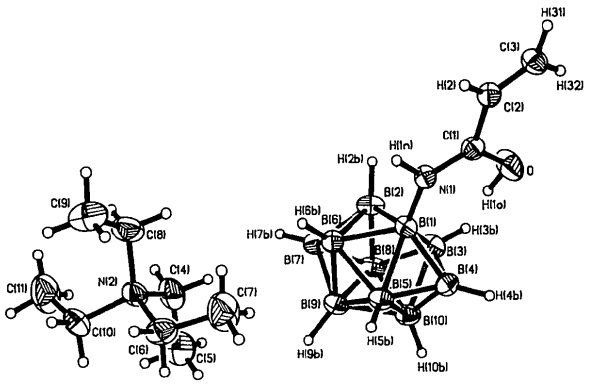

Fig. 1. *ORTEP* drawing of the molecule. Thermal ellipsoids scaled to enclose 30% probability. H atoms are represented as spheres of arbitrary radii.

radii of boron and nitrogen (1·58 Å), but is significantly longer than B=N (1·34 Å) and delocalized B—N (1·44 Å) distances (Niedenzu & Dawson, 1965). A high degree of double-bond character of the N—C bond [1·288 (4) Å] and planarity of the entire amide moiety [121·7 (3)°] are consistent with the microwave measurements on formamide, and have been invoked to explain a relatively high rotational barrier about the C—N bond to make the structure of amides a relatively rigid one. Furthermore, O-protonated amide, as in (I), is greatly stablized by resonance (Streitwieser & Heathcock, 1985).

The slightly distorted tetrahedral geometry of the $(C_2H_5)_4N^+$ ion with an average C—N—C bond angle of 111·3 (3)° is unexceptional and deserves no special comment.

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Platelet Activating Factor Antagonist Design: Structure of Methyl *trans*-5-(3,4-Dimethoxyphenyl)-2,3,4,5-tetrahydro-2-oxo-4-furancarboxylate

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Abstract. $C_{14}H_{16}O_6$, $M_r = 280{\cdot}28$, monoclinic, $P2_1/c$, $a = 6{\cdot}070$ (2), $b = 9{\cdot}526$ (5), $c = 22{\cdot}418$ (5) Å, $\beta = 94{\cdot}32$ (2)°, $V = 1293$ Å^3, $Z = 4$, $D_x = 1{\cdot}44$ g cm^{-3}, λ(Mo $K\alpha$) = 0·71073 Å, $\mu = 0{\cdot}71$ cm^{-1}, $F(000) = 592$, $T = 293$ K, final $R = 0{\cdot}043$ for 1400 observed [$F_o \geq 5\sigma(F_o)$] reflections. The observed structure confirms a *trans* stereorelationship for the two substituents and an envelope conformation for the lactone ring. There is no crystallographically imposed symmetry. An analysis of the closest contacts in the cell lattice reveals two types of intermolecular interactions for this compound.

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Introduction. Platelet activating factor (PAF) is produced in a diversity of stimulated cells, and it is being attributed an increasingly significant role as a mediator of biochemical and physiological events (Venuti, 1985; McManus, 1986). PAF-induced pulmonary, intravascular, and cardiovascular alterations have been implicated casually in the development of pulmonary, vascular, and cardiac diseases of both immune and non-immune origin (McManus, 1986; Wu, Biftu & Doebber, 1986). The binding of radiolabeled PAF to isolated blood platelets has been demonstrated, suggesting that the binding of PAF to specific receptor sites is the first step in its biological functions (McManus, 1986; Hwang, Lam, Biftu, Beattie & Shen, 1985). Specific and potent PAF receptor antagonists would block this key binding step and could be used to clarify further the biological role of this phospholipid ether. At the same time, new PAF antagonists have good potential of becoming efficacious pharmaceutical agents. X-ray crystallographic studies are useful to characterize the geometry and conformations of therapeutics (Codding, 1988), while an understanding of the intermolecular interactions within the crystal lattice provides information about the nature of the biological receptor site. We now wish to report the first of our studies on the design of new PAF antagonists that employ such a crystallographic approach. Herein we describe the X-ray crystal structure and an analysis of the closest intermolecular contacts for methyl *trans*-5-(3,4-dimethoxyphenyl)-2,3,4,5-tetrahydro-2-oxo-4-furancarboxylate, a γ-lactone analogue of Merck, Sharp & Dohme's potent PAF antagonist L-652,731 (Wu *et al.*, 1986; Hwang *et al.*, 1985; Biftu *et al.*, 1986).

Experimental. The title compound was prepared in 66% yield by decarboxymethylation of dimethyl 5-(3,4-dimethoxyphenyl)-2,3,4,5-tetrahydro-2-oxo-3,4-furandicarboxylate (Peterson, Do & Surjasasmita, 1988) with potassium acetate in refluxing glacial acetic acid (Mandell, Singh, Gresham & Freeman, 1965). Product purification was effected by flash chromatography on silica gel eluting with 40% ethyl acetate in hexane. Crystals (m.p. 369–370 K) were obtained by slow evaporation of a methanol solution of the title compound. The X-ray structure was in full agreement with the spectral and analytical data. Physical data: IR (KBr) 3000, 2950, 2840, 1770, 1720, 1600, 1590, 1510, 1450, 1430, 1260, 1250, 1220, 1200, 1160, 1145, 1130, 1020, 980, 950, 910, 815, 765, 685 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6·95–6·82 (*m*, 3 H), 5·59 (*d*, $J = 7·53$ Hz, 1 H), 3·89 (*s*, 6 H), 3·77 (*s*, 3 H), 3·35 (*ddd*, $J = 9·66$, 8·88, 7·53 Hz, 1 H), 3·02 (*dd*, $J = 17·62$, 8·88 Hz, 1 H), 2·90 (*dd*, $J = 17·62$, 9·66 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50 MHz) 173·91, 171·22, 149·62, 149·47, 130·16, 118·15, 111·29, 108·66, 82·28, 56·01, 55·96, 52·68, 48·56, 32·55. Analysis calculated for $C_{14}H_{16}O_6$: C, 60·00; H, 5·75%; found C, 60·03; H, 6·06%. D_m not determined. Crystal 0·13 × 0·25 × 0·28 mm. Enraf–Nonius CAD-4 diffractometer, graphite-monochromated Mo $K\alpha$. Cell constants from setting angles of 25 reflections ($\theta > 20°$). Correction for Lorentz–polarization effect. $\theta_{max} = 50°$; h 0 to 7, k 0 to 11, l −26 to 26. Standard reflections observed every 3600 s of data collection time, 400; 060; 0,0,14. Variation = ±1%. 2641 reflections measured, 1400 independent observed reflections [$F_o \geq 5\sigma(F_o)$]. Structure solved utilizing *MULTAN* (Germain, Main & Woolfson, 1971) direct-methods program. Geometrically constrained hydrogen atoms were placed 0·95 Å from the bonded carbon atom with a fixed isotropic thermal parameter $B = 5·5$ Å^2 and allowed to ride on that atom. The methyl hydrogen atoms were located from a difference Fourier map and included with fixed contributions ($B = 5·5$ Å^2). Scattering factors and anomalous-dispersion corrections from *International Tables for X-ray Crystallography* (1974); structure refined with *SHELX*76 (Sheldrick, 1976). $\sum w(|F_o| - |F_c|)^2$ minimized, weights = $[\sigma(F_o)^2 + 0·00004F_o^2]^{-1}$, 181 parameters varied. $R = 0·043$, $wR = 0·044$, $S = 1·04$, Δ/σ in final least-squares refinement cycle < 0·01, $\Delta\rho < 0·3$ e Å^{-3} in final difference map.

Discussion. Fractional coordinates and B_{eq} values are given in Table 1,* bond distances and angles in Table 2, and an *ORTEP* drawing (Johnson, 1976) in Fig. 1. A cell plot is provided in Fig. 2.

As expected, the *trans* stereochemical disposition of the 4-methoxycarbonyl and 5-aryl moieties was maintained during the decarboxymethylation reaction (Peterson, Rogers & Do, 1988). Consistent with this finding is the C(5)–C(4)–C(3)–C(11) torsion angle of −84·5° and the relatively large (7·53 Hz) vicinal hydrogen coupling constant between C(4)–H and C(3)–H. The lactone ring exists in an envelope conformation with ring atoms O(1), C(1), C(2), and C(4) defining a plane to within 0·016 Å. Ring atom C(3) and the carbonyl oxygen atom O(2) deviate from this plane by 0·516 and 0·040 Å, respectively. The aromatic ring atoms C(5) through C(10) are planar to within 0·021 Å and this plane intersects the lactone ring plane at an angle of 107·7°. There is some bond-angle compression about C(2), C(3) and C(4) from that usually associated with sp^3 hybridized carbon because of the ring geometry in this compound. The angle C(1)–C(2)–C(3) is 102·8 (2)°, C(2)–C(3)–C(4) is 102·4 (2)°, and O(1)–C(4)–C(3) is 103·4 (2)°. As a

* Lists of structure factors, anisotropic thermal parameters, least-squares-planes results, torsion angles, and final fractional coordinates for hydrogen atoms have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51395 (8 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Final fractional coordinates for* $C_{14}H_{16}O_6$

	x	y	z	B_{eq}(Å^2)*
O(1)	0·1704 (4)	0·1739 (2)	0·17186 (9)	2·24
O(2)	0·1421 (4)	0·3926 (2)	0·2061 (1)	2·74
O(3)	0·3372 (4)	−0·1777 (2)	0·28533 (9)	2·28
O(4)	0·3440 (4)	−0·0102 (2)	0·35573 (9)	2·38
O(5)	0·3130 (4)	−0·3462 (2)	0·04987 (9)	2·42
O(6)	0·6664 (4)	−0·2346 (2)	0·01364 (9)	2·40
C(1)	0·1782 (5)	0·2708 (3)	0·2164 (1)	2·08
C(2)	0·2319 (6)	0·1995 (3)	0·2750 (1)	2·19
C(3)	0·3452 (5)	0·0657 (3)	0·2571 (1)	1·74
C(4)	0·2285 (5)	0·0344 (3)	0·1955 (1)	1·88
C(5)	0·3582 (5)	−0·0397 (3)	0·1505 (1)	1·69
C(6)	0·2754 (5)	−0·1621 (3)	0·1235 (1)	1·86
C(7)	0·3840 (5)	−0·2268 (3)	0·0789 (1)	1·75
C(8)	0·5766 (5)	−0·1655 (3)	0·0596 (1)	1·82
C(9)	0·6624 (5)	−0·0475 (3)	0·0880 (1)	1·99
C(10)	0·5549 (5)	0·0152 (3)	0·1335 (1)	1·94
C(11)	0·3389 (5)	−0·0558 (3)	0·2996 (1)	1·83
C(12)	0·3518 (7)	−0·1169 (4)	0·4019 (1)	3·02
C(13)	0·1450 (7)	−0·4248 (4)	0·0750 (2)	2·92
C(14)	0·8298 (6)	−0·1600 (4)	−0·0155 (1)	2·49

* $B_{eq} = \frac{4}{3}(a^2\beta_{11} + b^2\beta_{22} + c^2\beta_{33} + ab\cos\gamma\beta_{12} + ac\cos\beta\beta_{13} + bc\cos\alpha\beta_{23})$.

Table 2. *Bond distances* (Å) *and angles* (°) *for* $C_{14}H_{16}O_6$

O(1)–C(1)	1·358 (4)	O(1)–C(4)	1·464 (3)
O(2)–C(1)	1·200 (4)	O(3)–C(11)	1·204 (4)
O(4)–C(11)	1·330 (3)	O(4)–C(12)	1·450 (4)
O(5)–C(7)	1·365 (3)	O(5)–C(13)	1·416 (4)
O(6)–C(8)	1·366 (3)	O(6)–C(14)	1·419 (4)
C(1)–C(2)	1·493 (4)	C(2)–C(3)	1·517 (4)
C(3)–C(4)	1·533 (4)	C(3)–C(11)	1·502 (4)
C(4)–C(5)	1·500 (4)	C(5)–C(6)	1·391 (4)
C(5)–C(10)	1·383 (4)	C(6)–C(7)	1·383 (4)
C(7)–C(8)	1·399 (4)	C(8)–C(9)	1·383 (4)
C(9)–C(10)	1·387 (4)		

C(1)–O(1)–C(4)	110·9 (2)	C(11)–O(4)–C(12)	116·3 (3)
C(7)–O(5)–C(13)	117·5 (2)	C(8)–O(6)–C(14)	116·2 (2)
O(1)–C(1)–O(2)	121·3 (3)	O(1)–C(1)–C(2)	109·4 (3)
O(2)–C(1)–C(2)	129·3 (3)	C(1)–C(2)–C(3)	102·8 (2)
C(2)–C(3)–C(4)	102·4 (2)	C(2)–C(3)–C(11)	116·4 (2)
C(4)–C(3)–C(11)	112·9 (3)	O(1)–C(4)–C(3)	103·4 (2)
O(1)–C(4)–C(5)	108·0 (2)	C(3)–C(4)–C(5)	117·7 (3)
C(4)–C(5)–C(6)	119·7 (3)	C(4)–C(5)–C(10)	121·0 (3)
C(6)–C(5)–C(10)	119·2 (3)	C(5)–C(6)–C(7)	120·8 (3)
O(5)–C(7)–C(6)	124·4 (3)	O(5)–C(7)–C(8)	115·8 (3)
C(6)–C(7)–C(8)	119·7 (3)	O(6)–C(8)–C(7)	115·4 (3)
O(6)–C(8)–C(9)	125·3 (3)	C(7)–C(8)–C(9)	119·2 (3)
C(8)–C(9)–C(10)	120·6 (3)	C(5)–C(10)–C(9)	120·3 (3)
O(3)–C(11)–O(4)	124·4 (3)	O(3)–C(11)–C(3)	125·1 (3)
O(4)–C(11)–C(3)	110·4 (3)		

result of this geometric angle compression, the C(2)–C(3)–C(11) and C(3)–C(4)–C(5) external bond angles broaden to 116·4 (2) and 117·7 (3)°, respectively. Bond lengths about C(3) and C(4) are normal, however. The C(2)–C(3) bond length is 1·517 (4) Å while the distance between C(3) and C(4) is 1·533 (4) Å.

Analysis of the closest intermolecular contact distances in the cell lattice reveals two features that may provide clues to the molecular nature of the PAF receptor site. The most prominent closest atom interaction is likely dipole–dipole in character and occurs between the lactone carbonyl of one molecule and the methoxycarbonyl carbonyl of another molecule. At closest contact, C(11) lies 2·954 (4) Å away from O(2) in another molecule at x, $y-1$, z, while the corresponding intermolecular distance for O(3) and C(1) is 3·164 (4) Å. Although a carbonyl stacking interaction of this type is not possible for L-652,731, it could be important in the binding of other known PAF antagonists to the platelet receptor site (Braquet & Godfroid, 1986; Godfroid & Braquet, 1986). Intermolecular van der Waals interactions may also play a role in stabilizing the crystal lattice. The non-hydrogen to hydrogen contact distances from O(5) to H(1)C(12)

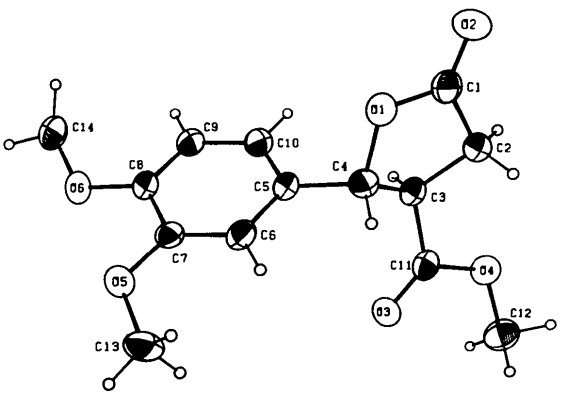

Fig. 1. Thermal-ellipsoid plot of the title compound showing the atom-numbering scheme. The hydrogen-atom radii are arbitrarily reduced.

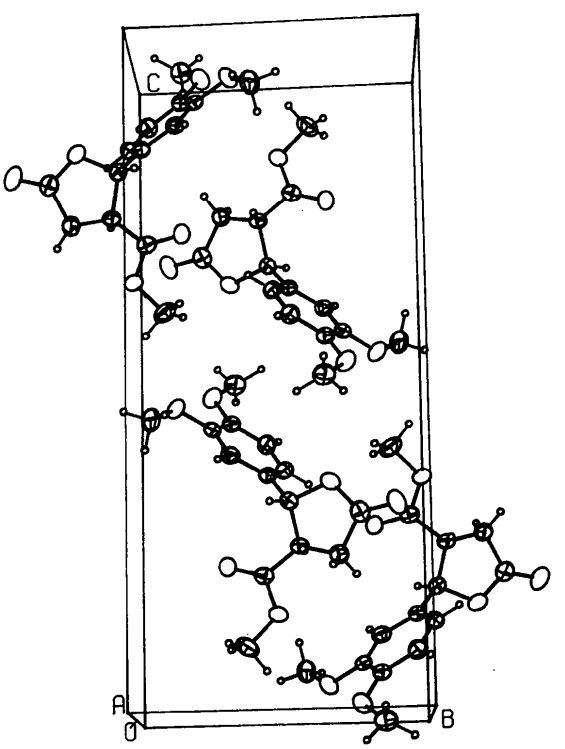

Fig. 2. Cell plot of the title compound.

and O(6) to H(2)C(12) on a neighboring molecule at x, $-y-0.5$, $z-0.5$ are 2·697 (2) and 2·827 (2) Å, respectively. Investigations of several other analogues of L-652,731 are now in progress in our laboratory to ascertain the possible biological significance of these intermolecular interactions and their relevance in the design of more potent and specific antagonists.

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Structure of Columbin, a Diterpenoid Furanolactone from *Tinospora cordifolia* Miers

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Abstract. (1*S*,4*R*,5*R*,8*S*,10*R*,12*S*)-4-Hydroxy-15,16-epoxycleroda-2,13(16),14-trieno-17,12:18,1-biscarbolactone, $C_{20}H_{22}O_6$, $M_r = 358·2$, m.p. = 453–454 K, orthorhombic, $P2_12_12_1$, $a = 7·3869$ (6), $b = 11·986$ (1), $c = 19·896$ (2) Å, $V = 1761·65$ Å^3, $Z = 4$, $D_x = 1·351$, D_m(by flotation) = 1·349 g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 8·36$ cm^{-1}, $F(000) = 760$, $T = 295$ K, $R = 0·0432$ for 1662 observed reflections. Two terpene rings, two δ-lactones, two methyl groups, a tertiary hydroxyl group and a β-substituted furan ring are present in the structure. The H atoms at C(12) and C(8) are α- and β-oriented. The terpene ring *A* is locked into a boat conformation by the C(1)–C(4) lactone bridge. The furan ring is attached equatorially at atom C(12). The hydroxyl group is involved in intramolecular hydrogen bonding.

Introduction. The medicinal properties of the plant *Tinospora cordifolia* have been studied extensively and many compounds have been isolated from this plant. The structural investigation of the title compound was undertaken to determine the stereochemistry.

Experimental. Dried and finely powdered stems of the plant were used for extraction with chloroform in a Soxhlet apparatus. Repeated column chromatography

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