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SYNTHESIS AND MOLECULAR STRUCTURE OF 3-(2-ARYL-2-OXOETHYL)-3-METHOXY-2-OXO-2,3-DIHYDROIMIDAZO-[1,2-*a*]PYRIDINE HYDROCHLORIDES

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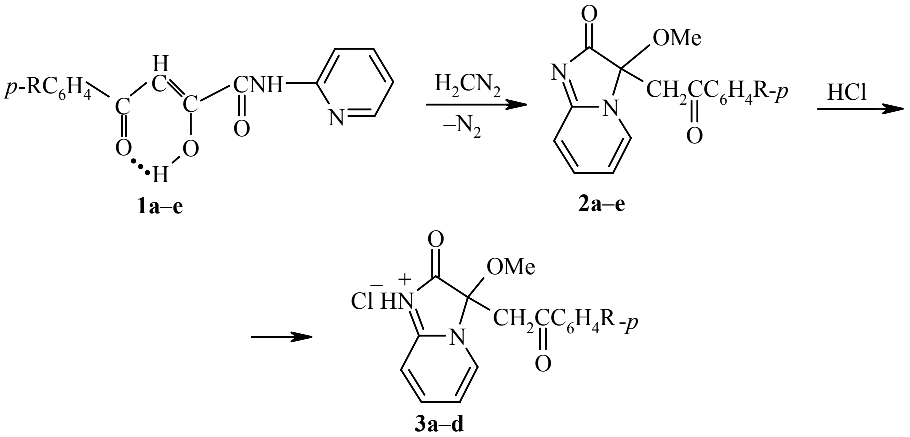
Reactions between 2-pyridylamides of Z-4-aryl-2-hydroxy-4-oxobut-2-enoic acids with diazomethane have been used to synthesize 3-(2-aryl-2-oxoethyl)-3-methoxy-2-oxo-2,3-dihydroimidazo[1,2-a]pyridines, which form hydrochlorides with hydrochloric acid. The structure of the latter has been demonstrated by XRD for the hydrochloride of 3-methoxy-2-oxo-3-(2-phenyl-2-oxoethyl)-2,3-dihydroimidazo[1,2-a]pyridine.

Keywords: hydrochlorides, substituted imidazo[1,2-*a*]pyridines, molecular and crystal structures.

Imidazo[1,2-*a*]pyridines have various forms of biological activity. Some of their derivatives act on the central nervous system [1, 2] and have cardiotonic [3], antiseptic [4, 5], anti-inflammatory, and analgesic [6] effects, and also show activity against HIV infections [7].

This paper continues research in the synthesis of imidazo[1,2-*a*]-pyridine derivatives and the search for biologically active compounds in that series [8], for which we have examined the reactions of N-(2-pyridyl)amides of *Z*-4-aryl-2-hydroxy-4-oxobut-2-enoic acids **1a-e** with diazomethane.



1–3 a R = H, **b** R = Me; **1c**, **2c** R = MeO, **1d**, **2d**, **3c** R = Cl, **1e**, **2e**, **3d** R = Br

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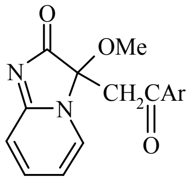
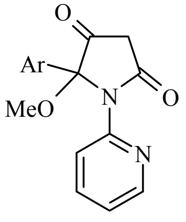
The reactions give 3-(2-aryl-2-oxoethyl)-3-methoxy-2,3-dihydro-2-oxoimidazo[1,2-*a*]pyridines **2a-e** with yields from 32 to 48% (Tables 1 and 2). The imidazo[1,2-*a*]pyridines **2a, b, d, e** on interaction with HCl smoothly form salts **3a-d** (Tables 1 and 2).

The spectral characteristics of compounds 2a-e (structure **A**) are given in Table 2 but do not allow one to exclude unambiguously the alternative for the structure of 2-aryl-2-methoxy-1-(2-pyridyl)tetrahydropyrrole-3,5-diones (**B**), and consequently for the salts **3** obtained from compounds **2** one retains the two possibilities for the structure, each of which is capable of forming salts. In this connection, an X-ray structure study has been made on compound **3a** and this established the existence of compounds **2** in the form **A**.



A



B

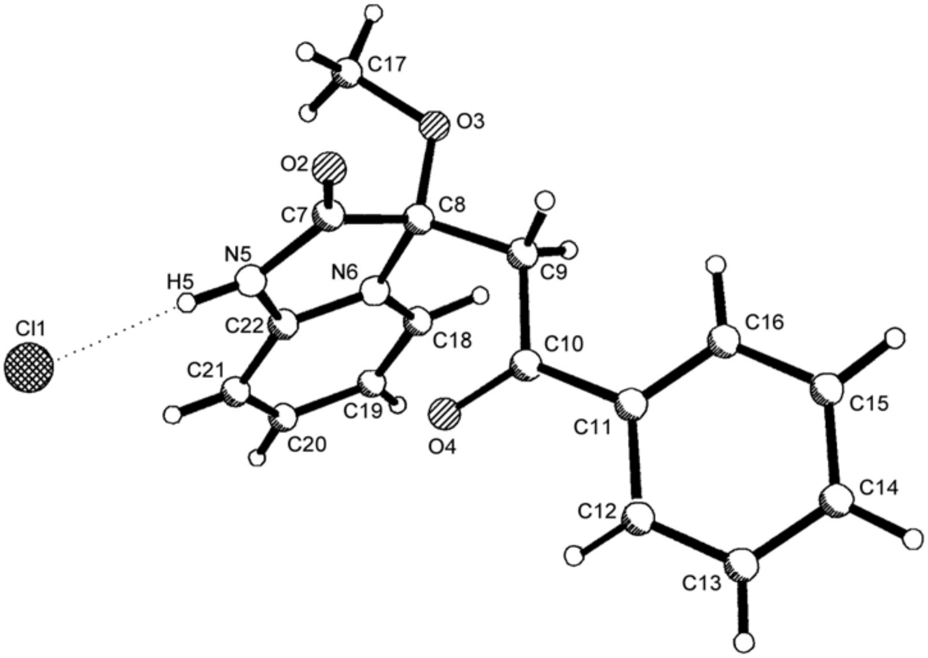
The crystals of **3a** consist of chlorine anions and organic cations. The figure shows the structure of the $C_{16}H_{15}N_2O_3^+$ cation. The distribution of the bond lengths in the planar bicyclic fragment (Tables 3 and 4) indicates complete double-bond delocalization in it.

TABLE 1. Physiochemical Characteristics of Compounds **2a-e, 3a-d**

Compound	Empirical formula	Found, % / Calculated, % C	H	N	Hal	mp, °C	Yield, %
2a	$C_{16}H_{14}N_2O_3$	68.14 68.08	5.03 5.00	9.84 9.92		197-197.5	47
2b	$C_{17}H_{16}N_2O_3$	68.87 68.91	5.40 5.44	9.43 9.45		201.5-203	48
2c	$C_{17}H_{16}N_2O_4$	65.46 65.38	5.19 5.16	8.89 8.97		174.5-176	34
2d	$C_{16}H_{13}ClN_2O_3$	60.73 60.67	4.12 4.14	8.78 8.84	11.12 11.19	207-208	39
2e	$C_{16}H_{13}BrN_2O_3$	53.15 53.21	3.65 3.63	7.79 7.76	22.21 22.12	223-224	32
3a	$C_{16}H_{15}ClN_2O_3$	60.11 60.29	4.87 4.74	8.60 8.79	11.29 11.12	214-216	73
3b	$C_{17}H_{17}ClN_2O_3$	61.26 61.36	5.24 5.15	8.59 8.42	10.50 10.65	209-210	68
3c	$C_{16}H_{14}ClN_2O_3$	54.59 54.41	3.82 4.00	8.05 7.93	20.19 20.08	220-222	59
3d	$C_{16}H_{14}BrClN_2O_3$	48.21 48.33	3.33 3.55	6.92 7.05	29.17 29.01	226-228	54

There is a certain lengthening of the bonds C(7)–C(8) 1.557 and N(6)–C(8) 1.494 Å probably on account of steric overload on the atom C(8). The benzoylmethylene group is planar. The bond lengths and valence angles in it have the usual values and require no comments. The planarity of the benzoylmethylene fragment is almost orthogonal (87°) to the plane of the bicycle and has a bisector orientation. The atom O(4) lies above the plane of the imidazole ring at a distance of 2.60 Å. The chlorine atom is linked to N(5) by a fairly strong hydrogen bond. The N(5)…Cl distance is 3.025 Å, while H(5)…Cl – 2.13 Å. There are no other shortened intermolecular contacts in the crystal.

The salts **3** have biological activity, which will be reported later.



Structure of compound **3a** molecule.

TABLE 2. Spectral Characteristics of Compounds **2a-e** and **3a-d**

Compound	IR spectrum, ν, cm^{-1}		^1H NMR spectrum, δ, ppm		
	$C=O_{cycle}$	C=O	CH_3, s	CH_2, s	Ar, m
2a	1723	1650 br.	3.12	3.82	7.51
2b	1703	1663	3.12, 3.32	3.75	7.35
2c	1712	1670	3.11, 3.85	3.71	7.22
2d	1714	1678	3.08	3.66	7.37
2e	1716	1680	3.15	3.78	7.65
3a	1721 br.				
3b	1727 br.		3.15, 3.82	3.70	7.35
3c	1726 br.				

TABLE 3. Main Bond Lengths *d* in Molecule of Compound **3a**

Bond	*d*, Å	Bond	*d*, Å
O(2)–C(7)	1.200(2)	C(10)–C(11)	1.482(2)
O(3)–C(8)	1.389(2)	O(3)–C(17)	1.442(2)
O(4)–C(10)	1.221(2)	N(5)–C(22)	1.365(2)
N(5)–C(7)	1.368(2)	N(6)–C(22)	1.351(2)
N(6)–C(18)	1.354(2)	N(6)–C(8)	1.497(2)
C(7)–C(8)	1.555(2)	C(8)–C(9)	1.514(2)
C(9)–C(10)	1.508(2)		

TABLE 4. Valence Angles (ω) in Molecule of Compound **3a**

Angle	ω, deg	Angle	ω, deg	Angle	deg
C(8)–O(3)–C(17)	116.5(2)	C(9)–C(8)–C(7)	112.9(2)	O(3)–C(8)–N(6)	111.3(2)
C(22)–N(5)–C(7)	111.3(2)	O(4)–C(10)–C(11)	121.7(2)	N(6)–C(8)–C(9)	113.2(1)
C(22)–N(6)–C(8)	110.9(1)	O(4)–C(10)–C(9)	119.8(2)	N(6)–C(8)–C(7)	99.7(1)
O(2)–C(7)–N(5)	127.8(2)	C(11)–C(10)–C(9)	118.5(2)	C(10)–C(9)–C(8)	115.2(1)
N(5)–C(7)–C(8)	107.6(2)	C(22)–N(6)–C(18)	122.3(2)	N(6)–C(22)–N(5)	110.3(2)
O(3)–C(8)–C(9)	106.2(1)	C(18)–N(6)–C(8)	126.8(1)	N(6)–C(22)–C(21)	120.7(2)
O(3)–C(8)–C(7)	113.8(1)	O(2)–C(7)–C(8)	124.6(2)	N(5)–C(22)–C(21)	129.0(2)

EXPERIMENTAL

The IR spectra were recorded with a UR-20 and Specord M-80 instrument in oil, while the ^{1}H NMR spectra were recorded with a RYa-2310 (60 MHz) instrument or Bruker WR-80 SV (80 MHz) in DMSO-d_6 and $CDCl_3$, internal standard HMDS (δ 0.05 mp). The course of the reaction was checked and the purity of the synthesized materials was verified by TLC on Silufol UV-254 plates in the solvent system ether-benzene-acetone 10:9:1.

3-(2-Aryl-2-oxoethyl)-3-methoxy-2,3-dihydro-2-oxoimidazo[1,2-*a*]pyridines 2a-e. To a solution of 2-pyridylamide of *Z*-4-aryl-2-hydroxy-4-oxobut-2-enoic acid **1a-e** (0.01 mol) in benzene (30 ml) we added a solution of diazomethane (0.03 mol) in ether (45 ml) and stirred the mixture for 3 h at -5 to 0°C. The deposit was filtered off and recrystallized from benzene.

Hydrochlorides of 3-(2-Aryl-2-oxoethyl)-3-methoxy-2,3-dihydro-2-oxoimidazo[1,2-*a*]pyridines 3a-d. A solution of compounds **2, a, b, d,** and **e** (0.01 mol) in 5% HCl (20 ml) was extracted with chloroform (15 ml). The water layer was separated and evaporated, and the residue was recrystallized from acetone.

X-ray Structure Study of Compound 3a. Euhedral prismatic crystals were obtained in 5% hydrochloric acid, $C_{16}H_{14}N_2O_3 \cdot HCl$, monoclinic syngony $a = 12.444(2)$, $b = 9.137(1)$, $c = 13.603(3)$ Å, $\beta = 83.02(3)°$, $V = 1535.2(5)$ Å^3, $M = 318.75$, $d_{calc} = 1.379$ g/cm^3, space group $P2_1/c$.

The experimental reflections were recorded with a KM-4 (KUMA DIFFRACTION) automatic 4-circle diffractometer with monochromatized CuKα radiation in the angular range $3.6<\theta<79.8°$, and in all we measured 2535 independent reflections. No absorption corrections were applied ($\mu = 2.331$ mm^{-1}). The structure was determined by a direct statistical method followed by a series of calculations on the electron-density map. The hydrogen atoms were localized objectively from a difference synthesis calculated after refining the nonhydrogen atoms in the isotropic approximation. Full-matrix anisotropic least-squares refinement (isotropic for the hydrogen atoms) was terminated at $R_1 = 0.0342$ ($wR_2 = 0.0969$) from 2064 reflections having $I > 2\sigma(I)$ and $R_1 = 0.0530$ ($wR_2 = 0.1098$) from the complete set. All the calculations were performed with an AT PC on the programs SHELX-86 [9] and SHELX l-93 [10].

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