Tetrahedron Letters,Vol.30,No.9,pp 1111-1114,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

ANTAGONISTS OF PLATELET ACTIVATING FACTOR FROM SWIETENIA MAHOGANI (L.) JACQ

Shigetoshi Kadota,[a] Lamek Marpaung,[a] Tohru Kikuchi,[a,*] and Hisao Ekimoto[b]

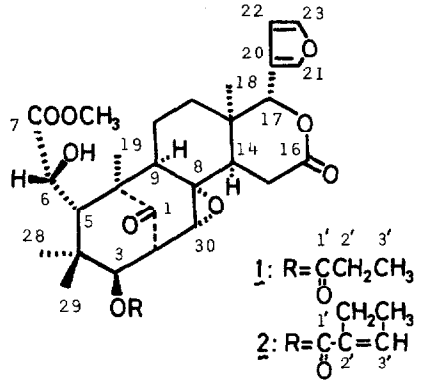
Research Institute for Wakan-Yaku (Oriental Medicines), Toyama Medical and Pharmaceutical University,[a] 2630 Sugitani, Toyama 930-01, Japan, Research Laboratories Pharmaceuticals Group Nippon Kayaku Co., Ltd.,[b] 31-12, Shimo 3-chome, Kita-ku, Tokyo 115, Japan

Summary: The structures of swietemahonin A (1), E (2), and 3-acetylswietenolide (3), isolated as antagonists of platelet activating factor from the ether extract of Swietenia mahogani (L.) Jacq., were determined based on the 2-D NMR spectroscopy.

In our search for biologically significant substances from medicinal plants in Indonesia, we have isolated three new tetranortriterpenoids, swietemahonin A (1), E (2), and 3-acetylswietenolide (3), from the cotyledons of Swietenia mahogani (L.) Jacq.[1] and found that they exhibit antagonistic effects on platelet activating factor (PAF).[2] This paper describes the isolation and structure elucidation of these new tetranortriterpenoids.

The cotyledons (700 g) of S. mahogani, collected in Medan, *North Sumatera-Indonesia*, were pulverized and extracted with ether at room temperature and then with boiling MeOH. The ether extract yielded an oil and a solid precipitate. The oily fraction of the ether extract was roughly separated by silica gel column chromatography using benzene, benzene-CH_2Cl_2, CH_2Cl_2, and MeOH-CH_2Cl_2. The MeOH-CH_2Cl_2 eluates were further separated by a combination of preparative TLC and HPLC to give swietemahonin A (1)(52 mg), E (2)(34 mg), and 3-acetylswietenolide (3)(56 mg), along with known swietenine (4)[3] and swietenolide (5).[4]

Swietemahonin A (1), colorless needles (from AcOEt-isopropyl ether), mp 174 - 174.5°C, $[\alpha]_D$ -12.16 ($CHCl_3$), has the molecular formula $C_{30}H_{38}O_{10}$ (M^+ 558.2478, calcd. 558.2464) and its IR spectrum showed the presence of a hydroxyl (3500 cm^{-1}), a lactone (1735 cm^{-1}), an ester (1720 cm^{-1}), a ketone (1700 cm^{-1}), and a furan (1500 and 870 cm^{-1}). The ^1H and ^{13}C NMR and



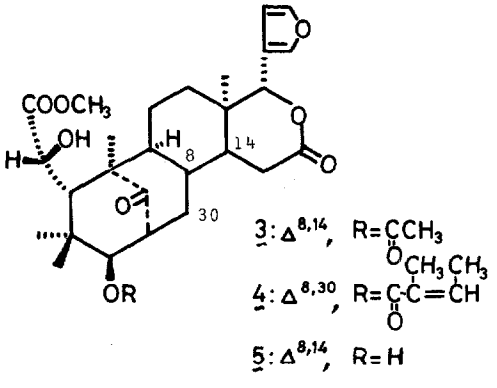


Table I. ^{1}H-NMR Spectral Data of Swietemahonin A (1), E (2), 3-Acetylswietenolide (3), Swietenine (4), and Swietenolide (5)

Compd / ^{1}H	1	2	3	4	5
2	3.54 dd (9.5, 2.5)	3.61 dd (9.5, 2.5)	3.15 ddd (10, 6, 2.5)	3.52 ddt (10, 8, 1.5)	3.04 ddd (10, 5.5, 2.5)
3	4.94 d (9.5)	4.84 d (9.5)	4.82 d (10)	4.64 d (10)	3.58 d (10)
5	3.27 br s	3.36 br s	3.22 br s	3.50 br s	3.25 br s
6	4.46 br s	4.46 br s	4.55 br s	4.56 br s	4.54 br s
15 α	2.79 dd (17, 7)	2.71 dd (17.5, 7.5)	3.47 dt (21, 3)	2.83 dd (18, 5)	3.46 dt (21, 2.5)
15 β	3.27 dd (17, 12.5)	3.16 dd (17.5, 12)	3.69 dt (21, 1.5)	2.76 dd (18, 2)	4.03 dt (21, 1)
18	1.05 s	1.04 s	1.03 s	0.97 s	0.99 s
19	1.34 s	1.35 s	1.42 s	1.45 s	1.40 s
28	1.11 s	1.12 s	1.09 s	1.12 s	1.00 s
29	0.88 s	0.92 s	0.80 s	0.89 s	0.88 s
30	3.20 d (2.5)	3.10 d (2.5)	2.15 m 2.81 dd (15.5, 2.5)	5.34 dt (8.0, 2)	2.01 dd (14.5, 5.5) 3.19 dd (14.5, 2.5)
2'	2.50 q (7.5)		2.15 s		
2'-CH_3		1.94 s		1.82 s	
3'	1.24 t (7.5)	7.01 qq (6.0, 1.5)		6.87 qq (7.0, 1.5)	
3'-CH_3		1.93 br d (6.0)		1.74 br d (7.0)	
$COOCH_3$	3.92 s	3.95 s	3.84 s	3.76 s	3.82 s

δ values in $CDCl_3$. Values in parentheses are coupling constants (Hz).

^{1}H-^{1}H and ^{1}H-^{13}C COSY[5] of 1 indicated the presence of a ketone (δ_C 213.51), a methyl ester (δ_H 3.92; δ_C 175.62 and 53.50), a propionyl (δ_H 1.24 and 2.50; δ_C 9.24, 27.52, and 173.14), a lactone (δ_H 5.12; δ_C 80.37 and 171.20), a furan (δ_H 6.39, 7.43, and 7.44; δ_C 109.89, 140.69, 143.44, and 120.62), a hydroxymethine (δ_H 4.46; δ_C 72.40), an epoxide (δ_H 3.20; δ_C 60.17 and 63.23), four tert-methyl groups (δ_H 0.88, 1.05, 1.11, and 1.34; δ_C 22.72, 26.86, 23.10, and 17.01), and three quarternary sp^3 carbons (δ_C 35.91, 39.78, and 48.54)(Table I and III).

The above data led us to suppose that the structure of swietemahonin A might be 1.

At this stage, we measured the ^{1}H-^{13}C long-range COSY[5] of 1 in order to confirm the assumed structure (1). As expected, the ^{13}C-signals at δ 213.51 (C-1) and at δ 175.62 (C-7) showed long-range correlations with the ^{1}H-signals at δ 1.34 (19-H_3), 3.20 (30-H), and 3.54 (2-H) and at δ 3.27 (5-H), 3.92 ($COOCH_3$), and 4.46 (6-H), respectively (Fig. 1). In turn, the ^{13}C-signal at δ 173.14 (C-1') was correlated with the ^{1}H-signals at δ 1.24 (3'-H_3), 2.50 (2'-H_2), and 4.94 (3-H), and the signal at δ 171.20 (C-16) with the ^{1}H-signals at δ 2.79, 3.27 (15-H_2), and 5.12 (17-H). Also some other significant long-range correlations are shown by arrows in formula in Fig. 1. Thus the planar structure of 1 was proved.

The relative stereochemistry of 1 was determined on the basis of the coupling constants of each protons and the results of NOE experiments. Irradiation at the 29-H_3 and 18-H_3 caused the increase of signal intensity of the 28-, 2'-, 5-, 3-, and ester methyl-protons and the 12-, 14-, 17-, 22-, and 21-protons, respectively, and irradiation at the 28-H_3 and 19-H_3 enhanced the signal intensity of the 19- and 3-protons and the 28-, 9-, and 6-protons, respectively.

Therefore the structure of swietemahonin A was proved to be 1.

Swietemahonin E (2), colorless needles (from AcOEt-isopropyl ether), mp 151 - 152°C,

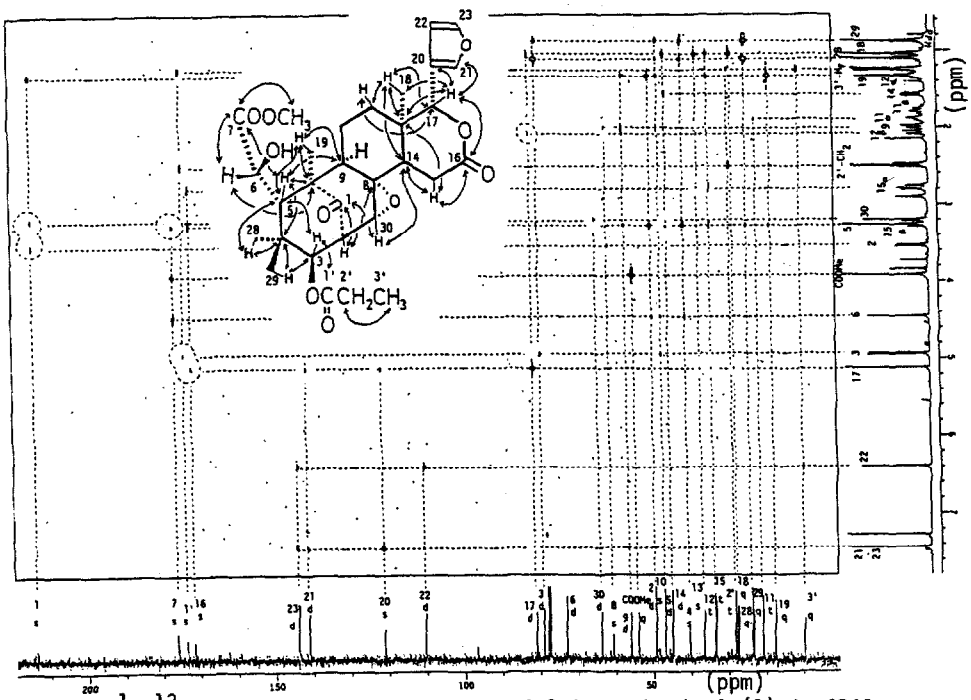


Fig. 1. ^{1}H-^{13}C Long-range COSY Spectrum of Swietemahonin A (1) in $CDCl_3$

$[\alpha]_D$ -20.69 ($CHCl_3$), has the molecular formula $C_{32}H_{40}O_{10}$ (M^+ 584.2605, calcd. 584.2620) and it showed the IR spectrum very similar to that of 1. The ^{1}H and ^{13}C NMR spectra are almost identical with those of 1 except for the appearance of the signals due to the tigloyl residue instead of the signals due to the propionyl residue in 1. (Table I and III). From these comparisons of ^{1}H and ^{13}C NMR data, it was concluded that in the structure of 2, the propionyl residue of 1 was replaced by the tigloyl residue at C-3.

Table II. *Inhibition of Rabbit Platelet Aggregation*

Compound	Inhibition (%)
swietemahonin A (1)	97.4
swietemahonin E (2)	91.7
3-acetylswietenolide (3)	91.6
swietenine (4)	none
swietenolide (5)	35.2

Concentration of PAF (final 7.5×10^{-8} M)
Concentration of sample (final 100 μg/ml)

3-Acetylswietenolide (3), $C_{29}H_{36}O_9$, colorless needles, mp 136 - 138°C, $[\alpha]_D$ -17.76 ($CHCl_3$), showed the ^{1}H-NMR spectrum closely similar to that of 5, except for the down-field shift of a proton doublet (δ 4.82) assignable to the 3-H (Table I). Acetylation of 3 gave a diacetate, which was identified as 3,6-diacetylswietenolide by comparing the spectral data with those reported in the literature.[6] Therefore 3 was considered to be the 3-acetyl derivative of 5.

The inhibitory effects on rabbit platelet aggregation[7] of these tetranortriterpenoids are listed in Table II. It was found that swietemahonin A (1) showed the most strong anti-PAF activity.

Although various compounds such as ginkgolides, triazolobenzodiazepines, benzofuranoid neolignans, and furanoid lignans have been reported as antagonists of PAF,[8] our present results

Table III. ^{13}C-NMR Spectral Data of Swietemahonin A (1), E (2), 3-Acetylswietenolide (3), Swietenine (4), and Swietenolide (5)

Compd / ^{13}C	1	2	3	4	5
1	213.51 (s)	213.70 (s)	217.59 (s)	216.53 (s)	219.80 (s)
2	48.68 (d)	49.01 (d)	47.86 (d)	48.95 (d)	49.99 (d)
3	78.44 (d)	79.13 (d)	79.94 (d)	78.41 (d)	78.50 (d)
4	39.78 (s)	40.05 (s)	38.72 (s)	39.04 (s)	39.66 (s)
5	46.26 (d)	46.16 (d)	45.22 (d)	45.47 (d)	44.00 (d)
6	72.40 (d)	72.39 (d)	73.33 (d)	72.87 (d)	73.57 (d)
7	175.62 (s)	175.85 (s)	175.45 (s)	175.97 (s)	175.83 (s)
8	60.17 (s)	60.30 (s)	128.52 (s)	138.28 (s)	129.05 (s)
9	55.45 (d)	55.08 (d)	53.59 (d)	57.56 (d)	52.96 (d)
10	48.54 (s)	48.65 (s)	53.23 (s)	50.39 (s)	53.99 (s)
11	20.38 (t)	20.63 (t)	18.96 (t)	21.28 (t)	18.74 (t)
12	32.91 (t)	32.59 (t)	29.76 (t)	34.64 (t)	29.08 (t)
13	35.91 (s)	35.65 (s)	38.08 (s)	36.73 (s)	37.81 (s)
14	44.30 (d)	43.52 (d)	131.46 (s)	45.09 (d)	130.75 (s)
15	32.65 (t)	32.50 (t)	33.59 (t)	29.57 (t)	33.15 (t)
16	171.20 (s)	170.78 (s)	169.44 (s)	168.45 (s)	171.43 (s)
17	80.37 (d)	80.86 (d)	80.92 (d)	76.71 (d)	80.51 (d)
20	120.62 (s)	120.93 (s)	120.72 (s)	121.38 (s)	120.81 (s)
21	140.69 (d)	140.63 (d)	141.12 (d)	140.54 (d)	141.06 (d)
22	109.89 (d)	109.82 (d)	109.70 (d)	109.24 (d)	109.80 (d)
23	143.44 (d)	143.48 (d)	143.09 (d)	143.20 (d)	142.88 (d)
30	63.23 (d)	63.04 (d)	33.89 (t)	123.66 (d)	33.80 (t)
18	26.86 (q)	27.06 (q)	18.41 (q)	21.28 (q)	17.91 (q)
19	17.01 (q)	17.07 (q)	17.53 (q)	16.53 (q)	17.91 (q)
28	23.10 (q)	23.24 (q)	23.33 (q)	22.80 (q)	23.22 (q)
29	22.72 (q)	23.24 (q)	23.08 (q)	23.05 (q)	23.63 (q)
1'	173.14 (s)	166.77 (s)	170.29 (s)	166.92 (s)	———
2'	27.52 (t)	127.88 (s)	21.14 (q)	127.77 (s)	———
3'	9.24 (q)	139.54 (d)	———	139.02 (d)	———
2'-CH_3	———	12.34 (q)	———	11.75 (q)	———
3'-CH_3	———	14.70 (q)	———	14.64 (q)	———
$COOCH_3$	53.50 (q)	53.47 (q)	53.17 (q)	53.28 (q)	53.23 (q)

δ values in $CDCl_3$. The multiplicities of carbon signals were determined by means of the off-resonance and are indicated as (s), (d), (t), and (q). Assignments were done by the use of ^{1}H-^{13}C COSY and ^{1}H-^{13}C long-range COSY.

provided the first examples of tetranortriterpenoids having antagonistic effects on PAF. Several tetranortriterpenoids were also isolated from S. mahogani and the investigation of their structures and anti-PAF activities is currently in progress.

References and Notes

1) D. A. H. Taylor, *J. Chem. Soc. Chem. Commun.*, 1969, 58.
2) E. J. Corey, Chung-Pin Chen, and M. J. Parry, *Tetrahedron Lett.*, 29, 2899 (1988).
3) J. D. Connolly, R. Henderson, R. McCrindle, K. H. Overton, and N. S. Bhacca, *J. Chem. Soc.*, 1965, 6935.
4) J. D. Connolly, R. McCrindle, K. H. Overton, and W. D. C. Warnock, *Tetrahedron*, 24, 1507 (1968).
5) A. Bax, "Two-Dimensional NMR in Liquids", D. Reidal Publishing Co., Dordrecht, Holland, 1982; R. Ben and H. Gunther, *Angew. Chem. Int. Ed. Engl.*, 22, 350 (1983).
6) K. C. Chan, T. S. Tang, and H. T. Toh, *Phytochemistry*, 15, 429 (1976).
7) Platelet-rich plasma (PRP) was made by centrifuging the blood of rabbit at 200 g for 10 min, and platelet-poor plasma (PPP) was made at 1400 g for 10 min. Aggregation was measured by the changes in turbidity with Aggregometer, model RMA-31 (Rikadenki Kogyo, Japan) at 37°C. The aggregometer was adjusted in sensitivity to give light transmission values of 0 and 100 % for PRP and PPP, respectively. Inhibition of aggregation was assayed by comparing the change in the transmitted light in PAF-treated PRP with that in the sample-treated PRP.
8) P. Braquet, L. Touqui, T. Y. Shen, and B. B. Vargaftig, *Pharmacol. Rev.*, 39, 98 (1987).

(Received in Japan 2 December 1988)