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THE CRYSTAL STRUCTURE OF 1-(3',4'-DIMETHOXYPHENYL)-2-(THIOPHENOXY)-1-PROPANONE, A PLATELET-ACTIVATING FACTOR (PAF-ACETHER) ANTAGONIST

CARLITO LARIUCCI, LEON ÍTALO BRASIL HOMAR,
Departamento de Física, Instituto de Matemática e Física - Universidade Federal de Goiás, C.P. 131, 74001-970 Goiânia, GO

PEDRO HENRIQUE FERRI
Departamento de Química Orgânica, Instituto de Química e Geociências - Universidade Federal de Goiás, C.P. 131, 74001-970 Goiânia, GO

LOURIVALDO SILVA SANTOS
Departamento de Química, Centro de Ciências Exatas e da Natureza, Universidade Federal do Pará, 66000-000 Belém, PA

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The crystal structure of a sulphur analogue of 8,4'-oxyneolignan derivative, **1**, with anti-PAF-acether activity has been determined from single-crystal X-ray diffraction data. The compound crystallizes in monoclinic space group $P2_1/c$ with a = 6.153(3), b = 16.718(3), c = 15.156(5) Å, β = 95.18(4)°, V = 1552(1) Å^3. Full-matrix least-squares refinement of 191 structural parameters gave R = 0.060 for 2004 observed [$I > 3\sigma(I)$] reflexions.

Key Words: 1-(3',4'-dimethoxyphenyl)-2-(thiophenoxy)-1-propanone, Crystal structure, Platelet-Activating Factor.

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INTRODUCTION

The Platelet-Activating Factor (PAF-acether) is an etherphospholipid mediator implicated in a diverse range of pathological conditions including asthmatic and inflammatory process, various cardiovascular disorders, acute graft rejeiction, endotoxic shock and immune responses regulation [1]. In addition to synthetic PAF-acether receptor antagonists having PAF analogous structure, PAF-acether antagonists of natural origin having various structures have been isolated from Brazilian and Chinese medicinal plants [2]. The natural neolignan benzofuranoid kadsurenone isolated from *Piper futokdsura* [3] is a potent inhibitor of [^{3}H]-PAF-acether binding to rabbit platelet membrane and PAF-acether induced platelet aggregation [4]. Later the synthetic 2,5-diaryltetrahydrofuran derivatives belonging to the subgroup of neolignans have been reported as PAF-acether antagonists [5].

Recently [6,7] the sulphur analogue of 8,4'-oxyneolignan derivative, **1**, shown selective antagonistic activity in PAF-acether-induced platelet aggregation and anti-PAF-acether effects in mouse PAF-induced pleurisy and vascular permeability. In an attempt to further these studies, the crystal structure of 1-(3',4'-dimethoxyphenyl)-2-(thiophenoxy)-1-propanonem, **1**, is described in this paper. The X-ray results enable conclusions to be drawn about the geometry of structural elements of this new PAF-acether antagonist.

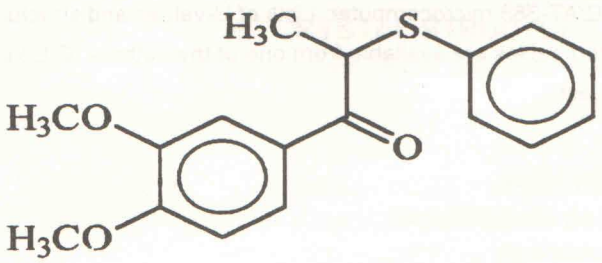

Figure 1

EXPERIMENTAL

Strutural Determination

Crystal and experimental data for **1** are given in Table 1. Diffracted intensity data were recorded with a Nonius CAD-4 X-ray diffractometer with graphite-monochromated Mo$K\alpha$ radiation. The intensities were corrected for Lorentz and polarization effects. The unit cell dimensions were determined from diffractometer setting angles for 22 reflections. The atomic coordinates of all non-hydrogen atoms were determined by direct methods [8] and by electron density calculations, H atoms placed at their calculated positions. Intensities statistics indicated a centric structure, and a plausible solution was obtained within space group $P2_1/c$. Final R and wR, omitting unobserved reflections, are 0.060 and 0.069 respectively.

TABLE 1

Crystal and Experimental Data for 1-(3',4'-dimethoxyphenyl)-2-(thiophenoxy)-1-propanone, **1**, $C_{17}H_{18}O_3S$

Mr	302
Crystal System	Monoclinic
Space Group	$P2_1/c$ (No. 14)
Unit Cell Dimensions/Å or °	a = 6,153(3)
	b = 16,718(3)
	c = 15,156(5)
	β = 95,18(4)
	V = 1552(1)
Z	4
Dc/gcm^{-1}	1.208
M.p./ C	59-61 (Metanol)
μ(Mo$K\alpha$)/mm^{-1}	1.72
Crystal size/mm	0.70 x 0.40 x 0.35
Reflections for cell determination	22
θ(range)deg	0-25
Scan mode	zig-zag
2θ range/	0-50
Total No. of independent reflections measured	2453
No. of observed independent reflections [$I>3\sigma(I)$]	2004
Method used to solve structure	Direct methods (SHELXS 86)
	Electron density difference map
No. of parameters refined	191
Weights calculated according to	$[\sigma^2 F_o + 0.0003 \mid F_o \mid^2]^{-1}$
R	0.060
Maximum residual electron density/e Å^{-3}	0.39

Some further details concerning the refinement of the structure are given in Table 2. Neutral atomic scattering factors as well as $\Delta f'$ a nd $\Delta f''$ were taken from International Tables for X-Ray Crystallography [9]. Calculations were carried out a PC/AT-386 microcomputer. Lists of U-values and structure factors tables are available from one of the authors (C.L.) on request.

TABLE 2

Atomic fractional coordinates and B_{eq} for 1-(3',4'-methoxyphenyl)-2-(thiophenoxy)-1-propanone, **1**, *$C_{17}H_{18}O_3S$. Space group $P2_1/c$. $B_{eq}=4/3\Sigma_{ij}B_{ij}\mathbf{a}_i\mathbf{a}_j$.*

Atom	x	y	z	B_{eq}
C(1)	0.5711(7)	0.0708(2)	0.3890(3)	5.4(1)
C(2)	0.3254(5)	0.1541(2)	0.4592(2)	3.7(1)
C(3)	0.1471(6)	0.1573(2)	0.5106(2)	3.9(1)
C(4)	-0.0741(7)	0.0847(2)	0.6033(3)	6.1(2)
C(5)	0.0493(5)	0.2306(2)	0.5257(2)	3.9(1)
C(6)	0.1304(5)	0.2993(2)	0.4902(2)	3.8(1)
C(7)	0.3076(5)	0.2971(2)	0.4407(2)	3.3(9)
C(8)	0.4051(5)	0.2231(2)	0.4251(2)	3.4(1)
C(9)	0.3941(6)	0.3733(2)	0.4069(2)	3.8(1)
C(10)	0.6004(6)	0.3722(2)	0.3611(2)	3.9(1)
C(11)	0.7209(7)	0.4521(2)	0.3671(3)	6.1(2)
C(12)	0.6606(5)	0.2577(2)	0.2262(2)	3.6(1)
C(13)	0.8688(6)	0.2408(2)	0.2641(2)	4.3(1)
C(14)	0.9692(6)	0.1706(3)	0.2419(3)	5.5(1)
C(15)	0.8647(8)	0.1178(2)	0.1821(3)	5.5(1)
C(16)	0.6628(7)	0.1358(2)	0.1432(3)	5.1(1)
C(17)	0.5566(6)	0.2043(2)	0.1655(2)	4.4(1)
O(1)	0.4054(4)	0.0799(1)	0.4464(2)	5.3(9)
O(2)	0.0844(4)	0.0861(1)	0.5417(2)	5.4(1)
O(3)	0.2987(4)	0.4360(2)	0.4171(2)	6.0(1)
S	0.5148(2)	0.3457(1)	0.2458(1)	4.8(3)

TABLE 2

*Atomic fractional coordinates and B_{eq} for 1-(3',4'-methoxyphenyl)-2-(thiophenoxy)-1-propanone, **1**, $C_{17}H_{18}O_3S$. Space group $P2_1/c$. $B_{eq}=4/3\Sigma_{ij}B_{ij}a_ia_j$ (Cont.)*

Atom	x	y	z
H1(C1)	0.6162	0.0085	0.3861
H2(C1)	0.7117	0.1056	0.4134
H3(C1)	0.5126	0.0912	0.3236
H1(C4)	-0.1055	0.0236	0.6214
H2(C4)	-0.2232	0.1116	0.5741
H3(C4)	-0.0151	0.1179	0.6618
H(C5)	-0.0887	0.2337	0.5648
H(C6)	0.0535	0.3560	0.5016
H(C8)	0.5435	0.2204	0.3861
H(C10)	0.7158	0.3299	0.3922
H1(C11)	0.8673	0.4477	0.3331
H2(C11)	0.7638	0.4669	0.4358
H3(C11)	0.6166	0.4983	0.3366
H(C13)	0.9519	0.2821	0.3105
H(C14)	1.1310	0.1568	0.2716
H(C15)	0.9431	0.0625	0.1663
H(C16)	0.5847	0.0958	0.0941
H(C17)	0.3936	0.2167	0.1362

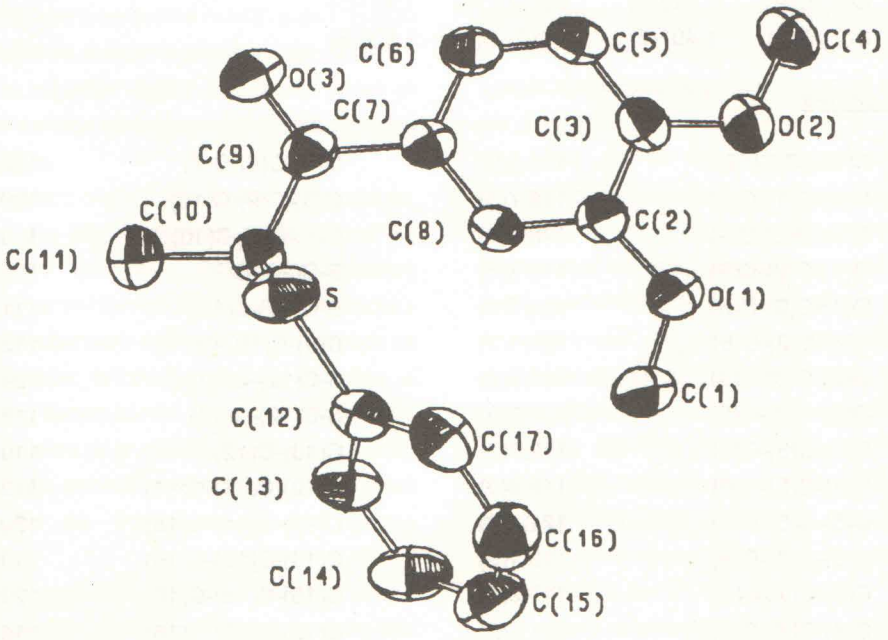

Fig. 2 - *The 1-(3',4'-dimethoxyphenyl)-2-(thiophenoxy)-1-propanone (**1**) molecule showing the atomic numbering*

Crystal structure of 1-(3',4'-dimethoxyphenyl)-2-(thiophenoxy)-1-propanone, 1

Fractional atomic coordinates and equivalent isotropic thermal parameters are given in Table 2, and bond distances and angles in Table 3. Fig. 2 shows the molecule and the atomic labelling. The crystal consists of four molecules held together by Van der Waals forces. The aromatic C-C bond distance are normal (mean value 1.384 Å) as are the C-H bond distance. The $C(sp^3)$-$O_{methoxy}$ bond distances (mean value 1.409 Å) agress well with those observed in a series of lignoid-related compounds [10, 11] and is in accordance with typical C-O single bond values. The $C(sp^2)$-$O_{methoxy}$ bond distances (mean value 1.352 Å) are also similar to those observed in other lignoid model compounds, and shows partial double-bond character. Wthin the limits of experimental error, the rings' carbon atoms are situated in the aromatic rings planes, mean deviations being close to 0.004 and 0.008. The methoxy oxygen atoms are almost coplanar with the respective ring [O(1), 0.017 Å; O(2), 0.035 Å], while the methoxy carbon atoms C(1) and C(4) are not [0.171 and 0.205 Å, respectively]. The thiophenoxy atom (S) is slightly twisted [0.050 Å] out of the benzene ring plane as was also found in phenoxy analogues [10, 11]. The bond distance between the thiophenoxy atom (S) and the C(12) shows partial double-bond character. The two benzene ring planes form an angle of 72.20(9)° with respect to each other.

TABLE 3

Bond distance (Å) and angles (°) in 1-(3',4'-methoxyphenyl)-2-(thiophenoxy)-1-propanone, 1, $C_{17}H_{18}O_3S$.

Bond distances

S -C(10)	1.833(3)	C(2)-C(8)	1.373(4)	C(12)-C(13)	1.385(5)
S -C(12)	1.762(3)	C(3)-C(5)	1.393(5)	C(12)-C(17)	1.395(5)
O(1)-C(1)	1.407(5)	C(5)-C(6)	1.381(5)	C(13)-C(14)	1.382(6)
O(1)-C(2)	1.355(4)	C(6)-C(7)	1.379(4)	C(14)-C(15)	1.382(6)
O(2)-C(3)	1.349(4)	C(7)-C(8)	1.404(4)	C(15)-C(16)	1.360(6)
O(2)-C(4)	1.410(5)	C(7)-C(9)	1.489(4)	C(16)-C(17)	1.376(5)
O(3)-C(9)	1.218(4)	C(9)-C(10)	1.501(5)		
C(2)-C(3)	1.403(5)	C(10)-C(11)	1.526(5)		

Bond angles

C(10)-S-C(12)	104.8(2)	O(3)-C(9)-C(7)	120.1(3)
C(1)-O(1)-C(2)	118.7(3)	O(3)-C(9)-C(10)	120.4(3)
C(3)-O(2)-C(4)	118.9(3)	C(7)-C(9)-C(10)	119.5(3)
O(1)-C(2)-C(3)	115.3(3)	S-C(10)-C(9)	105.2(2)
O(1)-C(2)-C(8)	124.7(3)	S-C(10)-C(11)	111.4(3)
C(3)-C(2)-C(8)	120.1(3)	C(9)-C(10)-C(11)	112.8(3)
O(2)-C(3)-C(2)	115.0(3)	S-C(12)-C(13)	124.5(3)
O(2)-C(3)-C(5)	125.3(3)	S-C(12)-C(17)	115.8(2)
C(2)-C(3)-C(5)	119.7(3)	C(13)-C(12)-C(17)	119.7(3)
C(3)-C(5)-C(6)	119.4(3)	C(12)-C(13)-C(14)	119.3(3)
C(5)-C(6)-C(7)	121.4(3)	C(13)-C(14)-C(15)	120.7(4)
C(6)-C(7)-C(8)	119.1(3)	C(14)-C(15)-C(16)	119.7(4)
C(6)-C(7)-C(9)	119.3(3)	C(15)-C(16)-C(17)	120.9(4)
C(8)-C(7)-C(9)	121.6(3)	C(12)-C(17)-C(16)	119.7(3)
C(2)-C(8)-C(7)	120.3(3)		

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REFERENCES

1. BRAQUET, P.; CHABRIER, P.E. & MENCIA-HUERTA, J.M. 1987. Advanced Inflammation Research. Vol. 12, Reven Press, New York.

2. BIFTER, T. & STEVENSON, R. 1987. Phytotheraphy Research, 3, 97.

3. CHANG, M.N.; HAN, G.-Q.; ARISON, B.H.; SPRINGER, J.P., HWANG, S.-B. & SHEN, T.Y. 1985. Phytochemistry, 24, 2079.

4. SHEN, T.Y.; HWANG, S.-B.; CHANG, M.N., DOEBBER, T.Y.; LAM, M.-H.; WU, M.S.; WANG, X.; HAN, G.-Q. & LEE, R.Z. 1985. Proc. Natl. Acac. Sci. USA, 82, 672.

5. GIROTRA, N.N.; BIFTU, T.; PONPIPOM, M.W.; ACTON, J.J.; ALBERTS, A.W.; BACH, T.N.; BALL, R.G.; BUGIANESI, R.L.; PARSONS, W.H.; CHABALA, J.C.; DAVIES, P.; DOEBBER, T.W.; DOHERTY, J.; GRAHAM, D.W., HWANG, S.-B.; KUO, C.H.; LAM, M.-H.; LUELL, S.; MACINTYRE, D.E.; MEURER, R.; ROBERTS, C.D.; SAHOO, S.P. & WU, M.S. 1992. J. Med. Chem., 35, 3474.

6. SANTOS, L.S.1991. Síntese e Atividade Biológica de Neolignanas 8.O.4', Derivados e Compostos Correlatos. Tese de Doutorado, IQ/UNICAMP.

7. FIERRO, I.M. 1989. Análogos Sintéticos de Neolignanas com Potencial Atividade Anti-PAF. 1989. Tese de Mestrado, ICB-UFRJ/FIOCRUZ.

8. SHELDRICK, G. M. 1986. SHELXS 86. Crystal Structure Solution Computer Program, University of Göttingen, FRG.

9. CROMER, D.T. & WABER, J.T. 1974. International Tables for X-Ray Crystallography, Vol. IV, Kynoch Press, Birmingham.

10. STOMBERG, R.; HAUTEVILLE, M. & LUNDQUIST, K. 1988. Acta Chem. Scand., Ser. B 42, 697.

11. JOHANSSON, A.; LUNDQUIST, K. & STOMBERG, R. 1992. Acta Chemi. Scand., 46, 901.