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SYLVONE, A NEW FURANOID LIGNAN OF PIPER SYLVATICUM

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Abstract - The structure of a novel 2,3,4- trisubstituted furanoid lignan, designated sylvone, was established as 1 from detailed spectroscopical and chemical studies.

We undertook the chemical investigation of the species Piper sylvaticum Roxb. in connection with our work on the systematic screening of Indian Piper plants. We have previously reported the isolation, characterisation and synthesis of amide, lignan and flavonoid constituents from this species [1-8]. The present communication reports the structure elucidation of another new compound, a novel furanoid lignan designated sylvone. To our knowledge only a few compounds of such structural pattern are known [9,10].

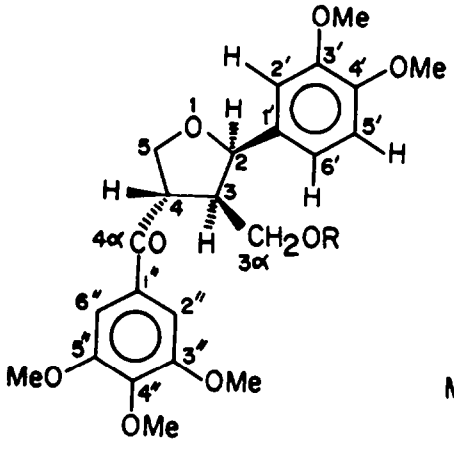
RESULTS AND DISCUSSION

Sylvone, 1, $C_{23}H_{28}O_8$ (M^+ 432), m.p. 138-139°, $[\alpha]_D^{21}$ + 9.6°($CHCl_3$), was obtained from the petrol extracts of the seeds. It exhibited UV maxima at 283, 219 and 207 mm (logϵ 4.10, 4.42 and 4.48) which did not show any significant alkali-shift thus ruling out the presence of phenolic or enolic functions. IR and NMR absorption spectra showed signals for an hydroxyl [IR(KBr) 3550 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) : δ 1.32, 1H,br.s, disappeared on deuteration] and conjugated carbonyl groups [IR(KBr) 1660 cm^{-1}; ^{13}C NMR (20 MHz), $CDCl_3$) : δ 198.4]. IR bands at 1575, 1500, 1450, 1410, 845, 810, 735, 720 and 710 cm^{-1} suggested the presence of substituted benzene rings. Its ^1H NMR spectrum also showed the presence of five aromatic methoxyls [δ 3.78(3H,s), 3.77 (6H,s) and 3.72 (6H,s)] and five aromatic protons as two singlets at δ 6.70 (3H, 2', 5' and 6'-H)and 7.26 (2H, 2" and 6"-H). Seven aliphatic protons appeared in the region δ 2.7-δ 4.9.

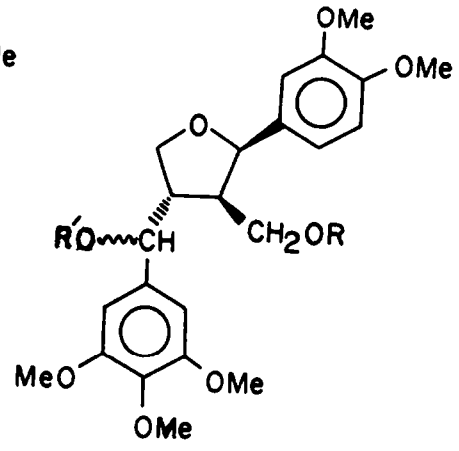
Sylvone on $NaBH_4$ reduction furnished two products of which one was an amorphous dihydro-compound 2, $C_{23}H_{30}O_8$ (M^+434). This compound lacked the characteristic signals for carbonyl in IR and ^{13}C NMR spectra. Thus a single conjugated carbonyl was present in sylvone.

Acetylation of 1 yielded an amorphous mono-acetate 3, $C_{25}H_{30}O_9$ (M^+ 474), which exhibited the characteristic bands for an acetoxy group in its IR($CHBr_3$) [1730, 1240 cm^{-1}] and ^1H NMR spectra [δ1.76, 3H, s]. Since the 2H signal at δ 3.27 shifted to δ 3.71 on acetylation, it was apparent that the hydroxy was incorporated in a hydroxymethylene group.

Reductive acetylation of 1 with Zn dust, glacial HOAc and Ac_2O gave a product 4, $C_{27}H_{34}O_{10}$ (M^+518). Its IR showed the absence of both the hydroxyl and conjugated carbonyl absorptions of sylvone (1). Instead, strong bands appeared at 1750 and 1240 cm^{-1} indicating the presence of acetoxy groups. Its ^1H NMR (80 MHz, $CDCl_3$) showed two acetoxy signals at δ 1.84 and 2.11. These results were compatible with the reduction of the conjugated carbonyl in sylvone followed by di-acetylation.



1 : R = H
3 : R = Ac



2 : R = R′ = H
4 : R = R′ = Ac

The structure and stereochemistry of sylvone could be settled as 1 from a detailed study of its ^1H and ^{13}C NMR including extensive decoupling, solvent-induced shift and NOE studies.

The substitution pattern of one of the two aromatic rings of sylvone (1) was settled as 3,4-dimethoxyphenyl from (i) the close correspondence in ^{13}C-NMR chemical shifts of six carbons (three CH and three quaternary) with those of the 3,4-dimethoxyphenyl rings in diaeudesmin[9]; (ii) the three protons of this ring, which appeared as a singlet at δ 6.70 in $CDCl_3$, were clearly differentiated in C_6D_6-$CDCl_3$ and C_6D_6, the splitting pattern corresponding to a 1,2,4-trisubstituted benzene.

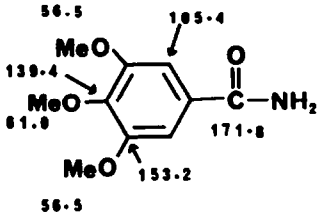
The presence of a 3,4,5-trimethoxybenzoyl moiety was apparent from the following observations : (i) the appearance of only four ^{13}C NMR signals for the six aromatic carbons thus indicating symmetrical substitution; (ii) the similarity

in ^{13}C chemical shifts of the ring and methoxyl carbons to those of trimethylgallamide (5); (iii) the comparative downfield position in sylvone of the two ortho-protons (δ 7.26 in $CDCl_3$; δ 7.52 in C_6D_6), which suffered a marked upfield shift to δ 6.78 ($CDCl_3$) in dihydrosylvone.

The ^{13}C-NMR spectrum of sylvone exhibited signals for three methines (δ48.2, 49.4 and 80.5) and two methylenes (δ60.9, 67.9) in the region for sp^3 carbons. It was apparent that both methylenes were adjacent to oxygen atoms while the methine at lowest field was obviously flanked by both an oxygen as well as an aryl ring. From the data presented so far and from biogenetic considerations structure (1), without stereochemical implications, could be proposed for sylvone. This was confirmed by the following decoupling studies which established the actual sequence of non-aromatic carbons. Irradiation of 3-H (δ 2.75, 1H, br.dq, J_d = 2.8 Hz and $J_q \approx$ 6.3 Hz) caused 2-H (δ 4.89, 1H, d, J = 6.3 Hz) and the 3α-methylene protons (δ 3.27, 2H, d, J = 6.4 Hz) to collapse to singlets. The 4-H (δ4.15, 1H, m), 5α-H (δ 4.09, 1H, distorted t), and 5β-H (δ4.28, 1H, t, J =7.8 Hz) signals formed a tightly coupled ABC system. The 4-H simplified to distorted t on irradiation of 3-H. The differentiation of 4-H from 5α-H and 5β-H was more marked in C_6D_6 solution. The 3-H signal itself simplified to a double doublet ($J_1 \approx$ 6.5 Hz and $J_2 \approx$ 2.8 Hz) and to a quartet (J = 6.4 Hz) on separate irradiation of 3α-methylene protons and 4-H respectively. The ^{13}C NMR chemical shifts of C-2 (δ80.5), C-3 (δ49.4) and C-1' (δ130.0) were very similar to those of the corresponding centres in diaeudesmin (δ84.0, 49.5 and 131.4 respectively) and different from those in epi-eudesmin (δ87.5, 54.4 and 133.5 respectively)[9]. This suggested a cis-orientation of the C-2 and C-3 substituents as in diaeudesmin. The relative stereochemistry of sylvone was firmly established as 1 on the basis of NOE experiments (Table 1).

Table 1. NOE Enhancements in 360 MHz ^1H-NMR of Sylvone

Proton Irradiated	NOE Enhancement (%)
2-H	6.6 (3-H), 2.3 (2'-H)
3-H	13.9 (2-H), 2.8 (4-H), 2.6 (CH_2OH)
4-H	3.3 (3-H), 9.7 (5β-H), 2.3 (CH_2OH)
5α-H)	3.5 (2-H), 18.3 (5β-H)
5β-H	9.7 (4-H), 26.3 (5α-H)
3-CH_2OH	3.9 (3-H), 1.3 (6'-H)



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The large NOE enhancement observed for the 2-H, 3-H pair led to the conclusion that these were in cis-orientation. On the other hand the small NOE enhancements for the 3-H, 4-H pair confirmed their trans-relationship.

Thus sylvone has the structure and relative stereochemistry (1). It is a member of a very rare class of furanoid lignans of which only very few examples are known [9,10]. ^1H NMR decoupling experiments with sylvone monoacetate indicated that no skeletal rearrangement had occurred during acetylation and confirmed its structure as 3. Decoupling experiments of the dihydro-product (2) also indicated that no skeletal rearrangement had taken place during its formation. The removal of deshielding influence of the carbonyl of sylvone resulted in the upfield

shift of 4-H (~δ2.56) in 2, which was coupled to 4α-methine (δ4.66, d, J = 3.9 Hz). In $CDCl_3$, one of the C_5-proton signals was obscured by the methoxyl signals. Addition of C_6D_6 to the $CDCl_3$ solution caused this proton to move outside the methoxyl region and appear as a triplet. Irradiation of 4-H caused both the C_5-proton triplets to collapse to doublets.

EXPERIMENTAL

M.ps were recorded on a Köfler block and are uncorrected. The UV spectrum was obtained with a Varian-634S spectrometer in aldehyde-free ethanol and IR spectra with Beckman IR-20 or Pye-Unicam 1025 spectrometer. ^{1}H NMR spectra were recorded at 360, 200 and 80 MHz in $CDCl_3$ and d_6-benzene and ^{13}C NMR spectra were recorded at 20 MHz in $CDCl_3$. The chemical shifts are expressed in ppm downfield from TMS. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, dd, double doublet; f.s., fine splitting; obs., obscured; br, broad; w, weak.

Analytical samples were routinely dried over P_2O_5 *in vacuo* at room temp. Na_2SO_4 was normally used for drying organic solvents and extracts. Si gel was used for column chromatography and Si gel G for TLC.

Isolation of sylvone (1): Air-dried powdered seeds (2 kg) were extracted with petrol (b.p.60-80°) in a Soxhlet apparatus for 72 hr. The extract was concd and chromatographed. Benzene-$CHCl_3$(1/9) eluates afforded sylvone 1, as colourless crystals, m.p.138-139° (MeOH-$CHCl_3$), $[\alpha]_D^{21}$ +9.6° ($CHCl_3$), R_f = 0.5 (Benzene /AcOEt = 2/3 and 3% MeOH-$CHCl_3$); UV(EtOH) λ_{max} nm(log ε) = 207 (4.48),219 (4.42), 283 (4.10); $\lambda_{max}^{EtOH-NaOH}$ nm (log ε) = 223 (4.34) , 282.5 (4.05); 1_H NMR (360 MHz, $CDCl_3$): data in text. ^{1}H NMR (200 MHz, d_6-benzene) ~δ 1.37 (1H, br.s, -OH); 2.80 (1H, q with f.s,3-H); [3.21 (1H, d, J= 6.5 Hz), 3.22 (1H, d, J = 9.5 Hz), 3α-H,H']; [3.32, 3.35 (12H,s), 3.68 (3H, s), OCH_3 protons]; [~4.16 (2H, m), ~4.45 (1H, m), 5-CH_2 and 4-H]; 5.20 (1H, d, J=6.5 Hz, 2-H); 6.44 (1H, d, J= 7.5Hz, 5'-H); 6.67 (1H, s, 2'-H); 6.70 (1H, d, J= 7.5 Hz, 6'-H); 7.52 (2H, s, 2" and 6"-H). ^{13}C NMR (20 MHz, $CDCl_3$) δ 80.5 (d, C-2); 49.4 (d, C-3); 48.2 (d, C-4); 67.9 (t, C-5); 130.0 (s, C-1'); 130.6 (s, C-1"); 110.7 (d, C-2'); 105.9 (d, C-2" and C-6"); 148.3 (s, C-3'); 152.4 (s, C-3" and C-5"); 147.6 (s,C-4'); 142.1 (s,C-4"); 108.6 (d, C-5'); 117.3 (d, C-6'); 60.9 (t, C-3α); 198.1 (s, C-4α); [55.2 (q), 55.5 (q), C-3', C-4', C-3" and C-5"-OCH_3]; 60.1 (q. C-4"-OCH_3). MS (m/z); 432 (M^+), 414 (M^+-H_2O), 398, 384, 369, 233, 232, 229, 210, 195, 194, 193, 180, 167, 166;(Found : C, 63.55; H, 6.73; Calc. for $C_{23}H_{28}O_8$: C, 63.88; H, 6.48%).

Sylvone mono-acetate (3) : Sylvone (40 mg, 0.09 mmol), Ac_2O (10 mL) and afew drops of pyridine were kept at room temp. for 48 hours. The mixture was diluted with H_2O, neutralised with aq. $NaHCO_3$ and then extracted with $CHCl_3$. The organic layer was removed, washed, dried and concd. After removal of excess pyridine, only one product was obtained which was purified by prep TLC. IR ($CHBr_3$) 1730 (s, acetoxy C=O), 1670 (m, conjugated C=O), 1580, 1500, 1460, 1410 (s, aromatic), 1240, 1160, 1125 (s, C-O-C), 1025 (m, C-OH), 860, 760 cm^{-1} (substituted phenyl). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.76 (3H, s, CO_2CH_3); 3.14

(1H,m,slightly simplified on irr. at 4.44 and simplified on irr. at 4.00, 3-H); 3.71 (2H, dd, J= 6.0 and 8.5 Hz, collapsed to two s on irr. at 3.14, 3α-H, H'); [3.89 (9H, s), 3.83 (3H, s) and 3.81 (3H, s), $OC\underline{H}_3$ protons]; 4.00 (2H, m, collapsed to s on irr. at 4.44 and simplified on irr. at 3.14, 5-H); 4.44 (1H, t with f.s., J = 11 Hz, collapsed to s on irr. at 4.00, 4-H); 5.05 (1H, d, J=6.5 Hz, collapsed to s on irr. at 3.14, 2-H); 6.82 (3H, s, 2', 5' and 6'-H); 7.22 (2H, s, 2" and 6"-H). (Found: C, 63.01; H, 6.67; Calc. for $C_{25}H_{30}O_9$: C, 63.28; H, 6.37%).

Sylvone diacetate (4) : Sylvone (50 mg, 0.11 mmol), glacial HOAc (1 mL), Ac_2O (1 mL) and a very small amount of Zn dust was stirred well and warmed for 30 min. The mixture was diluted with H_2O and filtered. The filtrate was neutralised with aq. $NaHCO_3$ and extracted with $CHCl_3$. The extract was washed with H_2O, dried and evapd. to give sylvone diacetate as a liquid mass which was purified by prep. TLC. IR (Film) 1750 (s, acetoxy C=O), 1600 (s), 1530 (s) 1475 (m), 1430 (m) (aromatic), 1240 (br), 1140 (m) (C-O-C). ^{1}H NMR (80 MHz, $CDCl_3$) δ 1.84 (3H, s, 3α-$CO_2C\underline{H}_3$); 2.11 (3H, s, 4α-CO_2 $C\underline{H}_3$); ~2.69 (2H, m, 3-H and 4-H); 3.67 (2H, dd, J =7.7 and 8.2 Hz, 3α-H, H'); [3.84 (3H, s), 3.86 (6H, s), 3.88 (6H, s), $OC\underline{H}_3$-protons]; 5.00 (1H, d, J=6Hz, collapsed to s on irr. at ~2.66, 2-H); 5.73 (1H, d, J =8.4Hz, collapsed to s on irr. at ~2.66, 4α-H); 6.57 (1H, s, 2"-H); 6.83 (3H, s, 2', 5' and 6'-H); 7.35 (1H, s, 6"-H); (Found : C, 62.25; H, 6.78; calc. for $C_{27}H_{34}O_{10}$: C, 62.53; H, 6.61%).

Reduction of sylvone by $NaBH_4$: Sylvone (80 mg, 0.18 mmol) in MeOH (5 mL) was treated with excess $NaBH_4$ and kept at room temp. for 48 hr. The mixture was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was washed and dried. The solvent was removed and the residue on prep. TLC yielded two amorphous products, the dihydroproduct, 2, R_f = 0.45 (Benzene/AcOEt = 2/3) and a second product, R_f = 0.5 (Benzene/AcOEt = 2/3).

Dihydrosylvone (2): IR ($CHBr_3$) 3550 -3200 (br.m, -OH), 1590, 1510, 1460 (m) and 1420 (w) (aromatic), 1255 (m, C-O-C and C-OH), 1150-1050 (s, C-O-C) and 820-780 cm^{-1} (m, substituted phenyl). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.18 (2H, s, $O\underline{H}$); 2.28 (1H, m, 3-H); 2.56 (1H, m, changed to q, J = 4.3Hz, on irr. at 2.28, 4-H); [3.15 (1H, dd, J =6.3 and 3.1Hz, simplified to d, J=6.7 Hz on irr. at 2.28), 2.98 (1H, dd, J =6.3 and 3.1 Hz, simplified to d, J = 6.7 Hz on irr. at 2.28 and pattern changed on irr. at 2.56), 3α-H, H']; 3.80 (1H, obs., 5-H'); [3.84 (3H,s), 3.80 (6H, s) and3.78 (6H, s), $-OC\underline{H}_3$ protons]; 4.21 (1H, t, J = 4.7 Hz, changed to d, J = 5.1 Hz on irr. at 2.56 and splitting pattern changed on irr. at ~3.80 at diff. decoupler settings and collapsed to d, J= 4.7 Hz on irr. at 2.56, 5-H); 4.66 (1H, d, J =3.9Hz, changed to s on irr. at 2.56, 4α-H); 4.87 (1H, d, J =3.9Hz, collapsed to s on irr. at 2.28, 2-H); 6.54 (3H, s, 2', 5' and 6'-H); 6.78 (2H, s, 2" and 6"-H). (Found : C, 63.22; H, 6.77; Calc. for $C_{23}H_{30}O_8$: C, 63.58; H, 6.96%).

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