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SYNTHESIS AND MOLECULAR STRUCTURE OF 3,7-DIMETHYL-2-[N-(4-METHYLPYRIDYL-2)-4-HYDROXY-3-METHYL-5-OXOPYRROLEN-3-YL-2]IMIDAZO[1,2-*a*]PYRIDINE

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Heterocyclization of 2-chloroepoxy-1,1-diethoxy-2.3-butane with 2-amino-4-methylpyridine occurred with participation of all three potential electrophilic centers to give 3,7-dimethyl-2-[N-(4-methylpyridyl-2)-4-hydroxy-3-methyl-5-oxopyrrolen-3-yl]imidazo[1,2-a]pyridine, the structure of which was determined by X-ray crystallography.

Keywords: 1-amino-4-methylpyridine, α-chlorooxirane, α-hydroxy acid, imidazo[1,2-*a*]pyridine, heterocyclic carbaldehyde.

The presence in α-chloroepoxides of type **1** of a potential aldehyde group – the acetal fragment – predetermines the high reactivity of these electrophilic reagents. We have shown that acetal-containing α-chlorooxiranes [1] are suitable starting reagents for the synthesis of five- and six-membered heterocyclic carbaldehydes and their derivatives [2-4].

To widen the synthetic potential of these substrates and to obtain polyheterocycles we have studied the condensation of α-chlorooxirane **1** with the aminopyridine **2**. The reaction occurred in boiling isopropanol over 3 h to give the heterocycle **9**.

The very unexpected formation of compound **9**, the structure of which was proved by ^{1}H NMR and X-ray crystallography, may occur as shown in the scheme (r.p. 1900).

Heterocyclization occurs in the first step to form the acetal **3** which is easily converted into the carbaldehyde **4** in the acid medium. An unusual condensation of the polyaminal **5**, formed by reaction of the aldehyde **4** with a second molecule of aminopyridine **2,** with the product of the rearrangement of α-chlorooxirane – the α-chloro ketone **6** – then occurs, accompanied by the formation of a new carbon-carbon bond. In previous investigations we have shown that heterosubstituted α-chloroacetals in acid media underwent redox processes which led to the synthesis of α-hydroxy acids [5]. Evidently the intermediate α-keto acetal **7** was converted similarly to the hydroxy acid **8**. The latter was transformed into the final product **9** by intramolecular condensation.

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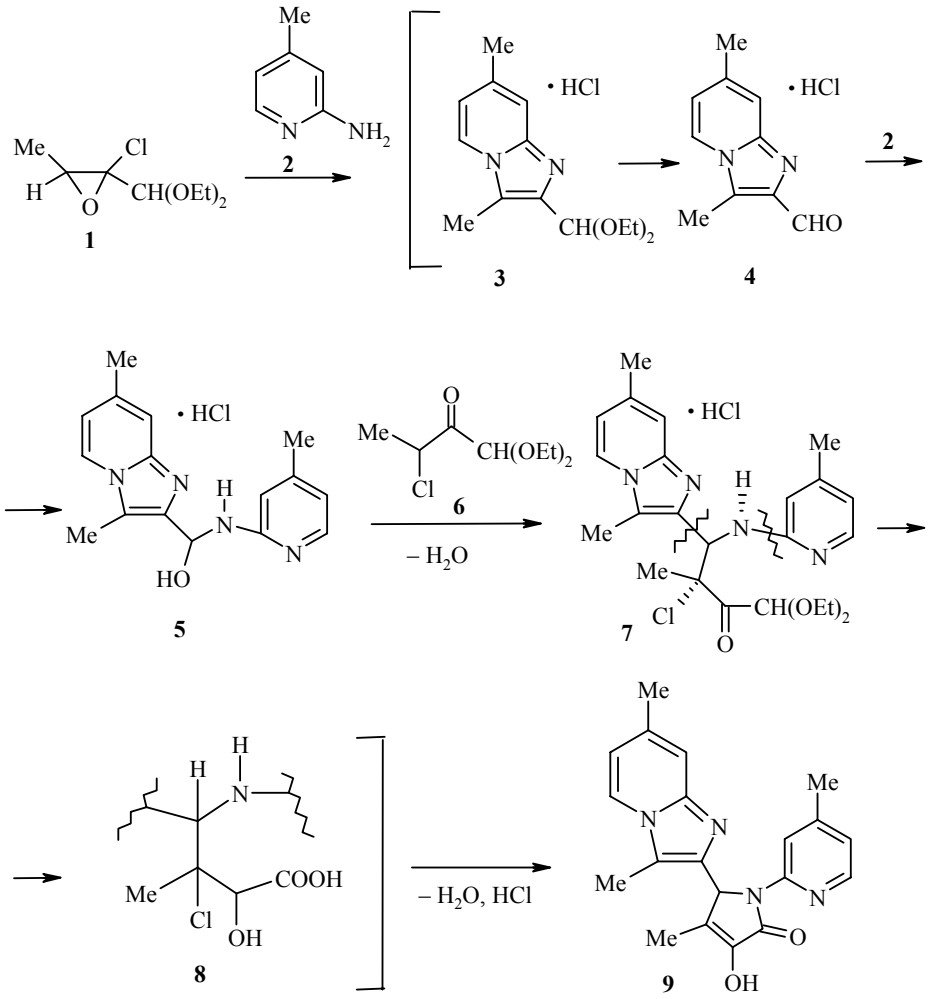

The IR spectrum of compound **9** contains intense absorptions at 1660-1650 and 1630-1620 cm^{-1} characteristic of stretching vibrations of C=N and C=C bonds in conjugated systems. The intense absorption maximum at 1690 cm^{-1} is characteristic of the stretching vibration of a carbonyl group. The stretching vibration of an OH group occurs at 3210 cm^{-1} in the high frequency region of the spectrum of the heterocycle.

In the ^1H NMR spectrum of compound **9** the signals of the protons of the methyl group on the five-membered heterocycle were observed at 1.6 ppm and those of the pyridine methyl group at 2.2 ppm. The methyne proton appeared in the 6.05 ppm region. The signals of the vinyl protons of the pyridine and imidazole fragments overlapped and were observed in the 6-8-7.2 and 7.9-8.1 ppm regions, and that for the hydroxy group at 9.25 ppm.

The structure of compound **9** was established by X-ray crystallography. Since the crystal was centrosymmetric, compound **9** exists as a racemate (Fig. 1).

Compound **9** consists of three unsaturated heterocyclic units joined by single bonds. The bicyclic imidazopyridine unit is planar within limits of 0.019(3) A. The distribution of bond lengths in this unit corresponds to the proposed structural formula and also indicates considerable conjugation in this bicyclic system, leading to lengthening of the double bonds and shortening of the single bonds. Nevertheless complete "levelling" of the bonds, as in benzene, was not observed.

The five-membered oxopyrrolene ring is also planar within limits of 0.013(3) A, despite the presence of the sp^3-hybridized $C_{(12)}$ atom. The bond lengths correspond to localized bonds, conjugation is absent (this is in agreement with the concept that an sp^3-atom does not transmit conjugation). The methylpyridine substituent at

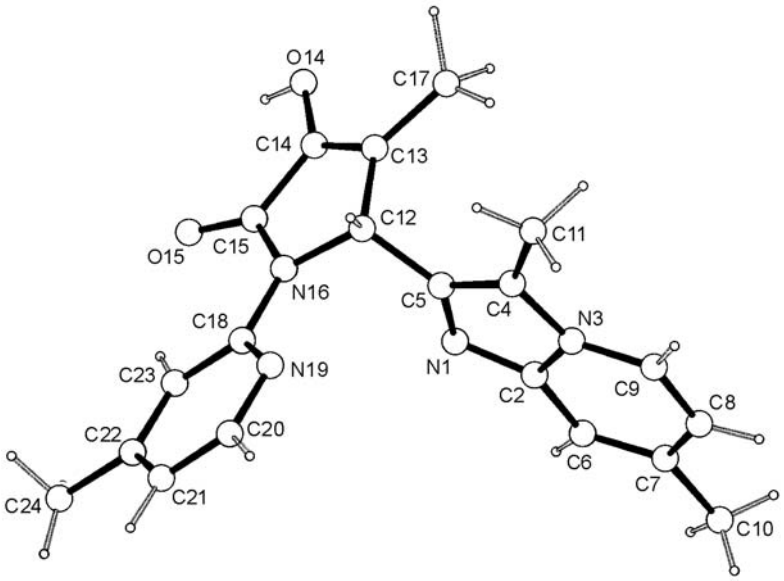

Fig. 1. Geometry of molecule **9** in the crystal.

the nitrogen atom is planar and the interfacial angle between the plane of the aromatic ring and the five-membered ring is 13.3(1)°, i.e., these rings are almost coplanar. Evidently the shortening of the $N_{(16)}$–$C_{(18)}$ and $N_{(16)}$–$C_{(15)}$ bonds, accompanied by the lengthening of the C=O bond, indicates conjugation of the lone pair of the nitrogen atom with the π-system of the double bond and the aromatic ring.

In the crystal of compound **9** the hydroxy group forms an intermolecular hydrogen bond of the O–H···N type (Fig. 2) with a nitrogen atom of the imidazopyridine unit to form centrosymmetric dimers. The parameters of the hydrogen bond are: $O_{(14)}$–H···$N_{(1)}$, (*-x*, 2 - *y*, *-z*), $O_{(14)}$–H 0.98(3), $O_{(14)}$···$N_{(1)}$ 2.680(3), H···$N_{(1)}$ 1.71(3) A, angle $O_{(14)}$–H···$N_{(1)}$ 169(3)°.

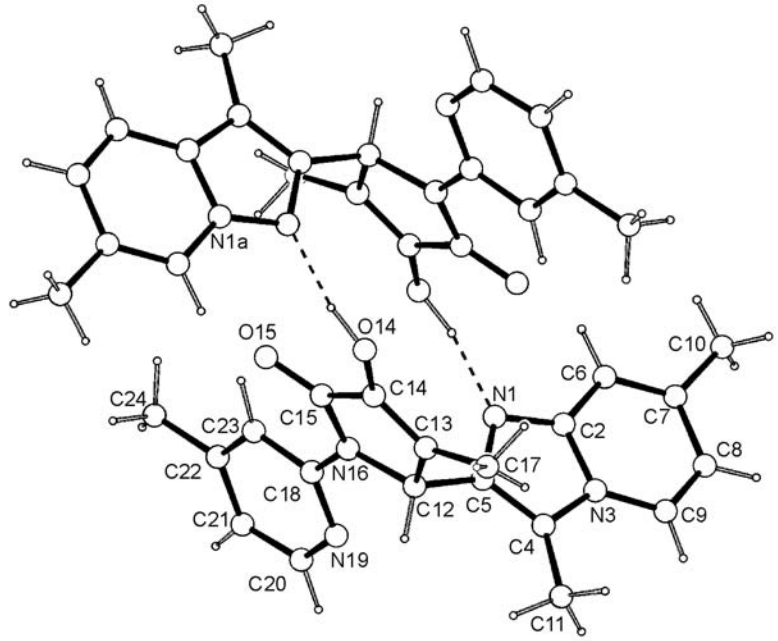

Fig. 2. Hydrogen bonds in the crystal of molecule **9**.

As the results of this and preceding studies have shown, when nucleophilic reagents, in particular aminopyridines, react with the α-chlorooxirane **1**, the presence of an acetal group in the latter facilitates the occurrence of unusual reactions, which are accompanied by formation of new C–C bonds, α-hydroxy acids, and bis-heterocyclic systems.

TABLE 1. Bond Lengths (*d*) in Molecule **9**

Bond	*d*, Å	Bond	*d*, Å	Bond	*d*, Å
$O_{(14)}$–$C_{(14)}$	1.347(3)	$N_{(19)}$–$C_{(18)}$	1.343(3)	$C_{(12)}$–$C_{(13)}$	1.498(3)
$O_{(15)}$–$C_{(15)}$	1.218(3)	$N_{(19)}$–$C_{(20)}$	1.337(3)	$C_{(13)}$–$C_{(14)}$	1.335(3)
$N_{(1)}$–$C_{(2)}$	1.330(3)	$C_{(2)}$–$C_{(6)}$	1.401(5)	$C_{(13)}$–$C_{(17)}$	1.492(3)
$N_{(1)}$–$C_{(5)}$	1.372(4)	$C_{(4)}$–$C_{(5)}$	1.372(3)	$C_{(14)}$–$C_{(15)}$	1.463(3)
$N_{(3)}$–$C_{(2)}$	1.389(3)	$C_{(4)}$–$C_{(11)}$	1.489(4)	$C_{(18)}$–$C_{(23)}$	1.401(3)
$N_{(3)}$–$C_{(4)}$	1.386(4)	$C_{(5)}$–$C_{(12)}$	1.499(4)	$C_{(20)}$–$C_{(21)}$	1.374(3)
$N_{(3)}$–$C_{(9)}$	1.381(3)	$C_{(6)}$–$C_{(7)}$	1.362(4)	$C_{(21)}$–$C_{(22)}$	1.403(3)
$N_{(16)}$–$C_{(12)}$	1.475(3)	$C_{(7)}$–$C_{(8)}$	1.425(4)	$C_{(22)}$–$C_{(23)}$	1.368(3)
$N_{(16)}$–$C_{(15)}$	1.384(3)	$C_{(7)}$–$C_{(10)}$	1.500(5)	$C_{(22)}$–$C_{(24)}$	1.498(3)
$N_{(16)}$–$C_{(18)}$	1.386(3)	$C_{(8)}$–$C_{(9)}$	1.342(5)		

TABLE 2. Bond Angles (ω) in Molecule **9**

Angle	ω, deg.	Angle	ω, deg.	Angle	ω, deg.
$C_{(2)}N_{(1)}C_{(5)}$	106.1(2)	$N_{(1)}C_{(5)}C_{(12)}$	121.0(2)	$O_{(14)}C_{(14)}C_{(15)}$	122.2(2)
$C_{(2)}N_{(3)}C_{(4)}$	107.6(2)	$C_{(4)}C_{(5)}C_{(12)}$	127.2(3)	$C_{(13)}C_{(14)}C_{(15)}$	110.4(2)
$C_{(2)}N_{(3)}C_{(9)}$	121.0(3)	$C_{(2)}C_{(6)}C_{(7)}$	120.0(2)	$O_{(15)}C_{(15)}N_{(16)}$	126.9(2)
$C_{(4)}N_{(3)}C_{(9)}$	131.4(2)	$C_{(6)}C_{(7)}C_{(8)}$	118.9(3)	$O_{(15)}C_{(15)}C_{(14)}$	126.6(2)
$C_{(12)}N_{(16)}C_{(15)}$	110.5(2)	$C_{(6)}C_{(7)}C_{(10)}$	121.9(3)	$N_{(16)}C_{(15)}C_{(14)}$	106.5(2)
$C_{(12)}N_{(16)}C_{(18)}$	123.0(2)	$C_{(8)}C_{(7)}C_{(10)}$	119.2(2)	$N_{(16)}C_{(18)}N_{(19)}$	115.8(2)
$C_{(15)}N_{(16)}C_{(18)}$	126.0(2)	$C_{(7)}C_{(8)}C_{(9)}$	121.5(3)	$N_{(16)}C_{(18)}C_{(23)}$	122.0(2)
$C_{(18)}N_{(19)}C_{(20)}$	116.8(2)	$N_{(3)}C_{(9)}C_{(8)}$	119.3(2)	$N_{(19)}C_{(18)}C_{(23)}$	122.1(2)
$N_{(1)}C_{(2)}N_{(3)}$	110.0(3)	$N_{(16)}C_{(12)}C_{(5)}$	112.8(2)	$N_{(19)}C_{(20)}C_{(21)}$	124.9(2)
$N_{(1)}C_{(2)}C_{(6)}$	130.7(2)	$N_{(16)}C_{(12)}C_{(13)}$	102.8(2)	$C_{(20)}C_{(21)}C_{(22)}$	118.2(2)
$N_{(3)}C_{(2)}C_{(6)}$	119.2(2)	$C_{(5)}C_{(12)}C_{(13)}$	111.7(2)	$C_{(21)}C_{(22)}C_{(23)}$	117.8(2)
$N_{(3)}C_{(4)}C_{(5)}$	104.9(2)	$C_{(12)}C_{(13)}C_{(14)}$	109.7(2)	$C_{(21)}C_{(22)}C_{(24)}$	120.9(2)
$N_{(3)}C_{(4)}C_{(11)}$	122.0(2)	$C_{(12)}C_{(13)}C_{(17)}$	123.7(2)	$C_{(23)}C_{(22)}C_{(24)}$	121.3(2)
$C_{(5)}C_{(4)}C_{(11)}$	133.1(3)	$C_{(14)}C_{(13)}C_{(17)}$	126.5(2)	$C_{(18)}C_{(23)}C_{(22)}$	120.2(2)
$N_{(1)}C_{(5)}C_{(4)}$	111.3(3)	$O_{(14)}C_{(14)}C_{(13)}$	127.4(2)		

TABLE 3. Basic Torsion Angles (τ) in Molecule **9**

Angle	τ, deg.	Angle	τ, deg.
$C_{(18)}N_{(16)}C_{(12)}C_{(5)}$	-67.2(3)	$C_{(20)}N_{(19)}C_{(18)}N_{(16)}$	-178.9(2)
$C_{(18)}N_{(16)}C_{(15)}O_{(15)}$	4.6(4)	$N_{(1)}C_{(5)}C_{(12)}N_{(16)}$	-33.6(3)
$C_{(18)}N_{(16)}C_{(15)}C_{(14)}$	-173.3(2)	$N_{(1)}C_{(5)}C_{(12)}C_{(13)}$	81.6(3)
$C_{(12)}N_{(16)}C_{(18)}N_{(19)}$	-7.3(4)	$C_{(4)}C_{(5)}C_{(12)}N_{(16)}$	154.9(2)
$C_{(12)}N_{(16)}C_{(18)}C_{(23)}$	172.6(2)	$C_{(4)}C_{(5)}C_{(12)}C_{(13)}$	-89.9(3)
$C_{(15)}N_{(16)}C_{(18)}N_{(19)}$	163.7(3)	$C_{(5)}C_{(12)}C_{(13)}C_{(14)}$	-120.0(2)
$C_{(15)}N_{(16)}C_{(18)}C_{(23)}$	-16.4(4)	$C_{(5)}C_{(12)}C_{(13)}C_{(17)}$	59.3(4)

EXPERIMENTAL

IR spectra of nujol mulls were recorded on a UR-20 spectrometer, X-ray crystallography was carried out with an automatic four-circle Enraf-Nonius CAD-4 diffractometer at 20°C, and ^{1}H NMR spectra of DMSO-d_6 solutions with HMDS as internal standard (δ 0.05 ppm) were recorded with a Tesla BW-567 (100 MHZ) machine.

3,7-Dimethyl-2-[N-(4-methylpyridyl-2)-4-hydroxy-3-methyl-5-oxopyrrolen-3-yl-2]imidazo[1,2-*a*]-pyridine (9). Oxirane **1** (3.00 g, 1.17 mmol) on 2-propanol (25 ml) was added with stirring to a solution of 2-amino-4-methylpyridine (1.26 g, 1.17 mmol) in absolute 2-propanol (10 ml). The reaction mixture was boiled for 3 h, the solvent was removed in vacuum , and a 2:3 mixture of ether and acetone was added to the residue. The crystals of compound **9** which formed were filtered off. Yield 2.70 g (43%); mp 254°C (2-propanol). IR spectrum, ν, cm^{-1}: 3210 (OH), 1690 (C=O). 1660 (C=N), 1620 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.60 (6H, s, 2CH_3); 2.25 (6H, s, 2CH_3); 6.05 (1H, s, CH–N); 6.80-7.20 (2H, m, Py); 7.90-8.10 (4H, m, Py); 9.25 (1H, br. s, OH). Found, %: N 16.20. $C_{20}H_{20}N_4O_2$. Calculated, %: N 16.09.

X-ray Crystallographic Analysis. Crystals of **9**, $C_{20}H_{20}N_4O_2$, triclinic. At 20°C a = 8.911(8), b = 9.404(9), c = 11.72(1) Å; α = 74.2(1), β = 72.29(8), γ = 72.65(9)°; V = 875(2) Å^3; Z = 2; d_{calc} = 1.32 g·cm^{-1}; space group $P1-$ ($P1$ bar).

The lattice parameters and the intensities of 3805 reflexions, 2356 of which had $I > 3\sigma$, were measured on an automatic four-circle Enraf-Nonius CAD-4 diffractometer at 20°C (λCuKα, graphite monochromator, ω/2θ scanning, θ ≤ 75°). No decrease in the intensities of three control reflexions was observed during data collection. Calculation of adsorption (μCu 6.7 cm^{-1}) was not carried out because it was so small.

The structure was solved by direct methods using the SIR programme [6] and refined initially in the isotropic and then in the anisotropic approximation. The hydrogen atoms were revealed by a difference synthesis and then refined in the remaining cycles isotropically. The final values of the residual factors were R = 0.049, R_w = 0.054 for 2086 independent reflexions with $F^2 \geq 3\sigma$. All calculations were carried out on a DEC Alfa Station 200 using the MoIEN suite of programmes [7]. Analyses of the intermolecular interactions and figures of the structure were obtained with the help of the PLATON programme [8].

The geometry of the molecule is shown in Fig. 1. Bond lengths, bond angles, and torsion angles are given in Tables 1-3 respectively.

Atomic coordinates of the structure have been deposited in the Cambridge Crystal Structure Data Bank (reference number CCBC 602046).

REFERENCES

1. F. I. Guseinov, S. Sh. Tagiev, and V. V. Moskva, *Zhur. Org. Khim.,* **31**, 1131 (1995).
2. F. I. Guseinov and N. A. Yudina, *Khim. Geterotsikl. Soedin.,* 1143 (1997). [*Chem. Heterocycl. Comp.,* **33**, 1001 (1997)].
3. F. I. Guseinov and N. A. Yudina, *Khim. Geterotsikl. Soedin.,* 124 (1998). [*Chem. Heterocycl. Comp.,* **34**, 115 (1998)].
4. F. I. Guseinov and N. A. Yudina, in: *36th IUPAC Congress, Book of Abstr.,* Geneva (1997), p. 476.
5. F. I. Guseinov and N. A. Yudina, in: *Chemistry and Use of Phosphor-, Sulfa- and Silico-organic Compounds. St.Petersburg Meeting-98, Book of Abstracts* [in Russian], St. Petersburg (1998), p.82.
6. A. Altomare, G. Cascarano, C. Giacovazzo, and D. Viterbo, *Acta Crystallogr.,* **A47**, 744 (1991).
7. L. H. Straver, A. J. Schierbeck, *MoIEN Structure Determination System,* Nonius B. V. (1994).
8. A. L. Spek, PLATON for Windows, version 98. *Acta Crystallogr.,* **A46**, 34 (1990).