New Constituents of *Artocarpus rigida*

by **Horng-Huey Ko** and **Chun-Nan Lin***

School of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan 807, Republic of China

and **Sheng-Zehn Yang**

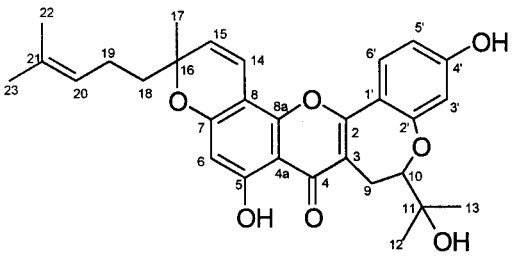
Department of Forest Resource, Management and Technology, National Pintung University of Science and Technology, Ping Tung Hsien, Taiwan 912, Republic of China

Four new phenolic compounds containing an oxepine ring, artocarpols B (**1**), C (**2**), D (**3**), and E (**4**), were isolated from the root bark of *Artocarpus rigida*. The structures, including relative configurations, were elucidated by means of spectroscopic data.

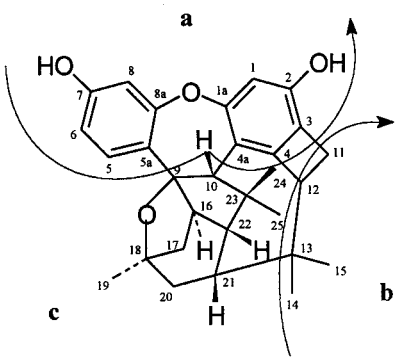
1. Introduction. – Various constituents isolated from the bark of *Artocarpus rigida* (Moraceae) have been reported [1][2]. Recently, we isolated and characterized a novel phenolic compound containing an oxepine ring, artocarpol A (**5**), which strongly inhibited superoxide formation in phorbol 12-myristate 13-acetate (PMA) stimulated rat neutrophils [3]. In a continued search for new bioactive constituents from this plant, four new phenolic compounds containing an oxepane ring, artocarpols B (**1**), C (**2**), D (**3**), and E (**4**) were isolated from the root bark. In the present paper, the structure elucidations of the four new compounds are reported.

2. Results and Discussion. – The molecular formula of artocarpol B (**1**) was determined to be $C_{30}H_{32}O_7$ by HR-EI-MS (*m/z* 504.2156 (M^+), $\pm$0.8 mmu error) which was consistent with the ^{1}H- and ^{13}C-NMR data. The IR absorptions of **1** implied the presence of OH (3435 cm^{-1}), conjugated CO (1653 cm^{-1}), and aromatic-ring (1606 cm^{-1}) moieties. The UV spectrum of **1** resembled that of compound A [4]. The ^{1}H-NMR data of **1** were very similar to those of compound A, except for the lack of signals due to a 2,2-dimethylpyran ring and the appearance of signals due to a 2-methyl-2-(4-methylpent-3-enyl)pyran ring [4]. The EI-MS spectrum of **1** gave significant fragments at *m/z* 489 ($[M-Me]^+$, 421 ($[489-C_5H_8]^+$), 403 ($[421-H_2O]^+$), and 361 ($[403-C_3H_6]^+$). On the basis of the above evidence, artocarpol B was characterized as **1**. The ^{13}C-NMR spectrum of **1** (*Table 1*) was assigned by conducting ^{1}H-decoupled, DEPT, ^{1}H,^{13}C COSY, and ^{1}H,^{13}C long-range correlation experiments and supported the structural assignment.

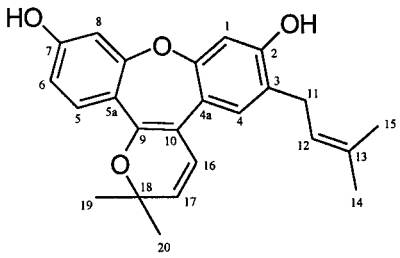
The molecular formula of artocarpol C (**2**) was determined to be $C_{29}H_{32}O_4$ by HR-EI-MS (*m/z* 444.2300 (M^+), $\pm$0.1 mmu error), which was consistent with the ^{1}H- and ^{13}C-NMR data. The IR absorptions of **2** were indicative of OH (3352 cm^{-1}) and aromatic ring moieties (1609 cm^{-1}), and the UV spectrum was similar to that of artocarpol A (**5**) [3]. The ^{1}H- and ^{13}C-NMR spectra (*Tables 1* and *2*) revealed signals due to a trisubstituted and a pentasubstituted benzene moiety, four aliphatic



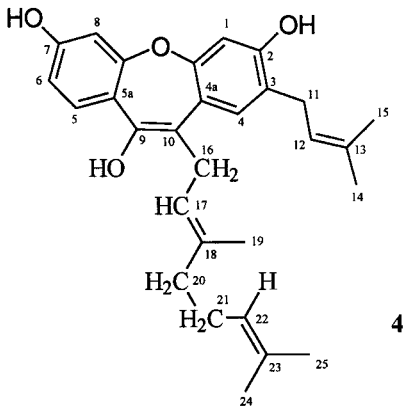
1



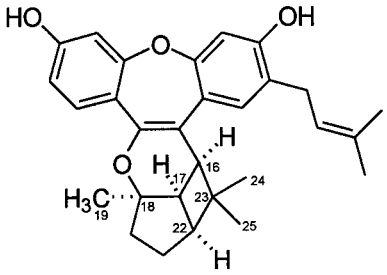
2



3



4



5

Figure. *Structures of* **1**–**5**

Table 1. *^{13}C-NMR Data* (δ in ppm) *of* **1**, **3**, *and* **4**[a]). Arbitrary numbering (see *Fig.*).

	1[b])	**3**	**4**[b])		**1**[b])	**3**	**4**[b])
C(1)		105.0	105.5	C(15)	128.0	25.7	25.6
C(1a)		153.5	153.6	C(16)	81.2	116.6	27.3
C(2)	159.1	152.1	153.3	C(17)	27.3	129.7	123.8
C(3)	117.4	120.3	120.4	C(18)	42.1	76.0	137.8
C(4)	181.8	107.3	106.4	C(19)	23.3	27.6	17.6
C(4a)	104.5	130.2	131.9	C(20)	124.7	27.6	26.3
C(5)	157.7	121.1	121.0	C(21)	132.2		39.5
C(5a)		122.8	122.1	C(22)	17.6		122.4
C(6)	94.9	112.0	111.9	C(23)	25.7		133.9
C(7)	161.1	154.4	153.8	C(24)			16.0
C(8)	105.5	98.2	98.4	C(25)			25.6
C(8a)	160.5	155.2	155.6	C(1′)	114.5		
C(9)	25.1	149.2	153.1	C(2′)	156.0		
C(10)	91.0	120.3	120.4	C(3′)	108.6		
C(11)	72.4	25.6	27.3	C(4′)	162.6		
C(12)	25.1	123.6	122.5	C(5′)	111.9		
C(13)	27.5	131.1	131.6	C(6′)	131.1		
C(14)	116.3	18.1	17.1				

[a]) The number of protons directly attached to each C-atom was verified by DEPT experiments. [b]) Signals obtained by ^{1}H,^{1}H COSY, HMQC, HMBC, and NOESY techniques and comparison with the corresponding reported data [3].

quarternary C-atoms, and five CH, three CH_2, and five tertiary Me groups. The three partial structures **a**–**c** (see *Fig.*) were deduced from extensive analysis of the 1D and 2D NMR data, including those from COSY, HMQC, HMBC, and NOESY experiments in $CDCl_3$ (*Table 2*), which established the proposed structure for artocarpol C (**2**).

The ^{1}H-NMR, ^{1}H,^{1}H-COSY, HMQC, and HMBC data of **2** suggested the partial structure **a** (*Fig.*). For partial structure **b** (*Fig.*), the connectivity CH_2(11)/H–C(12) was clearly revealed by the COSY data. The Me(14) and Me(15) groups and CH(12) of **b** were located at C(13) by HMBC cross-peaks Me(14)/C(15), Me(15)/C(14), Me(14)/C(13), Me(15)/C(13), Me(14)/C(12), and Me(15)/C(12). For partial structure **c** (*Fig.*), the connectivities CH_2(20)/H–C(22) and H–C(16)/CH_2(17) were clearly revealed by COSY. Me(24), Me(25), and CH(22) of **c** were located at C(23), by the HMBC cross-peaks Me(24)/C(25), Me(25)/C(24), Me(24)/C(23), Me(24)/C(22), and Me(25)/C(22), Me(19) and CH_2(20) at C(18) by the HMBC cross-peaks Me(19)/C(18), Me(19)/C(20), and H_α–C(20)/C(19), and finally CH(10) and the quarternary C(9) at C(23) and C(16), respectively, by the HMBC cross-peaks H–C(10)/C(22), Me(24)/C(22), Me(25)/C(22), Me(24)/C(10), Me(25)/C(10), and H–C(22)/C(9). The above correlations also established the connectivity C(9)–O–C(18) (C(9) and C(18) at δ 95.8 and 85.0, resp.).

H_α–C(11) and H–C(12) showed HMBC correlations with C(3), thus establishing the connection of partial structures **a** and **b** by the bonds C(11)–C(3) and C(12)–C(4). In addition, the HMBC correlation Me(14)/C(21) suggested that partial structures **b** and **c** were connected by the C(13)–C(21) bond. HMBC Correlation H–C(22)/C(9) and NOESY interactions H–C(10)/Me(24), Me(24)/H_α–C(11), and H_β–C(17)/H_β–C(20) showed that partial structures **a** and **c** were connected by the C(10)–C(4a) and C(9)–C(5a) bonds and suggested the connectivities C(16)–C(22), and C(17)–C(18).

The NOESY correlations H–C(16)/H_α–C(17) and H–C(16)/Me(19) suggested the α-configuration for H–C(16) and Me(19) in **2**, and the NOESY correlations Me(14)/H–C(21), H–C(21)/H–C(22), H–C(22)/Me(25), Me(25)/H–C(10), H–C(10)/H–C(22) and H_β–C(11)/H–C(12) was in accordance with the β-configuration for H–C(10), H–C(12), H–C(21), and H–C(22).

In the EI-MS of **2**, the base peak at *m*/*z* 361 was attributed to the fragment M–Me – **b** – H]$^+$ (see *Fig.*). This and characteristic peaks at *m*/*z* 429 ([M – Me]$^+$) and 198 ([361 – **c** – 15]$^+$ (see *Fig.*) also supported the structure of **2**.

Table 2. *^{1}H- and ^{13}C-NMR Data* (δ in ppm, J in Hz) *of* **2** *in $CDCl_3$*. Arbitrary numbering (see *Fig.*).

	δ(H)	δ(C)	HMBC (^{1}H)	^{1}H,^{1}H–NOESY[a])
H–C(1)	6.42 (d, J = 2.4)	107.3		
C(1a)		154.9		
C(2)		150.1		
C(3)		124.9	2.67 (*H*–C(11)), 2.83 (*H*–C(12))	
C(4)		140.8		
C(4a)		117.6		
H–C(5)	6.97 (d, J = 8)	126.9		
C(5a)		121.8		
H–C(6)	6.39 (dd, J = 8, 2.4)	106.7		
C(7)		161.3		
H–C(8)	6.35 (d, J = 2.4)	99.0		
C(8a)		156.2		
C(9)		95.8	2.83 (*H*–C(22))	
H–C(10)	3.49 (s)	57.2	0.95 (Me(24)), 1.00 (Me(25))	
H_α–C(11)	2.67 (dd, J = 16.4, 1.2)	27.0	2.83 (*H*–C(12))	
H_β–C(11)	2.99 (dd, J = 16.4, 8.8)			
H–C(12)	2.83 (m)	37.2	2.67 (H_α–C(11)), 1.07 (Me(14)), 0.55 (Me(15))	H_β–C(11)/H–C(12)
C(13)		40.9	1.07 (Me(14)), 0.55 (Me(15))	
Me(14)	1.07 (s)	32.9	0.55 (Me(15))	Me(14)/H–C(21), H–C(22)
Me(15)	0.55 (s)	19.3	1.07 (Me(14))	
H–C(16)	2.38 (m)	42.1		H–C(16)/H_α–C(17), Me(19)
H_α–C(17)	1.67 (dd, J = 14, 8.4)	24.9		H_α–C(17)/H_β–C(20)
H_β–C(17)	1.81 (m)			H_β–C(17)/H_β–C(20)
C(18)		85.0	1.19 (Me(19))	
Me(19)	1.19 (s)	23.8	1.53 (H_α–C(20))	
H_α–C(20)	1.53 (dd, J = 12.8, 4.0)	42.4	1.19 (Me(19))	
H_β–C(2b)	2.03 (dd, J = 12.8, 6.4)			
H–C(21)	2.38 (m)	46.7	1.07 (Me(14)), 0.55 (Me(15))	H–C(21)/H–C(22)
H–C(22)	2.83 (m)	53.1	0.95 (Me(24)), 1.00 (Me(25)), 3.49 *H*–C(10))	H–C(22)/Me(25)
C(23)		37.0	0.95 (Me(24))	
Me(24)	0.95 (s)	23.5	1.00 (Me(25))	
Me(25)	1.00 (s)	27.0	0.95 (Me(24)), 2.83 (*H*–C(22))	

[a]) Only key interactions.

The molecular formula of artocarpol D (**3**) was determined to be $C_{24}H_{24}O_4$ by HR-EI-MS (m/z 376.1675 (M^+), ±0.1 mmu error), which was consistent with the ^{1}H- and ^{13}C-NMR data. The IR absorptions of **3** were indicative of OH (3386 cm^{-1}) and aromatic-ring moieties (1602 cm^{-1}), and the UV spectrum was similar to that of artocarpol A (**5**) [3]. The ^{1}H-NMR spectrum of **3** showed five aromatic-proton signals, proton signals of a γ,γ-dimethylallyl group, and proton signals of a 2,2-dimethyl-2*H*-pyran moiety. In the ^{13}C-NMR spectrum of **3** (*Table 1*), the δ of C(1) to C(15) were almost identical to corresponding data of **5** [3]. Based on the above results, the 2,2-dimethyl-2*H*-pyran moiety was fused at C(9)–C(10). Therefore, artocarpol D was characterized as **3**.

The molecular formula of artocarpol E (**4**) was determined to be $C_{29}H_{34}O_4$ by HR-EI-MS (m/z 446.2457 (M^+), ±0.0 mmu error), which was consistent with the ^{1}H- and

^{13}C-NMR data. The IR absorptions of **4** were indicative of OH (3379 cm^{-1}) and aromatic-ring moieties (1619 and 1592 cm^{-1}). The UV spectrum was similar to that of artocarpol A (**5**) [3]. The ^{1}H-NMR spectrum of **4** showed five aromatic proton signals, a phenolic proton signal, proton signals of a γ,γ-dimethylallyl group, and proton signals of a geranyl group. In the ^{13}C-NMR spectra of **4** (*Table 1*), the chemical shift values of C(1) to C(15) were almost identical to corresponding data of **3**. Based on the above results, the geranyl group was located at C(10). Therefore, artocarpol E was characterized as **4**. The data obtained from the MS, and from the ^{13}C-NMR and HMBC spectra also supported the structure assignment of **4**.

The following long-range correlations were established by HMBC for the geranyl side chain of **4**: CH_2(16)/C(4a), C(9), and C(18); CH(17)/C(19) and C(20); CH_2(20)/C(17), C(18) and C(21); CH_2(21)/C(20) and C(22); H–C(22)/C(21), C(24), and C(25).

Artocarpols A (**5**), C (**2**), D (**3**), and E (**4**) are the first natural products containing an oxepine ring with a novel skeleton. Further experiments are required to elucidate their biogenetic formation.

This work was supported by a grant from the *National Science Council of Republic of China* (NSC 88-2314-B 037-037).

Experimental Part

General. M.p.: Uncorrected. Optical rotations: *Jasco* model *DIP-370* digital polarimeter. UV Spectra: *Jasco-UV-VIS* spectrophotometer; λ_{max} (log ε) in nm. IR Spectra: *Hitachi-260-30* spectrophotometer; $\nu\sim$ in cm^{-1}. ^{1}H- and ^{13}C-NMR Spectra: *Varian-Unity-400* spectrometer; 400 and 100 MHz, resp.; δ in ppm, J in Hz. MS: *JMS-HX-100* mass spectrometer; *m/z* (rel %).

Plant Material. Root (8.5 kg) of *A. rigida* were collected at Ping-Tung Hsien, Taiwan, in July 1998. A voucher specimen (9801) is deposited in the laboratory of medicinal chemistry.

Extraction and Isolation. The root barks (0.79 kg) of *A. rigida* were chipped and extracted with $CHCl_3$ at r.t. The extract (57 g) was subjected to column chromatography (silica gel). Elution with cyclohexane/CH_2Cl_2/acetone 3.5 : 2 : 1 yielded **1** (23 mg) and **2** (9 mg). Elution with cyclohexane/CH_2Cl_2/acetone 3.5 : 4.5 : 1 yielded **3** (14 mg) and **4** (25 mg).

Artocarpol B (=*8,9-Dihydro-6,12-dihydroxy-9-(1-hydroxy-1-methylethyl)-3-methyl-3-(4-methylpent-3-enyl)-3*H,*7*H-*pyrano[2,3 : 7,8][1]benzopyrano[3,2-*d*][1]benzoxepin-7-one*; **1**): Yellow amorphous powder (from cyclohexane/acetone). $[\alpha]_D^{25} = -2.4$ ($c = 0.1$, acetone). UV (MeOH) 210 (4.60), 231 (4.51), 289 (4.561), 307 (sh, 4.42), 348 (4.44). UV (MeOH + $AlCl_3$): 210, 255, 327 (sh), 375. UV (MeOH + NaOMe): 218, 238 (sh), 275 (sh), 288, 310 (sh). IR (KBr): 3435, 1653, 1606. ^{1}H-NMR ((D_6)acetone, 400 MHz; for numbering, see *Fig.*): 1.34 (*s*, Me(12)); 1.36 (*s*, Me(13)); 1.45 (*s*, Me(17)); 1.56 (*s*, Me(22)); 1.63 (*s*, Me(23)); 1.7–1.8 (*m*, 2 H–C(18)); 2.1–2.2 (*m*, 2 H–C(19)); 2.59 (*dd*, $J = 16.8$, 9.6, H–C(9)); 3.52 (*dd*, $J = 16.8$, 2.0, H–C(9)); 4.01 (*dd*, $J = 9.6$, 2.0, H–C(10)); 5.12 (*t*, $J = 7.2$, H–C(20)); 5.72 (*d*, $J = 10$, H–C(15)); 6.46 (*s*, H–C(6)); 6.66 (*d*, $J = 2.8$, H–C(3′)); 6.73 (*d*, $J = 10$, H–C(14)); 6.75 (*dd*, $J = 8.8$, 2.8, H–C(5′)); 7.98 (*d*, $J = 8.8$, H–C(6′)); 13.5 (*s*, OH–C(5)). ^{13}C-NMR: *Table 1*. EI-MS (70 eV): 504 (13, M^+), 489 (4), 421 (100), 403 (6), 361 (7), 347 (6), 333 (12), 203 (15). HR-EI-MS: 504.2156 ($C_{30}H_{32}O_7^+$; 504.2148).

Artocarpol C (=*1,2,11,12,13,14,15,15a-Octahydro-15,15,18,18-tetramethyl-11,9b,14-ethanylylidene-1,13-methano-9b*H-*benzo[*b*]cyclobuta[*g*]oxocino[2,3-*d*][1]benzoxepin-3,7-diol*; **2**): Amorphous powder (from $CHCl_3$). $[\alpha]_D^{25} = -12$ ($c = 0.05$, $CHCl_3$). UV (MeOH): 215 (3.86), 295 (3.16). IR ($CHCl_3$): 3452, 1609. ^{1}H-NMR: *Table 2*. ^{13}C-NMR: *Table 1*. EI-MS (70 eV): 444 (11, M^+), 429 (12), 395 (17), 361 (100), 305 (7), 198 (15). HR-EI-MS: 444.2300 ($C_{29}H_{32}O_4^+$; calc. 444.2301).

Artocarpol D (=*11,11-Dimethyl-2-(3-methylbut-2-enyl)-11*H-*dibenzo[*b,f*]pyrano[2,3-*d*]oxepin-3,7-diol*; **3**): Oil. UV (MeOH): 216 (3.31), 342 (3.25). IR ($CHCl_3$): 3386, 1602. ^{1}H-NMR ($CDCl_3$, 400 MHz; for numbering, see *Fig.*): 1.43 (*s*, Me(19), Me(20)); 1.70 (*s*, Me(14)); 1.75 (*s*, Me(15)); 3.47 (br. *d*, $J = 6.8$, 2 H–C(11)); 5.18 (*t*, $J = 6.8$, H–C(12)); 5.63 (*d*, $J = 9.6$, H–C(17)); 6.66 (*s*, H–C(1)); 6.69 (*s*, H–C(4)); 6.73

(*d*, *J* = 9.6, H–C(16)); 6.78 (*dd*, *J* = 8.4, 2.0, H–C(6)); 6.97 (*d*, *J* = 2.0, H–C(8)); 7.35 (*d*, *J* = 8.4, H–C(5)) [3]. ^{13}C-NMR: *Table 1*. EI-MS (70 eV): 376 (48, M^+), 333 (9), 321 (8), 305 (12), 293 (10), 239 (10). HR-EI-MS: 376.1675 ($C_{24}H_{24}O_4^+$; calc. 376.1675).

Artocarpol E (=*2-[(2*E*)-3,7-Dimethylocta-2,6-dienyl]-2-(3-methylbut-2-enyl)dibenzo[*b,f*]oxepin-3,7,10-triol*; **4**): Oil. UV (MeOH): 220 (3.53), 253 (sh; 3.00), 296 (3.06). IR ($CHCl_3$): 3379, 1619, 1592. ^{1}H-NMR ($CDCl_3$, 400 MHz; for numbering, see *Fig.*): 1.60 (*s*, Me(19)); 1.62 (*s*, Me(14)); 1.63 (*s*, Me(24)); 1.70 (*s*, Me(15), Me(25)); 2.03 (*m*, 2 H–C(21)); 2.07 (*m*, 2 H–C(20)); 3.21 (br. *d*, *J* = 6.4, 2 H–C(11), 2 H–C(16)); 5.06 (*t*, *J* = 5.2, H–C(17)); 5.22 (*m*, H–C(22)); 5.25 (*m*, H–C(12)); 5.71 (br. *s*, OH–C(2)); 6.57 (*s*, H–C(1)); 6.59 (*s*, H–C(4)); 6.85 (*dd*, *J* = 8.4, 2.0, H–C(6)); 7.03 (*d*, *J* = 2.0, H–C(8)); 7.43 (*d*, *J* = 8.4, H–C(5)) [3][5]. ^{13}C-NMR: *Table 1*. EI-MS (70 eV): 446 (31, M^+), 431 (4), 403 (13), 391 (6), 377 (6), 361 (18), 335 (15), 321 (31), 307 (20), 293 (18), 267 (33), 251 (14), 213 (24), 123 (49), 69 (100). HR-EI-MS 446.2457 ($C_{29}H_{34}O_4^+$; calc. 446.2457).

REFERENCES

[1] Y. Hano, R. Inami, T. Nomura, *Heterocycles* **1990**, *31*, 2173.
[2] Y. Hano, R. Inami, T. Nomura, *Heterocycles* **1993**, *35*, 1341.
[3] M. I. Chung, H. H. Ko, M. H. Yen, C. N. Lin, S. Z. Yang, T. T. Tsao, J. P. Wang, *Helv. Chim. Acta*. **2000**, *83*, 1200.
[4] T. Nomura, T. Fukai, S. Yamada, M. Katayanagi, *Chem. Pharm. Bull*. **1978**, *26*, 1394.
[5] T. Nomura, T. Fukai, T. Shimada, I. S. Chen, *Planta Med*. **1983**, *49*, 90.

Received June 5, 2000