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SYNTHESIS AND X-RAY CRYSTAL STRUCTURE OF 1,4-DIHYDRO-2,6-DIMETHYL-4-(2'-ISOPROPYLPHENYL)-3,5-PYRIDINE-DICARBOXYLIC ACID DIMETHYL ESTER: A NIFEDIPINE ANALOGUE

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Abstract: We report the synthesis and X-ray crystal structure of 1,4-dihydro-2,6-dimethyl-4-(2'-isopropylphenyl)-3,5-pyridine-dicarboxylic acid dimethyl ester (**4**), an analogue of the 1,4-dihydropyridine calcium channel antagonist, nifedipine. Solution state NOE data indicate the presence of both rotameric forms. The solid state shows exclusively one rotamer of **4** (that in which the 2'-isopropyl substituent is *syn* with C4H, which is also the major solution state rotamer). The 3,5-methyl esters adopt an *ap/sp* orientation with respect to the dihydropyridine double bonds in the solid state.

4-Aryl-1,4-dihydropyridines (aryl-DHPs) such as nifedipine (**5**) are calcium channel antagonists that are used clinically for the treatment of angina and hypertension. All pharmacologically potent aryl-DHP calcium channel antagonists have asymmetrically substituted 4-aryl rings.[1] When the DHP ring is replaced by an asymmetric mimic, the C4 enantiospecificity of biopotency is very high.[2] These structure-activity features argue for a distinct rotameric preference about the C4-C1' bond in the receptor bound state. As a result, considerable speculation and experimentation has been aimed at deriving the rotameric preference and barrier to this rotation.[3] The two low energy rotameric conformations place the ring planes orthogonal to one another.

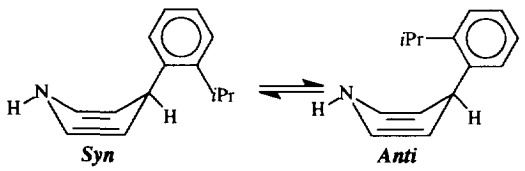

Figure 1. Definitions of *syn* and *anti* rotamers. Substituents on the dihydropyridine ring omitted for clarity.

The rotamers are designated *syn*- (with C2' substituent closest to the C4H) and *anti*- (with the 2' substituent facing away from the C4H) (Figure 1). Crystallographic examination has shed some light on the solid state rotameric preferences about the ring juncture but the question of the solution state conformation remains largely unanswered.[4] Compound **4** (in which the 2'-nitro group of nifedipine was replaced with an isopropyl moiety) was synthesized as a potential probe for rotational preference studies. We report the synthesis, X-ray crystal structure, NMR-derived rotameric preference and an estimate of the biological activity of **4**. Comparison with other crystal structures provides new insight into the effect of *syn/anti* rotameric preference upon the pucker of the dihydropyridine ring.

Using the method of Meyers and Mihelich, *ortho*-anisic acid was condensed with 2-methyl-2-amino-1-propanol followed by cyclization to the 2-anisyl-4,4-dimethyloxazoline.[5] This aryl oxazoline was then reacted with the isopropyl Grignard. The pseudo-chelation of the magnesium in the Grignard by both the nitrogen of

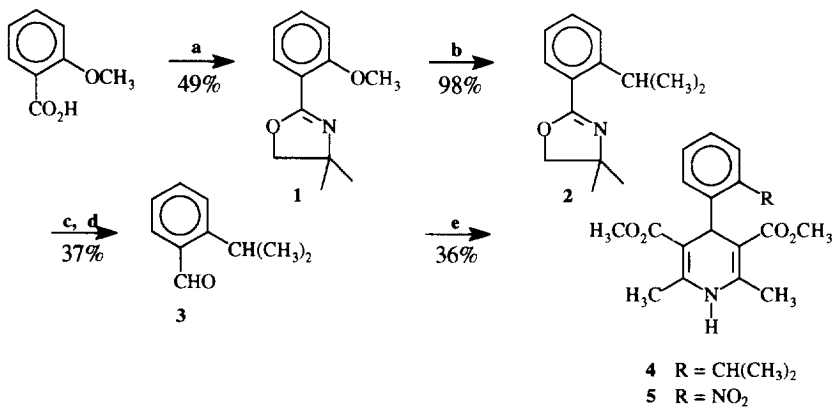

Figure 2. Preparation of **4**. **a**: 2-methyl-2-amino-1-propanol/$SOCl_2$; **b**: *i*PrMgCl/THF; **c**: $CH_3I/CH_3CH_2NO_2$, $NaBH_4$ /EtOH; **d**: PCC/CH_2Cl_2; **e**: Methylacetoacetate/NH_4OH/MeOH.[7]

the oxazoline and the oxygen of the aryl-methoxy group directs the Grignard to exclusive substitution at the *ortho-* position. Quaternization of the nitrogen with methyl iodide followed by reductive removal of the oxazoline with $NaBH_4$ gave the alcohol[6] which was readily oxidized to the substituted aldehyde with pyridinium chlorochromate (PCC). Subsequent employment of the Hantzsch pyridine synthesis,[8] with the omission of the final oxidation to the pyridine, afforded dihydropyridine **4** in 36% yield (Figure 2).

NMR studies of **4** employed a Bruker AMX500 spectrometer with 20 mM samples in $CDCl_3$. The solution state rotameric preference about the C4-C1' bond was determined using a standard difference NOE protocol as was employed in analogous studies of other 4-aryl-1,4-dihydropyridines.[9a,b] At ambient temperature and at 206 K, NOE's were seen from C4H to both the 2'-isopropyl methine and C6'H, with the former being substantially larger. This indicates that the more highly populated rotamer is that with the 2'-isopropyl substituent *syn* with C4H. The data were not of sufficient quality to provide quantitative determination of the rotameric populations, but a substantial *syn* preference is evident.

The X-ray crystal structure of **4** (Figure 3) was determined at Bristol-Myers Squibb using the same instrumentation and methods as those reported by Rovnyak.[10] The solid state shows an exclusive population of the rotamer with the 2'-isopropyl substituent *syn* with C4H. This is the same rotameric preference adopted by the 2'-nitro group in **5** in the solid state. Crystal packing forces and thermodynamic stability are assumed to be responsible for the appearance of only one rotameric form in the solid state even though solution state data indicate the presence of both.

In the X-ray crystal structure of **4**, the phenyl ring is 5.7° off of the perpendicular bisector of the dihydropyridine ring and the 2'-isopropyl group has a lateral tilt of <1° with respect to the phenyl ring (see Table 1). These angles are 12.5° and 35.9°, respectively in **5**. The methyl esters in positions 3 and 5 of the dihydropyridine ring adopt different rotameric dispositions about their respective dihydropyridine - ester carbonyl carbon bonds in both **4** and **5**. In compound **4**, the ester in the 3 position of the dihydropyridine ring assumes the antiperiplanar conformation (ester carbonyl with respect to dihydropyridine double bond) while the ester in the 5 position adopts the synperiplanar conformation. The ester dispositions are the same in **5**.

Table 1. Aquisition parameters and selected torsion angles for the X-ray crystal structures of **4**.[11]

Temperature, K	295
a, Å	8.256(1)
b, Å	32.388(2)
c, Å	14.059(1)
Space Group	P_{bca}
N_{uni}[b]	3313
N_{obs}[c]/N_{var}[d]	1318/226
R/R_w	0.067/0.077
Torsions:[e]	
N1-C2-C3-C4:	8.0
C2-C3-C4-C5:	-24.3
C3-C4-C5-C6:	25.4
C4-C5-C6-N1:	-10.4
C5-C6-N1-C2:	-9.1
C6-N1-C2-C3:	10.3
C2-C3-C10-O12:	176.7
C6-C5-C9-O11:	13.0
C3-C10-O14-C16:	-179.4
C5-C9-O13-C15:	-178.7
C1'-C2'-C1"-C2":	-120.4
C3-C4-C1'-C2':	112.2

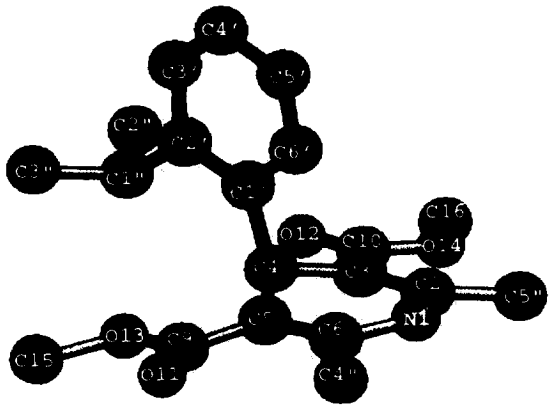

Figure 3. X-ray crystal structure of **4**.

The dihydropyridine ring of **4** in the solid state is a flattened boat as in other 4-aryl-1,4-dihydropyridine X-ray crystal structures. However, it is somewhat more puckered than many other nifedipine analogues. In compound **4**, C4 and N1 form angles of 21.3° and 8.4°, respectively, with the plane described by the four sp^2 carbons in the dihydropyridine ring. These angles in nifedipine, **5**, are 17.0° and 8.0°, respectively. The influence of rotameric preference on DHP ring pucker can be gauged from the DHP ring conformations of the 2'-chloro derivative, which exists in both rotameric forms.[4] With the clorine atom *syn*, the C4-plane angle is 23.3° while the N1-plane angle is 11.7°. However, when the chlorine is *anti*, these angles are 14.2° and 8.9°, respectively. This "flattening" effect is presumed to be due to the electronic repulsion between the chlorine and N1 in the *anti* rotamer. For comparison, the 2',6'-dichloro analog, which can never be in the *syn* form, is even flatter with a C4-plane angle of 5.8° and an N1-plane angle of 4.8°.[9a]

The sum of the absolute values of the six interior torsion angles of **4** is 87.5°. This parameter has been shown to correlate with pharmacologic potency as a calcium channel antagonist (the smaller this sum, the greater the biological activity).[12] For reference, the analogous sum in nifedipine (**5**) is 72.1°,[13] while it is 63.3° and 98.2° for the chlorine *anti* and chlorine *syn* forms of the 2'-chloro derivative, respectively. The sum of the interior torsions for the 2',6'-dichloro derivative is only 27.4°.[9a] These data can be used for the prediction of IC_{50}'s for inhibition of a tonic response in guinea pig ileal longitudinal muscle. IC_{50} values of 0.14 nM and 7.8 nM are obtained for the chlorine *anti* and chlorine *syn* forms of the 2'-chloro derivative, respectively. The average of these IC_{50}'s (3.9 nM) is quite close to the observed value of 3.1 nM.[14] Based on the same model, a predicted IC_{50} for the 2'-isopropyl derivative (**4**) is on the order of 2.3 nM, very close to the observed IC_{50} of 2.2 nM for nifedipine (**5**).[12] Given the similarity in ester disposition between **4** and **5** and the substantial *syn* rotameric preference of the 2'-isopropyl analog (**4**), assessment of the biopotency of **4** should serve to define the importance of the electronic properties of the 2'-substituent in aryl-DHP calcium channel antagonists.

Acknowledgements

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7. **1,4-Dihydro-2,6-dimethyl-4-(2'-isopropylphenyl)-3,5-pyridine-dicarboxylic acid dimethyl ester (4).** 2-Isopropylbenzaldehyde (**3**) (4.18 g; 28.2 mmol) was taken up in 25 mL of absolute methanol in an aerosol dispersion tube.[9a] Aqueous ammonia (30%; 3.8 mL; 35.2 mmol NH_3) and 6.1 mL (56.4 mmol) methylacetoacetate and a magnetic stirbar were added. The reaction was heated at 80°C at 35 - 40 psi for 16 h during which time the solution turned yellow. The solution was then cooled and the solvent removed to give a yellowish solid. Purification was effected by recrystallization from absolute methanol to give pale yellow crystals that were washed with a small quantity of ice-cold ether and air dried, (3.48 mg; 10.15 mmol; 36%). ^{1}H NMR: ($CDCl_3$) δ 7.30 (dd, 1H, J=7.8 Hz, J=1.5 Hz), 7.20 (dd, 1H, J=7.8 Hz, J=1.2 Hz), 7.11 (overlapping dd, 1H, J=7.2 Hz, J=1.5 Hz), 7.02 (overlapping dd, 1H, J=7.8 Hz, J=1.5 Hz), 5.61 (bs, 1H, NH), 5.36 (s, 1H, C4H), 3.73 (sept, 1H, J=6.8 Hz), 3.63 (s, 6H), 2.33 (s, 6H), 7.53 (d, 6H, J=6.8 Hz); HRMS: calculated for $C_{20}H_{25}NO_4$ 343.1784, found 343.1797; mp: 149-152°C; MS: *m/z* 343 ($M^{+\circ}$, 4.1), 238 (22.7), 224 (100.0), 224 (100), 210 (5.9), 165 (3.5), 131 (3.2), 91 (2.8).

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11. (a) The crystals of **4** were colorless plates recrystallized from absolute methanol using slight heating with slow evaporation. The study gave a cell containing 8 molecules with the formula $C_{20}H_{25}NO_4$. The hydrogens were not refined and are excluded for clarity. (b) Number of symmetry-independent reflections. (c) Number of reflections with $I \geq 3\sigma(I)$ used in least-squares refinement. (d) Number of refined variables. (e) Angles are reported in degrees.

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