Phytochemistry, Vol 27, No 5, pp 1537–1539, 1988
Printed in Great Britain

0031 9422/88 $3.00+0.00
Pergamon Press plc

CLERODANE DERIVATIVES FROM *GRANGEA MADERASPATANA*

PAHUP SINGH, SUNITA JAIN and JASMIN JAKUPOVIC*

Department of Chemistry, University of Rajasthan, Jaipur 302004, India; *Institute of Organic Chemistry, Technical University of Berlin, D-1000 Berlin 12, F R G

(*Received* 29 *June* 1987)

Key Word Index—*Grangea maderaspatana*; Compositae, diterpenes, clerodane derivatives; *nor*-diterpenes, *seco*-clerodanes

Abstract—The aerial parts of *Grangea maderaspatana* afforded in addition to compounds isolated previously eight new ones, five clerodane derivatives, a *nor*-clerodane, a *seco*-clerodane and *nor-seco*-clerodane The structures were elucidated by high field NMR spectroscopic methods.

INTRODUCTION

The aerial parts of *Grangea maderaspatana* Poir. have been investigated chemically. In addition to acetylenic compounds, flavones and sesquiterpenes some characteristic diterpenes like hardwickiic acid, the corresponding 1,2-dehydro derivative and centipedic acid were reported [1, 2]. A reinvestigation afforded several further compounds. The results are discussed in this paper.

RESULTS AND DISCUSSION

The extract of the aerial parts of *G. maderaspatana* afforded in addition to compounds isolated previously [1, 2] phytol, lupeol, *p*-hydroxybenzoic acid, the phenyl alanine derivative **11** [3], the diterpenes hardwickiic acid and strictic acid [4], and the corresponding 15,16-butenolides [5] **2, 3** and **5–10** which were isolated as their methyl esters.

The structure of **2a** was deduced from its ^{1}H NMR spectrum (Table 1) which was close to that of the corresponding alcohol **1a** [1]. As expected the H-2 signal was shifted downfield (δ5.42, *ddd*) and an acetoxy methyl singlet (δ2.08) was present.

The ^{1}H NMR spectrum of **3a** (Table 1) was close to that of **4a** [1, 4]. However, several signals were slightly different. Spin decoupling allowed the assignment of nearly all signals and by NOE difference spectroscopy the configurations at all chiral centers could be determined. Clear effects between H-19 and H-10 (10%), H-17 and H-10 (6%), H-20 and H-17 (5%), H-10 (12%) and H-2 (7%) required a *cis*-relationship of H-10, H-17, H-19 and H-20.

The molecular formula of **5** and its methyl ester **5a** indicated that this diterpene differed from the known 2-desoxy derivative of **1** [1, 2] by one additional oxygen. The ^{1}H NMR spectrum (Table 1) indicated that **5a** was the corresponding 15,16-butenolide. Accordingly, the signals of the furan protons were replaced by a triplet at δ7.09 and a two proton quartet at 4.76 while the remaining signals were nearly identical with those of the corresponding furan derivative [1, 2].

The ^{1}H NMR spectrum of **6a** (Table 1) was close to that of **5a** However, the two proton signal at δ4.76 was replaced by a broadened singlet at δ5.75 (1H) and two additional methoxy signals were visible (δ3.58 and 3.57). Furthermore, the H-17 signal was doubled. Accordingly, the epimeric 15-methoxy derivatives of **5a** were present which could not be separated.

The ^{1}H NMR spectrum of **7a** (Table 1) indicated that again epimeric 15-methoxy derivatives were present which differed from **6a** by an additional 1,2-double bond. Therefore the spectrum was in part close to that of **4a** and **6a**. Again the H-17 doublet was split while all other signals were identical for both epimers

The ^{1}H NMR spectrum of **8a** (Table 1) was in part close to that of **5a**. However, two methoxy signals and the molecular formula ($C_{19}H_{30}O_4$) required the presence of a *nor*-clerodane. The absence of signals for furan protons and the fragmentation pattern in the mass spectrum showed that a methyl propionate side chain was at C-9.

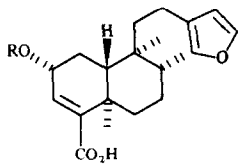
The ^{1}H NMR spectrum of **9a** (Table 1) was close to that of methyl strictic acid ester [1, 4] and in part to that of **6a** indicating that a 15-methoxy strictic acid derivative with a 15,16-butenolide group was present. As none of the signals were doubled most probably only one epimer was present. The relative configuration at C-15 could not be determined.

The ^{1}H NMR spectrum of **10a** (Table 1) and its molecular formula indicated that again a *nor*-diterpene was present. Accordingly, similar fragments as in the case of **8a** were observed

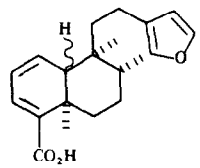
The isolation of strictic acid and the related compounds **9** and **10** again supports the proposed relevance of the dienes **3** and **4** as a precursor of strictic acid [4].

EXPERIMENTAL

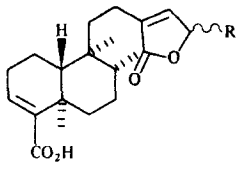
The air-dried aerial parts (1 kg, supplied by M/S United Chemicals and Allied Products, Calcutta, voucher deposited at RUBL, Herbarium Jaipur, India) were extracted with Et_2O–petrol–MeOH (1·1·1) at room temp for 24 hr Evapor-



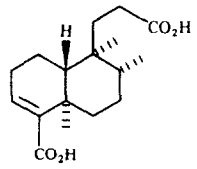
1 R = H
2 R = Ac



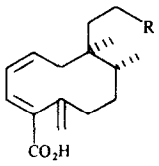
3 10α-H
4 10β-H

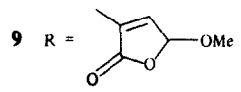


5 R = H
6 R = OMe
7 R = OMe
Δ[1]



8

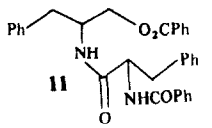




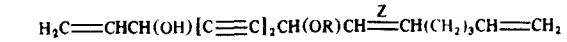
9 R =

10 R = CO_2H

1a–10a are the corresponding methyl esters



11



12 R = H
13 R = Ac

ation of the solvent at red. pres. furnished a greenish semi-solid mass which was disolved in 200 ml MeOH and left overnight in the refrigerator After filtration, the filtrate was concd and chromatographed over silica gel and gave the following fractions Fraction 1 (petrol), Fr 2 (petrol–Et_2O, 3.1), Fr. 3 (petrol–Et_2O, 1 1) and Fr. 4 (Et_2O). Fraction 1 displayed a single spot on TLC (petrol) and gave 20 mg of α-humulene Fraction 2 was a yellowish syrupy liquid and separated on TLC (C_6H_6–CH_2Cl_2, 1.1) affording 100 mg of phytol, 5 mg of 3-hydroxy-8-acetoxypentadeca-1,9,14-trien-4,6-diyne **13**, 20 mg of lupeol and 200 mg of a complex mixture of diterpene acids Therefore it was subjected to methylation with ethereal CH_2N_2 and followed by the usual work-up Its separation on TLC was again difficult It was finally separated by HPLC (MeOH–H_2O, 9 1) RP 18 (analytical) furnishing 15 mg **3a** (R_t 11 8 min), 50 mg of strictic acid methyl ester (R_t 12.7 min), 85 mg mixture of centipedic acid methyl ester and **4a** (R_t 15 min) and 50 mg of hardwickiic acid methyl ester (R_t 16 6 min). Fraction 3 on TLC (C_6H_6–CH_2Cl_2–Et_2O, 4 5 4.5 1) gave 3 mg of 3,8-dihydroxypentadeca-1,9,14-trien-4,6-diyne (**12**), 7 mg of *p*-hydroxybenzoic acid and a complex mixtrue of diterpene lactones The latter was subjected to methylation with CH_2N_2 and separated by HPLC (MeOH–H_2O, 9 1) affording 10 mg of **9a** (R_t 6 6 min), 25 mg of a mixture of **6a** and **7a** (R_t 7 2 min) (which could only be separated by HPLC giving 15 mg of **6a** and 8 mg of **7a**), 12 mg of **10a** (R_t 7 9 min), 5 mg of **8a** (R_t 9 4 min) and 21 mg of **2a** (R_t 12 4 min) Fraction 4 was a yellowish solid mass and separated on TLC (C_6H_6–CH_2Cl_2–Et_2O, 1 1 1) yielding 65 mg of a mixture of 5,3′-dihydroxy-3,6,7,4′,5′-pentamethoxyflavone and lactone **5a** (R_t 0 35), which was further separated by HPLC (MeOH–H_2O, 9 1), 10mg of the 15-desmethoxy derivative of **9a** (R_f 0 30), 7 mg of **11** (R_f 0 40) and 20 mg of 5-hydroxy-3,6,7,3′,4′,5′-hexamethoxyflavone (R_f 0 42)

2α-Acetoxyhardwickiic acid (**2**) Isolated as its methyl ester **2a** Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1} 1760, 1730, (OAc), 1715 (C=C–CO_2R); MS *m/z* (rel int) 388 224 $[M]^+$ (12) (calc for $C_{23}H_{32}O_5$ 388 224), 346 $[M-ketene]^+$ (12), 345 $[M-MeCO]^+$ (22), 328 $[M-AcOH]^+$ (4), 314 $[345-OMe]^+$ (8), 313 $[345-MeOH]^+$ (9), 299 $[314-Me]^+$ (6), 95 (34), 81 (38) and 61 (100), $[\alpha]_D$ −1 1° ($CHCl_3$, *c* 2 07)

10-epi-Nidoresedic acid (**3**) Isolated as its methyl ester **3a** Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1}. 1700 (C=C–C=C–CO_2R), MS *m/z* (rel int) 328 203 $[M]^+$ (8) (calc for $C_{21}H_{28}O_3$ 328 203), 313 $[328-Me]^+$ (8), 297 $[M-OMe]^+$ (4), 285 $[313-CO]^+$ (10), 151 (98) and 81 (100), $[\alpha]_D$ −66 1° ($CHCl_3$, *c* 1 0)

16-Oxo-15,16H-hardwickiic acid (**5**) Isolated as its methyl ester **5a** Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1} 1770 (γ-lactone), 1715 (C=C–CO_2R), MS *m/z* (rel int). 314 188 $[M-MeOH]^+$ (100) (calc for $C_{20}H_{26}O_3$ 314 188), 315 $[M-OMe]^+$ (20), 299 $[314-Me]^+$ (2), 271 $[299-CO]^+$ (10), 139 (30), 107 (26) and 61 (50), $[\alpha]_D$ −62° ($CHCl_3$, *c* 1 38)

15-Methoxy-16-oxo-15,16H-hardwickiic acid (**6**) Isolated as its methyl ester **6a** Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1} 1780 (γ-lactone), 1710 (C=C–CO_2R), MS *m/z* (rel int) 344 198 $[M-MeOH]^+$ (20) (calc for $C_{21}H_{28}O_4$ 344 198), 329 $[344-Me]^+$ (20), 297 $[329-MeOH]^+$ (1) and 61 (100), $[\alpha]_D$ −30 8° ($CHCl_3$, *c* 0 37)

15-Methoxy-16-oxo-nidoresedic acid (**7**) Isolated as its methyl ester **7a** Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1} 1775 (γ-lactone), 1710 (C=C–C=C–CO_2R), MS *m/z* (rel int). 374 209 $[M]^+$ (2) (calc for $C_{22}H_{30}O_5$ 374 209), 342 $[M-MeOH]^+$ (30), 327 $[342-Me]^+$ (90), 295 $[327-MeOH]^+$ (20) and 128 (100), $[\alpha]_D$ −120.8° ($CHCl_3$, *c* 0 23)

nor-*Hardwickiic acid* (**8**) Isolated as its methyl ester **8a** Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1} 1730 (CO_2R), 1710 (C=C–CO_2R), MS *m/z* (rel. int) 322 214 $[M]^+$ (5) (calc for $C_{19}H_{30}O_4$ 322 214), 291 $[M-OMe]^+$ (20), 290 $[M-MeOH]^+$ (100), 275 $[290-Me]^+$ (5), 260 $[275-Me]^+$ (4), 235 $[M-CH_2CH_2CO_2Me]^+$ (12), 203 $[235-MeOH]^+$ (20), 175 $[203-CO]^+$ (20) and 69 (100), $[\alpha]_D$ −36° ($CHCl_3$, *c* 0 10)

15-Methoxy-16-oxo-15,16H-strictic acid (**9**) Isolated as its methyl ester **9a**. Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1} 1780 (γ-lactone), 1720 (C=C–C=C–CO_2R), 1250, MS *m/z* (rel int) 374 209 $[M]^+$ (8) (calc for $C_{22}H_{30}O_5$ 374 209), 343 $[M-OMe]^+$ (10), 342 $[M-MeOH]^+$ (12), 327 $[342-Me]^+$ (6), 310 $[342-MeOH]^+$ (8) and 61 (100), $[\alpha]_D$ −135° ($CHCl_3$, *c* 0 24)

nor-*Strictic acid* (**10**) Isolated as its methyl ester **10a** Colourless gum, IR $\nu_{max}^{CCl_4}$ cm^{-1} 1730 (CO_2R), 1710 (C=C–C=C–CO_2R); MS *m/z* (rel int) 320 198 $[M]^+$ (8) (calc for $C_{19}H_{28}O_4$ 320 198), 289 $[M-OMe]^+$ (12), 288 $[M-MeOH]^+$ (18), 273 $[288-Me]^+$ (8), 256 $[288-MeOH]^+$ (10), 201 $[288-CH_2CH_2CO_2Me]^+$ (24), 173 $[201-CO]^+$ (30) and 55 (100), $[\alpha]_D$ −26° ($CHCl_3$, *c* 0 41)

Table 1 ^{1}H NMR spectral data of compounds **2a**, **3a** and **5a–10a** ($CDCl_3$, 400 MHz, TMS as internal standard)

H	**2a***	**3a**†	**5a**	**6**‡	**7a**‡	**8a**	**9a**	**10a**
1	+	6.01 *br dd*	+	+	6.15 *m*	+	5.40 *br dd*	5.35 *br dd*
2	5.42 *ddd*	6.18 *br dd*	+	+		+	5.93 *br d*	5.93 *br d*
3	6.42 *br d*	6.64 *br d*	6.60 *br dd*	6.60 *br dd*	6.73 *m*	6.58 *dd*	7.25 *ddd*	7.25 *ddd*
10	+	2.15 *br d*	+	+	2.29 *br s*	+	2.26 *br dd* 1.78 *br d*	2.22 *br dd* +
14	6.30 *br s*	6.20 *br s*	7.09 *tt*	6.76 *dt*	6.75 *dt*	—	6.77 *br s*	—
15	7.34 *dd*	7.31 *dd*	4.76 *dt*	5.75 *dt*	5.74 *dt*	—	5.74 *br s*	—
16	7.23 *br s*	7.13 *br s*	—	—	—	—	—	—
17	0.86 *d*	1.02 *d*	0.83 *d*	0.81(0.82) *d*	0.87(0.86) *d*	0.84 *d*	0.78 *d*	0.81 *d*
19	1.35 *s*	1.17 *s*	1.26 *s*	1.27 *s*	1.08 *s*	1.27 *s*	5.06 *br s* 4.84 *br s*	5.06 *br s* 4.84 *br s*
20	0.78 *s*	0.92 *s*	0.78 *s*	0.77 *s*	0.91 *s*	0.79 *s*	0.73 *s*	0.69 *s*
OMe	3.70 *s*	3.72 *s*	3.68 *s*	3.68 *s*	3.72 *s*	3.68 *s*	3.77 *s*	3.77 *s*
				3.58(3.57) *s*	3.57 *s*	3.66 *s*	3.57 *s*	3.69 *s*

+ Unassigned multiplets

*OAc: 2.08 *s*.

†H-6α 1.40 *ddd*, H-6β 2.48 *ddd*, H-7α 1.24 *dddd*, H-7β 1.62 *m*, H-8 1.84 *ddq*, H-11 2.14 *ddd*, H-11′ 1.60 *m*, H-12 2.24 *ddd*, H-12′ 2.07 *ddd*.

‡values in parenthesis for epimer

J [Hz]. 8,17 = 7, compounds **2a** and **3a**: 15,16 = 15,17 = 1.5; compound **2a**: 1,2 = 2, 1′,2 = 7, 2,3 = 2.5; compound **3a** 1,2 = 10; 1,10 = 2,3 = 5.5, 6α,6β = 6α,7β = 7α,7β = 13.5; 6α,7α = 6β,7α = 6β,7β = 7α,8 = 7β,8 = 3.5, 11,11′ = 11,12 = 12,12′ = 11′,12′ = 13, 11,12′ = 11′,12 = 5; compounds **5a**, **6a** and **8a**· 2,3 = 3; 2′,3 = 4, compounds **5a–7a**: 12,14 = 12,15 = 14,15 = 1.5, compounds **9a** and **10a**: 1,2 = 1,10 ≈ 12; 1,3 = 2,3 = 3,10′ ≈ 2.5.

REFERENCES

1. Pandey, R. C., Singhal, A. K., Barua, N. C., Sharma, R. P., Baruah, J. N., Watanabe, K., Kulanthaivel, P. and Herz, W. (1984) *Phytochemistry* **23**, 391.
2. Bohlmann, F. and Mahanta, P. K. (1979) *Phytochemistry* **18**, 1067.
3. Talapatra, S. K., Pal, M. K., Mallik, A. K. and Talapatra, B. (1983) *J. Nat. Prod.* **46**, 140.
4. Bohlmann, F. and Fritz, U. (1978) *Phytochemistry* **17**, 1769.
5. Singh, P., Sharma, M. C., Joshi, K. C. and Bohlmann, F. (1985) *Phytochemistry* **24**, 190.