Crystal Structures and Pharmacological Activity of Calcium Channel Antagonists: 2,6-Dimethyl-3,5-dicarbomethoxy-4-(unsubstituted, 3-methyl-, 4-methyl-, 3-nitro-, 4-nitro-, and 2,4-dinitrophenyl)-1,4-dihydropyridine

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The molecular structures of 2,6-dimethyl-3,5-dicarbomethoxy-4-phenyl-1,4-dihydropyridine and the 3-methyl-, 4-methyl-, 3-nitro-, 4-nitro-, and 2,4-dinitrophenyl derivatives were determined by X-ray diffraction methods. The dihydropyridine ring in each of the compounds exists in a boat-type conformation. However, the degree of ring puckering varies among the compounds. The observed ring distortions were found to be influenced to a great extent by the position of the substituent in the 4-phenyl ring and the conformation about the interring bond. The distortion at the apical nitrogen of the dihydropyridine ring was found to be linearly related to that at the apical tetrahedral carbon. A correlation was observed between the pharmacological activities of this class of calcium channel antagonists, determined by their ability to inhibit the Ca^{2+}-dependent muscarinic mechanical responses of guinea pig ileal longitudinal smooth muscle, and the magnitude of the 1,4-dihydropyridine ring puckering; the more active compounds exhibited the smallest degree of ring distortion from planarity.

Calcium ion plays a vital role in a large number of cellular processes, including excitation–contraction and stimulus–secretion.[1-3] The regulation of the intracellular concentration of this ion makes possible the control of such Ca^{2+}-dependent processes. One means of accomplishing this is by the use of agents known as calcium channel antagonists, which inhibit the movement of calcium through certain membrane channels.[2,4,5]

Structurally diverse groups of organic compounds are known to be effective as calcium antagonists.[2,4,5] The most potent class of antagonists comprises derivatives of 1,4-dihydropyridine (Figure 1), of which the most widely known agent is Nifedipine [2,6-dimethyl-3,5-dicarbomethoxy-4-(2-nitrophenyl)-1,4-dihydropyridine].[5,6] These compounds exert a profound negative inotropic effect on herat muscle and a marked relaxation of smooth muscle. Studies carried out to date suggest that the diverse pharmacological activities of these antagonists results from a fundamentally similar mode of action and that they act at specific membrane sites rather than through nonspecific membrane interactions.[7,8]

Structure–activity correlations derived for the dihydropyridine antagonists indicate that the nature and position of the substitution in the aryl ring are exceedingly important determinants of activity.[9-11] The effect of the substituents on activity was observed to be relatively independent of their electronic character but correlated well with a parameter, B_1, reflecting their size. In a previous structural study on four compounds of this series of antagonists, there was an indication that the substituted aryl ring could influence the degree of puckering of the 1,4-dihydropyridine ring, which in turn may be related to activity.[11] With the aim of further clarifying the relationship of structure with the activity of this important class of calcium channel antagonists, we determined the structures of six other members of this class.

Experimental Section

Crystals of the six compounds were grown by slow evaporation of methanol solutions. The crystallographic and experimental data for these materials are summarized in Table I. The unit cell parameters of each crystal were obtained by a least-squares fit of the diffractometer (SYNTEX PT) settings (χ, ϕ, and 2θ) for 15 high order reflections. The diffraction intensities were collected by the $\theta/2\theta$ scan procedure using graphite-monochromatized Mo Kα radiation (λ 0.71069 Å). The crystals were maintained at approximately −150 °C during the data collection by means of a stream of cold nitrogen. The intensities were corrected for Lorentz and polarization effects, but corrections for absorption were not deemed necessary.

The structures were solved by direct methods using the program MULTAN.[12] They were refined by difference electron density maps and least-squares analyses. The weights applied in the least squares were obtained from the standard deviation in the intensities, $\sigma(I)$, taken as $\sigma(I) = [C_T + (0.02C_N)^2]^{1/2}$, where C_T is the total number of counts and C_N is the next peak count. The final R values (reliability indexes) for the refined structures are listed in Table I.

The atomic form factors used in the calculations are those of Doyle and Turner[13] for the nonhydrogen atoms and of Stewart, Davidson, and Simpson[14] for hydrogen. The computer programs used are described by Groth.[15]

The positional parameters for the non-hydrogen atoms of the six structures are listed in Table IV (see paragraph at the end of paper concerning supplementary material). The coordinates of the hydrogen atoms, the thermal parameters for all the atoms, and the structure factors are available from the authors.

Results and Discussion

The molecular structures of the six compounds are shown in Figures 2–7, together with their atomic labeling

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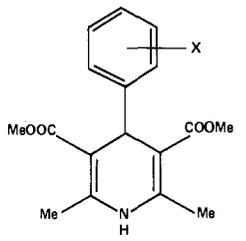

Figure 1. Structure of 2,6-dimethyl-3,5-dicarbomethoxy-4-aryl-1,4-dihydropyridines: X = H (I), 3-NO_2 (II), 4-NO_2 (III), 2,4-$(NO_2)_2$ (IV, 4-Me (V), and 3-Me (VI).

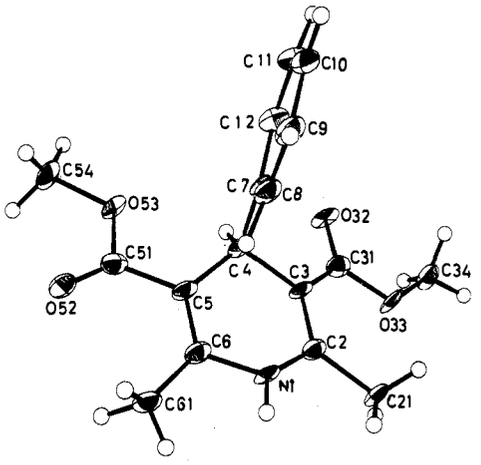

Figure 2. An ORTEP drawing of 2,6-dimethyl-3,5-dicarbomethoxy-4-phenyl-1,4-dihydropyridine (I).

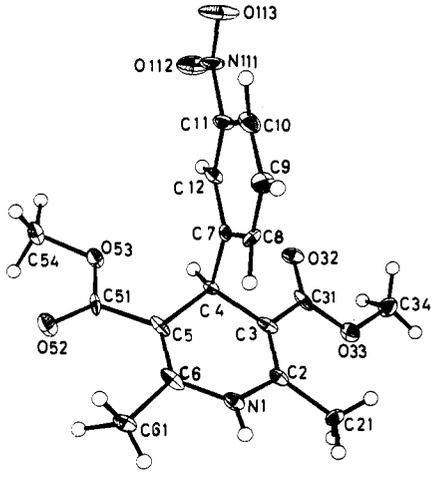

Figure 3. An ORTEP drawing of 2,6-dimethyl-3,5-dicarbomethoxy-4-(3-nitrophenyl)-1,4-dihydropyridine (II).

schemes. The atomic labeling convention adopted reflects the observed chiral nature of the molecules. This is brought about by the conformational differences found for the carbomethoxy substituents at positions 3 and 5 of the dihydropyridine ring and the twist of the phenyl group at position 4. The convention used to label the ring atoms defines C3 as that position bearing the carbonyl function of the carbomethoxy group trans to the neighboring ring double bond.

The intramolecular bonding parameters involving the nonhydrogen atoms of the molecules are presented in Tables V and VI (see paragraph at the end of paper concerning supplementary material). the bond lengths and angles about the molecular framework common to the six structures are similar. The values for these parameters also agree with those reported for other 1,4-dihydropyridine calcium channel antagonists and related compounds.[11] None of these quantitites deviate from the values that were expected for such structures.[16]

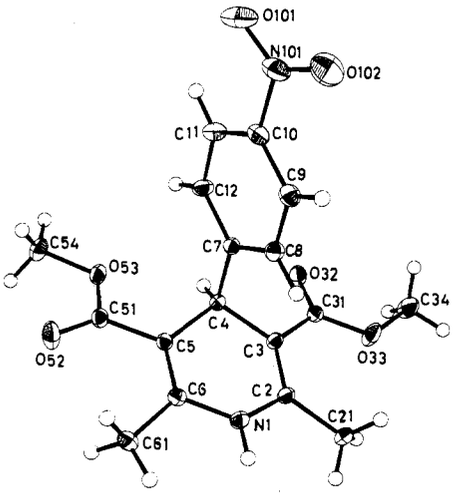

Figure 4. An ORTEP drawing of 2,6-dimethyl-3,5-dicarbomethoxy-4-(4-nitrophenyl)-1,4-dihydropyridine (III).

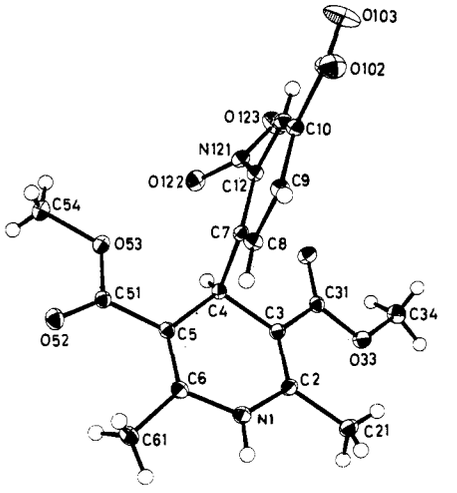

Figure 5. An ORTEP drawing of 2,6-dimethyl-3,5-dicarbomethoxy-4-(2,4-dinitrophenyl)-1,4-dihydropyridine (IV).

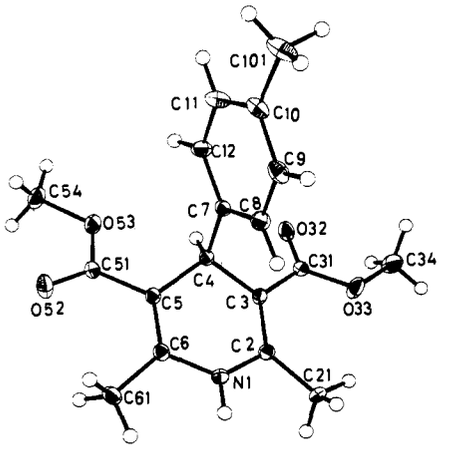

Figure 6. An ORTEP drawing of 2,6-dimethyl-3,5-dicarbomethoxy-4-(4-methylphenyl)-1,4-dihydropyridine (V).

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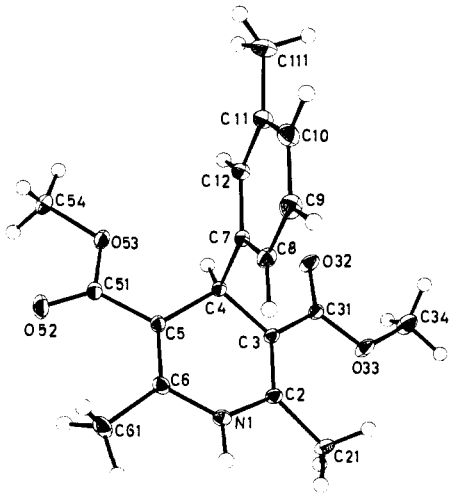

Figure 7. An ORTEP drawing of 2,6-dimethyl-3,5-dicarbomethoxy-4-(3-methylphenyl)-1,4-dihydropyridine (VI).

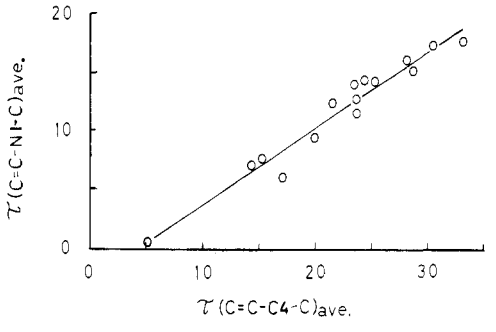

Figure 8. Correlation of the dihydropyridine ring distortion of C4 with that at N1. The degree of puckering at each atom is defined by the average of the torsion angles calculated about the two ring bonds involving these atoms. The slope, intercept, and correlation coefficient obtained by linear regression are 0.065, -2.85, and 0.97, respectively.

The conformation of the 1,4-dihydropyridine ring is best described in terms of the torsion angles about the intraring bonds (Table II). These angles reflect the displacement of the ring atoms from coplanarity; all the torsion angles would be zero in a planar system. A perusal of the magnitude and sign of these torsion angles (first six rows of Table II) for the six compounds plus a variety of other 1,4-dihydropyridine derivatives shows that the greatest ring distortions always occur at the nitrogen (N1) and the tetrahedral carbon (C4). Both atoms are displaced in the same direction from the ring and form the apexes of a boat-type conformation.

The degree of the ring distortions at N1 and C4 is directly reflected in the magnitude of the torsion angles about the ring bonds emanating from these two atoms. The torsion angles about the C4 ring bonds are, in all cases, greater than those for the N1 bonds (Table II), indicating that the puckering is greater at C4. The C4 distortion, which varies considerably among the compounds, is linearly related to that at the nitrogen (Figure 8): the greater the displacement of C4 from the ring, the larger is the ring distortion at N1. The direct coupling of these distortions is brought about by the relative inflexibility of the ring double bonds.

The differences in the degree of dihydropyridine ring puckering observed in the compounds results from a composite of factors. These can best be discussed by referring

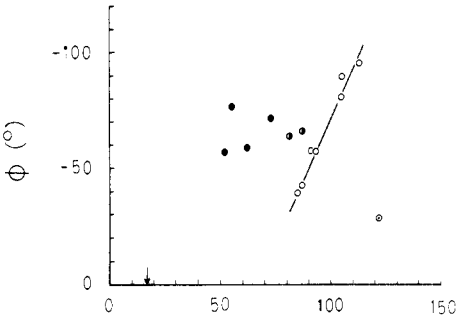

Figure 9. A plot of the interring conformational angle (ϕ) against the distortion from planarity of the dihydropyridine ring ($\sum 1\tau 1$). Key: open circles, compounds I–III, V, VI, and VIII; half-filled circles, compounds XII and XIII; filled circles, compounds IV, VII, and IX; circle with dot, compound XI; arrow, compound XIV.

to Figure 9. In this figure the distortion of the dihydropyridine ring from planarity (defined as the sum of the absolute values of the six ring torsion angles, $\sum 1\tau 1$) is plotted against the conformation about the interring bond (defined as the C8–C7–C4–C3 torsion angle, ϕ). The lack of any significant steric strain imposed by substituents on the dihydropyridine ring in *N*-benzyl-1,4-dihydronicotinamide (XIV)[20] results in a minimal amount of dihydropyridine ring distortion. On the other hand, the ring puckering is much more pronounced in the other compounds as a result of the repulsive forces between the ring substituents. Those compounds containing an ortho substituent on the phenyl ring other than hydrogen (filled circles) exhibit the least amount of ring puckering of the series. The phenyl ring in these derivatives, on the average, bisects the dihydropyridine ring, with the C8 hydrogen residing approximately over the center of the ring. The nonbonded interactions between the carbomethoxy groups on C3 and C5 and the C12 substituent are minimized by this conformation and, in turn, cause the dihydropyridine to be flatter than those compounds containing only hydrogens in the ortho-position.

A greater dispersion of ϕ values is found among those compounds having only *o*-phenyl hydrogens. With only a few exceptions, the phenyl ring conformation (ϕ) in these compounds is directly related to the observed dihydropyridine ring puckering (the correlation coefficient of the line drawn through open circles in Figure 9 is 0.96). Crystal packing forces are apparently the cause of the deviation from this relationship for the β-pyridyl compounds XII and XIII (half-filled circles).[18,19] In these crystals the pyridine nitrogen is involved in a strong intermolecular hydrogen bond with the N1 hydrogen. The deviation of compound XI is not as easily explained. However, if the labeling of the dihydropyridine ring for this compound is reversed, that is, if C_2 becomes C_6, C_3 becomes C_5, etc., which is equivalent to redefining ϕ as the C8–C7–C4–C5 torsion angle, the point falls close to the line. This suggests that the linear relationship between ϕ and $\sum 1\tau 1$ observed for most of the compounds may have a counterpart with an opposite slope. Further studies are clearly required to test this postulate, the significance of which may arise from the underlying chirality of the drug–receptor interacion. Consistent with this, 1,4-dihydropyridines with nonidentical ester functions at positions C3 and C5 are generally more active than their symmetrically substituted counterparts.[22]

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Table I. Crystallographic Data[a]

	I	II	III	IV	V	VI
a (esd), Å	7.376 (2)	14.833 (4)	10.495 (2)	11.800 (2)	10.244 (3)	15.106 (2)
b, Å	9.596 (3)	7.390 (2)	16.000 (3)	10.136 (2)	16.016 (6)	7.347 (1)
c, Å	11.663 (3)	15.685 (2)	10.702 (2)	15.050 (2)	10.709 (2)	17.392 (2)
α, deg	110.54 (2)	90	90	90	90	90
β, deg	95.08 (2)	109.92 (2)	115.80 (2)	109.27	114.93 (2)	123.47 (1)
γ, deg	99.78 (2)	90	90	90	90	90
space group	$P\bar{1}$	$P2_1/n$	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/c$
Z	2	4	4	4	4	4
maximum 2θ, deg	45	60	70	70	70	75
total no. of unique data	2002	2877	4669	4637	4688	6529
intensities $>2.5\sigma(I)$	1507	2246	4308	4089	3793	5979
R (usual)	0.065	0.107	0.032	0.046	0.075	0.052
R (weighted)	0.070	0.131	0.037	0.041	0.066	0.035

[a] I = 2,6-dimethyl-3,5-dicarbomethoxy-4-phenyl-1,4-dihydropyridine; II = 2,6-dimethyl-3,5-dicarbomethoxy-4-(3-nitrophenyl)-1,4-dihydropyridine; III = 2,6-dimethyl-3,5-dicarbomethoxy-4-(4-nitrophenyl)-1,4-dihydropyridine; IV = 2,6-dimethyl-3,5-dicarbomethoxy-4-(2,4-dinitrophenyl)-1,4-dihydropyridine; V = 2,6-dimethyl-3,5-dicarbomethoxy-4-(4-methylphenyl)-1,4-dihydropyridine; VI = 2,6-dimethyl-3,5-dicarbomethoxy-4-(3-methylphenyl)-1,4-dihydropyridine.

Table II. Selected Torsion Angles (degrees) and Relative Pharmacological Activity of Compounds I-XIV[a,b]

								VII								
atom	atom	atom	atom	I	II	III	IV	V	VI	1	2	VIII	IX	X	XI	XII	XIII	XIV
N1	C2	C3	C4	10.6	6.5	6.6	9.2	6.6	7.1	3.1	4.8	10.5	10.6	10.3	9.4	4.8	3.4	1.8
C2	C3	C4	C5	−29.3	−24.1	−23.2	−17.3	−23.3	−25.1	−13.5	−16.1	−29.0	−22.0	−31.1	−32.8	−20.8	−21.9	−4.7
C3	C4	C5	C6	27.7	24.4	24.2	12.9	23.9	25.3	15.2	18.0	27.1	17.9	29.4	33.4	22.1	24.7	5.7
C4	C5	C6	N1	−6.7	−7.0	−8.6	−0.4	−7.7	−7.6	−6.2	−8.4	−5.6	−2.9	−7.0	−10.6	−7.2	−8.9	−3.9
C5	C6	N1	C2	−16.3	−14.2	−11.1	−9.9	−12.4	−14.2	−6.2	−5.1	−17.5	−11.3	−18.3	−17.5	−12.0	−12.5	0.1
C6	N1	C2	C3	14.1	14.4	12.1	5.3	13.0	14.4	7.9	7.0	14.8	7.4	16.4	18.1	13.2	15.5	0.9
C21	C2	C3	C31	5.6	4.8	2.2	8.4	1.9	3.5	−2.0	−0.3	6.3	9.9	10.5	5.7	2.1	−0.5	
C61	C6	C5	C51	2.6	−2.0	−2.5	6.2	−0.9	−3.1	0.2	−4.3	−0.1	5.6	−1.1	−4.3	−6.6	−5.8	
C2	C3	C31	O32	−177.0	−177.8	165.7	−174.2	157.8	173.5	−9.4	8.1	175.4	−169.9	174.2	169.3	−11.2	179.2	
C6	C5	C51	O52	4.1	7.1	13.0	5.5	15.9	11.4	13.3	5.3	11.8	9.1	4.3	2.0	2.9	7.3	
C3	C31	O33	C34	177.0	−177.9	−178.4	179.2	177.4	−177.2	174.6	176.2	−177.0	175.4	177.3	176.1	−176.9		
C5	C51	O53	C54	176.6	−178.5	179.5	−178.6	177.6	−178.8	−179.3	179.6	178.5	−179.8	178.6	−175.9	177.7		
C8	C7	C4	C3	−81.5	−57.8	−39.5	−77.0	−42.8	−58.2	−56.7	−62.8	−90.1	−73.5	−96.3	−29.3	−64.4	−66.4	
C12	C7	C4	C3	96.3	121.0	142.2	97.2	137.9	121.9	121.9	118.8	87.5	101.0	82.8	53.4	115.4	113.6	
C10	C11	N111	O113		−6.0													
C10	C11	N111	O112		178.3													
C11	C10	N101	O102			−169.4	173.3											
C11	C10	N101	O103			12.3	−6.1											
C7	C12	N121	O122				33.8						36.8					
C7	C12	N121	O123				−149.5						−141.1					
Adv SD				0.6	0.9	0.1	0.2	0.3	0.1									
rel act. (IX = 100)				18	130	0.16	<0.05	<0.05	4.6	600	600	0.005	100	1.7	~18			
absolute act., ID_{50},[c] M × 10^8				2.8	0.4	320	>5000	~5000	11	0.09		5000	0.51	30	3.0			

[a] I-VI are defined in footnote *a* of Table I. [b] VII = 2,6-dimethyl-3,5-dicarbomethoxy-4-(2,3,4,5,6-pentafluorophenyl)-1,4-dihydropyridine;[11] VIII = 2,6-dimethyl-3,5-dicarbomethoxy-4-[4-(dimethylamino)phenyl]-1,4-dihydropyridine;[11] IX = 2,6-dimethyl-3,5-dicarbomethoxy-4-(2-nitrophenyl)-1,4-dihydropyridine;[11] X = 2,6-dimethyl-3,5-dicarbomethoxy-4-(3-cyanophenyl)-1,4-dihydropyridine;[11] XI = diethyl 2,6-dimethyl-4-phenyl-1,4-dihydro-3,5-pyridinedicarboxylate;[17] XII = 2,6-dimethyl-3,5-dicarbethoxy-4-(β-pyridyl)-1,4-dihydropyridine;[18] XIII = 2,6-dimethyl-3,5-diacetyl-4-(β-pyridyl)-1,4-dihydropyridine;[19] XIV = *N*-benzyl-1,4-dihydronicotinamide.[20] [c] ID_{50} measured against slow component or tonic response in guinea pig ileal longitudinal smooth muscle induced by the muscarinic agonist *cis*-2-methyl-4-[(dimethylamino)methyl]-1,3-dioxolane methiodide.[11,21]

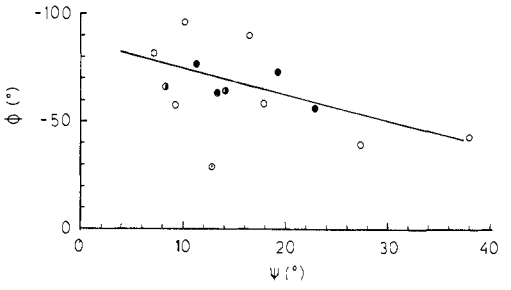

Figure 10. The interring conformational angle (ϕ) plotted against the sum of torsion distortions of the C3 and C5 substituents (Ψ). Ψ is defined as the sum of the absolute differences between the C2–C3–C31–O32 and C6–C5–C51–O52 torsion angles and their respective ideal values of either 0° or 180°. Key: same as in Figure 9.

Table III. Intermolecular Hydrogen Bonds

	I	II	III	IV	V	VI
acceptor O	O32	O32	O32	O52	O32	O32
N···O, Å	2.944	3.014	2.953	2.943	2.945	2.964
H···O, Å	2.14	2.17	2.07	2.05	2.11	2.05
N-H···O, deg	157.4	170.4	165.3	164.0	166.8	168.4

Free rotation of the phenyl ring about the C4–C7 bond is restricted in part by the carbomethoxy groups at C3 and C5. These groups are able to rotate about the C3–C31 and C5–C51 bonds to accomodate a particular phenyl ring conformation. The influence of the conformational angle (ϕ) on the torsional distortion of these groups (sum of the absolute differences between the observed torsion angles about the C3–C31 and C5–C51 bonds and their ideal conformation, Ψ) is illustrated in Figure 10. There is a general trend (correlation coefficient for line is 0.65) for this distortion to be larger with smaller negative ϕ values.

The phenyl ring in all the compounds examined is in a "priapic" orientation at C4. Though this is the sterically preferred conformation, there is still a considerable amount of strain present in the molecule as a result of nonbonded interactions involving the ortho substituents of the phenyl ring. The strain is relieved in a number of ways, most notably by the puckering of the dihydropyridine ring (discussed above), distortion of the angles around C4 from their ideal tetrahedral values, and a slight extension of the exocyclic C4–C7 bond [usual length of a C(phenyl)–C(tetrahedral) bond is 1.51 Å].[16]

The nitro groups in compounds II, III, IV, and IX are twisted out of coplanarity with the phenyl ring about their exocyclic C–N bonds (Table II). The rotation about this bond is much larger for the ortho-substituted group, more than 20° higher than for the meta- or para-substituted analogues, since it experiences much greater steric strain.

In each of the crystal structures, the hydrogen on N1 participates in an intermolecular hydrogen bond with a neighboring carbonyl oxygen. The parameters associated with these interactions are presented in Table III. Similar intermolecular bonding was also found in the previously reported structures of compounds VII to XI. An exception to this characteristic N1–H···O=C type bonding is observed in the β-pyridyl analogues (compounds XII and XIII),[18,19] where the hydrogen acceptor is the pyridine ring nitrogen. The differences in the hyrogen bonding parameters found for the various compounds are insignificant, indicating that the degree of ring puckering at N1 does not influence the strength of the interaction. Aside from the hydrogen bond, there are no other short intermolecular contacts in these structures which are suggestive of directional-type bonding.

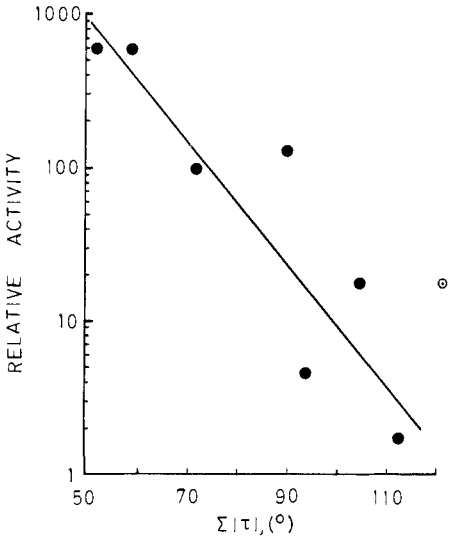

Figure 11. Correlation between biological activity (inhibition of guinea pig ileal longitudinal smooth muscle mechanical responses) and distortion from planarity of dihydropyridine ring ($\sum|\tau|$). Circle with dot is for compound XI, other circles are for compounds I, II, VI, VII (molecules 1 and 2), IX, and X.

A fairly extensive array of 1,4-dihydropyridine-type calcium antagonists have been synthesized and pharmacologically tested in an effort to formulate structure–activity relationships.[2,4,9,10] The activities of these compounds, whether measured on smooth muscle or cardiac muscle preparations, show the same general trends in structure–activity relationships.[4] The activities of the compounds studied in this paper, defined as the concentration that produces a 50% inhibition of the muscarinic receptor-mediated calcium ion dependent contraction of guinea pig ileal longitudinal smooth muscle, are listed in Table II and are also expressed relative to that of Nifedipine (compound IX = 100). The ortho-substituted analogues are generally the most active compounds, with the order of potency being ortho ≥ meta ≫ para. Large para substituents have a very detrimental effect on the relative potency. These general trends have been noted in a number of previously reported studies.[2,4,9,10]

The available structure–activity relationship studies have shown that the activities of these compounds are relatively independent of the electronic character (electron releasing or withdrawing) of the phenyl substituents but are highly dependent on their size.[2,9,10] Rodenkirchen and co-workers[10] found an excellent correlation between the negative inotropic activity in isolated cardiac muscle and a substituent constant, B_1, which is a measure of the substituent's minimum width. This correlation suggests that subtle topological differences between the compounds might be responsible for their markedly different activities. We therefore examined the possibility that a correlation might exist between pharmacological activity and one or more structural parameters derived from the X-ray study.

A good linear correlation was found between the degree of ring puckering ($\sum|\tau|$) and the relative activity of the parent unsubstituted compound and ortho and meta derivatives (Figure 11). A linear regression analysis of the points in this graph (excluding compound XI) provided a slope, intercept, and correlation coefficient of −0.03, 4.95, and 0.89, respectively. This correlation excludes compounds carrying para substituents in the phenyl ring whose activity is greatly reduced relative to that predicted from this correlation. This striking decrease in activity for the

(22) Meyer, H.; Bossert, F.; Wehinger, E.; Stoepel, K.; Vater, W. *Arzneim.-Forsch.* **1981**, *31*, 407.

latter compounds may arise from steric limitations of the binding of these substituents to the calcium receptor site. The β-pyridyl compound also deviates markedly from this correlation. This compound is crystallographically unique in this series because the pyridyl nitrogen is involved in an intermolecular H bond with the N1 of the 1,4-dihydropyridine ring.

Though based on only six compounds, the correlation in Figure 11 is remarkable in two respects: (1) it provides definitive clues on how the potency of these compounds might be enhanced, and (2) it is the first time, to the authors' knowledge, that crystallographic data have been directly incorporated into a quantitative structure–activity relationship.

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Supplementary Material Available: Fractional atomic coordinates (Table IV), intramolecular bond distances (in angstroms) (Table V), and intramolecular bond angles (in degrees) (Table VI) for structures I–VI (6 pages). Ordering information is given on any current masthead page.

Preparation and Antiinflammatory Activity of 2- and 4-Pyridones

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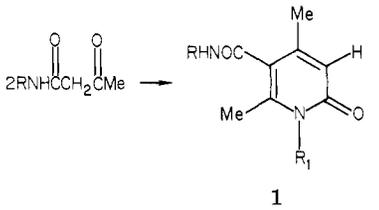
Several *N*-alkyl- and *N*-arylacetoacetamides have been self-condensed to form pyridones. *N*-Alkylacetoacetamides give 2-pyridones, while *N*-arylacetoacetamides give 4-pyridones. In an attempt to develop nonacidic, nonsteroidal antiiflammatory agents, the pyridones were tested in a carrageenan-induced pedal edema assay in rats. While the 2-pyridones were not active, 9 of 17 4-pyridones tested were active, and one compound (**4g**) had antiinflammatory efficacy in a dose–response assay (ED_{50} values). Most compounds were considered nontoxic by determination of approximate LD_{50} values in mice by a standard multidimensional observational assay.

The continued interest in nonacidic, nonsteroidal, safe antiinflammatory agents is an ongoing search in most pharmaceutical laboratories. The separation of antiinflammatory activity from GI toxicity, however, has been a key factor in the search for safer compounds, since it is generally agreed that gastric irritation is associated in some way with the acidic nature of such drugs.[1,2] It is reported that pyridones and their hydrogenated products piperidones exhibit good antiinflammatory activity. For example, 3-phenyl-2(1*H*)-pyridone[3a] is said to have a high degree of antiinflammatory activity and, similarly, 1-cycloalkoxy-2(1*H*)-pyridones[3b,c] exhibit the same activities. The hydrogenated products, 2-piperidones, are said to be antiinflammatory, antipyretic, and analgesic compounds.[1c] In our continued effort to discover biologically active molecules, we found that the self-condensation of *N*-alkyl- and *N*-arylacetoacetamides yielded 2- and 4-pyridones, respectively. In view of the above reported pharmaceutical activity for similar compounds, the effect of the 2- and 4-pyridones on the antiinflammatory response was evaluated in the carrageenan-induced pedal edema assay in rats.

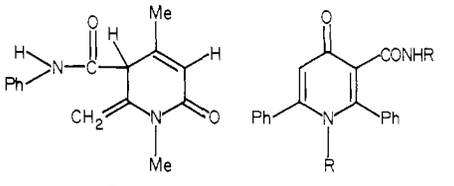
The 2- and 4-pyridones used in this study were prepared by the self-condensation of acetoacetamides. Self-condensations of acetoacetamides under both thermal and acid-catalyzed conditions has been the subject of a number of investigations. In 1960 a German patent by Ehm[4] described the self-condensation of a number of alkyl- and arylacetoacetamides to give 2-pyridones 1 (eq 1).



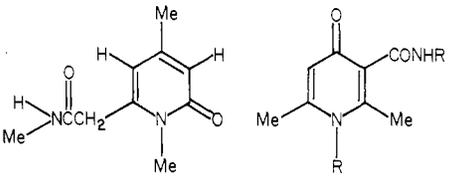
(1)

1

In 1966, Bukac and Sebenda[5] described a similar self-condensation for *N*-methyl- and *N*-ethylacetoacetamides. Subsequently, the isomeric structure **2** was proposed for



2 **3**



5 **4**

the compounds produced.[6] Zankowska-Jasinka et al.[7] have described the self-condensation of benzoylacetamides under acidic conditions to form 4-pyridones **3**; in a related paper,[8] they described the succinic acid dichloride cata-

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(1) E. Arrigoni-Martelli, "Inflammation and Antiinflammatories", Wiley, New York, 1977, p 208.
(2) K. D. Rainsford, K. Brane, and M. W. Whitehouse, "Aspirin and Related Drugs: Their Actions and Uses", Birkhauser, Verlag, Basel, Switzerland, 1977, p 67.
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