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PLAUNOL A AND B, NEW ANTI-ULCER DITERPENELACTONES FROM CROTON SUBLYRATUS

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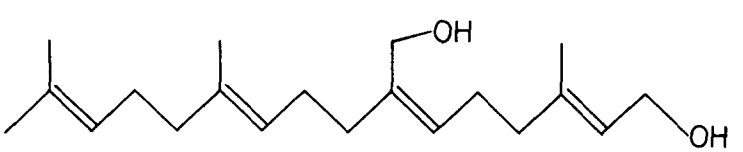
Summary: Two new diterpenelactones named plaunol A (2) and B (3) exhibiting anti-Shay ulcer activity were isolated from Thai medicinal plant, Croton sublyratus. Structure of 2 was determined by X-ray analysis of its p-bromobenzoate and structure of 3 was deduced from the results of chemical correlation and the spectral data.

Pharmacological screening directed toward to find antipeptic ulcer substances of plant origin led us to find that acetone extract of a crude drug named Plau-noi in Thailand, identified with stem of Croton sublyratus Kurz (Euphorbiaceae), showed significant inhibitory activities against reserpine-ulcer in mouse and Shay-ulcer in rat. From anti-reserpine ulcer active fraction, 18-hydroxygeranylgeraniol (1) was isolated[1], and from anti-Shay ulcer active fraction, new diterpenelactones designated as plaunol A (2) and B (3) were isolated by silica gel column chromatography. This paper describes structural elucidation and anti-Shay ulcer activity of 2 and 3.

Plaunol A (2): $C_{20}H_{20}O_6$ (m/e 356 (M^+), 338, 95, 94, 81); mp 214-7°; $[\alpha]_D^{23}$ -61.7° (c 1.0, acetone); ir ($\nu_{cm^{-1}}^{nujol}$) 3150, 1505, 878 (furan), 1735, 1725 (α,β-unsaturated γ-lactone), 1645, 885 (>C=C<); pmr (δ in d_6-acetone) 7.58 (1H, m), 7.53 (1H, m), 6.76 (1H, t, J=3 Hz), 6.52 (1H, m), 5.47 (1H, d, J=6 Hz), 5.24 (1H, d, J=2 Hz), 5.19 (1H, d, J=1 Hz), 5.15 (1H, t, J=6 Hz), 5.03 (1H, s), 4.98 (1H, dd, J=12/7 Hz), 3.0-2.1 (10H).

Plaunol B (3): $C_{20}H_{20}O_6$ (m/e 356 (M^+), 338, 95, 94, 81); mp 184.5°; $[\alpha]_D^{24}$ +41.4° (c 0.35, acetone); ir ($\nu_{cm^{-1}}^{nujol}$) 3140, 1505, 878 (furan), 1750 (γ-lactone),



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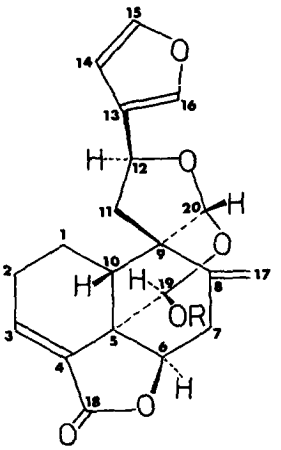
1725 (α,β-unsaturated γ-lactone), 1635, 895 (>C=C<); pmr (δ in d_6-acetone) 7.66 (1H, m), 7.57 (1H, m), 6.64 (1H, dd, J=4/3 Hz), 6.52 (1H, m), 5.66 (1H, t, J=9 Hz), 5.26 (1H, d, J=2 Hz), 4.92 (1H, d, J=1 Hz), 4.73 (1H, dd, J=12/7 Hz), 3.90 (1H, d, J=11 Hz), 3.56 (1H, d, J=11 Hz), 3.1-1.6 (9H).

Treatment of 2 with p-bromobenzoyl chloride in pyridine at room temperature gave mono-p-bromobenzoate (4): mp 198-200°; $[\alpha]_D^{24}$-115.8° (c 1.0, acetone); MS (m/e) 540, 538 (M^+); ir ($\nu_{cm^{-1}}^{nujol}$) 1765, 1735, 1675; pmr (δ in d_6-acetone) 7.93 (2H, d, J=9 Hz) 7.72 (2H, d, J=9 Hz), 7.63 (1H, m), 7.54 (1H, m), 6.89 (1H, dd, J=4/3 Hz), 6.56 (1H, m), 6.49 (1H, br s), 5.29 (1H, d, J=2 Hz), 5.27 (1H, d, J=2 Hz), 5.25 (1H, m), 5.23 (1H, dd, J=12/6 Hz), 5.16 (1H, br s), 3.1-2.1 (9H). To determine the molecular structure of 4, X-ray analysis was undertaken. The crystals were found to have monoclinic space group $P2_1$ (Z=2) and cell dimensions were a=13.347(1), b=7.215(1), c=13.087(1) Å, β=114.01(1)°. Intensity data of 1987 independent reflections were collected on a Rigaku automatic diffractometer within the 2θ limit of 128°. The structure was solved by heavy atom technique and block diagonal least squares refinement reduced the R-factor to the final value of 0.081. The stereoscopic view in Fig. 2 shows the absolute configuration of this compound which was determined by the anormalous dispersion method. Since no isomerization of the hydroxyl group at C-19 of 2 was observed in the acylation conditions, the stereochemistry of this position must be retained in the structure of 4. The absolute structure of plaunol A was decided as 2 having an ent-clerodane type structure.

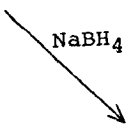
The structure of plaunol B is assumed to be a furanoditerpene having a primary alcohol as shown in structure 3 by comparison of functional groups suggested from the spectral data with that of 2, in addition to downfield shift of the carbinyl protons (δ3.90, 3.56) in plaunol B to δ4.40 in the pmr spectrum of its monoacetate. Evidence for this structure was provided by the results of chemical conversion which follow. Reduction of 3 with excess $NaBH_4$ in ethanol (50-55°, 14 hr) gave 3,4-dihydroplaunol B: mp 127°; MS (m/e) 358 (M^+); ir ($\nu_{cm^{-1}}^{nujol}$) 1780, 1760; pmr (δ in d_6-acetone) 7.63 (2H, m), 6.51 (1H, m), 5.70 (1H, dd, J=9/6 Hz), 5.02 (1H, m), 4.80 (1H, m), 4.71 (1H, dd, J=10/7 Hz), 3.88 (2H, m), 3.25-1.4 (13H), and 5: mp 180°; $[\alpha]_D^{23}$-109° (c 0.97, $CHCl_3$); MS (m/e) 360 (M^+), 342, 324, 97 (base), 95, 94, 81; ir ($\nu_{cm^{-1}}^{nujol}$) 3530, 3350, 3140, 1765, 1755, 1640, 1503, 995, 875; pmr (δ in d_6-acetone) 7.42 (2H, m), 6.40 (1H, m), 5.32 (1H, d, J=4 Hz), 5.15 (1H, m), 4,84 (1H, m), 4.82 (1H, m), 4.70 (1H, dd, J=4/1 Hz), 4.54 (1H, dd, J=8/7 Hz), 4.35 (1H, d, J=11.5 Hz), 4.32 (1H, dd, J=11.5/1.5 Hz), 3.02 (1H, dd, J=16/8 Hz), 2.85-1.4 (12H).

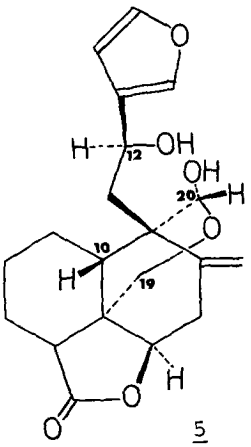
Acetylation of 5 gave diacetate and oxidation with pyridinium chlorochromate in methylene chloride yielded 6, whose ir spectrum showed the presence of three carbonyl groups, 1780 (γ-lactone), 1735 (δ-lactone) and 1680 cm^{-1} (conjugated ketone). Therefore, one of the two hydroxyl groups of 5 is attached to C-12 conjugated with furan ring, and the other is on the hemiacetal structure



2 R=H, plaunol A

4 R=CO-C6H4-Br





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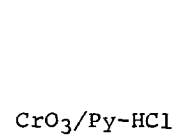

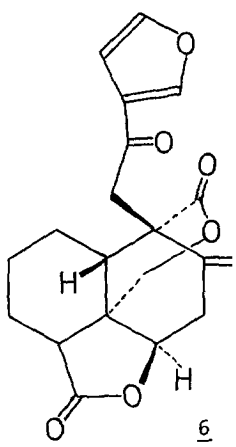

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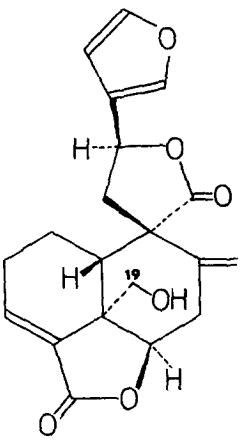


3 plaunol B

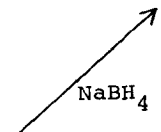
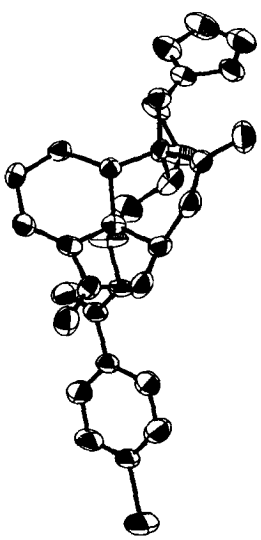


Fig. 1



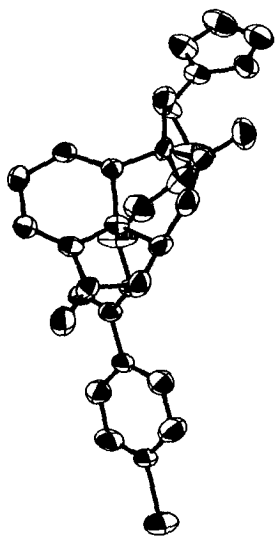


Fig. 2

Position of the hemiacetal hydroxyl group is concluded to be at C-20, not at C-19, because 5 is obtained under reduction conditions from 3 bearing the primary alcohol at C-19. Furthermore, in pmr spectrum of 5, a long-range coupling (J=1 Hz) between the hydrogens of δ4.70 (H-20) and δ2.38 (H-10) shows the stereochemistry at C-20 as R configuration. The absolute configuration of 5 established by a positive Cotton effect (Θ_{231}^{EtOH} +10900) in its CD curve[2] is consistent with that of 4 decided by X-ray analysis.

On the other hand, by excess $NaBH_4$ reduction in ethanol (room temperature, overnight), 2 gave 3,4-dihydroplaunol A: mp 163-4°; MS (m/e) 358 (M^+); ir ($\nu_{cm^{-1}}^{nujol}$) 1790; pmr (δ in $CDCl_3$) 7.36 (2H, m), 6.33 (1H, m), 5.73 (1H, s), 5.28 (1H, s), 5.08 (1H, t, J=7 Hz), 4.85 (1H, m), 4.75 (1H, m), 4.82 (1H, dd, J=10/7 Hz), 3.0-1.5 (13H), and 5, the latter of which was identical with that from 3 in all physical constants and spectral data. Thus, the absolute structure of plaunol B was decided as structure 3.

Finally, results of anti-Shay ulcer activity in rat are shown in Table I[3].

Table I

	Dose (mg/kg, ip)	No. of rats	Inhibition %
plaunol A	3	5	0
	10	5	0
plaunol B	3	5	55
	10	5	85

REFERENCES

1. A. Ogiso, E. Kitazawa, M. Kurabayashi, A. Sato, S. Takahashi, H. Noguchi, H. Kuwano, S. Kobayashi, and H. Mishima, Chem. Pharm. Bull., 26, 3117 (1978)
2. T. Komori, M. Arita, Y. Ida, T. Fujikura, T. Kawasaki, and K. Sekine, Liebigs Ann. Chem., 1973, 978.
3. H. Shay, S.A. Komarov. S.S. Fels, D. Meranze, M. Gruenstein, and H. Spielt, Gastroenterology, 5, 43 (1945).

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