ARTONINS A AND B, TWO NEW PRENYLFLAVONES FROM THE ROOT BARK OF ARTOCARPUS HETEROPHYLLUS LAMK.

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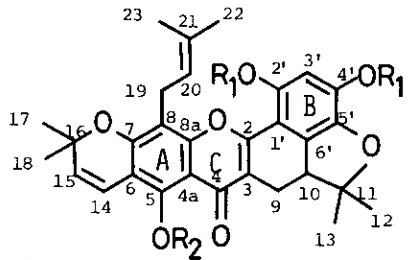
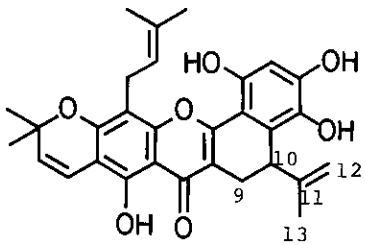
Abstract —— Two new prenylflavones, artonins A (**1**) and B (**2**), were isolated from the root bark of Artocarpus heterophyllus Lamk. (Moraceae), along with two known prenylflavones, heterophyllin (**3**) and cycloheterophyllin (**4**). The structures of artonins A and B were shown to be **1** and **2**, respectively, on the basis of the X-ray crystallographic analysis, spectroscopic data, and chemical evidence.

We already reported a series of isoprenoid-substituted phenolic compounds isolated from the moraceous plants.[1] In continuation of these studies, we examined the phenolic constituents of the root bark of Artocarpus heterophyllus, Indonesian moraceous plant. On the constituents of the plant, Venkataraman et al. reported a series of isoprenoid-substituted flavones.[2] This paper describes the characterization of two new prenylflavones, artonins A (**1**) and B (**2**), isolated from the root bark of A. heterophyllus Lamk.

The dried root bark (1 Kg) of A. heterophyllus, collected in Indonesia, was extracted with n-hexane, benzene, and acetone, successively. From the benzene extract (30 g), artonins A (**1**, 14 mg) and B (**2**, 48 mg) were isolated, along with two known compounds, heterophyllin (**3**, 300 mg)[3] and cycloheterophyllin (**4**, 1 g)[3], by using successively column chromatography, preparative tlc, hplc analysis, and gel filtration. Artonin A (**1**), yellow prisms (MeOH), mp 239-240 °C, $[\alpha]_D^{20}$ 0° (MeOH), exhibited positive ferric chloride reaction and magnesium hydrochloric acid test, and gave the EI-ms spectrum which showed the molecular ion peak at m/z 502. The ^{13}C nmr spectrum indicated the presence of thirty carbons (Table 2). Treatment of **1** with acetic



1: $R_1=R_2=H$
1a: R_1=Ac, $R_2=H$
1b: $R_1=R_2$=Ac



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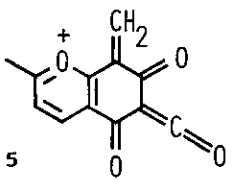

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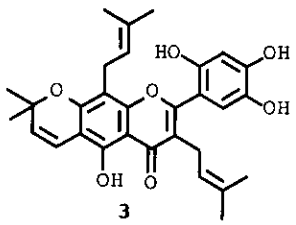

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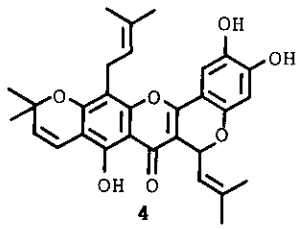

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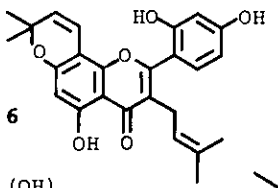

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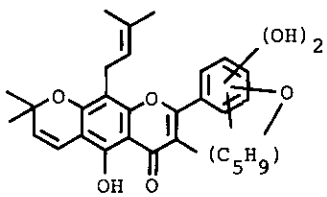
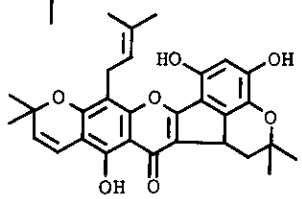


1'



1"

Table 1 ^{1}H Nmr chemical shifts (ppm) for C-14-H and C-15-H

	C-14-H	C-15-H
1a	6.73	5.62
1b	6.49	5.76
Δ	+0.24	-0.14

measured in $CDCl_3$

Fig. 1

Table 2 ^{13}C Nmr chemical shifts of **1**, **2**, and **4**

	1[a]	**2**[a]	**4**[b]		**1**[a]	**2**[a]	**4**[b]
C-2	161.6	161.8	155.7	C-9	20.5	22.4	68.5
C-3	112.6	111.3	108.3	C-10	47.6	38.1	121.1
C-4	181.7	181.5	177.8	C-11	93.7	151.5	137.6
C-4a	105.0	105.3	104.5	C-12	28.4	111.8	25.4
C-5	154.5	154.6	152.8	C-13	22.9	22.0	18.3
C-6	105.9	105.7	104.7	C-14	116.4	116.4	114.9
C-7	157.0	156.9	155.7	C-15	128.9	128.9	128.5
C-8	108.3	108.2	107.1	C-16	78.4	78.4	77.6
C-8a	155.3	155.2	153.7	C-17	28.4	28.4	27.6
C-1'	105.3	107.0	105.6	C-18	28.4	28.4	27.5
C-2'	151.5	150.9	152.3	C-19	22.0	22.1	21.0
C-3'	105.4	103.6	104.5	C-20	123.7	123.5	121.9
C-4'	147.0	145.4	150.4	C-21	131.7	131.8	131.1
C-5'	138.0	136.7	141.0	C-22	25.9	25.9	25.4
C-6'	133.7	129.8	109.0	C-23	18.2	18.1	17.8

solvent; a: acetone-d_6 b: DMSO-d_6

anhydride in pyridine gave a diacetate (**1a**, $FeCl_3$ test: positive)[4] and a triacetate (**1b**, $FeCl_3$ test: negative)[5]. These results suggest that the composition of artonin A (**1**) is $C_{30}H_{30}O_7$ and has three hydroxyl groups in the structure. The ir and uv spectra of **1** disclosed the following data: uv λ_{max}^{MeOH} nm (logε): 206 (4.65), 238 (4.31), 295 (4.43), 385 (4.29); ir ν_{max}^{KBr} cm^{-1}: 3570, 3560, 3150 (br), 1650, 1605, 1550, 1475, 1430. The uv spectrum closely resembled that of cycloheterophyllin (**4**). From the above results, the compound **1** is a flavone derivative like cycloheterophyllin (**4**). The ^1H nmr spectrum (acetone-$\underline{d}_6$) was analysed by comparison with those of **3** and **4**, and showed the signals of the following protons: 1) protons in a *r*,*r*-dimethylallyl (prenyl) group, δ 1.63, 1.80 (each 3H, br s, C-21-CH_3), 3.44, 3.62 (each 1H, br dd, $\underline{J}$=8 and 14 Hz, C-19-H), 5.32 (1H, br t, $\underline{J}$=8 Hz, C-20-H), 2) protons in a 2,2-dimethylpyran ring, δ 1.47 (6H, s, C-16-CH_3 x 2), 5.72 (1H, d, $\underline{J}$=10 Hz, C-15-H), 6.68 (1H, d, $\underline{J}$=10 Hz, C-14-H), 3) an aromatic proton, δ 6.41 (1H, s, C-3'-H), 4) a proton in a hydrogen-bonded hydroxyl group, δ 13.69 (1H, s, C-5-OH). The chemical shift values of these protons were almost the same as those of the relevant protons of **3** and **4**, while the proton signal at C-6' position was not observed in the spectrum. The EI-ms spectrum of **1** showed the following significant fragment ions: $\underline{m/z}$ 487 (M^+-CH_3, base peak), 459 (M^+-C_3H_7), 446 (M^+-C_4H_8), and 215 (**5**). This result suggests that a prenyl group and a 2,2-dimethylpyran ring are located in the A ring. The linear structure for the pyran ring was confirmed by the acetylation shift value of the olefinic protons in the pyran ring. The changes in chemical shift values of the diacetate (**1a**) and the triacetate (**1b**) indicate that the C-14-H is *peri* to C-5-OH (Table 1).[6] In the ^{13}C nmr spectrum of **1**, the chemical shift values of the carbon atoms of A ring, pyran ring, and prenyl group were similar to those of the relevant carbon atoms of **4**. From the above results, the partial structure (**1'**) can be proposed. The ^1H nmr spectrum of **1** showed the signals of the remaining protons as follows: 1) protons of two methyl groups, δ 1.33, 1.66 (each 3H, s, C-11-CH_3), 2) ABX type protons, δ 2.36 (1H, t, $\underline{J}$=15 Hz, C-9-H), 3.21 (1H, dd, $\underline{J}$=7 and 15 Hz, C-10-H), 3.41 (1H, dd, $\underline{J}$=7 and 15 Hz, C-9-H). These two methyl signals and the signals of an ABX type can be attributed to the isoprenoid moiety located at the C-3 position. This assumption was supported by the presence of two methyls (δ 22.9 and 28.4), a methylene (δ 20.5), a methine (δ 47.6), and an oxygenated sp^3 quaternary (δ 93.7) carbon atom in the ^{13}C nmr spectrum of **1** (Table 2). On the other hand, it has been reported that the oxidative cyclization occurred between a hydroxyl group at the C-2' position and a prenyl group located at the

C-3 position in the case of 3-prenylated flavones such as morusin (**6**).[7] The above results being taken into consideration, it was suggested that the C-C and the ether linkages have taken place between the B ring and the isoprenoid substituent located at the C-3 position. Thus two possible structures, **1** and **1'**, were proposed for artonin A. To determine the structure, the X-ray crystallographic analysis of **1** was carried out and the following crystal data were obtained: $C_{30}H_{30}O_7 \cdot H_2O$, molecular weight=520.58, triclinic, space group P1, lattice constants, a=9.765(7) Å, b=13.099(7) Å, c=5.724(2) Å, α=100.87(4)°, β=93.45(4)°, γ=68.43(5)°, V=668.6 Å^3, Z=1, and the final R value 0.10. The crystal structure of **1** was determined as shown in Fig. 2, and the formula **1** was confirmed as the structure of artonin A. Artonin B (**2**), yellow needles (benzene), mp 219-222 °C, $[\alpha]_D^{20}$ 0° (MeOH), exhibited positive $FeCl_3$ and Mg-HCl tests, and gave the EI-ms spectrum which showed the molecular ion peak at m/z 502. The ^{13}C nmr spectrum indicated the presence of thirty carbons (Table 2). These results suggest that the composition of artonin B (**2**) is $C_{30}H_{30}O_7$. The ir and uv spectra of **2** disclosed the following data: uv λ_{max}^{MeOH} nm (log ε): 210 (4.55), 235 (sh 4.41), 295 (4.54), 381 (4.40); ir ν_{max}^{KBr} cm^{-1}: 3550, 3500, 3400, 3200 (br), 1650, 1625, 1605, 1600, 1540, 1505, 1480, 1470, 1430. The uv and EI-ms spectra of **2** closely resembled those of artonin A (**1**). The ^1H nmr spectrum of **2** was also similar to that of **1**, while the signals of two methyl groups in the 2,2-dimethyldihydrofuran ring of **1** were not observed in the spectrum of **2**. In the spectrum (acetone-d_6), the signals of the following protons were observed: 1) protons in a prenyl group, δ 1.62, 1.79 (each 3H, br s, C-21-CH_3), 3.41, 3.64 (each 1H, br dd, J=8 and 14 Hz, C-19-H), 5.26 (1H, br t, J=8 Hz, C-20-H), 2) protons in a 2,2-dimethylpyran ring, δ 1.45, 1.46 (each 3H, s, C-16-CH_3), 5.72

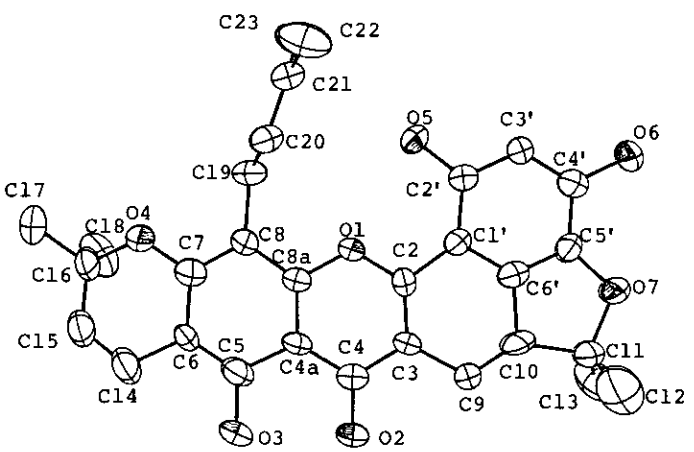


Fig. 2
The crystal structure of artonin A (**1**)

(1H, d, J=10 Hz, C-15-H), 6.68 (1H, d, J=10 Hz, C-14-H), 3) an aromatic proton, δ 6.68 (1H, s, C-3'-H), 4) protons in an isopropenyl group, δ 1.78 (3H, s, C-11-CH_3), 4.32, 4.65 (each 1H, br s, C-12-H), 5) ABX type protons, δ 2.44 (1H, dd, J= 7 and 16 Hz, C-9-H), 3.42 (1H, dd, J=2 and 16 Hz, C-9-H), 4.00 (1H, br d, J=7 Hz, C-10-H), 6) a proton in a hydrogen-bonded hydroxyl group, δ 13.03 (1H, s, C-5-OH). In the ^{13}C nmr spectrum of **2**, the chemical shift values of all the carbon atoms except those of C-6' and of the isoprenoid moiety located at the C-3 position were similar to those of the relevant carbon atoms of **1**. From the above data, compound **2** seems to be a structural isomer modified to the isopropenyl group from the 2,2-dimethyldihydrofuran ring of **1**. To corroborate this assumption, the following experiment was carried out. A 5% hydrochloric acid-methanol solution of **2** was allowed to stand for three days at room temperature, and then the product was purified by preparative tlc. The mp, ir, and nmr spectral data of the product were in fair agreement with those of artonin A (**1**). From the above results, the formula **2** was confirmed as the structure of artonin B.

Both artonins A (**1**) and B (**2**) have unique structure in which the C-C linkage takes place between the C-6' position of the B ring and the C-10 position of isoprenoid moiety located at the C-3 position. Taking no optical activities[8] into account, artonins A (**1**) and B (**2**) are biogenetically assumed to be derivatives from heterophyllin (**3**) through the oxidative coupling reaction as shown in Fig. 3.[9,10]

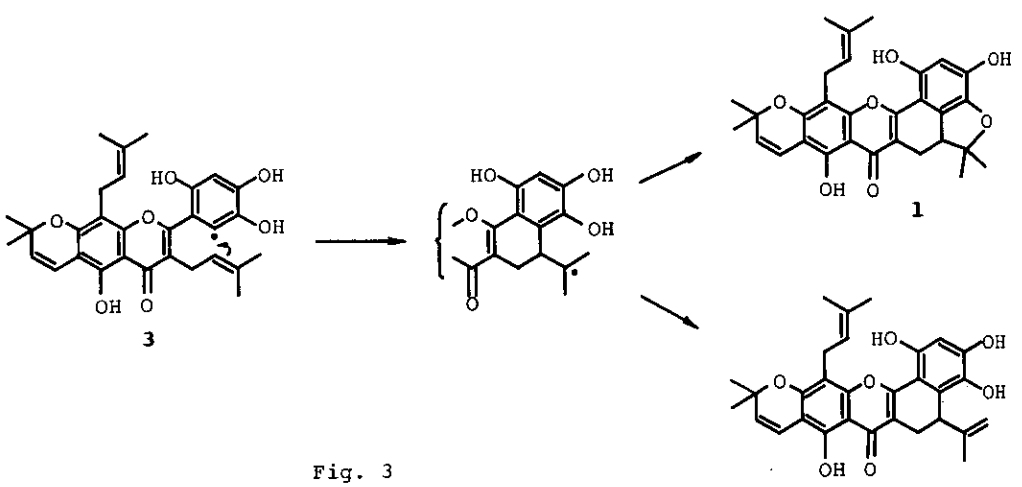


Fig. 3

REFERENCES AND NOTES

1. T. Nomura, "Progress in the Chemistry of Organic Natural Products", Splinger-Verlag, Wien, New York, 1988, **53**, pp. 87-201.

2. a) K. Venkataraman, Recent Dev. Chem. Nat. Carbon Compd., 1976, **7**, 39 and the references cited therein; b) K. Venkataraman, Phytochemistry, 1972, **11**, 1571 and the references cited therein.

3. A.V. Rama Rao, M. Varadan, and K. Venkataraman, Indian J. Chem., 1971, **9**, 7. However, the datailed data for heterophyllin (**3**) have not been cited therein. Our data for **3** are as follows: yellow needles, mp 202-204 °C, $FeCl_3$ test (+), Mg-HCl test (+). EI-Ms m/z 504 (M^+), 489 (base peak), 461, 449, 431, 405, 215. Uv λ_{max}^{MeOH} nm (logε): 206 (4.60), 283 (4.59), 342 (4.03). Ir ν_{max}^{KBr} cm^{-1}: 3420, 3380, 1653, 1635, 1615, 1570, 1525, 1474, 1448, 1430 (sh). ^1H Nmr (acetone-d_6): δ 1.46 (9H, s), 1.57, 1.61, 1.66 (each 3H, s), 3.16, 3.34 (each 2H, br d, J=7 Hz), 5.14, 5.17 (each 1H, m), 5.74 (1H, d, J=10 Hz), 6.60 (1H, s), 6.70 (1H, d, J=10 Hz), 6.85 (1H, s), 13.49 (1H, s).

4. Diacetate (**1a**) was obtained as yellow needles, mp 220-221 °C, and positive to $FeCl_3$ test. The spectral data are as follows: EI-Ms m/z: 586 (M^+), 571, 544, 529. Ir ν_{max}^{KBr} cm^{-1}: 3450 (br), 1780, 1650, 1605. ^1H Nmr ($CDCl_3$): δ 1.40, 1.45, 1.46, 1.66, 1.68, 1.79 (each 3H, s, C-11-CH_3, C-16-CH_3 and C-21-CH_3), 2.32, 2.34 (each 3H, s, $COCH_3$), 2.51 (1H, t, J=15 Hz, C-9-H), 3.29 (1H, dd, J=7 and 15 Hz, C-10-H), 3.4-3.5 (3H, m, C-9-H and C-19-H x 2), 5.19 (1H, br t, J=7 Hz, C-20-H), 5.62 (1H, d, J=10 Hz, C-15-H), 6.73 (1H, d, J=10 Hz, C-14-H), 6.75 (1H, s, C-3'-H), 13.13 (1H, s, C-5-OH).

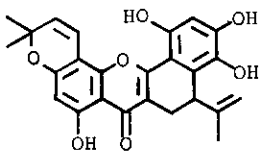
5. Triacetate (**1b**) was obtained as colorless needles, mp 180 °C, and negative to $FeCl_3$ test. The spectral data are as follows: EI-Ms m/z: 628 (M^+), 586, 571, 543, 529. Ir ν_{max}^{KBr} cm^{-1}: 1770, 1640 (sh), 1620, 1600, 1190. ^1H Nmr ($CDCl_3$): δ 1.37, 1.48, 1.49, 1.66, 1.67, 1.80 (each 3H, s, C-11-CH_3, C-16-CH_3 and C-21-CH_3), 2.31, 2.34, 2.47 (each 3H, s, $COCH_3$), 2.47 (1H, t, J=15 Hz, C-9-H), 3.28 1H, dd, J=7 and 15 Hz, C-10-H), 3.39 (1H, dd, J=7 and 15 Hz, C-9-H), 3.51, 3.59 (each 1H, br dd, J=7 and 14 Hz, C-19-H), 5.22 (1H, br t, J=7 Hz, C-20-H), 5.76 (1H, d, J=10 Hz, C-15-H), 6.49 (1H, d, J=10 Hz, C-14-H), 6.74 (1H, s, C-3'-H).

6. a) A. Arnone, G. Cardillo, L. Merlini, and R. Mondelli, Tetrahedron Lett., 1967, 4201; b) B. Jackson, P.J. Owen, and F. Sheinmann, J. Chem. Soc. (C), 1971, 3389.

7. T. Nomura and T. Fukai, Heterocycles, 1981, **15**, 1531 and the references cited therein.

8. The result of the X-ray crystallographic analysis of **1** also indicated that artonin A (**1**) is a mixture of C-10(S) and C-10(R)-artonin A.

9. Recenly, Sultanbawa et al. reported the structure of two pyranodihydrobenzoxanthones, artobiloxanthone (**7**) and cycloartobiloxanthone (**8**) from the bark of Artocarpus nobilis [M.U.S. Sultanbawa and S. Surendrakumar, Phytochemistry, 1989, **28**, 599]. Both of **7** and **8** have the same partial structure as artonins A (**1**) and B (**2**).



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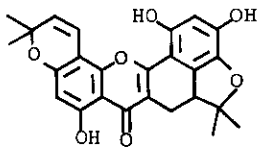

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10. We contributed the abstract paper for the structure determination of artonins A and B to the Organizing Comitties of 109th Annual Meeting of the Pharmaceutical Society of Japan (November, 19th, 1988). In the paper, we proposed the formula **1** and **2** for the structure of artonins A and B, respectively [109th Annual Meeting of the Pharmaceutical Society of Japan, Abstract Papers, Vol. III, p. 161, April, 1989, Nagoya, Japan].

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