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SESQUITERPENOID AND DISULPHIDE DERIVATIVES FROM *FERULA ASSA-FOETIDA*

TETSUYA KAJIMOTO, KIYOSHI YAHIRO and TOSHIHIRO NOHARA*

Faculty of Pharmaceutical Sciences, Kumamoto University 5-1 Oe-honmachi, Kumamoto 862, Japan

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Key Word Index—*Ferula assa-foetida*, Umbelliferae; root resin; disulphides; coumarin-sesquiterpene complexes.

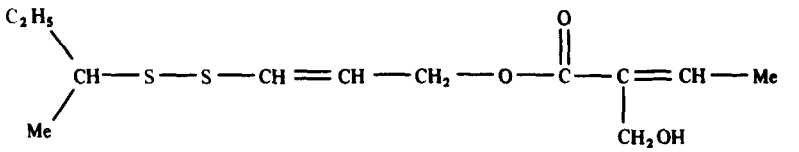
Abstract—Three new compounds asadisulphide, asacoumarin A and asacoumarin **B** were isolated from asa foetida, the resin prepared from the root or rhizome of *Ferula assa-foetida*. The first compound was shown to be the derivative of *sec*-butyl propenyl disulphide that was isolated from the same material, and the other two were characterized as umbelliferone-sesquiterpene complexes.

Asa foetida, the resin obtained from *Ferula assa-foetida* L., has been used for the seasoning in Afganistan and Persia, and due to its sedative effect, is mentioned in most pharmacopoeias. Concerning the chemical structures of the contents, farnesiferol A, B, C and *sec*-butyl propenyl disulphide were reported by Jeger *et al.* in 1958 [1], but nothing has been reported since. Further, the structures of the farnesiferols were based only on chemical degradation experiments. In this paper, we report the chemical structures of three new compounds isolated from this resin.

Asa foetida purchased in the market in China was extracted with methanol at room temperature and the extract was partitioned between ethyl acetate and water. The organic layer was subjected to a combination of silica gel, alumina, Bondapak C-18 column chromatography with various solvent systems (Chart 1) to yield compounds **1**–**3**.

Compound **1**, shows signals due to 12 carbons in the ^{13}C NMR spectrum, and its ^{1}H NMR spectrum gave well-separated signals (see Experimental). The ^{1}H–^{1}H COSY spectrum revealed that there are correlations between the downfield shifting olefinic proton at δ 7.00 (*q*) and the methyl proton at δ 1.91 (*d*), between olefinic protons at δ 6.39 (*d*) and δ 6.01 (*dt*) which is also correlated with the methylene signal δ 4.69 (*d*), and between ethyl signal at δ 1.00 (*t*) and 1.74–1.5 (*m*) and methine proton at δ 2.82 (*m*) which is also correlated with methyl signal at δ 1.30 (*d*). These data are in accord with **1** for this compound. This structure was confirmed by alkaline hydrolysis, which gave $EtMeCHSSCH=CHCH_2OH$.

Compound **2**, shows 24 carbon signals containing the nine carbon signals ascribable to umbelliferone in the ^{13}C NMR spectrum. This suggests that **2** is a complex of a sesquiterpene and umbelliferone. Since there are four methyl signals at δ 25.8, 17.9, 17.1, 14.0 and six olefinic



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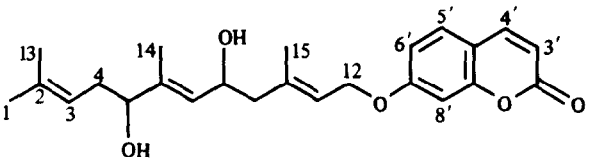

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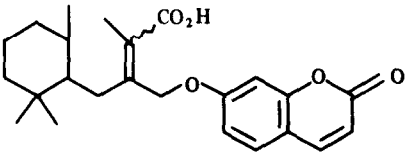

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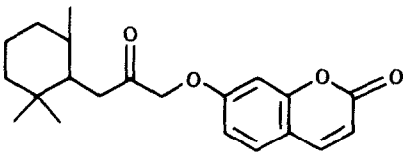

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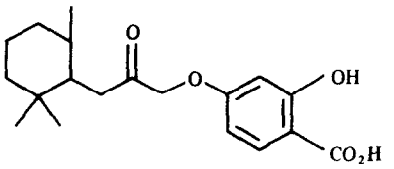

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carbons at δ 139.7, 138.5, 134.8, 128.4, 121 8, 119.8 among the other 15 signals in the ^{13}C NMR spectrum except for those of the umbelliferone unit, the C-15 unit is probably a derivative of farnesol. Moreover, acetylation of **2** afforded the diacetate, which showed the oxygenated carbon signals at δ 76.6 (*d*), 66.1 (*d*) being ascribable to the secondary alcohols. These facts and the coupling patterns of the olefinic protons at δ 5.57 (*t*), 5.44 (*d*), 5.07 (*t*) in the ^1H NMR spectrum are in accord with structure **2** for this compound Furthermore, the correlation between the triplet proton signal at δ 5 07 and two methyl signals at δ 1.71 and 1.63 in the ^1H–^1H COSY spectrum and also the mass fragment peak at *m/z* 329 (M^+ –CH_2–CH =CMe_2) confirms the correctness of this structure. It is worthwhile to note that the previously reported farnesiferols might be artifacts derived from **2**

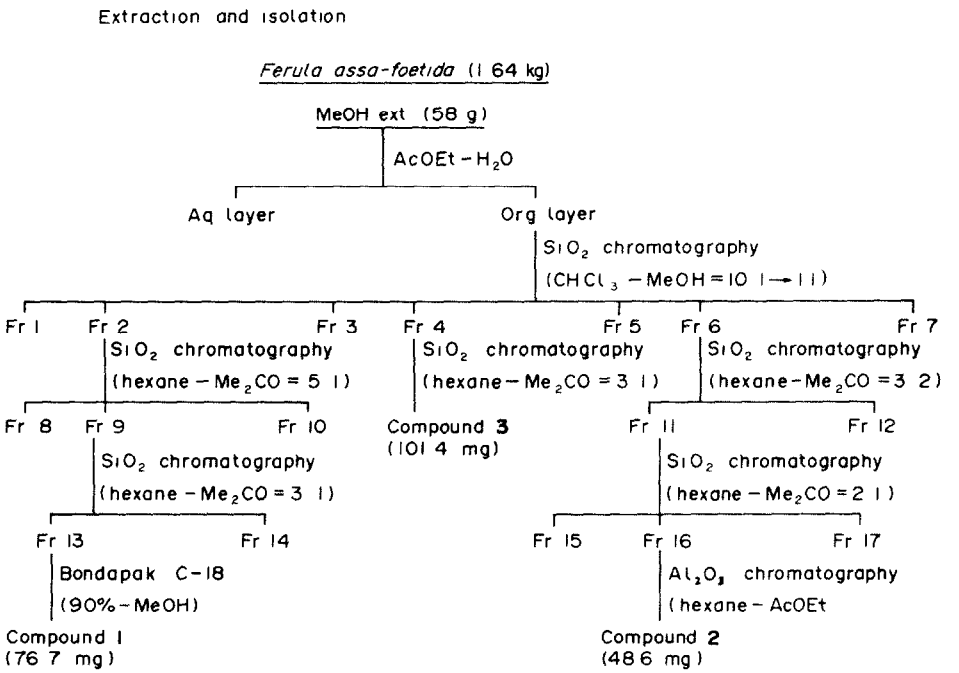
Compound **3**, showed 24 carbon signals containing the nine signals originated for umbelliferone in the ^{13}C NMR spectrum, as in the case of **2** The ^1H NMR spectrum showed well-separated signals; however, the strong signal at δ 1.90 consists of several protons. The ^1H–^{13}C COSY spectrum clarified that one methyne proton, one pair of methylene protons and a part of another methylene protons belong to the signal at δ 1.90 The ^1H–^1H COSY spectrum showed the existence of the sesquiterpene side chain as in **3**, and four residual signals are at δ 180 1, 129 6, 126 2 and 20.2 in the ^{13}C NMR spectrum can also be assigned to this side chain This structure for **3** was confirmed by mild ozonolysis [2] to yield **4** and **5**

EXPERIMENTAL

Isolation The methanol extract (58 g) of asa foetida, the resin obtained from the root or rhizome of *Ferula assa-foetida* L., purchased in the market in China, was separated as shown in Chart 1 to give a total of three substances

Asadisulphide (**1**) Colourless oil, $[\alpha]_D$ +24 0° ($CHCl_3$, *c* 0.4) $\nu_{max}^{CHCl_3}$ 3600, 1700 cm^{-1} MS *m/z* 276 084 (M^+) ^{13}C NMR ($CDCl_3$) δ 167 0 (*s*), 141 1 (*d*), 133 2 (*d*), 131 8 (*s*), 122 6 (*d*), 64 1 (*t*), 56 8 (*t*), 48 2 (*d*), 28 9 (*t*), 20 1 (*q*), 14 2 (*q*), 11 4 (*q*) ^1H NMR ($CDCl_3$) δ 7 00 (1H, *q*, *J* = 7 0 Hz, MeC<u>H</u>=), 6.39 (1H, *d*, *J* = 14 6 Hz, S–CH =), 6 01 (1H, *dt*, *J* = 14 6 and 6 6 Hz, CH_2–C<u>H</u> =), 4 69 (2H, *d*, *J* = 6 6 Hz, –CH_2OCO), 4 36 (2H, *s*, –CH_2OH), 2 82 (1H, *m*, CH–S), 2 50 (1H, *br s*, –OH), 1 91 (3H, *d*, *J* = 7 0 Hz, =CH<u>Me</u>), 1 74–1 51 (2H, *m*, AB type, Me<u>C</u>H_2CH–), 1 30 (3H, *d*, *J* = 6.9 Hz, <u>Me</u>CH–), 1 00 (3H, *t*, *J* = 7 3 Hz, <u>Me</u>CH_2–).

Alkaline hydrolysis of **1** Compound **1** (94 mg) in 3% KOH–MeOH was left for 3 hr at room temperature The reaction mixture was neutralized with HCl and the solvent evapd The residue was extracted with $CHCl_3$ and treated as usual, and purified by chromatography over a silica gel (*n*-hexane–acetone = 3 · 1) to yield EtMeCHSSCH=$CHCH_2$OH (48 mg) ^1H NMR ($CHCl_3$) δ 6 30 (1H, *d*, *J* = 15.0 Hz), 6 05 (1H,



dt, J = 15.0 and 5.8 Hz), 4 18 (2H, *d*, J = 5.8 Hz), 2 85–2.80 (1H, *m*), 1.75–1.50 (2H, *m*), 1.30 (3H, *d*, J = 6 6 Hz), 0.99 (3H, *t*, J = 7 3 Hz) $\nu_{max}^{CHCl_3}$ 3616, 1622 cm^{-1}

Asacoumarin A (2) Colourless oil, $[\alpha]_D$ +7.0° ($CHCl_3$; *c* 0.7). $\nu_{max}^{CHCl_3}$ 3616, 3448, 1728, 1614 cm^{-1}. ^{13}C NMR ($CDCl_3$) δ161 9 (*s*), 161.2 (*s*), 155.8 (*s*), 143.4 (*d*), 139 7 (*s*), 138.5 (*s*), 134.8 (*s*), 128.7 (*d*), 128.4 (*d*), 121.8 (*d*), 119.8 (*d*), 113.1 (*d*), 112.9 (*d*), 112.5 (*s*), 101.5 (*d*), 76 6 (*d*), 66 1 (*d*), 65.2 (*t*), 47 3 (*t*), 34.0 (*t*), 25.8 (*q*), 17 9 (*q*), 17.1 (*q*), 14.0 (*q*). ^1H NMR ($CDCl_3$) δ7.64 (1H, *d*, J = 9.5 Hz, 4'-H), 7.36 (1H, *d*, J = 8 4 Hz, 5'-H), 6.83 (1H, *dd*, J = 8.4 and 2.6 Hz, 6'-H), 6.80 (1H, *d*, J = 2.6 Hz, 8'-H), 6.24 (1H, *d*, J = 9.5 Hz, 3'-H), 5.57 (1H, *t*, J = 6.2 Hz, 11-H), 5.44 (1H, *d*, J = 8.4 Hz, 7-H), 5.07 (1H, *t*, J = 7.0 Hz, 3-H), 4.58 (3H, *m*, 8-H and 12-H_2), 3.99 (1H, *t*, J = 6.7 Hz, 5-H), 1.82, 1.71, 1.70, 1.63 (each 3H, *s*, 4 × Me). MS *m/z* 329, 162, 69

Diacetate of 2. Colourless oil ^1H NMR ($CDCl_3$) δ 7 63 (1H, *d*, J = 9.5 Hz), 7.36 (1H, *d*, J = 8 5 Hz), 6 82 (1H, *dd*, J = 2.5 and 8.5 Hz), 6.79 (1H, *d*, J = 2.5 Hz), 6.24 (1H, *d*, J = 9 5 Hz), 5.68 (1H, *dt*, J = 8 5 and 5 9 Hz), 5.48 (1H, *t*, J = 6.2 Hz), 5.36 (1H, *d*, J = 8.5 Hz), 5 07 (1H, *t*, J = 6 5 Hz), 4.98 (1H, *t*, J = 7.0 Hz), 4.56 (2H, *d*, J = 6 2 Hz), 2.44–2.20 (4H, *m*), 2.04, 1.99 (each 3H, *s*, 2 × MeCO), 1.79, 1 74, 1 67, 1 60 (each 3H, *s*, 4 × Me).

Asacoumarin B (3). Colourless amorphous powder, $[\alpha]_D$ −13.3° ($CHCl_3$, *c* 0.4) $\nu_{max}^{CHCl_3}$ 3700, 1728, 1712, 1616 cm^{-1}. ^{13}C NMR ($CDCl_3$) δ180.1 (*s*), 162.9 (*s*), 161.4 (*s*), 155 9 (*s*), 143.5 (*d*), 129 6 (*s*), 128 6 (*d*), 126.2 (*s*), 113 1 (*d*), 112.8 (*d*), 112.3 (*s*), 101.2 (*d*), 71.7 (*t*), 42.7 (*d*), 40.8 (*s*), 34.9 (*d*), 32.1 (*t*), 31.9 (*t*), 24.5 (*t*), 22.4 (*q*), 22.1 (*t*), 20.2 (*q*) × 2, 16.0 (*q*). ^1H NMR δ7.63 (1H, *d*, J =9.5 Hz), 7.34 (1H, *d*, J=8.8 Hz), 6 82 (1H, *dd*, J=8.8 and 2.5 Hz), 6.75 (1H, *d*, J=2 5 Hz), 6 24 (1H, *d*, J=9 5 Hz), 3 88 (1H, *d*, A part of AB, J=8 1 Hz), 3.70 (1H, *d*, B part AB, J=8.1 Hz), 2 95 (1H, *dd*, J=5.5 and 11.0 Hz), 2.51 (1H, *br d*, J=13.9 Hz), 2 21 (2H, *m*), 1.90 (4H, *m*), 1 62 (3H, *s*), 1.61 (1H, *d*, A part of AB, J =13.1 Hz), 1.45 (3H, *s*), 1.20 (1H, *dd*, B part of AB, J=13.1 and 4.5 Hz), 1.15 (3H, *s*), 0.92 (3H, *d*, J=7.0 Hz).

Ozonolysis of 3 Into the MeOH (5.0 ml) soln of compound 3 (70 mg) was blown dry O_3 at −72° until the colour changed to pale violet. After the reaction, the excess O_3 was blown out with air and small amount of Me_2S was added and stirred for 1 day at room temp., and evapd the solvent. The residue was purified by chromatography over a silica gel (*n*-hexane–AcOEt = 2·1) to afford two products, compound 4 (27 mg) and compound 5 (15 mg).

Compound 4. Colourless amorphous powder, ^1H NMR δ7.64 (1H, *d*, J=9.5 Hz), 7.38 (1H, *d*, J=8.5 Hz), 6.84 (1H, *dd*, J=8.5 and 2 2 Hz), 6.81 (1H, *d*, J = 2 2 Hz), 6 26 (1H, *d*, J = 9.5 Hz), 3.88 (1H, *d*, A part of AB, J = 9 0 Hz), 3.82 (1H, *d*, B part of AB, J = 9.0 Hz), 1.35, 1.25 (each 3H, *s*), 0.96 (3H, *d*, J = 7.0 Hz)

Compound 5 Colourless amorphous powder ^1H NMR δ11.5 (1H, *s*), 9 72 (1H, *s*), 7.43 (1H, *d*, J = 8 6 Hz), 6 54 (1H, *dd*, J = 8.6 and 2.2 Hz), 6.42 (1H, *d*, J = 2.2 Hz), 3.88 (1H, *d*, A part of AB, J =9.0 Hz), 3.81 (1H, *d*, B part of AB, J = 9.0 Hz), 1.34, 1.23 (each 3H, *s*), 0 94 (3H, *d*, J = 7.2 Hz).

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SESQUITERPENE LACTONES FROM *INULA HELENIUM*

VLATKA VAJS,* DRAGOSLAV JEREMIĆ, SLOBODAN MILOSAVLJEVIĆ and SLOBODAN MACURA

Institutes for Chemistry and Physical Chemistry, Faculty of Science, University of Belgrade, Studentski trg 16, P.O Box 550, 11001 Belgrade, Yugoslavia, *Institute for Chemistry, Technology and Metallurgy, Njegoševa 12, 11000 Belgrade, Yugoslavia

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Key Word Index—*Inula helenium*, Compositae; 11(13)-dehydroeriolin; 2α-hydroxyalantolactone; 4α,5α-epoxy-10α,14-H-inuviscolide; carabrone.

Abstract—The isolation of 11(13)-dehydroeriolin [a germacranolide also known as 11(13)-dehydroivaxillin], 2α-hydroxyalantolactone, 4α,5α-epoxy-10α,14-H-inuviscolide (the major component) and carabrone from the aerial parts of *Inula helenium* is reported. The first two lactones were isolated for the first time from this plant.

INTRODUCTION

Extensive chemotaxonomic studies of *Inula* species [1], all grown from seeds originating from botanical gardens, revealed a variety of sesquiterpene lactones in *Inula helenium* (i.e. eudesmanolides, germacranolides, guaianolides and their 4,5-*seco*-analogues and one member of the pseudoguaianolide group). The main lactone constituents in roots were eudesmanolides (alantolactone and isoalantolactone) whereas in the aerial parts, which contained a much smaller overall quantity of lactones, germacranolides were the major lactones together with smaller amounts of eudesmanolides.

An investigation of the chemical constituents of the aerial parts of *Inula helenium*, collected during flowering from the locality near Belgrade, is reported in this paper.