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ISOLATION OF A NEW NEOLIGNAN, MAGNOSALICIN, FROM MAGNOLIA SALICIFOLIA

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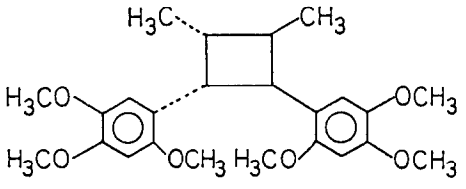
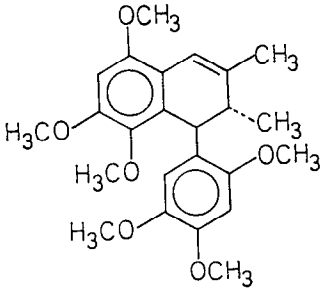
Abstract-A new neolignan named magnosalicin (**4**) was isolated as a biologically active compound from the buds of Magnolia salicifolia, which have been used as a Chinese medicinal drug, especially for nasal allergy. A unique arrangement of substitution groups on a tetrahydrofuran ring indicates magnosalicin (**4**) being a neolignan. Its biogenetical formation mechanism is also discussed.

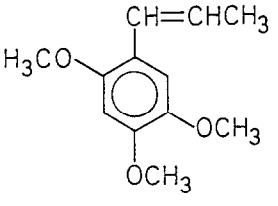
Buds of Magnolia salicifolia Maxim. are known as an oriental medicinal drug, "Shin-i" (Japanese name), which has been used especially for nasal allergy and nasal empyema. Several alkaloids have been isolated from this medicinal drug and shown to have neuromuscular blocking activity.[1] Recently isolation and structural elucidation of two neolignans, magnosalin (**1**) and magnoshinin (**2**), have been reported[2] and the structures of the neolignans indicate their close biogenetical relationship to asarone (**3**). In the course of our studies on antiallergy compounds contained in medicinal plants, a chloroform extract of this medicinal drug showed a significant antiallergy activity in passive cutaneous anaphylaxis (PCA) test, the most commonly used bioassay test to evaluate antiallergy effect to Type I allergy.[3] The extract also showed inhibitory effect to histamine release from rat peritoneal mast



MAGNOSALIN (1)



MAGNOSHININ (2)



ASARONE (3)

cells induced by compound 48/80.[4] The latter in vitro bioassay has been shown to have good correlation with PCA test.

Following to these findings we attempted to isolate antiallergy compounds contained in the chloroform extract. The chloroform extract was chromatographed on silica gel and eluted fractions were monitored by the mast cell bioassay test. Non-polar fractions containing essential oil were less effective. A separate analysis by GC-MS revealed that the chloroform extract contained fenchone, camphor, α-terpineol, safrol, caryophyllene oxide, eugenol methyl ether, iso-eugenol methyl ether, myristicine, veratraldehyde and asarone. Repeated fractionation with silica gel column chromatography finally gave a crystalline compound, named magnosalicin, which showed a significant inhibitory effect to histamine release in the mast cell bioassay test using compound 48/80 as a challenger (21.2 % inhibition at 10^{-3} M). Magnosalicin gave following physical and spectroscopical data; mp 134.5 - 135° C. High MS m/z: 432.2170, Calcd for $C_{24}H_{32}O_7$ 432.2146. MS m/z (relative intensity): 432 (40, M^+), 383 (100, $M^+ - CH_3\text{-}CHO$), 220 (38) and 205 (59). The molecular formula of magnosalicin (**4**) differs from that of magnosalin (**1**) only by one oxygen atom. The ^{1}H-NMR spectrum of magnosalicin (Fig. 1) showed the presence of two secondary methyl groups, four methine protons, six methoxy groups and four aromatic protons, indicating that although magnosalicin is not a symmetrical compound, it is very similar to magnosalin (**1**). The chemical shift and coupling constant values of four methine signals at δ 2.32 (m), 3.61 (dd, J=8.5, 10.5 Hz), 4.61 (m) and 4.98 (d, J=9.0 Hz), revealed a possible sequence of the four methine

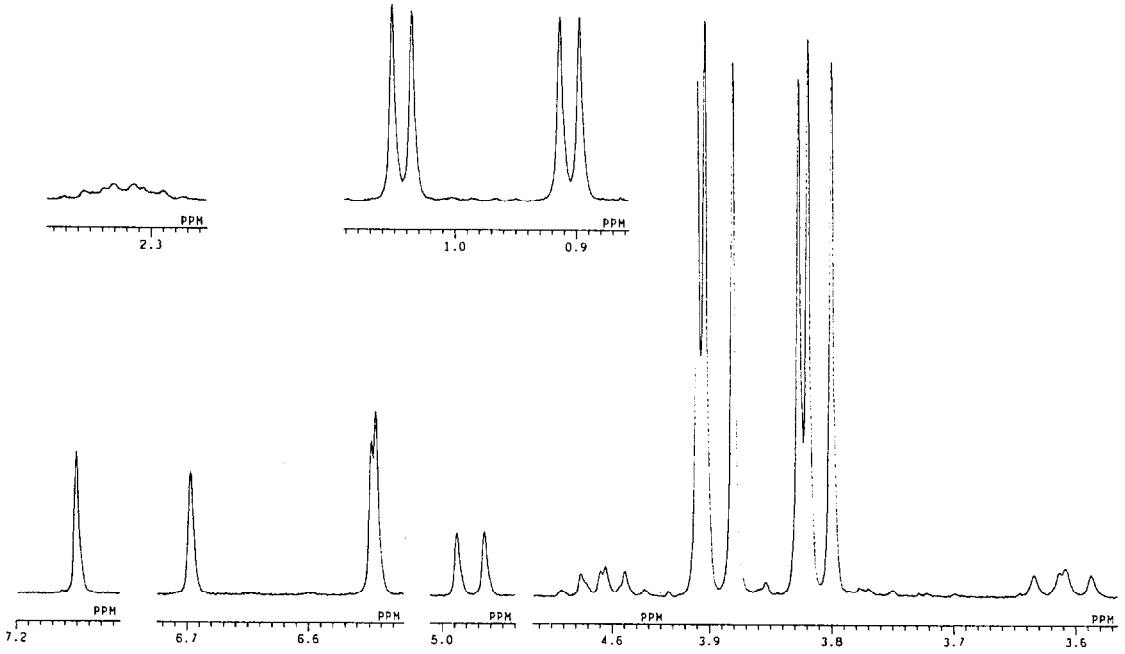


Fig. 1 ^{1}H-NMR spectrum of magnosalicin (4)

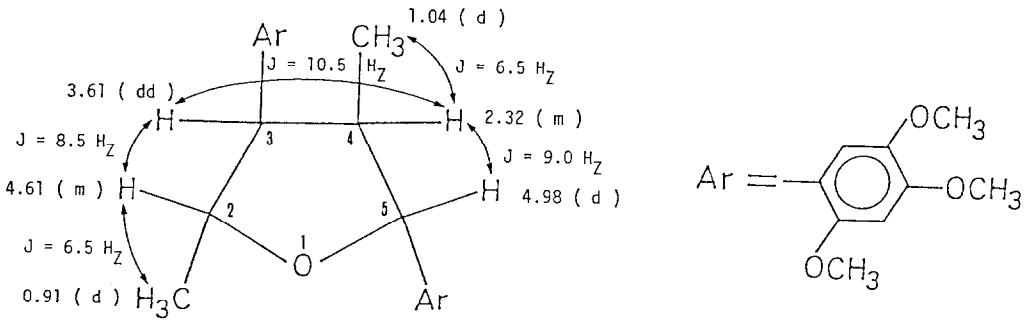


Fig. 2 A planar structrue of magnosalicin (**4**) and ^{1}H-NMR data

carbons in which the both terminal methine groups bonded to oxygen atom, indicating the presence of a tetrahydrofuran ring. (Fig. 2) Thus emerged structure (**4**) is somewhat unusual as a lignan having a tetrahydrofuran ring, because in normal lignans two phenyl groups are present at C-2 and C-5, and two methyl groups at C-3 and C-4. This is due to the reaction mechanism of lignan biosynthesis and magnosalicin (**4**) is therefore a new type neolignan formed by a differnt biosynthetic mechanism. Finally the structure of magnosalicin (**4**) including stereochemistry was unambiguously established by a X-ray analysis. The crystal recrystallized from methanol was monoclinic space group $P2_1/a$ with four molecules in a cell of dimensions, a=1.4725(7), b=17.796(8), c=9.100(4) Å; β=104.47 , D_x=1.34 g cm^{-3}, V=2309.03 Å^3. The space group indicates magnosalicin (**4**) being a racemate. Reflection data were recorded on a Philips PW-1100 diffractometer with graphite monochromated CuKα radiation. The cell parameters were determined by the least square method. A total of 3063 reflections were collected as above the 2σ(I) level within a range of 3-78° (θ). The structure was solved by the direct method (MULTAN) and refined by block diagonal least squares. A final R value was 0.0573 with anisotropic temperature

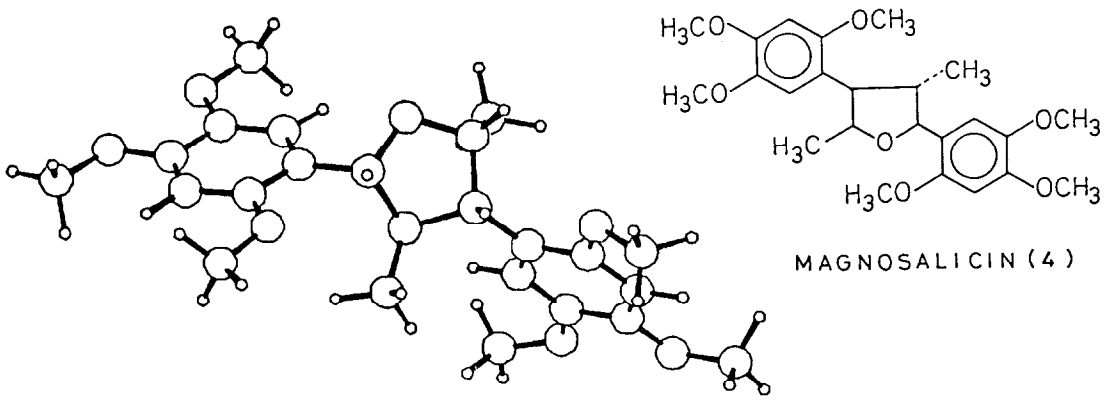


Fig. 3 PLUTO drawing of magnosalicin (**4**)

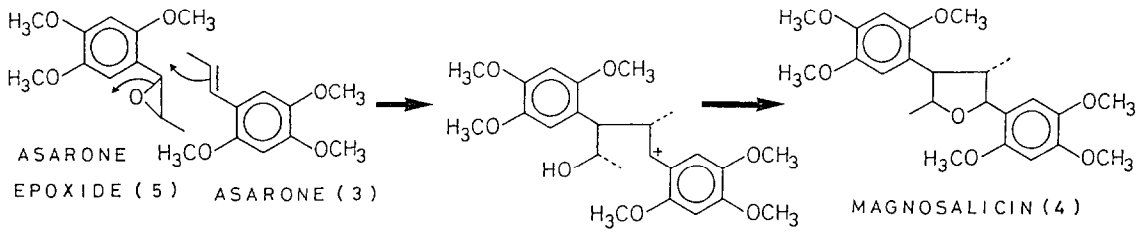


Chart 1. Biogenesis of magnosalicin (4)

factors for 24 carbon and 7 oxygen atoms and isotropic temperature factors for 32 hydrogen atoms.[5)]

The biogenesis of magnosalicin (**4**) may be rationally explained by a condensation reaction between asarone epoxide (**5**) and asarone (**3**) as shown in Chart 1. The reaction initiates with C-O bond cleavage of the epoxide (**5**) followed by C-C bond formation with the other molecule of asarone (**3**). Thus formed carbonium ion or its equivalent finally cyclizes to give magnosalicin (**4**). The biogenetical consideration on magnosalicin (**4**) suggests that asarone (**3**) is the common precursor of the three neolignans (**1**, **2** and **4**) isolated from M. salicifolia, because asarone (**3**) is a constituent of essential oil contained in this plant.

References and Note

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5) The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK. Any request should be accompanied by the full literature citation for this communication.

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