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MOLECULAR AND CRYSTAL STRUCTURES AND CHEMICAL PROPERTIES OF 2,6-DIMETHYL-4-PHENYL-3,5-DIETHOXYCARBONYL-1,4-DIHYDROPYRIDINE

A. F. Mishnev, A. E. Shvets,
Ya. Ya. Bleidelis, G. Ya. Dubur,
A. É. Sausin', and V. K. Lusis

UDC 548.737+547.827

The molecular and crystal structures of 2,6-dimethyl-4-phenyl-3,5-diethoxycarbonyl-1,4-dihydropyridine were determined by x-ray diffraction analysis. The following crystallographic data were obtained: $a = 9.754(2)$, $b = 7.401(1)$, $c = 24.384(5)$ Å, $\beta = 92.61(2)°$, $Z = 4$, $d_{calc} = 1.24$ g-cm^{-3}, space group $P2_1/c$. The structure was decoded from 1531 reflections, the intensities of which were measured with a $P2_1$ automatic diffractometer and refined by the method of least squares within the total matrix anisotropic approximation to $R = 0.061$. The dihydropyridine ring has a boat conformation. Packing of the molecules in the crystal is realized at the van der Waals distances and is stabilized by an $N_1-H\ldots O_{15}$ hydrogen bond (2.98 Å). From the data on the geometry of the molecule, the compound is closer to aminovinylcarbonyl compounds, whereas according to the data on the conformation, it is closer to Meisenheimer compounds than to pyridine derivatives. The C=O bond length corresponds to its length in esters and acid amides, despite the exceptionally low reactivity of this group in 3,5-dicarbonyl-1,4-dihydropyridines.

To determine the geometry and configuration of the 2,6-dimethyl-4-phenyl-3,5-diethoxycarbonyl-1,4-dihydropyridine (I) molecule and to understand its reactivity we subjected it to an x-ray diffraction study.

The intensities of the reflections were measured with a $P2_1$ automatic four-circle diffractometer using a 0.25 by 0.2 by 0.1 mm light-yellow single crystal. The following crystallographic data on the unit cell of a crystal of the composition $C_{19}H_{23}NO_4$ were obtained by the procedure of autoindexing and calculation of the orientation matrix by the method of least squares (MLS):

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1229-1234, September, 1977. Original article submitted September 14, 1976.

TABLE 1. Coordinates of the Atoms and Anisotropic Temperature

Atoms	x	y	z	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
N1	−0,1638(4)	1,1273(5)	0,0502(2)	3,84(23)	1,45(20)	3,61(22)	−0,21(18)	−0,54(19)	0,34(18)
C2	−0,2279(5)	0,9928(7)	0,0189(2)	3,23(27)	2,03(26)	2,52(25)	0,19(23)	−0,02(21)	0,02(24)
C3	−0,2153(5)	0,8196(7)	0,0368(2)	2,48(24)	1,96(27)	2,52(25)	−0,19(20)	−0,08(19)	−0,30(21)
C4	−0,1515(5)	0,7808(6)	0,0938(2)	2,52(22)	1,81(23)	2,46(23)	−0,18(20)	−0,39(20)	0,05(20)
C5	−0,0416(5)	0,9239(7)	0,1079(2)	2,52(25)	2,52(28)	2,70(25)	−0,09(22)	−0,28(21)	−0,14(22)
C6	−0,0590(5)	1,0951(7)	0,0892(2)	2,94(27)	2,57(28)	2,95(27)	−0,32(22)	−0,27(22)	−0,10(23)
C7	0,0193(5)	1,2636(7)	0,1049(2)	3,91(28)	3,23(28)	4,59(29)	−1,73(25)	−0,50(23)	0,08(25)
C8	−0,3033(6)	1,0629(7)	−0,0311(2)	5,52(33)	2,76(30)	3,71(29)	0,68(24)	−0,59(25)	0,59(24)
C9	0,0753(5)	0,8777(8)	0,1454(2)	2,89(29)	3,71(33)	2,85(27)	−0,02(26)	0,25(23)	−0,38(26)
O10	0,1630(4)	0,9793(5)	0,1638(2)	4,26(20)	4,60(22)	5,02(22)	−1,45(19)	−1,74(17)	0,34(19)
O11	0,0786(3)	0,6980(5)	0,1569(1)	3,16(18)	3,45(21)	4,14(20)	0,30(15)	−1,16(15)	0,23(17)
C12	0,1860(5)	0,6359(8)	0,1962(2)	3,27(28)	4,35(32)	5,14(33)	0,28(25)	−1,77(25)	0,76(28)
C13	0,1451(7)	0,6656(9)	0,2537(2)	7,94(43)	6,77(42)	3,58(32)	1,10(34)	−1,30(30)	0,48(32)
C14	−0,2660(5)	0,6596(8)	0,0069(2)	3,22(27)	3,02(31)	1,95(25)	−0,23(24)	0,01(21)	0,08(24)
O15	−0,2371(4)	0,5067(5)	0,0197(2)	6,41(25)	1,63(18)	4,54(20)	−0,01(17)	−2,27(17)	0,24(17)
O16	−0,3505(3)	0,6968(4)	−0,0368(1)	5,01(20)	2,43(18)	3,04(18)	−0,00(15)	−1,40(16)	−0,16(15)
C17	−0,3971(5)	0,5434(7)	−0,0704(2)	5,26(31)	2,60(28)	2,98(27)	−0,59(24)	−1,43(24)	−0,25(23)
C18	−0,4797(7)	0,6210(8)	−0,1177(2)	7,82(40)	4,37(34)	4,84(34)	−0,63(31)	−2,16(30)	−0,68(29)
C19	−0,2568(5)	0,7790(7)	0,1373(2)	2,54(25)	2,26(25)	2,34(24)	−0,63(22)	−0,57(20)	0,29(21)
C20	−0,3764(5)	0,8816(7)	0,1332(2)	3,02(26)	3,06(28)	3,57(28)	0,33(24)	−0,04(23)	0,47(24)
C21	−0,4682(5)	0,8849(8)	0,1749(2)	3,54(29)	4,35(33)	3,80(30)	0,49(26)	0,41(25)	0,33(27)
C22	−0,4433(6)	0,7877(8)	0,2226(2)	3,85(30)	5,63(36)	3,26(29)	−1,10(29)	−0,13(24)	0,42(28)
C23	−0,3252(6)	0,6826(9)	0,2271(2)	4,25(31)	6,65(40)	2,88(29)	−1,06(30)	−0,64(26)	1,79(29)
C24	−0,2338(5)	0,6795(7)	0,1851(2)	2,57(25)	4,34(32)	3,59(29)	−0,05(23)	−0,29(23)	0,92(26)

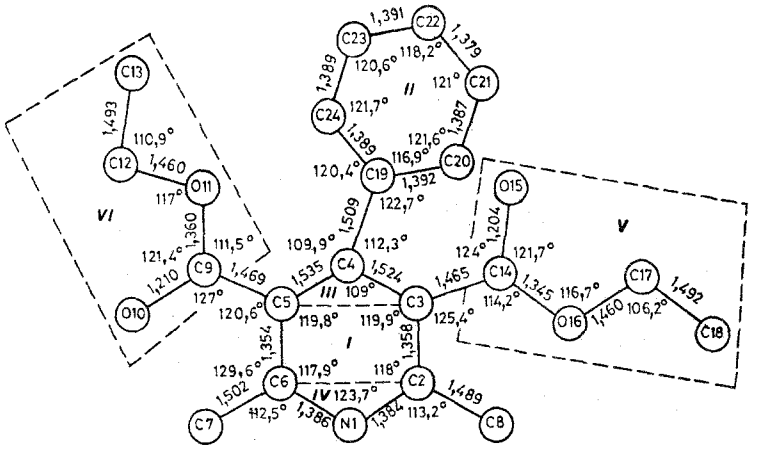


Fig. 1. Bond lengths and valence angles.

$a = 9.754$ (2) Å	$M = 329.42$
$b = 7.401$ (1) Å	$d_{calc} = 1.24$ g·cm^{-3}
$c = 24.384$ (5) Å	$Z = 4$
$\beta = 92.61$ (2)°	$\mu(CuK_\alpha) = 7.2$ cm^{-1}
$V = 1758.36$ (54) Å^3	Space group $P2_1/c$
	$F_{000} = 704$

The intensities of 1876 independent nonzero reflections were measured by the method of $\theta/2\theta$ scanning with monochromatic copper emission (with a graphite monochromator) up to $2\theta_{max} = 100°$. A total of 1531 reflections with $I \geq 1.96\sigma$ was used in the calculation.

The I structure was decoded under "on line" conditions with the aid of a system for the determination of XTL structures. The model of the molecule was found by a direct method from a MULTAN program [1]. We calculated eight variants of the phases, one of which with a maximum ABSFOM value of 1.1837 made it possible by means of E synthesis to localize all 24 nonhydrogen atoms. Refinement of the structure within the total matrix isotropic approximation by the method of least squares (MLS) led to R = 0.132. Two cycles of MLS refinement within the anisotropic approximation (217 parameters) reduced R to 0.087.

The positions of all 23 of the hydrogen atoms of the molecule were found from differential synthesis. The C–H distances ranged from 0.83 to 1.23 Å and were not refined. Two cycles of total matrix refinement for the nonhydrogen atoms with allowance for all of the hydrogen atoms ($B_{isotr} = 4.0$ Å^{-2}) led to a final R value of 0.061.

The coordinates of the atoms and the anisotropic temperature factors are presented in Table 1. The bond lengths and valence angles are given in Fig. 1. The accuracies in the determination of the interatomic distances and the valence angles were as follows: $\Delta r < 0.01$ Å, and $\Delta\alpha \sim 0.5°$.

The basis of the I molecule is the 3,5-dicarbonyl-1,4-dihydropyridine system, which, as seen from the x-ray diffraction data, in this case differs substantially from the heteroaromatic system of pyridine. With respect to the 1,4-dihydropyridine system, there are x-ray diffraction data available for 1-benzyl- [2] and 1-propyl-1,4-dihydronicotinamide [3, 4]. However, the accuracy in the determination of the geometrical characteristics of the 1-propyl-1,4-dihydronicotinamide molecule in [3, 4] is insufficient for comparison with the data from the present research. In [2] the 1,4-dihydronicotinamide fragment is close with respect to the lengths of the valence bonds to the 1,4-dihydropyridine fragment of the I structure. The valence angles in these rings are also extremely different in the two studies. The C=O bond length is also 0.05 Å shorter than the length reported in [2].

It is apparent from the structures of pyridine hydrochloride [5], 2- and 3-aminopyridines [6, 7], and 2-amino-5-methylpyridine hydrochloride [8] that the pyridine ring has a planar structure. The 1,4-dihydropyridine ring in 1-benzyl- [2] and 1-propyl-1,4-dihydronicotinamide [3, 4] molecules was also found to be planar. In contrast to [2-4], the 1,4-dihydropyridine ring in the I molecule is considerably deformed and has a boat conformation. The III and IV triangles formed by the C_3, C_4, C_5 and C_2, N_1, C_6 atoms are deviated to one side with respect to the I plane by 28.4 and 15.7°, respectively (see Fig. 1). The C_4 and N_1 atoms deviate from the plane of I by 0.42 and 0.18 Å, respectively.

Since 3,5-diethoxycarbonyl-1,4-dihydropyridines are formally analogs of aminovinylcarbonyl compounds, it seems expedient to compare their structures with systems that contain aminovinylcarbonyl groupings. Thus

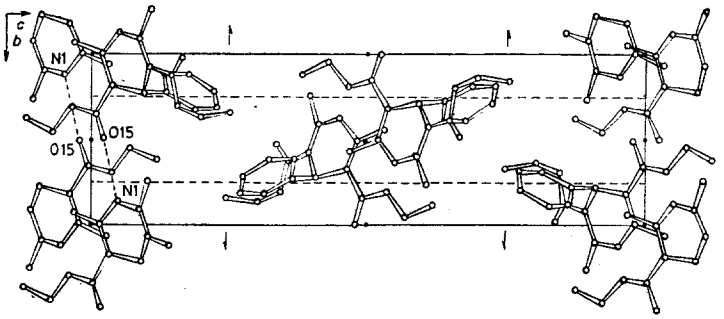


Fig. 2. Projection of the structure on the bc plane.

comparison with, for example, cyclic aminovinyl ketones [9, 10] actually shows the similarity in the corresponding structural fragments of the molecules of these classes of compounds.

Analysis of the interatomic distances and valence angles in the 1,4-dihydropyridine fragment of I shows their symmetrical character in the ring in the N_1-C_4 direction; this should have been expected, considering the symmetrical orientation of the substituents along this direction. The C–N bond length (average value 1.38 Å) is greater than the lengths in pyridines (average values 1.33 [6], 1.34 [7], 1.33 and 1.36 Å [8]). The C–N bond length is also greater than the length of the exocyclic C–N bond in aminovinyl ketone molecules (1.35 [9] and 1.33 Å [10]).

The average C_2-C_3 and C_5-C_6 bond lengths of 1.36 Å are shorter than the corresponding bonds in pyridine molecules [5-7, 11, 12], in which they range from 1.37 to 1.42 Å. The lengths of these bonds in structure I are extremely close to the length of the C=C bond in aminovinyl ketone structures (1.37 to 1.35 Å) [9, 10]. This attests to partial conjugation of the aminovinylcarbonyl grouping. The lengths of the C_3-C_{14} and C_5-C_9 bonds (average value 1.47 Å) are also extremely close to the values in aminovinyl ketone molecules (1.44 and 1.46 Å) [9, 10]. They are all shortened as compared with the lengths of single bonds; this also indicates a certain amount of conjugation in the system.

The C_4 atom has sp^3 hybridization. The hydrogen atom bonded to the tetrahedral C_4 atom, determined from differential synthesis, forms a C_4-H bond of 1.15 Å and is shielded on all sides by C_{19}, C_3, C_5, C_{14}, C_{24}, C_9, O_{11}, and O_{15} atoms at distances ranging from 2.15 to 2.76 Å; this may be the reason for its relative chemical inertness, which is manifested in the decreased rate constant for the reaction of I with hydrogen acceptors as compared with 2,6-dimethyl-3,5-diethoxycarbonyl-1,4-dihydropyridine [13]. The angles between the II plane and the I and III planes are 88.6 and 44.2°, respectively.

The $C_2N_1C_6$ valence angle (123.7°) is increased as compared with the valence angle in pyridine systems [6, 7, 11, 12], in which it is, respectively, 117.5°, 117.7°, 117.4°, and 116.2°; it also coincides with the value in [8] (123.6°), but is lower than the value in [5] (128°). The sum of the valence angles about the N_1 atom is 356° (the length of the N–H bond determined from differential synthesis is 1.09 Å), which indicates its sp^2 hybridization, as in the case of aminovinyl ketone structures [9, 10].

The average value of the C–C bond length in the benzene ring (III) is 1.39 Å and coincides, within the limits of the experimental error, with the value in crystalline benzene (1.392 Å) [14].

The geometry of the ester fragments of the molecule is extremely close to the geometry in the methyl formate molecule [15] and in the corresponding fragments of ethyl 2,4,4-triphenyl-1,2-diazetidin-3-one-1-carboxylate [16] and pyrocalciferyl 3,5-dinitrobenzoate [17].

The planes of ester fragments V and VI are deflected in the opposite direction from the I plane (14.4 and 21.9°) as compared with the planes of the II-IV fragments (88.6, 28.4, and 157°).

One should note the trans orientation of the O_{11} and O_{15} atoms of the carbonyl groups with respect to the $C_{13}\ldots C_{18}$ atomic chain, i.e., this compound exists in the crystal state in the form of the trans-s-cis-trans-s-trans rotational isomer.

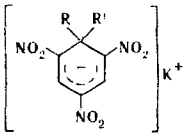
The N_1, C_4, C_{19}, and C_{22} atoms almost lie in a single plane. The deviations from the average plane are as follows: N_1 (0.00 Å), C_4 (–0.02 Å), C_{19} (0.03 Å), and C_{22} (–0.01 Å).

The C_{14}, O_{15}, O_{16}, C_{17}, and C_{18} atoms, which form an average plane (V), deviate from it by 0.02, –0.00, –0.03, –0.01, and 0.01 Å, respectively. The C_9, O_{10}, O_{11}, C_{12}, and C_{13} atoms deviate more significantly from

the average plane (VI): −0.32, 0.25, −0.18, 0.57, and −0.32 Å. The V and VI average planes form angles of 14.4 and 21.9°, respectively, with the I plane. The $C_{14}=O_{15}$ group is consequently in better conjugation with the divinylamine system than the $C_9=O_{10}$ carbonyl group.

Packing of the molecules in the crystal is realized at van der Waals distances and is stabilized by an $N_1-H\ldots O_{15}$ hydrogen bond (2.98 Å), which connects the molecules in infinite chains. The projection of the structure on the bc plane is given in Fig. 2.

The structure of dihydropyridine I has some characteristics that are similar to those of Meisenheimer compounds, the ring of which also contains a tetrahedral carbon atom (C_1) that forms valence angles with the remaining ring atoms that are close to the angles in I (109° for IIa [18], 107.8° for IIb [19], and 109° for IIc [20]).



IIa-c

IIa R = R' = OC_2H_5; b R = R' = OCH_3; c R = H, R' = CH_2COCH_3

The C_2, C_3, C_5, and C_6 atoms in IIc form a common plane, while the C_1 and C_4 atoms deviate from this plane by 0.30 and 0.11 Å, respectively, and exist in a cis orientation. The C_2-C_3 and C_5-C_6 bond lengths in IIa are 1.347 Å, as compared with 1.353 and 1.356 Å in IIb, which is very close to the corresponding bond lengths in I.

3,5-Di(alkoxycarbonyl)-1,4-dihydropyridines are also vinylogs of amides (or, more precisely, urethanes). The interatomic distance of the C=O grouping in amides ranges from 1.21 to 1.28 Å [21-23], i.e., I is no exception in this respect. However, its ester groups are inert with respect to attack by nucleophilic reagents (the hydroxide ion, amines, etc.). This cannot be explained by steric shielding by the adjacent methyl and phenyl groups, since similar properties are displayed by the 4-unsubstituted compound, but the corresponding heteroaromatic systems (2,6-dimethyl-3,5-diethoxycarbonylpyridines), even those that are substituted in the 4 position, have normal reactivities of the ester groups. The reason for the unusual properties in this case apparently should be sought in the specific conjugated 3,5-diethoxycarbonyl-1,4-dihydropyridine structure.

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