THE STRUCTURE OF 1,2,4,4,6-PENTAMETHYL-1,4-DIHYDROPYRIDINE--3,5-DICARBONITRILE

Jiří NOVOTNÝ[a], Antonín KURFÜRST[b] and Bohumil KRATOCHVÍL[a]

[a] *Department of Solid State Chemistry,*
Prague Institute of Chemical Technology, 166 28 Prague 6 and
[b] *Department of Organic Chemistry,*
Prague Institute of Chemical Technology, 166 28 Prague 6

The crystal and molecular structure of 1,2,4,4,6-pentamethyl-1,4-dihydropyridine-3,5-dicarbonitrile was solved by direct methods and anisotropically refined by the full-matrix least-squares method to a final R value of 0·045 for 1 280 observed reflections ($I > 3\sigma(I)$). The compound crystallizes in the *Pbca* space group with lattice parameters of $a = 12\cdot021(1)$, $b = 14\cdot271(2)$, $c = 13\cdot465(1)$ Å, $Z = 8$. The six-membered 1,4-dihydropyridine ring of the title compound assumes the boat conformation, while the 1,4-dihydropyridine ring in the related compound, 1-ethyl-2,4,4,6-tetramethyl-1,4-dihydropyridine-3,5-dicarbonitrile, has the envelope conformation. The difference in the fluorescence intensities of these substances can be explained on the basis of this conformational difference. No intermolecular hydrogen bonds were found in the structure, indicating that the crystal is held together by van der Waals interactions.

In the last twenty years, 1,4-dihydropyridines have become increasingly important, primarily because of their importance in medicine[1]. These substances, with general formula *I*, act as Ca^{2+} antagonists during interaction with the cell membrane

I

IIa, R = CH₃
IIb, R = C₂H₅
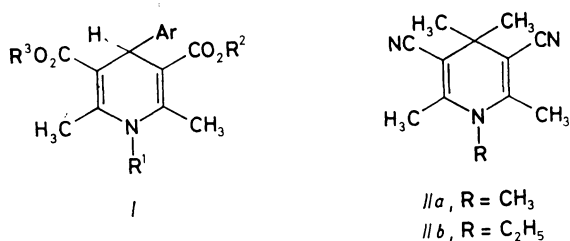
proteins, i.e. they block passage of Ca^{2+} ions through the membrane. Consequently detailed knowledge of the structures of 1,4-dihydropyridines is very important in elucidation of the relationship between the structure and the biological action. At present, a number of structures of 1,4-dihydropyridines have been found by dif-

fraction methods[2-15], where the dihydropyridine ring mostly has the boat conformation. 1,4-Dihydropyridines have been employed in other fields[1,16] in addition to their biological applications. For example, some 1,4-dihydropyridine derivatives have been found to have interesting luminescence properties[17-22]. Of the type-*II* compounds, *IIb* is employed in the scintillation technique[23]. Study of the fluorescence of a number of analogous type-*II* derivatives with long alkyl chains (ref.[22]) revealed that substance *IIb* exhibits the most intense fluorescence in the crystal state. The intensity of the fluorescence of type-*II* compounds decreases with increasing alkyl length (from methyl to pentyl) and only substance *IIb* constitutes an important exception to this trend. It is thus probable that the conformation of the fluorophore in the crystal state will be different for substance *IIb* than for the other type-*II* compounds. The X-ray structural analysis of substance *IIb* has already been carried out[24] and consequently this work deals with solution of the structure of substance *IIa*. As the fluorescence intensity increases with increasing planarity of the molecule in S_1 (ref.[25]) and the Stokes shift is approximately the same[22,26] for both substances *IIa* and *IIb*, then it can be assumed that the dihydropyridine ring in the ground state of *IIa* will be less planar than in *IIb*.

EXPERIMENTAL

The title compound, 1,2,4,4,6-pentamethyl-1,4-dihydropyridine-3,5-dicarbonitrile, *IIa*, $C_{12}H_{15}N_3$ (201·3) was prepared by the published procedure[22]. M.p. 172—174°C, ref.[22]: m.p. 169—170°C. Crystals for X-ray structural analysis were obtained by slow crystallization from an ethanolic solution.

Crystal Structure Determination

Orthorhombic, space group *Pbca*, $a = 12\cdot021(1)$, $b = 14\cdot271(2)$, $c = 13\cdot465(1)$ Å, $V = 2\ 309\cdot8(2)$ Å^3, $Z = 8$, $\varrho_o = 1\cdot16(3)$, $\varrho_c = 1\cdot157$ g cm^{-3}, $\mu = 0\cdot67$ cm^{-1}, $F(000) = 864$, MoK$_\alpha$, $\lambda = 0\cdot71073$ Å. The density was measured by the flotation method in a diiodomethane--toluene mixture at 23°C. The parameters for the intensity data set, structural solution and refinement are listed in Table I.

DISCUSSION

The final coordinates and the equivalent isotropic thermal parameters for the non-H atoms are listed in Table II and the bond distances, bond angles and endocyclic torsion angles are given in Table III.* The optimal least-squares planes fitted through the atoms of the molecule are given in Table IV. A perspective view of the molecule with the atomic numbering scheme is depicted in Fig. 1 and the molecular packing is shown in Fig. 2.

---

* Tables of the $|F_o|$, F_c, values, anisotropic temperature factors and H-atom positions are available on request from the authors.

The bond distances and angles in the molecule correspond to the expected values. The six-membered dihydropyridine ring assumes the boat conformation, with the C1, C2, C4 and C5 atoms located close to one plane and the N1 and C3 atoms at

TABLE I

Data collection and structure refinement parameters

Crystal dimensions	$0.25 \times 0.20 \times 0.15$ mm
Diffractometer used	Enraf–Nonius CAD4 equipped with a graphite monochromator
Scan technique	$\omega/2\Theta$
No. and Θ range of reflections for lattice parameter refinement	19; $10.2—15.8°$
Maximum value of $(\sin \Theta)/\lambda$	0.703 Å^{-1}
Range of h, k and l	$0 \rightarrow 16$, $0 \rightarrow 19$, $0 \rightarrow 18$
Standard reflections	$-1, 3, -2; 1, 2, -2$
Standard reflections monitored in interval, intensity fluctuation	120 min; 1%
Total number of reflections measured; 2Θ range	3 779; $2\Theta \leqq 60°$
No. of observed reflections	1 280
Criterion for observed reflections	$I > 3\sigma(I)$
Method used to solve structure	Direct methods, subsequent difference Fourier
Method used to find H-atoms	Located from difference Fourier map and refined isotropically
Function minimized	$\sum w(\lvert F_o \rvert - \lvert F_c \rvert)^2$
Weighting scheme	$w = 4F_o^2/[\sigma(F_o^2)]^2$
Parameters refined	197
Value of R	0.045
Value of wR	0.054
Value of S	1.362
Ratio of max. LS shift to e.s.d. (Δ/σ)	0.03
Max. and min. heights in final $\Delta\varrho$ map	0.15; -0.14 e Å^{-3}
Source of atomic scattering factors	SDP system (ref.[27])
Program used	SDP system
Computer used	DEC PDP 11/73

TABLE II

Positional ($.10^4$) and equivalent isotropic thermal parameters. $B_{eq} = \frac{4}{3}\sum_i\sum_j B_{ij}\boldsymbol{a}_i\boldsymbol{a}_j$

| Atom	x	y	z	B_{eq}, Å^2
N1	2577(2)	5239(1)	5363(1)	3·41(4)
N2	5121(2)	3981(2)	7742(2)	5·71(6)
N3	5040(2)	7800(2)	4733(2)	5·22(5)
C1	3144(2)	4668(2)	6035(2)	2·97(4)
C2	4034(2)	5013(1)	6516(2)	2·96(4)
C3	4379(2)	6038(2)	6474(2)	3·18(4)
C4	3990(2)	6384(2)	5466(2)	2·98(4)
C5	3096(2)	6033(2)	4998(2)	3·08(4)
C6	2744(2)	3677(2)	6155(2)	4·23(6)
C7	4629(2)	4423(2)	7184(2)	3·69(5)
C8	5639(2)	6143(2)	6587(2)	5·54(6)
C9	3775(3)	6586(2)	7294(2)	4·93(6)
C10	4559(2)	7171(2)	5046(2)	3·66(5)
C11	2630(2)	6447(2)	4055(2)	4·54(6)
C12	1481(2)	4952(2)	4982(2)	5·22(6)
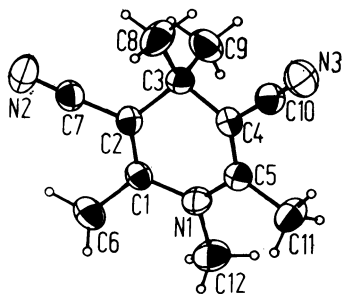
FIG. 1

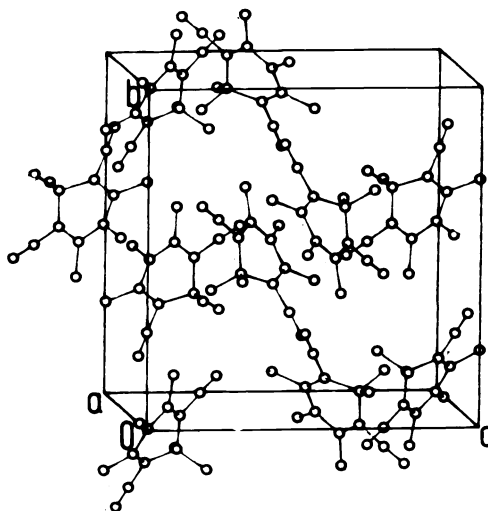Perspective view of the title compound with the atomic numbering scheme

FIG. 2

Crystal packing

positions well outside this plane. In contrast, this ring in the related compound, 1-ethyl-2,4,4,6-tetramethyl-1,4-dihydropyridine-3,5-dicarbonitrile (see ref.[24]) has the envelope conformation. The difference in the observed fluorescence intensities between these compounds can probably be explained on the basis of this different conformation. A plane can be ideally fitted through the C12, N1, C3, C8 and C9 atoms. This plane is almost perpendicular to the plane of the dihydropyridine ring (with a dihedral angle of 89·78(8)°).

No intermolecular hydrogen bonds were found in the structure. Examination of the intermolecular distances between the non-H atoms indicates that the crystal is

TABLE III
Interatomic distances (Å), angles (°) and selected torsion angles (°)

Bond	Bond length	Bond	Bond length
N1–C1	1·395(3)	C2–C7	1·426(3)
N1–C5	1·385(3)	C3–C4	1·519(3)
N1–C12	1·473(3)	C3–C8	1·530(4)
N2–C7	1·146(3)	C3–C9	1·536(4)
N3–C10	1·149(3)	C4–C5	1·342(4)
C1–C2	1·343(3)	C4–C10	1·432(3)
C1–C6	1·503(3)	C5–C11	1·509(3)
C2–C3	1·522(4)		

Atoms	Angle	Atoms	Angle
C1–N1–C5	119·2(2)	C4–C3–C8	111·3(2)
C1–N1–C12	120·1(2)	C4–C3–C9	109·4(2)
C5–N1–C12	120·5(2)	C8–C3–C9	110·3(3)
N1–C1–C2	119·2(2)	C3–C4–C5	123·0(2)
N1–C1–C6	117·6(2)	C3–C4–C10	117·4(2)
C2–C1–C6	123·2(3)	C5–C4–C10	119·4(3)
C1–C2–C3	123·4(2)	N1–C5–C4	119·9(2)
C1–C2–C7	119·2(2)	N1–C5–C11	117·0(2)
C3–C2–C7	117·0(2)	C4–C5–C11	123·1(3)
C2–C3–C4	105·2(2)	N2–C7–C2	177·2(3)
C2–C3–C8	111·1(2)	N3–C10–C4	177·9(3)
C2–C3–C9	109·5(2)		
C5–N1–C1–C2	17·8(3)	C1–C2–C3–C4	−29·4(3)
C1–N1–C5–C4	−17·4(3)	C2–C3–C4–C5	29·8(3)
N1–C1–C2–C3	8·3(3)	C3–C4–C5–N1	−9·1(3)

TABLE IV

Least squares planes fitted through the atoms in the molecule. Each plane is defined as $AX + BY + CZ - D = 0$

Atoms	Deviation from the plane, Å	Atoms	Deviation from the plane, Å
	Plane I[a]		Plane II[b]
C1*	0·003(2)	C12*	−0·001(3)
C2*	−0·002(2)	N1*	0·001(2)
C4*	0·002(2)	C3*	less than 0·000
C5*	−0·003(2)	C8*	less than 0·000
N1	−0·185(2)	C9*	less than 0·000
C3	−0·382(2)		

Plane III[c]

(the plane fitted through the atoms of the dihydropyri-
dine ring in 1-ethyl-2,4,6-tetramethyl-1,4-dihydro-3,5-
-pyridinedicarbonitrile — see ref.[24])

C1*	0·020	C2[i]*	−0·015
C2*	−0·015	C3[i]*	0·001
C3*	0·001	N10*	0·007

[a] $A = 0·6021$, $B = −0·4552$, $C = −0·6559$, $D = −6·0914$, $\chi^2 = 5$; [b] $A = −0·0212$, $B = 0·8093$, $C = −0·5871$, $D = 1·7421$, $\chi^2 = 0$; [c] $A = −0·7011$, $B = 0$, $C = −0·7131$, $D = −1·7413$. The planes are fitted only through the atoms designated by an asterisk.

stabilized by van der Waals interactions alone; the shortest distances are $N2 - C6^i = 3·51(3)$ Å and $C12 - C12^{ii} = 3·56(3)$ Å, where i: $x + 1/2$, y, $1·5 - z$ and ii: $\bar{x}$, $1 - y$, $1 - z$.

REFERENCES

1. Kuthan J., Kurfürst A.: Int. Eng. Chem., Drug Res. Develop. *21*, 191 (1982).
2. Krajewski J., Urbanczyk-Lipkowska Z., Gluzinski P.: Acta Crystallogr., B *33*, 2967 (1977).
3. Mishnev A. F., Shvec A. E., Bleidelis Y., Duburs G., Sausins A., Lusis V. K.: Khim. Geterot-sikl. Soedin. *1977*, 1229.
4. Krajewski J., Urbanczyk-Lipkowska Z., Gluzinski P.: Cryst. Struct. Commun. *6*, 787 (1977).
5. Hempel A., Gupta M. P.: Acta Crystallogr., B *34*, 3815 (1978).
6. Triggle A. M., Shefter E.,Triggle D. J.: J. Med. Chem. *23*, 1442 (1980).
7. Bundule M. F., Keeme A. A., Bleidelis Y., Bieseniece E., Uldrikis J., Duburs G.: Zh. Strukt. Khim. *22*, 124 (1981).
8. Fossheim R.: Acta Chem. Scand., B *39*, 785 (1985).

9. Fossheim R., Svarteng K., Mostad A., Romming Ch., Schefter E., Triggle D. J.: J. Med. Chem. *25*, 126 (1982).

10. Tacke R., Bentlage A., Sheldrick W. S., Ernst L., Towart R., Stoepel K.: Z. Naturforsch., B *37*, 443 (1982).

11. Schauer C. K., Anderson O. P., Natale N. R., Quincy D. A.: Acta Crystallogr., C *42*, 884 (1986).

12. Fossheim R.: J. Med. Chem. *29*, 305 (1986).

13. Fossheim R.: Acta Chem. Scand., B *40*, 777 (1986).

14. Fossheim R.: Acta Chem. Scand., B *41*, 581 (1987).

15. Fossheim R., Joslyn A., Solo A. J., Luchewski E., Rutledge A., Triggle D. J.: J. Med. Chem. *31*, 300 (1988).

16. Eisner U., Kuthan J.: Chem. Rev. *72*, 1 (1972).

17. Dittmer D. C., Blidner B. B.: J. Org. Chem. *38*, 2873 (1973).

18. Kano K., Matsuo T.: Bull. Chem. Soc. Jpn. *49*, 3269 (1976).

19. Kano K., Matsuo T.: Tetrahedron Lett. *1975*, 1389.

20. Kikugawa K., Ido Y.: Lipids *19*, 600 (1984).

21. Kikigawa K., Ido Y., Mikami A.: J. Am. Oil Chem. Soc. *61*, 1574 (1984).

22. Kuthan J., Paleček J.: Collect. Czech. Chem. Commun. *39*, 3711 (1974).

23. Gilar O., Pavlíček Z., Jursová L.: Tesla Electron. *8*, 87 (1975).

24. Huml K., Ječný J., Kutschabsky L., Reck G.: Acta Crystallogr., B *35*, 444 (1979).

25. Berlman I. B.: J. Phys. Chem. *74*, 3985 (1970).

26. Kurfürst A., Luňák S., Jr., Nepraš M.: Unpublished results.

27. Frenz B. A. and Associated, Inc., College Station, Texas 77840 and Enraf–Nonius, Delft, Holland: *SDP. Structure Determination Package*, Delft 1985.

Translated by M. Štulíková.