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THREE NEW FLAVANS FROM THE ROOT OF *DAPHNE ODORA* THUNB.

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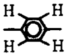
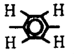
From the root of *Daphne odora* Thunb. (Chinese crude drug, Ruixanggen, Thymelaeaceae) three new flavans, daphnodorin A (**1**), daphnodorin B (**2**) and daphnodorin C (**3**) have been isolated. Their structures were established by chemical and spectroscopic means.

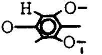
KEYWORDS ―― *Daphne odora*; Thymelaeaceae; flavan; daphnodorin A; daphnodorin B; daphnodorin C; Ruixanggen

The root of *Daphne odora* Thunb. is called "Ruixanggen" in China. It is used to treat stomachache, bruises and bites by venomous snakes.

Recently, the authors investigated this plant in order to study its phenolics and isolated three new flavans named daphnodorin A (**1**), daphnodorin B (**2**) and daphnodorin C (**3**) in addition to coumarins such as daphnin, daphnetin, daphnoretin and umbelliferone. This paper deals with the structure elucidation of these compounds.

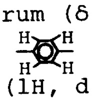
Daphnodorin A (**1**), $C_{30}H_{22}O_9$, yellow crystalline powders, mp 185 - 186°C(dec.), Gibbs Ts + (greenish brown). ORD(c=0.19, dioxane)$[\alpha]^{22}$(nm): -63.16°(589), -84.21°(550), -105.26°(500), -168.42°(450), -252.63°(400), -926.36°(350), -1347.37°(338), -842.11°(330). CD(c=0.0011, dioxane) $\Delta\varepsilon^{23}$max(nm): -0.7(263), +2.7(289), -3.3(322). $UV\lambda_{max}^{dioxane}$nm(log ε): 217(4.58), 307(4.58). $IR\nu_{max}^{Nujol}cm^{-1}$: 3250, 1615, 1510. From the ^{1}H-NMR spectrum (δ, DMSO-d_6) of **1**, the presence of the following skeletons and groups in the molecule were deduced: 4-oxyphenyl × 2 [7.39, 6.78(each 2H, d, J=8.8 Hz), 6.85, 6.60(each 2H, d, J=8.8 Hz)], 2,8(or 6)-disubstituted 5,7-dioxy-3,4-dihydrobenzopyran [6.58(1H, s), 4.86(1H, br d, J=9.4 Hz), 2.64(2H, m), 2.22, 1.70(each 1H, m)], 2,4,6-trioxyphenyl [5.74(2H, s)], phenolic OH × 6 [12.42, 11.52(each 1H,br), 10.51, 9.73, 9.60, 9.27(each 1H, s)]. The ^{13}C-NMR spectrum (δ, DMSO-d_6) (Table I) exhibited signals due to twenty seven sp^2 carbons ($>$C=O, $=\overset{|}{C}-O$ × 9, $=\overset{|}{C}-$ × 6, =CH- × 11) and three sp^3 carbons ($-CH_2-$ × 2, $-\overset{|}{C}H-O-$), and those signals were well assigned to the skeletons and groups revealed in the ^{1}H-NMR spectrum. The acetylation of **1** with acetic anhydride and pyridine gave a hexaacetate (**4**), and then the methylation of **1** with CH_2N_2 gave a pentamethyl ether (**5**). In the ^{1}H-NMR spectrum of both **4** and **5**, two aromatic protons of 2,4,6-trioxyphenyl occurred as AB type signals [**4**: 6.68, 6.39(each 1H, d, J=2.3 Hz), **5**: 5.97, 5.94(each 1H, d, J=2.3 Hz)], and in that of **5** a signal due to a chelated hydroxy group appeared at 13.46. Further, the ^{1}H-NMR of **4** and **5** exhibited two acetyl signals (1.68 and 1.99) and a methoxyl signal (3.26) shifted to a higher field, respectively. **5** was methylated with CH_3I to give a hexamethyl ether, whose ^{1}H-NMR spectrum exhibited an aromatic proton signal (5.99, 2H, s) due to 2,4,6-trioxyphenyl group, and a methoxyl signal (3.46, 6H, s) shifted to the higher field. From these ^{1}H-NMR data, it became evident that the 2,4,6-trioxyphenyl moiety was linked at a carbonyl group and was held in the position by magnetic shielding. **5** was decomposed upon heating in acetic acid with H_2SO_4 to give 4-methoxybenzoic acid (**6**), 3,5-dimethoxyphenol (**7**), 2-hydroxy-4,6-dimethoxybenzoic acid (**8**) and furanoflavan (**9**) whose structure was determined to be formula 9 from the following spectral data; ORD(dioxane)$[\alpha]^{23}$(nm): 0°(700 - 360), $IR\nu_{max}^{CHCl_3}cm^{-1}$: 1630, 1615, 1590, 1505. $UV\lambda_{max}^{dioxane}$nm(log ε): 221(4.38), 247(4.01), 256(4.00), 306sh (4.41), 319(4.48), 334sh(4.30). Mass m/z: 416(28, M^+), 282(100, M-134), 267(61, 282-Me), 134(35, M-282). ^1H-NMR (δ, $CDCl_3$): 7.68, 6.93(each 2H, br d, J=8.8 Hz, 

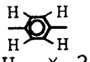
), 7.38, 6.93(each 2H, br d, J=8.8 Hz, 

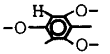
), 6.89(1H, d, J=0.9 Hz, =CH-), 6.66(1H, d, J=0.9 Hz, 

), 3.85(3H, s, OCH_3), 3.81(6H, s, OCH_3 x 2), 5.06(1H, dd, J=10.3, 2.1, $Ar-CH_2-CH_2-\overset{|}{C}\underline{H}-O-$), 2.85, 2.73(each 1H, m, $Ar-C\underline{H_2}-CH_2-\overset{|}{C}H-O-$), 2.26, 2.07(each 1H, m, $Ar-CH_2-C\underline{H_2}-\overset{|}{C}H-O-$), the irradiation of the OCH_3 signal at δ 3.85 resulted in an 18.5% NOE enhancement of the aromatic proton signal at 6.66 but no NOE enhancement of the proton signal at 6.89.1)

From the above evidence, the structure of **1** was represented as formula 1 .

Daphnodorin B (**2**), $C_{30}H_{22}O_{10}$, yellow crystalline powders, mp 215 - 217°C(dec.), Gibbs Ts + (greenish brown). ORD(c=0.22, dioxane)$[\alpha]^{22}$(nm): -107.62°(589), -143.50° (550), -193.31°(500), -269.06°(450), -287.00°(400), -1721.97°(350). CD(c=0.0013, dioxane) $\Delta\varepsilon^{23}$max(nm): -1.7(264), +2.1(287), -4.7(314), +0.5(360). $UV\lambda_{max}^{dioxane}$nm(log ε): 215(4.57), 301(4.57). $IR\nu_{max}^{Nujol}cm^{-1}$: 3250, 1625, 1600, 1500. The ^1H-NMR spectrum (δ, DMSO-d_6) of **2** was very similar to that of **1** except that signals due to a 3-hydroxy-3,4-dihydropyran ring were observed instead of the signals due to the 3,4-dihydropyran ring; 4-oxyphenyl X 2 [7.39, 6.78(each 2H, br d, J=8.8 Hz), 6.86, 6.58 (each 2H, br d, J=8.8 Hz)], 2,8-disubstituted 3,5,7-trioxy-3,4-dihydrobenzopyran [6.59(1H, s), 5.03(1H, d, J=5.2 Hz, OH), 4.57(1H, d, J=7.4 Hz), 3.73(1H, m), 2.74 (1H, dd, J=16.5, 5.5 Hz), 2.50(1H, dd, J=16.5, 8.5 Hz)], 2,4,6-trioxybenzoyl [5.70 (2H, s)], phenolic OH X 6 [12,50, 11.19(each 1H, br), 10.47, 9.73, 9.61, 9.23(each 1H, s)]. The ^{13}C-NMR spectrum (δ, DMSO-d_6) of **2** was also very similar to that of **1** except for signals due to a dihydropyran ring (Table I). The acetylation of **2** with acetic anhydride and pyridine gave a heptaacetate (**10**), and then the methylation of **2** with CH_2N_2 gave a pentamethyl ether (**11**). **11** was decomposed upon heating in acetic acid with H_2SO_4 to give **6**, **7**, **8** and furanofravan (**12**) which was determined by the ^1H-NMR spectrum (δ, $CDCl_3$) to be the 3-acetoxy derivative of **9**; 7.71, 6.95(each 2H, d, J=8.8 Hz, 

), 7.31, 6.87(each 2H, d, J=8.8 Hz, 

), 6.93(1H, d, J=0.7 Hz, =CH-), 6.70(1H, d, J=0.7 Hz, 

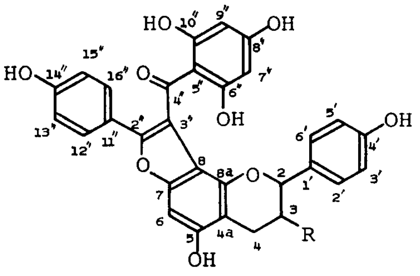
), 3.85(6H, s, OCH_3 x 2), 3.80(3H, s, OCH_3), 5.43(1H, m, $Ar-CH_2-\overset{O}{C}\underline{H}-\overset{|}{C}H-O-$), 5.23(1H, d, J=5.9 Hz, $Ar-CH_2-\overset{O}{C}H-\overset{|}{C}\underline{H}-O-$), 2.93(1H, dd, J=17.0, 5.3 Hz, $Ar-C\underline{H_2}-\overset{O}{C}H-\overset{|}{C}H-O-$), 2.81(1H, dd, J=17.0, 5.8 Hz, $Ar-C\underline{H_2}-\overset{O}{C}H-\overset{|}{C}H-O-$), 1.99(3H, s). Consequently, the structure of **2** was represented as formula 2 .

Daphnodorin C (**3**), $C_{30}H_{22}O_9$, off-white crystalline powders, mp 233 - 235°C(dec.), Gibbs Ts + (reddish brown). ORD(c=0.21, dioxane)$[\alpha]^{22}$(nm): -262.9°(589), -338.0° (550), -469.5°(500), -657.3°(450), -1164.3°(400), -4507.0°(350), -7211.3°t(342), 0° (332), +5558.7°p(316), 0°(306). CD(c=0.0018, dioxane) $\Delta\varepsilon^{23}$max(nm): -23.9(275), +5.4 (305), -18.0(329). $UV\lambda_{max}^{dioxane}$nm(log ε): 222(4.84), 283(4.45), 322(3.72). $IR\nu_{max}^{Nujol}$ cm^{-1}: 3450, 3250, 1680, 1640, 1620, 1530. From the ^1H-NMR spectrum (δ, DMSO-d_6) of **3**, the presence of the following skeletons and groups in the molecule were deduced; 4-oxyphenyl X 2 [7.04, 6.68(each 2H, d, J=8.8 Hz), 6.85, 6.59(each 2H, d, J=8.8 Hz)], monosubstituted 2,4,6-trioxybenzene moiety [5.83, 5.52(each 1H, d, J=1.7 Hz)], $-\overset{|}{C}H-$ [5.47(1H, s)], 2,8(or 6)-disubstituted 5,7-dioxy-3,4-dihydrobenzopyran [6.10(1H, s,

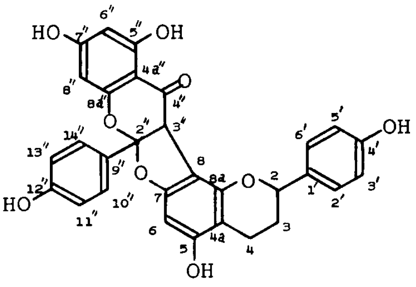
Table I. ^{13}C-NMR Chemical Shifts of 1, 2 and 3 in DMSO-d_6, δ (ppm) from TMS

Carbon	1	2	Carbon	3
C-2	76.04(d)	80.53(d)	C-2	75.89(d)
C-3	19.55(t)	66.52(d)	C-3	19.29(t)
C-4	29.08(t)	28.64(t)	C-4	28.25(t)
C-4a	104.50(s)	103.43(s)	C-4a	102.57(s)*
C-5	153.65(s)	153.83(s)	C-5	160.80(s)
C-6	89.30(d)	89.69(d)	C-6	89.37(d)**
C-7	148.25(s)	147.59(s)	C-7	172.42(s)
C-8	110.01(s)	109.80(s)	C-8	102.66(s)*
C-8a	152.24(s)	152.58(s)	C-8a	152.40(s)
C-1'	131.45(s)	129.20(s)	C-1'	131.14(s)
C-2'	125.91(d)	127.49(d)	C-2'	126.06(d)
C-3'	114.65(d)*	114.59(d)*	C-3'	114.84(d)
C-4'	157.36(s)**	157.58(s)**	C-4'	157.65(s)
C-5'	114.65(d)*	114.59(d)*	C-5'	114.84(d)
C-6'	125.91(d)	127.49(d)	C-6'	126.06(d)
C-2"	146.37(s)	146.79(s)	C-2"	93.91(s)
C-3"	117.12(s)	117.27(s)	C-3"	90.87(d)
C-4"	194.56(s)	194.57(s)	C-4"	193.30(s)
C-5"	105.74(s)	105.95(s)	C-4a"	102.78(s)
C-6"	165.23(s)	165.53(s)***	C-5"	159.10(s)
C-7"	94.44(d)	94.69(d)****	C-6"	96.10(d)
C-8"	165.87(s)	165.97(s)	C-7"	157.71(s)
C-9"	94.44(d)	94.59(d)****	C-8"	89.42(d)**
C-10"	164.16(s)	165.47(s)***	C-8a"	168.00(s)
C-11"	121.22(s)	121.39(s)	C-9"	123.42(s)
C-12"	126.48(d)	126.75(d)	C-10"	129.00(d)
C-13"	115.60(d)*	115.80(d)*	C-11"	114.84(d)
C-14"	156.12(s)**	156.45(s)**	C-12"	156.26(s)
C-15"	115.60(d)*	115.80(d)*	C-13"	114.84(d)
C-16"	126.48(d)	126.75(d)	C-14"	129.00(d)

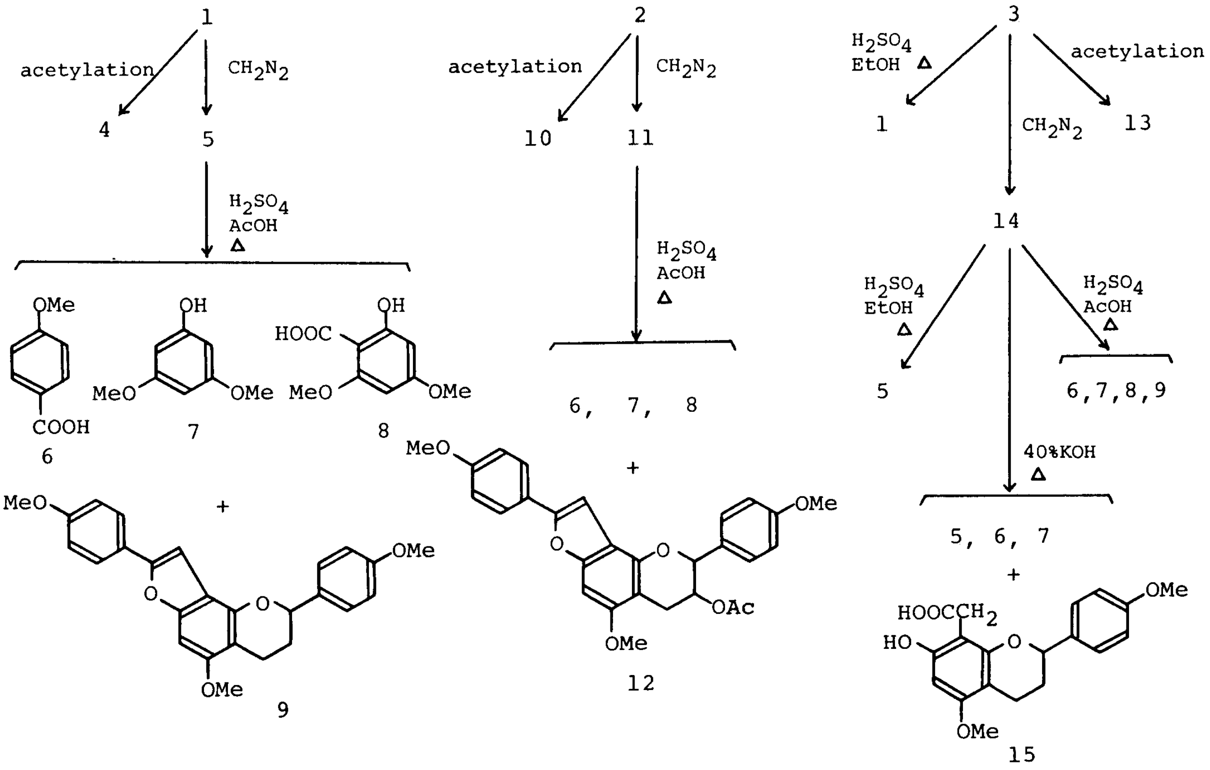
Asterisks: Assignment may be interchangeable in each column.



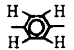
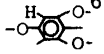
1: R= H
2: R= OH



3



4.78(1H, d, J=10.4 Hz), 2.55(2H, m), 2.27, 1.55(each 1H, m)], phenolic OH X 5[10.63, 10.42, 9.88, 9.50, 9.25(each 1H, s)]. The ^{13}C-NMR spectrum (δ, DMSO-d_6) of 3 exhibited signals due to twenty five sp^2 carbons (>C=O, $=\overset{|}{C}$-O x 8, $=\overset{|}{C}$- x 5, =CH- x 11) and five sp^3 carbons ($-\overset{|}{\underset{|}{C}}-$, $-\overset{|}{C}H-$ x 2, $-CH_2-$ x 2), and those signals were well assigned to the skeletons and groups revealed in the ^{1}H-NMR spectrum. The acetylation of **3** with acetic anhydride and pyridine gave a pentaacetate (**13**) and the methylation of **3** with CH_2N_2 gave a pentamethyl ether (**14**). In the ^{1}H-NMR spectra of **13** and **14**, an acetyl signal and a methoxyl signal were not shifted upfield in comparison with those of **4** and **5**. From the above evidence, it was estimated that 3 has a flavan skeleton, which formed some condensed ring with the monosubstituted 2,4,6-trioxybenzene moiety unlike **1** and **2**.

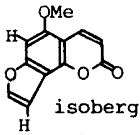
The treatment of **3** and **14** with H_2SO_4 in EtOH gave **1** and **5**, respectively. Further, **14** was decomposed upon heating in AcOH with H_2SO_4 to give **6**, **7**, **8** and **9**, and upon alkaline hydrolysis to give **5**, **6**, **7** and 8-carboxymethyl-7-hydroxy-5,4'-dimethoxyflavan (**15**) whose structure was decided from the following spectral data; ^{1}H-NMR (δ DMSO-d_6): 8.96(1H, br, COOH), 7.32, 6.92(each 2H, d, J=8.6 Hz, ), 6.05(1H, s, ), 5.66(1H, s, OH), 4.95(1H, dd, J=10.3, 2.0, Ar-CH_2-CH_2-$\overset{|}{C}\underline{H}$-O-), 2.50(2H, m, Ar-$C\underline{H}_2$-$CH_2$-$\overset{|}{C}H$-O-), 2.12, 1.80(each 1H, m, Ar-CH_2-$C\underline{H}_2$-$\overset{|}{C}H$-O-), 3.75, 3.67(each 3H, s, OCH_3 x 2), 3.40, 3.33(each 1H, d, J=16.0 Hz, Ar-$C\underline{H}_2$-COOH). MS m/z: 326(18, M-H_2O), 192(9, M-134), 134(100, M-192). IRν_{max}^{Nujol}cm^{-1}: 3450, 3200-2500, 1680, 1620, 1510. From the above results, the structure of **3** was represented as formula 3 .

Moreover, the stereochemistry of **1**, **2** and **3** are now in progress by CD and X-ray analysis. However, the relative configuration between C-2 and C-3 of **2** was determined to be *trans* by the comparison of the ^{1}H-NMR spectra with those of catechin and epicatechin.[2)]

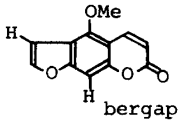
ACKNOWLEDGEMENT We are greatly indebted to Prof. A. Numata and Miss M. Nabae of this College of Pharmacy for the measurement of NMR spectra. We also thank Dr. H. Komura of Suntry Institute for Bioorganic Reseach, and Prof. S. Matsunaga and Miss M. Kurimoto of this College of Pharmacy for the measurement of the CD and Mass spectra.

REFERENCES AND NOTES

1) In the ^{1}H-NMR spectrum of isobergapten, a long range coupling (J=1.0 Hz) between the proton of C-6 and the proton of the β-position of the furan ring was observed, and the irradiation of the OCH_3 signal of C-5 at δ 3.96 resulted in a 17.3% NOE enhancement of the proton signal of C-6 at δ 6.88. In the case of bergapten, a long range coupling (J=1.0 Hz) between the proton of C-8 and the proton of the β position of the furan ring was observed, and the irradiation of the OCH_3 signal of C-5 at δ 4.27 resulted in a 6.5% NOE enhancement of the proton signal of the β position of the furan ring at δ 7.02.



isobergapten



bergapten

2) G. Nonaka, O. Kawahara and I. Nishioka, Chem. Pharm. Bull., 31, 3906 (1983).

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