Synthesis and molecular structure of 6-aryl-3-ethoxycarbonyl-4-hydroxypyridazines

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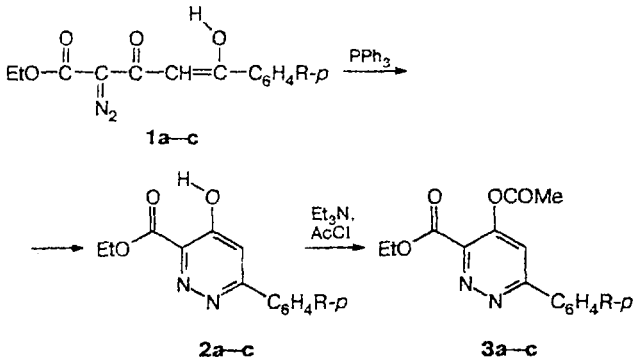
Ethyl *Z*-5-aryl-2-diazo-5-hydroxy-3-oxopent-4-enoates interact with triphenylphosphine to give 6-aryl-3-ethoxycarbonyl-4-hydroxypyridazines (Ar = Ph, 4-MeC_6H_4, 4-ClC_6H_4). Quantum-chemical calculations (MNDO) were performed to estimate the tautomeric equilibrium in the latter using a 6-phenyl-substituted derivative as an example. Acetylation of the 4-hydroxypyridazines led to 4-acetoxy-6-aryl-3-ethoxycarbonylpyridazines. The structure of the latter was confirmed by an X-ray diffraction analysis of 4-acetoxy-3-ethoxycarbonyl-6-(*p*-tolyl)pyridazine.

Key words: diazo compounds, substituted pyridazines, acylation, molecular and crystal structure.

In continuation of the study of the chemical transformations of diazocarbonyl compounds,[1] we studied the interaction of ethyl *Z*-5-aryl-2-diazo-5-hydroxy-3-oxopent-4-enoates (**1a—c**) with triphenylphosphine. This reaction results in the formation of 6-aryl-3-ethoxycarbonyl-4-hydroxypyridazines (**2a—c**) (Tables 1 and 2) and triphenylphosphine oxide (Scheme 1).

Scheme 1



The spectral characteristics of compounds **2a—c** presented in Table 2 do not allow one to exclude unambiguously an alternative structure of 6-aryl-3-ethoxycarbonyl-1,4-dihydropyridazine-4-ones for them. Because of this, we performed[2] quantum-chemical calculations for the molecule of compound **2a** in its hydroxy (**A**) and oxo (**B**) forms in an MNDO approximation with optimization of the geometry (bond lengths, valence and torsion angles). The standard values of the geometric

Table 1. The physicochemical characteristics of compounds **2a—c** and **3a—c**

Compound	Yield (%)	M.p. /°C	Found / Calculated (%) C	H	N	Cl	Molecular formula
2a	65	196—198	64.02 / 63.94	4.68 / 4.95	11.32 / 11.47	—	$C_{13}H_{12}N_2O_3$
2b	50	222—223	65.35 / 65.10	5.35 / 5.46	10.63 / 10.85	—	$C_{14}H_{14}N_2O_3$
2c			56.15 / 56.03	4.15 / 3.98	10.11 / 10.05	12.86 / 12.72	$C_{13}H_{11}ClN_2O_3$
3a	76	237—238 (decomp.)	63.08 / 62.93	4.73 / 4.93	8.61 / 8.78	—	$C_{15}H_{14}N_2O_4$
3b	55	98—99	64.27 / 63.99	5.47 / 5.37	9.62 / 9.33	—	$C_{16}H_{16}N_2O_4$
3c	59	129—131 (decomp.)	56.31 / 56.17	4.20 / 4.09	8.54 / 8.73	10.92 / 11.05	$C_{15}H_{13}ClN_2O_4$

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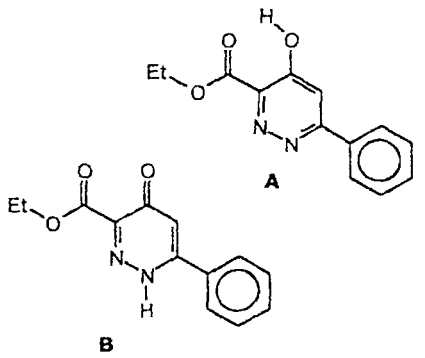
Table 2. The spectral characteristics of compounds **2a—c** and **3a—c**

Compound	IR, ν/cm^{-1}				^{1}H NMR, δ				
	CH	COO	C=C, C=N	OH	CH	CH_3	CH_2	Ar	OH
2a		1728 br	1603	3210	6.72 s	1.28 t	4.28 q	7.55 m	13.48 br.s
2b		1730 br	1607	3196	6.82 s	1.28 t, 2.35 s	4.28 q	7.55 m	
2c		1720 br	1595	3220	6.72 s	1.28 t	4.24 q	7.56 m	13.38 br.s
3a	3056	1776, 1718	1590		8.32 s	1.38 t, 2.38 s	4.42 q	7.77 m	
3b	3068	1778, 1718	1582		8.25 s	1.28 t, 2.38 d	4.42 q	7.65 m	
3c	3076	1780, 1734	1584		8.35 s	1.35 t, 2.45 s	4.45 q	7.92 m	

parameters of the phenyl substituent were used without optimization.



The enthalpies ($\Delta_f H$), full energies (E_{full}), and dipole moments (μ) of the forms **A** and **B** of compound **2a**, obtained from the quantum-chemical calculations, are given below.

	A	**B**
$\Delta_f H$/kJ mol^{-1}	−286.10	−215.36
E_{full}/eV	−3212.11	−3211.38
μ/D	3.09	6.18

It follows from the calculated values of the enthalpies and full energies of the molecules that the hydroxy form **A** is more stable in the pair of **A** and **B**. According to the calculations, the pyridazine ring is planar, and the benzene ring is turned relative to the plane of the heterocycle, forming a torsion angle of 110.3°. It should be noted that the acylation of compounds **2a—c** with acetyl chloride results in the exclusive isolation of 4-acetoxy-6-aryl-3-ethoxycarbonylpyridazines (**3a—c**) (see Table 1) as reaction products, whereas isomeric *N*-acyl derivatives are entirely absent. The structure of compound **3b** was also confirmed by X-ray diffraction analysis. Its structure is shown in Fig. 1, and the bond lengths and valence angles are listed in Table 3.

The pyridazine ring is planar with double bonds completely delocalized. Unlike the data calculated for compound **2a**, the planes of the heterocycle and the tolyl fragment in compound **3b** are almost coplanar: the torsion angle C(3)C(4)C(5)C(10) is equal to −10.8°. The planar ethoxycarbonyl group is also coplanar to the plane of the pyridazine ring. The torsion angle C(2)C(1)C(14)O(3) is equal to 2.3°. However, judging from the lengths of the C(4)—C(5) (1.480(3) Å) and C(1)—C(14) (1.498(3) Å) bonds, the conjugation of the

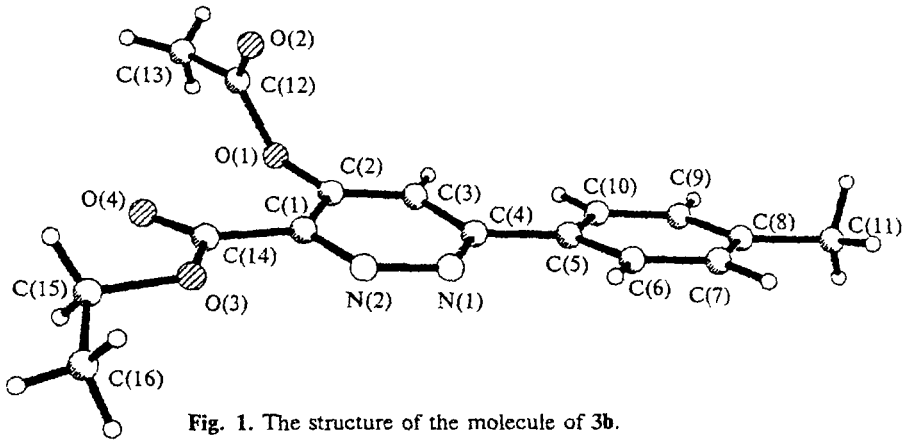


Fig. 1. The structure of the molecule of **3b**.

Table 3. The main geometric parameters of the molecule of compound **3b**

Bond	d/Å	Bond	d/Å
O(1)—C(12)	1.380(2)	C(3)—C(4)	1.386(3)
O(1)—C(2)	1.383(2)	C(4)—C(5)	1.480(3)
O(2)—C(12)	1.186(3)	C(5)—C(6)	1.385(3)
O(3)—C(14)	1.319(2)	C(5)—C(10)	1.386(3)
O(3)—C(15)	1.453(2)	C(6)—C(7)	1.374(3)
O(4)—C(14)	1.206(2)	C(7)—C(8)	1.392(3)
N(1)—N(2)	1.324(2)	C(8)—C(9)	1.368(3)
N(1)—C(4)	1.344(3)	C(8)—C(11)	1.502(3)
N(2)—C(1)	1.337(2)	C(9)—C(10)	1.382(3)
C(1)—C(2)	1.391(3)	C(12)—C(13)	1.473(3)
C(1)—C(14)	1.498(3)	C(15)—C(16)	1.487(4)
C(2)—C(3)	1.363(3)		

Angle	ω/deg	Angle	ω/deg
C(12)—O(1)—C(2)	116.0(2)	C(10)—C(5)—C(4)	122.3(2)
C(14)—O(3)—C(15)	116.1(2)	C(7)—C(6)—C(5)	122.0(2)
N(2)—N(1)—C(4)	120.0(2)	C(6)—C(7)—C(8)	120.8(2)
N(1)—N(2)—C(1)	121.0(2)	C(9)—C(8)—C(7)	117.3(2)
N(2)—C(1)—C(2)	121.0(2)	C(9)—C(8)—C(11)	121.7(2)
N(2)—C(1)—C(14)	115.2(2)	C(7)—C(8)—C(11)	121.0(2)
C(2)—C(1)—C(14)	123.8(2)	C(8)—C(9)—C(10)	122.2(2)
C(3)—C(2)—O(1)	118.4(2)	C(9)—C(10)—C(5)	120.7(2)
C(3)—C(2)—C(1)	118.0(2)	O(2)—C(12)—O(1)	121.6(2)
O(1)—C(2)—C(1)	123.6(2)	O(2)—C(12)—C(13)	127.5(2)
C(2)—C(3)—C(4)	118.8(2)	O(1)—C(12)—C(13)	110.8(2)
N(1)—C(4)—C(3)	121.0(2)	O(4)—C(14)—O(3)	123.9(2)
N(1)—C(4)—C(5)	115.6(2)	O(4)—C(14)—C(1)	123.9(2)
C(3)—C(4)—C(5)	123.3(2)	O(3)—C(14)—C(1)	112.2(2)
C(6)—C(5)—C(10)	117.1(2)	O(3)—C(15)—C(16)	107.6(2)
C(6)—C(5)—C(4)	120.7(2)		

pyridazine ring with the tolyl and ethoxycarbonyl substituents, which are coplanar to it, is absent. The fact that the molecule becomes more planar is probably due to a packing effect. The plane of the acetoxy group forms a torsion angle of 67.3° relative to the heterocycle, and the torsion angle C(1)C(2)O(1)C(12) is equal to 66.9°. All bond lengths and valence angles in the molecule have ordinary values and there are no shortened intermolecular contacts in the crystal.

Experimental

IR spectra were recorded on a UR-20 instrument and a Specord instrument in Vaseline oil. ^{1}H NMR spectra were recorded on an RYa-2310 spectrometer (60 MHz) in DMSO-d_6. The course of the reaction and the homogeneity of the compounds synthesized were controlled by TLC on Silufol UV-254 plates in a benzene—ether—acetone (10 : 9 : 1) system.

6-Aryl-3-ethoxycarbonyl-4-hydroxypyridazines (2a—c). A solution of ethyl *Z*-5-aryl-2-diazo-5-hydroxy-3-oxopent-4-enoate (**1a—c**) (0.01 mol) and Ph_3P (0.01 mol) in 50 mL of anhydrous ether was kept at ~20 °C for 48—72 h. The reaction mixture was cooled to +4 °C, and the precipitate that formed was filtered off and recrystallized from dioxane.

Table 4. The coordinates of the atoms (×10^4) and the isotropic thermal parameters (×10^3) in the molecule of compound **3b**

Atom	x	y	z	U_{eq}
O(1)	8054(1)	494(1)	2172(1)	42(1)
O(2)	8033(2)	2074(2)	3330(1)	62(1)
O(3)	7490(1)	3937(1)	449(1)	47(1)
O(4)	8929(2)	2664(2)	1241(2)	64(1)
N(1)	4694(2)	1740(2)	752(1)	41(1)
N(2)	5696(2)	2430(2)	687(1)	41(1)
C(1)	6804(2)	2050(2)	1128(1)	34(1)
C(2)	6938(2)	920(2)	1677(1)	34(1)
C(3)	5915(2)	185(2)	1710(2)	36(1)
C(4)	4787(2)	619(2)	1240(1)	33(1)
C(5)	3607(2)	−62(2)	1288(1)	35(1)
C(6)	2486(2)	514(2)	971(2)	48(1)
C(7)	1375(2)	−86(2)	1027(2)	55(1)
C(8)	1338(2)	−1317(2)	1391(2)	44(1)
C(9)	2445(2)	−1888(2)	1701(2)	50(1)
C(10)	3565(2)	−1281(2)	1666(2)	44(1)
C(11)	127(3)	−1981(3)	1444(3)	62(1)
C(12)	8553(2)	1188(2)	3025(2)	40(1)
C(13)	9753(2)	663(2)	3463(2)	49(1)
C(14)	7861(2)	2903(2)	958(2)	39(1)
C(15)	8459(2)	4785(2)	189(2)	52(1)
C(16)	7895(3)	5683(3)	−614(3)	66(1)
H(3)	6028(22)	−590(23)	2055(20)	53
H(6)	2519(26)	1253(27)	718(23)	72
H(7)	521(32)	386(28)	761(26)	83
H(9)	2404(29)	−2635(27)	1995(24)	74
H(10)	4330(26)	−1750(24)	1927(21)	66
H(11a)	−533(34)	−1518(31)	1440(29)	93
H(11b)	69(32)	−2213(28)	2191(30)	93
H(11c)	−14(32)	−2662(32)	993(28)	93
H(13a)	9821(31)	27(28)	3108(26)	74
H(13b)	9554(31)	−1(26)	3922(26)	74
H(13c)	10334(28)	1207(26)	3772(24)	74
H(15a)	9064(31)	4254(26)	−85(25)	79
H(15b)	8879(31)	5160(28)	772(27)	79
H(16a)	8431(34)	6273(32)	−837(27)	99
H(16b)	7247(35)	6236(28)	−312(28)	99
H(16c)	7617(36)	5225(31)	−1262(31)	99

4-Acetoxy-6-aryl-3-ethoxycarbonylpyridazines (3a—c). A solution of AcCl (0.01 mol) in 10 mL of anhydrous toluene and Et_3N (0.01 mol) were added to a solution of compounds (**2a—c**) (0.01 mol) in 30 mL of anhydrous toluene. The reaction mixture was stirred at ~20 °C for 14 h. The precipitate that formed was filtered off, the filtrate was concentrated, and the residue was recrystallized from EtOH.

The X-ray diffraction study of compound 3b. Crystals of compound **3b** are monoclinic. Main crystallographic data: a = 10.869(2), b = 10.630(2), c = 12.818(3) Å, β = 96.20(3)°, V = 1472.3(5) Å^3, molecular weight 300.31, d = 1.355 g cm^{-3}, Z = 4, space group $P2_1/n$. Unit cell parameters and an experimental set of reflections were obtained on an automatic four-circle KUMA DIFFRACTION diffractometer using monochromatic Cu-Kα radiation. Independent reflections (2529) were measured in the angle range of 5 < θ < 68°. Corrections for absorption were not introduced. The structure was solved by a direct statistic method. The coordinates of hydrogen atoms were determined geometrically. The root-mean-square refinement was

performed in a full-matrix anisotropic approximation. The isotropic thermal parameters of hydrogen atoms were not refined, but fixed equal to values that are a factor of 1.5 greater than the corresponding parameters of non-hydrogen atoms. The final R value obtained from 1604 reflections with $I > 2\sigma(I)$ is equal to 0.050. All computations were performed on a PC/AT using the SHELX-86 [3] and SHELXL-193 [4] programs. The coordinates of atoms are listed in Table 4.

The quantum-chemical calculations for the A and B forms of compound 2a were performed by the MNDO [2] method on a PC/AT.

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A simple synthesis of 4-amino-6-methyl-1,1,1-trifluoro(trichloro)hepta-3,5-dien-2-ones and 2,2-dimethyl-6-trifluoromethyl-2,3-dihydro-4-pyridone

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Treatment of 2,2-dimethyl-6-trifluoro(trichloro)methyl-2,3-dihydro-4-pyrones with ammonia gives 4-amino-1,1,1-trifluoro(trichloro)-6-methylhepta-3,5-dien-2-ones. Under similar conditions 1,1,1-trifluoro-2-hydroxy-6-methylhepta-2,5-dien-4-one and 6-chloro-1,1,1-trifluoro-2-hydroxy-6-methylhept-2-en-4-one cyclize into 2,2-dimethyl-6-trifluoromethyl-2,3-dihydro-4-pyridone.

Key words: aminodienones, β-diketones, dihydropyrones, ammonia, heterocyclization; 2,3-dihydro-2,2-dimethyl-6-trifluoromethyl-4-pyridone.

Earlier,[1] we demonstrated that the condensation of trifluoroacetonitrile with mesityl oxide in the presence of *N*-ethylanilinemagnesium bromide leads to 2-amino-1,1,1-trifluoro-6-methylhepta-2,5-dien-4-one (**1**), whose acid hydrolysis can give, depending on reaction conditions, either 1,1,1-trifluoro-2-hydroxy-6-methylhepta-2,5-dien-4-one (**2**) or its cyclic isomer, 2,2-dimethyl-6-trifluoromethyl-2,3-dihydro-4-pyrone (**3**). The cyclization of dienone **2** into dihydropyrone **3** is catalyzed by acids, while the reverse process occurs under the action of sodium ethoxide.

In continuation of studies on the properties of these compounds, we found that dihydropyrone **3** treated with an aqueous 25% solution of ammonia at room temperature undergoes ring opening to give 4-amino-1,1,1-trifluoro-6-methylhepta-3,5-dien-2-one (**4**) isomeric to aminodienone **1**, while dienone **2**, under similar conditions, undergoes heterocylization into 2,2-dimethyl-6-trifluoromethyl-2,3-dihydro-4-pyridone (**5**). The yields of products **4** and **5** are 46 and 37%, respectively, and a competitive reaction is the cleavage of compounds **2** and **3** under the action of ammonia into mesityl oxide and CF_3COONH_4. The treatment of 6-chloro-1,1,1-trifluoro-2-hydroxy-6-methylhept-2-en-4-one (**6**), obtained upon acidic hydrolysis of chloroaminoenone (**7**) described earlier,[1] with aqueous ammonia can also result in dihydropyridone **5** (Scheme 1).

In the preparative synthesis of compounds **4** and **5**, the more readily available ethyl trifluoroacetate rather than trifluoroacetonitrile is recommended. Its condensation with mesityl oxide in the presence of sodium methoxide followed by the isolation of the product through a copper chelate gives dienone **2** in a high yield.[2] The same reaction can also be used to obtain dihydropyrone **3**, if the condensation product is isolated by vacuum distillation, without the stage of formation of a copper chelate.

2,2-Dimethyl-6-trichloromethyl-2,3-dihydro-4-pyrone (**8**) behaves similarly to dihydropyrone **3**.[3] Its

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