Drug Research and Production Unit[1], Department of Pharmaceutics[2], Obafemi Awolowo University, Ile-Ife, Nigeria, and Institut für Pharmazeutische Technologie[3], Westfälische Wilhelms-Universität, Münster, Germany

New constituents of *Piper guineense* fruit and leaf

S. K. Adesina[1], A. S. Adebayo[1], S. K. O. Adesina[2], R. Gröning[3]

Received August 16, 2002, accepted November 19, 2002

Prof. S. K. Adesina, Drug Research and Production Unit, Faculty of Pharmacy, Obafemi Awolowo University, Ile-Ife, Nigeria
sadesina@oauife.edu.ng

Pharmazie 58: 423–425 (2003)

Fourteen compounds were isolated from the fruits and leaves of *Piper guineense* Schum and Thonn (Piperaceae). Two of those were regarded to be new natural compounds, *N*-pyrrolidyl-2,4-octadecadienamide and *N*-piperidyl-2,4-octadecadienamide.

1. Introduction

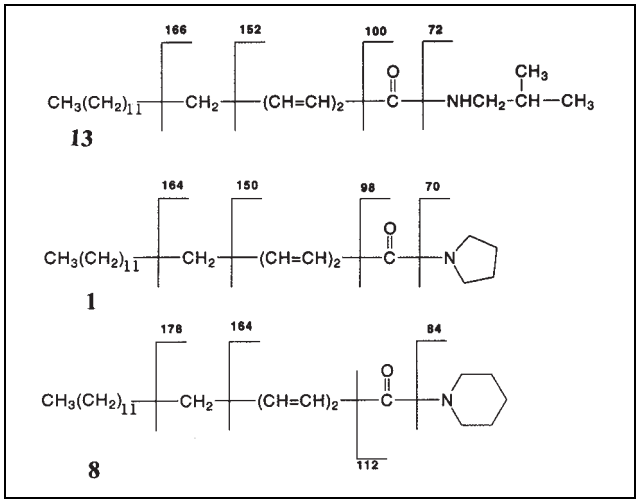
Piper guineense Schum and Thonn (Piperaceae), (syn. *P. leonense* DC and *P. famechonii* DC) is well known for its pungent and aromatic fruits which have medicinal and food value [1]. Extensive chemical investigations [2–11] of the fruit have led to the isolation of several amides, lignans and sterols, many of which exhibit remarkable biological activity. The powdered fruit and some chemical compounds isolated from the fruit have shown antimicrobial [12], insecticidal [13–16] and anticonvulsant properties [17]. The result of our work on the stem [1] led to the identification of many new compounds hitherto unreported in this plant and encouraged this re-investigation of the leaf and fruit. We now report on the occurrence of many new constituents of both the fruit and leaf.

2. Investigations, results and discussion

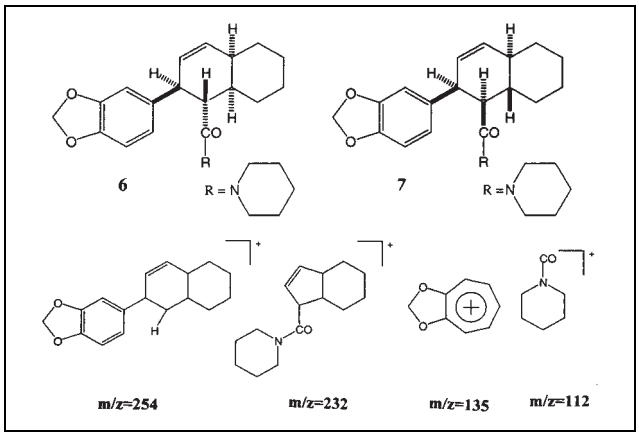
The pentane and chloroform extracts of the fruit were subjected separately to GC/MS analyses. As was observed for the pulverized stem [1], various chemical compounds including monoterpene hydrocarbons, alcohols, ketones (with $GC_{tR} = 11.39$ min–23.97 min), sesquiterpene and other terpenoid substances (with $GC_{tR} = 27.22$ min–45.57 min and mass ranges 134, 136, 204, 220, 222–236), and free fatty acids ($GC_{tR} = 47.92$ min–55.34 min, mass ranges 256–312) occurred as the major components eluted within 48 min of the elution programme. In addition to these volatile constituents, many chemical compounds identified earlier were confirmed to be present. These include the isobutylamides – pellitorine (m/z = 223, $GC_{tR} = 48.88$ min) *N*-isobutyl-2,4-dodecadienamide (m/z = 251,$GC_{tR} = 59.05$ min), 3,4-methylenedioxycinnamic acid isobutylamide (fagaramide, m/z = 247, $GC_{tR} = 59.35$ min), *N*-isobutyl-2,4-tetradecadienamide (m/z = 279, $GC_{tR} = 60.63$ min), *N*-isobutyl-2,4-hexadecadienamide (m/z = 307, $GCt_R = 66.39$ min), *N*-isobutyl-2,4-octadecadienamide {(m/z = 335, $GCt_R = 71.40$ min (**13**)}, *N*-isobutyl-2,4-eicosadienamide (m/z = 363, $GC_{tR} = 75.95$ min), Δαβ-dihydropiperlonguminine (m/z = 275, $GC_{tR} = 62.15$ min), piperlonguminine (m/z = 273, $GC_{tR} = 67.38$ min) and guineense (m/z = 383, $GC_{tR} = 95.16$ min); the pyrrolidines – trichostachine (m/z = 271, $GC_{tR} = 69.93$min), Δαβ-dihydrowisanidine (m/z = 303, $GC_{tR} = 71.22$min) and wisanidine (okolasin, m/z = 301, GC_{tR} 74.50 min): the piperidines – Δαβ-dihydropiperine (m/z = 287, $GC_{tR} = 67.74$ min), piperine (m/z = 285, $GC_{tR} = 70.38$ min), Δαβ-dihydrowisanine (m/z = 317, $GC_{tR} = 71.79$ min), wisanine (m/z = 315, $GC_{tR} = 74.80$ min), the lignan sesamin (m/z = 354, $GC_{tR} = 80.42$ min) and sterols – campesterol (m/z = 400, $GC_{tR} = 82.84$ min), stigmasterol (m/z = 412, $GC_{tR} = 83.99$) and sitosterol (m/z = 414, $GC_{tR} = 86.31$ min).

Fourteen compounds, two of which have been identified as new natural products were the new constituents of the fruit. These include *N*-pyrrolidyl-2,4-octadecadienamide (**1**), *N*-piperidyl-2,4-hexadecadienamide (**2**) which is the piperidyl analogue of *N*-isobutyl-2,4-hexadecadienamide earlier isolated from the same fruit [2] and stem [1], and its higher homologue, *N*-piperidyl-2,4-octadecadienamide (**8**). Others include the three structurally-related piperstachine alkaloids – cyclopiperstachine (**3**) cyclostachine B(**4**), cycloguineense A (**6**) and their stereoisomers, vitamins (**9, 10**) and *N*-pyrrolidyl-2,4-eicosadienamide (trichonine, **11**). Piperettine (**12**), the higher homologue of piperine earlier isolated from the stem and the lignan arctigenin methyl ether (**14**) were also identified along with *N*-piperidyl-3,4-methylenedioxycinnamoylamide (**15**) which is the *N*-piperidyl analogue of fagaramide.

Similarly, a detailed examination of the leaf chloroform extracts revealed the presence of monoterpene hydrocarbons, terpenoid substances and twenty-one other new constituents. This is a first detailed report on the constituents of the leaf. Three aliphatic amides identified included *N*-isobutyl-2, 4-decadienamide (pellitorine), *N*-isobutyl-2,4-hexadecadienamide and *N*-isobutyl-2,4-eicosadienamide. Aromatic amides identified were *N*-isobutyl-5-(3,4-methylenedioxyphenyl)-2-pentenamide (= Δαβ-dihydropiperlonguminine), *N*-isobutyl-5-(3,4-methylenedioxyphenyl)-2,4-pentadienamide (= piperlonguminine), *N*-piperidyl-5-(3,4-methylenedioxyphenyl)-2-pentenamide (= Δαβ-dihydropiperine), *N*-piperidyl-5-(3,4-methylenedioxyphenyl)-3-pentenamide (= Δβγ-dihydropiperine), *N*-pyrrolidyl-5-(2-methoxy-4,5-methylenedioxyphenyl)-2-pentaenamide-(Δαβ-dihydrowisanidine), *N*-piperidyl-5-(2-methoxy-4,5-



The fragmentation patterns of *N*-isobutyl-2,4-octadecadienamide (**13**), *N*-pyrrolidyl-2,4-octadecadienamide (**1**) and *N*-piperidyl-2,4-octadecadienamide (**8**)



The fragmentation patterns of *Cycloguineense* A (**6**) and *Cycloguineense* B (**7**)

methylenedioxyphenyl)-2-pentenamide (= Δαβ-dihydrowisanine, *N*-pyrrolidyl-5-(3,4-methylenedioxyphenyl)-2,4-pentadienamide (trichostachine), *N*-piperidyl-5-(3,4-methylenedioxyphenyl)-2,4-pentadienamide (= piperine), *N*-pyrrolidyl-5-(2-methoxy-4,5-methylenedioxyphenyl-2,4-pentadienamide (= wisanidine = okolasin = 6-methoxy trichostachine) and *N*-piperidyl-5-(2-methoxy-4,5-methylenedioxyphenyl)-2,4-pentadienamide (wisanine). Other new constituents of the leaf included the lignans sesamin and arctigenin methyl ether, vitamin E, campesterol, stigmasterol and sitosterol which were also identified from the fruit extracts.

These structures were readily deduced from their fragmentation patterns, and retention times, the structure of their hydrogenated products and their chromatographic behaviour. The discovery of pyrrolidyl, isobutyl and piperidyl derivatives of octadeca-2,4-dienoic acid in the fruit is interesting as these derivatives of two lower homologues of this compound, that is, deca-2,4-dienoic and dodeca-2,4-dienoic were found to occur in the stem part [1]. As would be expected in oil bearing plants, aliphatic acid amide derivatives seem to occur more in *Piper guineense* fruit than in the stem and leaf.

The various fruit samples collected in October/November 1995, June 1996 and April/May 2001 and examined under similar conditions gave similar patterns/profiles of constituents thus ruling out the issue of variation due to the time of collection. There could, however, be variations in the concentration of individual compounds. The accumulation of a large number of amide alkaloids, in *Piper guineense* fruit and stem will continue to be of immense value in the protection and preservation of some selected farm products from insect infestation or attack since these insecticidal components are well distributed in the fruit, stem and leaf.

3. Experimental

3.1. Plant material

Piper guineense fruit was sourced routinely from a plant identified earlier as Ife Herb 264 [1]. Collection of the fruits occurred in October/November 1995, June 1996 and April/May 2001.

3.2. Apparatus, methods

The general experimental procedures were as described for *Piper guineense* stem [1]. Preliminary screening was achieved by GC/MS investigation of extracts. Freshly-collected fruits (200 g) were milled and covered with methanol (A.R. grade 1 L) with shaking and extracted overnight at RT. Further processing [1] led to the recovery of a pentane extract residue (8.2 g) and a $CHCl_3$ extract residue (8.4 g), parts of which were separately subjected to GC/MS analysis.

For the isolation of compounds, milled fruit (2.38 kg) was exhaustively extracted in MeOH for 72 h in the dark and was processed further to MeOH residue (211.36 g). This residue was processed further [1] to leave a viscous, oily $CHCl_3$ residue (58.3 g). Portions of this were chromatographed and analyzed into six fractions, PgfrO1-PgfrO6. The general isolation and identification procedures including spectroscopic analysis, catalytic hydrogenation, co-chromatography and alkaline hydrolysis were also as described previously [1].

3.3. Compounds characterized

3.3.1. N-piperidyl-3,4-methylenedioxycinnamoylamide (**15**)

Detected in $PgfrO_4$. $GC_{tR} = 65.21$ min – EIMS (m/z, % int.): 259 (M^+, 48), 258 (M^+-H, 15), 175 (M^+-Piperidyl, 61), 174 (26), 147 (12), 145 (M^+-2 H–CO-Piperidyl, 48), 135 (100), 117 (20), 113 (15), 89 (27), 84 (16), 77 (18). New constituent of the fruit but previously isolated from *Piper novae-hollandiae* [22]. Catalytic hydrogenation gave a product, $GC_{tR} = 59.70$ min – EIMS (m/z, % int.): 261 (M^+, 55), 260 (M^+-1, 10), 232 (4), 204 (6), 175(8), 149 (M^+-CO-piperidyl, 12), 148 (M^+-CO-piperidyl-H, 100), 147 (27), 135 (50), 126 (M^+-135, 91), 112 (5), 91 (33), 84 (18), 77 (29).

3.3.2. N-pyrrolidyl-2,4-octadecadienamide (**1**)

Detected as a minor component in fraction PgfrO3. $GC_{tR} = 71.05$ min – EIMS (m/z, % int.): 333 (M^+, 7), 318 (1), 305 (12), 304 (7), 262 (6), 234 (6), 206 (6), 192 (9), 178 (17), 164 (18), 152 (20), 150 {–(CH=CH)$_2$–CO-pyrrolidyl, 100}, 124 (–CH=CH–CO-pyrrolidyl, 10), 113 {–$(CH_2)_7CH_3$, 30}, 98 (CO-pyrrolidyl, 20), 70 (pyrrolidyl, 18), 15 (12). Like trichonine (**11**), it gave a key fragment at m/z 150. It gave a hydrogenated product $GC_{tR} = 7.78$ min – EIMS (m/z, % int.): 337 (M^+, 2), 126 (CH_2)$_2$–CO-pyrrolidyl, 23), 113 (–CH_2–CO-pyrrolidyl + H, 100), 98 (CO-pyrrolidyl, 17), 85 (6), 72 (15), 70 (pyrrolidyl, 24), 55 (12).

3.3.3. N-piperidyl-2,4-hexadecadienamide (**2**)

Obtained also as a minor component of the fruit, detected in $PgfrO_4$. $GC_{tR} = 71.72$ min – EIMS (m/z, % int.): 319 (M^+, 25), 290 (M^+-CH_2CH_3, 5), 276 (6), 262 (10), 248 (12), 234 (11), 220 (M^+-$CH_3(CH_2)_6$–, 11), 206 (24), 192 (M^+-$CH_3(CH_2)_8$–, 100), 178 (44), 164 {–(CH=CH)$_2$–CO-piperidyl, 92}, 150 (36), 138 (–CH=CH–CO-piperidyl, 98), 127 (31), 112 (CO-piperidyl, 20), 84 (piperidyl, 59). Its hydrogenated product had a $GC_{tR} = 68.04$ min – and had major ions at m/z 323 (M^+, 2,) 140 (–$(CH_2)_2$–CO-piperidyl, 25), 127 (M^+-$(CH_2)_{13}$–CH_3 + H, 100), 112 (CO-piperidyl, 35), 84 (piperidyl, 25). It is a known constituent of the stem [1].

3.3.4. Cyclopiperstachine (**3**)

Identified in PgfrO4. $GC_{tR} = 71.98$ min – EIMS (m/z, % int.): 355 (M^+, 100), 282 (M^+-$NHCH_2$–CH–$(CH_3)_2$–H, 16), 255 (M^+-CO-isobutyl, 44), 256 (28), 254 (53), 220 (55), 201 (7), 152 (31), 148 (33), 135 (86), 121 (46), 115 (34), 91 (45), 103 (22), 79 (22). Analytical data identical with literature [1, 19]. Furnished a hydrogenated product with $GC_{tR} =$ 69.98 min and EIMS [m/z, % int.]: 357 (M^+, 60), 222 (100), 223 (12), 204 (7), 136 (16), 135 (31), 123 (31), 115 (12), 72 (6) as expected. It is a new constituent of the fruit.

3.3.5. Cyclostachine B (**4**)

Detected in PgfrO4. $GC_{tR} = 73.96$ min – EIMS (m/z, % int.): 353 (M^+, 60), 323 (25), 254 (M^+-CO-pyrrolidyl, 12), 255 (12), 252 (15), 240 (20), 228 (34), 218 (100), 150 (21), 135 (46), 98 (CO-pyrrolidyl, 42), 70 (pyrrolidyl, 23), 55 (20). Mass spectral data identical with published data [19]. Known component of the stem, furnished a hydrogenated product, EIMS (m/z, % int.): 355 (M^+, 97) as expected.

3.3.6. Cyclostachine A (**5**)

Detected in PgfrO4. $GC_{tR} = 75.03$ min – EIMS (m/z, % int.): 353 (M^+, 100), 323 (5), 282 (10), 270 (22), 255 (30), 254 (M^+-CO-pyrrolidyl, 65), 240 (27), 218 (62), 212 (22), 150 (25), 135 (62), 98 (CO-pyrrolidyl, 52), 70 (pyrrolidyl, 20), 55 (30). First report in this fruit. Mass spectral data identical with literature [1, 19]. Furnished a hydrogenated product $GC_{tR} = 74.41$ min – EIMS (m/z, % int.): 355 (M^+, 100), 284 (3), 257 (19), 256 (94), 242 (4), 220 (55), 214 (20), 135 (63), 98 (26), 70 (31), 55 (26). Cyclostachine A and B are isomers.

3.3.7. Cycloguineense A (**6**)

Component of fraction PgfrO4. $GC_{tR} = 75.47$ min – EIMS (m/z, % int.): 367 (M^+, 100), 368 ($M^+ + 1$, 19) 337 (10), 255 (12), 254 (M^+-CO-piperidyl, 32), 240 (34), 232 (80), 228 (35), 138 (33), 135 (54), 127 (26), 112 (CO-piperidyl, 68), 86 (25), 84 (piperidyl, 38), 69 (33). Mass spectral pattern as reported [1]. It is a new natural product with the piperidine moiety substituting for the pyrrolidine moiety in cyclostachine and the isobutyl group in cyclopiperstachine. Had a hydrogenated product with $GC_{tR} = 74.21$ min and major ions at m/z 369 (M^+, 62), 256 (6), 235 (17), 234 (100), 140 (43), 135 (30), 27 (23), 112 (43), 86 (38), 84 (23).

3.3.8. Cycloguineense B (**7**)

Detected in PgfrO4. $GC_{tR} = 76.20$ min – EIMS (m/z, % int.): 367 (M^+, 100), 368 ($M^+ + 1$, 34), 324 (4), 284 (13), 255 (M^+-CO-piperidyl + H, 30), 254 (M^+-CO-piperidyl, 85), 240 (25), 232 (60), 212 (20), 164 (22), 152 (13), 135 (65), 112 (CO-piperidyl, 57), 103 (13), 84 (piperidyl, 28), 69 (28). Isomeric to the compound eluted at $GC_{tR} = 75.47$ min and identified as cycloguineense A, a new natural product earlier described from the stem [1]. Its hydrogenated product had a $GC_{tR} = 75.68$ min with major ions occurring at m/z 369 (M^+, 60), 257 (21), 256 (100), 234 (30), 214 (10), 154 (19), 135 (41), 127 (47), 112 (15), 103 (23), 84 (15) as expected. These fragmentation patterns for (**6**) and (**7**) are consistent with the scheme of Joshi et al. [19] displayed in this paper.

3.3.9. N-Piperidyl-2,4-octadecadienamide (**8**)

Component of fraction PgfrO4. $GC_{tR} = 76.56$ min – EIMS (m/z, % int.): 347 (M^+, 22), 248 {M^+-$CH_3(CH_2)_6$–, 11}, 235 (12), 234 {M^+-$CH_3(CH_2)_7$–, 11}, 220 {M^+-$CH_3(CH)_8$–, 21}, 206 {M^+-$CH_3(CH_2)_9$–, 20}, 192 {M^+-$CH_3(CH_2)_{10}$–, 83}, 178 (37), 164 {(CH=CH)$_2$–CO-piperidyl, 86}, 150 (50), 138 (CH=CH–CO-piperidyl, 100), 127 (60), 112 (CO-piperidyl, 47) 84 (piperidyl, 77), 55 (17). It is a new natural product identified as the piperidyl analogue of the known isobutyl-2,4-octadecadienamide (**13**) earlier isolated from this source [3]. Its hydrogenated product had $GC_{tR} = 72.73$ min with major ions at m/z 351 (M^+, 3), 220 (3) 196 (5), 182 (4), 141 (5), 140 (23), 127 (100), 112 (CO-piperidyl, 46), 86 (17), 84 (20), 70 (25).

3.3.10. Gamma-tocopherol (vitamin E) (**9**)

Isolated in PgfrO1: $GC_{tR} = 77.65$ min – EIMS (m/z % int.): 416 (M^+, 13) 417 ($M^+ + 1$, 2), 191 (18), 152 (15), 151 (100), 113 (5), 81 (12), 69 (12), 55 (20). Spectroscopic data and chromatographic behaviour identical with the reference synthetic sample obtained commercially.

3.3.11. Alpha-tocopherol (= 5,7,8-trimethyltocol, vitamin E) (**10**)

Identified in PgfrO1. $GC_{tR} = 80.57$ min – EIMS (m/z, % int.): 430 (M^+, 15), 285 (2), 205 (10), 166 (10), 165 (100), 121 (4), 90 (4), 69 (6). Mass spectral pattern and chromatographic behaviour identical with the sample obtained commercially.

3.3.12. N-Pyrrolidyl-2,4-eicosadienamide (= trichonine) (**11**)

Component of $PgfrO_3$ $GC_{tR} = 81.73$ min – EIMS (m/z, int.): 361 (M^+, 19), 346 (M^+-CH_3, 3), 304 {M^+-$CH_3(CH_2)_3$–, 4}, 234 {M^+-$CH_3(CH_2)_8$–, 12}, 220 {M^+-$CH_3(CH_2)_9$–, 12}, 178 {M^+-$CH_3(CH_2)_{12}$–, 18}, 164 {M^+-$CH_3(CH_2)_{13}$, 25}, 150 for {(CH=CH)$_2$–CO-pyrrolidyl, 100), 113 (for $CH_3(CH_2)_7$–, 85), 55 (17). Its hydrogenated product had a major ion at m/z 365 and in agreement with that published [20]. It is a new constituent of the fruit.

3.3.13. Piperidyl-7-(3,4-methylenedioxyphenyl)-hepta-2,4,-6-trienamide (= piperettine) (**12**)

Isolated in PgfrO3. $GC_{tR} = 83.79$ min – EIMS (m/z, % int.): 311 (M^+, 22), 227 (M^+-piperidyl, 24), 226 (M^+-piperidyl-H, 73), 225 (14), 199 (M^+-CO-piperidyl, 40), 198 (20), 169 (67), 141 (100), 115 (78), 112 (16), 84 (23). It is a new constituent of the fruit earlier identified from the stem [1]. It gave a hydrogenated product with $GC_{tR} = 72.16$ min and major ions at EIMS (m/z, % int.): 317 (M^+, 14), 232 (6), 182 (34), 148 (32), 140 (66), 135 (59), 127 (100), 112 (CO-piperidyl, 66), 86 (41), 84 (23), 77 (32), 70 (35), 60 (22) as expected.

3.3.14. Arctigenin methyl ether (**14**)

Detected in PgfrO5. $GC_{tR} = 90.08$ min – EIMS (m/z, % int.): 386 (M^+, 10), 354(3), 203 (12), 177 (13), 161 (16), 152 (20), 151 (100), 149 (68), 135 (48), 121 (16), 107 (12), 91 (12), 77 (19), 71 (24), 55 (20). New constituent of the fruit unaffected by hydrogenation experiments. A known lignan with a 2,3-bis(substituted benzyl)-butyrolactone unit previously isolated from *Zanthoxylum lemairie* [21].

Acknowledgements: Thanks are due to the Obafemi Awolowo University, Ile-Ife for financial support (URC Grant No. 1427 EI), to the DAAD for a fellowship to SKA and to the Institutes for Pharmaceutical Chemistry and Organic Chemistry, Westfälische Wilhelms-University, Münster, for GC/MS and other laboratory facilities.

References

1 Adesina, S. K.; Adebayo, A. S.; Adesina, S. K. O.; Gröning, R.: Pharmazie **57**, 622 (2002)
2 Okogun, J. I.; Ekong, D. E. U.: J. Chem. Soc. Perkin **1**, 2195 (1974)
3 Tackie, A. N.; Dwuma-Badu, D.; Ayim, J. S. K.; El Sohly, H. N.; Knapp, J. E.; Slatkin, D. J.; Schiff, P. L.: Phytochemistry **14**, 1888 (1975)
4 Dwuma-Badu, D.; Ayim, J. S. K.; Dabra, T. T.; El Sohly, H. N.; Knapp, J. E.; Slatkin, D. J.; Schiff, P. L. Jr.: Lloydia **38**, 343 (1975)
5 Dwuma-Badu, D.; Ayim. J. S. K..; Dabra, T. T.; El Sohly, H. N.; Knapp, J. E.; Slatkin, D. J.; Schiff, P. L. Jr.: Lloydia **39**, 60 (1976)
6 Dwuma-Badu, D.; Ayim, J. S. K.; Dabra, T. T.; El Sohly, H. N.; El Sohly, M. A.; Knapp, J. E.; Slatkin, D. J.; Schiff, P. L. Jr.: Phytochemistry **15**, 822 (1976).
7 Sondengam, B. L.; Kimbu, S. F.; Connolly, J. D.: Phytochemistry **16**, 1295 (1977)
8 Okogun, J. I.; Sondengam, B. L.; Kimbu, S. F.: Phytochemistry **16**, 1295 (1977)
9 Addae-Mensah, I.; Torto, F. G.; Oppong, I. V.; Baxter, I.; Sanders, J. K. M.: Phytochemistry **16**, 483 (1977)
10 Sondengam, B. L.; Kimbu, S. F.: Tetrahedron Lett. **I**, 69 (1977)
11 Sondengam, B. L.; Kimbu, S. F.; Njimi, T.; Okogun J. I.; Ekong, D. E. U.: Tetrahedran Lett. **4**, 367 (1977)
12 Mitscher, L. A.; Leu, R.; Bathala, M. S.; Wu, W.; Beal, J. L.: Lloydia **35**, 157 (1972)
13 Jacobson, M. in: M. Jacobson and D. G. Crosby (Eds), Naturally Occurring Insecticides, p. 139, Mercel Decker Inc. New York 1971
14 Olaifa, J. I.; Erhun, W. O.: Insect. Sci. Application **9**, 55 (1988)
15 Su Helen, C. F.; Sondengam, B. L.: J. Ga. Ent. Soc. **15**, 47 (1980)
16 Oji, O.: Fitoterapia **62**, 179 (1991)
17 Abila, B.; Richens, A.; Davies, J. A.: J. Ethnopharmacol. **39**, 113 (1993)
18 Gbewonyo, W. S.; Candy, D. J.: Toxicon **30**, 1037 (1992)
19 Joshi, B. S.; Viswanathan, N.; Gawad, D. H.; Balakrishnan, V.; von Phillipsborn, W: Helv. Chim. Acta **58**, 2295 (1975)
20 Singh, J.; Dhar, K. L.; Atal, C. K.: Tetrahedron Lett. **24**, 2119 (1971)
21 Adesina, S. K.; Olugbade, T. A.; Akinwusi, D. D.; Bergenthal, D.: Pharmazie **52**, 720 (1997)
22 Loder, J. W.; Moorhouse, A.; Russell, G. B.: Aust. J. Chem. **22**, 1531 (1969)