CONFORMATIONAL AND HYDROGEN BONDING DETAILS OF C_4-HETEROCYCLE 1,4-DIHYDROPYRIDINES IN THE SOLID STATE

By

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Chapter I

INTRODUCTION AND BACKGROUND

Calcium

Ca^{2+} is the major extracellular divalent cation in human systems. The normal adult man and woman possess about 1300 and 1000 g of Ca^{2+}, respectively, of which more than 99% is in bone. Ca^{2+} is present in small amounts in extracellular fluids and to a minor extent within cells, where its ionized concentration is about 0.1 μM. In response to hormonal, electrical or mechanical stimuli, a temporary increase in Ca^{2+} flux raises this concentration to about 1 μM, permitting interactions with specific Ca^{2+} binding proteins that activate specific processes. The major Ca^{2+} binding protein in all organisms is calmodulin, it binds four moles of Ca^{2+} per mole of protein. Ca^{2+} is essential for many important processes, including neuronal excitation, neurotransmitter release, muscle contraction, membrane integrity and blood coagulation. In addition, Ca^{2+} serves a second messenger function for the actions of many hormones [1].

Calcium antagonists

Calcium antagonists, also referred to as calcium-channel blocking drugs, constitute an important class of pharmaceuticals. Part of the larger family of antiarrhythmics, they have been the subject of much interest in the past 20 years. This

does not come as much of a surprise when one considers the clinical and fundamental relevance of these compounds. Therapeutically, calcium antagonists are widely used in the treatment of angina, hypertension and certain types of cardiac arrhythmia. From a research perspective, they are widely valued as tools in the study of calcium metabolism in physiological processes [2].

Mechanism of action

Calcium-channel blockers inhibit the entry of calcium into the cell or inhibit its mobilization from the intracellular stores in both cardiac and smooth muscle cells. Therefore, they mimic the effect of Ca^{2+} withdrawal and hence block contraction.
Cytosolic Ca^{2+} concentrations may be increased by various contractile stimuli. Many hormones and neurohormones increase Ca^{2+} influx through so-called receptor-operated channels, while voltage-sensitive, or "potential-operated", channels regulate the influx of calcium via the membrane potential [3].

Experimentally, the action of calcium-channel inhibitors has been shown to be membrane potential or "voltage" dependent. In fact, the channel inhibition is much more pronounced under depolarized rather than hyperpolarized conditions [4-7]. This is explained by the modulated receptor hypothesis [8, 9] which assumes that the affinity of a drug for the channel is "state" dependent (Cf Figure 1). However, variations in voltage also influence the configuration of the receptor which is allosteric. Thus, in the inactivated state the receptor allows for a higher lock and key affinity of the drug than in the resting state.

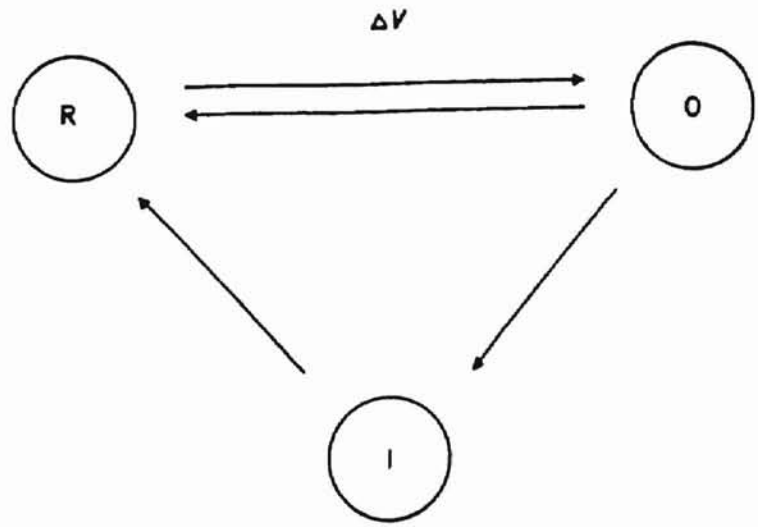


Figure 1: Potential-dependent states of the Ca^{2+} channel (R= resting state, O= open state, I= inactivated state)

Voltage-sensitive channels contain domains of homologous sequence that are arranged in tandem within a single large subunit. In addition to the major channel-forming subunit (termed α_1), Ca^{2+} channels contain several other associated subunits (termed α_2, β, γ and δ) [10].

Voltage-sensitive Ca^{2+} channels have been divided into at least three subtypes based on their conductivities and sensitivities to voltage [10, 11]. The channels best characterized to date are the L, N and T subtypes. Only the L-type channel is sensitive to dihydropyridine Ca^{2+} channel blockers.

Overall, the effect of calcium channel inhibitors is to prolong the time of recovery from the inactivated state. In so doing, in-coming depolarization pulses are kept from inducing contraction in the cardiac or smooth muscle.

1,4-Dihydropyridines: Structural details and background.

1,4 –Dihydropyridines constitute the largest class of calcium antagonists. In fact, their facile synthesis has led to their intensive study. They have the added interest of displaying both agonistic and antagonistic activity for very similar chemical structures.

Studies indicate that their activity derives from their interaction with a receptor site located in the alpha 1 subunit of the calcium channel found in both cardiac and smooth muscle.

Structure-activity studies have shown that certain structural details correlate with increased pharmaceutical activity [12]. It is thought that ring A (Cf Figure 2) should be in a shallow boat form with the substituent at C_4 in a pseudo-axial position. If the substituent at C_4 is a ring, the plane of that ring should be perpendicular to the plane of C_2, C_3, C_5 and C_6 which forms the base of the dihydropyridine boat. However, aromatization of the A ring which occurs upon light induced oxidation of the DHP, destroys activity [13, 14].

It has been suggested that the presence of ester groups at the 3 and 5 positions produces optimal activity. Previous work in this lab has shown that the esterification groups at these positions should be small in volume (isopropyl or smaller) for optimal activity [13-15]. Coplanarity of the C=O bond of the ester group with the adjacent conjugated double bond of the A ring is normally seen in the crystal structure. Thus conformation may be anti-periplanar (ap) or syn-periplanar (sp) (Figure 2). It has been suggested that the conformation of these carbonyl groups should be ap at C_5 for maximum hydrogen bonding efficiency in the docking site [16].

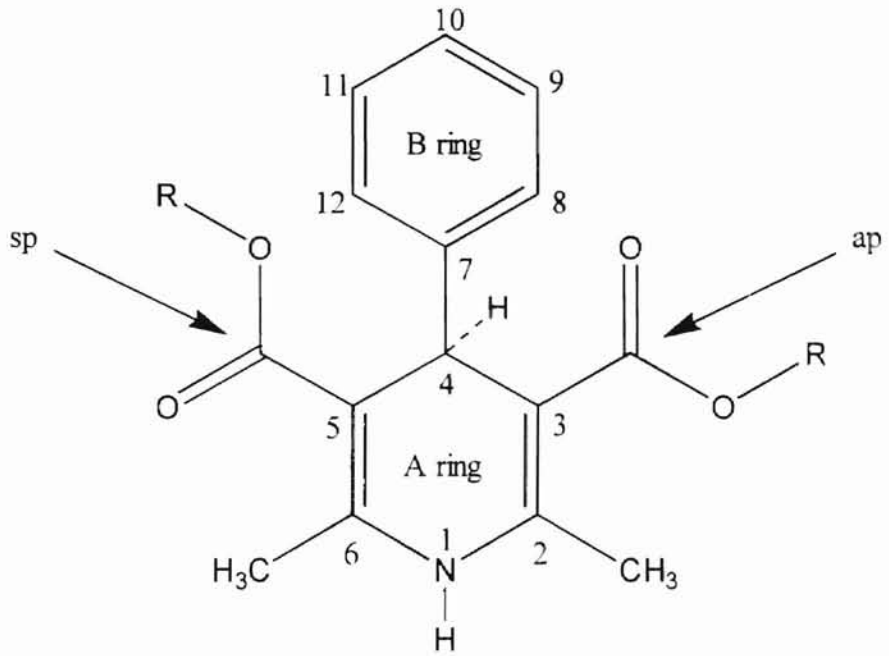


Figure 2: Illustration of the sp and ap conformation of the ester substituents. Standard view with C_4 hydrogen pointing back.

Other studies have shown that the presence of electronegative substituents on the B ring increases the ability of DHP compounds to inhibit calcium influx. This increase in drug efficiency is position dependent, with enhanced activity seen in the order: ortho >meta >>para [12]. Rovnyak *et al.* suggested that there is a preferred 'prow-forward' conformation with the B ring substituent on the same side as the C_4 hydrogen (synperiplanar, *sp*) instead of, following rotation of the B ring, the substituents lying above the dihydropyridine ring in a 'prow-over' (*ap*, antiperiplanar) conformation. (Cf Figure 3).

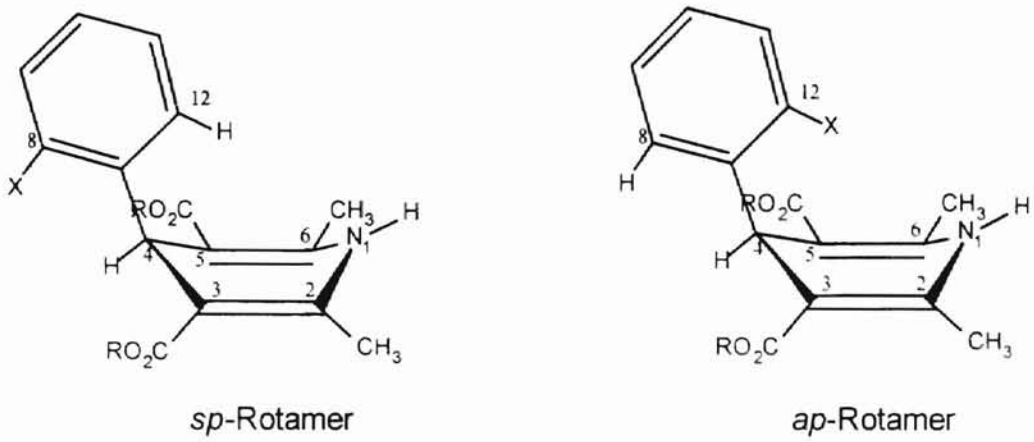


Figure 3: Illustration of the *sp* and *ap* conformation of the phenyl substituents

As a part of studies designed to pinpoint the conformational characteristics associated with biological activity (i.e. of affinity with the slow calcium channel receptor site), many research groups have examined the crystal structures of derivatives from the 1,4-dihydropyridine family. DHPs with benzene as the B ring constitute the bulk of compounds studied by X-ray crystallography (Cf Table 1) and serve as the foundation for most of the structure activity relationship studies.

Nonetheless, dihydropyridine derivatives with heterocyclic substituents at C_4 have also been a subject of interest (Cf Table 2).

These studies underline the importance of two conformational details: the orientation of 1) the B ring, when it is substituted, and 2) the ester carbonyls.

1) B ring orientation

In the solid state, the synperiplanar geometry is widely favored [16]. Theoretical calculations also indicate a preference for the *sp* conformer rather than the *ap* conformer [17, 18]. A study conducted by Kappe *et al.* further shows that the energy difference

between rotamers is more pronounced for ortho substituted B rings, with differences ranging from 1.5 to 3.6 kcal/mol [19]. The thermodynamic preference for the *sp* conformer in solution can also be confirmed through NMR spectroscopy by measurement of the Nuclear Overhauser effects of the ortho hydrogen atom with the C_4 hydrogen (Cf Figure 2) [16, 20, 21].

In the solid state, an overwhelming number of DHPs are found to adopt the *sp* conformation. However, there are categories of dihydropyridine derivatives which take on the *ap* conformation including 3-cyano analogues of nifedipine and bicyclic dihydropyridines [12, 16]. The 2-chloro nifedipine derivative is the only example in the literature of a DHP compound seen in both *sp* and *ap* conformations. These were observed within the same crystal unit cell [21].

Though the *sp* form is usually favored in the crystal, in solution, the energy difference between the two rotamers is small. Thus interactions with the biologically active site may involve either rotamer. A drug molecule may easily alter B ring conformation to adapt to the receptor site.

Interestingly, when one considers DHP derivatives with heterocyclic B rings (Cf Tables 2 and 3), the preference for the *sp* conformer is not followed. In fact the rotameric preference, as observed in the solid state, is in favor of the *ap* comformer (8(*ap*):6(*sp*)). Taking into consideration only the ortho substituted compounds which, according to theoretical calculations, have stronger bias towards the *sp* geometry, leads to an *ap*/*sp* rotameric ratio of 6/3 [17]. Natale *et al.* attribute this conformational bias to crystal packing forces [22].

2) Ester carbonyl conformation

Assuming a favored coplanar arrangement of the ester carbonyl with the adjacent double bond of the dihydropyridine ring, three conformations are possible in principle for the ester groups: sp/sp, {sp/ap, ap/sp} and ap/ap. An analysis of X-ray crystallographic studies on aryl substituted DPH derivatives has shown a preference for the {sp/ap, ap/sp} and sp/sp arrangements in crystals. There is only one example of an ap/ap conformer in the literature [23]. In the presence of ortho substituents, there is a pronounced preference for the sp/sp conformation whereas in their absence, the asymmetric {sp/ap, ap/sp} arrangement is favored [16].

A similar analysis of the crystal structures of the heterocyclic compounds in Table 3 yields conflicting results. Indeed, in this case, the carbonyl conformational preference for dihydropyridines with ortho substituted B rings is {sp/ap, ap/sp} at a ratio of 4 to 3 (sp/sp). Compounds with meta substituted B rings maintain their preference for the asymmetric conformation.

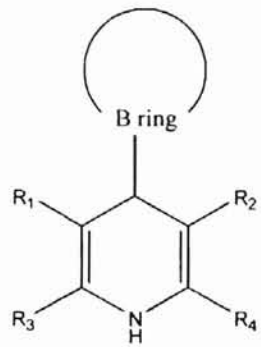
Preference for a particular ester conformation at the calcium channel receptor has been widely postulated [12, 16, 24]. However literature discussions of conformational characteristics associated with high calcium antagonistic activity differ in conclusions. Kappe *et al.* consider that the left ester (5 position) functionality must be sp for optimum antagonistic activity whereas both Sagar *et al.* and Schleifer conclude that an 5ap/3sp arrangement is needed [25, 26]. Fossheim on the other hand estimates antagonistic activity to be dependent only on the presence of any sp oriented ester carbonyl [24].

Differential hydrogen bonding of carbonyl groups might explain the purported conformer preference. Based on solid state studies, Triggle *et al.* claim that ortho substituted DPHs can only form hydrogen bonds to sp oriented carbonyl oxygens.

This conclusion is based on substituted B rings sterically hindering rearrangement to the ap position. Other X-ray diffraction studies substantiate this proposition [27]. Gaudio *et al.* adopt a more flexible point of view considering hydrogen bonding of ester carbonyls in the ap conformation to the receptor site to be more difficult when the B ring has a bulky ortho substituent [18].

Table 3 gives the observed hydrogen bonding patterns for C_4-heterocyclic substituted DHPs found in the literature. When a heteroatom present in the B ring is not involved, ortho substituted derivatives show a preference for hydrogen bonding in the crystal via sp oriented carbonyl groups at a ratio of 4:3 while compounds with meta substituents hydrogen bond exclusively through carbonyl groups in the ap conformation.

Table 1. 1,4-Dihydropyridines studied by X-ray crystallography.



R_1	R_2	R_3	R_4	B ring	B ring substituents	Reference
$CO_2CH_2CH_3$	$CO_2CH_2CH_3$	CH_3	CH_3	Phenyl	H	28
CO_2CH_3	CO_2CH_3	CH_3	CH_3	Phenyl	2-CF_3	29
CO_2CH_3	CO_2CH_3	CH_3	CH_3	Phenyl	2-Cl	21
CO_2CH_3	CO_2CH_3	CH_3	CH_3	Phenyl	H	30
CO_2CH_3	CO_2CH_3	CH_3	CH_3	Phenyl	3-NO_2	30
$CO_2CH(CH_3)_2$	$CO_2CH_2CH_2OCH_3$	CH_3	CH_3	Phenyl	3-NO_2	31, 32
CO_2CH_3	CO_2CH_3	CH_3	CH_3	Phenyl	2-NO_2	33

CO_2CH_3	CO_2CH_3	CH_3	CH_3	Phenyl	3-CH_3	30
CO_2CH_3	CO_2CH_3	CH_3	CH_3	Phenyl	4-CH_3	30
CO_2CH_3	CO_2CH_3	CH_3	CH_3	Phenyl	4-NO_2	30
CO_2CH_3	CO_2CH_3	CH_3	CH_3	Phenyl	3-CN	33
CO_2CH_3	CO_2CH_3	CH_3	CH_3	Phenyl	2,4-$(NO_2)_2$	30
CO_2CH_3	CO_2CH_3	CH_3	CH_3	Phenyl	2, 3, 4, 5, 6-F_5	33
CO_2CH_3	$CO_2CH_2CH_2CH(CH_3)_2$	CH_3	CH_3	Phenyl	2-NO_2	34
NO_2	CO_2CH_3	CH_3	CH_3	Phenyl	2-CF_3	35
CO_2CH_3	$CO_2(C_5H_7N)$-$CH_2C_6H_5$	CH_3	CH_3	Phenyl	3-NO_2	36
CO_2CH_3	$CO_2CH_2CH_3$	CH_3	CH_3	Phenyl	2-NH_2	37
$CO_2CH_2CH_3$	$CO_2CH_2CH_2CH(CH_3)_2$	CH_3	CH_3	Phenyl	2,3-Cl_2	27
CO_2CH_3	$CO_2CH_2CH_2CH(CH_3)_2$	CH_3	CH_3	Phenyl	H	34
CO_2CH_3	$CO_2CH_2CH_2CH(CH_3)_2$	CH_3	CH_3	Phenyl	3-NO_2	34
CO_2CH_3	$CO_2CH_2CH_2CH(CH_3)_2$	CH_3	CH_3	Phenyl	3-CN	34
CO_2CH_3	$CO_2CH_2CH_2CH(CH_3)_2$	CH_3	CH_3	Phenyl	3-OCH_3	34
CO_2CH_3	$CO_2CH_2CH_2CH(CH_3)_2$	CH_3	CH_3	Phenyl	4-F	34
CO_2CH_3	$CO_2CH_2CH_2CH(CH_3)_2$	CH_3	CH_3	Phenyl	2-CF_3	34
$C(O)N(CH_2CH_3)_2$	$C(O)N(CH_2CH_3)_2$	CH_3	CH_3	Phenyl	2,4-Cl_2	38

$C(O)NHCH_3$	$C(O)NHCH_3$	CH_3	CH_3	Phenyl	2-CF_3	39
$C(O)NHCH_3$	$C(O)NHCH_3$	CH_3	CH_3	Phenyl	2-Methyl	39
$C(O)NHCH_3$	$C(O)NHCH_3$	CH_3	CH_3	Phenyl	2-Methoxy	39
$C(O)NHCH_3$	$C(O)NHCH_3$	CH_3	CH_3	Phenyl	2,4-Dichloro	39
$CO_2CH_2CH_2OCH_3$	$CO_2CH_2CH_2ONO_2$	CH_3	CH_3	Phenyl	3-NO_2	40
CO_2CH_3	$CO_2CH_2CH_2ONO_2$	CH_3	CH_3	Phenyl	3-NO_2	41
CO_2CH_3	$CO_2CH_2CH_3$	CH_3	CH_3	Phenyl	3-NO_2	31
CO_2CH_3	$CO_2CH_2CH_2CH(CH_3)_2$	CH_3	CH_3	Phenyl	4-Cl	34
CO_2CH_3	$CO_2CH_2CH_2CH(CH_3)_2$	CH_3	CH_3	Phenyl	3-CF_3	34
CO_2CH_3	CO_2CH_3	CH_3	CH_3	Phenyl	4-$N(CH_3)_2$	33
$CO_2CH_2C(CH_3)_3$	$CO_2CH_2C(CH_3)_3$	CH_3	CH_3	Phenyl	3-NO_2	42
$CO_2CH(CH_3)_2$	CO_2CH_3	CH_3	CH_3	Phenyl	3-NO_2	43
CO_2CH_3	CO_2CH_3	CH_3	CH_3	Phenyl	2-Cl, 3-NO_2	21
CO_2CH_3	CO_2CH_3	CH_3	CH_3	Phenyl	2-Cl, 4-NO_2	21
CO_2CH_3	CO_2CH_3	CH_3	CH_3	Phenyl	2-Cl, 5-NO_2	21
$CO_2CH_2CH_3$	$CO_2CH_2CH_3$	CH_3	CH_3	Phenyl	2-(9-anthryl)	44
CO_2CH_3	CO_2CH_3	CH_3	CH_3	Phenyl	4'-(4H-4-oxo-1-benzopyran-2-yl	23

Table 2. Dihydropyridines with hetero B rings studied by x-ray crystallography.

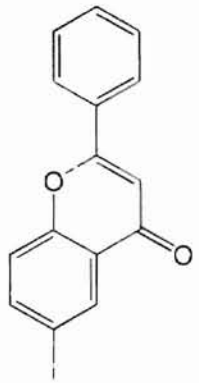
R_1	R_2	R_3	R_4	B ring	B ring substituents	[Reference] / (Compound)
$CO_2CH_2CH{=}CH_2$	$CO_2CH_2CH{=}CH_2$	CH_3	CH_3	I		[45] / (1)
CN	CN	CH_3	CH_3	II	2-CN	[46] / (2)
$CO_2CH(CH_3)_2$	CN	CH_3	CH_3	III	R=2-naphthyl	[44] / (3)
$CO_2CH_2CH_3$	CN	CH_3	CH_3	III	R=8-naphthyl	[44] / (4)
CO_2CH_3	CO_2CH_3	CH_3	CH_3	IV		[20] / (5)
$CO_2CH(CH_3)_2$	NO_2	CH_3	CH_3	IV		[24] / (6)
CO_2CH_3	CO_2CH_3	CH_3	CH_3	V		[20] / (7)
CO_2CH_3	CO_2CH_3	CH_3	CH_3	VI		[20] / (8)
CO_2CH_3	CO_2CH_3	CH_3	CH_3	VII		[20] / (9)
$CO_2CH_2CH_3$	$CO_2CH_2CH_3$	CH_3	CH_3	VIII	5-Para-tolyl	[47] / (10)
CO_2CH_3	CO2CH(C6H5)(CH2C5H5N)	CH_3	CH_3	IX		[48] / (11)

$CO_2CH_2CH_3$	$CO_2CH_2CH_3$	CH_3	CH_3	X	5-Methyl, 3-phenyl	[49] / (12)
$CO_2CH_2CH_3$	$CO_2CH_2CH_3$	CH_3	CH_3	X	R_1=Methyl R_2=1-naphthyl	[22] / (13)
$CO_2CH_2CH_3$	$CO_2CH_2CH_3$	CH_3	CH_3	XI		[50] / (14)
$CO_2CH_2CH_3$	$CO_2CH_2CH_3$	CH_3	CH_3	XII		[50] / (15)

Table 3. Conformational and hydrogen bonding details for compounds from table 2.

Compound (Cf Table 2)	Substituent position / heteroatom position	Rotamer	Ester conformation	Hydrogen bonding
(3)	Ortho/ β N	ap	5sp / 3CN	N_1-H---N_1'(Ring B pyridine N)
(4)	Ortho / β N	ap	5sp / 3CN	N_1-H---N_1'(Ring B pyridine N)
(5)	Ortho / none	sp	5sp / 3ap	N_1-H---O_3 N_1-H---O_5
(6)	Ortho / none	ap	5sp / 3sp	N_1-H---O_3 and O_5 (Bifurcated H-bond to both carbonyl Os)
(8)	Ortho / none	sp	5ap / 3sp	N_1-H---O_5
(12)	Ortho / β O and N	sp	5sp / 3sp	N_1-H---N_2 (Isoxazolyl N)
(13)	Ortho / β O and N	ap	5sp / 3sp	N_1-H---O_3 N_1-H---O_5
(14)	Ortho / α and β N	ap	5sp / 3ap	N_1-H---O_1 (Quinoxaline O)
(15)	Ortho / α and β N	ap	5sp / 3ap	N_1-H---O_1 (Quinoxaline O)
(1)	Meta / none	ap	5ap / 3sp	N_1-H---O_2 (Ether oxygen of flavone C ring)
(2)	Meta / α	ap	5CN / 3CN	N_1-H---N_4 (Cyano nitrogen)
(7)	Meta / none	sp	5ap / 3sp	N_1-H---O_5
(9)	Meta / none	sp	5sp / 3ap	N_1-H---O_3
(10)	Meta / α	sp	5sp / 3ap	N_1-H---O_3
(11)	None / α	ap and sp	sp / sp	N_1-H---solvant molecule

Figure 4. DHP heterocyclic C_4 substituents.



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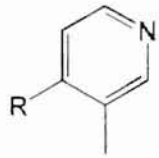

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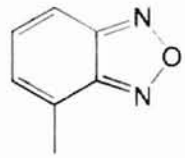

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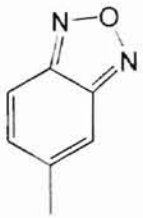

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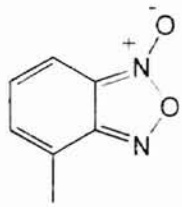

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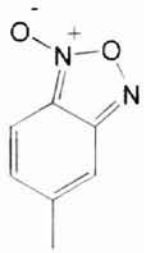

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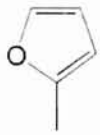

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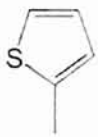

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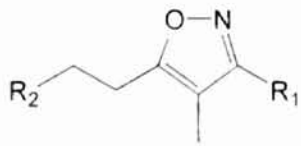

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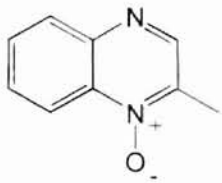

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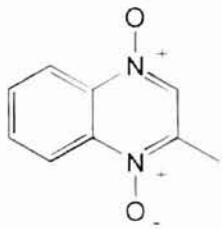


XII

Molecular modeling studies

A long series of molecular modeling studies published in the 80's and 90's using Sybyl [12, 51] led to expectation of a docking pattern involving the insertion of ring B of the DHP molecule into a specific turn of a protein helix purported to be a suitable receptor site [31]. This approach was justified: these studies yielded relative binding energies which paralleled the activities of the same compounds tested in vivo and studies with proteins lacking this cleft showed no DHP binding [52].

Following this direction, further molecular modeling conducted using Sybyl [51] suggested that the binding efficiency of DHPs was related to the number of hydrogen bonds formed between drug and protein. These hydrogen bonds involved arginine amino acid residues found on opposite sides of the receptor pocket. This molecular modeling software does not, however, permit flexibility of the drug molecule or of the receptor protein. The conformation of the drug molecule is fixed (energy minimized or other) and the drug is driven in to the rigid receptor site. A 'best fit' is determined and the derived binding energy used to quantify binding efficiency. Thus, during docking, ester groups substituted at C_3 and C_5 of ring A of the DHP molecule could not change conformation, the B ring could not rotate about the C_4-C_7 bond and the conformation of the A ring was fixed in a shallow boat conformation with N_1 and C_4 upward.

More recent programming algorithms (i.e. FLEXIDOC [53] and GOLD [54]) allow rotation about designated bonds of the drug molecule and of the receptor itself and thus a more realistic approach to *in vivo* behavior.

Crystallization and co-crystallization as a tool for assessment of docking geometry.

A drug molecule recognizes its receptor site via affinity processes (i.e. establishment of positive interactions; hydrogen bonding, dipole-dipole interactions and Van der Waals attractions) which are also responsible for binding strength. Hydrogen bonding is the strongest of these interactions.

Crystallization, where interactions with neighboring molecules are maximized, parallels the above process. Indeed, as a drug approaches a protein, it probes the surface for any complementary interactions. Establishing this complementarity proceeds through conformational variation which allows positive interactions to be optimized. This is the same methodology that a molecule displays when it deposits itself onto the surface of a forming crystal. The way in which a molecule changes to adapt to its receptor in a protein is very similar to the way that a molecule seeks out the 'best fit' to a crystal surface.

Thus the crystallographic conformation represents an energy minimum conformation of the drug in the environment of the crystal and may be indicative of the affinity-maximizing molecular recognition process taking place in vivo.

By correlating the hydrogen bonding patterns observed in the solid state to the conformational details of the molecules studied, insight into the active docking geometry of the DHP ligands can be obtained.

Protein-ligand interactions are modulated through conformational variability and crystallization involves interactions between identical molecules which can display only limited conformational variability. Co-crystallization of a drug molecule with a different compound can be employed as an intermediate and more realistic approach to modeling the molecular recognition process [55].

Therefore this thesis study set out to obtain insight into the molecular recognition process of derivatives of the 1,4-dihydropyridine family by studying the hydrogen bonding/conformational patterns observed in the crystalline state (influence of hydrogen bonding upon the conformation of the carbonyl groups and on the orientation of substituents on the B ring). Our expectations were that a DHP molecule will respond to the environment of the crystal with changes similar to those exhibited on docking with a receptor site.

Chapter II

CRYSTALLOGRAPHY

The main goal of X-ray crystallography is the acquisition of a detailed model of the three-dimensional contents of a crystal at the atomic level. Knowledge of the atomic positions yields a wealth of information: bond lengths and angles, intermolecular interactions, molecular packing, conformation, and hydrogen bonding.

In the crystalline state, there exists a very high degree of internal order and symmetry. The molecules, atoms, or ions in the crystal are arranged in a precise regular way, a motif which is repeated over and over in all directions. It is this property of crystals that allows the diffraction of X-rays and the subsequent solution of a crystal structure. Most crystals are very regular in shape with sharp faces and edges, but this characteristic is not sufficient to define a crystal. A crystal must have a pattern that repeats in three dimensions, which defines the crystal lattice.

The basic "building block" in a crystal is the unit cell. The unit cell is characterized by its cell edges (a, b, and c) and angles (α, β, and γ). The crystal system to which a unit cell belongs is defined by the relationship between these edges and angles. There are seven possible crystal systems (Table 4).

Table 4.The seven crystal systems

Crystal system	Unit cell shape	Bravais lattices
Triclinic	$a \neq b \neq c$ $\alpha \neq \beta \neq \gamma \neq 90°$	P
Monoclinic	$a \neq b \neq c$ $\alpha = \gamma = 90°, \beta \neq 90°$	P, C
Orthorhombic	$a \neq b \neq c$ $\alpha = \beta = \gamma = 90°$	P, C, I, F
Tetragonal	$a = b \neq c$ $\alpha = \beta = \gamma = 90°$	P, I
Trigonal	$a = b = c$ $\alpha = \beta = \gamma \neq 90°$ $\gamma < 120$	P
Hexagonal	$a = b \neq c$ $\alpha = \beta = 90°, \gamma = 120°$	P
Cubic	$a = b = c$ $\alpha = \beta = \gamma = 90°$	P, I, F

The unit cell of a crystal may also contain a variety of symmetry elements relating atoms or molecules to each other. These include:

Center of symmetry: The point about which inversion of an object occurs.

Mirror Plane: A plane of reflection which must be perpendicular to an axis and parallel to one of the crystal faces.

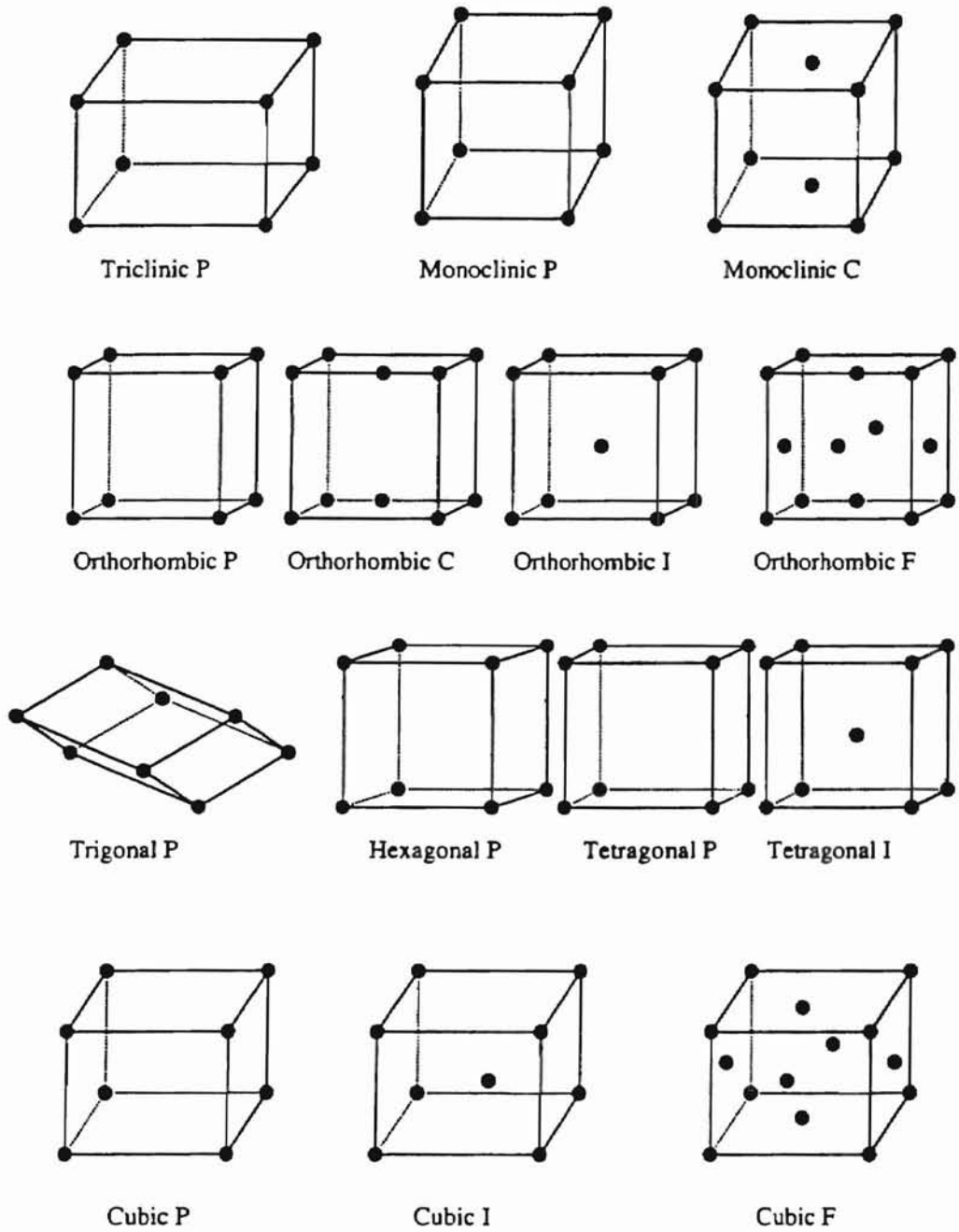
Rotation Axis: An n-fold rotation axis in which the rotation through $2\pi/n$ (n=1, 2, 3 or 4) leaves the appearance of the motif unchanged.

Glide Plane: The combination of a mirror reflection and a translation.

Screw axis: The combination of a rotation and a translation.

Inversion axis: The combination of a rotation axis with a center of symmetry.

Figure 5. The 14 bravais lattices.



The crystal lattice can be classified as primitive (P), face centered (A, B, C, or F) or body centered (I). Fourteen Bravais lattices result when the crystal system is combined with these lattice types. The combination of the fourteen Bravais lattices with the symmetry elements produces a total of 230 possible space groups. Each crystal crystallizes in a specific space group that characterizes that crystalline structure [56].

Since crystals have the highly ordered structure described above, they are capable of diffracting radiation in a manner similar to an optical grating. The diffraction pattern of a crystal is much more complicated because a crystal exhibits three-dimensional periodicity thus producing diffraction in all directions of space [56]. The diffraction of an X-ray by a crystal obeys the mathematical relationship called Bragg's Law:

$$n\lambda = 2d_{hkl} \sin\theta \qquad (1)$$

where n is an integer, λ is the wavelength of the incident radiation, d_{hkl} is the interplanar spacing or distance between the regularly oriented layers of a set of (hkl)-planes, θ is the angle of incidence and the angle of diffraction of the X-ray beam. Bragg's law, thus, describes the relationship between the wavelength of the incident radiation, the distance between the parallel planes of the crystal, and the angles at which specific diffracted beams will be observed. Bragg's law must be satisfied in order for coherent diffraction to occur.

The diffraction pattern of a crystal is characteristic of the unit cell and the distribution of the atoms present. The intensities of the diffracted reflections are determined by the type of atoms present and their relative positions within the unit cell. Different elements have different abilities to scatter X-rays, which are dependent on the number of electrons the element has. The "heavier" the atom, the greater it's ability to scatter the X-ray beam. Each crystal has a diffraction pattern which is characteristic of its structure.

The intensity data collected from a crystal supply all the information necessary to solve the molecular structure of that crystal. However, the intensities of these reflections are influenced by a number of other factors which must be taken into account. The raw intensity data (I_{meas}) must be corrected for these various effects before it can be used to solve the structure. This correction process is known as *data reduction* and involves the application of corrections for X-ray background intensity (i), Lorentz (ii) and polarization (iii) factors, absorption effects (iv) and decomposition (v) due to radiation or air damage.

(i) Background: When a reflection intensity is measured, it is usually accompanied by a certain amount of scattered "background" radiation which must be eliminated to obtain the true intensity [56, 57]. This correction is calculated as follows:

$$I_{int} = (I_{meas} - L_{bg} - R_{bg}) \times \text{Scan speed} \qquad (2)$$

where:

I_{int} : Integrated Intensity

I_{meas} : Measured Intensity

L_{bg} : Left background (Measured before reflection)

R_{bg} : Right background (Measured after reflection)

The error in this intensity measurement is given by:

$$\sigma I_{int} = (I_{meas} + L_{bg} - R_{bg})^{1/2} \times \text{Scan speed} \qquad (3)$$

where:

σI_{int} : The standard deviation of I_{int}

(ii) Lorentz factor: The Lorentz correction (L) takes into account the different lengths of time that the various Bragg reflections spend in the diffracting position.

Indeed, if the crystal rotates at a constant speed, certain reflections (i.e. high 2θ reflections) will be in optimum diffraction geometry for shorter periods of time. The Lorentz factor corrects for this effect and is given by:

$$L = (\sin 2\theta)^{-1} \qquad (6)$$

(iii) Polarization factor: The polarization factor is a function of the Bragg angle. As the data is collected, θ is varied. In so doing, the nature of the X-ray beam and the efficiency of diffraction vary. A normal X-ray beam is unpolarized and contains two limiting components, one parallel to the reflecting plane ($I_{\parallel}$) and one perpendicular to the reflecting plane ($I_{\perp}$). These components are diffracted by the crystal monochromator with different efficiencies. At lower 2θ, the $I_{\parallel}$ and $I_{\perp}$ components are diffracted with approximately equal efficiency. At higher 2θ however, the efficiency of diffraction of the $I_{\perp}$ component decreases dramatically, causing the diffracted beam to become partially polarized and the measured diffraction intensity to drop.

The polarization factor, P, is a function of 2θ and is independent of the geometry of data collection. It is calculated using the following expression.

$$P = (1 + \cos^2 2\theta) / 2 \qquad (5)$$

The combination of the Lorentz and polarization factors results in what is known as the Lorentz-polarization factor (LP):

$$LP = (1 + \cos^2 2\theta) / 2\sin 2\theta \qquad (7)$$

(iv) Absorption factor: As an X-ray beam passes through a crystal, its intensity is reduced as a result of its absorption by the material in the crystal. The extent of this absorption depends on what elements are present in the compound, the path length of the

beam through the crystal, and the wavelength of the incident X-ray beam. The absorption factor (A) is defined by the following mathematical expression:

$$A = (1 / V) \int e^{-\mu L} dv \qquad (8)$$

where V is the volume of the crystal, μ is the linear absorption coefficient which is defined as the absorption per mm of material passed through and L is the path length through the crystal of the beam diffracted by the volume dv.

v) Decomposition: Exposure of a crystal to X-rays is often harmful and can lead to its deterioration through a variety of processes (formation of free radicals, loss of solvent of crystallization, heating of the crystal, exposure to air ...etc). Radiation induced damage causes Bragg reflections to change intensity as a function of time. This damage can be monitored by measuring a set of reference reflections at regular intervals throughout the data collection. The correction for this effect is given by:

$$D = I_{orig} / I_{ave} \qquad (9)$$

where:

I_{orig} : starting intensity of a standard reflection

I_{ave} : average current and last intensity measurements of the standard reflection

Once all of the above corrections have been taken into account (data reduced), the total corrected intensity may be calculated by:

$$I_{corr} = I_{int} \times (LP)^{-1} \times A^{-1} \times D \qquad (10)$$

where:

I_{int} : the integrated intensity (after background corrections)

I_{corr} : the overall corrected intensity

The reflection is considered to be observed if $I_{int} = 2\sigma(I_{int})$ and is used in the solution of the crystal structure.

I_{int} is related to the structure factor (F) by:

$$| F | = (K\ I_{corr})^{1/2} \qquad (4)$$

where:

K : constant, dependent upon beam intensity and machine constants.

The structure factor can be calculated, theoretically, once the positions of the atoms are known. Also, this factor is used in the calculation of electron density maps from which the position of the atoms can be determined. The relationship between F and I depends on the corrections listed above and must be taken into account in order to convert I into $| F_{obs} |$ which is used in the subsequent structure solution.

X-rays scattered by a crystal have a particular combination of amplitude and phase which is termed the structure factor (F). The structure factor may be calculated from the positions of the atoms in the cell, their ability to scatter X-rays, and the phase angle, α_{hkl} (i. e. the difference in period, expressed as an angle, between the wave resulting from a specific set of planes and a wave resulting from scattering at the origin). where:

$$| F_{hkl} | = \{ (A_{hkl})^2 + (B_{hkl})^2 \}^{1/2}$$

$$A_{hkl} = \Sigma_j\ f_j \cos 2p\ (hx_j + ky_j + lz_j\ )$$

$$B_{hkl} = \Sigma_j\ f_j \sin 2p\ (hx_j + ky_j + lz_j\ )$$

$$\alpha_{hkl} = \tan^{-1} (B_{hkl} / A_{hkl})$$

and f_j is the individual atomic scattering factor and x_j, y_j, z_j are the positional parameters in the unit cell of atom j.

In order to acquire a three dimensional picture of the scattering matter (the electron distribution), a three dimensional Fourier synthesis must be performed. The number of electrons per unit volume or the electron density at any point in the cell with [x, y, z] coordinates, represented by $\rho(xyz)$ is given by:

$$\rho(xyz) = (1/V_c)\, \Sigma_h \Sigma_k \Sigma_l \,|\, F_{hkl} \,|\, \cos\,[2\pi\,(hx + ky + lz) - \alpha_{hkl}] \qquad (13)$$

where:

V_c : the volume of the unit cell

F_{hkl} : structure factor for the particular set of indices h.k.l

α_{hkl} : phase angle

Therefore, if $|F|$ and α were known, ρ could be computed for all values of x, y and z and these values could be plotted to obtain a three-dimensional electron density map. However, only the scattering magnitude can be measured experimentally, not the phase angle. This value must be derived from the values of A and B from previously known similar structures or by purely analytical methods. This is what is known as the phase problem in X-ray crystallography. In order to solve a structure, a certain number of the phase angles must be determined approximately in order to compute an initial model from which to complete the structure. This problem has been solved mainly by two mathematical approaches: the Patterson method and direct methods.

The Patterson method is based on the idea that the phase angle is dominated by the scattering induced by the heavy atoms and can be used in structures containing elements with a higher molecular weight than sulfur.

The second approach, most commonly used to obtain the positional parameters of an organic structure is called direct methods, and is applicable to both light and heavy atom structures. Direct methods is a way of determining the phase(s) based on relationships among the intensities of the reflections themselves. The practical objective

of direct methods is to phase enough reflections to provide an identifiable representation of the molecule. The first step in this solution requires the conversion of the observed intensities into normalized structure factors by the following equation [56]:

$$| E_{hkl} |^2 = | F_{hkl} |^2 / \varepsilon \Sigma_j f_j^2 \qquad (15)$$

where:

$|E_{hkl}|$ = normalized structure factor

f_j = the scattering factor of the jth atom

ε : the epsilon factor takes into account the crystal class and the deviation of the average intensities of certain groups of Bragg reflections from those of the general Bragg reflections.

This equation is applied in shells of 10°θ. Once the structure factors are normalized, the effects of the decline in atomic scattering power with increasing 2θ are eliminated.

The phases may be derived directly from the magnitudes of E_{hkl}. This value will allow the calculation of an electron density map from which to derive a suitable structure.

In defining the electron density the following equation holds:

$$\rho(xyz) = (1/V_c)\, \Sigma_h \Sigma_k \Sigma_l \,|\, F_{hkl} \,|\, \cos\, [2\pi\, (hx + ky + lz) - \alpha_{hkl}] \qquad (16)$$

where:

V_c : the volume of the unit cell

F_{hkl} : structure factor for the particular set of indices h.k.l

α_{hkl} : phase angle

In a centrosymmetric cell, this equation simplifies to:

$$\rho(xyz) = (1/V_c)\, \Sigma_h \Sigma_k \Sigma_l \pm |\, F_{hkl} \,|\, \cos 2\pi\, (hx + ky + lz) \qquad (17)$$

The phase angle may be simplified because in a centrosymmetric cell, with each atom at x, y, z, there is an equivalent atom at -x, -y, -z, therefore the phase angle can only be 0 or π (hence the $\pm$ sign in front of the structure factor). Thus, the electron density map can be constructed from equation (17), if the signs of a significant number of structure factors are known.

Phases can be initially assigned by the use of what is known as Harker-Kasper inequalities. These inequalities provided the first method of determining the phase of one reflection in terms of its magnitude and those of others. The inequalities that were derived are given below:

$$U^2_{hkl} \leq 1/2 + 1/2\ [U(2h, 2k, 2l)] \qquad (18)$$

$$U^2_{hkl} \leq 1/2 \pm 1/2\ |\ U(2h, 2k, 2l)\ | \qquad (19)$$

where u is the unitary structure factor.

These equations are significant because the only unknown is the phase (or sign) of U(2h, 2k, 2l). The quantity U^2_{hkl} must be positive. For example, if U^2_{hkl} is equal to 0.60 and | U(2h, 2k, 2l) | is equal to 0.20, then it follows that the sign of U(2h, 2k, 2l) must be positive. Only then will equation (19) be satisfied.

Once a few initial phases are determined, it is possible to define relations among them. These relationships are based on the fact that the electron density can never be negative and that electron density consists of discrete spherically symmetric atoms. For centrosymmetric structures, it can be shown that for any structure factor F_{hkl}, the phase is determined by the products of all of the phases of the pairs of structure factors whose indices add to give (hkl). Thus F_{213} depends on the products of the phases of F_{322} and F_{-1-11}, F_{604} and F_{-41-1}, and so on. This relationship is described in the following equation introduced by Sayre:

$$s(F_{h1k1l1}) \bullet s(F_{h2k2l2}) \approx s(F_{h1+h2,\ k1+k2,\ l1+l2}) \qquad (20)$$

This is known as the triplet product sign relationship, where s means " sign of " and ≈ means "is probably equal to". s(h, k, l) may be considered as ±1, and $(h_1k_1l_1)$, $(h_2k_2l_2)$ and $(h_1+h_2, k_1+k_2, l_1+l_2)$ are strong reflections with high | E | values. The triplet product sign relationship is used to expand the number of known phases. Therefore, if two of the signs in the equation are known, the third can be deduced. However, only a limited number of phases can be determined from the triplet relationship. A method termed symbolic addition is used to expand the number of phases known.

In symbolic addition, one starts with a limited number of phases and uses them in connection with equation (20) to build a large enough set of known phases in order to produce a recognizable electron density representation of the structure. The preliminary step in symbolic addition is the calculation of the E values for the entire data set as given in equation (15). For all the E values that are greater than a chosen minimum, a list is compiled of all the triples of reflections belonging to this set for which the indices sum to zero. The list of strongest relationships is used to select those reflections that are most often and most reliably interconnected, and of these, appropriate ones are chosen for origin determination. In the centrosymmetric case, the origin is placed on one of the centers of symmetry in the unit cell. In any primitive, centrosymmetric space group in the triclinic, monoclinic, or orthorhombic systems, arbitrary signs can be allocated to three reflections in order to specify the origin. These form a basic set from which more phases can be defined by using the triplet product relationships. For example, if the signs of 601 and 133 are +1, then 734 is generated by the combination of these and its sign will be positive:

$$s(734) \approx s(601) \cdot s(133) = +1 \cdot +1 = +1$$

Many times these starting reflections will combine to relate to two new ones and imply their phases by equation (20). The next step then involves the assignment of a new, strong reflection as a variable, a, b, or c. This variable stands for a general phase in the non-centrosymmetric case or a sign in the centrosymmetric case. These variables are

then used to determine other phases exactly or in terms of one or more variables. This series is continued until a sufficient number of reflections have been phased to provide an initial structural model.

Once enough phases have been determined, an electron density map (E-map) is calculated with the | E | values instead of the | F | values.

$$\rho(xyz) = (1/V_c) \pm| E_{hkl} | \cos 2\pi (hx + ky + lz) \qquad (21)$$

A trial model is derived from the E-map.

When the initial model is defined, the phased structure factors (F_{calc}) can be calculated and their magnitudes compared with those that have been measured (F_{obs}). This is performed by a least squares refinement method (refinement). Least-squares refinement modifies the atomic positional parameters of the calculated structure to improve the least-squares fit. This procedure then identifies any missing atoms (using the difference Fourier $| F_{obs} | - | F_{calc} |$. The correctness of the model is given by the 'Residual Factor', R_f, defined as:

$$R_f = \Sigma \, | \, | F_{obs} | - | F_{calc} | \, | \, / \, \Sigma \, | F_{obs} | \qquad (22)$$

Once this initial R factor is determined, refinement of the total set of atom positions in the crystal structure is performed using the least-squares method. As the model approaches completion, the difference between F_{obs} and F_{calc} is reflected in a lower R_f value.

The atom positions are first refined using isotropic temperature parameters. Each atom has an associated temperature parameter. This value, a measure of the thermal vibration of the atom, effectively spreads the electron cloud over a larger spherical

volume. This factor reflects the decrease in the atomic scattering factors as 2θ increases. The scattering factor for an atom at rest is given by the following equation:

$$\exp \{ -B_{iso} (\sin^2\theta) / I^2\} \qquad (23)$$

where B_{iso} is the isotropic thermal parameter, which is equal to $8\pi^2 <u^2>$, where $<u^2>$ is the mean square displacement of the atom from its equilibrium position. However, the atomic scattering behavior is more accurately defined by an anisotropic thermal parameter given by:

$$\exp -(b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{13}hl + b_{23}kl) \qquad (24)$$

where b_{ij} is the individual anisotropic thermal parameter of the atom. The refinement is continued using the anisotropic form of the temperature parameter which provides more accurate positional parameters and hence a better R_f for the structure. These anisotropic thermal parameters describe an ellipsoidal electron distribution of the electron density.

Hydrogen atom positions are normally calculated using idealized geometry, unless the intensity data is sufficiently good to allow them to be located from the difference Fourier map. When all atoms have been located, an appropriate weighting scheme and extinction correction can be applied. The structural refinement is considered complete when the R_f factor reaches a value of between 3% - 6% and all atom bond lengths and angles are reasonable.

Tables of crystal information (cell dimensions), data collection conditions, anisotropic thermal parameters, positional parameters and bond distances and angles are now prepared. A table of final F_{obs} and F_{calc} structure factors is printed. Three dimensional drawings of the molecule and/or the unit cell are prepared to show the atoms as ellipsoids of 50% probability. From these data, structural characteristics such as bond type, hydrogen bonding parameters, and conformation can be studied.

Chapter III

EXPERIMENTAL

Synthesis

The compounds studied were prepared via a synthetic procedure known as the Hantzsch dihydropyridine synthesis [58], a "one pot" synthesis in which all the reactants are mixed in an alcohol solvent (CH_3OH or CH_3CH_2OH) and refluxed for 4-12 hours (Figure 6). The product usually crystallizes out of the mother liquor. However, evaporation of the alcohol solvent, and replacement with another solvent, usually CH_3CN, was often employed in order to obtain crystals.

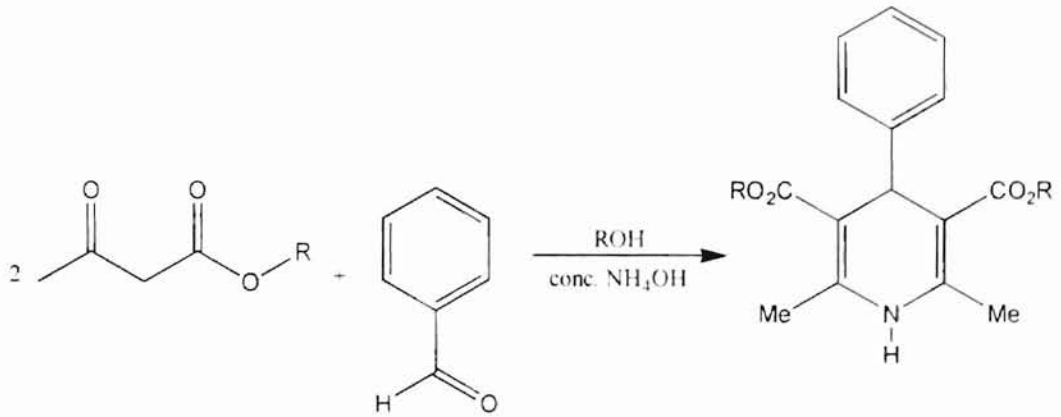


Figure 6: General Hantzsch synthesis of 4-phenyl-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl).

4-(2-Pyrrolyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (I)

A solution of 2-pyrrol-carboxaldehyde (1.64 g; 17.2 mmol), 4 g (34.3 mmol) of methyl acetoacetate and 1.21 g (34.3 mmol) of concentrated ammonium hydroxide was refluxed for 12 h in 30 mL of methanol. The methanol was removed under vacuum and the yellow solid dissolved in acetonitrile which was dried over anhydrous $MgSO_4$ and then filtered. Yellow rhombohedral crystals formed upon slow evaporation of the acetonitrile solution, mp = 200-202 °C.

4-(3-Furyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (II)

3-Furan-carboxaldehyde (0.822 g; 8.56 mmol), 1.99 g (17.1 mmol) of methyl acetoacetate and 0.599 g (17.1 mmol) of concentrated ammonium hydroxide were mixed in 30 mL of methanol and refluxed for 12 h. The methanol was removed by distillation under reduced pressure and the yellow solid dissolved in acetonitrile which was dried over $MgSO_4$. The acetonitrile solution was filtered and left to stand. Slow evaporation at room temperature led to yellow rhombohedral crystals, mp = 173-174.5 °C.

4-(3-Bromo-2-furyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (III)

5 Bromo-2-furan-carboxaldehyde (1.42 g; 8.09 mmol), 1.88 g (16.2 mmol) of methyl acetoacetate and 0.566 g (16.2 mmol) of concentrated ammonium hydroxide were mixed in 30 mL of methanol and refluxed for 12 h. The methanol was removed by rotary evaporation and the remaining yellow solid dissolved in acetonitrile. After the solution was dried over $MgSO_4$ and filtered, it was left standing at room temperature. Crystals suitable for X-ray diffraction formed from the solution, mp = 168.5-170.5 °C.

4-(2-Thiophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (IV)

2-Thiophene-carboxaldehyde (0.912 g; 8.14 mmol), methyl acetoacetate (1.89 g; 16.3 mmol) and 0.570 g (16.3 mmol) of concentrated ammonium hydroxide were mixed in 30 mL of methanol and refluxed for 12 h. The methanol was removed under vacuum and the residual yellow solid was dissolved in acetonitrile.The solution was dried ($MgSO_4$) and filtered. Slow evaporation of the dried acetonitrile solution allowed the formation of yellow rhombohedral crystals, mp = 186.5-188 °C.

4-(3-thiophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (V)

3-Thiophene-carboxaldehyde (0.912 g; 8.14 mmol), methyl acetoacetate (1.89 g; 16.3 mmol) and 0.570 g (16.3 mmol) of concentrated ammonium hydroxide were mixed in 30 mL of methanol and refluxed for 12 h. The methanol was removed under vacuum and the residual yellow solid dissolved in acetonitrile .The solution was then dried over $MgSO_4$ and filtered. Yellow rhombohedral crystals formed upon slow evaporation of the filtrate, mp = 196-197.5 °C.

4-(5-(1,3-Benzodioxole)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (VI)

1,3-Benzodioxole-5-carboxaldehyde (2.18 g, 14.50 mmol), methyl acetoacetate (3.36 g, 29.0 mmol) and concentrated ammonium hydroxyde (1.02 g, 29.0 mmol) were mixed in methanol and allowed to reflux for 5 h. The resulting yellow solution was

concentrated under vacuum and dried over $MgSO_4$ and filtered. Upon slow evaporation of the solution, yellow rhombohedral crystals formed, mp = 196-198 °C

4-(3-Pyridyl)2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (VII)

3-Formylpyridine (1.77 g, 16.6 mmol), methyl acetoacetate (3.84 g, 33.1 mmol) and concentrated ammonium hydroxyde (1.16 g, 33.1 mmol) were mixed in methanol and heated under reflux for 5 h. The resulting yellow solution was concentrated under vacuum, dried over $MgSO_4$ and then filtered. Crystals suitable for X-Ray diffraction formed from the solution, dec ~ 220 °C.

4-(3(1-Methyl-1*H*-indole))-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (VIII)

1-Methyl-1H-indole-3-carboxaldehyde (2.25 g, 14.1 mmol), methyl acetoacetate (3.28 g, 28.2 mmol) and concentrated ammonium hydroxyde (0.985 g, 28.2 mmol) were mixed in methanol and heated under reflux for 5 h. The resulting yellow solution was concentrated by rotary evaporation, dried ($MgSO_4$) and filtered. Crystals, suitable for X-Ray diffraction, formed upon slow evaporation of the solution, mp = 187-189 °C.

4-(3-Bromo-6-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (IX)

3-Bromo-6-methoxy-benzaldehyde (2.62 g, 12.2 mmol), methyl acetoacetate (2.83 g, 24.4 mmol) and concentrated ammonium hydroxyde (0.854 g, 24.4 mmol) were mixed in methanol and allowed to reflux for 5 h. The methanol was removed under

vacuum and the residual yellow solid was dissolved in acetonitrile. The solution was then dried over $MgSO_4$ and filtered. Crystals formed from the filtrate which were suitable for X-ray diffraction, mp = 199.5-201 °C.

Triphenylphosphine oxide / 4-(4-bromo-2-thiophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) co-crystal. (X)

4-Bromo-2-thiophene-carboxaldehyde (1.24 g; 6.48 mmol), methyl acetoacetate (1.50 g; 13.0 mmol) and 0.453 g (13.0 mmol) of concentrated ammonium hydroxide were mixed in 30 mL of methanol and refluxed for 12 h. The methanol was removed under vacuum leaving a yellow solid behind.

The methyl-2,6-dimethyl-4-(4-bromo-2-thiophenyl)-1,4-dihydropyridine-3,5-dicarboxylate (1.25 g, 3.24 mmol) and triphenylphosphine oxide (0.900 g, 3.24 mmol) were mixed in toluene. The mixture was allowed to stand at room temperature until crystals formed.

4-(2,5-Dimethoxy-phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) ap-rotamer. (XI)

Ethyl-2,6-dimethyl-4-(2,5-dimethoxy-phenyl)-1,4-dihydropyridine-3,5-dicarboxylate (0.250 g, 6.43 x 10^{-4} mol), previously synthesized in this lab, and nitrobenzene (0.079 g, 6.43 x 10^{-4} mol) were mixed in ethanol. The mixture was left to evaporate slowly at room temperature until crystals appeared.

Note: Melting points were determined using a Mel-Temp capillary apparatus and are uncorrected.

Crystallography

Crystals of each compound were chosen for X-ray diffraction. A single crystal was mounted on a glass fiber held in a brass support. The brass pin was placed in a goniometer head and mounted on a Siemens P4 automated four-circle diffractometer equipped with a PC-486DX computer (Figure 7). The crystals were irradiated with molybdenum radiation at an average wavelength of 0.71073 Å (a weighted average of $k\alpha 1$ and $k\alpha 2$). Unit cell dimensions were determined using the centered angles from 25 to 50 independent strong reflections which were refined by least-squares methods using the automated procedure in XSCANS [59]. The intensity data were collected at room temperature using a variable scan rate, a θ-2θ scan mode and a scan range of 0.6° below $k\alpha_1$ and 0.6° above $k\alpha_2$ to a maximum 2θ value (normally 50.0° or the observed diffraction limit of the crystal). Backgrounds were measured at the ends of the scan range for a combined time equal to the total scan time. After every 97 reflections, the intensities of three standard reflections were remeasured to check for crystal decomposition. The raw data were corrected for Lorentz, polarization, absorption, decomposition, centering and background effects. Subsequently, redundant and space group forbidden data were removed.

Observed reflections ($F \geq 4.0\ \sigma F$) were used to arrive at the non-hydrogen atom positions by direct methods using SHELXS [60-62] Refinement of the scale factor,

positional and anisotropic thermal parameters for all atoms was carried out using either XLS (refinement on F) or SHELXL [63] (refinement on F^2) to convergence.

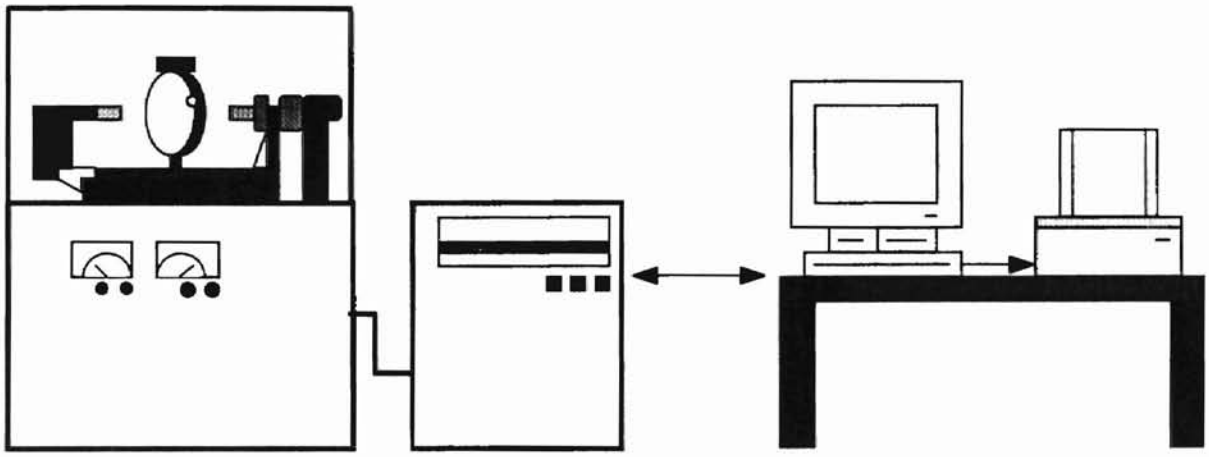


Figure 7. Schematic of Siemens P4 automated 4-circle diffractometer with PC-486DX computer and printer

Scattering factors were taken from the International Tables for Crystallography [64]. Hydrogen atom positions were calculated using idealized geometry. The profile fitting technique for data reduction was employed. A weighting scheme $\left(w = \frac{1}{\sigma^2(F) + |g|F^2} \right)$ and extinction correction were applied at the last stages of refinement. Final refinement led to the agreement factor, R_w.

Chapter IV

RESULTS AND DISCUSSION

Eleven new 1,4-dihydropyridine derivatives were synthesized, crystallized and characterized by X-ray crystallography. 4-(2-Pyrrolyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) (I), 4-(3-furyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) (II), 4-(3-bromo-2-furyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) (III), 4-(2-thiophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) (IV), 4-(3-thiophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) (V), 4-(5-(1,3-benzodioxole)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) (VI), 4-(3-pyridyl)2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) (VII), 4-(3(1-methyl-1*H*-indole))-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) (VIII), 4-(3-bromo-6-methoxy-phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) (IX) were synthesized using the Hantzsch reaction. Triphenylphosphine oxide / 4-(4-bromo-2-thiophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) co-crystal (X) and 4-(2,5-dimethoxy phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(ethoxycarbonyl) (XI) were also synthesized.

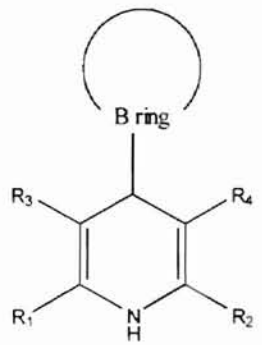
All of the DHPs investigated (Cf Table 5) contained heterocycles at C_4.

Heteroatoms included oxygen (II, III, VI and VIII), nitrogen (I and VII) and sulfur (IV, V and X) atoms. The position of these heteroatoms in the B rings varied. The rings themselves contained 5 and 6 members. Compounds III and X had, in addition, halides substituted on the heterocycles. Compounds IX and XI contained no hetero atoms but had electron pairs present on substituents on the 4-phenyl group.

There are few examples of heterocycle-subsituted (B ring) DHPs in the literature. The range of compounds studied was chosen to provide multiple views of the participation of heteroatoms in hydrogen bonding and thus receptor site bonding and the consequences of a heteroatom in the B ring on DHP conformation. Furthermore, the structures of compounds I through XI were to be examined for hydrogen bonding patterns involving carbonyl groups. Positions 2 and 6 on the A ring (Cf Figure 2) were substituted with methyl groups as the literature [65] indicates these to be necessary for optimal activity. Methyl esters were substituted at positions 3 and 5 as previous work in this lab has shown that small alkyl esters produce more potent calcium antagonists [13].

Earlier molecular modeling of dihydropyridines docking in the supposed receptor site using Sybyl [51] was limited by the inability of the program to incorporate flexibility of either the protein receptor pocket or the drug molecule. More recent programming algorithms (i.e. FLEXIDOC [53] and GOLD [54]) allow rotation about designated bonds of the drug molecule and of the receptor itself and thus a more realistic approach to *in vivo* behavior.

Table 5. Synthesized 1,4-Dihydropyridines.



Compound	R_1	R_2	R_3	R_4	B ring	B ring substituents
I	CH_3	CH_3	CO_2CH_3	CO_2CH_3	2-Pyrrolyl	
II	CH_3	CH_3	CO_2CH_3	CO_2CH_3	3-Furyl	
III	CH_3	CH_3	CO_2CH_3	CO_2CH_3	5-Furryl	2-Br
IV	CH_3	CH_3	CO_2CH_3	CO_2CH_3	2-Thiophenyl	
V	CH_3	CH_3	CO_2CH_3	CO_2CH_3	3-Thiophenyl	
VI	CH_3	CH_3	CO_2CH_3	CO_2CH_3	6-Benzodioxole	
VII	CH_3	CH_3	CO_2CH_3	CO_2CH_3	3-Pyridyl	
VIII	CH_3	CH_3	CO_2CH_3	CO_2CH_3	3-Indole	N-methyl
IX	CH_3	CH_3	CO_2CH_3	CO_2CH_3	Phenyl	2-Methoxy, 5-Br
X (co-crystal)	CH_3	CH_3	CO_2CH_3	CO_2CH_3	2-Thiophenyl	4-Br
XI	CH_3	CH_3	$CO2CH_2CH3$	$CO2CH_2CH3$	Phenyl	2,5-Dimethoxy

Unfortunately, modeling studies using this second generation software, frequently lead to inconsistencies [66]; one DHP molecule docking A ring first, another merely lying on the surface of the protein coil and other DHP molecules opting to dock at other sites entirely. These nonsensical results were consistently obtained for all of the

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compounds modeled, both those DHPs synthesized and dihydropyridines of well known activity (i.e. antagonists: nifedipine, nitrendipine and R Bay K8644; Agonist: S Bay K8644) which were chosen as standards. The relative binding energies obtained in these studies are inconsistent with activities established from *in vivo* studies and inconsistent with each other. Thus modeling was abandoned as a tool for evaluating potential potency.

This prompted the need for other approaches to the study of structure activity relationships for this class of compounds and led to a need for further understanding of the molecular recognition process.

Crystallization is a sequence of events which are, in many ways, similar to those exhibited by a drug molecule in docking to a receptor. Both processes involve a molecule orienting itself to a surface in a fashion which is dictated by the recognition and maximization of positive interactions including hydrogen bonds, dipole-dipole interactions and Van der Waals forces. The strongest of these interactions are hydrogen bonds. Therefore, in order to gain knowledge of the molecular recognition characteristics of the heterocycle containing dihydropyridine derivatives synthesized, their hydrogen bonding patterns in the crystalline state were closely examined.

The crystal structures of compounds I through XI led to the results presented in Table 6. Tabulated are the conformations of the ester carbonyl groups, details of hydrogen bonding and observed interplanar A/B ring angles.

B ring orientation:

The 4-heterocyclic and 4-substituted aryl DHPs studied show a preference for the *sp*, prow-forward, rotamer in the solid state. Two ortho-substituted derivatives, which

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have a bicyclic indole ring (VIII) and a disubstituted benzene ring at their respective C_4 positions in the molecule, adopt the *sp* conformation as does the 2,5-dimethoxyphenyl DHP (XIbis) crystallized from ethanol. This follows the well established trend observed for DHP B ring conformation. The C_4-indole derivative (VIII) does not behave like the other members of the C_4-bicyclic structures in the literature which tend to adopt the *ap* conformation [12]. The literature examples of heterocycle containing compounds adopt the *ap* conformation more often then the alternate *sp* geometry. These *ap* rotamer DHPs have benzodioxazole [24], naphthyl substituted isoxazol [22] pyridine [44], quinoxaline [20, 50] and flavone B rings [45].

This phenomenon, which contradicts empirical trends and theoretical calculations favoring the *sp* rotamer, has been attributed to crystal packing forces [106] and the increased steric inhibition of the *sp* conformation resulting from the proximity of the C_4 hydrogen and the B ring [44].

Table 6. Conformational and hydrogen bonding information for compounds I-XI.

Compound	B ring substitution / heteroatom position.	Rotamer	A/B ring interplanar angle (°)	Ester carbonyl conformation	Hydrogen bond	Hydrogen bond length (Å)	N-H-X angle (°)
VIII	Ortho and meta alkyl / β N	sp	88.5	5sp / 3sp	$N\text{-}H_1a\text{---}O_3'$	2.114	172.7
IX	Ortho methoxy and meta Br / none	sp	92.4	5ap / 3sp	$N\text{-}H_1a\text{---}O_5'$	2.162	26.1
XI	Ortho methoxy	ap	93.8	5sp / 3ap	$N\text{-}H_1a\text{---}O_3'$	2.201	163.1
XI bis	Ortho methoxy	sp	88.3	5sp / 3ap	$N\text{-}H_1a\text{---}O_3'$	1.910	163.4
III	Meta Br / α O	ap	91.4	5sp / 3ap	$N\text{-}H_1a\text{---}O_3'$	2.130	170.0
VI	Meta alkyl	sp	93.3	5sp / 3ap	$N\text{-}H_1a\text{---}O_3'$	2.138	168
X (co-crystal)	Meta Br / α sulfur	sp	79.9	5sp / 3sp	$N\text{-}H_1a\text{---}O_1$ (Phosphinyl O)	1.955	166.1
I	None / α N	sp	81.9	5sp / 3ap	$N\text{-}H_1a\text{---}O_3'$	2.141	166.6
					$N_{11}\text{-}H_{11}$(ring B)---O_5'	2.259	127.4
II	None / β O	ap	80.9	5ap / 3sp	$N\text{-}H_1a\text{---}O_5'$	2.207	160.2
IV	None / α S	sp(80%) ap(20%)	98.8	5ap / 3ap	$N\text{-}H_1a\text{---}O_3'$	2.073	160.4
V	None / β S	ap(93%) sp(7%)	98.3	5ap / 3ap	$N\text{-}H_1a\text{---}O_5'$	2.113	168.7
VII	None / β N	sp	88.5	5ap / 3sp	$N\text{-}H_1a\text{---}N_9$ (B ring)	2.133	157.5

Molecules with meta substituents also prefer the *sp* geometry with 2 of 3 molecules adopting it. The bromine substituted furan derivative (III) is seen in the *ap* geometry whereas structures VI and X with bicyclic and five membered B rings respectively have the *sp* conformation. Classification of meta bromo furan (III) DHP is complicated by the presence of a heteroatom at the alpha position in the B ring (Cf Figures 8 and 9) plus a bromine substituted at the meta position. The alpha oxygen atom present has a lone pair in the plane of the ring but the bromine has three unshared pairs of its own. It is unclear why this molecule shows an *ap* conformation. One might have expected the profusion of lone pairs on the same side of the five membered ring would lead to that side of the molecule preferring the prow forward position.

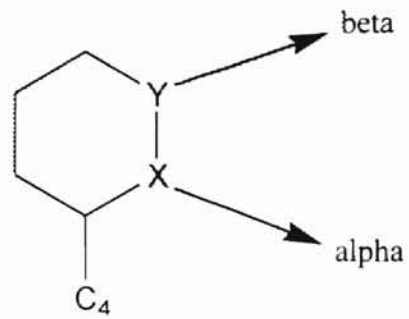


Figure 8. Alpha and beta positions on B ring.

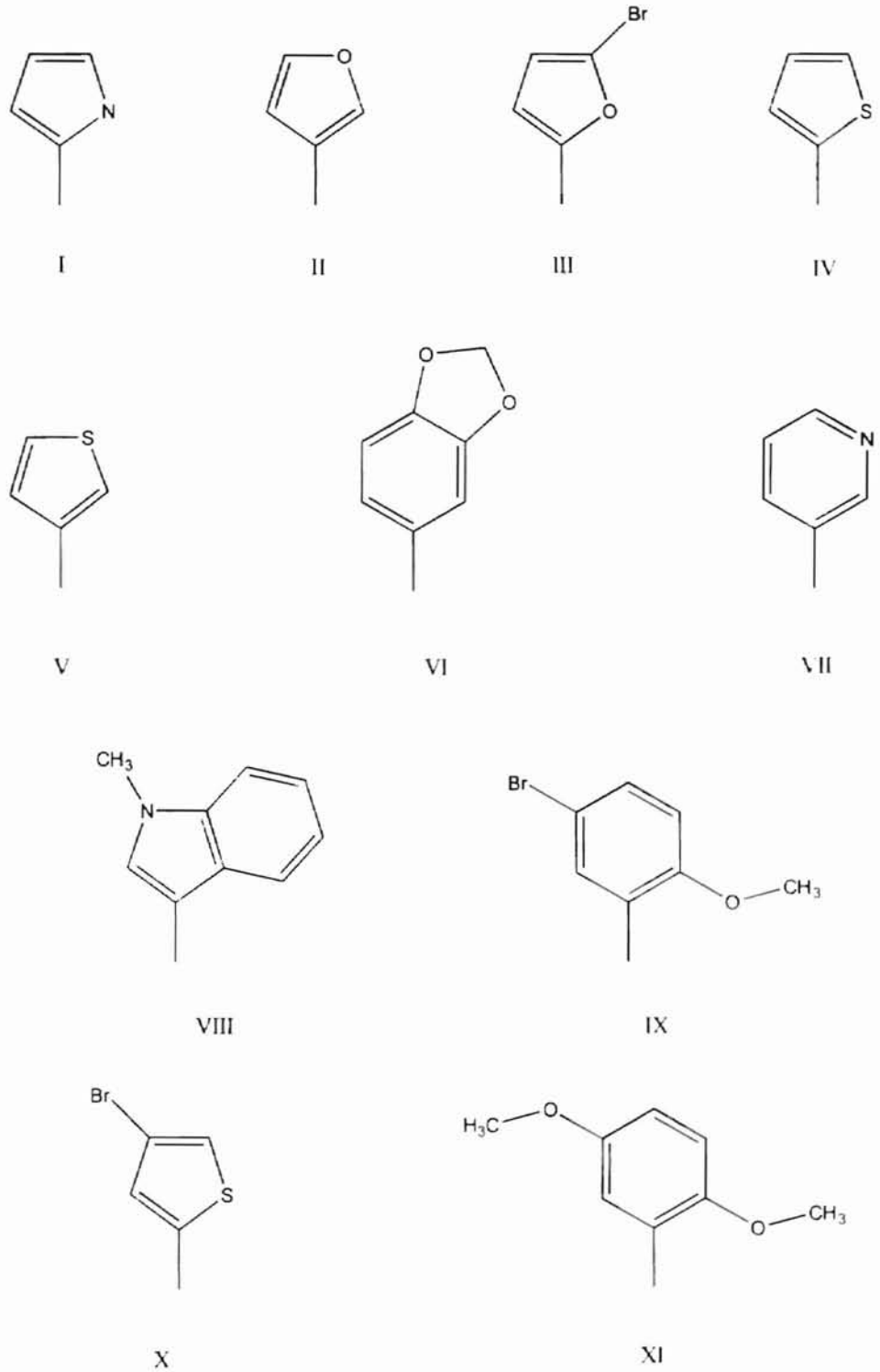
The potential importance of the position occupied in the B ring by heteroatoms has been pointed out. If the lone pairs on the oxygen, nitrogen and sulfur containing heterocycles of the DHPs synthesized are considered as substituents with unshared pairs projecting out in space, they ought to contribute to a preference for an *sp* conformation pattern where the atoms are in the prow forward position. Examination of compounds I.

II, IV, V and VII shows the two α-hetero B ring containing derivatives (I and IV), to be predominantly *sp* where as the β-hetero B ring DHPs are both *sp* and *ap*.

DHPs IV and V cannot be considered as having either totally ortho or meta-like substitutions as the sulfur position in the thiophene B rings is disordered in the solid state. In both cases there is a marked preference for a particular orientation: the thiophene in compound IV has the prow-forward conformation about 80% of the time while that of compound V, which has the sulfur in the meta position, corresponds to the folded-over conformation 97 out of 100 times.

The heterocyclic DHP derivatives in this study do not follow the conformational trend reported in the literature. They fall into the extensively documented patterns of the larger group going into the prow-forward position seen for the aryl substituted family of dihydropyridines. Considering the range of sizes of the hetero B rings in compound I-VIII and X, it is quite obvious that steric bulk of the B ring is not the controlling factor. The observed *sp* B ring conformational preference has been shown to be influenced by the bulk of the ortho and meta substituents on the B ring and also by the alpha and beta heteroatoms present in the ring, although to a lesser extent.

Figure 9. C_4 heterocycles of DHPs I-XI.



A/B ring orthogonality

The relative orientations of the A and B rings may be quantified by the interplanar angle between the plane formed by atoms C_2, C_3, C_5 and C_6 of ring A and the plane of ring B. In aryl substituted DHPs, the B ring is usually found to subtend an angle close to 90° with the base of the A ring in the solid state. This conformational characteristic has been linked to biological activity. It has been reported that the less the B ring deviates from orthogonality with the A ring, the higher the calcium antagonistic activity [27]. Langs and Triggle [35] have postulated from the results of solid state studies on dihydropyridines that ortho substituents on the B ring impose a more orthogonal relationship between A and B rings.

Compounds VIII, IX and XI have ortho substituted B rings. These DHPs have the following respective ortho substituents: benzene ring residue, methoxy and methoxy. Their average deviation from a 90° A/B ring interplanar angle is 2.35°. The meta substituted derivatives which include the two bromo thiophene containing DHPs (III and X) and the bicyclic B ring structure VI have an average angular deviation of 4.93° from orthogonality. Thus Langs and Triggle's postulate is substantiated by the compounds studied.

If the dihydropyridines synthesized are now classified according to the size of their B rings, five membered rings constituting one category, six membered and bicyclic rings making up the other, the difference in A/B ring orientation is obvious. Compounds with five membered B rings have an average deviation of 7.63° from orthogonality while the bigger six membered and bicyclic B rings have an average deviation of 2.37°. The fact that smaller five membered B rings deviate substantially more from a 90° angle with

the base of the A ring confirms the importance of steric effects in maintaining a condition of orthogonality.

Ester conformation:

In the crystal, derivatives I-VIII and X, which have heteroatom-containing B rings, prefer the {sp/ap, ap/sp} ester carbonyl conformation with 6 compounds out of 9 adopting it, all of them having carbonyl functionalities coplanar to the adjacent A ring double bond. DHP X has an sp/sp arrangement while dihydropyridines IV and V are found with the unprecedented ap/ap geometry. The crystal structures for compounds IX and XI yield respective ester conformations of 5ap/3sp and 5sp/3ap.

According to Goldmann and Stoltefuss (1991) ortho substituents on B rings enhance bias toward the most energetically favorable sp/sp arrangement of the ester carbonyls in dihydropyridines [16]. This opinion was supported by ab initio and semi-empirical calculations and studies of dihydropyridines in the crystalline state [12][17][18][67]. This was not verified by the crystal structures of the heterocyclic DHPs found in the literature and it is not verified by the structures of compounds I, III, IV and V. Of the six ortho and ortho-like substituted B ring compounds in this study, only two, the indole-substituted DHP (VIII) and the thiophene substituted DHP, co-crystallized with triphenylphosphine (X) had the (sp/sp) conformation. DHP VIII with its bulky benzene fused pyrrole B ring was a good candidate for steric restriction of the ester carbonyls to the sp/sp conformation. Molecules IV and V display the ap/ap geometry. There is but a single example in the literature (dimethyl-1,4-dihydro-2,6-dimethyl-4-[4'-(4H-4-oxo-1-benzopyran-2-yl)phenyl]-3,5-pyridine dicarboxylate) of such a

conformation being seen in the solid state for any 1,4-dihydropyridine type drug [23]. Compounds IV and V have small thiophene B rings which will diminish some of the steric interactions unfavorable to the ap/ap arrangement. However, it seems that factors other than steric ones must be at work as the literature example of an ap/ap conformation has a phenyl B ring with a very bulky bicyclic (two fused six membered rings) substituent, albeit in the para position.

Hydrogen bonding patterns

The hydrogen bonding patterns observed in the crystal structures of the compounds were tabulated (Cf Table 6). With the exception of compound VIII, all of the hydrogen bonds involving carbonyl oxygen atoms as acceptors, involve the ap oriented carbonyl group. Seven out of nine DHPs synthesized have intermolecular hydrogen bonds involving the amine hydrogen in the A ring and an ap oriented carbonyl oxygen atom of an adjacent molecule. As the molecules synthesized are symmetric, there is an almost even distribution of 5ap to 3ap carbonyl groups involved (3 (5ap) to 4 (3ap)). Triggle's prediction that steric hindrance would prevent ap carbonyl groups being involved in hydrogen bonding is not verified. Steric effects on the conformation of the compounds are seen. In 5 out of the 7 cases where ap hydrogen bonding is seen, the B ring deviates from orthogonality by twisting in the direction that minimizes steric interaction between the substituent and the ap carbonyl group. In the case of compounds I, VI and IX the B ring twists away from the hydrogen bonding carbonyl group with respective deviations of 8.1, 3.3 and 2.4 degrees from the plane bisecting the A ring and passing through C_4 and N_1. Compounds II and III in the folded-over rotameric

conformation avoid any interactions between the heteroatoms and the hydrogen bonds to the ap oriented carbonyl groups. The two thiophene substituted DHPs IV and V which both adopt the rare ap/ap conformation are less easily interpreted.

Derivative VIII shows hydrogen bonding taking place to a carbonyl group in the sp conformation. In the solid state, compound VII is involved in hydrogen bonding but the acceptor atom is not a carbonyl oxygen atom. The acceptor atom is a nitrogen atom of the B ring of an adjacent molecule.

Compound VII is the only compound which shows hydrogen bonding involving the heteroatom present in the B ring.

Thus the presence of heteroatoms in the B ring of 1,4-dihydropyridines apparently does not appreciably influence the hydrogen bonding patterns observed in the solid state for DHP molecules. Because the hydrogen bonds observed in the crystal structures of compounds I-XI involved ester carbonyl oxygens as acceptor atoms and because conformation of the carbonyl functionality participating in the hydrogen bond was, with one exception (VIII), exclusively ap, it would seem that formation of the hydrogen bond is responsible for 'turning' the conformation of the carbonyl group to ap. Sp geometry is energetically more favorable than ap and should otherwise be favored over the former.

Co-crystallization

Crystallization parallels the molecular recognition process of a ligand binding to a receptor site. However, the variety of interactions, positive or otherwise, are limited to those possible with identical neighboring molecules. Therefore co-crystallization of the

DHP with another molecule which allows the introduction of more conformational and functional variety represents a more realistic approach to mimicking the docking process.

Triphenylphosphine oxide was co-crystallized with 4-(4-bromo-2-thiophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). This resulted in the DHP adopting an *sp* rotameric orientation and an sp/sp ester carbonyl conformation while being hydrogen bonded to the phosphinyl oxygen via the dihydropyridine amine hydrogen. The DHP was never successfully crystallized independently therefore its conformational characteristics cannot be compared to those seen in the co-crystal. Nonetheless, the fact that co-crystallization of the molecule was possible illustrates the receptor-like effect of the triphenylphosphine without which the DHP did not posess enough affinity to its neighbors to allow crystallization. It was suggested that carbonyl groups would be found in sp conformation except when the carbonyl oxygen atom was involved in hydrogen bonding. Thus the co-crystallized dihydropyridine crystal structure (X) substantiates the previous observations.

An attempt at co-crystallizing 4-(2,5-dimethoxy phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(ethoxycarbonyl) and nitrobenzene from an ethanol solution yielded a surprising and unprecedented result. When crystallized alone from ethanol, the DHP (XIbis) is found as the *sp* rotamer [68]. The crystal found in the DHP-nitrobenzene mixture (XI) switched rotameric preferences to *ap*. Both rotamers crystallize with sp/sp ester conformation and show hydrogen bonding involving the same carbonyl oxygen at the 3 position. The only notable difference between derivatives XI and XIbis is in their A/B ring interplanar angle with the deviation from 90° for the *sp* compound being more

than twice that of the *ap* conformer (3.8° versus 1.7°). This result shows that varying the solution environment of crystallization influences the molecular recognition process as evidenced by the change in conformation and therefore justifies the co-crystallization approach. Altering the rotameric preference of a dihydropyridine in the solid state has not only never been seen before, but it has never been discussed. The crystal which yielded the *ap* rotamer was only found after examination of four or five crystals, the others corresponding to the previously known DHP rotamer (XIbis).

This result implies that the conclusions drawn from published solid state conformational studies may be less definitive than thought. These studies were conducted in normal fashion; assuming that the crystal chosen for crystallographic study was representative of all crystals formed. Secondly, these studies did not take into account the influence of the crystallization environment. If crystallization from ethanol gives the *sp* rotamer but crystallization from ethanol and nitrobenzene gives the *ap* isomer, what isomer would be formed in organic solvents of varying polarity (DMSO, acetone, hexane, glycine) or an aqueous solution under physiological conditions?

Conclusion

This thesis study set out to evaluate the effects of the presence of having a heteroatom in the B ring of DHPs on conformational and hydrogen bonding patterns in the solid state. Crystallization was considered to mimic the process of a drug binding to a receptor site and seen as a tool to study molecular recognition.

The presence of heteroatoms in the B ring of the DHP structures was found to contribute to the *sp* rotameric preference but to a lesser degree than ortho or meta

substitution. The molecular recognition process of hydrogen bonding was found to induce the carbonyl group involved to adopt the ap conformation. Also, the heteroatoms in the B rings did not participate in any hydrogen bonding as observed in the solid state.

This work has established that crystallization conditions can influence the conformational flexibility of 1,4-dihydropyridines and that co-crystallization can be used as an aide in evaluating molecular recognition processes.

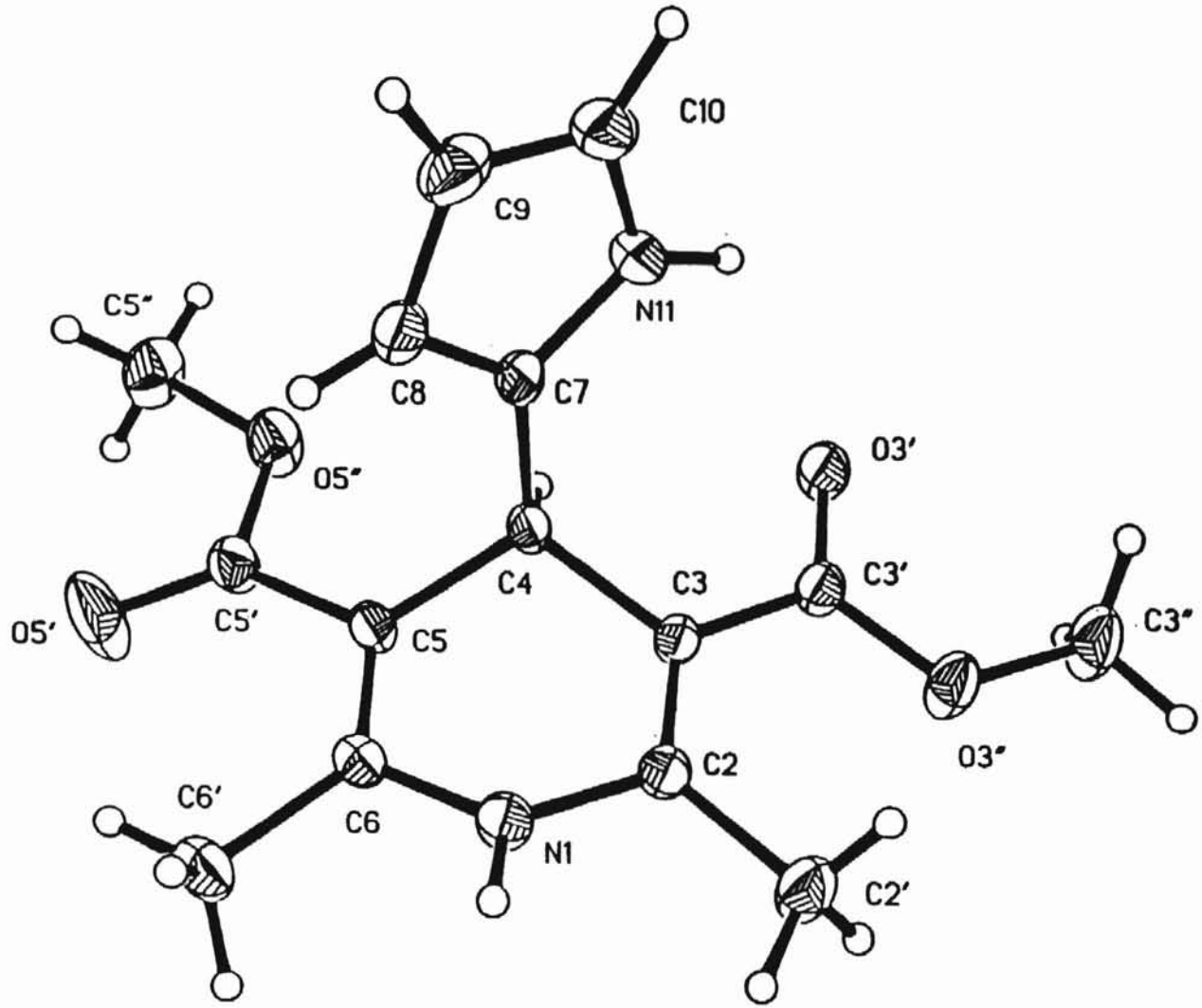


Figure 10. Projection view of 4-(2-pyrrolyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (I)

Table 7. Crystal data for 4-(2-pyrrolyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (I)

Empirical formula	$C_{15}H_{18}N_2O_4$	
Formula weight	290.3	
Temperature	301 K	
Wavelength	0.71073 Å	
Crystal system, space group	Triclinic, P1	
Unit cell dimensions	a= 7.401(4) Å	α= 65.77(4) °
	b= 7.738(5) Å	β= 65.96(3) °
	c= 7.906(5) Å	γ= 77.38(4) °
Volume	376.8(4) $Å^3$	
Z, Calculated density	1, 1.279 mg/m^3	
Absorption coefficient	0.094 mm^{-1}	
F(000)	154	
Crystal size	0.1 x 0.1 x 0.2 mm	
Theta range for data collection	1.75 to 30.0°	
Index ranges	$-1 \leq h \leq 10$, $-10 \leq k \leq 10$, $-10 \leq l \leq 11$	
Reflections collected/ unique/	2603 / 2603 (R_{int}= 0.0)	
Reflections observed	1937 ($F > 4.0\sigma$ (F))	
Goodness-of-fit	1.22	
Final R indices [I> 2 sigma (I)]	R= 5.03, wR= 5.79	
R indices (all data)	R= 0.0726, wR= 0.3591	
Extinction coefficient	-0.009(3)	
Largest diff. peak and hole	0.30 and -0.21 $eÅ^{-3}$	

Table 8. Atomic coordinates (Å) and equivalent isotropic displacement coefficients ($Å^2$) for 4-(2-pyrrolyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (I)

Atom	x	y	z	Ueq[a]
N(1)	0.4742	0.8149	0.6790	0.038(1)
C(2)	0.6517(6)	0.8896(5)	0.5347(5)	0.033(1)
C(2')	0.6348(7)	1.0103(6)	0.3352(6)	0.050(2)
C(3)	0.8163(6)	0.8490(5)	0.5867(5)	0.030(1)
C(3')	1.0070(6)	0.9329(5)	0.4614(5)	0.034(1)
C(3")	1.1961(7)	1.1572(7)	0.1540(6)	0.063(2)
O(3')	1.1528(5)	0.8871(5)	0.5102(5)	0.045(1)
O(3")	1.0107(5)	1.0690(5)	0.2855(5)	0.052(1)
C(4)	0.8082(6)	0.6943(5)	0.7885(5)	0.028(1)
C(5)	0.5988(6)	0.6880(5)	0.9427(6)	0.032(1)
C(5')	0.5739(6)	0.6073(6)	1.1569(5)	0.039(1)
C(5")	0.7422(7)	0.4844(6)	1.3866(6)	0.056(2)
O(5')	0.4209(5)	0.5747(7)	1.2948(5)	0.099(2)
O(5")	0.7466(6)	0.5728(5)	1.1827(5)	0.051(1)
C(6)	0.4403(6)	0.7369(6)	0.8824(6)	0.035(1)
C(6')	0.2238(6)	0.7182(6)	1.0085(6)	0.052(2)
C(7)	0.8773(6)	0.5004(5)	0.7696(5)	0.032(1)
C(8)	0.7746(7)	0.3405(5)	0.8473(6)	0.044(1)
C(9)	0.9116(8)	0.1992(6)	0.7796(6)	0.056(2)
C(10)	1.0883(8)	0.2762(6)	0.6645(6)	0.056(2)
N(11)	1.0692(6)	0.4597(5)	0.6589(5)	0.044(1)

a: Equivalent isotropic U defined as one third of the trace of the orthogonalized Uij tensor

Table 9. Bond lengths (Å) and angles (°) for 4-(2-pyrrolyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (I)

Bond lengths	
N(1)-C(2)	1.390(4)
N(1)-C(6)	1.397(4)
C(2)-C(2')	1.509(6)
C(2)-C(3)	1.373(7)
C(3)-C(3')	1.459(6)
C(3)-C(4)	1.539(5)
C(3')-O(3')	1.224(6)
C(3')-O(3")	1.350(5)
C(3")-O(3")	1.447(6)
C(4)-C(5)	1.528(5)
C(4)-C(7)	1.523(6)
C(5)-C(5')	1.490(6)
C(5)-C(6)	1.364(7)
C(5')-O(5')	1.195(5)
C(5')-O(5")	1.328(7)
C(5")-O(5")	1.459(6)
C(6)-C(6')	1.504(6)
C(7)-C(8)	1.375(6)
C(7)-N(11)	1.379(5)
C(8)-C(9)	1.437(6)
C(9)-C(10)	1.349(7)
C(10)-N(11)	1.380(7)

Bond angles	
C(2)-N(1)-C(6)	123.6(3)
N(1)-C(2)-C(2')	113.3(4)
N(1)-C(2)-C(3)	118.5(3)
C(2')-C(2)-C(3)	128.2(3)
C(2)-C(3)-C(3')	125.6(3)
C(2)-C(3)-C(4)	118.8(3)
C(3')-C(3)-C(4)	115.5(4)
C(3)-C(3')-O(3')	123.6(3)
C(3)-C(3')-O(3")	114.6(4)
O(3')-C(3')-O(3")	121.8(4)
C(3')-O(3")-C(3")	117.3(4)
C(3)-C(4)-C(5)	110.8(3)
C(3)-C(4)-C(7)	111.0(4)
C(5)-C(4)-C(7)	110.1(3)
C(4)-C(5)-C(5')	118.5(4)
C(4)-C(5)-C(6)	119.3(4)
C(5')-C(5)-C(6)	121.8(3)
C(5)-C(5')-O(5')	126.5(5)
C(5)-C(5')-O(5")	112.0(3)
O(5')-C(5')-O(5")	121.5(4)
C(5')-O(5")-C(5")	117.1(3)
N(1)-C(6)-C(5)	118.8(3)
N(1)-C(6)-C(6')	112.9(4)
C(5)-C(6)-C(6')	128.3(4)
C(4)-C(7)-C(8)	130.4(3)
C(4)-C(7)-N(11)	122.2(4)
C(8)-C(7)-N(11)	107.4(4)
C(7)-C(8)-C(9)	107.0(4)
C(8)-C(9)-C(10)	107.9(4)
C(9)-C(10)-N(11)	108.0(4)
C(7)-N(11)-C(10)	109.6(4)

Table 10. Atomic displacement coefficients ($Å^2$)[a] for 4-(2-pyrrolyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (I)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	0.028(1)	0.048(2)	0.037(1)	-0.007(1)	-0.016(1)	-0.008(1)
C(2)	0.029(2)	0.036(1)	0.033(1)	-0.004(1)	-0.013(1)	-0.008(1)
C(2')	0.043(2)	0.057(2)	0.041(2)	-0.009(2)	-0.022(2)	0.000(1)
C(3)	0.029(1)	0.030(1)	0.027(1)	-0.004(1)	-0.009(1)	-0.006(1)
C(3')	0.034(2)	0.037(2)	0.030(1)	-0.006(1)	-0.013(1)	-0.007(1)
C(3")	0.051(2)	0.069(2)	0.045(2)	-0.028(2)	-0.013(2)	0.010(2)
O(3')	0.030(1)	0.055(1)	0.040(1)	-0.011(1)	-0.014(1)	-0.003(1)
O(3")	0.043(1)	0.059(1)	0.040(1)	-0.021(1)	-0.018(1)	0.009(1)
C(4)	0.022(1)	0.036(1)	0.022(1)	-0.002(1)	-0.008(1)	-0.008(1)
C(5)	0.026(2)	0.037(1)	0.029(1)	-0.002(1)	-0.005(1)	-0.013(1)
C(5')	0.033(2)	0.051(2)	0.029(1)	0.001(1)	-0.010(1)	-0.013(1)
C(5")	0.064(3)	0.071(3)	0.032(2)	-0.007(2)	-0.024(2)	-0.011(2)
O(5')	0.039(2)	0.186(4)	0.032(1)	-0.005(2)	-0.001(1)	-0.014(2)
O(5")	0.044(1)	0.079(2)	0.029(1)	-0.006(1)	-0.015(1)	-0.015(1)
C(6)	0.027(2)	0.040(2)	0.034(2)	-0.002(1)	-0.009(1)	-0.012(1)
C(6')	0.028(2)	0.068(2)	0.047(2)	-0.003(2)	-0.010(2)	-0.013(2)
C(7)	0.033(2)	0.038(1)	0.022(1)	0.000(1)	-0.012(1)	-0.007(1)
C(8)	0.050(2)	0.038(2)	0.032(1)	-0.005(2)	-0.010(1)	-0.007(1)
C(9)	0.088(3)	0.036(2)	0.041(2)	0.003(2)	-0.022(2)	-0.014(1)
C(10)	0.062(3)	0.050(2)	0.041(2)	0.017(2)	-0.014(2)	-0.018(2)
N(11)	0.037(2)	0.048(1)	0.038(1)	0.007(1)	-0.008(1)	-0.016(1)

a:The anisotropic displacement exponent takes the form $-2\pi^2 (h^2 a^{*2} U_{11} + \ldots + 2hka * b * U_{12})$

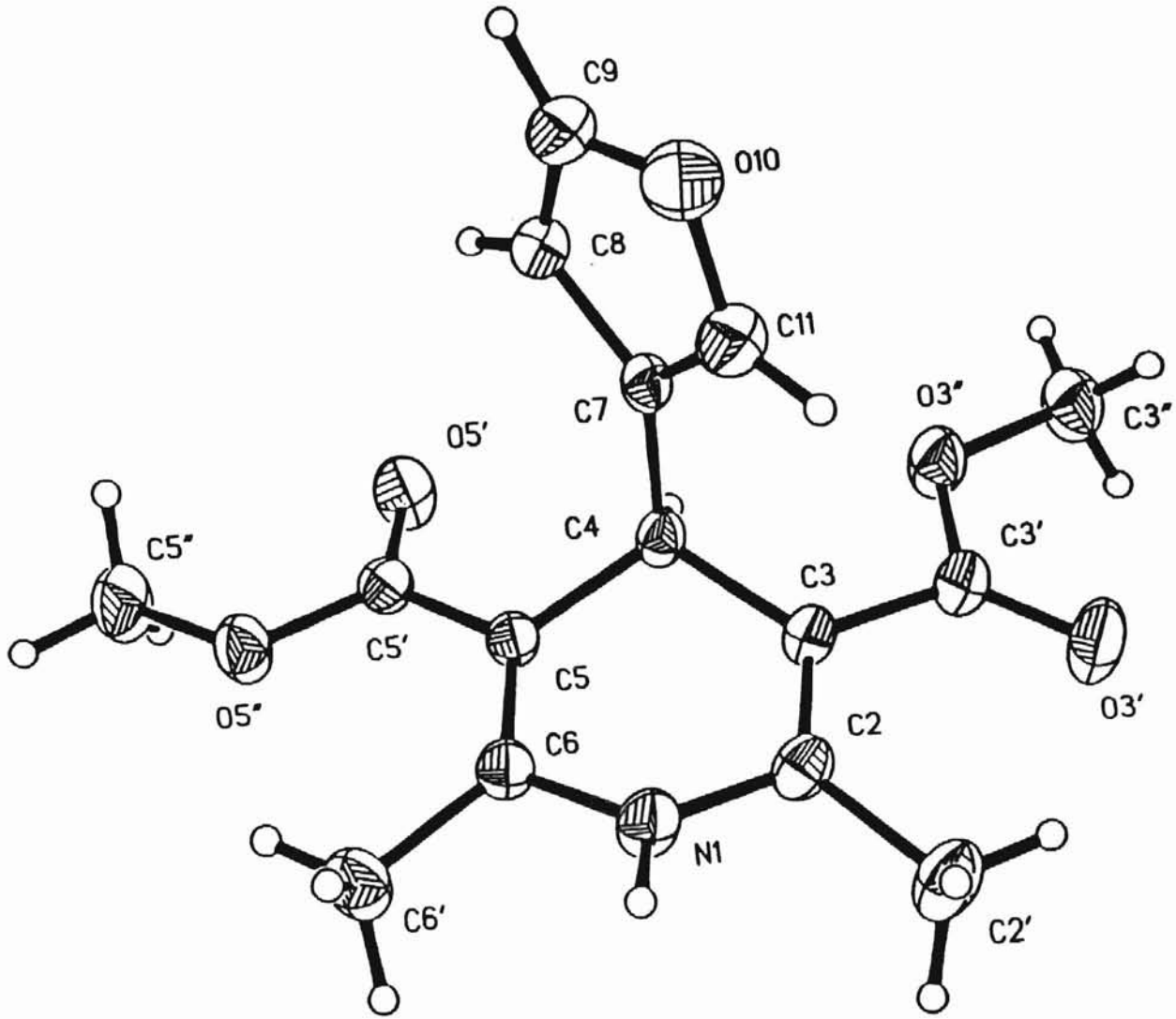


Figure 11. Projection view of 4-(3-furyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (II)

Table 11. Crystal data for 4-(3-furyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (II)

Empirical formula	$C_{15}H_{17}NO_5$	
Formula weight	291.3	
Temperature	301 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/c$	
Unit cell dimensions	a= 11.172(6) Å	α= 90.0 °
	b= 7.487(5) Å	β= 93.49(4) °
	c= 18.218(8) Å	γ= 90.0 °
Volume	1521.3(15)$Å^3$	
Z, Calculated density	4, 1.272 mg/m^3	
Absorption coefficient	0.096 mm^{-1}	
F(000)	616	
Crystal size	0.2 x 0.2 x 0.1 mm	
Theta range for data collection	1.75 to 30.0 °	
Index ranges	$-1 \leq h \leq 15, -10 \leq k \leq 1, -25 \leq l \leq 25$	
Reflections collected/ unique/	5740/ 4436 (R_{int}= 3.37)	
Reflections observed	2343 ($F > 5.0\sigma(F)$)	
Goodness-of-fit	1.48	
Final R indices [I> 2 sigma (I)]	R= 5.31, wR= 6.61	
R indices (all data)	R= 0.1043, wR= 0.0890	
Extinction coefficient	-0.0007(6)	
Largest diff. peak and hole	0.29 and -0.18e$Å^{-3}$	

Table 12 Atomic coordinates (Å) and equivalent isotropic displacement coefficients ($Å^2$) for 4-(3-furyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (II)

Atom	x	y	z	Ueq[a]
N(1)	0.6145(2)	0.1020(2)	0.4159(1)	0.048(1)
C(2)	0.7067(2)	0.0670(3)	0.4687(1)	0.043(1)
C(2')	0.7525(3)	0.2331(3)	0.5087(1)	0.062(1)
C(3)	0.7444(2)	-0.1067(3)	0.4794(1)	0.040(1)
C(3')	0.8382(2)	-0.1523(3)	0.5376(1)	0.045(1)
C(3")	0.9541(2)	-0.3909(4)	0.5936(1)	0.066(1)
O(3')	0.8905(2)	-0.0496(3)	0.5803(1)	0.076(1)
O(3")	0.8610(2)	-0.3312(2)	0.5396(1)	0.059(1)
C(4)	0.6968(2)	-0.2551(3)	0.4275(1)	0.038(1)
C(5)	0.5716(2)	-0.2072(3)	0.3932(1)	0.038(1)
C(5')	0.4973(2)	-0.3619(3)	0.3685(1)	0.041(1)
C(5")	0.3214(2)	-0.4692(4)	0.3004(2)	0.074(1)
O(5')	0.5211(2)	-0.5179(2)	0.3857(1)	0.063(1)
O(5")	0.3996(1)	-0.3214(2)	0.3242(1)	0.059(1)
C(6)	0.5387(2)	-0.0300(3)	0.3846(1)	0.041(1)
C(6')	0.4274(2)	0.0476(3)	0.3452(1)	0.058(1)
C(7)	0.7827(2)	-0.2901(3)	0.3672(1)	0.041(1)
C(8)	0.7801(2)	-0.4380(3)	0.3158(1)	0.055(1)
C(9)	0.8695(3)	-0.4109(4)	0.2711(1)	0.069(1)
O(10)	0.9309(2)	-0.2565(3)	0.2893(1)	0.073(1)
C(11)	0.8756(2)	-0.1861(4)	0.3486(1)	0.057(1)

a: Equivalent isotropic U defined as one third of the trace of the orthogonalized Uij tensor

Table 13. Bond lengths (Å) and angles (°) for 4-(3-furyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (II)

Bond lengths	
N(1)-C(2)	1.390(3)
N(1)-C(6)	1.400(3)
C(2)-C(2')	1.515(3)
C(2)-C(3)	1.377(3)
C(3)-C(3')	1.483(3)
C(3)-C(4)	1.533(3)
C(3')-O(3')	1.217(3)
C(3')-O(3")	1.364(3)
C(3")-O(3")	1.457(3)
C(4)-C(5)	1.539(3)
C(4)-C(7)	1.525(3)
C(5)-C(5')	1.479(3)
C(5)-C(6)	1.384(3)
C(5')-O(5')	1.234(3)
C(5')-O(5")	1.352(3)
C(5")-O(5")	1.460(3)
C(6)-C(6')	1.513(3)
C(7)-C(8)	1.449(3)
C(7)-C(11)	1.358(3)
C(8)-C(9)	1.342(4)
C(9)-O(10)	1.376(4)
O(10)-C(11)	1.381(3)

Bond angles	
C(2)-N(1)-C(6)	123.6(2)
N(1)-C(2)-C(2')	113.1(2)
N(1)-C(2)-C(3)	118.9(2)
C(2')-C(2)-C(3)	127.9(2)
C(2)-C(3)-C(3')	121.0(2)
C(2)-C(3)-C(4)	120.3(2)
C(3')-C(3)-C(4)	118.5(2)
C(3)-C(3')-O(3')	127.0(2)
C(3)-C(3')-O(3")	111.6(2)
O(3')-C(3')-O(3")	121.4(2)
C(3')-O(3")-C(3")	116.4(2)
C(3)-C(4)-C(5)	110.8(2)
C(3)-C(4)-C(7)	111.1(2)
C(5)-C(4)-C(7)	110.1(2)
C(4)-C(5)-C(5')	114.9(2)
C(4)-C(5)-C(6)	119.9(2)
C(5')-C(5)-C(6)	125.2(2)
C(5)-C(5')-O(5')	123.7(2)
C(5)-C(5')-O(5")	115.1(2)
O(5')-C(5')-O(5")	121.2(2)
C(5')-O(5")-C(5")	117.0(2)
N(1)-C(6)-C(5)	118.7(2)
N(1)-C(6)-C(6')	112.4(2)
C(5)-C(6)-C(6')	128.8(2)
C(4)-C(7)-C(8)	127.5(2)
C(4)-C(7)-C(11)	127.3(2)
C(8)-C(7)-C(11)	105.2(2)
C(7)-C(8)-C(9)	106.9(2)
C(8)-C(9)-O(10)	111.0(2)
C(9)-O(10)-C(11)	105.6(2)
C(7)-C(11)-O(10)	111.2(2)

Table 14. Anisotropic displacement coefficients ($Å^2$)[a] for 4-(3-furyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (II)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	0.060(1)	0.029(1)	0.055(1)	-0.003(1)	-0.007(1)	0.002(1)
C(2)	0.053(1)	0.034(1)	0.042(1)	-0.007(1)	0.002(1)	-0.001(1)
C(2')	0.082(2)	0.040(1)	0.062(1)	-0.011(1)	-0.008(1)	-0.006(1)
C(3)	0.045(1)	0.037(1)	0.037(1)	-0.005(1)	-0.003(1)	-0.002(1)
C(3')	0.051(1)	0.045(1)	0.038(1)	-0.005(1)	-0.003(1)	-0.001(1)
C(3")	0.065(1)	0.071(2)	0.059(1)	0.009(1)	-0.019(1)	0.005(1)
O(3')	0.090(1)	0.062(1)	0.072(1)	-0.008(1)	-0.037(1)	-0.010(1)
O(3")	0.069(1)	0.050(1)	0.055(1)	0.007(1)	-0.023(1)	0.001(1)
C(4)	0.043(1)	0.030(1)	0.038(1)	-0.002(1)	-0.007(1)	0.000(1)
C(5)	0.039(1)	0.033(1)	0.040(1)	0.000(1)	-0.002(1)	0.000(1)
C(5')	0.041(1)	0.037(1)	0.045(1)	-0.002(1)	0.001(1)	-0.002(1)
C(5")	0.058(1)	0.067(2)	0.092(2)	-0.015(1)	-0.022(1)	-0.017(2)
O(5')	0.064(1)	0.034(1)	0.088(1)	-0.006(1)	-0.019(1)	0.004(1)
O(5")	0.052(1)	0.046(1)	0.078(1)	-0.003(1)	-0.021(1)	-0.008(1)
C(6)	0.045(1)	0.034(1)	0.043(1)	-0.001(1)	-0.001(1)	0.002(1)
C(6')	0.055(1)	0.043(1)	0.076(2)	0.005(1)	-0.012(1)	0.003(1)
C(7)	0.042(1)	0.042(1)	0.038(1)	0.005(1)	-0.009(1)	0.000(1)
C(8)	0.053(1)	0.058(2)	0.051(1)	0.005(1)	-0.006(1)	-0.013(1)
C(9)	0.068(2)	0.091(2)	0.048(1)	0.017(2)	-0.002(1)	-0.017(1)
O(10)	0.065(1)	0.095(2)	0.060(1)	-0.004(1)	0.015(1)	-0.003(1)
C(11)	0.061(1)	0.059(2)	0.052(1)	-0.003(1)	0.004(1)	-0.003(1)

a:The anisotropic displacement exponent takes the form: $-2\pi^2 (h^2 a^{*2} U_{11} + \ldots + 2hka * b * U_{12})$

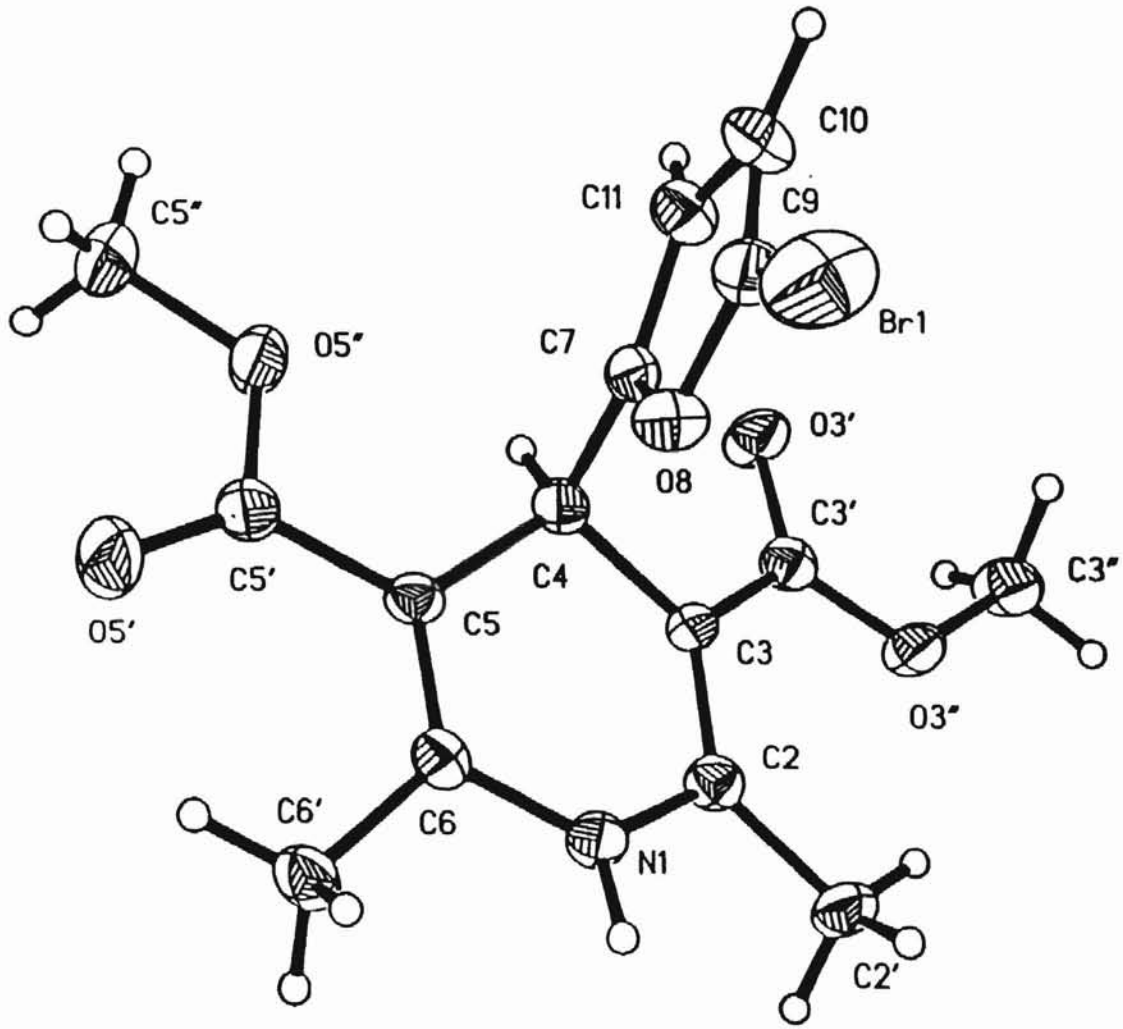


Figure 12. Projection view of 4-(3-bromo-2-furyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (III)

Table 15. Crystal data for 4-(3-bromo-2-furyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (III)

Empirical formula	$C_{15}H_{16}BrNO_5$	
Formula weight	370.2	
Temperature	301 K	
Wavelength	0.71073 Å	
Crystal system, space group	Triclinic, P1 bar	
Unit cell dimensions	a= 7.526(4) Å	α= 103.19(3) °
	b= 10.626(6) Å	β= 103.52(5) °
	c= 11.845(6) Å	γ= 109.27(4) °
Volume	820.3(8)Å^3	
Z, Calculated density	2, 1.499 mg/m^3	
Absorption coefficient	2.527 mm^{-1}	
F(000)	376	
Crystal size	0.2 x 0.2 x 0.1 mm	
Theta range for data collection	1.75 to 30.0 °	
Index ranges	$-10 \leq h \leq 1$, $-13 \leq k \leq 14$, $-16 \leq l \leq 16$	
Reflections collected/ unique/	5571/ 4607 (R_{int}= 3.26)	
Reflections observed	1926 ($F > 4.5\sigma$ (F))	
Goodness-of-fit	1.56	
Final R indices [I> 2 sigma (I)]	R= 5.98, wR= 6.92	
R indices (all data)	R= 0.1398, wR= 0.0894	
Extinction coefficient	-0.0013	
Largest diff. peak and hole	0.80 and -0.55 eÅ^{-3}	

Table 16. Atomic coordinates (Å) and equivalent isotropic displacement coefficients ($Å^2$) for 4-(3-bromo-2-furyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (III)

Atom	x	y	z	Ueq[a]
N(1)	0.8259(6)	0.7670(4)	0.9396(4)	0.040(2)
C(2)	0.6993(7)	0.7265(5)	1.0054(4)	0.038(2)
C(2')	0.7871(8)	0.6855(6)	1.1110(5)	0.052(3)
C(3)	0.5118(7)	0.7325(5)	0.9706(4)	0.035(2)
C(3')	0.3655(7)	0.7041(5)	1.0350(4)	0.039(2)
C(3")	0.2615(8)	0.6178(7)	1.1887(5)	0.060(3)
O(3')	0.2066(5)	0.7205(4)	1.0051(3)	0.055(2)
O(3")	0.4111(5)	0.6551(4)	1.1281(3)	0.052(2)
C(4)	0.4394(7)	0.7610(5)	0.8506(4)	0.036(2)
C(5)	0.6155(7)	0.8477(5)	0.8172(4)	0.035(2)
C(5')	0.5800(8)	0.9266(6)	0.7330(5)	0.044(2)
C(5")	0.3283(10)	0.9881(7)	0.6230(6)	0.074(4)
O(5')	0.6953(6)	0.9912(5)	0.6887(4)	0.076(3)
O(5")	0.3877(5)	0.9166(4)	0.7049(4)	0.060(2)
C(6)	0.7980(7)	0.8391(5)	0.8576(4)	0.037(2)
C(6')	0.9846(7)	0.9034(5)	0.8242(5)	0.044(2)
C(7)	0.2998(7)	0.6255(5)	0.7482(4)	0.038(2)
O(8)	0.3894(5)	0.5433(4)	0.6942(3)	0.049(2)
C(9)	0.2342(9)	0.4246(6)	0.6088(5)	0.052(3)
Br(1)	0.3035(1)	0.2937(1)	0.5122(1)	0.091(1)
C(10)	0.0553(10)	0.4261(6)	0.6064(5)	0.061(3)
C(11)	0.0966(8)	0.5554(6)	0.6967(5)	0.054(3)

a. Equivalent isotropic U defined as one third of the trace of the orthogonalized Uij tensor

Table 17. Bond lengths (Å) and angles (°) for 4-(3-bromo-2-furyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (III)

Bond lengths	
N(1)-C(2)	1.389(7)
N(1)-C(6)	1.387(7)
C(2)-C(2')	1.498(9)
C(2)-C(3)	1.401(8)
C(3)-C(3')	1.472(8)
C(3)-C(4)	1.533(7)
C(3')-O(3')	1.247(7)
C(3')-O(3")	1.344(7)
C(3")-O(3")	1.468(8)
C(4)-C(5)	1.539(7)
C(4)-C(7)	1.502(5)
C(5)-C(5')	1.474(8)
C(5)-C(6)	1.386(8)
C(5')-O(5')	1.218(8)
C(5')-O(5")	1.368(7)
C(5")-O(5")	1.440(10)
C(6)-C(6')	1.531(8)
C(7)-O(8)	1.400(7)
C(7)-C(11)	1.367(7)
O(8)-C(9)	1.368(5)
C(9)-Br(1)	1.883(7)
C(9)-C(10)	1.345(10)
C(10)-C(11)	1.422(8)

Bond angles	
C(2)-N(1)-C(6)	124.3(5)
N(1)-C(2)-C(2')	114.1(5)
N(1)-C(2)-C(3)	118.5(5)
C(2')-C(2)-C(3)	127.4(5)
C(2)-C(3)-C(3')	125.9(5)
C(2)-C(3)-C(4)	119.4(5)
C(3')-C(3)-C(4)	114.6(4)
C(3)-C(3')-O(3')	123.2(5)
C(3)-C(3')-O(3")	115.6(5)
O(3')-C(3')-O(3")	121.1(5)
C(3')-O(3")-C(3")	116.5(5)
C(3)-C(4)-C(5)	111.6(4)
C(3)-C(4)-C(7)	110.9(4)
C(5)-C(4)-C(7)	112.5(4)
C(4)-C(5)-C(5')	119.0(5)
C(4)-C(5)-C(6)	119.1(5)
C(5')-C(5)-C(6)	121.6(5)
C(5)-C(5')-O(5')	128.3(6)
C(5)-C(5')-O(5")	110.4(5)
O(5')-C(5')-O(5")	121.3(6)
C(5')-O(5")-C(5")	117.4(5)
N(1)-C(6)-C(5)	119.5(5)
N(1)-C(6)-C(6')	112.9(5)
C(5)-C(6)-C(6')	127.6(5)
C(4)-C(7)-O(8)	116.1(4)
C(4)-C(7)-C(11)	134.6(6)
O(8)-C(7)-C(11)	109.2(4)
C(7)-O(8)-C(9)	105.3(4)
O(8)-C(9)-Br(1)	116.4(5)
O(8)-C(9)-C(10)	112.2(5)
Br(1)-C(9)-C(10)	131.4(4)
C(9)-C(10)-C(11)	105.9(5)
C(7)-C(11)-C(10)	107.4(6)

Table 18. Anisotropic displacement coefficients ($Å^2$)[a] for 4-(3-bromo-2-furyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (III)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	0.031(2)	0.049(2)	0.053(2)	0.023(2)	0.021(2)	0.024(2)
C(2)	0.032(3)	0.040(3)	0.044(3)	0.019(2)	0.014(2)	0.012(2)
C(2')	0.034(3)	0.071(4)	0.065(3)	0.029(3)	0.016(3)	0.037(3)
C(3)	0.030(3)	0.036(3)	0.039(2)	0.016(2)	0.009(2)	0.015(2)
C(3')	0.032(3)	0.044(3)	0.043(3)	0.016(2)	0.014(2)	0.016(2)
C(3")	0.039(3)	0.095(5)	0.059(3)	0.025(3)	0.026(3)	0.044(3)
O(3')	0.039(2)	0.088(3)	0.067(2)	0.040(2)	0.027(2)	0.046(2)
O(3")	0.035(2)	0.086(3)	0.059(2)	0.030(2)	0.025(2)	0.047(2)
C(4)	0.028(3)	0.041(3)	0.044(3)	0.018(2)	0.016(2)	0.016(2)
C(5)	0.029(3)	0.036(3)	0.040(2)	0.015(2)	0.010(2)	0.012(2)
C(5')	0.036(3)	0.045(3)	0.054(3)	0.018(3)	0.016(3)	0.020(2)
C(5")	0.062(4)	0.084(5)	0.093(5)	0.031(4)	0.020(4)	0.062(4)
O(5')	0.054(3)	0.107(4)	0.102(3)	0.037(3)	0.043(3)	0.076(3)
O(5")	0.047(2)	0.079(3)	0.081(3)	0.033(2)	0.029(2)	0.057(2)
C(6)	0.034(3)	0.033(3)	0.041(2)	0.012(2)	0.015(2)	0.009(2)
C(6')	0.035(3)	0.047(3)	0.057(3)	0.017(3)	0.022(2)	0.021(2)
C(7)	0.033(3)	0.044(3)	0.040(2)	0.015(2)	0.014(2)	0.021(2)
O(8)	0.041(2)	0.054(2)	0.046(2)	0.021(2)	0.008(2)	0.010(2)
C(9)	0.052(4)	0.044(3)	0.044(3)	0.012(3)	0.002(3)	0.012(2)
Br(1)	0.111(1)	0.079(1)	0.064(1)	0.051(1)	0.006(1)	-0.003(1)
C(10)	0.043(4)	0.049(3)	0.062(3)	-0.003(3)	0.001(3)	0.016(3)
C(11)	0.034(3)	0.060(4)	0.061(3)	0.009(3)	0.015(3)	0.025(3)

a:The anisotropic displacement exponent takes the form: $-2\pi^2 (h^2 a^{*2} U_{11} + \ldots + 2hka^* b^* U_{12})$

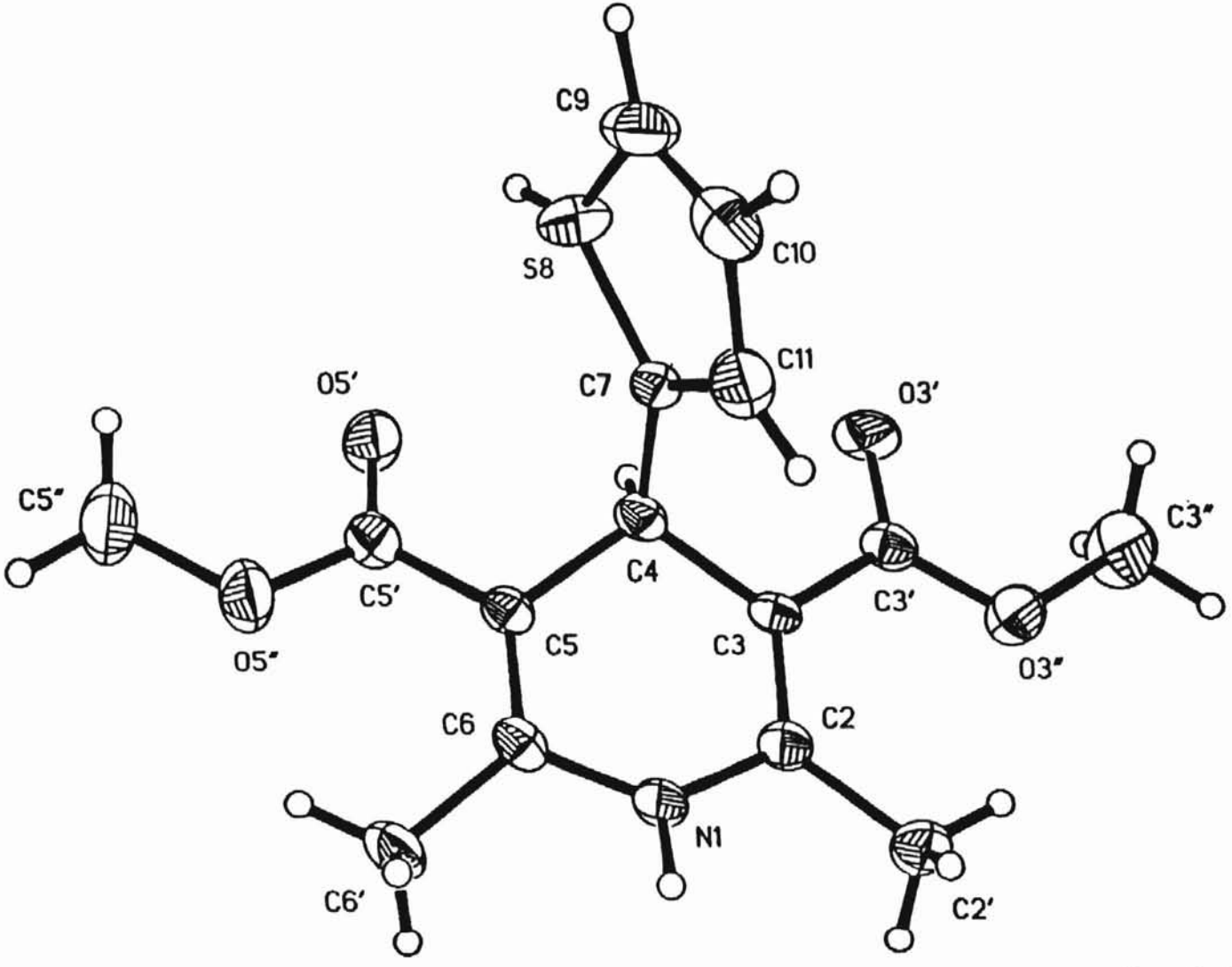


Figure 13. Projection view of 4-(2-thiophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (IV)

Table 19. Crystal data for 4-(2-thiophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (IV)

Empirical formula	$C_{15}H_{17}NO_4S$	
Formula weight	307.4	
Temperature	301 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/c$	
Unit cell dimensions	a= 10.428(5) Å	α= 90.00 °
	b= 10.273(5) Å	β= 98.13(4) °
	c= 14.799(9) Å	γ= 90.00 °
Volume	1568.7(14) $Å^3$	
Z, Calculated density	4, 1.301 mg/m^3	
Absorption coefficient	0.220 mm^{-1}	
F(000)	648	
Crystal size	0.2 x 0.2 x 0.3 mm	
Theta range for data collection	1.75 to 30.0 °	
Index ranges	$-1 \leq h \leq 14$, $-1 \leq k \leq 14$, $-20 \leq l \leq 20$	
Reflections collected/ unique/	5808 / 4583 (R_{int}= 4.27)	
Reflections observed	2102 ($F > 5.0\sigma$ (F))	
Goodness-of-fit	1.44	
Final R indices [I> 2 sigma (I)]	R= 0.0588, wR= 0.0711	
R indices (all data)	R= 0.1224, wR= 0.0884	
Extinction coefficient	-0.0011(3)	
Largest diff. peak and hole	0.52 and –0.20 $eÅ^{-3}$	

Table 20. Atomic coordinates (Å) and equivalent isotropic displacement coefficients ($Å^2$) for 4-(2-thiophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (IV).

Atom	x	y	z	Ueq[a]	Occupancy
N(1)	0.0826(3)	0.1943(3)	0.3924(2)	0.044(1)	
C(2)	0.0119(3)	0.2568(3)	0.4523(2)	0.037(1)	
C(2')	-0.0910(3)	0.3451(3)	0.4040(2)	0.052(1)	
C(3)	0.0419(3)	0.2340(3)	0.5441(2)	0.034(1)	
C(3')	-0.0283(3)	0.2874(3)	0.6158(2)	0.041(1)	
C(3")	-0.1914(4)	0.4220(5)	0.6604(3)	0.084(2)	
O(3')	0.0011(2)	0.2572(3)	0.6971(1)	0.058(1)	
O(3")	-0.1248(2)	0.3696(3)	0.5890(1)	0.061(1)	
C(4)	0.1599(3)	0.1544(3)	0.5812(2)	0.037(1)	
C(5)	0.2023(3)	0.0654(3)	0.5072(2)	0.036(1)	
C(5')	0.2839(3)	-0.0439(3)	0.5443(2)	0.044(1)	
C(5")	0.4379(4)	-0.2042(4)	0.5181(3)	0.080(2)	
O(5')	0.2943(2)	-0.0786(2)	0.6241(2)	0.061(1)	
O(5")	0.3499(3)	-0.1027(3)	0.4837(2)	0.070(1)	
C(6)	0.1670(3)	0.0924(3)	0.4166(2)	0.039(1)	
C(6')	0.2064(3)	0.0233(4)	0.3342(2)	0.056(1)	
C(7)	0.2707(3)	0.2434(3)	0.6202(2)	0.039(1)	
S(8)	0.3830(1)	0.2014(1)	0.7113(1)	0.063(1)	0.8069
C(8)	0.3830(1)	0.2014(1)	0.7113(1)	0.063(1)	0.1931
C(9)	0.4647(4)	0.3423(5)	0.7090(3)	0.071(2)	
C(10)	0.4127(4)	0.4210(4)	0.6422(3)	0.066(1)	
S(11)	0.2989(2)	0.3731(3)	0.5839(2)	0.069(1)	0.1931
C(11)	0.2989(2)	0.3731(3)	0.5839(2)	0.069(1)	0.8069

a: Equivalent isotropic U defined as the one third of the trace of the orthogonalized Uij tensor

Table 21. Bond lengths (Å) and angles (°) for 4-(2-thiophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (IV)

Bond lengths	
N(1)-C(2)	1.388(4)
N(1)-C(6)	1.383(4)
C(2)-C(2')	1.506(4)
C(2)-C(3)	1.372(4)
C(3)-C(3')	1.476(4)
C(3)-C(4)	1.514(4)
C(3')-O(3')	1.239(4)
C(3')-O(3")	1.330(4)
C(3")-O(3")	1.448(5)
C(4)-C(5)	1.539(4)
C(4)-C(7)	1.521(4)
C(5)-C(5')	1.467(4)
C(5)-C(6)	1.368(4)
C(5')-O(5')	1.224(4)
C(5')-O(5")	1.348(4)
C(5")-O(5")	1.434(5)
C(6)-C(6')	1.517(5)
C(7)-[S(8),C(8)]	1.711(3)
C(7)-[S(11),C(11)]	1.481(4)
C(7)-C(11)	1.481(4)
[S(8),C(8)]-C(9)	1.683(5)
C(9)-C(10)	1.332(6)
C(10)-[S(11),C(11)]	1.451(4)

Bond angles	
C(2)-N(1)-C(6)	124.1(2)
N(1)-C(2)-C(2')	112.5(2)
N(1)-C(2)-C(3)	119.1(3)
C(2')-C(2)-C(3)	128.4(3)
C(2)-C(3)-C(3')	125.6(3)
C(2)-C(3)-C(4)	120.7(3)
C(3')-C(3)-C(4)	113.6(2)
C(3)-C(3')-O(3')	121.7(3)
C(3)-C(3')-O(3")	117.0(2)
O(3')-C(3')-O(3")	121.4(3)
C(3')-O(3")-C(3")	116.1(3)
C(3)-C(4)-C(5)	111.3(2)
C(3)-C(4)-C(7)	110.4(2)
C(5)-C(4)-C(7)	110.3(2)
C(4)-C(5)-C(5')	113.5(2)
C(4)-C(5)-C(6)	120.8(3)
C(5')-C(5)-C(6)	125.7(3)
C(5)-C(5')-O(5')	123.5(3)
C(5)-C(5')-O(5")	114.7(3)
O(5')-C(5')-O(5")	121.8(3)
C(5')-O(5")-C(5")	116.9(3)
N(1)-C(6)-C(5)	118.8(3)
N(1)-C(6)-C(6')	112.3(2)
C(5)-C(6)-C(6')	128.9(3)
C(4)-C(7)-[S(8),C(8)]	123.1(2)
C(4)-C(7)-[S(11),C(11)]	125.6(2)
[S(8),C(8)]-C(7)-S(11)	111.3(2)
[S(8),C(8)]-C(7)-C(11)	111.3(2)
C(7)-[S(8),C(8)]-C(9)	93.4(2)
[S(8),C(8)]-C(9)-C(10)	112.6(3)
C(9)-C(10)-[S(11),C(11)]	116.6(4)
C(7)-[S(11),C(11)]-C(10)	106.1(3)

Table 22. Anisotropic displacement coefficients ($Å^2$)[a] for 4-(2-thiophenyl)-2,6-dimethyl 1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (IV)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	0.060(2)	0.052(2)	0.021(1)	0.010(1)	0.009(1)	0.002(1)
C(2)	0.042(2)	0.043(2)	0.027(1)	-0.001(1)	0.006(1)	0.000(1)
C(2')	0.059(2)	0.063(2)	0.033(2)	0.010(2)	0.007(1)	0.004(2)
C(3)	0.038(2)	0.041(2)	0.023(1)	-0.005(1)	0.005(1)	-0.003(1)
C(3')	0.039(2)	0.052(2)	0.031(1)	-0.005(2)	0.008(1)	-0.006(1)
C(3")	0.071(3)	0.122(4)	0.064(2)	0.032(3)	0.033(2)	-0.009(3)
O(3')	0.060(1)	0.088(2)	0.026(1)	0.004(1)	0.011(1)	-0.003(1)
O(3")	0.056(1)	0.089(2)	0.040(1)	0.025(1)	0.018(1)	0.000(1)
C(4)	0.047(2)	0.042(2)	0.023(1)	-0.001(1)	0.006(1)	-0.002(1)
C(5)	0.044(2)	0.036(2)	0.029(1)	-0.003(1)	0.008(1)	0.000(1)
C(5')	0.048(2)	0.042(2)	0.042(2)	-0.002(2)	0.008(1)	-0.001(1)
C(5")	0.079(3)	0.083(3)	0.082(3)	0.036(2)	0.019(2)	0.001(2)
O(5')	0.077(2)	0.065(2)	0.043(1)	0.021(1)	0.011(1)	0.014(1)
O(5")	0.084(2)	0.075(2)	0.053(1)	0.034(2)	0.020(1)	0.002(1)
C(6)	0.050(2)	0.040(2)	0.028(1)	-0.003(1)	0.011(1)	-0.005(1)
C(6')	0.081(2)	0.058(2)	0.031(2)	0.011(2)	0.013(2)	-0.006(2)
C(7)	0.042(2)	0.048(2)	0.028(1)	0.005(1)	0.002(1)	-0.005(1)
S(8)	0.060(1)	0.079(1)	0.044(1)	-0.004(1)	-0.014(1)	0.004(1)
C(8)	0.060(1)	0.079(1)	0.044(1)	-0.004(1)	-0.014(1)	0.004(1)
C(9)	0.051(2)	0.101(3)	0.057(2)	-0.009(2)	-0.003(2)	-0.027(2)
C(10)	0.065(2)	0.064(2)	0.072(3)	-0.010(2)	0.019(2)	-0.0.20(2)
S(11)	0.057(2)	0.066(2)	0.080(2)	0.005(1)	0.004(1)	-0.019(1)
C(11)	0.057(2)	0.066(2)	0.080(2)	0.005(1)	0.004(1)	-0.019(1)

a: The anisotropic displacement exponent takes the form: $-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2hka^*b^*U_{12})$

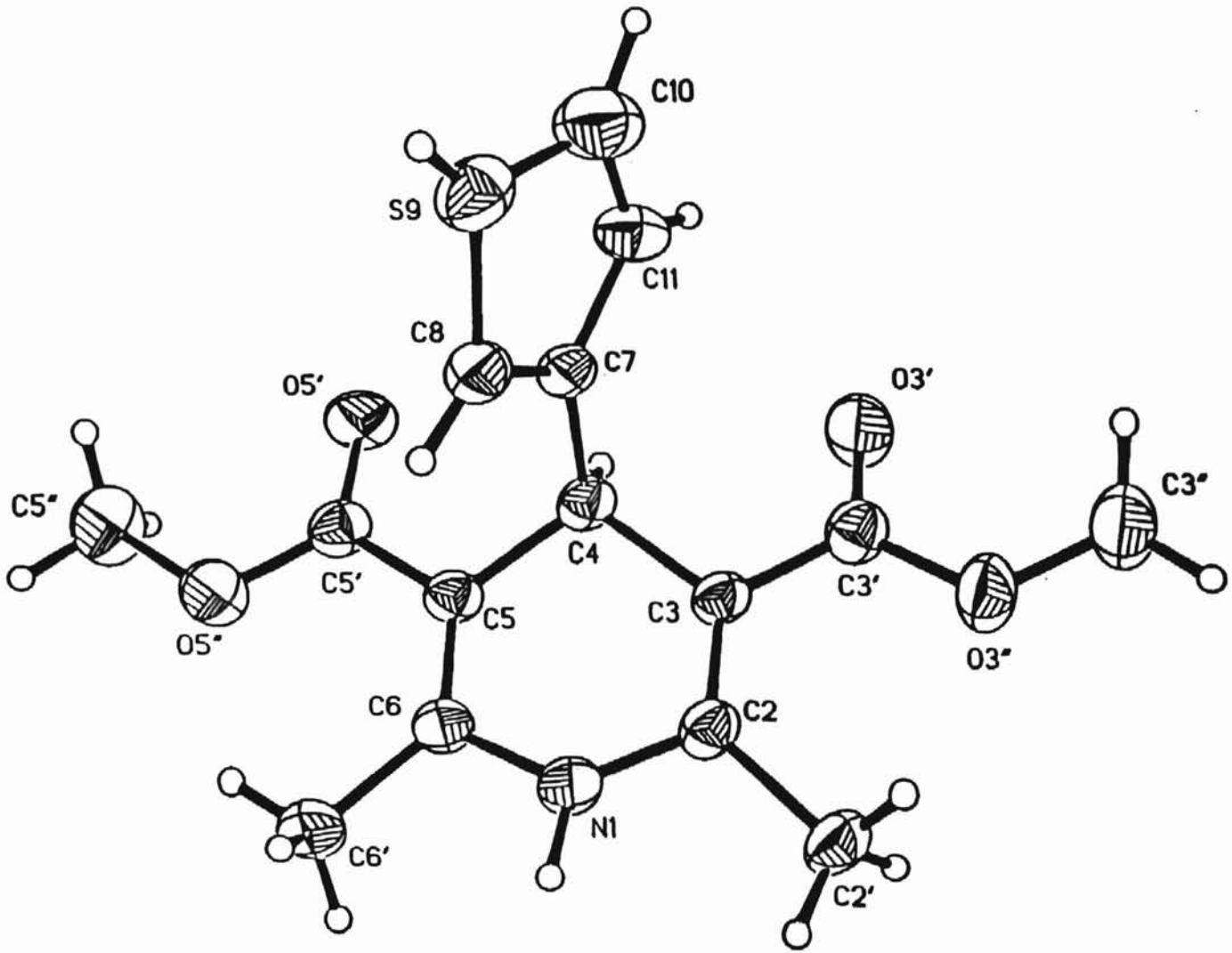


Figure 14. Projection view of 4-(3-thiophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (V)

Table 23. Crystal data for 4-(3-thiophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (V)

Empirical formula	$C_{15}H_{17}NO_4S$	
Formula weight	307.4	
Temperature	301 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/c$	
Unit cell dimensions	a= 10.67(2) Å	α= 90.00 °
	b= 10.39(2) Å	β= 98.30(0) °
	c= 15.03(4) Å	γ= 90.00 °
Volume	1649(9) $Å^3$	
Z, Calculated density	4, 1.238 mg/m^3	
Absorption coefficient	0.210 mm^{-1}	
F(000)	648	
Crystal size	0.1 x 0.2 x 0.1mm	
Theta range for data collection	1.75 to 30.0 °	
Index ranges	$-1 \leq h \leq 14$, $-14 \leq k \leq 1$, $-21 \leq l \leq 21$	
Reflections collected/ unique/	5937 / 4749 (R_{int}= 0.032)	
Reflections observed	1804 ($F > 4.5\sigma$ (F))	
Goodness-of-fit	1.81	
Final R indices [I> 2 sigma (I)]	R= 0.0633, wR= 0.079	
R indices (all data)	R= 0.1834, wR= 0.5464	
Extinction coefficient	0.0033(10)	
Largest diff. peak and hole	0.23 and –0.37 $eÅ^{-3}$	

Table 24. Atomic coordinates (Å) and equivalent isotropic displacement coefficients ($Å^2$) for 4-(3-thiophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl. (V)

Atom	x	y	z	Ueq[a]	Occupancy
N(1)	0.5856(3)	0.3060(3)	-0.1062(2)	0.058(1)	
C(2)	0.6704(3)	0.4070(3)	-0.0814(2)	0.054(1)	
C(2')	0.7089(4)	0.4779(4)	-0.1637(2)	0.071(2)	
C(3)	0.7069(3)	0.4328(3)	0.0095(2)	0.049(1)	
C(3')	0.7885(3)	0.5412(3)	0.0464(3)	0.057(1)	
C(3")	0.9407(4)	0.7033(4)	0.0202(3)	0.092(2)	
O(3')	0.8024(3)	0.5747(2)	0.1271(2)	0.078(1)	
O(3")	0.8526(3)	0.6027(3)	-0.0139(2)	0.083(1)	
C(4)	0.6651(3)	0.3415(3)	0.0825(2)	0.050(1)	
C(5)	0.5446(3)	0.2649(3)	0.0451(2)	0.048(1)	
C(5')	0.4743(3)	0.2120(3)	0.1170(3)	0.055(1)	
C(5")	0.3103(4)	0.0778(5)	0.1617(3)	0.097(2)	
O(5')	0.5046(2)	0.2410(3)	0.1985(2)	0.073(1)	
O(5")	0.3774(2)	0.1306(3)	0.0900(2)	0.075(1)	
C(6)	0.5123(3)	0.2439(3)	-0.0472(2)	0.051(1)	
C(6')	0.4079(3)	0.1591(3)	-0.0953(2)	0.066(1)	
C(7)	0.7757(3)	0.2506(3)	0.1199(2)	0.052(1)	
C(8)	0.7943(3)	0.1293(3)	0.0847(3)	0.063(1)	
S(9)	0.9277(1)	0.0528(1)	0.1420(1)	0.079(1)	0.9325
C(9)	0.9277(1)	0.0528(1)	0.1420(1)	0.079(1)	0.0675
C(10)	0.9627(4)	0.1830(4)	0.2120(3)	0.101(2)	0.0675
S(10)	0.9627(4)	0.1830(4)	0.2120(3)	0.101(2)	0.9325
C(11)	0.8737(3)	0.2806(4)	0.1939(2)	0.070(1)	

a: Equivalent isotropic U defined as the one third of the trace of the orthogonalized Vij tensor

Table 25. Bond lengths (Å) and angles (°) for 4-(3-thiophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (V)

Bond lengths	
N(1)-C(2)	1.401(5)
N(1)-C(6)	1.419(6)
C(2)-C(2')	1.546(6)
C(2)-C(3)	1.391(6)
C(3)-C(3')	1.482(6)
C(3)-C(4)	1.564(6)
C(3')-O(3')	1.249(6)
C(3')-O(3")	1.369(6)
C(3")-O(3")	1.450(6)
C(4)-C(5)	1.547(6)
C(4)-C(7)	1.553(6)
C(5)-C(5')	1.505(6)
C(5)-C(6)	1.398(6)
C(5')-O(5')	1.258(5)
C(5')-C(5)-C(6)	125.4(3)
C(5)-C(5')-O(5')	121.8(3)
C(5')-O(5")	1.352(5)
C(5")-O(5")	1.481(7)
C(6)-C(6')	1.519(6)
C(7)-C(8)	1.392(6)
C(7)-C(11)	1.446(6)
C(8)-[S(9),C(9)]	1.746(6)
S(9)-[S(10),C(10)]	1.721(6)
C(9)-[S(10),C(10)]	1.721(6)
[S(10),C(10)]-C(11)	1.389(7)

Bond angles	
C(2)-N(1)-C(6)	124.5(3)
N(1)-C(2)-C(2')	112.3(3)
N(1)-C(2)-C(3)	119.0(3)
C(2')-C(2)-C(3)	128.7(3)
C(2)-C(3)-C(3')	125.5(3)
C(2)-C(3)-C(4)	120.3(3)
C(3')-C(3)-C(4)	114.2(3)
C(3)-C(3')-O(3')	123.8(4)
C(3)-C(3')-O(3")	115.4(3)
O(3')-C(3')-O(3")	120.8(3)
C(3')-O(3")-C(3")	117.6(3)
C(3)-C(4)-C(5)	111.3(3)
C(3)-C(4)-C(7)	110.1(3)
C(5)-C(4)-C(7)	111.5(3)
C(4)-C(5)-C(5')	113.6(3)
C(4)-C(5)-C(6)	120.9(3)
C(5)-C(5')-O(5")	116.9(3)
O(5')-C(5')-O(5")	121.3(4)
C(5')-O(5")-C(5")	116.3(3)
N(1)-C(6)-C(5)	118.1(3)
N(1)-C(6)-C(6')	113.5(3)
C(5)-C(6)-C(6')	128.4(3)
C(4)-C(7)-C(8)	123.8(3)
C(4)-C(7)-C(11)	125.1(3)
C(8)-C(7)-C(11)	111.1(3)
C(7)-C(8)-[S(9),C(9)]	112.1(3)
C(8)-[S(9),C(9)]-[S(10),C(10)]	91.9(2)
[S(9),C(9)]-[S(10),C(10)]-C(11)	111.9(3)
C(7)-C(11)-C(10)	113.0(4)
C(7)-C(11)-S(10)	113.0(4)

Table 26. Anisotropic displacement coefficients ($Å^2$)[a] for 4-(3-thiophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (V)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	0.079(2)	0.070(2)	0.026(2)	-0.012(1)	0.009(1)	-0.003(1)
C(2)	0.065(2)	0.054(2)	0.045(2)	-0.002(2)	0.015(2)	0.003(2)
C(2')	0.096(3)	0.074(2)	0.046(2)	-0.013(2)	0.020(2)	0.010(2)
C(3)	0.059(2)	0.054(2)	0.034(2)	-0.001(1)	0.009(2)	0.002(1)
C(3')	0.064(2)	0.057(2)	0.052(3)	-0.001(2)	0.014(2)	0.000(2)
C(3")	0.100(3)	0.094(3)	0.086(3)	-0.032(3)	0.025(3)	0.001(2)
O(3')	0.099(2)	0.084(2)	0.051(2)	-0.026(1)	0.014(1)	-0.014(1)
O(3")	0.102(2)	0.088(2)	0.063(2)	-0.038(2)	0.026(2)	-0.003(1)
C(4)	0.063(2)	0.056(2)	0.033(2)	-0.001(2)	0.012(2)	0.000(1)
C(5)	0.053(2)	0.056(2)	0.037(2)	0.000(1)	0.008(1)	0.000(1)
C(5')	0.053(2)	0.067(2)	0.049(3)	0.004(2)	0.013(2)	0.007(2)
C(5")	0.088(3)	0.136(4)	0.075(3)	-0.035(3)	0.040(2)	0.008(3)
O(5')	0.083(2)	0.108(2)	0.029(2)	-0.012(1)	0.012(1)	0.001(1)
O(5")	0.070(2)	0.107(2)	0.053(2)	-0.025(1)	0.022(1)	0.001(1)
C(6)	0.058(2)	0.058(2)	0.038(2)	-0.002(2)	0.009(2)	-0.002(2)
C(6')	0.076(2)	0.079(2)	0.041(2)	-0.010(2)	0.007(2)	-0.002(2)
C(7)	0.057(2)	0.064(2)	0.035(2)	-0.005(2)	0.010(2)	0.007(2)
C(8)	0.065(2)	0.065(2)	0.060(2)	-0.001(2)	0.010(2)	0.008(2)
S(9)	0.071(1)	0.079(1)	0.088(1)	0.013(1)	0.016(1)	0.021(1)
C(9)	0.071(1)	0.079(1)	0.088(1)	0.013(1)	0.016(1)	0.021(1)
C(10)	0.086(3)	0.141(4)	0.073(3)	0.002(2)	0.002(2)	0.022(2)
S(10)	0.086(3)	0.141(4)	0.073(3)	0.002(2)	0.002(2)	0.022(2)
C(11)	0.071(2)	0.088(3)	0.049(2)	0.005(2)	-0.002(2)	0.000(2)

a. The anisotropic displacement exponent takes the form: $-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2hka^*b^*U_{12})$

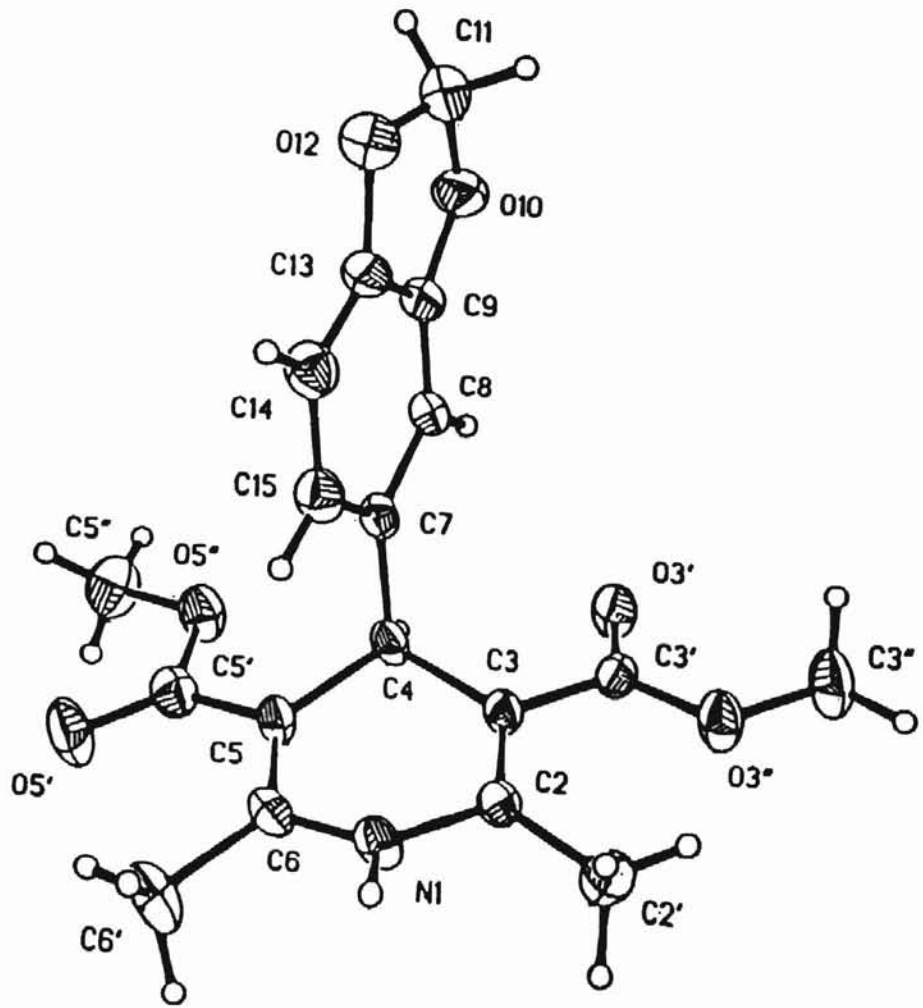


Figure 15. Projection view of 4-(5-(1,3-benzodioxole)2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (VI)

Table 27. Crystal data for 4-(5-(1,3-benzodioxole)2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (VI)

Empirical formula	$C_{18} H_{19} N O_6$	
Formula weight	345.3	
Temperature	301 K	
Wavelength	0.71073 Å	
Crystal system, space group	Triclinic, P1 bar	
Unit cell dimensions	a= 7.498(6) Å	α= 100.92(2) °
	b= 9.698(6) Å	β= 97.49(3) °
	c= 12.374(7) Å	γ= 99.73(3) °
Volume	860.0(10)$Å^3$	
Z, Calculated density	2, 1.334 mg/m^3	
Absorption coefficient	0.101 mm^{-1}	
F(000)	364	
Crystal size	0.2 x 0.3 x 0.1 mm	
Theta range for data collection	1.75 to 30.0 °	
Index ranges	$-10 \leq h \leq 1$, $-13 \leq k \leq 13$, $-17 \leq l \leq 17$	
Reflections collected/ unique/	6058 / 4999 (R_{int}= 0.0924)	
Reflections observed	1199 ($F > 4.0\sigma$ (F))	
Goodness-of-fit	1.09	
Final R indices [I> 2 sigma (I)]	R= 0.0560, wR= 0.0618	
R indices (all data)	R= 0.2008, wR= 0.1210	
Extinction coefficient	0.0031(9)	
Largest diff. peak and hole	0.21 .and –0.21 $eÅ^{-3}$	

Table 28. Atomic coordinates (Å) and equivalent isotropic displacement coefficients ($Å^2$) for 4-(5-(1,3-benzodioxole)2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (VI)

Atom	x	y	z	Ueq[a]
N(1)	0.7863(5)	0.2920(4)	0.4189(4)	0.048(2)
C(2)	0.6542(7)	0.2434(5)	0.4805(5)	0.042(2)
C(2')	0.7340(7)	0.1888(6)	0.5790(5)	0.055(3)
C(3)	0.4752(7)	0.2518(5)	0.4456(4)	0.039(2)
C(3')	0.3236(8)	0.2198(6)	0.5111(5)	0.042(2)
C(3")	0.2260(8)	0.1213(7)	0.6594(6)	0.069(3)
O(3')	0.1691(5)	0.2424(4)	0.4859(3)	0.056(2)
O(3")	0.3697(5)	0.1616(4)	0.5969(4)	0.061(2)
C(4)	0.4170(7)	0.2916(5)	0.3347(4)	0.039(2)
C(5)	0.5800(7)	0.3828(5)	0.3012(4)	0.041(2)
C(5')	0.5418(9)	0.4729(6)	0.2227(5)	0.052(3)
C(5")	0.3064(9)	0.5686(7)	0.1267(6)	0.074(3)
O(5')	0.6508(6)	0.5393(4)	0.1763(4)	0.079(2)
O(5")	0.3587(5)	0.4776(4)	0.2011(3)	0.060(2)
C(6)	0.7544(7)	0.3746(5)	0.3408(5)	0.046(2)
C(6')	0.9301(7)	0.4472(6)	0.3073(6)	0.065(3)
C(7)	0.3315(7)	0.1552(5)	0.2450(4)	0.039(2)
C(8)	0.1408(7)	0.1029(6)	0.2249(5)	0.045(2)
C(9)	0.0702(8)	-0.0206(7)	0.1469(5)	0.050(3)
O(10)	-0.1130(5)	-0.0870(5)	0.1095(4)	0.068(2)
C(11)	-0.1080(10)	-0.2210(7)	0.0374(6)	0.078(3)
O(12)	0.0749(7)	-0.2166(4)	0.0125(4)	0.073(2)
C(13)	0.1828(9)	-0.0968(6)	0.0886(5)	0.054(3)
C(14)	0.3697(9)	-0.0504(6)	0.1044(5)	0.056(3)
C(15)	0.4429(8)	0.0775(6)	0.1838(5)	0.048(2)

a:Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 29. Bond lengths (Å) and angles (°) for 4-(5-(1,3-benzodioxole)2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (VI)

Bond lengths	
N(1)-C(2)	1.400(8)
N(1)-C(6)	1.388(8)
C(2)-C(2')	1.512(9)
C(2)-C(3)	1.376(8)
C(3)-C(3')	1.503(8)
C(3)-C(4)	1.524(8)
C(3')-O(3')	1.226(7)
C(3')-O(3")	1.328(8)
C(3")-O(3")	1.450(8)
C(4)-C(5)	1.535(8)
C(4)-C(7)	1.538(6)
C(5)-C(5')	1.457(9)
C(5)-C(6)	1.356(8)
C(5')-O(5')	1.223(8)
C(5')-O(5")	1.374(8)
C(5")-O(5")	1.453(9)
C(6)-C(6')	1.531(8)
C(7)-C(8)	1.406(7)
C(7)-C(15)	1.415(8)
C(8)-C(9)	1.364(7)
C(9)-O(10)	1.393(6)
C(9)-C(13)	1.395(9)
O(10)-C(11)	1.440(8)
C(11)-O(12)	1.440(9)
O(12)-C(13)	1.401(6)
C(13)-C(14)	1.374(9)
C(14)-C(15)	1.405(7)

Bond angles	
C(2)-N(1)-C(6)	123.2(5)
N(1)-C(2)-C(2')	113.0(4)
N(1)-C(2)-C(3)	117.7(5)
C(2')-C(2)-C(3)	129.2(5)
C(2)-C(3)-C(3')	123.3(5)
C(2)-C(3)-C(4)	121.3(5)
C(3')-C(3)-C(4)	115.3(5)
C(3)-C(3')-O(3')	122.9(6)
C(3)-C(3')-O(3")	114.3(5)
O(3')-C(3')-O(3")	122.7(6)
C(3')-O(3")-C(3")	116.7(5)
C(3)-C(4)-C(5)	110.5(4)
C(3)-C(4)-C(7)	109.9(4)
C(5)-C(4)-C(7)	112.4(4)
C(4)-C(5)-C(5')	118.3(5)
C(4)-C(5)-C(6)	120.2(5)
C(5')-C(5)-C(6)	121.4(5)
C(5)-C(5')-O(5')	127.8(6)
C(5)-C(5')-O(5")	112.5(5)
O(5')-C(5')-O(5")	119.7(6)
C(5')-O(5")-C(5")	117.0(5)
N(1)-C(6)-C(5)	119.9(5)
N(1)-C(6)-C(6')	113.4(5)
C(5)-C(6)-C(6')	126.7(6)
C(4)-C(7)-C(8)	120.3(5)
C(4)-C(7)-C(15)	120.9(4)
C(8)-C(7)-C(15)	118.7(4)
C(7)-C(8)-C(9)	118.8(5)
C(8)-C(9)-O(10)	128.5(6)
C(8)-C(9)-C(13)	121.6(5)
O(10)-C(9)-C(13)	109.9(5)
C(9)-O(10)-C(11)	105.1(5)
O(10)-C(11)-O(12)	108.7(5)
C(11)-O(12)-C(13)	104.9(5)
C(9)-C(13)-O(12)	109.7(5)
C(9)-C(13)-C(14)	122.1(5)
O(12)-C(13)-C(14)	128.1(6)
C(13)-C(14)-C(15)	116.5(6)
C(7)-C(15)-C(14)	122.3(5)

Table 30. Anisotropic displacement coefficients ($Å^2$)[a] for 4-(5-(1,3-benzodioxole)2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (VI)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	0.027(3)	0.059(3)	0.066(4)	0.014(2)	0.017(2)	0.022(3)
C(2)	0.035(3)	0.051(4)	0.041(4)	0.007(3)	0.010(3)	0.010(3)
C(2')	0.038(4)	0.079(4)	0.052(4)	0.017(3)	0.008(3)	0.017(3)
C(3)	0.033(3)	0.047(3)	0.039(3)	0.008(3)	0.011(3)	0.014(3)
C(3')	0.040(4)	0.051(3)	0.037(4)	0.009(3)	0.006(3)	0.015(3)
C(3")	0.060(4)	0.093(5)	0.077(5)	0.027(4)	0.035(4)	0.048(4)
O(3')	0.036(2)	0.086(3)	0.059(3)	0.021(2)	0.017(2)	0.032(2)
O(3")	0.042(2)	0.090(3)	0.067(3)	0.022(2)	0.023(2)	0.043(3)
C(4)	0.027(3)	0.046(3)	0.049(4)	0.005(3)	0.012(3)	0.020(3)
C(5)	0.037(3)	0.049(3)	0.045(4)	0.010(3)	0.016(3)	0.020(3)
C(5')	0.053(4)	0.048(4)	0.055(4)	0.009(3)	0.016(3)	0.011(3)
C(5")	0.097(6)	0.068(4)	0.073(5)	0.034(4)	0.015(4)	0.034(4)
O(5')	0.075(3)	0.082(3)	0.093(4)	0.005(3)	0.031(3)	0.053(3)
O(5")	0.054(3)	0.068(3)	0.071(3)	0.021(2)	0.016(2)	0.036(2)
C(6)	0.041(4)	0.039(3)	0.057(4)	-0.001(3)	0.018(3)	0.010(3)
C(6')	0.046(4)	0.061(4)	0.094(5)	0.005(3)	0.029(4)	0.025(4)
C(7)	0.037(3)	0.039(3)	0.043(4)	0.002(3)	0.005(3)	0.017(3)
C(8)	0.040(4)	0.050(4)	0.043(4)	-0.001(3)	0.011(3)	0.013(3)
C(9)	0.038(4)	0.058(4)	0.048(4)	-0.006(3)	0.002(3)	0.016(3)
O(10)	0.052(3)	0.078(3)	0.062(3)	-0.006(2)	0.010(2)	0.004(2)
C(11)	0.085(6)	0.079(5)	0.057(5)	-0.017(4)	0.004(4)	0.022(4)
O(12)	0.078(3)	0.063(3)	0.068(3)	-0.002(3)	0.007(3)	0.008(2)
C(13)	0.066(5)	0.037(3)	0.051(4)	-0.005(3)	0.002(4)	0.009(3)
C(14)	0.056(4)	0.056(4)	0.060(4)	0.012(4)	0.020(4)	0.012(4)
C(15)	0.039(4)	0.055(4)	0.053(4)	0.012(3)	0.011(3)	0.015(3)

a: The anisotropic displacement exponent takes the form: $-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2hka^*b^*U_{12})$

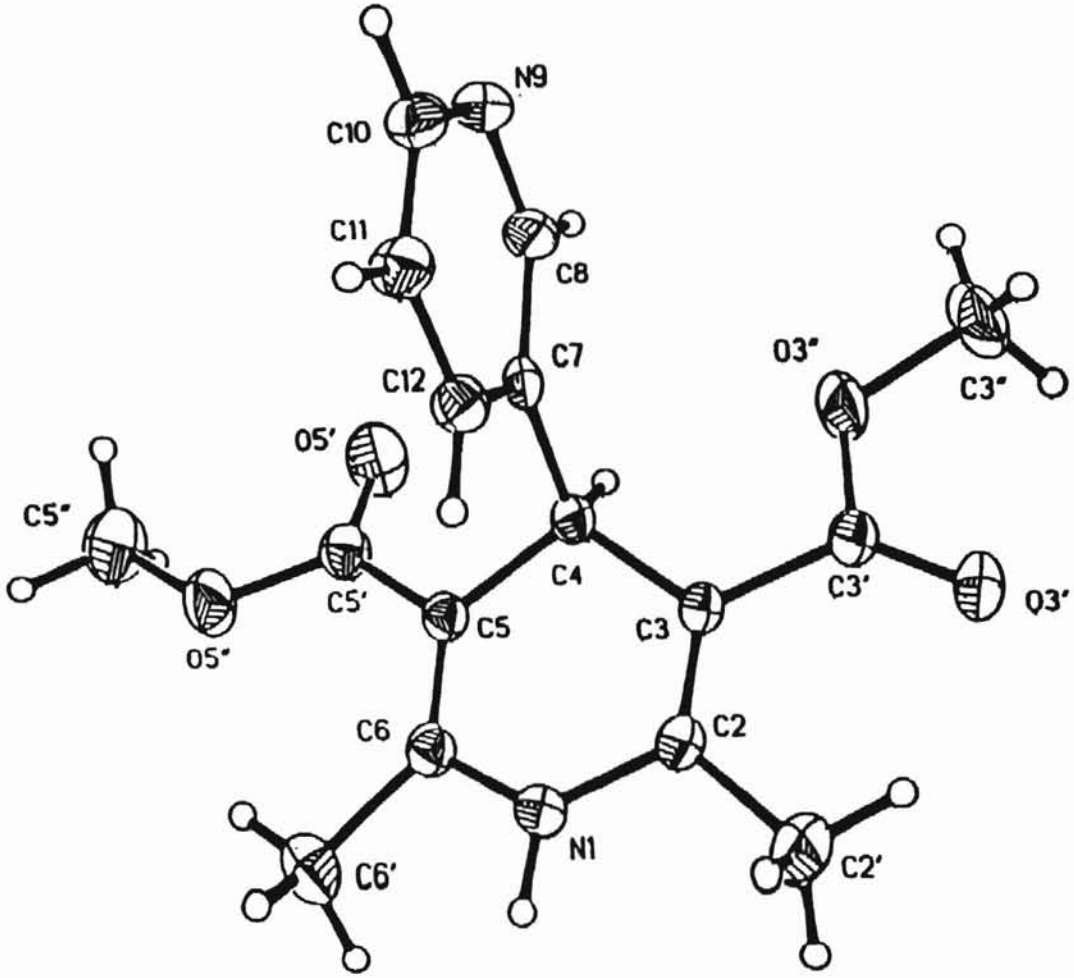


Figure 16. Projection view of 4-(3-pyridyl)2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (VII)

Table 31. Crystal data for 4-(3-pyridyl)2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (VII)

Empirical formula	$C_{16} H_{18} N_2 O_4$	
Formula weight	302.3	
Temperature	301 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/c$	
Unit cell dimensions	a= 8.525(5) Å	α= 90.00 °
	b= 22.070 Å	β= 111.240(0) °
	c= 8.996(9) Å	γ= 90.00 °
Volume	1577(2)Å^3	
Z, Calculated density	4, 1.273 mg/m^3	
Absorption coefficient	0.092 mm^{-1}	
F(000)	640	
Crystal size	0.05 x 0.1 x 0.1 mm	
Theta range for data collection	1.75 to 30.0 °	
Index ranges	$-1 \leq h \leq 11$, $-1 \leq k \leq 30$, $-12 \leq l \leq 12$	
Reflections collected/ unique/	5677 / 4591 (R_{int}= 0.0810)	
Reflections observed	2329 ($F > 4.5\sigma$ (F))	
Goodness-of-fit	1.38	
Final R indices [I> 2 sigma (I)]	R= 0.0534, wR= 0.0675	
R indices (all data)	R= 0.0988, wR= 0.0828	
Extinction coefficient	0.0005(5)	
Largest diff. peak and hole	0.23 .and –0.22 eÅ^{-3}	

Table 32. Atomic coordinates (Å) and equivalent isotropic displacement coefficients ($Å^2$) for 4-(3-pyridyl)2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (VII)

Atom	x	y	z	Ueq[a]
N(1)	0.4078(2)	0.6255(1)	1.0689(2)	0.042(1)
C(2)	0.5473(2)	0.6527(1)	1.0520(3)	0.039(1)
C(2')	0.6272(3)	0.7008(1)	1.1783(3)	0.061(1)
C(3)	0.5973(2)	0.6357(1)	0.9297(3)	0.037(1)
C(3')	0.7527(3)	0.6602(1)	0.9139(3)	0.043(1)
C(3")	0.9200(3)	0.6564(1)	0.7490(4)	0.069(1)
O(3')	0.8512(2)	0.6969(1)	1.0000(2)	0.069(1)
O(3")	0.7756(2)	0.6360(1)	0.7839(2)	0.059(1)
C(4)	0.4886(2)	0.5934(1)	0.7969(2)	0.034(1)
C(5)	0.3643(2)	0.5573(1)	0.8512(2)	0.036(1)
C(5')	0.2901(3)	0.5044(1)	0.7481(3)	0.043(1)
C(5")	0.0603(4)	0.4346(2)	0.6543(4)	0.085(2)
O(5')	0.3516(3)	0.4803(1)	0.6612(3)	0.074(1)
O(5")	0.1393(2)	0.4864(1)	0.7517(2)	0.070(1)
C(6)	0.3276(3)	0.5748(1)	0.9806(3)	0.038(1)
C(6')	0.2097(3)	0.5443(1)	1.0501(3)	0.056(1)
C(7)	0.3918(2)	0.6292(1)	0.6439(2)	0.032(1)
C(8)	0.4164(3)	0.6198(1)	0.4992(3)	0.045(1)
N(9)	0.3311(3)	0.6498(1)	0.3619(2)	0.051(1)
C(10)	0.2153(3)	0.6905(1)	0.3656(3)	0.048(1)
C(11)	0.1828(3)	0.7037(1)	0.5024(3)	0.048(1)
C(12)	0.2734(3)	0.6730(1)	0.6435(3)	0.041(1)

a:Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 33. Bond lengths (Å) and angles (°) for 4-(3-pyridyl)2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (VII)

Bond lengths	
N(1)-C(2)	1.390(3)
N(1)-C(6)	1.398(3)
C(2)-C(2')	1.523(4)
C(2)-C(3)	1.369(4)
C(3)-C(3')	1.484(4)
C(3)-C(4)	1.535(3)
C(3')-O(3')	1.222(3)
C(3')-O(3")	1.362(4)
C(5)-C(5')	1.483(3)
C(5)-C(6)	1.367(4)
C(5')-O(5')	1.210(4)
C(5')-O(5")	1.356(4)
C(6)-C(6')	1.519(4)
C(7)-C(8)	1.407(4)
C(7)-C(12)	1.397(3)
C(8)-N(9)	1.357(3)
N(9)-C(10)	1.343(4)
C(10)-C(11)	1.388(4)
C(11)-C(12)	1.398(3)

Bond angles	
C(2)-N(1)-C(6)	123.0(2)
N(1)-C(2)-C(2')	112.9(2)
N(1)-C(2)-C(3)	119.9(2)
C(2')-C(2)-C(3)	127.3(2)
C(2)-C(3)-C(3')	121.7(2)
C(2)-C(3)-C(4)	121.1(2)
C(3')-C(3)-C(4)	117.1(2)
C(3)-C(3')-O(3')	127.8(2)
C(3)-C(3')-O(3")	110.5(2)
O(3')-C(3')-O(3")	121.7(2)
C(5')-C(5)-C(6)	125.3(2)
C(5)-C(5')-O(5')	124.2(2)
C(5)-C(5')-O(5")	114.1(2)
O(5')-C(5')-O(5")	121.6(2)
N(1)-C(6)-C(5)	119.7(2)
N(1)-C(6)-C(6')	112.4(2)
C(5)-C(6)-C(6')	127.9(2)
C(8)-C(7)-C(12)	116.8(2)
C(7)-C(8)-N(9)	124.0(2)
C(8)-N(9)-C(10)	117.4(2)
N(9)-C(10)-C(11)	123.2(2)
C(10)-C(11)-C(12)	118.8(2)
C(7)-C(12)-C(11)	119.9(2)

Table 34. Anisotropic displacement coefficients ($Å^2$)[a] for 4-(3-pyridyl)2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (VII)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	0.039(1)	0.053(1)	0.036(1)	-0.004(1)	0.017(1)	-0.006(1)
C(2)	0.031(1)	0.048(1)	0.035(1)	-0.002(1)	0.008(1)	0.000(1)
C(2')	0.055(1)	0.075(2)	0.050(1)	-0.017(1)	0.017(1)	-0.022(1)
C(3)	0.026(1)	0.045(1)	0.037(1)	-0.002(1)	0.007(1)	0.000(1)
C(3')	0.029(1)	0.054(1)	0.042(1)	-0.001(1)	0.008(1)	0.003(1)
C(3")	0.044(1)	0.088(2)	0.088(2)	-0.006(1)	0.041(1)	0.000(2)
O(3')	0.045(1)	0.099(1)	0.062(1)	-0.033(1)	0.017(1)	-0.019(1)
O(3")	0.038(1)	0.081(1)	0.068(1)	-0.013(1)	0.030(1)	-0.017(1)
C(4)	0.027(1)	0.040(1)	0.036(1)	0.001(1)	0.012(1)	-0.001(1)
C(5)	0.029(1)	0.039(1)	0.037(1)	0.001(1)	0.010(1)	0.002(1)
C(5')	0.042(1)	0.039(1)	0.048(1)	-0.002(1)	0.015(1)	0.001(1)
C(5")	0.082(2)	0.080(2)	0.089(2)	-0.045(2)	0.025(2)	-0.025(2)
O(5')	0.069(1)	0.074(1)	0.090(2)	-0.015(1)	0.041(1)	-0.038(1)
O(5")	0.059(1)	0.079(1)	0.078(1)	-0.035(1)	0.030(1)	-0.029(1)
C(6)	0.032(1)	0.043(1)	0.038(1)	0.001(1)	0.011(1)	0.005(1)
C(6')	0.055(1)	0.065(2)	0.057(2)	-0.012(1)	0.030(1)	0.001(1)
C(7)	0.025(1)	0.041(1)	0.033(1)	-0.007(1)	0.011(1)	-0.005(1)
C(8)	0.042(1)	0.057(1)	0.039(1)	0.002(1)	0.020(1)	-0.004(1)
N(9)	0.054(1)	0.067(1)	0.035(1)	-0.004(1)	0.019(1)	0.001(1)
C(10)	0.049(1)	0.051(1)	0.039(1)	-0.003(1)	0.010(1)	0.008(1)
C(11)	0.045(1)	0.050(1)	0.046(1)	0.009(1)	0.012(1)	0.007(1)
C(12)	0.038(1)	0.048(1)	0.039(1)	0.005(1)	0.016(1)	-0.002(1)

a: The anisotropic displacement exponent takes the form: $-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2hka^*b^*U_{12})$

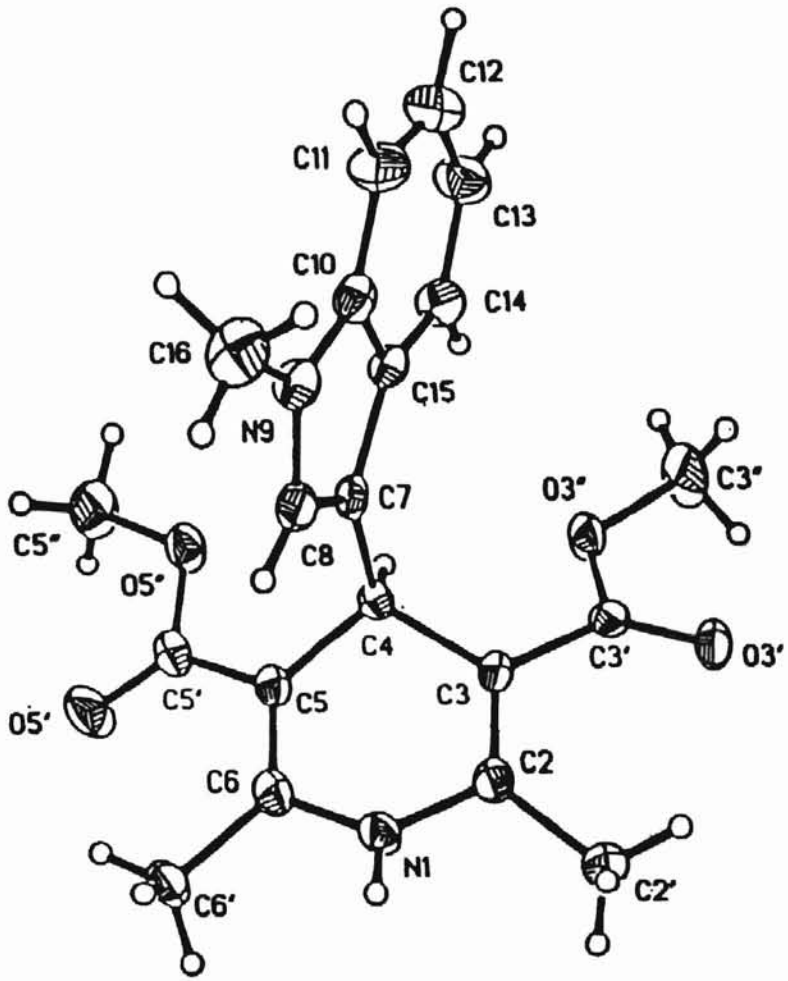


Figure 17. Projection view of 4-(3(1-methyl-1H-indole))-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (VIII)

Table 35. Crystal data for 4-(3(1-methyl-1H-indole))-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (VIII)

Empirical formula	$C_{20}H_{22}N_2O_4$	
Formula weight	354.4	
Temperature	301 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1$	
Unit cell dimensions	a= 8.209(5) Å	α= 90.00 °
	b= 10.524(4) Å	β= 95.560(0) °
	c= 10.856(5) Å	γ= 90.00 °
Volume	933.5(8)Å^3	
Z, Calculated density	2, 1.261 mg/m^3	
Absorption coefficient	0.088 mm^{-1}	
F(000)	376	
Crystal size	0.2 x 0.2 x 0.2 mm	
Theta range for data collection	1.75 to 30.0 °	
Index ranges	$-1 \leq h \leq 11$, $-1 \leq k \leq 14$, $-15 \leq l \leq 15$	
Reflections collected/ unique/	3725 / 3139 (R_{int}= 0.0415)	
Reflections observed	1970 ($F > 4.0\sigma(F)$)	
Goodness-of-fit	1.20	
Final R indices [I> 2 sigma (I)]	R= 0.0580, wR= 0.0593	
R indices (all data)	R= 0.0907, wR= 0.0673	
Extinction coefficient	0.0040(7)	
Largest diff. peak and hole	0.39 and –0.27 eÅ^{-3}	

Table 36. Atomic coordinates (Å) and equivalent isotropic displacement coefficients ($Å^2$) for 4-(3(1-methyl-1H-indole))-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (VIII)

Atom	x	y	z	Ueq[a]
N(1)	0.3046(4)	0.6629	0.4939(3)	0.038(1)
C(2)	0.3595(4)	0.5465(5)	0.4522(3)	0.034(1)
C(2')	0.5123(5)	0.4993(5)	0.5277(4)	0.054(1)
C(3)	0.2714(4)	0.4867(4)	0.3572(3)	0.031(1)
C(3')	0.3222(5)	0.3606(4)	0.3124(3)	0.034(1)
C(3")	0.2353(7)	0.1831(5)	0.1846(5)	0.070(2)
O(3')	0.4565(3)	0.3108(4)	0.3339(3)	0.050(1)
O(3")	0.1995(3)	0.3054(4)	0.2394(2)	0.047(1)
C(4)	0.1225(4)	0.5539(4)	0.2873(3)	0.030(1)
C(5)	0.0471(4)	0.6481(4)	0.3737(3)	0.033(1)
C(5')	-0.1283(5)	0.6800(5)	0.3512(3)	0.041(1)
C(5")	-0.3709(5)	0.6535(7)	0.2138(4)	0.066(2)
O(5')	-0.2071(4)	0.7480(5)	0.4130(3)	0.071(1)
O(5")	-0.1995(3)	0.6222(4)	0.2472(3)	0.051(1)
C(6)	0.1438(4)	0.7051(4)	0.4664(3)	0.036(1)
C(6')	0.0972(5)	0.8138(5)	0.5486(4)	0.048(1)
C(7)	0.1746(4)	0.6220(5)	0.1722(3)	0.032(1)
C(8)	0.2473(5)	0.7403(5)	0.1673(3)	0.039(1)
N(9)	0.2878(4)	0.7667(4)	0.0492(3)	0.044(1)
C(10)	0.2407(4)	0.6645(5)	-0.0260(3)	0.039(1)
C(11)	0.2564(6)	0.6456(6)	-0.1530(4)	0.060(2)
C(12)	0.1955(6)	0.5337(6)	-0.2055(4)	0.064(2)
C(13)	0.1195(6)	0.4422(6)	-0.1365(4)	0.062(2)
C(14)	0.1053(5)	0.4597(5)	-0.0098(4)	0.047(1)
C(15)	0.1681(4)	0.5719(5)	0.0472(3)	0.035(1)
C(16)	0.3628(7)	0.8841(6)	0.0094(5)	0.067(2)

a:Equivalent isotropic U defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 37. Bond lengths (Å) and angles (°) for 4-(3(1-methyl-1H-indole))-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (VIII)

Bond lengths	
N(1)-C(2)	1.396(5)
N(1)-C(6)	1.397(5)
C(2)-C(2')	1.514(6)
C(2)-C(3)	1.356(5)
C(3)-C(3')	1.487(6)
C(3')-O(3')	1.223(5)
C(3')-O(3")	1.351(5)
C(4)-C(5)	1.535(6)
C(4)-C(7)	1.537(5)
C(5)-C(5')	1.475(5)
C(5)-C(6)	1.359(5)
C(5')-O(5')	1.211(6)
C(5')-O(5")	1.364(5)
C(6)-C(6')	1.522(7)
C(7)-C(8)	1.384(7)
C(7)-C(15)	1.452(5)
C(8)-N(9)	1.384(5)
N(9)-C(10)	1.383(6)
N(9)-C(16)	1.464(7)
C(10)-C(11)	1.411(5)
C(10)-C(15)	1.425(6)
C(11)-C(12)	1.381(9)
C(12)-C(13)	1.403(8)
C(13)-C(14)	1.403(6)
C(14)-C(15)	1.408(7)

Bond angles	
C(2)-N(1)-C(6)	122.6(3)
N(1)-C(2)-C(2')	112.9(3)
N(1)-C(2)-C(3)	119.2(3)
C(2')-C(2)-C(3)	127.8(4)
C(2)-C(3)-C(3')	121.1(3)
C(3)-C(3')-O(3')	126.6(4)
C(3)-C(3')-O(3")	111.0(3)
O(3')-C(3')-O(3")	122.3(4)
C(5)-C(4)-C(7)	110.9(4)
C(4)-C(5)-C(5')	119.4(3)
C(4)-C(5)-C(6)	119.7(3)
C(5')-C(5)-C(6)	120.8(4)
C(5)-C(5')-O(5')	127.5(4)
C(5)-C(5')-O(5")	111.6(4)
O(5')-C(5')-O(5")	120.9(4)
N(1)-C(6)-C(5)	119.3(4)
N(1)-C(6)-C(6')	113.5(3)
C(5)-C(6)-C(6')	127.1(4)
C(4)-C(7)-C(8)	127.3(3)
C(4)-C(7)-C(15)	127.1(4)
C(8)-C(7)-C(15)	105.6(3)
C(7)-C(8)-N(9)	111.1(4)
C(8)-N(9)-C(10)	108.2(4)
C(8)-N(9)-C(16)	126.1(4)
C(10)-N(9)-C(16)	125.7(4)
N(9)-C(10)-C(11)	129.8(5)
N(9)-C(10)-C(15)	108.1(3)
C(11)-C(10)-C(15)	122.1(4)
C(10)-C(11)-C(12)	117.4(5)
C(11)-C(12)-C(13)	121.8(4)
C(12)-C(13)-C(14)	121.2(5)
C(13)-C(14)-C(15)	118.6(4)
C(7)-C(15)-C(10)	107.1(4)
C(7)-C(15)-C(14)	134.0(4)
C(10)-C(15)-C(14)	118.9(3)

Table 38. Anisotropic displacement coefficients ($Å^2$)[a] for 4-(3(1-methyl-1H-indole))-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (VIII)

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	0.037(2)	0.034(2)	0.042(1)	-0.001(1)	0.000(1)	-0.009(1)
C(2)	0.036(2)	0.033(2)	0.033(2)	0.001(2)	0.006(1)	0.003(2)
C(2')	0.054(3)	0.053(3)	0.053(2)	0.011(2)	-0.012(2)	-0.013(2)
C(3)	0.030(2)	0.028(2)	0.035(2)	0.005(2)	0.004(1)	0.005(1)
C(3')	0.043(2)	0.030(2)	0.030(2)	0.001(2)	0.004(2)	0.003(1)
C(3")	0.081(4)	0.035(2)	0.092(3)	0.008(2)	-0.011(3)	-0.027(2)
O(3')	0.045(2)	0.045(2)	0.059(2)	0.018(2)	-0.005(1)	-0.008(1)
O(3")	0.051(2)	0.031(1)	0.057(2)	0.009(1)	-0.003(1)	-0.010(1)
C(4)	0.031(2)	0.026(2)	0.033(2)	-0.001(2)	0.006(1)	0.000(1)
C(5)	0.035(2)	0.029(2)	0.037(2)	0.003(2)	0.008(1)	0.003(2)
C(5')	0.040(2)	0.037(2)	0.048(2)	0.003(2)	0.013(2)	-0.002(2)
C(5")	0.040(2)	0.077(3)	0.080(3)	0.011(3)	-0.006(2)	-0.014(3)
O(5')	0.049(2)	0.091(3)	0.072(2)	0.022(2)	0.007(2)	-0.031(2)
O(5")	0.035(1)	0.054(2)	0.062(2)	0.009(2)	0.000(1)	-0.012(2)
C(6)	0.040(2)	0.030(2)	0.038(2)	0.000(2)	0.010(2)	-0.001(2)
C(6')	0.050(2)	0.043(2)	0.052(2)	0.006(2)	0.007(2)	-0.015(2)
C(7)	0.027(2)	0.033(2)	0.036(2)	0.009(2)	0.004(1)	0.004(1)
C(8)	0.040(2)	0.037(2)	0.041(2)	0.004(2)	0.004(2)	0.004(2)
N(9)	0.049(2)	0.033(2)	0.050(2)	-0.005(2)	0.006(2)	0.009(1)
C(10)	0.037(2)	0.039(2)	0.042(2)	0.002(2)	0.005(2)	0.008(2)
C(11)	0.071(3)	0.068(3)	0.042(2)	-0.007(3)	0.015(2)	0.011(2)
C(12)	0.080(3)	0.075(3)	0.037(2)	0.003(3)	0.010(2)	-0.004(2)
C(13)	0.078(3)	0.059(3)	0.049(2)	-0.004(3)	0.004(2)	-0.013(2)
C(14)	0.055(3)	0.042(2)	0.045(2)	-0.006(2)	0.000(2)	0.001(2)
C(15)	0.029(2)	0.038(2)	0.039(2)	0.002(2)	-0.001(1)	0.003(2)
C(16)	0.083(4)	0.042(3)	0.078(3)	-0.012(3)	0.014(3)	0.019(2)

a: The anisotropic displacement exponent takes the form: $-2\pi^2(h^2a^{*2}U_{11} + \ldots + 2hka^*b^*U_{12})$

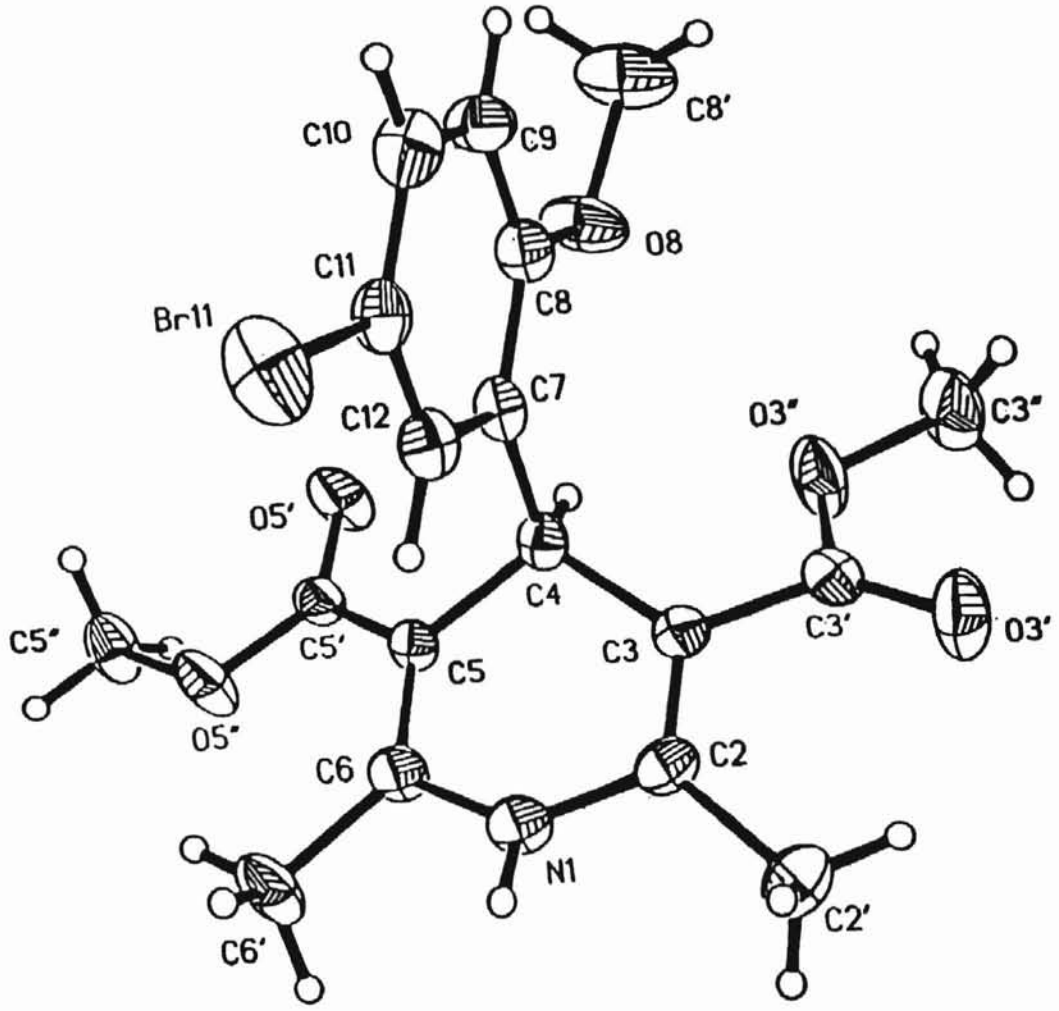


Figure 18. Projection view of 4-(3-bromo-6-methoxy-phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (IX)

Table 39. Crystal data for 4-(3-bromo-6-methoxy-phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (IX)

Empirical formula	$C_{18} H_{20} Br N O_5$	
Formula weight	410.26	
Temperature	301 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, C(2)/c	
Unit cell dimensions	a= 28.49(2) Å	α= 90.00 °
	b= 7.551(10) Å	β= 127.66 °
	c= 22.34(2) Å	γ= 90.00 °
Volume	3805(7) $Å^3$	
Z, Calculated density	8, 1.432 mg/m^3	
Absorption coefficient	2.187 mm^{-1}	
F(000)	1680	
Crystal size	0.1 x 0.1 x 0.01 mm	
Theta range for data collection	1.8 to 30.0°	
Index ranges	$-1 \leq h \leq 30$, $-8 \leq k \leq 1$, $-24 \leq l \leq 19$	
Reflections collected/ unique/	3205/ 2537 (R_{int}= 0.0740)	
Reflections observed	1716	
Goodness-of-fit	1.045	
Final R indices [I> 2 sigma (I)]	R= 0.0664, wR= 0.1736	
R indices (all data)	R= 0.1057, wR= 0.2056	
Extinction coefficient	0.0004(3)	
Largest diff. peak and hole	0.77 and –0.66 $eÅ^{-3}$	

Table 40. Atomic coordinates (Å) and equivalent isotropic displacement parameters ($Å^2$) for 4-(3-bromo-6-methoxy-phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (IX)

	x	y	z	U(eq)[a]
N(1)	-0.1458(3)	0.3587(7)	-0.3719(3)	0.50(2)
C(2)	-0.2030(3)	0.3253(9)	-0.3951(4)	0.42(2)
C(2')	-0.2434(3)	0.4868(10)	-0.4322(4)	0.056(2)
C(3)	-0.2159(3)	0.1590(9)	-0.3858(4)	0.41(2)
C(3)	-0.2778(3)	0.1059(10)	-0.4182(4)	0.46(2)
C(3')	-0.3419(3)	-0.1419(11)	-0.4486(6)	0.080(3)
O(3')	-0.3187(3)	0.2088(9)	-0.4389(4)	0.087(2)
O(3")	-0.2847(2)	-0.0729(8)	-0.4221(4)	0.74(2)
C(4)	-0.1671(3)	0.0156(9)	-0.3421(3)	0.40(2)
C(5)	-0.1177(3)	0.0527(9)	-0.3507(3)	0.37(2)
C(5')	-0.0879(3)	-0.1064(10)	-0.3512(4)	0.41(2)
C(5")	-0.0102(3)	-0.2220(11)	-0.3542(5)	0.066(2)
O(5')	-0.1010(2)	-0.2603(7)	-0.3488(3)	0.609(14)
O(5")	-0.0432(2)	-0.0711(7)	-0.3547(3)	0.65(2)
C(6)	-0.1067(3)	0.2247(9)	-0.3593(4)	0.43(2)
C(6')	-0.0572(3)	0.2967(11)	-0.3597(5)	0.065(2)
C(7)	-0.1420(3)	0.0096(9)	-0.2588(4)	0.38(2)
C(8)	-0.1538(3)	-0.1309(9)	-0.2277(4)	0.50(2)
C(8')	-0.2075(5)	-0.4097(12)	-0.2495(5)	0.092(3)
O(8)	-0.1886(3)	-0.2718(8)	-0.2754(3)	0.72(2)
C(9)	-0.1291(4)	-0.1285(11)	-0.1504(4)	0.059(2)
C(10)	-0.0936(3)	0.0105(11)	-0.1036(4)	0.058(2)
C(11)	-0.0820(3)	0.1499(10)	-0.1344(4)	0.50(2)
Br(11)	-0.0328(4)	0.3461(1)	-0.0705(1)	0.815(5)
C(12)	-0.1053(3)	0.1504(9)	-0.2099(4)	0.048(2)

a:U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 41. Bond lengths (Å) and angles (°) for 4-(3-bromo-6-methoxy-phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (IX)

Bond length	
N(1)-C(2)	1.397(9)
N(1)-C(6)	1.402(9)
C(2)-C(3)	1.360(9)
C(2)-C(2')	1.527(10)
C(3)-C(3')	1.497(10)
C(3)-C(4)	1.548(9)
C(3')-O(3')	1.231(9)
C(3')-O(3")	1.359(9)
C(3")-(3")	1.449(9)
C(4)-C(7)	1.534(9)
C(4)-C(5)	1.558(9)
C(5)-C(6)	1.377(10)
C(5)-C(5')	1.477(9)
C(5')-O(5')	1.233(8)
C(5')-O(5")	1.348(8)
C(5")-O(5")	1.473(9)
C(6)-C(6)'	1.517(10)
C(7)-C(8)	1.416(9)
C(7)-C(12)	1.422(9)
C(8)-C(9)	1.411(10)
C(8)-O(8)	1.400(9)
C(8')-O(8)	1.446(9)
C(9)-C(10)	1.388(11)
C(10)-C(11)	1.402(11)
C(11)-C(12)	1.386(10)
C(11)-Br(11)	1.938(7)

Bond angles	
C(2)-N(1)-C(6)	123.3(6)
C(3)-C(2)-N(1)	118.1(6)
C(3)-C(2)-C(2')	129.6(6)
N(1)-C(2)-C(2')	112.2(6)
C(2)-C(3)-C(3')	121.4(6)
C(2)-C(3)-C(4)	121.4(6)
C(3')-C(3)-C(4)	117.2(6)
O(3')-C(3')-O(3")	122.5(7)
O(3')-C(3')-C(3)	125.4(7)
O(3")-C(3')-C(3)	112.1(6)
C(3')-O(3")-C(3")	117.7(6)
C(7)-C(4)-C(3)	111.1(5)
C(7)-C(4)-C(5)	111.6(5)
C(3)-C(4)-C(5)	109.1(5)
C(6)-C(5)-C(5')	125.7(6)
C(6)-C(5)-C(4)	119.2(6)
C(5')-C(5)-C(4)	115.0(6)
O(5')-C(5')-O(5")	120.8(6)
O(5')-C(5')-C(5)	125.1(6)
O(5")-C(5')-C(5)	114.1(6)
C(5')-O(5")-C(5")	117.8(6)
C(5)-C(6)-N(1)	119.1(6)
C(5)-C(6)-C(6)'	129.2(6)
N(1)-C(6)-C(6)'	111.7(6)
C(8)-C(7)-C(12)	117.9(6)
C(8)-C(7)-C(4)	122.8(6)
C(12)-C(7)-C(4)	119.2(6)
C(9)-C(8)-C(7)	119.9(7)
C(9)-C(8)-O(8)	122.2(6)
C(7)-C(8)-O(8)	117.8(6)
C(8)-O(8)-C(8)'	120.5(6)
C(10)-C(9)-C(8)	121.4(7)
C(9)-C(10)-C(11)	118.7(7)
C(12)-C(11)-C(10)	121.2(7)
C(12)-C(11)-Br(11)	119.2(6)
C(10)-C(11)-Br(11)	119.6(5)
C(11)-C(12)-C(7)	120.8(7)

Table 42. Anisotropic displacement coefficients ($Å^2$)[a] for 4-(3-bromo-6-methoxy-phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl). (IX)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	0.060(4)	0.025(4)	0.068(4)	-0.003(3)	0.040(3)	-0.002(3)
C(2)	0.053(4)	0.031(4)	0.040(4)	-0.003(3)	0.026(3)	-0.001(3)
C(2)'	0.068(5)	0.039(5)	0.059(5)	-0.002(4)	0.038(4)	0.012(4)
C(3)	0.042(4)	0.043(5)	0.037(3)	-0.004(3)	0.023(3)	-0.001(3)
C(3)'	0.049(4)	0.050(5)	0.042(4)	-0.008(3)	0.031(4)	-0.004(4)
C(3)"	0.051(5)	0.059(6)	0.119(8)	-0.001(5)	0.046(5)	-0.014(4)
O(3')	0.057(4)	0.084(5)	0.124(5)	-0.002(4)	0.057(4)	0.014(4)
O(3")	0.043(3)	0.061(4)	0.112(5)	-0.012(3)	0.044(3)	-0.016(3)
C(4)	0.041(4)	0.033(4)	0.044(4)	-0.005(3)	0.025(3)	-0.005(3)
C(5)	0.037(3)	0.030(4)	0.041(4)	-0.006(3)	0.022(3)	-0.005(3)
C(5')	0.039(4)	0.039(5)	0.046(4)	0.001(3)	0.026(3)	-0.003(3)
C(5")	0.051(5)	0.050(5)	0.011(7)	-0.015(5)	0.056(5)	-0.002(4)
O(5')	0.071(3)	0.023(3)	0.113(4)	0.000(3)	0.069(4)	-0.002(3)
O(5")	0.070(3)	0.037(3)	0.120(5)	-0.011(3)	0.074(4)	-0.009(3)
C(6)	0.048(4)	0.027(4)	0.056(4)	-0.003(3)	0.032(4)	-0.005(3)
C(6)'	0.061(5)	0.041(5)	0.105(7)	-0.005(4)	0.058(5)	-0.014(4)
C(7)	0.036(3)	0.033(4)	0.045(4)	-0.008(3)	0.024(3)	-0.005(3)
C(8)	0.051(4)	0.036(5)	0.058(5)	-0.005(4)	0.032(4)	-0.002(4)
C(8)'	0.134(9)	0.057(6)	0.090(7)	-0.015(5)	0.070(7)	-0.045(6)
O8	0.099(4)	0.055(4)	0.065(3)	-0.012(3)	0.052(3)	-0.042(3)
C(9)	0.067(5)	0.060(6)	0.053(5)	0.008(4)	0.039(4)	0.003(4)
C(10)	0.059(5)	0.063(6)	0.046(4)	-0.011(4)	0.028(4)	0.000(4)
C(11)	0.041(4)	0.052(5)	0.049(4)	-0.013(4)	0.024(4)	0.006(4)
Br11	0.764(7)	0.956(9)	0.768(7)	-0.472(5)	0.490(6)	-0.326(5)
C(12)	0.048(4)	0.043(5)	0.56(4)	-0.005(4)	0.034(4)	0.004(4)

a:The anisotropic displacement exponent takes the form: $-2\pi^2 (h^2 a^{*2} U_{11} + \ldots + 2hka^* b^* U_{12})$

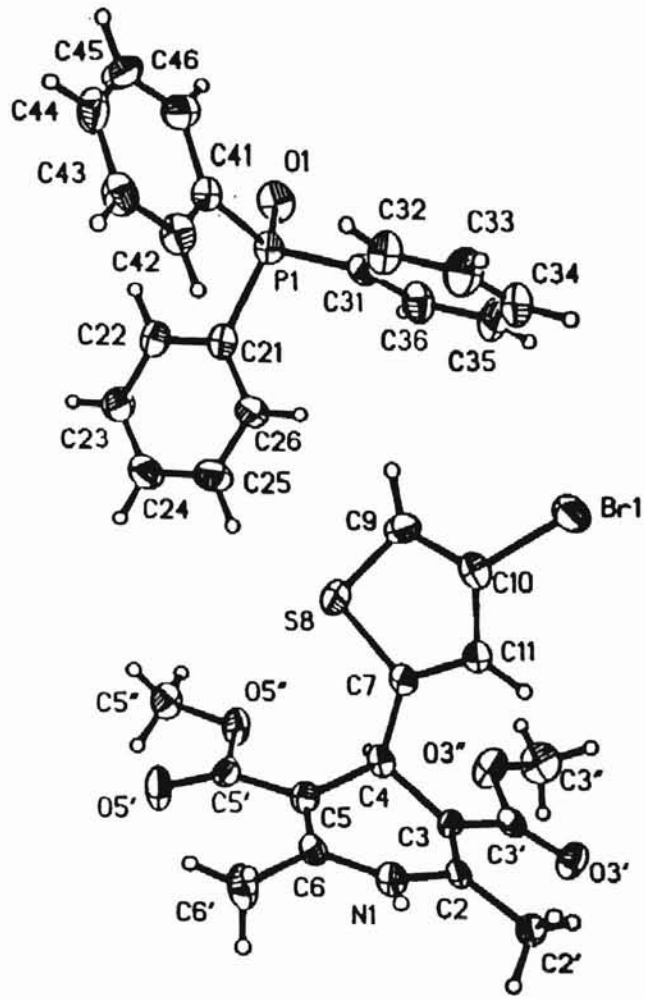


Figure 19. Projection view of triphenylphosphine oxide / 4-(4-bromo-2-thiophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) co-crystal. (X)

Table 43. Crystal data for triphenylphosphine oxide / methyl-2,6-dimethyl-4-(4-bromo-2-thiophenyl)-1,4-dihydropyridine-3,5-dicarboxylate co-crystal. (X)

Empirical formula	$C_{33}H_{31}BrNO_5PS$	
Formula weight	664.5	
Temperature	301 K	
Wavelength	0.71073 Å	
Crystal system, space group	Triclinic, P1bar	
Unit cell dimensions	a= 10.745(8) Å	α= 77.59(4) °
	b= 12.625(9) Å	β= 76.43(3) °
	c= 12.827(9) Å	γ= 72.40(6) °
Volume	1599(2) $Å^3$	
Z, Calculated density	2, 1.380 mg/m^3	
Absorption coefficient	1.441 mm^{-1}	
F(000)	684	
Crystal size	0.05 x 0.1 x 0.2 mm	
Theta range for data collection	1.8 to 60.0 °	
Index ranges	$-1 \leq h \leq 15$, $-17 \leq k \leq 17$, $-17 \leq l \leq 18$	
Reflections collected/ unique/	10710/ 9325 (R_{int}= 0.0713)	
Reflections observed	2877 ($F > 4.5\sigma(F)$)	
Goodness-of-fit	1.08	
Final R indices [I> 2 sigma (I)]	R= 0.0671, wR= 0.0897	
R indices (all data)	R= 0.2065, wR= 0.1596	
Extinction coefficient	-0.0010(3)	
Largest diff. peak and hole	0.77 and –0.66 $eÅ^{-3}$	

Table 44. Atomic coordinates (Å) and equivalent isotropic displacement parameters ($Å^2$) for triphenylphosphine oxide / 4-(4-bromo-2-thiophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) co-crystal. (X)

	x	y	z	U(eq)[a]
N(1)	0.2088(6)	0.3121(5)	0.0595(5)	0.046(3)
C(2)	0.2485(7)	0.3730(6)	0.1192(6)	0.036(3)
C(2')	0.3900(7)	0.3750(8)	0.853(7)	0.053(4)
C(3)	0.1560(7)	0.4263(5)	0.1972(6)	0.035(3)
C(3')	0.1884(8)	0.5015(6)	0.2558(6)	0.040(3)
C(3")	0.970(10)	0.6209(7)	0.3915(8)	0.071(5)
O(3')	0.2926(6)	0.5240(5)	0.2434(5)	0.064(3)
O(3")	0.0801(5)	0.5444(5)	0.3302(5)	0.060(3)
C(4)	0.0210(7)	0.4006(6)	0.2327(6)	0.035(3)
C(5)	-0.0213(7)	0.3762(6)	0.1346(6)	0.039(3)
C(5')	-0.1632(8)	0.4050(6)	0.1294(7)	0.042(3)
C(5")	-0.3828(8)	0.4978(7)	0.2153(7)	0.058(4)
O(5')	-0.2128(6)	0.3806(5)	0.0650(5)	0.066(3)
O(5")	-0.2398(5)	0.4624(4)	0.2112(5)	0.054(3)
C(6)	0.0754(8)	0.3256(6)	0.0573(6)	0.042(3)
C(6')	0.0565(9)	0.2844(9)	-0.0389(8)	0.071(5)
C(7)	0.0250(7)	0.3013(6)	0.3257(6)	0.039(3)
S(8)	-0.1160(2)	0.2537(2)	0.3825(2)	0.053(1)
C(9)	-0.0359(9)	0.1516(7)	0.4772(7)	0.054(4)
C(10)	0.0918(8)	0.1569(6)	0.4623(6)	0.044(3)
Br(1)	0.2116(1)	0.0600(1)	0.5542(1)	0.067(1)
C(11)	0.1290(7)	0.2397(6)	0.3777(6)	0.039(3)
P(1)	-0.5192(2)	0.1347(2)	0.8093(2)	0.043(1)
O(1)	-0.6061(6)	0.1817(5)	0.9075(5)	0.063(3)
C(21)	-0.5437(8)	0.2329(6)	0.6835(6)	0.044(3)
C(22)	-0.6745(9)	0.2805(8)	0.6674(8)	0.068(5)
C(23)	-0.7002(10)	0.3562(9)	0.5737(9)	0.080(5)
C(24)	-0.5987(10)	0.3839(8)	0.4952(8)	0.065(4)
C(25)	-0.4692(10)	0.3363(8)	0.5120(8)	0.067(5)
C(26)	-0.4415(9)	0.2623(7)	0.6040(7)	0.055(4)
C(31)	-0.3431(8)	0.1003(7)	0.8144(6)	0.048(4)
C(32)	-0.2539(9)	-0.0043(8)	0.8007(7)	0.063(4)
C(33)	-0.1200(10)	-0.0240(9)	0.8060(9)	0.082(5)
C(34)	-0.0779(11)	0.0592(10)	0.8293(9)	0.081(6)
C(35)	-0.1662(11)	0.1620(10)	0.8458(9)	0.083(6)
C(36)	-0.2982(10)	0.1840(8)	0.8383(8)	0.066(4)
C(41)	-0.5578(7)	0.0119(6)	0.7891(6)	0.042(3)

C(42)	-0.5035(9)	-0.0342(7)	0.6917(7)	0.058(4)
C(43)	-0.5410(10)	-0.1234(7)	0.6727(9)	0.068(5)
C(44)	-0.6285(11)	-0.1695(8)	0.7505(10)	0.076(5)
C(45)	-0.6841(10)	-0.1262(9)	0.8479(10)	0.081(5)
C(46)	-0.6457(9)	-0.0369(8)	0.8684(8)	0.067(4)

a:U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 45. Bond lengths (Å) and angles (°) for triphenylphosphine oxide / 4-(4-bromo-2-thiophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) co-crystal. (X)

Bond lengths	
N(1)-C(2)	1.400(12)
N(1)-C(6)	1.398(11)
C(2)-C(2')	1.487(11)
C(2)-C(3)	1.364(9)
C(3)-C(3')	1.488(13)
C(3)-C(4)	1.525(11)
C(3')-O(3')	1.205(12)
C(3')-O(3")	1.371(9)
C(3")-O(3")	1.443(13)
C(4)-C(5)	1.551(12)
C(4)-C(7)	1.532(9)
C(5)-C(5')	1.471(11)
C(5)-C(6)	1.363(10)
C(5')-O(5')	1.215(13)
C(5')-O(5")	1.365(10)
C(5")-O(5")	1.456(9)
C(6)-C(6')	1.514(15)
C(7)-S(8)	1.741(9)
C(7)-C(11)	1.378(11)
S(8)-C(9)	1.739(8)
C(9)-C(10)	1.361(13)
C(10)-Br(1)	1.919(8)
C(10)-C(11)	1.411(10)
P(1)-O(1)	1.498(6)
P(1)-C(21)	1.831(8)
P(1)-C(31)	1.823(9)
P(1)-C(41)	1.804(9)
C(21)-C(22)	1.397(12)
C(21)-C(26)	1.393(11)
C(22)-C(23)	1.391(14)
C(23)-C(24)	1.375(14)
C(24)-C(25)	1.386(15)
C(25)-C(26)	1.370(12)
C(31)-C(32)	1.396(11)
C(31)-C(36)	1.401(16)
C(32)-C(33)	1.400(15)
C(33)-C(34)	1.372(20)
C(34)-C(35)	1.381(15)
C(35)-C(36)	1.383(16)
C(41)-C(42)	1.416(12)
C(41)-C(46)	1.392(12)
C(42)-C(43)	1.388(16)
C(43)-C(44)	1.364(15)
C(44)-C(45)	1.400(18)
C(45)-C(46)	1.404(18)

Bond angles	
C(2)-N(1)-C(6)	122.5(6)
N(1)-C(2)-C(2')	114.3(6)
N(1)-C(2)-C(3)	118.5(7)
C(2')-C(2)-C(3)	127.2(8)
C(2)-C(3)-C(3')	121.2(7)
C(2)-C(3)-C(4)	119.7(8)
C(3')-C(3)-C(4)	118.9(6)
C(3)-C(3')-O(3')	127.5(7)
C(3)-C(3')-O(3")	110.3(7)
O(3')-C(3')-O(3")	122.3(8)
C(3')-O(3")-C(3")	116.1(7)
C(3)-C(4)-C(5)	109.9(6)
C(3)-C(4)-C(7)	110.7(6)
C(5)-C(4)-C(7)	110.8(7)
C(4)-C(5)-C(5')	119.4(6)
C(4)-C(5)-C(6)	118.3(7)
C(5')-C(5)-C(6)	122.3(8)
C(5)-C(5')-O(5')	127.3(7)
C(5)-C(5')-O(5")	111.5(8)
O(5')-C(5')-O(5")	121.2(7)
C(5')-O(5")-C(5")	117.5(7)
N(1)-C(6)-C(5)	119.7(8)
N(1)-C(6)-C(6')	113.0(6)
C(5)-C(6)-C(6')	127.2(8)
C(4)-C(7)-S(8)	120.6(6)
C(4)-C(7)-C(11)	128.9(7)
S(8)-C(7)-C(11)	110.5(5)
C(7)-S(8)-C(9)	92.8(4)
S(8)-C(9)-C(10)	108.9(6)
C(9)-C(10)-Br(1)	121.6(6)
C(9)-C(10)-C(11)	116.0(7)

Br(1)-C(10)-C(11)	122.4(7)
C(7)-C(11)-C(10)	111.8(7)
O(1)-P(1)-C(21)	112.4(3)
O(1)-P(1)-C(31)	112.5(4)
C(21)-P(1)-C(31)	106.5(4)
O(1)-P(1)-C(41)	112.0(4)
C(21)-P(1)-C(41)	103.8(4)
C(31)-P(1)-C(41)	109.1(4)
P(1)-C(21)-C(22)	116.8(6)
P(1)-C(21)-C(26)	124.5(6)
C(22)-C(21)-C(26)	118.6(7)
C(21)-C(22)-C(23)	119.8(8)
C(22)-C(23)-C(24)	121.1(9)
C(23)-C(24)-C(25)	118.6(9)
C(24)-C(25)-C(26)	121.3(9)
C(21)-C(26)-C(25)	120.5(8)
P(1)-C(31)-C(32)	124.2(8)
P(1)-C(31)-C(36)	116.6(6)
C(32)-C(31)-C(36)	119.1(9)
C(31)-C(32)-C(33)	120.6(11)
C(32)-C(33)-C(34)	119.3(9)
C(33)-C(34)-C(35)	120.4(11)
C(34)-C(35)-C(36)	121.1(13)
C(31)-C(36)-C(35)	119.3(9)
P(1)-C(41)-C(42)	121.1(6)
P(1)-C(41)-C(46)	120.0(7)
C(42)-C(41)-C(46)	118.9(9)
C(41)-C(42)-C(43)	121.1(8)
C(42)-C(43)-C(44)	119.5(10)
C(43)-C(44)-C(45)	121.0(11)
C(44)-C(45)-C(46)	119.9(10)
C(41)-C(46)-C(45)	119.5(9)

Table 46. Anisotropic displacement coefficients ($Å^2$)[a] for triphenylphosphine oxide / 4-(4-bromo-2-thiophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) co-crystal. (X)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	0.042(4)	0.052(4)	0.046(4)	-0.006(3)	-0.006(3)	-0.027(3)
C(2)	0.030(4)	0.046(4)	0.032(4)	-0.001(3)	-0.011(3)	-0.011(3)
C(2')	0.035(5)	0.083(6)	0.039(5)	-0.011(4)	0.001(4)	-0.020(4)
C(3)	0.027(4)	0.038(4)	0.039(4)	-0.006(3)	-0.006(3)	-0.010(3)
C(3')	0.053(5)	0.037(4)	0.033(5)	-0.007(4)	-0.012(4)	-0.011(3)
C(3")	0.091(7)	0.067(6)	0.066(6)	-0.025(6)	0.001(5)	-0.047(5)
O(3')	0.049(4)	0.088(5)	0.070(4)	-0.029(3)	-0.004(3)	-0.037(3)
O(3")	0.051(4)	0.074(4)	0.066(4)	-0.023(3)	0.006(3)	-0.046(3)
C(4)	0.037(4)	0.033(4)	0.036(4)	0.000(3)	-0.006(3)	-0.021(3)
C(5)	0.039(5)	0.037(4)	0.046(5)	-0.008(4)	-0.010(4)	-0.013(4)
C(5')	0.039(5)	0.043(4)	0.048(5)	-0.017(4)	-0.011(4)	0.001(4)
C(5")	0.040(5)	0.058(5)	0.068(6)	0.003(4)	-0.016(4)	-0.010(4)
O(5')	0.046(4)	0.094(5)	0.072(4)	-0.015(3)	-0.024(3)	-0.030(4)
O(5")	0.030(3)	0.066(4)	0.065(4)	0.002(3)	-0.012(3)	-0.028(3)
C(6)	0.050(5)	0.045(4)	0.039(5)	-0.015(4)	-0.016(4)	-0.013(4)
C(6')	0.058(6)	0.100(7)	0.070(7)	-0.012(5)	-0.024(5)	-0.043(6)
C(7)	0.043(5)	0.050(5)	0.033(4)	-0.011(4)	-0.004(4)	-0.025(4)
S(8)	0.040(1)	0.064(1)	0.057(1)	-0.020(1)	-0.007(1)	-0.009(1)
C(9)	0.062(6)	0.059(5)	0.046(5)	-0.030(5)	0.002(4)	-0.012(4)
C(10)	0.049(5)	0.040(4)	0.044(5)	-0.004(4)	-0.013(4)	-0.014(4)
Br(1)	0.069(1)	0.071(1)	0.057(1)	-0.012(1)	-0.022(1)	0.001(1)
C(11)	0.033(4)	0.046(4)	0.038(5)	-0.004(4)	-0.004(4)	-0.018(4)
P(1)	0.043(1)	0.047(1)	0.039(1)	-0.006(1)	-0.001(1)	-0.023(1)
O(1)	0.059(4)	0.068(4)	0.058(4)	0.003(3)	0.000(3)	-0.038(3)
C(21)	0.042(5)	0.037(4)	0.055(5)	-0.005(4)	-0.009(4)	-0.021(4)
C(22)	0.044(6)	0.088(7)	0.072(7)	-0.024(5)	-0.016(5)	0.000(6)
C(23)	0.054(6)	0.083(7)	0.098(9)	-0.015(6)	-0.036(6)	0.018(6)
C(24)	0.064(6)	0.066(6)	0.058(6)	-0.010(5)	-0.019(5)	0.005(5)
C(25)	0.064(7)	0.076(7)	0.047(6)	-0.012(5)	0.001(5)	-0.001(5)
C(26)	0.042(5)	0.062(5)	0.049(6)	0.000(4)	-0.004(4)	-0.009(4)
C(31)	0.057(5)	0.050(5)	0.040(5)	-0.014(4)	-0.012(4)	-0.009(4)
C(32)	0.050(6)	0.070(6)	0.073(7)	-0.005(5)	-0.009(5)	-0.035(5)
C(33)	0.049(7)	0.086(8)	0.106(9)	0.001(6)	-0.010(6)	-0.034(7)
C(34)	0.058(7)	0.100(9)	0.090(8)	-0.021(7)	-0.031(6)	-0.005(7)
C(35)	0.078(8)	0.088(8)	0.105(9)	-0.045(7)	-0.041(7)	-0.004(7)
C(36)	0.067(7)	0.052(5)	0.085(7)	-0.007(5)	-0.034(6)	-0.016(5)
C(41)	0.035(4)	0.039(4)	0.050(5)	0.000(4)	-0.006(4)	-0.015(4)

C(42)	0.066(6)	0.045(5)	0.067(6)	-0.007(4)	-0.018(5)	-0.019(4)
C(43)	0.087(8)	0.052(5)	0.076(7)	-0.015(5)	-0.035(6)	-0.015(5)
C(44)	0.082(8)	0.047(6)	0.115(10)	-0.020(6)	-0.059(7)	-0.003(6)
C(45)	0.071(7)	0.076(7)	0.097(9)	-0.041(6)	-0.014(7)	0.013(6)
C(46)	0.064(6)	0.063(6)	0.068(6)	-0.016(5)	-0.009(5)	-0.004(5)

a:The anisotropic displacement exponent takes the form: $-2\pi^2 (h^2 a^{*2} U_{11} + \ldots + 2hka^* b^* U_{12})$

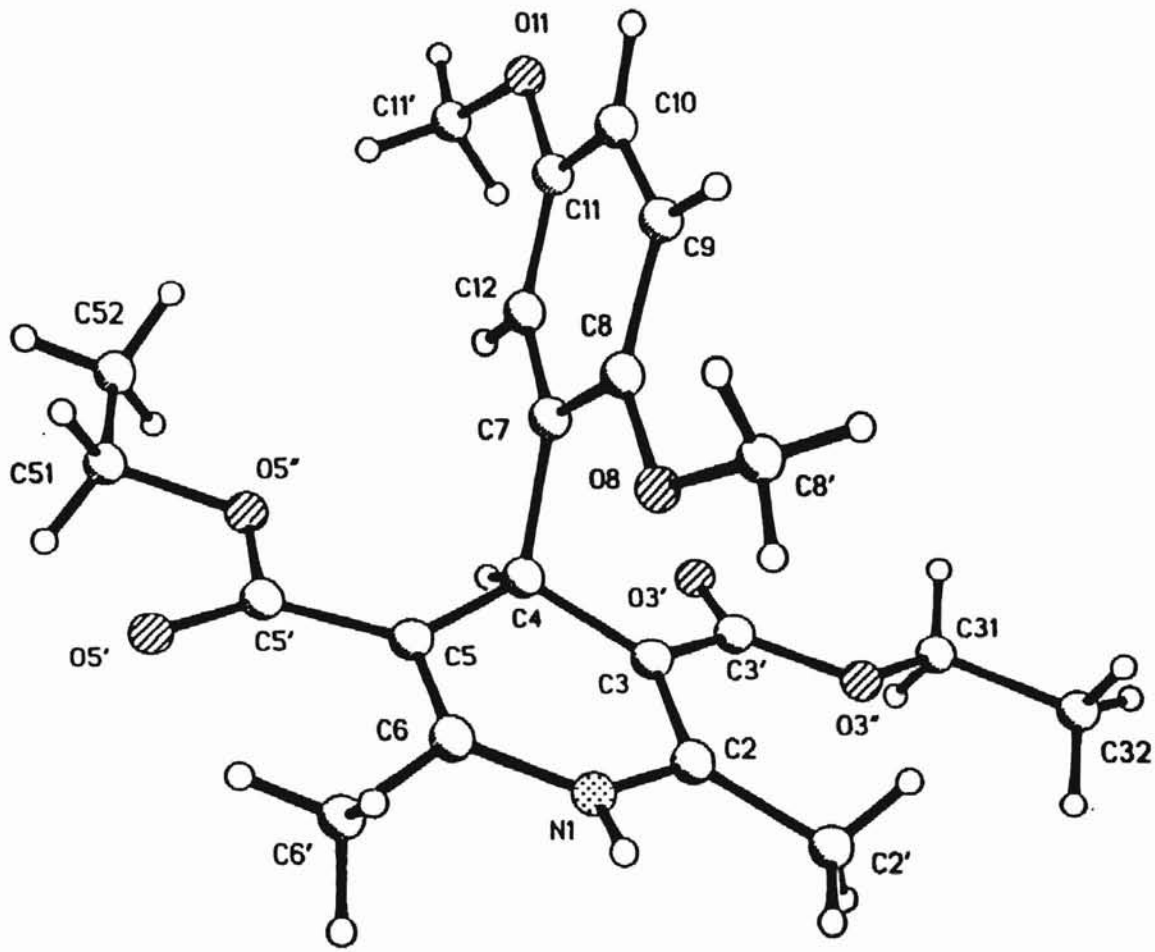


Figure 20. Projection view of 4-(2,5-methoxy-phenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(ethoxycarbonyl) *ap*-rotamer. (XI)

Table 47. Crystal data for ethyl-2,6-dimethyl-4-(2,5-methoxy phenyl)-1,4-dihydropyridine-3,5-dicarboxylate *ap*-rotamer. (XI)

Empirical formula	$C_{21}H_{27}BrNO_6$	
Formula weight	389.5	
Temperature	301 K	
Wavelength	0.71073 Å	
Crystal system, space group	Monoclinic, $P2_1/c$	
Unit cell dimensions	a= 7.696(4) Å	α= 90.00 °
	b= 8.699(5) Å	β= 76.43(10) °
	c= 30.635(13) Å	γ= 90.00 °
Volume	2057(2) $Å^3$	
Z, Calculated density	4, 1.257 mg/m^3	
Absorption coefficient	0.092 mm^{-1}	
F(000)	832	
Crystal size	0.05 x 0.2 x 0.2 mm	
Theta range for data collection	1.8 to 60.0 °	
Index ranges	$-10 \leq h \leq 1$, $-12 \leq k \leq 1$, $-43 \leq l \leq 43$	
Reflections collected/ unique/	8076/ 6009 (R_{int}= 0.0712)	
Reflections observed	721 ($F > 4.0\sigma(F)$)	
Goodness-of-fit	3.19	
Final R indices [I> 2 sigma (I)]	R= 0.0738, wR= 0.0781	
R indices (all data)	R= 0.3684, wR= 0.3119	
Extinction coefficient	none	
Largest diff. peak and hole	0.25 and –0.31 $eÅ^{-3}$	

Table 48. Atomic coordinates (Å) and equivalent isotropic displacement parameters ($Å^2$) for ethyl-2,6-dimethyl-4-(2,5-dimethoxy phenyl)-1,4-dihydropyridine-3,5-dicarboxylate *ap*-rotamer. (XI)

Atom	x	y	z	U(eq)[a]
N(1)	1.302(2)	-0.064(2)	0.0707(4)	0.053(8)
C(2)	1.161(2)	0.031(3)	0.0606(5)	0.048(9)
C(2')	1.212(2)	0.170(3)	0.0347(6)	0.060(9)
C(3)	0.998(2)	-0.013(3)	0.0766(5)	0.035(7)
C(3')	0.836(2)	0.070(3)	0.0646(5)	0.034(8)
C(31)	0.703(2)	0.294(3)	0.0352(6)	0.052(9)
C(32)	0.762(2)	0.448(3)	0.0178(6)	0.071(11)
O(3')	0.6898(14)	0.022(2)	0.0708(4)	0.055(6)
O(3")	0.8580(13)	0.209(2)	0.0459(4)	0.050(6)
C(4)	0.978(2)	-0.147(2)	0.1075(5)	0.030(7)
C(5)	1.126(2)	-0.258(3)	0.1049(6)	0.042(8)
C(5')	0.111(3)	-0.413(23)	0.1213(6)	0.040(8)
C(51)	0.914(2)	-0.603(3)	0.1506(6)	0.52(9)
C(52)	0.728(2)	-0.619(3)	0.1634(6)	0.079(11)
O(5')	1.218(2)	-0.512(3)	0.1242(6)	0.111(9)
O(5")	0.941(2)	-0.450(2)	0.1331(4)	0.055(6)
C(6)	1.278(2)	-0.207(3)	0.0891(6)	0.036(8)
C(6')	1.450(2)	-0.302(3)	0.0885(6)	0.064(11)
C(7)	0.937(2)	-0.097(3)	0.1549(6)	0.053(10)
C(8)	1.055(2)	0.000(3)	0.1773(6)	0.047(9)
C(8')	1.328(3)	0.151(3)	0.1749(6)	0.089(12)
O(8)	1.212(2)	0.037(2)	0.1571(4)	0.066(7)
C(9)	1.019(3)	0.061(2)	0.2206(7)	0.051(9)
C(10)	0.863(3)	0.014(3)	0.2394(6)	0.067(10)
C(11)	0.746(2)	-0.076(2)	0.2176(7)	0.040(8)
C(11')	0.478(3)	-0.218(3)	0.2194(6)	0.080(12)
O(11)	0.591(2)	-0.109(2)	0.2397(4)	0.076(7)
C(12)	0.785(2)	-0.128(3)	0.1752(6)	0.049(9)

a:U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor

Table 49. Bond lengths (Å) and angles (°) for ethyl-2,6-dimethyl-4-(2,5 dimethoxy phenyl)-1,4-dihydropyridine-3,5-dicarboxylate *ap*-rotamer. (XI)

Bond length	
N(1)-C(2)	1.40 (3)
N(1)-C(6)	1.38 (3)
C(2)-C(2')	1.49 (3)
C(2)-C(3)	1.40 (2)
C(3)-C(3')	1.49 (3)
C(3)-C(4)	1.51 (23)
C(3')-O(3')	1.22 (2)
C(3')-O(3")	1.35 (23)
C(31)-C(32)	1.51 (3)
C(31)-O(3")	1.44 (2)
C(4)-C(5)	1.49 (3)
C(4)-C(7)	1.55 (3)
C(5)-C(5')	1.45 (3)
C(5)-C(6)	1.34 (3)
C(5')-O(5')	1.20 (3)
C(5')-O(5")	1.39 (2)
C(51)-C(52)	1.48 (3)
C(51)-O(5")	1.46 (3)
C(6)-C(6')	1.56 (3)
C(7)-C(8)	1.42 (3)
C(7)-C(12)	1.35 (3)
C(8)-O(8)	1.39 (2)
C(8)-C(9)	1.45 (3)
C(8')-O(8)	1.44 (3)
C(9)-C(10)	1.40 (3)
C(10)-C(11)	1.37 (3)
C(11)-O(11)	1.40 (2)
C(11)-C(12)	1.41 (3)
C(11')-O(11)	1.43 (3)

Bond angles	
C(2)-N(1)-C(6)	121(2)
N(1)-C(2)-C(2')	113(2)
N(1)-C(2)-C(3)	117(2)
C(2')-C(2)-C(3)	130(2)
C(2)-C(3)-C(3')	122(2)
C(2)-C(3)-C(4)	122(2)
C(3')-C(3)-C(4)	116.5(14)
C(3)-C(3')-O(3')	125(2)
C(3)-C(3')-O(3")	116(2)
O(3')-C(3')-O(3")	119(2)
C(32)-C(31)-O(3")	106.5(14)
C(3')-O(3")-C(31)	116.9(14)
C(3)-C(4)-C(5)	112.6(14)
C(3)-C(4)-C(7)	113(2)
C(5)-C(4)-C(7)	112.7(14)
C(4)-C(5)-C(5')	122(2)
C(4)-C(5)-C(6)	118(2)
C(5')-C(5)-C(6)	120(12)
C(5)-C(5')-O(5')	130.2(20)
C(5)-C(5')-O(5")	112(2)
O(5')-C(5')-O(5")	118(2)
C(52)-C(51)-O(5")	109(2)
C(5')-O(5")-C(51)	116(2)
N(1)-C(6)-C(5)	124(2)
N(1)-C(6)-C(6')	111(2)
C(5)-C(6)-C(6')	125(2)
C(4)-C(7)-C(8)	119(2)
C(4)-C(7)-C(12)	124(2)
C(8)-C(7)-C(12)	117(2)
C(7)-C(8)-O(8)	118(2)
C(7)-C(8)-C(9)	122(2)
O(8)-C(8)-C(9)	119(2)
C(8)-O(8)-C(8')	122(2)
C(8)-C(9)-C(10)	116(2)
C(9)-C(10)-C(11)	122(2)
C(10)-C(11)-O(11)	116(2)
C(10)-C(11)-C(12)	120(2)
O(11)-C(11)-C(12)	124(2)
C(11)-O(11)-C(11')	116(2)
C(7)-C(12)-C(11)	123(2)

Table 50. Anisotropic displacement coefficients ($Å^2$)[a] for ethyl-2,6-dimethyl-4-(2,5-dimethoxy phenyl)-1,4-dihydropyridine-3,5-dicarboxylate *ap*-rotamer. (X)

	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)	0.031(9)	0.07(2)	0.054(11)	-0.010(11)	0.006(8)	0.005(11)
C(2)	0.038(11)	0.07(2)	0.040(13)	0.016(13)	-0.001(10)	0.027(13)
C(2')	0.038(11)	0.07(2)	0.073(14)	-0.014(12)	0.006(10)	0.021(13)
C(3)	0.026(9)	0.04(2)	0.040(12)	0.008(10)	-0.002(8)	0.003(11)
C(3')	0.051(13)	0.02(2)	0.034(12)	0.005(11)	0.012(10)	0.002(11)
C(31)	0.029(10)	0.07(2)	0.057(14)	0.010(12)	-0.007(10)	0.022(13)
C(32)	0.055(13)	0.09(3)	0.07(2)	0.02(2)	0.003(11)	0.01(2)
O(3')	0.034(7)	0.057(13)	0.075(9)	-0.006(8)	0.004(7)	0.031(9)
O(3")	0.028(7)	0.07(2)	0.052(8)	0.000(8)	-0.010(6)	0.029(8)
C(4)	0.041(11)	0.012(12)	0.038(11)	-0.025(11)	-0.006(9)	-0.009(11)
C(5)	0.019(10)	0.06(2)	0.050(13)	0.016(11)	0.002(9)	0.019(12)
C(5')	0.07(2)	0.00(2)	0.050(13)	-0.016(12)	-0.012(11)	-0.011(10)
C(51)	0.069(14)	0.02(2)	0.07(2)	-0.020(12)	-0.05(12)	-0.008(12)
C(52)	0.09(2)	0.06(2)	0.09(2)	-0.03(2)	0.005(14)	0.03(2)
O(5')	0.073(10)	0.09(2)	0.17(2)	0.035(11)	0.028(11)	0.07(2)
O(5")	0.041(7)	0.06(2)	0.062(9)	-0.015(8)	0.003(7)	0.013(8)
C(6)	0.040(12)	0.03(2)	0.040(12)	0.003(11)	0.003(9)	-0.022(11)
C(6')	0.041(11)	0.07(3)	0.08(2)	0.020(13)	-0.002(10)	0.008(14)
C(7)	0.028(11)	0.07(2)	0.06(2)	0.008(12)	-0.008(11)	-0.012(13)
C(8)	0.035(11)	0.04(2)	0.07(2)	-0.025(11)	0.016(12)	0.039(13)
C(8')	0.08(2)	0.09(3)	0.10(2)	-0.03(2)	-0.025(14)	0.01(2)
O(8)	0.053(8)	0.08(2)	0.066(10)	-0.029(10)	-0.030(7)	0.001(9)
C(9)	0.06(2)	0.009(14)	0.08(2)	0.019(12)	-0.025(12)	-0.034(12)
C(10)	0.071(14)	0.09(3)	0.040(13)	0.02(2)	-0.019(13)	-0.016(14)
C(11)	0.060(13)	0.000(11)	0.06(2)	0.000(11)	0.002(12)	0.015(11)
C(11')	0.07(2)	0.11(3)	0.06(2)	-0.001(17)	0.038(13)	0.032(16)
O(11)	0.080(10)	0.10(2)	0.048(9)	-0.006(11)	0.018(8)	-0.002(10)
C(12)	0.031(11)	0.07(2)	0.050(13)	0.028(11)	-0.007(10)	-0.016(12)

a:The anisotropic displacement exponent takes the form: $-2\pi^2 (h^2 a^{*2} U_{11} + \ldots + 2hka^* b^* U_{12})$

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