to provide (−)-liridinine (**7**) in 76% yield, $C_{19}H_{21}O_3N$, nmr (360 MHz) δ2.60 (s, 3H, NCH_3), 3.63 and 3.91 (2s, 6H, 2 x OCH_3), 7.20–7.33 (m, 3H, H-8,9,10), 8.23 (d, 1H, J_A=7.3 Hz, H-11); R_f 0.36 methanol-chloroform 5:95.

(−)-3-HYDROXYNORNUCIFERINE (**2**).—$C_{18}H_{19}O_3N$; λ max 219, 240 sh, 280, 292 sh nm (log ε 4.39, 3.90, 4.14, 4.04); λ min 250 nm (log ε 3.60); λ max MeOH–OH^- 225, 250 sh, 315 nm (log ε 4.20, 3.74, 4.17); λ min MeOH–OH^- 263 nm (log ε 3.51); ms *m/z* 297 (M^+, 60), 296 (100), 295 (33), 282 (24), 281 (14), 280 (48), 268 (14), 267 (11), 266 (21), 265 (21), 264 (13), 263 (16), 262 (12), 251 (12), 250 (17), 237 (26), 236 (12), 165 (11), 149 (12); cd Δε(nm), 0(315), +7.5(279), 0(252), −48 (240), 0(227), +29(219); R_f 0.12 diethylamine-chloroform 1:9.

(−)-*N*,*O*-DIACETYL-3-HYDROXYNORNUCIFERINE (**4**).—$C_{22}H_{23}O_5N$; nmr (200 MHz) δ2.16 and 2.22 (2s, 3H, $NCOCH_3$), 2.39 (s, 3H, $OCOCH_3$), 3.73 (1s, 3H, C-1 OCH_3), 3.92 (1s, 3H, C-2 OCH_3), 7.23–7.36 (m, 3H, H-8,9,10), 8.37 (m, 1H, H-11); ms *m/z* 381 (M^+, 32), 322 (71), 321 (46), 280 (91), 279 (43), 268 (62), 267 (100), 252 (27), 251 (27), 249 (28), 233 (22), 43 (22); R_f 0.44 methanol-chloroform 2:98.

N-METHYLATION OF **2**.—This was achieved with formaldehyde and formic acid to supply (−)-3-hydroxynuciferine (**8**) in 82% yield; $C_{19}H_{21}O_3N$; nmr (360 MHz) δ2.55 (3H, s, NCH_3), 3.72 (3H, s, C-1 OCH_3), 3.98 (3H, s, C-2 OCH_3), 7.15–7.30 (3H, m, H-8,9,10), 8.19 (1H, q, J_A= 7.8 Hz, J_B=0.8 Hz, H-11); ms *m/z* 311 (M^+, 75), 310 (100), 296 (70), 294 (58), 280 (42), 268 (38), 264 (31), 253 (15), 237 (46), 165 (10), 152 (7), 149 (7).

(−)-ISOPILINE (**6**).—$C_{18}H_{19}O_3N$; λ max 218, 267, 302 sh nm (log ε 4.43, 4.11, 3.76); λ min 243 nm (log ε 3.65); λ max MeOH–OH^- 218, 268 sh, 333 nm (log ε 4.38, 3.97, 3.67); λ min MeOH–OH^- 300 nm (log ε 3.51); nmr (200 MHz) δ3.90 and 3.97 (2s, 6H, 2 OCH_3), 7.23–7.37 (3H, m, H-8,9,10), 8.32 (d, 1H, J_A=7.6 Hz, H-11); cd Δε(nm), 0(318), +6.3(274), 0(251), −50(237), 0(224), +18 (217); R_f 0.71 diethylamine-chloroform 1:9.

(−)-*N*,*O*-DIACETYLISOPILINE (**6A**).—Obtained from acetylation of (−)-isopiline (**6**); $C_{22}H_{23}O_5N$; nmr (360 MHz) δ2.17 and 2.23 (2s, 3H, $NCOCH_3$), 2.35 (s, 3H, $OCOCH_3$), 3.89 and 3.90 (2s, 6H, 2 OCH_3), 7.22–7.36 (m, 3H, H-8,9,10), 7.94 (m, 1H, H-11); ms *m/z* 381 (M^+, 0.2), 292 (8), 280 (9), 269 (28), 268 (100), 236 (4), 209 (6), 165 (3), 153 (4).

(−)-NORANNURADHAPURINE (**3**).—$C_{18}H_{17}O_4N$; λ max 218 sh, 281, 298 sh, 317 sh nm (log ε 4.27, 3.87, 3.69, 3.46); λ min 256 nm (log ε 3.69); λ max MeOH–OH^- 220 sh, 258 sh, 284, 307 sh, 322 sh nm (log ε 4.22, 3.85, 3.75, 3.57, 3.49); λ min MeOH–OH^- 273 nm (3.73); ms *m/z* 311 (M^+, 44), 310 (100), 309 (28), 294 (18), 291 (17), 282 (19), 281 (30), 278 (27), 267 (18), 266 (44), 251 (12), 250 (13), 238 (12), 208 (16), 152 (14); cd Δε(nm), 0(320), +12(275), 0(255), −54(240), 0(227), +31(216); R_f 0.11 diethylamine-chloroform 1:9.

(−)-*N*,*O*-DIACETYLNORANNURADHAPURINE (**10**).—Acetylation of **3** under standard conditions afforded **10**; $C_{22}H_{21}O_6N$; nmr (360 MHz) δ2.15 and 2.22 (2s, 3H, $NCOCH_3$), 2.34 and 2.37 (2s, 3H, $OCOCH_3$), 3.86 and 3.88 (2s, 3H, OCH_3), 5.76 and 6.09 (2m, 2H, OCH_2O), 6.55 and 6.59 (2s, 1H,

H-3), 6.92 (m, 1H, H-10), 7.99 (d, 1H, J=8.2 Hz, H-11); ms m/z 395 (M^+, 36), 353 (18), 323 (22), 309 (11), 295 (14), 294 (42), 282 (40), 281 (100), 266 (16); R_f 0.44 methanol-chloroform 2:98.

(−)-NOROLIVEROLINE (11).—$C_{17}H_{15}O_3N$; λ max 233 sh, 245 sh, 265 sh, 272, 281 sh, 315 nm (log ε 4.09, 3.99, 4.01, 4.07, 3.97, 3.51); λ min 254, 301 nm (log ε 3.92, 3.40); ms m/z 281 (M^+, 92), 280 (100), 263 (73), 262 (60), 251 (44), 204 (42), 176 (52), 165 (42); cd Δε(nm), 0(299), +6.7(272), 0(252), −32(235), 0(222), positive tail near 215 nm; R_f 0.13 diethylamine-chloroform 1:9.

(−)-*N*,*O*-DIACETYLNOROLIVEROLINE (12).—Obtained by acetylation of **11** under standard conditions; $C_{21}H_{19}O_5N$, nmr (200 MHz) δ2.20 (s, 3H, $OCOCH_3$), 2.23 and 2.27 (2s, 3H, $NCOCH_3$), 6.02 and 6.13 (2m, 2H, OCH_2O), 6.25 (d, 1H, J=12.3 Hz, H-7), 6.59 and 6.63 (2s, 1H, H-3), 7.33–7.52 (m, 3H, H-8,9,10), 8.10 (m, 1H, H-11); R_f 0.59 methanol-chloroform 2:98.

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LITERATURE CITED

1. R. Hocquemiller, P. Cabalion, A. Bouquet and A. Cavé, *C.R. Acad. Sci. Paris, Serie C*, **285**, 447 (1977).
2. M. Shamma, S. Y. Yao, B. R. Pai and R. Charubala, *J. Org. Chem.*, **36**, 3253 (1971).
3. (a) A. Abdusamatov, R. Ziyaev and S. Y. Yunusov, *Chem. Nat. Compd.*, **11**, 829 (1975); (b) C.-L. Chen and H.-M. Chang, *Phytochemistry*, **17**, 779 (1978).
4. P. Wiriyachitra and M. P. Cava, *J. Org. Chem.*, **42**, 2274 (1977).
5. R. Ziyaev, A. Abdusamatov, S. Yu. Yunusov, M. R. Yagudaev and V. M. Malikov, *Khim. Prir. Soedin.*, **9**, 67 (1933). See also Ref. 3b.
6. B. Ringdahl, R. P. K. Chan, J. C. Craig, M. P. Cava and M. Shamma, *J. Nat. Prod.*, **44**, 80 (1981).
7. R. Hocquemiller, A. Cavé and A. Raharisololalao, *J. Nat. Prod.*, **44**, 551 (1981).
8. P. E. Sonnet and M. Jacobson, *J. Pharm. Sci.*, **60**, 1254 (1971).