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Winston F. Tinto, Patrick K. Jagessar, Patrick Ketwaru, William F. Reynolds, and Stewart McLean

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CONSTITUENTS OF *TRICHILIA SCHOMBURGKII*

WINSTON F. TINTO, PATRICK K. JAGESSAR, PATRICK KETWARU,

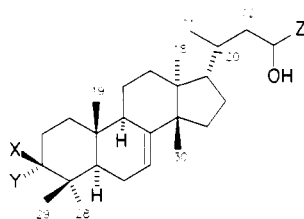*Centre for Natural Products Chemistry, University of Guyana, Georgetown, Guyana*

WILLIAM F. REYNOLDS, and STEWART MCLEAN*

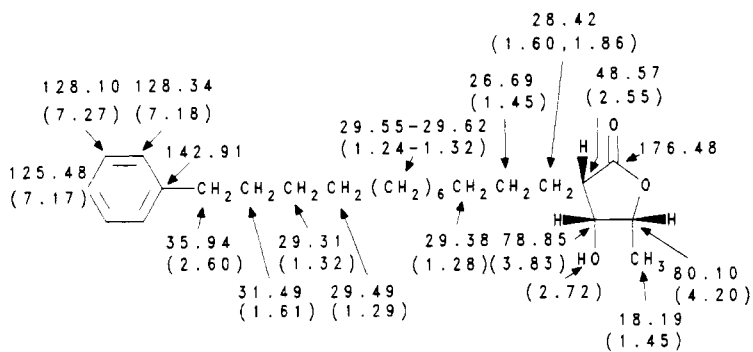*Department of Chemistry, University of Toronto, Toronto M5S 1A1, Canada*

ABSTRACT.—From *Trichilia schomburgkii*, we have isolated three protolimonoids (niloticin, dihydroniloticin, and piscidinol A), the limonoid 7-deacetoxy-7-oxogedunin, phytosterols, and the new compounds 2,3,4-trihydroxypregnan-16-one [9] and 2-(13-phenyltridecyl)-3-hydroxy-4-methylbutanolide [7]. Two-dimensional nmr spectroscopy has been used to establish the structures of the new compounds and to characterize the limonoid and protolimonoids.

Trichilia schomburgkii C. DC. (Meliaceae) is endemic to Guyana where it is a common subdominant forest tree in the near interior. From the leaves we have isolated three protolimonoids to which we have assigned structures **1–3**. Mulholland and Taylor (1) have reported the isolation of the same three protolimonoids from African *Turraea nilotica* (Meliaceae). From the bark we obtained the hydroxybutanolide **7**, closely related to the grandinolides described by Viera *et al.* (2) as constituents of *Iryanthera grandis* (Myristicaceae). The stems afforded the same butanolide **7**, a known limonoid, 7-deacetoxy-7-oxogedunin [**8**] (3,4), a novel steroid, 2,3,4-trihydroxypregnan-16-one [**9**], and phytosterols; the same constituents, except for **8**, were found in the roots. Each of the compounds isolated was investigated by standard spectroscopic methods, and 2D nmr spectroscopy was used to elucidate structures where these were not readily apparent from earlier data (5,6).
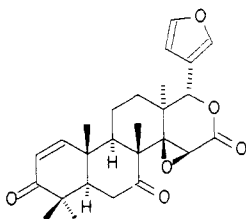
PROTOLIMONOIDS.—After the routine spectroscopic data for the three compounds isolated from the leaves had been collected, the long-range ^{1}H-^{13}C shift-correlated spectra of **1** and **3** were obtained. Our procedures for obtaining and analyzing these spectra have been described in detail previously (5,6). Sufficient cross peaks were obtained to assign the structures with a high degree of confidence, and the results are

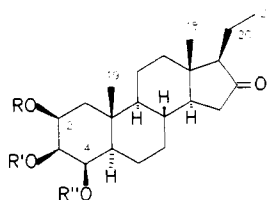**1** X+Y=O, Z =-CH-CMe$_2$ (with O)

2 X=OH, Y=H, Z =-CH-CMe$_2$ (with O)

3 X+Y=O, Z =-CH-CMe$_2$ (with OH OH)

4 X=H, Y=OH, Z =-CH-CMe$_2$ (with OH OH)

5 X=OH, Y=H, Z =-CH-CMe$_2$ (with OH OH)

6 X+Y=O, Z=-CH-CMe$_2$ (with OH Cl)

28.42
(1.60,1.86)

26.69   48.57
(1.45)   (2.55)

128.10 128.34
(7.27) (7.18)

29.55-29.62   O
(1.24-1.32)   H   176.48

142.91

125.48   O
(7.17)   CH₂ CH₂ CH₂ CH₂ (CH₂)₆ CH₂ CH₂ CH₂

35.94   29.31   29.38 78.85   H
(2.60)   (1.32)   (1.28)(3.83) HO   CH₃ 80.10
                                          (4.20)
31.49 29.49   (2.72)
(1.61) (1.29)   18.19
                                    (1.45)

7

8

9   R=R'=R″=H
10   R=R″=H; R'=Ac

condensed in Table 1, which lists assigned ¹H and ¹³C resonances. A complete shift-correlated spectrum was not obtained with the small amount of 2 available, and the structural and spectroscopic assignments for this compound are based on comparisons with 1 and 3 and with related compounds. Relatively few stereochemical assignments can be based solely on the data we have presented. Where vicinal ¹H-¹H coupling constants can be determined at sites in the polycyclic nucleus, the stereochemistry is clearly established. However, as others have done (1–4), we have assumed that the protolimonoids are derived from tirucallane; very recently, the absolute stereochemistry of hispidol B has been established unequivocally (7).

These protolimonoids or very closely related compounds have been reported several times previously, and they appear to occur in both the Meliaceae and the Rutaceae with a worldwide distribution. However, investigators have not always recognized the probable identity of their compounds with those described previously, and a certain amount of confusion in nomenclature has resulted. Mulholland and Taylor (1) obtained **1–3** from *Tu. nilotica* and named **1** niloticin and the others as its derivatives. Among the triterpenoids that Jolad *et al.* (8) isolated from Peruvian *Trichilia hispida* were hispidol A and hispidol B, to which they assigned structures **4** and **5**, respectively; configurational assignments were also made to centers in the side chain. In their investigation of Australian *Flindersia bourjotiana* (Rutaceae), Breen *et al.* (9) isolated a number of oxygenated tirucallane derivatives, including bourjotinolone C [**6**], which could be converted chemically to **1**; they postulated that the epoxide **1** was the true natural product and that **6** was an artifact of the isolation procedure. Purushothanan *et al.* (10) have assigned structures **3** and **5** to constituents of Indian *Walsura piscidia* (syn. *Walsura trifoliata*, *Trichilia coriaceae*, etc.) (Meliaceae) that they have named piscidinol A and piscidinol B, respectively. Compounds **1–3** and **5** have recently been identified among the protolimonoids of *Phellodendron chinense* (Rutaceae) (11).

7-DEACETOXY-7-OXOGEDUNIN.—The extract of the stems afforded a substance, mp 261–263°. One-, two-, and three-bond connectivities were determined from the

TABLE 1.   Assigned ^{13}C and ^{1}H Chemical Shifts for Compounds **1–3**.

Position		Compound						
		1			**2**		**3**	
	$n_H{}^a$	$\delta_C{}^b$	$\delta_H{}^c$	n_H	δ_C	n_H	δ_C	δ_H
1	2	38.47	1.44, 1.96	1	37.20	2	38.47	1.47, 1.91
2	2	34.85	2.22, 2.74	2	27.68	2	34.88	2.25, 2.76
3	0	216.80	—	1	79.24	0	217.09	—
4	0	47.80	—	0	38.96	0	47.83	—
5	1	52.26	1.70	1	50.62	1	52.24	1.72
6	2	24.29	<2.08>	2	23.94	2	24.29	<2.09>
7	1	117.91	5.29	1	118.05	1	117.86	5.31
8	0	145.64	—	0	145.57	0	145.70	—
9	1	48.39	2.25	1	48.92	1	48.38	2.27
10	0	34.94	—	0	34.94	0	34.95	—
11	2	18.19	<1.54>	2	18.09	2	18.24	<1.57>
12	2	33.52	1.61, 1.80	2	33.72	2	33.70	1.63, 1.82
13	0	43.48	—	0	43.59	0	43.46	—
14	0	51.15	—	0	51.19	0	51.13	—
15	2	33.93	1.47, 1.49	2	33.98	2	33.93	1.46, 1.50
16	2	28.69	1.19, 2.03	2	28.77	2	28.40	1.31, 2.00
17	1	53.20	1.54	1	53.26	1	53.73	1.49
18	3	21.71	0.79	3	21.72	3	21.99	0.82
19	3	12.72	0.98	3	13.10	3	12.75	1.01
20	1	33.46	1.36	1	33.58	1	33.59	1.39
21	3	19.84	0.93	3	19.92	3	18.84	0.92
22	2	40.60	1.39, 1.63	2	40.71	2	40.33	1.19, 1.88
23	1	69.15	3.55	1	69.31	1	69.66	4.12
24	1	68.44	2.64	1	68.44	1	74.87	3.16
25	0	60.17	—	0	60.28	0	74.30	—
26^d	3	24.80	1.31	3	24.88	3	27.35	1.32
27^d	3	19.77	1.30	3	19.83	3	26.23	1.30
28	3	24.47	1.03	3	27.61	3	24.88	1.05
29	3	21.53	1.09	3	14.73	3	21.55	1.11
30	3	27.33	1.00	3	27.23	3	27.35	1.02

^{a}Number of protons attached to designated carbon.
$^b{}^{13}$C chemical shift; 100 MHz, CDCl$_3$ solution.
$^c{}^1$H chemical shift for each proton; for pairs of CH$_2$ protons with chemical shift difference <0.02 ppm, <average value> is listed; 400 MHz, CDCl$_3$ solution.
^{d}Carbons at these sites cannot be distinguished from connectivity experiment.

^{13}C-^{1}H shift-correlated spectra, and the substance was assigned structure **8** from these data. Structure **8** was first assigned to a limonoid of *Cedrela odorata* (Meliaceae) by Bevan *et al.* (4); the same limonoid was subsequently isolated from *Carapa guianensis* (3). Very recently Kadota *et al.* (12) have isolated **8** from *Swietenia mahagoni* (Meliaceae) and have assigned ^{13}C and ^{1}H chemical shifts for it; their results are in substantial agreement with ours.

2,3,4-TRIHYDROXYPREGNAN-16-ONE [**9**].—Both stems and roots afforded a substance, C$_{21}$H$_{34}$O$_4$, mp 262–265°, with ir absorption at 3350 and 1737 cm^{-1}, which could be converted to mono-, di-, and tri-acetates. The monoacetate was chosen for detailed study by 2D nmr. Standard procedures were used to obtain ^{1}H-^{1}H COSY and one-bond ^{1}H-^{13}C shift-correlated spectra, and our XCORFE pulse sequence (13), with acquisition parameters optimized for polarization transfer from Me protons, was

used to obtain n-bond ^{1}H-^{13}C shift correlations. The results are summarized in Table 2. Cross peaks were observed between the protons of one methyl group (C-18) and the quaternary carbon (C-13), a methylene carbon (C-12), and two methine carbons (C-14 and C-17). The methine carbons could be distinguished because the C-17 carbon also showed a cross peak to the C-21 methyl protons. Cross peaks were observed between the protons of the remaining methyl (C-19) and the C-1, C-5, C-9, and C-10 carbons. These correlations in conjunction with the one-bond correlation and the COSY spectra led to the assignment of structure **10**, without stereochemistry, to the compound under study.

The relative stereochemistry in ring A was assigned from the observed ^{1}H-^{1}H coupling constants. All $^3J_{HH}$ couplings between vicinal neighbors in this ring were in the 4–5 Hz range, showing that these hydrogens have a gauche relationship, and the 2-OH and 4-OH must then both be axial. The trans A/B ring fusion and the equatorial orientation of the 3-OAc were indicated by several observations. Irradiation of the (axial) H-3 gave positive nOe enhancements (ca. 6–8%) for protons assigned as H-5 and H-1 (axial), whereas irradiation of the low-field OH proton (at C-2) gave a weak (ca. 2%) enhancement of the C-19 methyl protons, as well as partial saturation of the 4-OH proton (because of slow exchange). The stereochemical assignment at C-3 is also supported by the observation that the 3-OH in the parent triol is acetylated considerably faster than the other OH groups, which also show evidence of intramolecular hydrogen bonding. The most difficult assignment involved the relative stereochemistry of the C-18 methyl group and the ethyl group at C-17. However, irradiation of the C-18 methyl group protons produced about a 5% nOe enhancement of the C-20 methylene protons and a weaker (1–2%) enhancement of the C-21 methyl protons. This observation led us to place the methyl and ethyl groups in a cis relationship. Irradiation of the C-18 methyl

TABLE 2.   Assigned ^{13}C and ^{1}H Chemical Shifts and Long-Range Correlations for 2,3,4-Trihydroxypregnan-16-one Monoacetate [**10**].

Position	δ_C	δ_H	Cross peak to Me at δ_H:
1	43.41	1.28, 2.23	1.28 (C-19)
2	70.55	4.25 (OH 2.80)	
3	74.66	4.71	
4	74.78	3.93 (OH 2.55)	
5	49.50	1.24	1.28 (C-19)
6	25.43	1.40, 1.90	
7	32.29	1.01, 1.76	
8	33.87	1.58	
9	56.65	0.81	1.28 (C-19)
10	35.22	—	1.28 (C-19)
11	20.07	1.36, 1.53	
12	38.03	1.32, 1.90	0.68 (C-18)
13	42.19	—	0.68 (C-18)
14	50.42	1.39	0.68 (C-18)
15	38.44	1.75, 2.20	
16	219.45	—	
17	65.36	1.63	0.68 (C-18), 1.02 (C-21)
18	13.56	0.68	
19	17.09	1.28	
20	17.63	1.22, 1.60	
21	13.43	1.02 ˙	
CH$_3$$C$=O	170.26	—	
CH_3C=O	21.26	2.16	

group also led to significant (4–5%) enhancements for the C-15 proton at δ 1.75 and the C-11 proton at δ 1.36. These results were all consistent with the proposed stereochemical assignment. Other pregnan-16-one derivatives, toosendansterols A and B, have recently been isolated from *Melia toosendan* (Meliaceae) (14).

THE HYDROXYBUTANOLIDE 7.—The bark and stems afforded a white crystalline compound, $C_{24}H_{28}O_3$, mp 70–72°, to which we have assigned structure 7. The presence of a phenyl group, a hydroxyl function, a γ-lactone, a methyl group, and a polymethylene chain was apparent from an examination of the ir and nmr (^{1}H and ^{13}C) spectra. One-bond and n-bond ^{1}H-^{13}C shift-correlated spectra were obtained as described above. The structural features of the phenyl and γ-lactone termini of 7 were assigned from these data; the CH_2CH_2 units directly attached to the terminal rings were also assigned in this manner, but chemical shift differences of the remaining CH_2 units in the polymethylene chain were too small for this method to be taken further, and partial ^{13}C assignments for these units were made on the basis of ^{13}C relaxation measurements (and ^{1}H assignments followed from the one-bond connectivity experiment). Structure 7 has been labelled to show δ_C and, in parentheses, δ_H values. This compound is obviously structurally similar to the grandinolides and related γ-lactones of *Iryanthera* species (2), but there are important differences. The grandinolides occur as a mixture of components that differ in the length of the polymethylene chain; they have not been separated, but mass spectral evidence indicates that the major component has a chain of 19 CH_2 units, and minor components have other chain lengths (odd numbered), with 13 CH_2 units possibly being the smallest. Our compound 7 apears to be a homogeneous compound with 13 CH_2 units in the chain. Furthermore, the stereochemistry of 7 appears to be different from that of either the grandinolides (with both OH and Me trans to the polymethylene chain) or the related juruenolides (epimeric at the OH site) since both the methine ^{1}H chemical shifts and the vicinal ^{1}H-^{1}H coupling constants reported for these compounds differ significantly for those of 7. In 7, the proton α to C=O is coupled to the β proton with $^3J = 8.7$ Hz (and it has additional couplings of 5.7 and 7.5 Hz with the first CH_2 of the polymethylene chain); the β and γ protons have a 7.2 Hz coupling (and the γ proton has a further 6.3 Hz coupling with the protons of the attached Me). These vicinal coupling constants are consistent with the all-*cis* stereochemistry (15–17) depicted in 7, with the ring in an envelope conformation, the Me and the polymethylene chain pseudoequatorial, and the OH pseudoaxial.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Mp's were determined on a Thomas-Kofler micro hot stage. Spectrometers used were: a Nicolet 5DX FTIR (samples in KBr disks; selected ir absorptions reported in cm^{-1} units); a Cary 14 {samples in MeOH; uv absorptions reported as λ max nm (ϵ)]; a Varian XL-400 (^{1}H at 400 MHz; ^{13}C at 100 MHz); a Bell and Howell CEC21-490 [m/z values of significant peaks and intensity relative to base peak (%) reported]. A Perkin-Elmer 243B polarimeter was used to obtain [α]D values; cd was measured on a Jasco J-41A spectropolarimeter (samples in MeOH).

PLANT MATERIAL.—*Tr. schomburgkii* ssp. *schomburkii* was collected at a location on the Essequibo river near Groete Creek, Guyana in November 1987. Voucher specimens are deposited in the Herbarium of the University of Guyana and at the Institute of Systematic Botany, University of Utrecht, Netherlands.

EXTRACTION AND ISOLATION.—Dried leaves (700 g) were extracted with Me$_2$CO, and the gum obtained (13.8 g) was flash-chromatographed over Si gel with elution by hexane and then hexane/Me$_2$CO of increasing polarity. Compounds isolated were, in order of elution, 1 (1.86 g), 2 (55 mg), 3 (225 mg).

Bark (700 g) was extracted with CH$_2$Cl$_2$, and the gum obtained (13.3 g) was flash-chromatographed over Si gel with elution by hexane-CHCl$_3$ (1:1) and then CHCl$_3$. The later fractions were rechromatographed with elution by CHCl$_3$, and 7 (170 mg) was isolated.

Air-dried stems (1.6 kg) were extracted with MeOH, and the gum obtained (60 g) was partitioned between hexane and MeOH-H$_2$O (9:1); the aqueous phase was diluted to MeOH-H$_2$O (3:7), and extracted

with CHCl$_3$. The hexane extract on flash chromatography over Si gel with gradient elution by hexane/EtOAc afforded first a mixture of phytosterols, mp 153–154° (170 mg) [mainly stigmasterol and β-sitosterol] and then **7** (70 mg). The CHCl$_3$ extract was flash chromatographed over Si gel with gradient elution with CHCl$_3$/MeOH; limonoid **8** (12 mg) was isolated [CHCl$_3$-MeOH (49:1)] and later fractions [CHCl$_3$-MeOH (ca. 95:5)] were combined and rechromatographed with CHCl$_3$ elution to provide the steroid **9** (30 mg).

Protolimonoid **1**.—Crystals: mp 153–154° (hexane/Me$_2$CO); [α]D −68° (c = 0.1, CHCl$_3$); ir 3470, 1706; ms 456 (13), 369 ʹ(100), 325 (58). Identified as niloticin (1). Acetate mp 200–202°; ir 1737, 1708; ms 498 (32), 483 (100), 423 (60), 325 (79).

Protolimonoid **2**.—Crystals: mp 173–174° (hexane/Me$_2$CO); [α]D −43.5° (c = 0.12, CHCl$_3$); ir 3440; ms 458 (12), 371 (100), 353 (70). Identified as dihydroniloticin (1). Diacetate mp 160–162°; [α]D −34° (c = 0.096, CHCl$_3$); ir 1738, 1732.

Protolimonoid **3**.—Crystals: mp 202–204° (hexane/Me$_2$CO); [α]D −89° (c = 0.09, CHCl$_3$); ir 3560, 3440, 3380, 1697; ms 474 (11), 441 (15), 369 (100), 325 (49). Identified as piscidinol A (8) [=Mulholland and Taylor's "amorphous triol" (1)]. Diacetate mp 223–225° (8).

Hydroxybutanolide **7**.—Crystals: mp 71–72° (hexane/Me$_2$CO); [α]D −8.5° (c = 0.2, CHCl$_3$); ir 3430, 1735; ms 374 (100), 356 (21), 329 (16), 283 (25); exact mass 374.28168 (calcd for C$_{24}$H$_{38}$O$_3$, 374.28209).

Limonoid **8**.—White cubes: mp 261–263° from Me$_2$CO; [α]D −46° (c = 0.54, CHCl$_3$); ir 1738, 1713, 1670; uv 221 (7,000); fabms [M + 1]$^+$ 439 (25), 307 (22), 154 (100). Identified as 7-deacetoxy-7-oxogedunin (3,4).

2,3,4-Trihydroxypregnan-16-one [**9**].—White needles: mp 262–265° (Me$_2$CO/hexane); [α]D −124° (c = 0.08, CHCl$_3$); cd [θ]$_{298}$ −9.0 × 10^3; ir 3370, 1737; ms 350 (20), 332 (100), 288 (82), 264 (62), 246 (78); exact mass 350.2483 (calcd for C$_{21}$H$_{34}$O$_4$, 350.24571). Monoacetate (3-acetoxy-2,4-dihydroxy) [**10**] mp 198–201°; [α]D −81° (c = 0.16 in CHCl$_3$); ir 3459, 1731, 1243.

ACKNOWLEDGMENTS

LITERATURE CITED

1.   D.A. Mulholland and D.A.H. Taylor, *Phytochemistry*, **27**, 1220 (1988).
2.   P.C. Viera, M. Yoshida, O.R. Gottlieb, H.F. Paulino Filho, T.J. Nagem, and R.B. Filho, *Phytochemistry*, **22**, 711 (1983).
3.   W.D. Ollis, A.D. Ward, H. Meirelles De Oliviera, and R. Zelnik, *Tetrahedron*, **26**, 1637 (1970).
4.   C.W.L. Bevan, J.W. Powell, and D.A.H. Taylor, *J. Chem. Soc.*, 980 (1963).
5.   S. McLean, M. Perpick-Dumont, W.F. Reynolds, H. Jacobs, and S.S. Lachmansing, *Can. J. Chem.*, **65**, 2519 (1987).
6.   W.F. Reynolds, S. McLean, J. Poplawski, R.G. Enriquez, L.I. Escobar, and I. Leon, *Tetrahedron*, **42**, 3419 (1986).
7.   P. Bhandari, N. Chaichit, A.I. Gray, B.W. Skelton, P.G. Waterman, and A.H. White, *Aust. J. Chem.*, **41**, 1777 (1988).
8.   S.D. Jolad, J.J. Hoffmann, K.H. Schram, J.R. Cole, M.S. Tempesta, and R.B. Bates, *J. Org. Chem.*, **46**, 4085 (1981).
9.   G.J.W. Breen, E. Ritchie, W.T.L. Sidwell, and W.C. Taylor, *Aust. J. Chem.*, **19**, 455 (1966).
10. K.K. Purushothanan, K. Duraiswamy, J.D. Connolly, and D.S. Rycroft, *Phytochemistry*, **24**, 2349 (1985).
11. A.I. Gray, P. Bhandari, and P.G. Waterman, *Phytochemistry*, **27**, 1805 (1988).
12. S. Kadota, L. Marpaung, T. Kikuchi, and H. Ekimoto, *Chem. Pharm. Bull.*, **38**, 639 (1990).
13. W.F. Reynolds, D.W. Hughes, M. Perpick-Dumont, and R.G. Enriquez, *J. Magn. Reson.*, **63**, 413 (1985).
14. A. Inada, M. Kobayashi, and T. Nakanishi, *Chem. Pharm. Bull.*, **36**, 609 (1988).
15. R.N. Johnson, J.B. Lowry, and N.V. Riggs, *Tetrahedron Lett.*, 5113 (1967).
16. J. Altman, H. Gilboa, and O. Ben-Ishai, *Tetrahedron*, **33**, 3173 (1977).
17. M.P. Galache, P. Garcés, A.L. Esteban, E. Diez, and J. Guilleme, *Magn. Reson. Chem.*, **27**, 44 (1989).

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