PRODUCTS OF INTERACTION OF FERVENULIN-3-ONE-4-OXIDE WITH *o*-PHENYLENEDIAMINES

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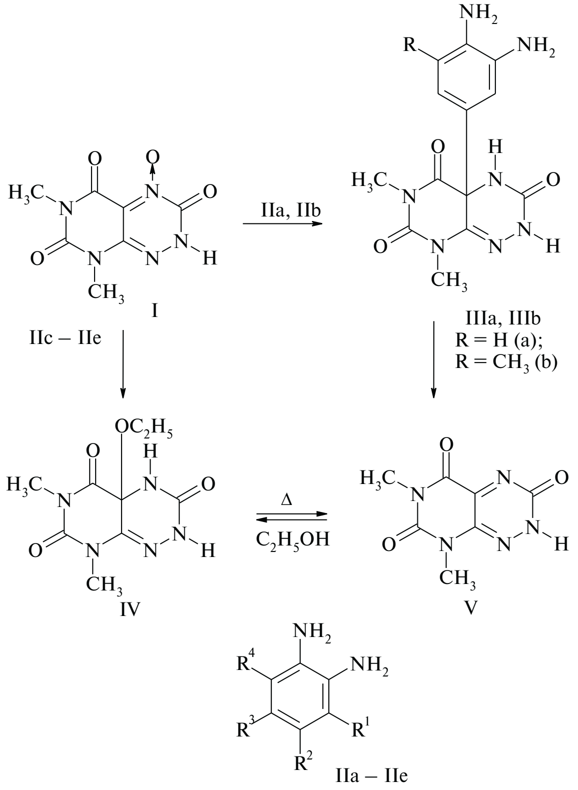
Pyrimidotriazine antibiotics were reported to exhibit a broad spectrum of pharmacological activity [1 – 3]. For example, reumycin – a representative of this series of compounds – is used as an antitumor drug [4].

As is known, fervenul-3-one smoothly reacts with various C-nucleophilic compounds with the formation of addition products with respect to the C_{4a} node atom of the pyrimidotriazine nucleus [5]. At the same time, the synthesis of new analogs of these compounds is hindered because of low availability of fervenul-3-one. Recently, one of the authors described fervenul-3-one-4-N-oxide and proposed a simple method for the synthesis of this compound from more available fervenulin-4-oxide [6].

Below we will demonstrate that fervenul-3-one-4-oxide (I) interacts with *o*-phenylenediamines (IIa, IIb) with the formation of known diaminophenyl derivatives IIIa and IIIb [5].

It is interesting to note that 4-chloro-, 4,5-dimethyl-, and 3,6-dimethoxyphenylenediamines (IIc – IIe) do not attach to the pyrimidotriazine nucleus and the reaction terminates by the formation of a colorless adduct with ethanol (IV). Heating compound IV may lead to detachment of the ethanol fragment with the formation of fervenulone V. Recrystallization of compound V from ethanol again leads to the formation of adduct IV.

The ^1H and ^{13}C NMR spectra of compounds IIIa and IIIb were described in [5]. The ^1H NMR spectra indicate that protons of the 2-NH and 4-NH groups exhibit a spin – spin coupling characterized by $J_{2,4} = 1.9$ Hz. The chemical shift and the character of splitting of the signals corresponding to these protons were affected neither by increasing temperature of the solution nor by adding deuterated solvents.[3] An important diagnostic feature of the 4a-substituted fervenulone derivatives is the presence of a tetrahedral node occupied by a carbon atom, the signal of which is observed at ~ 60 ppm in the ^{13}C NMR spectrum.



IIa: $R^1 = R^2 = R^3 = R^4 = H$;
IIb: $R^1 = CH_3, R^2 = R^3 = R^4 = H$;
IIc: $R^1 = R^3 = R^4 = H, R^2 = Cl$;
IId: $R^1 = R^4 = H, R^2 = R^3 = CH_3$;
IIe: $R^1 = R^4 = OCH_3, R^2 = R^3 = H$.

Taking into account the unusual structural features of the molecules of 4a-diaminophenyl derivatives, we have studied the crystal structure of compound IIIa by x-ray diffraction. It was found that IIIa crystallizes in the monoclinic system with $a = 12.424(6)$ Å, $b = 12.583(6)$ Å, $c = 18.242(6)$ Å, $\beta = 93.15(3)°$, $V = 2847(2)$ Å^3, $Z = 8$, space group $C2/c$. The structure was solved by direct method and refined by the least squares method in the full-matrix anisotropic approximation to final $R = 0.071$. The data for 1630 reflections were

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* The positions and temperature parameters of H atoms revealed by difference Fourier syntheses were not refined.

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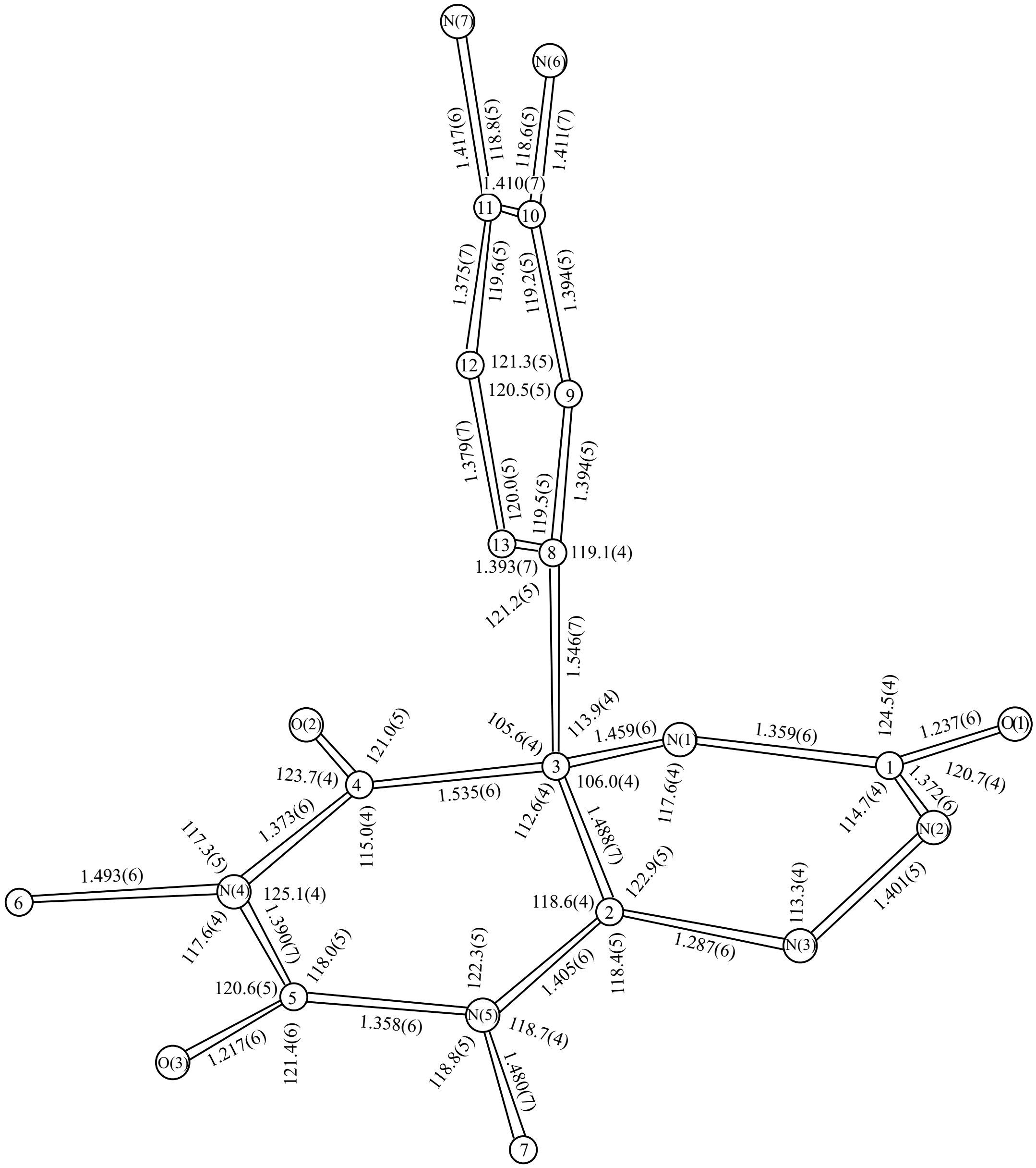

Fig. 1. Bond lengths (Å) and angles (deg) in IIIa molecule.

TABLE 1. Coordinates of Nonhydrogen Atoms (× 10^4)

Atom	*x/a*	*y/b*	*z/c*	Atom	*x/a*	*y/b*	*z/c*
O(1)	2024(3)	1923(3)	779(2)	C(2)	4918(4)	669(4)	1161(3)
O(2)	5431(3)	2181(3)	–462(2)	C(3)	4876(4)	1667(4)	723(2)
O(3)	7573(3)	–133(4)	857(2)	C(4)	5612(4)	1632(5)	75(3)
N(1)	3766(3)	1768(4)	428(2)	C(5)	6695(4)	285(5)	748(3)
N(2)	3263(3)	1061(4)	1520(2)	C(6)	7387(4)	1153(5)	–344(3)
N(3)	4157(3)	381(4)	1569(2)	C(7)	5973(5)	–850(5)	1691(3)
N(4)	6521(3)	1020(4)	186(2)	C(8)	5272(4)	2624(4)	1197(3)
N(5)	5858(3)	47(4)	1167(2)	C(9)	4980(4)	3648(4)	974(3)
N(6)	5060(3)	5577(4)	1178(2)	C(10)	5380(4)	4530(4)	1364(3)
N(7)	6484(4)	5274(4)	2381(2)	C(11)	6083(4)	4374(5)	1988(3)
C(1)	2967(4)	1629(4)	899(2)	C(12)	6362(4)	3357(5)	2200(3)
				C(13)	5981(4)	2486(5)	1808(3)

TABLE 2. Coefficients of the Mean-Square Plane Equations ($Ax + By + Cz = D$) and Deviations of Atoms (Å) for Some Planar Fragments of IIIa Molecule

No.	Plane											A	B	C	D
1	C(8) – 0.01	C(9) 0.00	C(10) 0.00	C(11) – 0.01	C(12) – 0.01	C(13) 0.01	C(2)* – 0.41	C(4)* 1.56	N(6)* – 0.06	N(7)* 0.00	N(1)* – 0.70	0.1238	0.4757	–11.3524	4.1097
2	N(1) – 0.02	N(2) 0.12	N(3) – 0.13	C(1) – 0.04	C(2) 0.62	C(3)						4.1343	9.7584	9.4386	3.7046
3	N(4) – 0.01	N(5) – 0.07	C(2) 0.04	C(4) – 0.01	C(5) 0.05	C(3) 0.40						4.5189	8.6641	11.0626	4.0468
4	N(1) – 0.12	N(2) 0.17	N(3) – 0.05	N(4) 0.01	N(5) – 0.11	C(1) – 0.07	C(2) – 0.08	C(4) 0.10	C(5) – 0.01			3.9533	9.2663	10.5557	3.7056

* Atoms not included in calculations for a given plane.

obtained with Syntex-PI diffractometer using Ni-filtered λCuK_{α} radiation ($\theta/2\theta$ scan technique, $3 \le 2\theta \le 120°$). The coordinates of nonhydrogen atoms in IIIa are listed in Table 1; the bond lengths and angles are indicated in Fig. 1.

The molecule of compound IIIa contains two six-membered heterocycles (pyrimidine and triazine) sharing the C(2) – C(3) bond and a diaminophenyl fragment connected to the C(3) atom. The pentaatomic fragments of the six-membered nitrogen-containing heterocycles are almost flat (except for the protruding C(3) atom), forming a dihedral angle of 7.4° (Table 2) and making angles 90.6 and 92.3° with the plane of the benzene ring. The phenyl group is rotated about C(3) – C(8) bond so that the plane of the benzene ring is almost perpendicular to the C(3) – C(4) bond: the torsion angles C(4)C(3)C(8)C(13) and C(4)C(3)C(8)C(9) are close to 90°. The tetrahedral coordination of C(3) atom results in a considerable shift of this atom [by 0.53 Å toward C(8)] from the median plane passing through atoms N(1) – N(5), C(1)C(2)C(5)C(4). The C(3) – C(8) bond length is somewhat greater as compared to the standard value $C_{sp3} - C_{sp2} = 1.50$ Å [7]. The other bond lengths in the heterocycle system are rather close to the corresponding standard values: the single bonds $C_{sp2} - N$ vary from 1.358(6) to 1.405(6) Å and the length of the double bond C(2) = N(3) is 1.287(6) Å. The molecule contains six active protons [two protons at each nitrogen in the amino groups and one proton at each of N(1) and N(2) atoms] capable of forming hydrogen bonds. However, only three of these protons are actually involved in H-bonds: O(1)…N(1) ($1/2 - x$, $1/2 - y$, z), O(1)…N(6) ($-1/2 + x$, $-1/2 + y$, z), and N(2)…N(7) ($-1/2 + x$, $-1/2 + y$, z). The donor – acceptor distances are 2.878, 3.090, and 2.952 Å (with the corresponding O–H and N – H distances being 1.88, 2.01, and 1.98 Å, respectively).

EXPERIMENTAL CHEMICAL PART

Reaction of fervenulin-3-one-4-oxide with *o*-phenylenediamines IIa and IIb. A mixture of 0.09 g (0.4 mmole) fervenulin-3-one-4-oxide (I), 0.1 ml concentrated HCl, and 0.087 g (0.8 mmole) *o*-phenylenediamine IIa was boiled in 7 ml ethanol for 3 h. The precipitate of 1,2,3,5,6,7,8,8a-octahydro-6,8-dimethyl-4a-(3,4-diaminophenyl)pyrimido[5,4-e][1,2,4]triazine-3,5-trione was separated by filtration. The aqueous hydrochloride solution was treated with sodium acetate to obtain a base of the target product IIIa (yield, 65%).

The target product IIIb was obtained using a similar procedure with *o*-phenylenediamine IIb (yield, 75%). Compounds IIa and IIIb are identical to the samples described in [5].

Reaction of fervenulin-3-one-4-oxide with *o*-phenylenediamines IIc – IIe. A mixture of 1.0 mmole) fervenulin-3-one-4-oxide (I), 1.0 mmole diamine, and 0.2 ml concentrated HCl was boiled in 5 ml ethanol for 1 h. Upon cooling, the precipitate of 2,3,4,4a,5,6,7,8-octahydro-4a-ethoxy-6,8-dimethylpyrimido[5, 4-e][1,2,4]triazine-3,5,7-trione IV was separated by filtration (yield, 70 – 75%). On heating to 150 – 155°C, compound IV converts into V with a quantitative yield. Compounds IV and V are identical to the samples described in [5].

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