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THE MOLECULAR STRUCTURE OF 4a, 5, 8, 8a-TETRA-HYDRO-11, 14-DIMETHOXY-7-METHYL-4a-(3-METHYL-2-BUTENYL)-5, 8a-*o*-BENZENO-1, 4-NAPHTHOQUINONE

S. K. AGARWAL and R. P. RASTOGI
Central Drug Research Institute, Lucknow, India

and

H. VAN KONINGSVELD*
Laboratory of Organic Chemistry, Delft University of Technology, Julianalaan 136,
2628 BL Delft, The Netherlands

and

K. GOUBITZ and G. J. OLTHOF
Laboratory of Crystallography, Amsterdam University, Nieuwe Achtergracht 166,
1018 WV Amsterdam, The Netherlands

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Abstract—A novel natural product, microphyllone, has been isolated from *Ehretia microphylla*† together with baurenol and ursolic acid. Spectroscopic techniques, derivative formation and finally X-ray diffraction have been utilized in the structure elucidation of microphyllone. The structure appears to be 4a, 5, 8, 8a - tetrahydro - 11, 14 - dihydroxy-7-methyl-4a-(3-methyl-2-butenyl)-5, 8a-*o*-benzeno-1, 4-naphthoquinone.

Ehretia microphylla Lamk. (= *Carmona retusa* (Vahl.) Masam. N.O. Boraginaceae) is reported to be medicinally useful in Indigenous System of Medicine.[1] The chemical constituents of some constituents of some species of *Ehretia* have been reported to be long chain aliphatic unsaturated acids, a triterpene (baurenol) and allantoin[2-4] but no work has been reported on this taxon. Since its alcoholic extract was found to exhibit mild antiinflammatory (carrageenin-induced edema in mice) and CNS depressant (barbiturate potentiation test in mice) activities,[5] a detailed structural study was undertaken, the results of which are presented here.

RESULTS

Spectroscopic data

The absorption bands in the IR spectrum of *microphyllone* (1) indicated the presence of OH, a tetra-substituted aromatic ring, an unsaturated CO, *cis*-di, and tri substituted double bonds.

The off resonance ^{13}C NMR spectrum shows that 14 unsaturated C atoms in the molecule are distributed as two carbonyl-C atoms, two aryloxy-, two arylmethine- and two aryl quaternary C atoms, two equivalent methine-, two other methine- and two quaternary C atoms. In the upfield region eight saturated carbons were observed which included three Me-, two methylene-, one methine- and two quaternary C atoms. The PMR spectrum further defined the structural features as an isopentenyl chain, an unsaturated fragment: $-CH_2C(Me){=}CHCH<$, two OH-groups, two *ortho* arylmethines and a *cis*-disubstituted double bond. Spectral studies of derivatives (Experimental 2–4) confirmed these assignments and gave evidence of the presence of only two phenolic OH-groups and of the vinylic nature of the three Me groups.

Thus, micropyllone should consist of four rings, one of which is a dihydroxylated tetrasubstituted phenyl ring having two *ortho*-H atoms, an isopentenyl chain, an unsaturated fragment $-CH_2C(Me){=}CHCH<$, two CO groups in conjugation with a *cis*-disubstituted double bond and two quaternary C atoms. Difficulties in building a unique three dimensional molecule from these constituent parts led us to study microphyllone by X-ray analysis.

X-Ray analysis

Because of the bad crystals of microphyllone itself a crystal of the dimethylether (Fig. 1, R = 3) was used instead. Yellow monoclinic crystals, space group $P2_1$ and $Z = 2$, were grown from MeOH at 5°. The unit-cell dimensions, deduced from measurements on a single-crystal diffractometer ($CuK_{\alpha_1} = 1.54051$ Å), are $a = 13.571(4)$, $b = 8.870(3)$, $c = 8.706(3)$ Å and $\beta = 103.68(4)°$. Three dimensional intensity data were collected up to $\theta = 68°$ with the CAD-3-Nonius diffractometer using CuK_α radiation. High intensities were reduced by Ni filters. No absorption correction was applied.

The structure was solved using the direct method program system SIMPEL[6]. Three reflections were chosen to fix origin and enantiomorph and 5 extra reflections were given symbolic phases. After the symbolic addition procedure 45 out of 300 reflections were

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*Author to whom correspondence should be addressed.

†The plant material was collected by Dr. K. K. Singh of CDRI from Tirupati Hills, Andhra Pradesh, India, and a voucher specimen No. 8183 is preserved in the herbarium of CDRI, Lucknow.

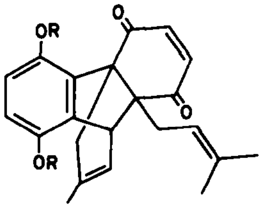
1, R = H
2, R = $COCH_3$
3, R = CH_3

Fig. 1. Microphyllone and its derivatives. The numbering of the atoms is as given in Fig. 2.

phased. The Σ_2 – consistency FOM Q, built in SIMPEL for the automatic determination of numerical values for the symbols, did not reveal the structure. Therefore, a recently developed enantiomorph specific criterion DELCRI[7], employing estimated phase sums for triplets, was used. It was successful in producing a fragment of 18 atoms, which was easily completed to a full image of the structure by a conventional recycling procedure. H atoms in the five Me groups could not be unequivocally located and were left out the refinement. The last cycle of blocked full-matrix anisotropic least squares refinement with fixed isotropic thermal parameters for the 11 non-methyl H atoms, converged to a final conventional R-index of 5.4% for 1810 observed ($> 2.85\,\sigma(I)$) reflections. The final non-hydrogen atomic coordinates, the temperature factors and their standard deviations (ESD's) as calculated from the refinement are given in Table 1. A list of F_0 and final F_c values is available on request.

Figure 2 shows an ORTEP[8] drawing of the molecule as determined by X-ray analysis. Table 2 summarizes the bond distances and bond angles between the non-H atoms. The molecule contains 3 6-membered rings. Both –C=O functions belong to one ring system. The tetra-substituted phenylring contains two –OMe groups. The third 6-membered ring shows the unsaturated fragment $-CH_2C(Me) = CHCH<$. The three rings are fused by a

Table 1. Final parameters with ESD's between parentheses. The fractional atomic coordinates are multiplied by 10^4. The expression for the anisotropic thermal parameters ($Å^2 \times 10^3$) is $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + a^*b^*hkU_{12} + a^*c^*hlU_{13} + b^*c^*klU_{23})]$

Atom	x/a	y/b	z/c	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C1	1088(4)	4378(7)	8876(6)	38(2)	59(3)	42(3)	0(3)	7(2)	-4(2)
C2	846(4)	2895(8)	9541(6)	45(3)	70(4)	56(3)	-15(3)	15(2)	1(3)
C3	1550(4)	1902(7)	10094(7)	59(3)	48(3)	63(3)	-8(3)	17(3)	7(3)
C4	2838(4)	2157(7)	10189(8)	52(3)	45(3)	52(3)	2(3)	13(2)	4(3)
C4a	2988(3)	3702(6)	9723(5)	38(2)	43(3)	34(2)	1(2)	4(2)	0(2)
C5	3770(3)	3523(6)	8739(6)	33(2)	53(3)	41(2)	9(2)	4(2)	0(2)
C6	4137(4)	5058(7)	8363(6)	38(2)	61(4)	50(3)	-7(3)	9(2)	1(3)
C7	3503(4)	6208(7)	8063(6)	42(3)	54(3)	51(3)	-11(3)	8(2)	-1(3)
C8	2390(4)	6055(6)	8114(6)	43(3)	43(3)	55(3)	2(2)	9(2)	4(3)
C8a	2098(3)	4437(6)	8448(5)	34(2)	43(3)	39(2)	0(2)	7(2)	-1(2)
C9	2136(3)	3409(6)	7038(5)	40(2)	43(3)	44(3)	-5(2)	10(2)	-3(2)
C10	3118(3)	2857(6)	7218(6)	41(2)	44(3)	46(3)	0(2)	11(2)	-2(2)
C11	3378(4)	1997(0)	6078(6)	50(3)	46(3)	47(3)	2(3)	15(2)	-2(3)
C12	2623(5)	1617(7)	4762(6)	70(4)	53(4)	48(3)	-3(3)	19(3)	-13(3)
C13	1649(4)	2157(7)	4544(6)	53(3)	59(4)	46(3)	-11(3)	10(2)	-8(3)
C14	1400(4)	3103(7)	5682(6)	41(3)	53(3)	42(3)	-11(2)	4(2)	-3(2)
C15	4703(4)	845(8)	5082(7)	72(4)	86(5)	61(3)	17(4)	33(3)	-13(4)
C16	-285(4)	3611(10)	4032(7)	39(3)	118(6)	64(4)	-5(4)	-12(3)	-12(4)
C17	3374(4)	4580(7)	11262(6)	42(3)	55(3)	44(3)	4(3)	4(2)	-8(3)
C18	2812(4)	5129(6)	12125(6)	45(3)	48(3)	43(3)	-6(2)	15(2)	-1(2)
C19	2454(4)	6523(7)	12482(6)	59(3)	54(3)	47(3)	9(3)	4(2)	-8(3)
C20	1671(5)	6890(10)	13438(8)	70(4)	127(7)	84(5)	20(5)	26(4)	-37(5)
C21	3066(7)	7875(8)	12109(10)	169(8)	42(4)	109(6)	-16(5)	61(6)	-10(4)
C22	3810(5)	7765(8)	7690(8)	80(4)	61(4)	83(4)	-25(4)	13(4)	16(4)
O1	503(3)	5434(5)	8745(5)	39(2)	70(3)	76(3)	12(2)	16(2)	5(2)
O2	3256(3)	1194(5)	10735(6)	76(3)	56(3)	109(3)	21(2)	26(3)	34(3)
O3	4380(3)	1556(6)	6354(4)	56(2)	79(3)	81(2)	18(2)	17(2)	-14(2)
O4	473(2)	3740*	5569(4)	38(2)	89(3)	47(2)	-3(2)	-1(1)	-10(2)

* Parameter was fixed during refinement.

Table 2. Bond distances (Å) and bond angles (°) in the heavy atom part of microphyllone.

Bond distances (Å)

1 = 1.503(9)
2 = 1.305(8)
3 = 1.474(8)
4 = 1.528(8)
5. = 1.546(7)
6 = 1.512(8)
7 = 1.320(8)
8 = 1.528(7)
9 = 1.535(8)
10 = 1.558(6)
11 = 1.504(7)
12 = 1.540(7)
13 = 1.394(7)
14 = 1.382(8)
15 = 1.386(7)
16 = 1.375(8)
17 = 1.399(8)
18 = 1.381(8)
19 = 1.528(6)
20 = 1.540(7)
21 = 1.493(8)
22 = 1.308(9)
23 = 1.528(10)
24 = 1.539(11)
25 = 1.516(10)
26 = 1.430(8)
27 = 1.474(6)
28 = 1.217(7)
29 = 1.213(7)
30 = 1.381(6)
31 = 1.361(6)

Bond angles (°)

1,2 = 121.7(5)
1,28 = 120.9(5)
2,3 = 123.5(6)
3,4 = 118.4(5)
3,29 = 120.3(5)
4,5 = 110.2(4)
4,10 = 110.2(4)
4,20 = 107.2(4)
4,29 = 121.1(5)
5,6 = 109.8(5)
5,10 = 99.4(4)
5,19 = 100.4(4)
5,20 = 112.3(4)
6,7 = 120.4(5)
6,19 = 108.3(4)
7,8 = 121.9(5)
7,25 = 123.8(5)
8,9 = 112.9(4)
8,25 = 114.3(5)
9,10 = 109.9(4)
9,11 = 111.8(4)
8,12 = 110.1(4)
10,11 = 112.9(4)
10,12 = 99.1(4)
10,20 = 117.5(4)
11,1 = 114.9(5)
11,12 = 112.4(4)
11,28 = 124.2(5)
12,13 = 108.3(4)
12,18 = 130.1(4)
13,14 = 121.3(4)
13,18 = 120.4(5)
13,19 = 107.7(4)
14,15 = 118.0(5)
14,19 = 130.7(4)
14,30 = 118.5(4)
15,16 = 121.8(5)
15,30 = 125.5(5)
16,17 = 119.8(4)
17,18 = 118.4(5)
17,31 = 124.9(4)
18,31 = 116.7(5)
20,21 = 118.9(4)
21,22 = 126.8(5)
22,23 = 120.8(6)
22,24 = 123.7(6)
23,24 = 115.5(6)
26,30 = 117.4(4)
27,31 = 116.8(4)

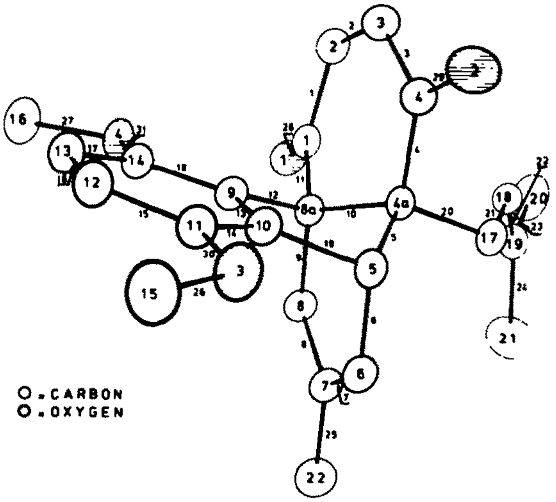

Fig. 2. Molecular conformation observed in the crystal structure of the dimethylether of microphyllone. Atomic numbering and thermal ellipsoids are given. For the sake of clarity hydrogen atoms are omitted.

5-membered ring bearing on one of its two saturated quarternary C atoms an isopentenyl chain. The dimethylether of microphyllone appears to be 4a, 5, 8, 8a - tetrahydro - 11, 14 - dimethoxy - 7 - methyl - 4a - (3 - methyl - 2 - butenyl) - 5, 8a - σ - benzeno - 1, 4 - naphthoquinone. In microphyllone itself two OMe groups are replaced by OH groups.

EXPERIMENTAL

IR spectra were measured on a Perkin–Elmer grating spectrophotometer model 177. PMR spectra were obtained on a 60 MHz instrument ($CDCl_3$: TMS int. std.), unless stated otherwise.

The powdered aerial parts of the plant (8 kg) was extracted with EtOH (90%). The total EtOH extract was concentrated under reduced pressure to a dark green viscous mass (350 g) which was exhaustively macerated with $CHCl_3$. The $CHCl_3$ extract was partitioned with 80% MeOH–$CHCl_3$ to give $CHCl_3$ (63 g) and 80% MeOH (13 g) souble fractions.

The residue from dark green $CHCl_3$ fraction was chromatographed on Si gel (1.5 kg). The C_6H_6 and C_6H_6-MeOH (1%) eluates gave substance A, identified as baurenol (mp 205–6° (11.0 g)). The successive elution of the column with C_6H_6-MeOH (3%) yielded a fraction (12.0 g) containing substance B which was charcoaled and rechromatographed over Si gel to give pure substance B, identified as ursolic acid (mp 290–1° (0.35 g)).

The dark brown MeOH (80%) soluble fraction was treated with charcoal and the residue (10 g) was chromatographed over Si gel; the C_6H_6-MeOH (6–8%) eluates crystallized from C_6H_6 as pale yellow needles (mp 179–80° (0.8 g)). This substance is called microphyllone.

Microphyllone. (Figure 1; R = 1). Mp 179–80° (C_6H_6). $[\alpha]_D$ −20.0° (*c* 2.0, $CHCl_3$). (Found: C, 75.15; H, 6.10. $C_{22}H_{22}0_4$ requires: C, 75.42; H, 6.28%). IR (KBr): 3375 (OH), 1670 (C=C–C=O), 1600, 1500, 808 (RR'R"R'"C_6H_2), 740'830 (*cis* RCH=CHR' and *cis* RCH=CR'R"). ^{1}H NMR (270 MHz): δ 1.47, 1.56, 1.60 (9H, s, C20, C21 and C22), 2.30, 2.47 (2H, dd, J = 7, 15 Hz, C17), 2.60, 2.88 (2H, d, J = 19 Hz, C8), 3.90 (1H, d, J = 6.5 Hz, C5) 4.95 (1H, t, J = 7 Hz, C18), 5.1 (2H, D_2O exch., O3 and O4), 5.8 (1H, brd, J = 7 Hz, C6), 6.38, 6.50 (2H, d, J = 8.5 Hz, C12 and C13), 6.45, 7.15 (2H, d, J = 10.5 Hz, C2 and C3). ^{13}C NMR: δ 203.5, 202.1 (2s, C1 and C4), 145.7, 142.7 (2s, C11 and C14), 140.0 (2d, C2 and C3), 138.5, 135.2 (2s, C9 and C10), 133.5, 131.4 (2s, C7 and C19), 122.6, 118.4, 117.0, 115.7 (4d, C6, C12, C13 and C18), 69.0, 59.5 (2s, C4a and C8a), 42.1 (d, C5), 33.5, 29.0 (2t, C8 and C17), 25.7, 22.1, 18.5 (3q, C20, C21 and C22). MS: $M^{\cdot +}$ 350.15.

Microphyllone diacetate (Figure 1; R = 2). $C_{26}H_{26}O_6$. To 50 mg of 1 in C_5H_5N 0.5 ml Ac_2O was added at room temp. After one night the C_5H_5N was removed yielding a mixture which was purified by Si gel chromatography ($CHCl_3$) as an amorphous powder. IR (KBr): 1755 (Ar–OCOR). ^{1}H NMR: no big differences from 1 except appearance of signals at δ2.0 (3H, s, OAc), 2.19 (3H, s, OAc) and disappearance of signals at 5.1 ppm.

Microphyllone dimethylether. (Figure 1; R = 3). 150 mg of 1 in dry acetone was refluxed with MeI and K_2CO_3 for 4 hr. 3 was purified by plc (C_6H_6–MeOH, 98:2). MP 77–9° (MeOH). (Found: C, 75.93; H, 6.97. $C_{24}H_{26}O_4$ requires C, 76.19; H, 6.87%). ^{1}H NMR: no big differences from 1 except appearance of signals at δ3.66 (3H, s, OMe), 3.79 (3H, s, OMe) and disappearance of signals at 5.1 ppm. MS: $M^{\cdot +}$ 378.

Hexahydro microphyllone. (4). $C_{22}H_{28}O_4$. 50 mg of 1 in alcohol was shaken with Pd/C (10%, 50 mg) in H_2 atmosphere for 4 hr. The hydrogenated product was purified on Si gel column ($CHCl_3$–MeOH; 97:3). Mp 210° ($CHCl_3$–C_6H_6). ^{1}H NMR: δ 0.83, 0.91 (9H, s, 3Me), 1.0–3.8 (17H), 6.38, 6.56 (2H, d, J = 8.5 Hz, C2 and C3). MS: $M^{\cdot +}$ 356.

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