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Two new abietane diterpenes from *Cordia latifolia*

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Abstract—Two new abietane diterpenes cordioic acid and cordifolic acid were isolated from the methanolic extract of *Cordia latifolia* stem bark. The structures of these diterpenes were elucidated using spectroscopic techniques. To the best of our knowledge, this is the first instance of isolation of diterpenoids from this source. Furthermore, cordifolic acid is a rare 2,3-*seco*-abietane suggestive of its biogenesis from 3-keto-analogue.

1. Introduction

Cordia latifolia (Boraginaceae) is a small deciduous tree growing nearly all over the Indo–Pak subcontinent. Practically every part of the tree is reported for its medicinal value in the indigenous system of medicine[1] and thus various groups of workers undertook studies on its chemical constituents and reported different classes of compounds, which include fatty acids,[2] sterols,[3] carbohydrate,[4–6] flavanone and flavanone glycosides,[7–11] triterpenoids and glycosides[12,13] and pyrrolizidine alkaloids.[14]

In the present study, two new abietane diterpenes cordioic acid (**1**) and cordifolic acid (**2**) were isolated from the methanolic extract of *C. latifolia* stem bark and their structures were determined by spectroscopic analysis.

2. Results and discussion

The molecular formula of compound **1** was established through HREIMS, which showed the molecular ion peak at *m/z* 330.1840 corresponding to the molecular formula $C_{20}H_{26}O_4$ (eight degrees of unsaturation). The IR spectrum displayed absorption bands attributable to carboxyl group (3100–2500 br, 1725 cm^{-1}), benzene ring (1599–1407 cm^{-1}, four peaks) and geminal methyls (1381 cm^{-1}). The ^1H NMR spectrum (Table 1) indicated the presence of an aromatic isopropyl moiety at δ 1.20 (6H, d, J=7.0 Hz), 2.80 (1H, septet, J=7.0 Hz), three aromatic protons at 7.14 (1H, d, J=8.1 Hz), 6.97 (1H, br d, J=8.1 Hz) and 6.86 (1H, br s) and one methyl singlet at δ 1.26 (3H, s).

The ^{13}C and DEPT NMR spectra (Table 1) suggested that **1** was a diterpenoid with a total of twenty carbons consisting of three methyls, five methylenes, five methines (including three aromatic CH) and seven quaternary carbons (including three aromatic and two carbonyl carbons). In the ^1H–^1H COSY spectrum, cross peaks between H-15 (δ 2.80) and the methyl protons at δ 1.20 (H-16, H-17) revealed that two methyls and one methine are part of an isopropyl group. The ^{13}C NMR spectrum further showed the presence of two carboxylic carbonyls at δ 183.3 and 183.4 and six aromatic carbons at δ 133.3 (C-8), 146.7 (C-9), 124.1 (C-11), 123.8 (C-12), 145.7 (C-13) and 126.9 (C-14). A detailed analysis of ^1H–^1H COSY, HMQC and HMBC spectra revealed that **1** is an abietane diterpenoid.[15,16] These structural features were supported by the HMBC spectrum in which cross peaks were observed for correlations between H-5 (δ 2.22) and C-3 (δ 36.7), C-4 (δ 47.3), C-6 (δ 21.7), C-7 (δ 29.9), C-9 (δ 146.7), C-10 (δ 51.4), C-18 (δ 183.3/183.4), C-19 (δ 16.2) and C-20 (δ 183.3/183.4) and between H-15 (δ 2.80) and C-12 (δ 123.8), C-13 (δ 145.7), C-14 (δ 126.9) and C-16/C-17 (δ 23.9) (Table 1). In the light of these observations the structure of compound **1** (Fig. 1) was established as abieta-8,11,13-trien-18,20-dioic acid. The assignments of proton and carbon nuclei are based on 2D NMR and compare well with the published values of similar partial structures,[15–17] which were also supportive for the carboxyl groups at C-4 and C-10. The values of C-4, C-5 and C-19 were particularly helpful in assigning the α disposition of the carboxyl group at C-4.[17]

The composition of **2** as $C_{20}H_{28}O_2$ (seven degrees of unsaturation) was evident from the molecular ion peak at *m/z* 300.2078 in the HREIMS spectrum. The IR spectrum displayed absorption bands attributable to carboxyl group (–O–H str., 3200–2500 cm^{-1} br; carbonyl str., 1720 cm^{-1}), benzene ring (1634–1459 cm^{-1}) and geminal methyls

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Table 1. ^{1}H and ^{13}C NMR data of compound **1** in $CDCl_3$[a]

Proton	δC[b]	δH[c,d]	^{1}H–^{1}H COSY	HMBC (H→C)
1	36.7	1.49–2.28 (m)	H-2	C-5, C-20
2	18.5	1.71, 1.82 (m)	H-1, H-3	C-1
3	37.9	1.49–2.28 (m)	H-2	—
4	47.3	—	—	—
5	44.6	2.22 (dd, 12.2, 2.5)	H-6	C-1, C-3, C-4, C-9, C-18
6	21.7	1.83, 1.85 (m)	H-5, H-7	C-5, C-7
7	29.9	2.65, 2.70 (m)	H-6	C-6, C-8
8	133.3	—	—	—
9	146.7	—	—	—
10	51.4	—	—	—
11	124.1	7.14 (d, 8.1)	H-12	C-8, C-12, C-13
12	123.8	6.97 (br d, 8.1)	H-11, H-14	C-9, C-11, C-13, C-14, C-15
13	145.7	—	—	—
14	126.9	6.86 (br s)	—	C-8, C-15
15	33.4	2.80 (septet, 7.0)	H-16, H-17	C-12, C-13, C-14, C-16/C-17
16	23.9	1.20 (d, 7.0)	H-15	C-13
17	23.9	1.20 (d, 7.0)	H-15	C-13
18	183.3[e]	—	—	—
19	16.2	1.26 (s)	—	C-3, C-4, C-5, C-18,
20	183.4[e]	—	—	—

[a] Assignments based on ^{1}H–^{1}H COSY, HMQC and HMBC experiments.
[b] Recorded at 125 MHz.
[c] Recorded at 500 MHz.
[d] Multiplicity and *J* values in hertz are given in parenthesis.
[e] Values may be interchanged.

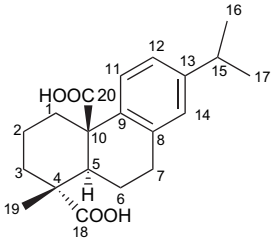

Figure 1. Structure of cordioic acid.

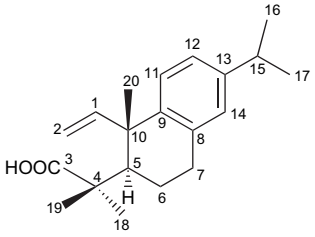

Figure 2. Structure of cordifolic acid (**2**).

(1383 cm^{-1}). The ^{1}H NMR spectrum revealed the resonances for a terminal double bond [δ 4.86 (1H, d, J=10.4 Hz), 4.83 (1H, d, J=17.2 Hz) and 5.68 (1H, dd, J=17.2, 10.4 Hz)], three aromatic protons [δ 7.08 (1H, d, J=8.1 Hz), 6.90 (1H, br d, J=8.0 Hz) and δ 6.79 (1H, br s)] suggestive of an *ortho–ortho* and *ortho–meta* coupled aromatic ring system, an isopropyl group [δ 1.13 (6H, d, J=6.8 Hz) and 2.73 (1H, septet, J=6.8 Hz)] and three methyl singlets [δ 1.10 (3H, s), 1.12 (3H, s) and 1.17 (3H, s)]. These proposals were supported by the ^{13}C NMR (broad band) DEPT spectra, which exhibited twenty carbons including five methyls, three methylenes (including one sp^2), six methines (including four sp^2) and six quaternary (including one carboxyl and three aromatic carbons).

Detailed analysis of the ^{1}H–^{1}H COSY and HMQC spectra of **2** demonstrated four structural units, three with correlated protons: –$CH(CH_3)_2$ (isopropyl), –^{5}CH–$^{6}CH_2$–$^{7}CH_2$–, $^{2}CH_2$=^{1}CH– and an *ortho–ortho*, *ortho–meta* coupled aromatic system as shown in Figure 2. These units were combined on the basis of heteronuclear multiple bond correlation (HMBC) (Table 2), which clarified the structure of **2** as 2,3-*seco*-abieta-1,8,11,13-tetraen-3-oic acid.

The stereochemistry of various centres was deduced from NOESY correlations, which were present between H-5/H-1, H-5/H-2, H-5/H-18 and H-19/H-20.

Compound **2** is a rare example of ring A *seco*-abietane derivative[18,19] and offers its interesting possible biogenesis through a Baeyer–Villiger oxidation of the 3-ketone followed by a fragmentation of the lactone to generate a carboxylic acid and an alkene.

3. Experimental

3.1. General experimental procedures

Column chromatography was carried out by using silica gel 60 (Merck Kieselgel 60, 70–230 mesh). TLC was taken on silica gel 60 PF_{254} (Merck); detection under UV lamp (λ_{max} 254, 366) and with I_2 spray. UV spectra were obtained using a Hitachi-U-3200 spectrophotometer. IR spectra were recorded on a Jasco A-302 spectrophotometer. NMR spectra were measured on Bruker AMX-500 spectrophotometer at 300 K. Mass spectra were obtained using Finnigan-Mat-311A spectrometer. Preparative HPLC was carried out on JAI LC-908W normal phase, column silica 12 nm, 20 cm× 250 nm, by using $CHCl_3$ as a mobile phase; loop was 3 ml; flow rate was 8.0 ml/min.

3.2. Plant material

The aerial parts of *C. latifolia* were collected from Karachi region during 2001 and identified by Mr. Jan-e-Alam,

Table 2. ^{1}H and ^{13}C NMR data of compound **2** in $CDCl_3$[a]

Proton	δC[b]	δH[c,d]	^{1}H–^{1}H COSY	HMBC (H→C)
1	147.2	5.68 (dd, 17.2, 10.4)	H-2	C-10, C-20
2a	112.6	4.86 (d, 10.4)	H-1	C-1, C-10
2b		4.83 (d, 17.2)		
3	181.5	—	—	—
4	47.0	—	—	—
5	48.8	1.85 (dd, 13.5, 3.0)	H-6	C-4, C-20
6	18.8	1.65, 1.70 (m)	H-5, H-7	—
7	29.6	2.62, 2.69 (m)	H-6	C-9
8	134.6	—	—	—
9	146.9	—	—	—
10	50.5	—	—	—
11	124.0	7.08 (d, 8.1)	H-12	C-9, C-12, C-13
12	123.7	6.90 (br d, 8.07)	H-11	C-9, C-11, C-14
13	145.6	—	—	—
14	126.7	6.79 (br s)	—	C-9, C-12
15	33.4	2.73 (septet, 6.8)	H-17	C-13
16/17	24.9	1.13 (d, 6.8)	H-15	C-13, C-15
18	29.3	1.17 (s)	—	C-3
19	23.8	1.10 (s)	—	C-3, C-4
20	16.8	1.12 (s)	—	C-1, C-9

[a] Assignments based on ^{1}H–^{1}H COSY, HMQC and HMBC experiment.
[b] Recorded at 125 MHz.
[c] Recorded at 500 MHz.
[d] Multiplicity and *J* values in hertz are given in parenthesis.

Department of Botany, University of Karachi. A voucher specimen (G.H. No. 68223) has been deposited in the herbarium of the same department. The bark of the stem was cut using hand chopper.

3.3. Extraction and isolation

The stem bark (5 kg) of *C. latifolia* was repeatedly (4×15 l) extracted with MeOH at room temperature. The combined methanolic extract was freed of the solvent in vacuo to a thick syrup, which was partitioned between EtOAc and H_2O. The EtOAc layer was washed with H_2O, dried (anhydrous Na_2SO_4) and evaporated under reduce pressure to give a gummy residue (400 g). It was divided into *n*-hexane soluble and insoluble fractions.

The *n*-hexane soluble fraction was extracted with 90% aq MeOH, which was extracted out with EtOAc after adding saline. The EtOAc phase was dried over Na_2SO_4 (anhydrous) and concentrated under vacuum. The residue left was divided into $CHCl_3$ soluble and insoluble fractions. The $CHCl_3$ soluble (100 g) fraction was subjected to gravity column chromatography (Merck Kieselgel 60, 70–230 mesh, 1500 g), which was eluted with $CHCl_3$, $CHCl_3$–MeOH in increasing order of polarity. As a result various fractions were obtained, which were combined on the basis of TLC to ultimately afford 37 fractions. Fraction 7 (50 mg) was purified over precoated silica gel 60 F_{254} aluminium sheets (20×10 cm; Merck) developed with *n*-hexane–EtOAc (7:3). Four bands were separated with the upper most band as the major component. It was further purified through HPLC to furnish compound **1** (12.0 mg) (JAI LC-908W, $CHCl_3$ as mobile phase, retention time 16 min). Fraction 19 (43.7 mg) was also purified over the same silica gel precoated sheets using *n*-hexane–EtOAc (7:3) solvent system affording three bands. Of these, the second band (27.4 mg) was further purified through HPLC to furnish **2** (15.2 mg) (JAI LC-908W, $CHCl_3$ as mobile phase, retention time 24 min).

3.4. Characteristics of each terpenoid

3.4.1. Cordioic acid (1). Amorphous solid; $[\alpha]_D^{27}$ +48.8 (*c* 0.15, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 288 (3.19), 266 (2.15) nm; IR (film) ν_{max} 3100–2500 br, 2927, 2858, 1725, 1599, 1527, 1449, 1407, 1381, 1275 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 1; HREIMS *m/z* 330.1840 [M^+] (calcd for $C_{20}H_{26}O_4$, 330.1831).

3.4.2. Cordifolic acid (2). Amorphous solid; $[\alpha]_D^{27}$ +76.3 (*c* 0.25, $CHCl_3$); UV (MeOH) λ_{max} (log ε) 290 (3.24), 267 (1.95) nm; IR (film) ν_{max} 3200–2500 br, 1634, 1601, 1459, 1383, 1277 cm^{-1}; ^{1}H and ^{13}C NMR data, see Table 2; HREIMS *m/z* 300.2078 [M^+] (calcd for $C_{20}H_{28}O_2$, 300.2089).

References and notes

1. Chopra, R. N.; Nayar, S. L.; Chopra, I. C. *Glossary of Indian Medicinal Plants*; C.S.I.R.: India, 1956; p 77.
2. Tiwari, R. D.; Srivastava, K. C.; Shukla, S.; Bajpai, R. K. *Planta Med.* **1967**, *15*, 240–244.
3. Tiwari, K. P.; Srivastava Smt, S. D. *Planta Med.* **1979**, *36*, 191–192.
4. Bhatty, M. K.; Shah, D. H.; Saeed, M. A.; Nasir, U. *Pak. J. Sci. Ind. Res.* **1978**, *21*, 162–163.
5. Ifzal, S. M.; Qureshi, A. *Pak. J. Sci. Ind. Res.* **1976**, *19*, 64–65.
6. Karawya, M. S.; Wassel, G. M.; Baghdadi, H. H.; Ammar, N. M. *Planta Med.* **1980**, *38*, 73–78.
7. Srivastava, S. K. *Indian J. Pharm. Sci.* **1980**, *42*, 95–96.
8. Chauhan, J. S.; Srivastava, S. K. *Indian J. Chem., Sect. B* **1977**, *15*, 760–761.
9. Srivastava, S. K.; Srivastava, S. D. *Phytochemistry* **1979**, *18*, 2058–2059.
10. Srivastava, S. K. *Indian Drugs* **1979**, *16*, 105–106.

11. Chauhan, J. S.; Srivastava, S. K.; Sultan, M. *Phytochemistry* **1978**, *17*, 334.
12. Chauhan, J. S.; Srivastava, S. K. *Phytochemistry* **1978**, *17*, 1005–1006.
13. Srivastava, S. K.; Srivastava, S. D.; Nigam, S. S. *J. Indian Chem. Soc.* **1983**, *60*, 202.
14. Wassel, G.; El-Menshawi, B.; Saeed, A.; Mahran, G.; El-Merzabani, M. *Pharmazie* **1987**, *42*, 709–711.
15. Levy, G. C. *Topics in Carbon-13 NMR Spectroscopy*; Wiley: New York, NY, London, Sydney, Toronto, 1976; Vol. 2.
16. Escudero, J.; Perez, L.; Rabanal, R. M.; Valverde, S. *Phytochemistry* **1983**, *22*, 585–587.
17. Chang, C. W. J.; Flament, I.; Matson, J. A.; Nishida, T.; Ohloff, G.; Wehrli, F. W.; Weinheimer, A. J. *Progress in the Chemistry of Organic Natural Products*; Herz, W., Grisebach, H., Kirby, G. W., Eds.; Springer: New York, NY, 1979; Vol. 36.
18. Charles, L.; Cantrell, S. L.; Richheimer, G. M.; Nicholas, B. K.; Schmidt, D.; Bailey, T. *J. Nat. Prod.* **2005**, *68*, 98–100.
19. Kuo-Chiou, H.; Jim-Min, F.; Shiachen, Y. *J. Nat. Prod.* **1995**, *58*, 1592–1595.