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

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The molecular crystal structure of 4-phenyl-3,5-diethoxycarbonyl-1,2,6-trimethyl-1,2-dihydropyridine has been investigated by x-ray structural analysis. The three-dimensional structural properties of the molecule have been compared against the large observed reactivity of the 3-ethoxycarbonyl group with respect to nucleophilic substitution reactions.

In studying the reactivity of diethyl ester derivatives of 1,2-dihydropyridine-3,5-dicarboxylic acids [1] it has been found that only the 3-ethoxycarbonyl group undergoes hydrolysis. In order to elucidate the steric factors which are responsible for this behavior characteristic among these compounds, we have carried out an x-ray crystal structure analysis of 4-phenyl-3,5-diethoxycarbonyl-1,2,6-trimethyl-1,2-dihydropyridine (I). The structural data have then been compared against the results of reactivity studies of this compound.

The independent portion of the unit cell in crystals of (I) contain two enantiomorphic molecules of compound I, with superimposable geometries (within experimental error); in Fig. 1 we have shown a molecular model of one of the enantiomers with an averaged geometry for the two molecules (cf. Fig. 1 and Table 1).

TABLE 1. Nonhydrogen Atom Coordinates ($\times 10^4$) for Crystallographically Independent Molecules of Compound I

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
$N_{(1)}$	7774(6)	7551(4)	5012(3)	$N'_{(1)}$	−2320(5)	2459(4)	−80(3)
$O_{(10)}$	12662(5)	9218(4)	5187(3)	$O'_{(10)}$	2421(5)	3932(4)	−356(2)
$O_{(11)}$	12112(4)	8531(3)	3917(2)	$O'_{(11)}$	2685(4)	4206(3)	926(2)
$O_{(15)}$	5621(5)	4301(4)	3620(3)	$O'_{(15)}$	−3505(5)	230(4)	1445(3)
$O_{(16)}$	7780(4)	4056(3)	3605(2)	$O'_{(16)}$	−1312(4)	38(4)	1484(2)
$C_{(2)}$	7015(6)	6783(5)	4261(4)	$C'_{(2)}$	−2608(6)	2193(5)	693(4)
$C_{(3)}$	7917(6)	6038(5)	4017(3)	$C'_{(3)}$	−1523(6)	1640(5)	950(3)
$C_{(4)}$	9453(6)	6619(5)	4133(3)	$C'_{(4)}$	−83(6)	2144(5)	806(3)
$C_{(5)}$	10139(6)	7813(5)	4629(3)	$C'_{(5)}$	277(6)	2998(5)	277(3)
$C_{(6)}$	9291(7)	8171(5)	5134(3)	$C'_{(6)}$	−896(7)	3008(5)	−225(3)
$C_{(7)}$	9994(8)	9218(5)	5809(3)	$C'_{(7)}$	−622(7)	3599(5)	−914(3)
$C_{(8)}$	6833(7)	7520(5)	3654(4)	$C'_{(8)}$	−2440(7)	3359(6)	1235(3)
$C_{(9)}$	11749(7)	8585(5)	4634(4)	$C'_{(9)}$	1870(7)	3737(5)	219(4)
$C_{(12)}$	13696(7)	9069(6)	3839(5)	$C'_{(12)}$	4324(7)	4737(6)	952(4)
$C_{(13)}$	13868(9)	8939(8)	3040(5)	$C'_{(13)}$	5036(7)	5263(7)	1740(4)
$C_{(14)}$	6983(7)	4741(5)	3725(3)	$C'_{(14)}$	−2213(7)	594(5)	1312(3)
$C_{(17)}$	6960(7)	2750(5)	3365(3)	$C'_{(17)}$	−1911(8)	−1012(6)	1845(4)
$C_{(18)}$	8143(8)	2255(5)	3250(4)	$C'_{(18)}$	−692(9)	−1389(6)	2032(4)
$C_{(19)}$	10479(6)	6040(4)	3855(3)	$C'_{(19)}$	1151(6)	1778(5)	1084(3)
$C_{(20)}$	11426(6)	5828(5)	4388(3)	$C'_{(20)}$	1743(6)	1178(5)	558(3)
$C_{(21)}$	12402(6)	5280(5)	4139(4)	$C'_{(21)}$	2902(7)	845(5)	815(4)
$C_{(22)}$	12436(7)	4988(6)	3363(4)	$C'_{(22)}$	3482(7)	1132(6)	1586(4)
$C_{(23)}$	11499(7)	5205(6)	2837(3)	$C'_{(23)}$	2914(7)	1741(6)	2108(3)
$C_{(24)}$	10525(6)	5730(5)	3081(3)	$C'_{(24)}$	1741(6)	2058(5)	1856(3)
$C_{(25)}$	6821(8)	7756(6)	5577(4)	$C'_{(25)}$	−3633(7)	2259(7)	652(4)

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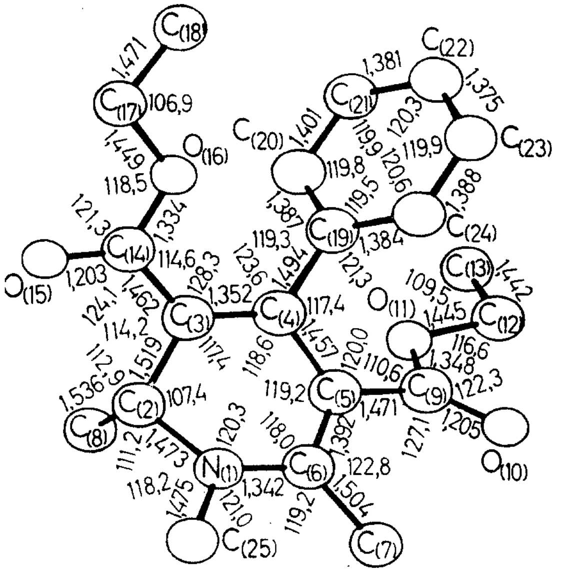


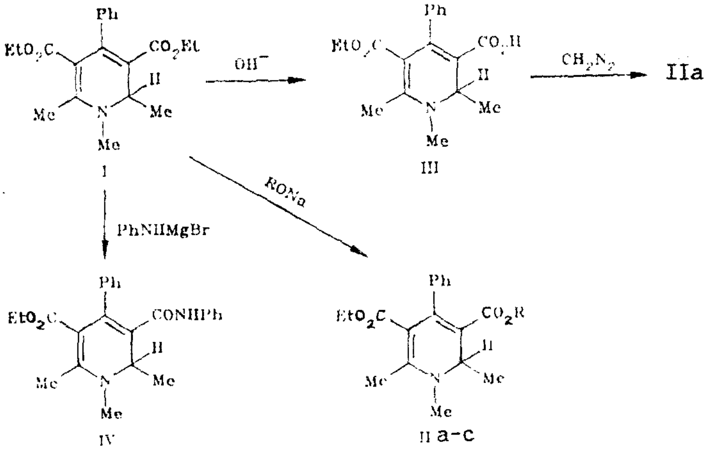
Fig. 1. Three-dimensional molecular model of compound I.

The 1,2-dihydropyridine ring in molecule I exists in a boat (tub) conformation. The $C_{(5)}$ and $C_{(2)}$ atoms deviate from the average plane of the other four atoms (±0.008 Å) by 0.190(5) and 0.539(6) Å, respectively. The $C_{(3)}$—$C_{(4)}$—$C_{(5)}$—$C_{(6)}$ torsional angle is equal to 18.4°. The $C_{(8)}$ atom is located in an axial position. The plane of the phenyl ring is rotated relative to the average plane of the 1,2-dihydropyridine ring by an angle of 125.4°. The carbonyl groups and double bond exist in the s-cis configuration.

Bond length analysis reveals that the double bonds in the 1,2-dihydropyridine ring are not strictly or rigorously localized. Thus, the $C_{(3)}$—$C_{(4)}$ distance equal to 1.351(9) Å indicates that this bond is conjugated with the 3-$COOC_2H_5$ group. The value of the $C_{(4)}$—$C_{(3)}$—$C_{(14)}$—$C_{(15)}$ torsional angle equal to 177(6)° is also consistent with conjugation between these molecular structural fragments. The $C_{(5)}=C_{(6)}$ double is even more elongated to 1.391(8) Å, and is thus conjugated with the 5-$COOC_2H_5$ group as well as with the unshared pair of electrons on the N atom. This latter degree of conjugation interaction results in contraction of the $C_{(6)}$—N bond distance to 1.342(8) Å, which corresponds with the C_{sp^2}—N bond length observed in enamines [2]. However, the $C_{(6)}$—$C_{(5)}$—$C_{(9)}$—$O_{(10)}$ torsional angle is equal to 35.1°, which suggests partial disruption of conjugation interaction between the 5-$COOC_2H_5$ functional group and the double bond in the ring. The geometry of the latter group is superimposable on the geometry observed for the corresponding fragment in the molecular structure of 4-phenyl-3,5-diethoxycarbonyl-2,6-dimethyl-1,4-dihydropyridine [3], while the geometry for the carbonyl functional group attached to $C_{(3)}$ is significantly different. This functional group enjoys maximum conjugation with the ring double bond, although the $O_{(16)}$ atom is in very close, substantial proximity to the $C_{(19)}$ atom. The distance between these two atoms is 2.729 Å, which is significantly shorter than the sum of the van der Waals radii. This leads to changes in the bond angles for the carbonyl group. The $C_{(4)}$—$C_{(3)}$—$C_{(14)}$ and $C_{(3)}$—$C_{(14)}$—$O_{(16)}$ bond angles are increased to 128.3 and 114.6°, respectively [for comparison, the $C_{(6)}$—$C_{(5)}$—$C_{(9)}$ and $C_{(5)}$—$C_{(9)}$—$O_{(11)}$ bond angles are equal to 120.7 and 110.6°]. It follows therefore that both ester functional groups experience steric strain. The overall molecular geometry of dihydropyridine I is similar to that observed for 4-(2′-nitrophenyl)-3,5-dimethoxycarbonyl-1,2,6-trimethyl-1,2-dihydropyridine [4]. In [4] it was found, however, that the 4-aryl ring and the 1,2-dihydropyridine ring were essentially coplanar.

Comparison of the PMR spectra of a variety of different esters of 4-phenyl-5-ethoxycarbonyl-1,2,6-trimethyl-1,2-dihydropyridine-3-carboxylic acid, along with the spectrum of 4-phenyl-5-ethoxycarbonyl-1,2,6-trimethyl-1,2-dihydropyridine [1], has made it possible for us to assign the signal at 3.53-3.56 ppm to the methylene protons in the 5-ethoxycarbonyl group, and the signal at 3.77-3.79 ppm to the CH_2 protons in the $COOCH_2CH_3$ group in the 3-position. The resonance signal for the methylene protons in the 3-$COOCH_2CH_3$ group always appears in the form of a sharp quartet, while the signal for the corresponding protons in the 5-$COOCH_2CH_3$ group appear in the form of a complex multiplet, suggesting hindered rotation in the latter functional group. It follows, therefore, that the ester functional group attached to the $C_{(5)}$ atom experiences greater steric hindrance in solution than the corresponding ester functional group in the $C_{(3)}$ position. This conclusion is consistent with the properties of dihydropyridine I. The

3-ethoxycarbonyl group is readily hydrolyzed by base and is more active as well in reactions with other nucleophiles. Reaction of diester I with the appropriate sodium alkoxides gave the corresponding methyl, isopropyl, and tert-butyl esters of 4-phenyl-5-ethoxycarbonyl-1,2,6-trimethyl-1,2-dihydropyridine-3-carboxylic acid III. The structures of compounds IIa-c were confirmed by synthesis of the methyl ester IIa from 4-phenyl-5-ethoxycarbonyl-1,2,6-trimethyl-1,2-dihydropyridine-3-carboxylic acid (III) and diazomethane. The 3-ethoxycarbonyl group in I also reacts with activated aniline (Bodru reaction) to give 4-phenyl-5-ethoxycarbonyl-1,2,6-trimethyl-1,2-dihydropyridine-3-carboxylic acid anilide (IV).



II a R=CH$_3$; b R= –CH(CH$_3$)$_2$; c R= –C(CH$_3$)$_3$

The structure of anilide IV was established based on its PMR spectrum and comparison with the spectra of diesters II. The methylene proton signal which appears as a multiplet at 3.62 ppm is assigned to the 5-COOCH$_2$CH$_3$ functional group in compound IV. The latter anilide derivative has also been obtained, along with its isomeric 4-phenyl-3-ethoxycarbonyl-1,2,6-trimethyl-1,2-dihydropyridine-5-carboxylic acid anilide, by reduction of 3-phenylcarbamoyl-4-phenyl-5-ethoxycarbonyl-1,2,6-trimethylpyridinium perchlorate, which will be reported in a separate publication.

EXPERIMENTAL

PMR spectra were obtained on a WH-90 spectrometer using CDCl$_3$ solutions versus TMS as internal standard.

Compound I crystallizes in the form of transparent yellow crystals in triclinic syngony. The principal crystallographic data for C$_2$OH$_{25}$O$_4$N are: a = 9.640(1), b = 12.119(1), c = 17.782(4) Å; α = 98.44(1)°, β = 94.31(1)°, γ = 112.6(1)°, ν = 1877.2 Å^3, M = 343.45; d$_{calc}$ = 1.22 g/cm^3, F$_{000}$ = 736, Z = 4, P1 space group. The intensities of 4963 independent reflections were measured by $\theta/2\theta$-scanning up to $2\theta_{max}$ = 120°. The calculations were performed based on 4019 reflections with $I \geq 1.96\sigma(I)$. The x-ray structural analysis was carried out on a Syntex P2$_1$ diffractometer (CuKα irradiation, graphite monochromator). The structure was solved using the XTL system for structure identification and was refined by full-matrix least squares using anisotropic approximations for all nonhydrogen atoms; the hydrogen atoms were not refined. The final R-factor was 0.082. The coordinates for the nonhydrogen atoms are given in Table 1.

The results of C, H, and N elemental analysis for compounds IIa-c and IV agreed with calculations.

Transesterification of 4-Phenyl-3,5-diethoxycarbonyl-1,2,6-trimethyl-1,2-dihydropyridine (I). A mixture of 0.86 g (25 mmoles) of dihydropyridine and 125 mmoles of the appropriate freshly prepared (sodium) alkoxide in 15 ml of the corresponding alcohol was refluxed for 6 h. The solvent was evaporated and the residue was treated with 50 ml hot water and then filtered. The yellow deposit of ester product which remained on the filter was recrystallized from ethyl alcohol. The acid III was isolated from the filtrate after acidification with dilute HCl.

4-Phenyl-5-ethoxycarbonyl-1,2,6-trimethyl-1,2-dihydropyridine-3-carboxylic Acid Methyl Ester (IIa, $C_{19}H_{23}NO_4$). Mp 113-114°C. PMR spectrum: 0.60 (3H, t, 5-COOCH$_2$CH$_3$); 1.22 (3H, d, 2-CH$_3$), 2.41 (3H, s, 6-CH$_3$), 3.18 (3H, s, 1-CH$_3$), 3.37 (3H s, 3-COOCH$_3$), 3.56 (2H, m, J = 7 Hz, 5-COOCH$_2$CH$_3$), 4.52 (1H, q, J = 5.6 Hz, 2-H), 7.13 ppm (5H, br.s, arom). Yield 0.77 g (93%).

Sample IIa did not give a melting-point depression and was identical in all characteristics with a sample of ester synthesized from acid III and diazomethane, according to [5].

4-Phenyl-5-ethoxycarbonyl-1,2,6-trimethyl-1,2-dihydropyridine-3-carboxylic Acid Isopropyl Ester (IIb, $C_{21}H_{27}NO_4$). Mp 109-111°C. PMR spectrum: 0.60 (3H, t, 5-$COOCH_2CH_3$), 0.77 and 0.87 (3H, d, $CH(CH_3)_2$), 1.22 (3H, d, 2-CH_3), 2.40 (3H, s, 6-CH_3), 3.18 (3H, s, 1-CH_3), 3.54 (2H, m, J = 7.0 Hz, 5-$COOCH_2CH_3$), 4.50 (1H, q, J = 6.5 Hz, 2-H), 4.71 [1H, q, J = 6.0 Hz, $CH(CH_3)_2$], 7.13 ppm (5H, br.s, arom.). Yield 0.55 g (61%).

4-Phenyl-5-ethoxycarbonyl-1,2,6-trimethyl-1,2-dihydropyridine-3-carboxylic Acid tert-Butyl Ester (IIc, $C_{22}H_{29}NO_4$). Mp 135-136°C. PMR spectrum: 0.59 (3H, t, 5-$COOCH_2CH_3$), 1.06 (9H, s, $C(CH_3)_3$), 1.22 (3H, d, 2-CH_3), 2.39 (3H, s, 6-CH_3), 3.18 (3H, s, 1-CH_3), 3.53 (2H, m, J = 7.0 Hz, 5-$COOCH_2CH_3$), 4.41 (1H, q, J = 6.5 Hz, 2-H), 7.17 ppm (5H, br.s, arom.). Yield 0.46 g (49%).

4-Phenyl-5-ethoxycarbonyl-1,2,6-trimethyl-1,2-dihydropyridine-3-carboxylic Acid Anilide (IV, $C_{24}H_{26}N_2O_3$). To a suspension of 0.96 g (0.02 moles) metallic magnesium in 20 ml absolute ether was added dropwise with stirring 3 ml (0.08 moles) ethyl bromide in 3 ml absolute ether at such a rate as to maintain gentle boiling of the solution. After ethyl bromide addition was complete the solution was refluxed until all of the magnesium had been converted into solution (~0.5 h); a solution of 1.82 ml (0.04 moles) aniline in 2 ml ether was added and refluxed an additional 0.5 h, and finally a solution of 3.43 g (20 mmoles) of dihydropyridine I in 150 ml absolute ether was added. The solution turned red and a dark precipitate appeared. The mixture was stirred at reflux for another 0.5 h. The mixture was then cooled and filtered to remove the precipitate, and the filtrate was treated with 100 ml 1 N HCl; the ether layer was separated and evaporated. The oily residue was dissolved in 8-10 ml chloroform and subjected to preparative chromatography on a silica gel (L40/100) plate (20 × 35 cm size, depth of the mobile layer 2-3 mm) using a solvent system composed of 9:7:1 chloroform—hexane—acetone. Two yellow bands were collected. The first band from the solvent front yielded 20-25% of the starting material I, the second consisted of anilide IV. Mp 140-142°C (from ethanol). PMR spectrum ($CDCl_3$): 0.62 (3H, t, 5-$COOCH_2CH_3$), 1.28 (3H, d, 2-CH_3), 2.46 (3H, s, 6-CH_3), 3.21 (3H, s, 1-CH_3), 3.62 (2H, m, J = 7.0 Hz, 5-$COOCH_2CH_3$), 4.67 (1H, s, J = 6.5 Hz, 2-H), 6.56 (1H, br.s, NH), 6.78-7.41 ppm (10H, m, arom.).

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