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Dibutyl 2,6-Dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, Diisobutyl 2,6-Dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate and Di-*tert*-butyl 2,6-Dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

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Abstract

The structures of dibutyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, $C_{23}H_{30}N_2O_6$, diisobutyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, $C_{23}H_{30}N_2O_6$, and di-*tert*-butyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, $C_{23}H_{30}N_2O_6$, members of the 1,4-dihydropyridine class of calcium antagonists, have been determined. Increasing the bulk of the esterification groups, as quantified in a cone-angle analysis, leads to greater perpendicularity of the dual ring system. This leads to conclusions about the potential activity of these compounds.

Comment

Nifedipine [2,6-dimethyl-3,5-dicarbomethoxy-4-(2-nitrophenyl)-1,4-dihydropyridine] is a calcium antagonist drug of the 1,4-dihydropyridine (DHP) type (Fig. 1). Compounds of this class are currently being used in the treatment of cardiovascular disorders such as angina and hypertension (Triggle, Langs & Janis, 1989; Hurwitz, Partridge & Leach, 1991).

Calcium antagonistic activity of members of the 1,4-dihydropyridine family is influenced by (*a*) the presence of the 1,4-dihydropyridine moiety, (*b*) alkyl groups (preferably methyl) substituted at the 2 and 6 positions, (*c*) ester groups at the 3 and 5 positions, (*d*) a phenyl substituent at position 4 and (*e*) an H atom on N1 (Triggle, Langs & Janis, 1989; Morad, Goldmann & Trentham, 1983; Loev, Goodman, Snader, Tedeschi & Macko, 1974; Janis, Silver & Triggle, 1987; Fig. 1).

The influence of the size of the esterification groups is not fully understood. Variation of the C3 and C5 ester alkyl groups has led to conflicting results. In an early investigation of various DHP derivatives, it was observed that an increase in the bulk of the ester side chain led to an increase in activity (Loev, Goodman, Snader, Tedeschi & Macko, 1974; Bolger, Gengo, Klockowski, Luchowski, Siegel, Janis, Triggle & Triggle, 1983). However, in a series of *meta*-nitro derivatives, activity appeared to decrease with an increase in the bulk of the ester alkyl groups (Rodenkirchen, Bayer, Steiner, Bossert, Meyer & Moeller, 1979; Suzuki, Shiratori, Murayama, Harada, Miyano & Takeya, 1989). Furthermore, another investigation revealed that for *ortho*-substituted phenyl derivatives, activity decreased as ester bulk increased and for *meta*-substituted phenyl derivatives, activity increased as bulk increased whereas for *para*-phenyl derivatives, activity was always observed to be low no matter what ester groups were present (Bossert, Horstmann, Meyer & Vater, 1979). The effect of the size of the ester side chain on the rest of the conformation is poorly understood.

All of the nifedipine derivatives examined by single-crystal X-ray diffraction (Triggle, Langs & Janis, 1989; Mehdi & Ravikumar, 1992) exhibit a flattened-boat conformation of the 1,4-dihydropyridine ring with the N atom at the prow and the phenyl ring in pseudo-axial position at the bow. Structure–activity studies have demonstrated that flattening of the boat conformation correlates with increased activity, presumably due to the concurrent change in position of the phenyl ring.

In the majority of the more than 30 crystal structures of members of the nifedipine family, the ester groups are found to be nearly coplanar with the nearest double bond in the DHP ring, with the carbonyl group oriented either *cis* (*sp*, synperiplanar) or *trans* (*ap*, antiperiplanar) to that bond (Fig. 1) (Triggle, Langs & Janis, 1989). In nifedipine itself, the carbonyls of the ester groups are *ap* and *sp* and thus point in opposite directions. It is thought that only the *sp* conformation of the ester group permits hydrogen bonding to the carbonyl O atom as

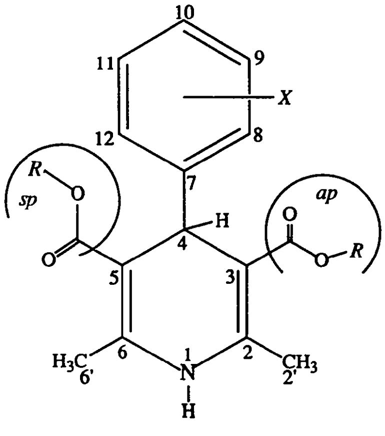

Fig. 1. 1,4-Dihydropyridine skeleton with the crystallographic numbering scheme illustrating *sp* and *ap* orientations of ester groups.

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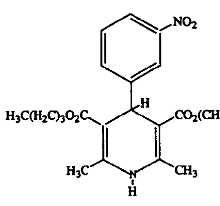
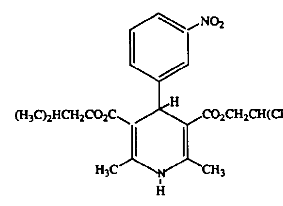
an acceptor atom when the drug binds to its receptor site (Triggle, Schefter & Triggle, 1980; Langs, Strong & Triggle, 1990).

It appears that *o*-phenyl substituted derivatives have a preference for *sp,sp* geometry, whereas the non-*o*-substituted derivatives prefer *sp,ap* geometry. This is consistent with the thesis that the DHP binding site is non-symmetrical on the receptor, and the probability of the ester groups being *ap,sp* oriented when binding is high.

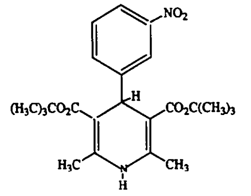
In order to observe the conformational effects of an extended ester side chain and increased bulk of the ester groups, the crystal structures of dibutyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, (I), diisobutyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, (II), and di-*tert*-butyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate, (III), were performed.



(I)



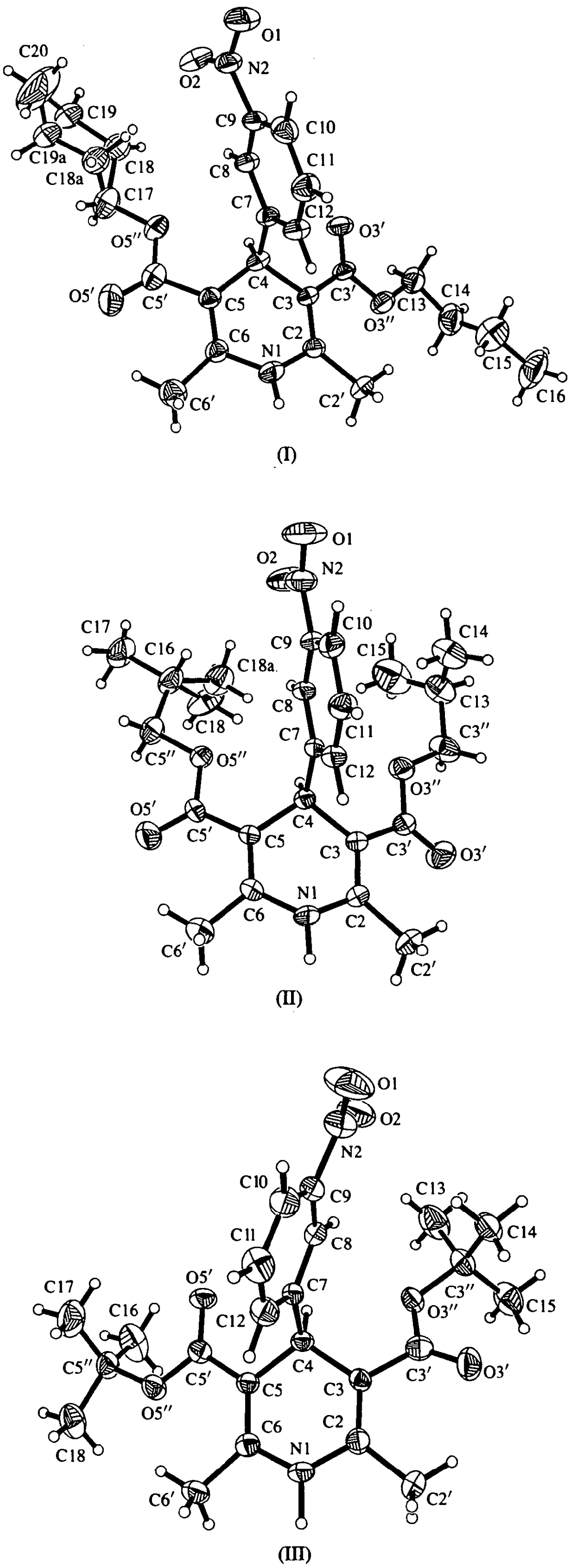
(II)



(III)

Compound (I) exhibits the same orientation of the ester groups as nifedipine (C3 *ap*, C5 *sp*). Compound (II) shows both esters in the *sp* conformation, similar to that of nimodipine (Langs, Strong & Triggle, 1990). Compound (III) shows the opposite orientation to that of nifedipine. The C3 ester is *sp*, whereas the C5 ester is *ap*.

When the plane of the phenyl ring is perpendicular to the plane of the base of the boat, activity increases (Loev, Goodman, Snader, Tedeschi & Macko, 1974; Triggle, Schefter & Triggle, 1980). The torsion angle that defines this parameter is C3—C4—C7—C12. The deviation from perfect bisection of the phenyl ring with respect to the DHP ring can be expressed as the difference between the torsion angle C3—C4—C7—C12 and the ideal value of 60°. Compound (II) exhibits the least deviation from the ideal value [8.8 (4)°]. Compounds (I) and (III) exhibit deviations of 14.8 (6) and 21.4 (5)°, respectively. The position of the ester alkyl groups in compound (II) may cause the phenyl ring to become more perpendicular (Fig. 2).



(I)

(II)

(III)

Fig. 2. Projection views of (I), (II) and (III). Displacement ellipsoids are plotted at the 50% probability level.

The sum, Σ, of the absolute values of the internal torsion angles of the DHP ring is a measure of its planarity (Table 7). Published structure–activity ratios indicate that increased planarity of this ring (Σ close to zero) correlate with higher activity of the compound. Larger Σ values are observed, in general, for parent compounds with the nitro group in the *meta* position. This is an indication of the decreased planarity of the DHP ring and hence the lower activity of compounds with a *meta* substituent. Compound (I) exhibits a Σ of 103.4 (6)°, compound (II) 100.7 (5)° and compound (III) 73.7 (6)°. Hence, the *tert*-butyl alkyl group causes the least deviation from planarity of the DHP ring.

A parameter that can be used to describe the space occupied by an ester alkyl group is the cone angle (Tolman, 1977). This is the angle that is swept out by the van der Waals radii of the groups attached to the carboxy O atom, assuming free rotation about the C3—C3′ or C5—C5′ bonds. The compound with the largest cone angle, (II), shows an *sp,sp* conformation of the ester carbonyl groups. In the *sp* conformation, the alkyl esterification group is extended towards and parallel to the phenyl ring. The smaller cone angle of (III) appears to correlate with greater flattening of the 1,4-DHP ring (Table 7).

Therefore, compound (III) should have higher activity, based on its Σ value. Compound (II) should exhibit high activity because of the orientation of its ester groups and the almost perfect bisection of the phenyl ring with respect to the DHP ring.

Experimental

All three title compounds were prepared by known synthetic methods (Hantzsch, 1882) and recrystallized from ethanol/water solution. Slow evaporation of an ethanol solution yielded yellow plate-like crystals in each case.

Compound (I)

Crystal data

$C_{23}H_{30}N_2O_6$
$M_r = 430.5$
Monoclinic
$P2_1/c$
$a = 11.358\,(4)$ Å
$b = 16.352\,(6)$ Å
$c = 12.999\,(5)$ Å
$\beta = 101.56\,(1)°$
$V = 2364.9\,(15)$ Å^3
$Z = 4$
$D_x = 1.209$ Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 47 reflections
$\theta = 4.033–12.674°$
$\mu = 0.088$ mm^{-1}
$T = 298$ K
Chunk
0.3 × 0.2 × 0.2 mm
Yellow

Data collection

Siemens *P*4 four-circle diffractometer
$\theta/2\theta$ scans
Absorption correction: none
5197 measured reflections
4160 independent reflections
1458 observed reflections [$F > 4.5\sigma(F)$]

$R_{\rm int} = 0.0568$
$\theta_{\rm max} = 25.0°$
$h = -13 \rightarrow 13$
$k = 0 \rightarrow 19$
$l = 0 \rightarrow 15$
3 standard reflections monitored every 97 reflections
intensity decay: 1.0%

Refinement

Refinement on F
$R = 0.0560$
$wR = 0.0612$
$S = 1.13$
4160 reflections
289 parameters
H-atom parameters not refined
$w = 1/[\sigma^2(F_o) + 0.0008F^2]$
$(\Delta/\sigma)_{\rm max} = 0.035$
$\Delta\rho_{\rm max} = 0.16$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.23$ e Å^{-3}

Extinction correction: *SHELXS*86 (Sheldrick, 1990)
Extinction coefficient: 0.0019 (4)
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2) for (I)*

$$U_{\rm eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$U_{\rm eq}$
N1	0.8738 (4)	0.1670 (3)	0.3466 (3)	0.059 (2)
N2	1.0175 (5)	0.0910 (4)	−0.1728 (4)	0.072 (2)
O1	0.9788 (4)	0.0460 (3)	−0.2493 (4)	0.108 (2)
O2	1.1108 (5)	0.1320 (3)	−0.1632 (3)	0.091 (2)
C2	0.8040 (4)	0.2257 (4)	0.2851 (4)	0.051 (2)
C2′	0.6925 (4)	0.2491 (3)	0.3277 (4)	0.066 (2)
C3	0.8420 (4)	0.2573 (3)	0.2001 (4)	0.046 (2)
C3′	0.7863 (4)	0.3253 (3)	0.1353 (4)	0.052 (2)
O3′	0.8149 (3)	0.3487 (2)	0.0536 (3)	0.072 (2)
O3″	0.6984 (3)	0.3675 (2)	0.1724 (3)	0.068 (2)
C4	0.9526 (4)	0.2196 (3)	0.1650 (4)	0.050 (2)
C5	1.0376 (4)	0.1813 (3)	0.2584 (4)	0.050 (2)
C5′	1.1678 (6)	0.1713 (4)	0.2552 (5)	0.066 (3)
O5′	1.2451 (4)	0.1392 (3)	0.3204 (4)	0.103 (2)
O5″	1.1933 (3)	0.2067 (3)	0.1678 (3)	0.081 (2)
C6	0.9943 (5)	0.1510 (3)	0.3422 (4)	0.054 (2)
C6′	1.0610 (5)	0.1039 (4)	0.4347 (4)	0.074 (3)
C7	0.9177 (4)	0.1577 (3)	0.0747 (3)	0.047 (2)
C8	0.9775 (4)	0.1547 (3)	−0.0105 (4)	0.055 (2)
C9	0.9469 (5)	0.0949 (4)	−0.0870 (4)	0.058 (2)
C10	0.8570 (5)	0.0368 (4)	−0.0860 (4)	0.067 (3)
C11	0.7992 (5)	0.0403 (4)	−0.0008 (5)	0.076 (3)
C12	0.8293 (5)	0.0991 (4)	0.0781 (4)	0.059 (2)
C13	0.6497 (5)	0.4405 (4)	0.1144 (5)	0.081 (3)
C14	0.5579 (6)	0.4803 (5)	0.1673 (6)	0.103 (3)
C15	0.4467 (7)	0.4379 (5)	0.1638 (7)	0.126 (4)
C16	0.3473 (7)	0.4826 (5)	0.2065 (8)	0.158 (5)
C17	1.3171 (5)	0.2006 (5)	0.1532 (6)	0.111 (4)
C18†	1.3232 (9)	0.227 (1)	0.042 (9)	0.096 (5)
C18*A*†	1.341 (2)	0.175 (3)	0.078 (3)	0.096 (5)
C19†	1.445 (1)	0.218 (1)	0.013 (1)	0.102 (6)
C19*A*†	1.462 (3)	0.169 (3)	0.061 (3)	0.102 (6)
C20	1.4820 (9)	0.1439 (8)	−0.0166 (10)	0.237 (9)

† Site occupancy = 0.5.

Table 2. *Selected geometric parameters (Å, °) for (I)*

N1—C2	1.391 (7)	C5—C6	1.375 (8)
N1—C6	1.406 (7)	C5′—O5′	1.211 (8)
N2—O1	1.244 (7)	C5′—O5″	1.357 (8)
N2—O2	1.238 (8)	O5″—C17	1.459 (7)
N2—C9	1.499 (8)	C6—C6′	1.499 (7)
C2—C2′	1.528 (8)	C13—C14	1.50 (1)
C2—C3	1.366 (7)	C14—C15	1.43 (1)
C3—C3′	1.461 (7)	C15—C16	1.53 (1)

C3—C4	1.548 (7)	C17—C18	1.52 (11)
C3′—O3′	1.232 (7)	C17—C18*A*	1.14 (4)
C3′—O3″	1.378 (7)	C18—C19	1.52 (2)
O3″—C13	1.460 (7)	C19—C20	1.37 (2)
C4—C5	1.526 (6)	C20—C19*A*	1.16 (3)
C4—C7	1.540 (7)	C18*A*—C19*A*	1.43 (4)
C5—C5′	1.496 (8)		
C2—N1—C6	123.5 (5)	C5—C5′—O5′	127.6 (6)
O1—N2—O2	123.9 (6)	C5—C5′—O5″	110.8 (5)
O1—N2—C9	117.7 (6)	O5′—C5′—O5″	121.6 (6)
O2—N2—C9	118.4 (5)	C5′—O5″—C17	116.9 (5)
N1—C2—C2′	112.5 (4)	N1—C6—C5	118.1 (4)
N1—C2—C3	119.3 (5)	N1—C6—C6′	113.8 (5)
C2′—C2—C3	128.1 (5)	C5—C6—C6′	128.1 (5)
C2—C3—C3′	125.7 (5)	C4—C7—C8	122.0 (4)
C2—C3—C4	119.6 (4)	C4—C7—C12	120.3 (5)
C3′—C3—C4	114.6 (4)	N2—C9—C8	117.9 (5)
C3—C3′—O3′	125.1 (5)	N2—C9—C10	118.6 (5)
C3—C3′—O3″	116.1 (5)	O3″—C13—C14	110.1 (5)
O3′—C3′—O3″	118.8 (5)	C13—C14—C15	117.5 (7)
C3′—O3″—C13	117.0 (4)	C14—C15—C16	117.6 (7)
C3—C4—C5	110.5 (4)	O5″—C17—C18	109.4 (6)
C3—C4—C7	112.7 (4)	O5″—C17—C18*A*	122.4 (17)
C5—C4—C7	111.2 (4)	C17—C18—C19	115.3 (23)
C4—C5—C5′	119.6 (5)	C17—C18*A*—C19*A*	124 (3)
C4—C5—C6	120.5 (5)	C18—C19—C20	120 (1)
C5′—C5—C6	119.7 (5)	C18*A*—C19*A*—C20	121 (3)
C6—N1—C2—C3	15.2 (7)	C3—C4—C5—C6	28.5 (6)
C2—N1—C6—C5	−14.7 (7)	C3—C4—C7—C8	138.6 (5)
O1—N2—C9—C10	12.9 (8)	C3—C4—C7—C12	−45.2 (6)
N1—C2—C3—C4	8.0 (7)	C6—C5—C5′—O5′	−0.8 (9)
C2—C3—C3′—O3′	−173.4 (5)	C4—C5—C6—N1	−9.1 (7)
C2—C3—C4—C5	−27.9 (6)		

Compound (II)

Crystal data

$C_{23}H_{30}N_2O_6$
$M_r = 430.5$
Triclinic
$P\bar{1}$
$a = 9.715\ (1)$ Å
$b = 10.932\ (1)$ Å
$c = 12.501\ (1)$ Å
$\alpha = 99.29\ (1)^\circ$
$\beta = 97.27\ (1)^\circ$
$\gamma = 116.35\ (1)^\circ$
$V = 1144.2\ (2)$ Å^3
$Z = 2$
$D_x = 1.249$ Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 41 reflections
$\theta = 4.151\text{–}12.402^\circ$
$\mu = 0.090$ mm^{-1}
$T = 298$ K
Chunk
0.3 × 0.2 × 0.2 mm
Yellow

Data collection

Siemens *P*4 four-circle diffractometer
$\theta/2\theta$ scans
Absorption correction: none
2623 measured reflections
2116 independent reflections
1557 observed reflections [$F > 4.0\sigma(F)$]

$R_{\text{int}} = 0.0267$
$\theta_{\max} = 19.98^\circ$
$h = -9 \rightarrow 9$
$k = -10 \rightarrow 0$
$l = 0 \rightarrow 12$
3 standard reflections monitored every 97 reflections intensity decay: 0.19%

Refinement

Refinement on F^2
$R(F) = 0.0574$
$wR(F^2) = 0.1595$
$S = 1.113$
2030 reflections

$\Delta\rho_{\max} = 0.526$ e Å^{-3}
$\Delta\rho_{\min} = -0.249$ e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick 1993)

291 parameters
H-atom parameters not refined
$w = 1/[\sigma^2(F_o^2) + (0.1127P)^2 + 0.3691P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{\max} = -0.057$

Extinction coefficient: 0.0185 (82)
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Table 3. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2) for (II)*

$$U_{\text{eq}} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
N1	0.1571 (4)	1.3679 (3)	0.7555 (3)	0.0552 (10)
C2	0.0591 (4)	1.3042 (4)	0.6512 (3)	0.0485 (11)
C2′	0.0753 (5)	1.4042 (4)	0.5777 (4)	0.0715 (14)
C3	−0.0388 (4)	1.1638 (4)	0.6240 (3)	0.0438 (10)
C3′	−0.1340 (5)	1.0906 (5)	0.5124 (4)	0.0558 (12)
C3″	−0.3525 (6)	0.8808 (5)	0.4012 (4)	0.083 (2)
O3′	−0.1169 (4)	1.1333 (4)	0.4300 (3)	0.0960 (12)
O3″	−0.2489 (3)	0.9624 (3)	0.5082 (2)	0.0615 (9)
C4	−0.0529 (4)	1.0797 (4)	0.7123 (3)	0.0421 (10)
C5	0.0995 (4)	1.1536 (4)	0.8032 (3)	0.0427 (10)
C5′	0.1406 (5)	1.0687 (4)	0.8656 (3)	0.0512 (11)
C5″	0.0532 (5)	0.8416 (4)	0.9004 (4)	0.0726 (14)
O5′	0.2639 (4)	1.1076 (3)	0.9309 (3)	0.0888 (11)
O5″	0.0256 (3)	0.9368 (3)	0.8438 (2)	0.0581 (9)
C6	0.1930 (4)	1.2933 (4)	0.8231 (3)	0.0497 (11)
C6′	0.3382 (5)	1.3819 (4)	0.9120 (4)	0.0770 (14)
C7	−0.1957 (4)	1.0546 (4)	0.7612 (3)	0.0373 (10)
C8	−0.2981 (4)	0.9218 (4)	0.7678 (3)	0.0461 (11)
C9	−0.4266 (4)	0.9001 (4)	0.8146 (3)	0.0501 (11)
C10	−0.4573 (5)	1.0072 (5)	0.8554 (3)	0.0594 (12)
C11	−0.3535 (5)	1.1411 (4)	0.8491 (3)	0.0596 (12)
C12	−0.2262 (5)	1.1634 (4)	0.8022 (3)	0.0513 (11)
C13	−0.4830 (6)	0.7517 (5)	0.4119 (4)	0.085 (2)
C14	−0.5874 (6)	0.7760 (6)	0.4794 (5)	0.107 (2)
C15	−0.4303 (9)	0.6617 (8)	0.4486 (7)	0.143 (3)
C16	−0.0779 (6)	0.6970 (4)	0.8513 (4)	0.0716 (14)
C17	−0.0544 (7)	0.5961 (5)	0.9142 (4)	0.097 (2)
C18†	−0.063 (3)	0.661 (3)	0.734 (4)	0.105 (10)
C18*A*†	−0.139 (3)	0.637 (3)	0.729 (3)	0.089 (7)
N2	−0.5339 (5)	0.7577 (5)	0.8197 (4)	0.0786 (12)
O1	−0.6409 (5)	0.7386 (4)	0.8662 (4)	0.120 (2)
O2	−0.5118 (5)	0.6613 (4)	0.7774 (4)	0.116 (2)

† Site occupancy = 0.5.

Table 4. *Selected geometric parameters (Å, °) for (II)*

N1—C2	1.376 (5)	C5′—O5′	1.213 (4)
N1—C6	1.379 (5)	C5′—O5″	1.330 (5)
C2—C3	1.353 (5)	C5″—O5″	1.446 (5)
C2—C2′	1.507 (5)	C5″—C16	1.483 (6)
C3—C3′	1.448 (5)	C6—C6′	1.485 (6)
C3—C4	1.529 (5)	C9—N2	1.457 (5)
C3′—O3′	1.199 (5)	C13—C15	1.405 (8)
C3′—O3″	1.336 (5)	C13—C14	1.481 (7)
C3″—O3″	1.440 (5)	C16—C18*A*	1.48 (4)
C3″—C13	1.460 (6)	C16—C18	1.50 (4)
C4—C7	1.519 (5)	C16—C17	1.531 (6)
C4—C5	1.534 (5)	N2—O1	1.209 (5)
C5—C6	1.344 (5)	N2—O2	1.220 (5)
C5—C5′	1.453 (5)		
C2—N1—C6	122.5 (3)	O5″—C5″—C16	108.5 (3)
C3—C2—N1	119.5 (3)	C5′—O5″—C5″	117.7 (3)
C3—C2—C2′	126.6 (4)	C5—C6—N1	119.3 (3)
N1—C2—C2′	113.9 (3)	C5—C6—C6′	127.2 (4)
C2—C3—C3′	121.3 (3)	N1—C6—C6′	113.5 (3)
C2—C3—C4	120.0 (3)	C8—C7—C4	120.3 (3)
C3′—C3—C4	118.7 (3)	C12—C7—C4	121.9 (3)
O3′—C3′—O3″	121.0 (4)	C10—C9—N2	118.7 (4)
O3′—C3′—C3	126.9 (4)	C8—C9—N2	118.7 (4)
O3″—C3′—C3	112.2 (3)	C15—C13—C3″	111.7 (5)
O3″—C3″—C13	110.6 (4)	C15—C13—C14	112.0 (6)
C3′—O3″—C3″	116.9 (3)	C3″—C13—C14	113.9 (4)

C7—C4—C3	112.2 (3)	C5″—C16—C18*A*	122.9 (13)
C7—C4—C5	111.4 (3)	C5″—C16—C18	105.1 (12)
C3—C4—C5	110.0 (3)	C5″—C16—C17	109.1 (4)
C6—C5—C5′	121.3 (3)	C18*A*—C16—C17	114.0 (15)
C6—C5—C4	120.4 (3)	C18—C16—C17	109.3 (16)
C5′—C5—C4	118.4 (3)	O1—N2—O2	122.0 (4)
O5′—C5′—O5″	121.0 (4)	O1—N2—C9	119.4 (5)
O5′—C5′—C5	126.5 (4)	O2—N2—C9	118.6 (4)
O5″—C5′—C5	112.5 (3)		
C6—N1—C2—C3	18.2 (5)	C2—N1—C6—C5	−19.1 (5)
N1—C2—C3—C4	6.5 (4)	C3—C4—C7—C8	130.0 (5)
C2—C3—C3′—O3′	16.1 (8)	C3—C4—C7—C12	−51.1 (4)
C2—C3—C4—C5	−26.4 (7)	N2—C9—C10—C11	−179.9 (5)
C3—C4—C5—C6	25.6 (7)	C8—C9—N2—O2	−3.8 (6)
C6—C5—C5′—O5′	−7.7 (5)	C10—C9—N2—O1	−4.8 (3)
C4—C5—C6—N1	−4.9 (4)		

Compound (III)

Crystal data

$C_{23}H_{30}N_2O_6$
M_r = 430.5
Monoclinic
$P2_1/n$
a = 11.142 (1) Å
b = 16.803 (2) Å
c = 13.384 (1) Å
β = 109.90 (1)°
V = 2356.1 (4) Å^3
Z = 4
D_x = 1.214 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 40 reflections
θ = 3.967–12.537°
μ = 0.088 mm^{-1}
T = 298 K
Chunk
0.3 × 0.2 × 0.2 mm
Yellow

Data collection

Siemens *P*4 four-circle diffractometer
$\theta/2\theta$ scans
Absorption correction: none
2898 measured reflections
2207 independent reflections
1383 observed reflections [$I > 2\sigma(I)$]

$R_{\rm int}$ = 0.1083
$\theta_{\max}$ = 20.02°
$h = -10 \rightarrow 10$
$k = 0 \rightarrow 16$
$l = 0 \rightarrow 12$
3 standard reflections monitored every 97 reflections intensity decay: 1.0%

Refinement

Refinement on F^2
$R(F)$ = 0.0542
$wR(F^2)$ = 0.1209
S = 1.123
2183 reflections
280 parameters
H-atom parameters not refined
$w = 1/[\sigma^2(F_o^2) + (0.0632P)^2 + 0.0108P]$ where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\max} = -0.004$
$\Delta\rho_{\max}$ = 0.141 e Å^{-3}
$\Delta\rho_{\min}$ = −0.197 e Å^{-3}
Extinction correction: none
Atomic scattering factors from *International Tables for Crystallography* (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4)

Table 5. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2) for (III)*

$$U_{\rm eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	$U_{\rm eq}$
N1	0.2005 (3)	0.2790 (2)	0.2687 (3)	0.0516 (11)
C2	0.1253 (5)	0.3456 (3)	0.2626 (4)	0.0489 (13)
C2′	0.1766 (5)	0.4011 (3)	0.3560 (4)	0.064 (2)
C3	0.0222 (4)	0.3576 (3)	0.1770 (3)	0.0405 (12)
C3′	−0.0543 (4)	0.4308 (3)	0.1659 (4)	0.0530 (14)
C3″	−0.2107 (5)	0.5140 (3)	0.0333 (4)	0.0588 (14)
O3′	−0.0569 (3)	0.4730 (2)	0.2389 (3)	0.0781 (12)
O3″	−0.1237 (3)	0.4454 (2)	0.0645 (3)	0.0519 (9)
C4	−0.0235 (4)	0.2945 (3)	0.0902 (3)	0.0402 (12)
C5	0.0825 (4)	0.2369 (3)	0.0938 (3)	0.0403 (12)
C5′	0.0597 (5)	0.1938 (3)	−0.0061 (4)	0.0459 (13)
C5″	0.1547 (5)	0.1038 (3)	−0.1047 (4)	0.0577 (14)
O5′	−0.0373 (3)	0.2026 (2)	−0.0818 (3)	0.0635 (11)
O5″	0.1557 (3)	0.1459 (2)	−0.0080 (2)	0.0565 (9)
C6	0.1864 (4)	0.2291 (3)	0.1830 (4)	0.0459 (13)
C6′	0.2957 (4)	0.1705 (3)	0.2042 (4)	0.065 (2)
C7	−0.1419 (4)	0.2523 (3)	0.0980 (3)	0.0404 (12)
C8	−0.2622 (5)	0.2790 (3)	0.0382 (4)	0.0468 (13)
C9	−0.3679 (5)	0.2456 (3)	0.0524 (4)	0.0532 (14)
C10	−0.3596 (5)	0.1851 (4)	0.1233 (5)	0.070 (2)
C11	−0.2408 (6)	0.1568 (3)	0.1795 (5)	0.073 (2)
C12	−0.1328 (5)	0.1909 (3)	0.1701 (4)	0.0588 (14)
C13	−0.2619 (6)	0.5080 (4)	−0.0860 (4)	0.098 (2)
C14	−0.3173 (5)	0.5039 (3)	0.0776 (5)	0.080 (2)
C15	−0.1387 (5)	0.5911 (3)	0.0685 (5)	0.084 (2)
C16	0.1405 (6)	0.1618 (4)	−0.1936 (4)	0.098 (2)
C17	0.0516 (6)	0.0426 (4)	−0.1351 (5)	0.102 (2)
C18	0.2851 (5)	0.0652 (3)	−0.0693 (5)	0.086 (2)
N2	−0.4927 (4)	0.2780 (3)	−0.0067 (5)	0.081 (2)
O1	−0.5837 (3)	0.2592 (3)	0.0187 (4)	0.133 (2)
O2	−0.5019 (4)	0.3253 (3)	−0.0779 (4)	0.103 (2)

Table 6. *Selected geometric parameters (Å, °) for (III)*

N1—C2	1.384 (6)	C4—C7	1.532 (6)
N1—C6	1.385 (5)	C5—C6	1.357 (6)
C2—C3	1.333 (6)	C5—C5′	1.464 (6)
C2—C2′	1.508 (6)	C5′—O5′	1.213 (5)
C3—C3′	1.475 (7)	C5′—O5″	1.345 (5)
C3—C4	1.526 (6)	C5″—O5″	1.473 (5)
C3′—O3′	1.216 (5)	C5″—C17	1.491 (7)
C3′—O3″	1.336 (5)	C5″—C16	1.505 (7)
C3″—O3″	1.472 (5)	C5″—C18	1.512 (6)
C3″—C13	1.506 (7)	C6—C6′	1.515 (6)
C3″—C14	1.507 (7)	C9—N2	1.452 (7)
C3″—C15	1.511 (7)	N2—O1	1.215 (6)
C4—C5	1.516 (6)	N2—O2	1.218 (6)
C2—N1—C6	123.0 (4)	C5′—C5—C4	113.3 (4)
C3—C2—N1	120.0 (4)	O5′—C5′—O5″	123.0 (4)
C3—C2—C2′	126.3 (5)	O5′—C5′—C5	122.1 (5)
N1—C2—C2′	113.6 (4)	O5″—C5′—C5	114.9 (4)
C2—C3—C3′	120.8 (4)	O5″—C5″—C17	110.2 (4)
C2—C3—C4	121.1 (4)	O5″—C5″—C16	110.5 (4)
C3′—C3—C4	118.1 (4)	C17—C5″—C16	111.5 (5)
O3′—C3′—O3″	123.0 (5)	O5″—C5″—C18	102.2 (4)
O3′—C3′—C3	125.2 (5)	C17—C5″—C18	111.0 (5)
O3″—C3′—C3	111.7 (5)	C16—C5″—C18	110.9 (5)
O3″—C3″—C13	102.9 (4)	C5′—O5″—C5″	122.4 (4)
O3″—C3″—C14	109.3 (4)	C5—C6—N1	119.5 (4)
C13—C3″—C14	110.2 (5)	C5—C6—C6′	128.1 (4)
O3″—C3″—C15	110.8 (4)	N1—C6—C6′	112.4 (4)
C13—C3″—C15	111.0 (5)	C8—C7—C4	119.9 (4)
C14—C3″—C15	112.3 (4)	C12—C7—C4	121.9 (4)
C3′—O3″—C3″	122.0 (4)	C10—C9—N2	118.7 (5)
C5—C4—C3	111.4 (3)	C8—C9—N2	118.6 (5)
C5—C4—C7	112.5 (4)	O1—N2—O2	122.2 (6)
C3—C4—C7	109.9 (3)	O1—N2—C9	119.0 (6)
C6—C5—C5′	125.9 (4)	O2—N2—C9	118.7 (6)
C6—C5—C4	120.8 (4)		
C6—N1—C2—C3	10.3 (6)	C4—C5—C6—N1	−5.2 (5)
N1—C2—C3—C4	6.8 (6)	C2—N1—C6—C5	−11.2 (5)
C2—C3—C3′—O3′	−22.4 (2)	C3—C4—C7—C8	93.7 (7)
C2—C3—C4—C5	−20.6 (7)	C10—C9—N2—O1	10.5 (7)
C3—C4—C5—C6	19.6 (7)	C10—C9—N2—O2	−172.0 (5)
C6—C5—C5′—O5′	178.1 (6)	C3—C4—C7—C12	−81.4 (1)

Table 7. *Structural parameters (°) for compounds (I), (II) and (III)*

Compound	Σ	Deviation	Ester conformation	Cone angle
(I)	103.4 (6)	14.8 (6)	*ap, sp*	52.7
(II)	100.7 (5)	8.8 (4)	*sp, sp*	56.2
(III)	73.7 (6)	21.4 (5)	*sp, ap*	48.4

Scan width 0.6° above $K\alpha_1$ and 0.6° below $K\alpha_2$, variable scan rate, background counts on each side of scan, refinement by full-matrix least-squares methods. H-atom positional parameters for compounds (I), (II) and (III) were calculated using ideal geometries and were allowed to ride on their attached atoms, C—H 0.97 and N—H 1.00 Å. Compounds (I), (II) and (III) display disorder of the H atoms attached to C2′. Compounds (I) and (III) also display disorder of the H atoms attached to C6′. Compound (I) has a disordered side chain where C18 and C19 show alternate positions of half occupancy each. Compound (II) displays disorder of C18 with an alternate position of half occupancy.

For all compounds, data collection: *XSCANS* (Siemens, 1991); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structures: *SHELXS*86 (Sheldrick, 1990). Program(s) used to refine structures: *SHELXS*86 for (I); *SHELXL*93 (Sheldrick, 1993) for (II) and (III). For all compounds, molecular graphics: *XP* (Siemens, 1990)

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: PA1223). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

Bolger, D. T., Gengo, P., Klockowski, R., Luchowski, E., Siegel, H., Janis, R. A., Triggle, D. J. & Triggle, A. M. (1983). *J. Pharmacol. Exp. Ther.* **225**, 291–301.

Bossert, V. F., Horstmann, H., Meyer, H. & Vater, W. (1979). *Arzneim. Forsch./Drug Res.* **29**, 226–229.

Hantzsch, A. (1882). *Justus Liebigs Ann. Chem.* **215**, 1–81.

Hurwitz, L., Partridge, L. D. & Leach, J. K. (1991). In *Calcium Channels: Their Properties, Functions, Regulation, and Clinical Relevance.* Boca Raton, Florida: CRC Press.

Janis, R. A., Silver, P. J. & Triggle, D. J. (1987). *Adv. Drug Res.* **16**, 309–591.

Langs, D. A., Strong, P. D. & Triggle, D. J. (1990). *J. Comput. Aided Mol. Des.* **4**, 215–230.

Loev, B., Goodman, M. M., Snader, K. M., Tedeschi, R. & Macko E. (1974). *J. Med. Chem.* **17**, 956–965.

Mehdi, S. & Ravikumar, K. (1992). *Acta Cryst.* C**48**, 1627–1630.

Morad, M., Goldmann, Y. E. & Trentham, D. R. (1983). *Nature (London)*, **304**, 635–638.

Rodenkirchen, R., Bayer, R., Steiner, R., Bossert, F., Meyer, H. & Moeller, E. (1979). *Naunyn-Schmiedeberg's Arch. Pharmakol.* **310**, 69–78.

Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.

Sheldrick, G. M. (1993). *SHELXL93. Program for the Refinement of Crystal Structures.* University of Göttingen, Germany.

Siemens (1990). *XP. Interactive Molecular Graphics Program.* Version 4.1. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

Siemens (1991). *XSCANS Users Manual.* Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

Suzuki, K., Shiratori, K., Murayama, B., Harada, N., Miyano, T. & Takeya, K. (1989). *J. Pharmacobiol. Dyn.* **12**, 293–298.

Tolman C. A. (1977). *Chem. Rev.* **77**, 313–341.

Triggle, D. J., Langs, D. A. & Janis, R. A. (1989). *Med. Res. Rev.* **9**, 123–180.

Triggle, A. M., Schefter, E. & Triggle, D. J. (1980). *J. Med. Chem.* **23**, 1442–1445.

Acta Cryst. (1996). C**52**, 2212–2215

(*E*)-6-Chloro-3-[2-(4-chlorophenylsulfonyl)-ethenyl]-4-chromanone, (*E*)-6-Bromo-3-[2-(4-bromophenylsulfonyl)ethenyl]-4-chromanone and (*E*)-3-[2-(4-Chlorophenylsulfonyl)ethenyl]-6-methoxy-4-chromanone

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Abstract

The structures of (*E*)-6-chloro-3-[2-(4-chlorophenylsulfonyl)ethenyl]-4-chromanone, $C_{17}H_{10}Cl_2O_4S$, (*E*)-6-bromo-3-[2-(4-bromophenylsulfonyl)ethenyl]-4-chromanone, $C_{17}H_{10}Br_2O_4S$, and (*E*)-3-[2-(4-chlorophenylsulfonyl)ethenyl]-6-methoxy-4-chromanone, $C_{18}H_{13}ClO_5S$, display similar bond angles and distances, but differ in the conformations of the ring systems.

Comment

Sulfones display activity as antibacterial and antifungal agents. Dapsone has been proven to be effective against leprosy, and diasone is found to be highly effective against streptococci and pneumococci infections (Kharesch, Stampa & Nudenberg, 1953). The antifungicidal activity of some unsaturated sulfones has been found to be dependent upon substituent and stereochemical effects (Hawthorne, 1960). (*E*)-3-[2-(Phenylsulfonyl)ethenyl]-4*H*-1-benzopyran-4-one and (*E*)-3-[2-(4-chlorophenylsulfonyl)ethenyl]-4*H*-1-benzopyran-4-one have been observed to display antifungal activity against *Curvularia lunata* and *Furasium oxysporum* (Mukundam, 1990).

In the interest of exploiting and increasing this activity, we have synthesized a series of compounds which are derived from these active antifungal agents but with substituents at the 6 position of the 4*H*-1-benzopyran-4-one ring and with variation of the *para* substituent on the phenyl ring: (*E*)-6-chloro-3-[2-(4-chlorophenylsulfonyl)ethenyl]-4-chromanone, (I), (*E*)-6-bromo-3-[2-(4-bromophenylsulfonyl)ethenyl]-4-chromanone, (II), and (*E*)-3-[2-(4-chlorophenylsulfonyl)ethenyl]-6-methoxy-4-chromanone, (III). Our aim was to observe the influences of these changes upon the