Polysulfide Derivatives from *Ferula foetida*

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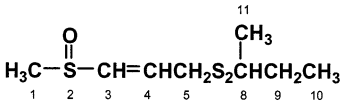
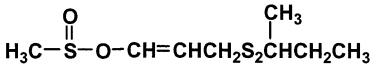
The ethyl acetate-soluble fraction from a methanol extract of *Ferula foetida* has afforded six new sulfide derivatives, (*E*)-3-methylsulfinyl-2-propenyl *sec*-butyl disulfide (foetisulfide A) (**1**), (*Z*)-3-methylsulfinyloxy-2-propenyl *sec*-butyl disulfide (foetisulfide B) (**2**), (*E*)-3-methylsulfinyloxy-2-propenyl *sec*-butyl disulfide (foetisulfide C) (**3**), bis(3-methylthio-2*E*-propenyl) disulfide (foetisulfide D) (**4**), 3,4,5-trimethyl-2-thiophenecarboxylic acid (foetithiophene A) (**5**), 3,4,5-trimethyl-2-(methylsulfinyloxymethyl)thiophene (foetithiophene B) (**6**), along with six known compounds. The structures of **1**−**6** were established on the basis of spectroscopic studies, with the elucidation of **5** confirmed by single-crystal X-ray crystallography.

Ferula foetida (Bunge) Regel (Umbelliferae) has been used in folk medicine as an anthelmintic, antirheumatic, antispasmodic, diuretic, and emmenagogue.[1,2] Up to the present, however, only a number of sesquiterpene coumarins and sulfide derivatives have been isolated from this plant.[2−6] Recently, the essential oil of the seed and gum portions of *Ferula foetida* was found to exhibit antifungal activity.[7] As part of our ongoing studies on medicinal plants from Uzbekistan,[8] we have begun a study on the chemical constituents of *F. foetida*. In this paper, we report the isolation and structure elucidation of six new sulfide derivatives, named foetisulfides A−D (**1**−**4**) and foetithiophenes A (**5**) and B (**6**). Compounds **1**−**6** were obtained from the ethyl acetate-soluble portion of a methanol extract of *F. foetida* roots, along with six known compounds.

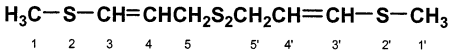


1 *E*

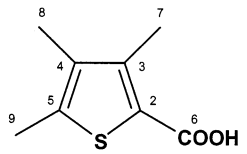


2 *Z*

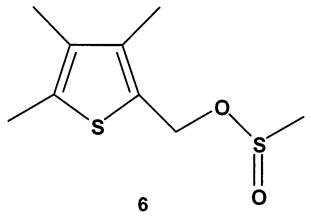
3 *E*



4 3,3'-*E*



5



6

Compound **1** (foetisulfide A) was obtained as an oil with an unpleasant smell. It was assigned the molecular formula $C_8H_{16}OS_3$ as found from its HREIMS (*m*/*z* 224.0339), and its IR spectrum showed sulfoxide group (1039 cm^{-1}) absorption. The ^1H NMR spectrum of **1** revealed the presence of one methylsulfinyl group [δ_H 2.63 (3H, s)], two coupled olefinic protons [δ_H 6.46 (1H, dt, J = 14.7, 6.2 Hz), 6.42 (1H, d, J = 14.7 Hz)], one methylene [δ_H 3.43 (2H, d, J = 6.2 Hz)], and one *sec*-butyl group [δ_H 2.76, 1.67, 1.51 (each 1H, m), 1.28 (3H, d, J = 6.8 Hz), 0.97 (3H, t, J = 7.3 Hz)]. The ^{13}C NMR spectrum of **1** showed three methyls, one double bond (δ_C 137.2 and 133.6), two methylenes, and one methine. Compound **1** was assumed to be a polysulfide derivative, the same as 2-butyl (*E*)-3-methylthioallyl disulfide, which has been reported from the same source.[9] The ^1H NMR spectral data of **1** were similar to those of 2-butyl (*E*)-3-methylthioallyl disulfide, except for the H-1, H-3, and H-4 signals. The downfield-shifted H_3-1 resonance (δ_H 2.63 in **1**; 2.27 in 2-butyl (*E*)-3-methylthioallyl disulfide) indicated the presence of a methylsulfinyl group in **1**. In the HMBC spectrum, the proton signal at δ_H 2.63 (H_3-1) correlated with the carbon signal at δ_C 137.2 (C-3), and the signal at δ_H 3.43 (H-5) correlated with the signals at δ_C 137.2 (C-3) and 133.6 (C-4). Analysis of the fragment ion peaks in the HREIMS (Figure 1) confirmed that the structure of **1** is (*E*)-3-methylsulfinyl-2-propenyl *sec*-butyl disulfide.

Foetisulfide B (**2**) had a molecular formula of $C_8H_{16}O_2S_3$ based on HREIMS. Its ^1H NMR spectrum showed two coupled olefinic protons [δ_H 6.62 (1H, d, J = 9.6 Hz), 5.73 (1H, dt, J = 9.6, 8.1 Hz)], one methylene [δ_H 3.90 (2H, d, J = 8.1 Hz)], and one *sec*-butyl group, similar to that of **1**. The downfield-shifted methyl (δ_H 2.89, in **2**; 2.63, in **1**)

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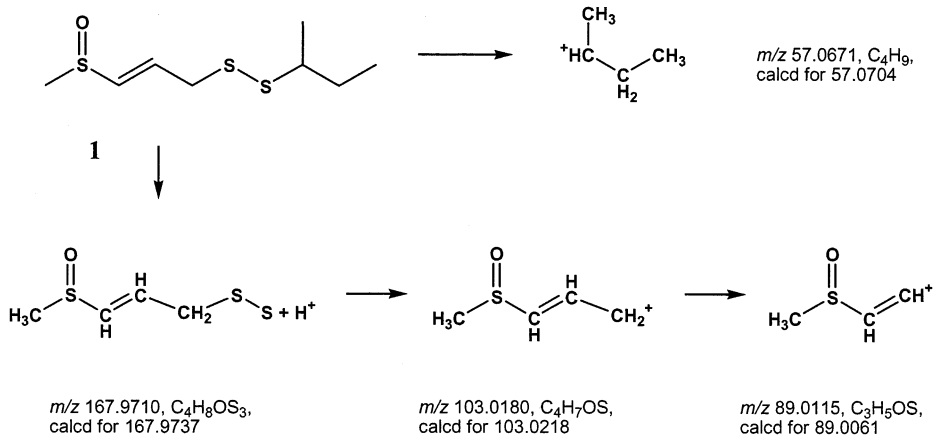

Figure 1. Mass spectral fragment peaks of **1**.

Table 1. ^{1}H and ^{13}C NMR Spectral Data of Compounds **1**−**4**[a]

position	**1**		**2**		**3**		**4**	
1	2.63 (s)	41.0	2.89 (s)	39.7	2.87 (s)	39.4	2.28 (s)	14.8
3	6.42 (d, 14.7)	137.2	6.62 (d, 9.6)	141.5	6.48 (d, 15.0)	138.0	6.25 (d, 14.6)	129.5
4	6.46 (dt, 14.7, 6.2)	133.6	5.73 (dt, 9.6, 8.1)	116.2	5.98 (dt, 15.0, 7.8)	114.5	5.36 (dt, 14.6, 7.8)	120.0
5	3.43 (d, 6.2)	40.1	3.90 (8.1)	54.8	3.78 (d, 7.8)	58.2	3.40 (d, 7.8)	42.4
8	2.76 (m)	48.3	2.84 (m)	48.8	2.84 (m)	48.4		
9a	1.67 (m)	29.0	1.70 (m)	28.7	1.70 (m)	29.0		
9b	1.51 (m)		1.56 (m)		1.56 (m)			
10	0.97 (t, 7.3)	11.5	1.00 (t, 7.4)	11.6	0.99 (t, 7.5)	11.6		
11	1.28 (d, 6.8)	20.2	1.32 (d, 6.8)	20.2	1.31 (d, 6.9)	20.2		

[a] $CDCl_3$ was used as solvent, and TMS as internal standard.

indicated the presence of one methylsulfinyloxy group. The ^{13}C NMR spectral data of **2** were similar to those of **1**, except for C-4 and C-5 (Table 1). Moreover, the fragment ion peaks in the HREIMS were supportive of the structure of **2** as (*Z*)-3-methylsulfinyloxy-2-propenyl *sec*-butyl disulfide.

Foetisulfide C (**3**) had the same molecular formula, $C_8H_{16}O_2S_3$, as **2** on the basis of the HREIMS. The ^{1}H and ^{13}C NMR spectral data closely matched those of **2**, except for the coupling constants of H-3 (J = 15.0 Hz) and H-4 (J = 15.0, 7.8 Hz) in **3** (Table 1). Thus, **3** was elucidated as (*E*)-3-methylsulfinyloxy-2-propenyl *sec*-butyl disulfide.

Foetisulfide D (**4**), $C_8H_{14}S_4$, revealed two coupled olefinic protons [δ_H 6.25 (1H, d, J = 14.6 Hz), 5.36 (1H, dt, J = 14.6, 7.8 Hz)], one methylene [δ_H 3.40 (2H, d, J = 7.8 Hz)], and one thiomethyl group (δ_H 2.28) from its ^{1}H NMR spectrum. The ^{13}C NMR spectrum showed four carbons and was similar to that of 2-butyl (*Z*)-3-methylthioallyl disulfide, except for the *sec*-butyl group signals in 2-butyl (*Z*)-3-methylthioallyl disulfide. From this information, **4** was concluded to be a sulfide dimer. By analysis of the fragment ion peaks in HREIMS, the structure of **4** was determined to be bis(3-methylthio-2*E*-propenyl) disulfide.

Foetithiophene A (**5**) was assigned a molecular formula of $C_8H_{10}O_2S$ from its HREIMS. Its ^{1}H NMR spectrum revealed three tertiary methyls (δ_H 2.41, 2.35, and 2.05). The ^{13}C NMR spectrum showed two double bonds, three methyls, and one carboxylic group. Compound **5** was assumed to be a thiophene derivative, similar to the synthetic compound 2,3,4,5-tetramethylthiophene.[10] In the HMBC spectrum, the methyl proton signal at δ_H 2.41 (H_3-7) correlated with the carbon signals at δ_C 149.9 (C-3), 139.2 (C-4), and 127.0 (C-2), and the signal at δ_H 2.05 (H_3-8) correlated with the signals at δ_C 149.9 (C-3), 143.3 (C-5), and 139.2 (C-4). Thus, **5** was proposed as 3,4,5-trimethyl-2-thiophenecarboxylic acid. Single-crystal X-ray analysis of **5** confirmed the assigned structure (Figure 2).

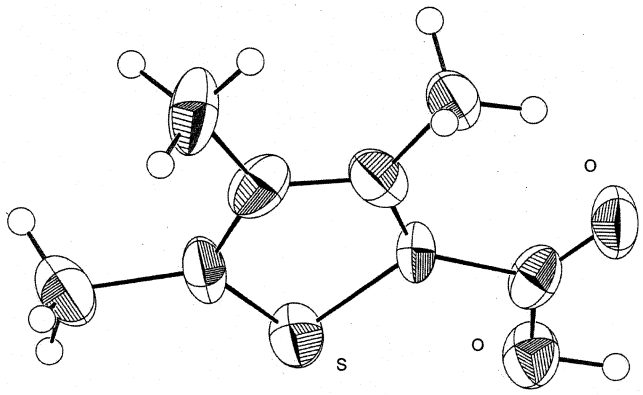

Figure 2. ORTEP drawing of compound **5**.

Foetithiophene B (**6**), $C_9H_{14}O_2S_2$, showed sulfinyl ester group absorption at 1128 cm^{-1} in its IR spectrum. The ^{1}H NMR spectrum revealed four tertiary methyls and one methylene. Comparison of the ^{13}C NMR spectrum of **6** with that of **5** indicated that **6** is also a thiophene derivative. In the HMBC spectrum, the proton signal at δ_H 2.13 (H_3-7) correlated with the signals at δ_C 139.3 (C-3), 134.1 (C-4), and 117.4 (C-2), the signal at δ_H 2.03 (H_3-8) correlated with the signals at δ_H 139.3 (C-3), 134.1 (C-4), and 133.9 (C-5), and the signal at δ_H 4.33 (H_2-6) correlated with the signals at δ_C 139.3 (C-3) and 117.4 (C-2). Moreover, the EIMS base peak at *m/z* 139.0595 ($C_8H_{11}S$, calcd for 139.0581) indicated the presence of a thiophene ring fragment. Thus, **6** was elucidated as 3,4,5-trimethyl-2-(methylsulfinyloxymethyl)-thiophene.

Six known compounds were identified from their spectral data by comparison with values reported in the literature as 2-butyl (*E*)-3-methylthioallyl disulfide,[9] 2-butyl (*Z*)-3-methylthioallyl disulfide,[9] rutadisulfide A,[11] falcarindiol,[12] 2,3,4,5-tetramethylthiophene,[10] and 5-allyl-1-methoxy-2,3-

methylenedioxybenzene.[13] The last three of these known compounds were isolated from *F. foetida* for the first time.

Experimental Section

General Experimental Procedures. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. UV spectra were run on a UV 2100 UV−vis recording spectrometer (Shimadzu). IR spectra were recorded on a 1720 infrared Fourier transform spectrometer (Perkin-Elmer). NMR experiments were run on a Bruker ARX-400 instrument. ^{1}H NMR was measured at 400 MHz, and ^{13}C NMR, at 100 MHz, both using TMS as internal standard. MS were obtained on JEOL DX-303 and SX-102A instruments. Chromatographic materials: silica gel 60 (Merck). HPLC: GPC (gel-permeation chromatography, Shodex H-2001, H-2002) and silica gel HPLC (YMC-Pack SIL-06 SH-043-5-06, 250 × 20 mm).

Plant Material. The roots of *Ferula foetida* (Bunge) Regel were collected in April 2000 at Farish, Uzbekistan, and identified by Prof. Dr. Olimjon K. Kodzhimatov (Uzbekistan Institute of Botany). A voucher specimen (J-0015/26042000) is deposited in Uzbekistan Institute of Botany and Botanical Garden, Uzbekistan.

Extraction and Isolation. The roots (1.56 kg) of *F. foetida* were crushed and extracted 3× with MeOH (20 L each) at 60 °C for 6 h. The MeOH extracts were concentrated in vacuo to give a residue (115 g), which was partitioned between EtOAc and H_2O. The EtOAc layer was concentrated to give a residue (23 g), which was chromatographed on a silica gel (800 g) column (80 × 850 mm). The column was eluted with solvent mixtures of increasing polarity [hexane−EtOAc (3:1, 3:2, 1:1, 1:2, and 1:4), EtOAc, EtOAc−MeOH (19:1, 9:1, 4:1) and MeOH] to give 16 fractions (fractions 1−16). Fraction 1 (0.6 g of 2.4 g) was chromatographed by GPC HPLC ($CHCl_3$) to give five fractions (fractions 1.1−1.5). Fraction 1.4 was separated by Si gel HPLC (hexane−EtOAc, 6:1) to give rutadisulfide A (6 mg) and 2,3,4,5-tetramethylthiophene (3 mg). A partial fraction 3 (0.5 g of 1.5 g) was chromatographed by GPC HPLC ($CHCl_3$) to give six fractions (fractions 3.1−3.6). Fraction 3.6 was separated by Si gel HPLC (hexane−EtOAc, 7:1) to yield 2-butyl (*E*)-3-methylthioallyl disulfide (4 mg), 2-butyl (*Z*)-3-methylthioallyl disulfide (5 mg), **4** (4 mg), and 5-allyl-1-methoxy-2,3-methylenedioxybenzene (10 mg). Combined fractions 7 and 8 (0.8 g) were chromatographed by GPC HPLC ($CHCl_3$) to give six fractions (fractions 7.1−7.6). Fraction 7.5 was separated by Si gel HPLC (hexane−EtOAc, 2:1) to give **3** (12 mg), **2** (8 mg), **6** (8 mg), and falcarindiol (4 mg). Fraction 7.6 was purified by preparative TLC ($CHCl_3$−MeOH, 95:5) to give **5** (8 mg, R_f = 0.55). Combined fractions 13+14 (4.9 g) were chromatographed over a Si gel column ($CHCl_3$−MeOH, 95:5) to give four fractions (fractions 13.1−13.4). Fraction 13.1 was then subjected to GPC−HPLC ($CHCl_3$) to give three fractions (fractions 13.1.1−13.1.3). Fraction 13.1.3 was separated by Si gel HPLC (hexane−EtOAc, 3:1) to give **1** (46 mg).

Foetisulfide A (*E*-3-methylsulfinyl-2-propenyl *sec*-butyl disulfide) (1): pale yellow oil; $[\alpha]_{25}^{D}$ −36.7° (*c* 1.1, MeOH); UV (MeOH) λ_{max} (log ϵ) 237 (3.36) nm; IR (KBr) ν_{max} 2964, 2922, 1457, 1418, 1375, 1286, 1039, 958 cm^{-1}; ^{1}H NMR ($CDCl_3$) data, see Table 1; ^{13}C NMR ($CDCl_3$) data, see Table 1; EIMS *m/z* 224 $[M]^+$ (60), 168 (99), 160 (100), 136 (92), 119 (73), 103 (98), 89 (99), 71 (98), 57 (95), 47 (99); HREIMS *m/z* 224.0339 (calcd for $C_8H_{16}OS_3$, 224.0363).

Foetisulfide B (*Z*-3-methylsulfinyloxy-2-propenyl *sec*-butyl disulfide) (2): pale yellow oil; $[\alpha]_{25}^{D}$ +8.8° (*c* 0.9, MeOH); UV (MeOH) λ_{max} (log ϵ) 233 (3.48) nm; IR (KBr) ν_{max} 2965, 2928, 1457, 1307, 1124, 967, 721 cm^{-1}; ^{1}H NMR ($CDCl_3$) data, see Table 1; ^{13}C NMR ($CDCl_3$) data, see Table 1; EIMS *m/z* 240 $[M]^+$ (62), 184 (43), 161 (73), 105 (100), 89 (11), 71 (47), 61 (40), 57 (99), 41 (99); HREIMS *m/z* 240.0306 (calcd for $C_8H_{16}O_2S_3$, 240.0312), 183.9697 (calcd for $C_4H_8O_2S_3$, 183.9686), 161.0500 (calcd for $C_7H_{13}S_2$, 161.0459), 78.9849 (calcd for CH_3O_2S, 78.9853), 57.0705 (calcd for C_4H_9, 57.0704).

Foetisulfide C (*E*-3-methylsulfinyloxy-2-propenyl *sec*-butyl disulfide) (3): pale yellow oil; $[\alpha]_{25}^{D}$ +27.5° (*c* 1.2, MeOH); UV (MeOH) λ_{max} (log ϵ) 239 (3.47) nm; IR (KBr) ν_{max} 2965, 2925, 1457, 1310, 1125, 968, 902, 762 cm^{-1}; ^{1}H NMR ($CDCl_3$) data, see Table 1; ^{13}C NMR ($CDCl_3$) data, see Table 1; EIMS *m/z* 240 $[M]^+$ (30), 184 (20), 161 (72), 145 (22), 120 (14), 105 (100), 87 (15), 79 (12), 71 (26), 57 (74), 43 (70); HREIMS *m/z* 240.0306 (calcd for $C_8H_{16}O_2S_3$, 240.0312).

Foetisulfide D [bis(3-methylthio-2*E*-propenyl) disulfide] (4): colorless oil; UV (MeOH) λ_{max} (log ϵ) 235 (3.78), 251 (3.81) nm; IR (KBr) ν_{max} 2922, 2852, 1542, 1508, 1457, 1220, 933 cm^{-1}; ^{1}H NMR ($CDCl_3$) data, see Table 1; ^{13}C NMR ($CDCl_3$) data, see Table 1; EIMS *m/z* 238 $[M]^+$ (4), 159 (3), 139 (8), 119 (19), 104 (6), 87 (100), 83 (19), 71 (11), 53 (8), 45 (40); HREIMS *m/z* 237.9979 (calcd for $C_8H_{14}S_4$, 237.9978), 119.0016 (calcd for $C_4H_7S_2$, 118.9989), 87.0319 (calcd for C_4H_7S, 87.0268).

Foetithiophene A (3,4,5-trimethyl-2-thiophenecarboxylic acid) (5): colorless needles; mp 166.0−166.5 °C; UV (MeOH) λ_{max} (log ϵ) 261 (3.91), 279 (3.82) nm; IR (KBr) ν_{max} 2924, 1654, 1458, 1372, 1288, 934 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.41 (3H, s, H_3-7), 2.35 (3H, s, H_3-9), 2.05 (3H, s, H_3-8); ^{13}C NMR ($CDCl_3$) δ 169.0 (s, C-6), 149.9 (s, C-3), 143.3 (s, C-5), 139.2 (s, C-4), 127.0 (s, C-2), 17.4 (q, C-7), 16.6 (q, C-9), 15.1 (q, C-8); EIMS *m/z* 170 $[M]^+$ (100), 155 (41), 125 (55), 101 (30), 83 (53), 73 (63), 55 (60), 41 (73); HREIMS *m/z* 170.0368 (calcd for $C_8H_{10}O_2S$, 170.0401), 125.0422 (calcd for C_7H_9S, 125.0425).

X-ray Crystallographic Analysis Data of Foetithiophene A (5).[14] A colorless triclinic crystal was obtained from *n*-hexane−EtOAc (1:1). Crystal size = 0.35 × 0.20 × 0.15 mm; cell parameters, a = 6.8620(7) Å, b = 7.8200(9) Å, c = 8.4580(8) Å, V = 419.87(8) Å^3, α = 81.359(6)° , β = 69.751(5)° , γ = 83.153(4)° , space group $P\bar{1}$ (Z = 2). Data collection was performed on a DIP image plate, the structure was solved by direct methods (maXus SIR92), and the final R and R_w values were 0.053 and 0.123, respectively, for 1326 observed reflections.

Foetithiophene B [3,4,5-trimethyl-2-(methylsulfinyloxymethyl)thiophene] (6): pale yellow oil; UV (MeOH) λ_{max} (log ϵ) 245 (3.25), 322 (2.12) nm; IR (KBr) ν_{max} 2925, 1457, 1292, 1128, 966 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.33 (2H, s, H-6), 2.83 (3H, s, sulfinylmethyl), 2.34 (3H, s, H_3-9), 2.13 (3H, s, H_3-7), 2.03 (3H, s, H_3-8); ^{13}C NMR ($CDCl_3$) δ 139.3 (s, C-3), 134.1 (s, C-4), 133.9 (s, C-5), 117.4 (s, C-2), 54.5 (t, C-6), 39.0 (q, sulfinylmethyl), 13.7 (q, C-7), 13.5 (q, C-9), 12.8 (q, C-8); EIMS *m/z* 218 $[M]^+$ (13), 181 (26), 155 (34), 139 (100), 124 (29), 113 (16), 105 (13), 91 (23), 77 (18), 59 (46), 43 (77); HREIMS *m/z* 218.0435 (calcd for $C_9H_{14}O_2S_2$, 218.0435), 139.0595 (calcd for $C_8H_{11}S$, 139.0581), 78.9850 (calcd for CH_3O_2S, 78.9854).

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(14) Crystallographic data for foetithiophene A (**5**) have been deposited with the Cambridge Crystallographic Data Center (CCDC187440). Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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