Synthesis and X-ray structure conformation of novel unsymmetrical 1,4-dihydropyridine

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Methyl 2,6-dimethyl-5-(2-methylphenylcarbamoyl)-4-(3-nitrophenyl)-1,4-dihydropyridine-2-carboxylate (3) was prepared by known Hantzch method and its structure was elucidated by X-ray diffraction method.

Keywords: 1,4-dihydropyridine, crystal structure, flattened boat

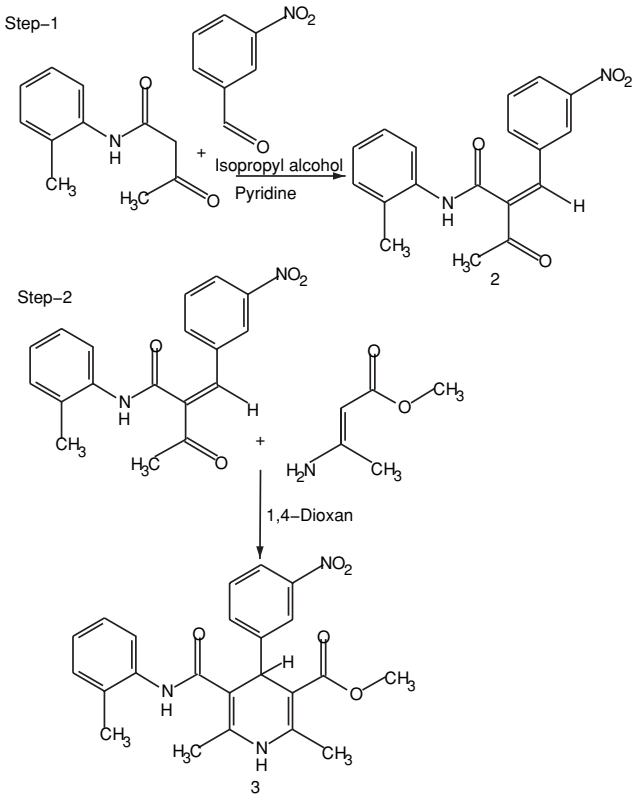
Among various cardiovascular 1,4-dihydropyridine (1,4-DHP) calcium channel antagonists,[1,2] Nifedipine, Darodipine and Flordipine are the compounds having symmetrical structure in their ester functionality at 3-and 5-position.[3,4] Other drugs like Nimodipine, Nicardipine, Nilvodipine, Falodipine, Isradipine, Reodipine, Amlodipine, Nitrendipine, Lacidipine, Bernidipine, Sangandipine, Benidipine, Furaldipine, Manidipine, AE-0047, SM-6586 and Toludipine are unsymmetric in differentiating ester linkage between 3-and 5-position in the drugs.[5–7]

However, in recent developments, these compounds are found to be active as antitubercular agents. The 2D and 3D QSAR studies has revealed some important points in drug design,[10,11] but hybrid structure was not synthesised. Very few compounds of this type are reported in literature.[12] This has prompted us to synthesise the unsymmetrical 1,4-DHP where at C5 carbamoyl function is introduced and on the other hand an esteric group is present.[8,9] This type of hybrid structure was undertaken for the synthesis and confirmation by single crystal X-ray diffraction method.

The compound 3 was synthesised in a two step reaction as shown in Scheme 1; 2 g of **3** was taken in 30 ml solvent mixture [ethanol + DMF (15ml: 7.5ml)]. 4 g charcoal was added and heated on a heating device for 8 minutes. The solution was filtered while hot through Whatmann 42 filter paper. The solution was kept in a slightly opened stoppered conical flask. The crystals (rectangular shape) were grown by thin film evaporation technique.

The X-ray structure analysis of **3** showed that the 1, 4-DHP ring in the structure has a flattened boat conformation (Fig.1) with C4 and N1 being –0.197(5)Å and –0.146(5)Å, respectively, from the plane defined by C2, C3, C5 and C6. The maximum deviation from their mean plane is 0.129(5)Å for C3. The degree of ring distortions at N1 and C4 is directly reflected in the magnitude of torsion angles emanating from these two atoms. The torsion angle value of C3–C4–C5–C6 (–29.35°) or C2–C3–C4–C5 (28.45°) is higher in the 1,4-DHP ring, which indicates that there is greater puckering at C4 than at N1. The 4-nitrophenyl ring occupies an axial position on C4 and thereby lies above the 1,4-DHP ring.

Another confirmation of the planarity of the 1,4-DHP ring is the sum of magnitudes of the six intra-ring torsion angles, ΣP, around the ring. For the compound under study, ΣP is 106.1°. This value is relatively more than reported nifedipine drug molecule *i.e.* 72°. Such a mild flatenning might have significant implications for the calcium modulatories of the above compound, as it has been suggested [13–15] that the most active compounds in the nifedipine and nisoldipine series possess the shallowest boat conformations.



Scheme 1

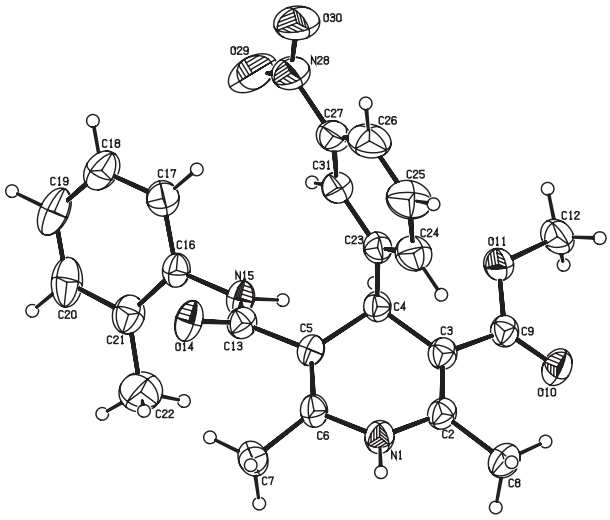


Fig. 1 Crystal structure of the molecule 3 at 50% probability.

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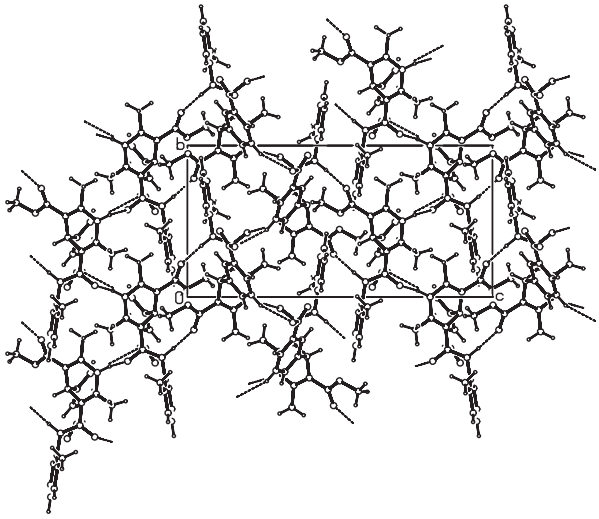

Fig. 2 Packing of the molecules down a axis. Dashed lines represent the hydrogen bonds.

The other structural characteristic of the molecule is the conformation of carbamoyl and carbamethoxy groups. Each group can be oriented in synperiplanar *(cis*) or antiperiplanar (*trans*) conformation with respect to the adjacent C=C of the 1,4-DHP ring. The torsion angles observed are C2–C3–C9–O10 (44.46°) and C6–C5–C13–O14 (11.95°), which indicate *cis/cis* conformation. The structure exhibits both intra and intermolecular hydrogen bonds of the type C–H...O and N–H...O, which helps in stabilising the crystal structure. The packing diagram of the molecules down a axis indicate that the molecules are linked by the hydrogen bonds forming an infinite chain (Fig. 2). In addition these chains are interlinked by the hydrogen bonds. The presence of hydrogen bonding in the crystal structure shows its major role in the calcium channel antagonist effect.[16,17] All H-bonds of acceptor atoms are at C3 and C5 substituent groups *i.e.* at O10, O14 respectively.

Experimental

The infrared spectrum was recorded on Shimadzu FT-IR-8400on KBr pellet.The frequency range is 400–4000 cm^{-1} . The ^1H NMR spectrum was analysed on Bruker AC (300 MHz) FT-NMR and deuterated chloroform ($CdCl_3$) was used as solvent, TMS being internal standard. The FAB MASS was recorded on JEOL SX 102/DA-6000. The elemental analysis was recorded on Carlo Erba EA-1108.

Preparation of 2-acetyl-N-*(2-methylphenyl)-3-(3-nitrophenyl) acrylamide* **(2)**: A mixture of 3 nitrobenzaldehyde (0.01 mol, 1.51 g) and 2'-methylacetoacetanilide (0.01 mol,) was taken in conical flask (250 ml) containing 50 ml isopropyl alcohol, stirred it on stirring device for 30 minutes and pyridine (0.5 ml) was added in reaction mixture. After 5h solid product was separated, the reaction was cooled. Solid product was filtered and washed with chilled isopropyl alcohol to give free solid product, which was crystallised in methanol. Yield 80%, m.p: 210°C. [Calculated % C 66.66, H 4.97, N 8.64, Found % C 66.65, H 4.98, N 8.65].

Preparation of methyl 2,6-dimethyl-5-(2-methylphenylcarbamoyl)-4-(3-nitrophenyl)-1,4-dihydropyridine-2-carboxylate **(3)**: A mixture of 2-acetyl-*N*-(2-methylphenyl)-3-(3-nitrophenyl)acrylamide (0.01 mol, 3.24 g) and methyl-3-amino crotonate (0.01 mol, 1.15 g) was taken in flat bottom flask and sufficient 1,4-dioxane was added, stirred and refluxed on stirring device. After several hours sticky mass obtained in reaction flask which was treated by diethyl ether and solid product was obtained in the flask. The solid product was filtered and washed with tetrahydrofuran, and further crystallised from DMF, Yield 25.5%, melting point: 236 °C. [Calculated % C 65.55, H 5.50, N 9.97, Found % C 65.58, H 5.51, N 9.94]. IR: 3205 cm^{-1}, 1708 cm^{-1}, 1676 cm^{-1}, 1596 cm^{-1}, 1446 cm^{-1}, 1282 cm, 1081cm^{-1}, 761 cm^{-1} . ^1H NMR: 1.99(s, 3H, COOCH3), 2.25 (s, 3H, CH3), 2.30 (s,3H,CH3), 3.60(s,3H, CH3), 5.13(s, 1H,=CH–), 7.09 (m, 4H, Ar–H), 7.30 (d, 1H, Ar–H), 7.45(t, 1H, Ar–H), 7.70(d, 1H, Ar–H), 7.98 (d, 1H, Ar–H), 8.17 (s, 1H, NH), 8.21 (s, 1H,CONH).

Crystal data: $C_{23}H_{23}N_3O_5$, 421.44, Monoclinic, $P2_1/n$, a = 11.201(2) Å,b = 19.723(3)Å,c = 11.084(2)Å, β = 117.944(5)°, V = 2163.1(7)° 11.084(2)$Å^3$, Z = 4, D_X = 1.294 Mg/m^3 , μ = 0.092 mm^{-1}, T = 296K. A single crystal of 3 of dimension 0.2 × 0.3 × 0.25 mm was chosen for X-ray diffraction studies.

The measurements were made on a DIPLabo Image Plate system with graphite monochromated radiation (MoK_α) from a sealed anode generator operated at 50 kV and 36 mA. Thirty six frames of reflection data were collected by oscillation method. Successive frames were scanned in steps of 3°/min with an oscillation range of 5°. Image processing and data reduction were carried out using Denzo[18]. All frames could be indexed with a monoclinic primitive lattice. The structure was solved by direct methods[19] and refined by least squares methods.[20] The final cycle of full-matrix least-squares refinement was based on 1748 observed reflections for $I > 2\sigma(I)$ and 303 variable parameters and converged with R = 0.0673 and ωR =0.1104. The hydrogen atoms were placed at chemically acceptable positions and were not included in the refinement. Full crystallographic details have been deposited at the Cambridge Crystallographic Centre (Ref. no. CCDC 261411).

We thank the Department of Chemistry, Saurashtra University, Rajkot for providing laboratory facility and DST, Government of India for financial assistance under the project SP/I2/FOO/93. Also M.M. would like to thank CSIR, Government of India for the award of a Senior Research Fellowship.

Received 29 September 2004; accepted 11 November 2004
Paper 04/2786

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