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4-BIARYL-SUBSTITUTED DIHYDROPYRIDINES WITH AN UNUSUAL ANTIPERIPLANAR CONFORMATION

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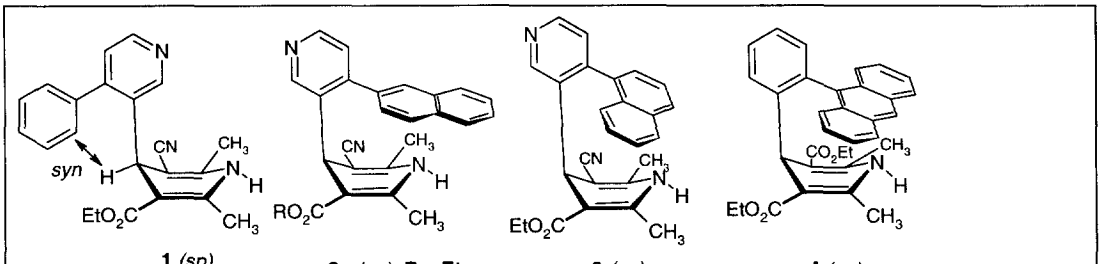
Abstract: We report X-ray crystal structures and NMR solution data of the unusual antiperiplanar conformation of 1,4-dihydro-5-cyano-2,6-dimethyl-4-biaryl-3-pyridine carboxylic acid esters with 3`-(4`-(1``- or 2``-naphthyl)pyridyl)- and 2`-(9``-anthracenyl) phenyl-residues as the biaryl moiety. This class might serve as a biological tool to identify which DHP-rotamer is responsible for the interaction with the biological receptor. © 1997 Elsevier Science Ltd.

4-Aryl-dihydropyridines[1] (DHPs) are pharmacologically effective both as calcium antagonists and as calcium agonists[2]. By rotation of the ortho- or meta-substituted aryl group about the pseudoaxial axis to the chair-shaped DHP ring, two conformations can exist: the antiperiplanar (*ap*) and the synperiplanar (*sp*) rotamers (cf. examples in fig. 1). Usually both forms exist as an equilibrium in solution, dominated by the *sp*-conformer, especially in the crystalline state[3]. Recently we have demonstrated, that it is possible to specifically trap each conformer by oxidation with different reagents.[4] We and others[3a,5] reasoned, that a biological receptor might have a similar preference for one rotamer. In order to identify the biologically active rotamer, it is necessary to have a DHP with a single defined conformation both in solution and in the solid state. Since no DHP is known to date which *exclusively* adopts the *ap*-form, we focused on searching for DHPs with this unusual conformation. For this purpose, we prepared a series of biarylaldehydes by palladium-catalyzed Suzuki-coupling or in analogy to Jutz et al.[6], and converted them into the corresponding DHPs by classical Hantzsch synthesis[7]. A selection of representative structures is shown in fig. 1.

Figure 1



1 *(sp)* **2a** *(ap)*: **R = Et** **2b** *(ap)*: **R = i-Prop** **3** *(ap)* **4** *(ap)*

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Figure 2: *X-ray crystal structures*[8] *of* ***2b*** *(left) and* ***3*** *(right) with ap-conformation*

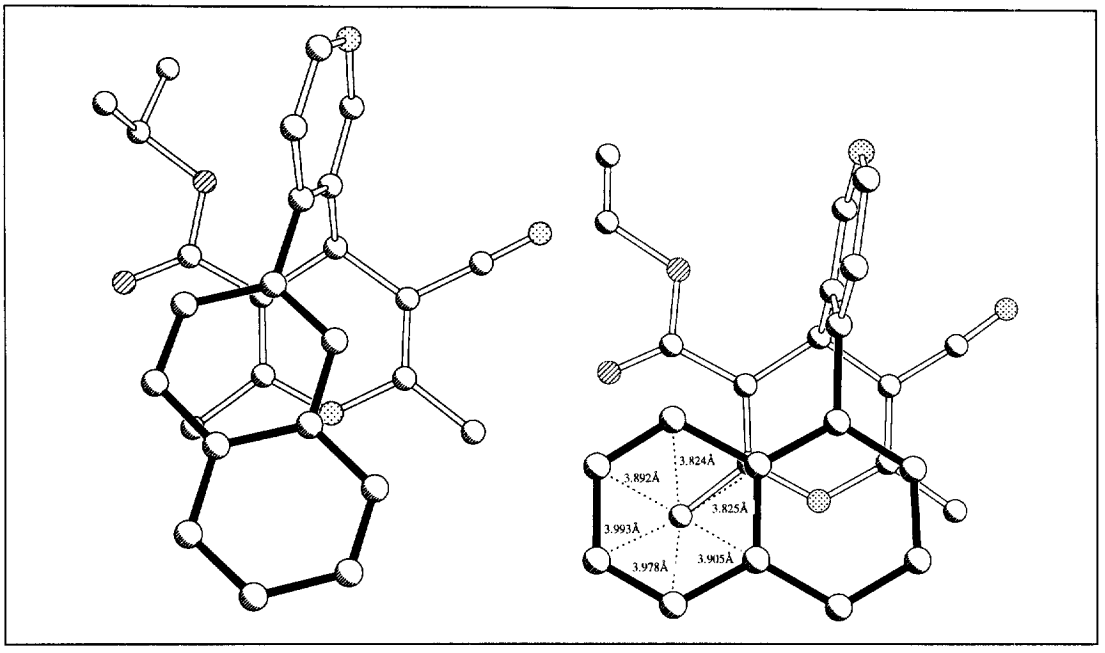


Table 1: *Chemical shifts (ppm) of* ***1, 2a, 3a, 3b*** *and* ***4*** *from 300 MHz-*^{1}*H-NMR-spectra in d* ^{6}*-DMSO*

Position	**1**	**2a**	**3a**	**3b**	**4**
CH3CH2 (t, 3H)	0.87	0.83	0.88	1.0	1.1 (6H)
CH3 (s, 3H)	1.93	1.92	0.96	0.97	0.8
CH3 (s, 3H)	2.15	2.10	1.87	1.76	0.8
CH3CH2 (m, 2H)	3.75-3.95	3.85	3.60-3.90	3.60-3.90	3.85-4.2 (4H)
H4 (s, 1H)	4.78	4.82	4.70	4.69	5.0
Pyr-H5` (d, 1H)	7.10	7.22	7.10	6.90-7.00	
aromatic	7.40 (m,1H,Ph) 7.47 (m,4H)	7.52-7.63 (m,3H) 7.90-8.05 (m,4H)	7.20 (t,2H) 7.41 (t,1H) 7.48-7.60 (m,2H) 7.95 (t,2H)	7.20 7.40 7.45-7.60 7.95 (t,2H)	see footnote [a]
Pyr-H6`(d, 1H)	8.40	8.46	8.50		
Pyr-H2` (s, 1H)	8.5	8.52	8.52		
NH-1 (s, 1H)	9.09 (s,1H)	9.5 (broad s, 1H)	8.10	8.10	6.7

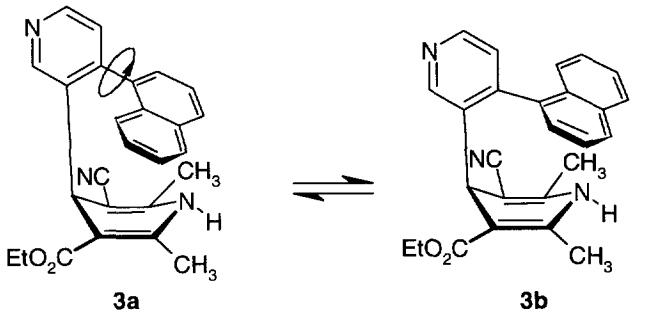
[a] aromatic hydrogens for **4**: 6.85 (d, 1H), 7.12 (d, 2H), 7.2 (t, 2H), 7.3 (t, 2H), 7.33-7.5 (m, 3H), 7.55 (d, 1H), 8.05 (d, 1H), 8.57 (s, 1H).

We tested the conformation of biaryl-DHPs **1, 2, 3** and **4** by NMR and x-ray crystallography. With **1** there was the expected shift of the 2,6-methyl groups of approx. 2 ppm in the NMR, which is typical for DHPs. Looking at DHP-H4 the ROESY-NMR showed an Overhauser effect with the pyridyl-H2' and the phenyl-H3'', H6'', indicating free rotation of the pyridyl group in relation to the DHP ring.

Analogs **2a** and **2b** also showed the DHP-methyl groups in the normal range (Tab. 1). However, the ROESY-NMR revealed a strong NOE effect between the pyridyl-H2' and DHP-H4. Additional cross-signals to the H1'' and H3'' of the naphthyl groups which occur in the 600 msec experiment are only very weak and can be adequately explained by spin diffusion effects. Therefore, an *ap*-rotamer was supposed, and this was confirmed by x-ray structural analysis of the well-crystallizing **2b** (Fig. 2)[8].

Freshly dissolved **3** shows a DHP-methyl-group at 1.9 ppm and the other, with a surprisingly strong high-field shift at 0.96 ppm (Tab. 1). This one is apparently located in the shielding anisotropy range of the naphthyl aromatic, which in an *ap*-rotameric form resides above a methyl group. The distance agrees with the calculations of Bovey[9] on the influence of aromatics on the chemical shift of protons. The suspected *ap*-form was also confirmed by x-ray structural analysis (Fig. 2)[8]. When **3** is in solution for prolonged periods, equilibrium with a second, atropisomeric form with comparable behaviour in terms of chemical shift gradually occurs. This can be attributed to rotation of the naphthyl ring about the biaryl axis (Fig. 3).

Figure 3



In **4** both 2,6-methyl groups exhibit the unusual high-field shift of 0.8 ppm. This speaks for an *ap*-conformation with simultaneous shielding of the two methyl groups by the anthracene group, which is double benzo-annelated in relation to the naphthyl group. Accordingly, for the DHP-H4 the ROESY-NMR shows only an intense Overhauser effect towards phenyl-H6'.

We have reported on DHPs which are present exclusively as *ap*-conformers both in solution and in crystalline form. As no charge-transfer bands were detected in the UV-Vis spectra, the thermodynamical driving force for adopting of the *ap*-conformation could be attributable to the increased steric inhibition of the *sp*-conformation and the non-binding interaction between aromatics and the DHP-dipole in the *ap*-form. For this last reason,

benzyl-substituted hydantoins[10], diketopiperazines[11] and triphenylbenzyldihydropyridines[12] are known to exist in a similar folded conformation.

Affinity values at the DHP-receptor in the resting state from calf hearts were determined for **1**, **2a** and **3** (IC50`s = 250, 100 and 270 nM, resp.), whereas **4** did not bind at all, probably due to sterical reasons. These data show, that the *sp*-form is no prerequisite for receptor-binding; **1** might bind in the *ap*-form as well, since we have demonstrated free rotation of the 4-substituent.

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[8] Crystallographic data for **2b** and **3** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication. Copies of the data can be obtained on application to The Director, CCDC, 12 Union Road, GB-Cambridge CB2 1EZ, UK (fax: Int. code +(1223)336-033; e-mail: teched@chemcrys.cam.ac.uk).

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