A SIMPLE METHOD FOR THE SYNTHESIS OF FERVENULIN-3-ONE-4-OXIDE

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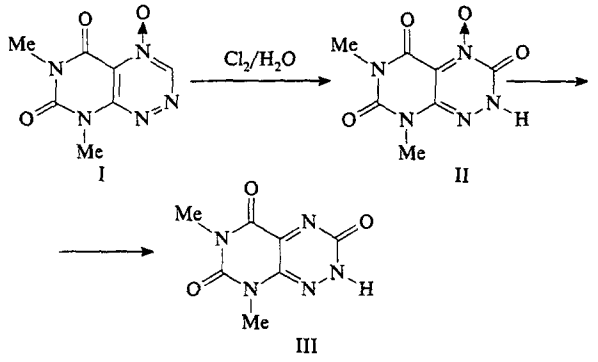
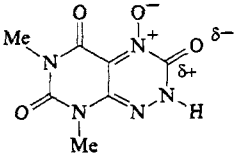
As is known, the antibiotic fervenulin (6,8-dimethyl-5,7-dioxo-5,6,7,8-tetrahydropyrimido[5,4-e][1,2,4]triazine) and its 3-alkyl or 3-arylsubstituted derivatives transformed into derivatives of xanthine [1], 6-azapurine [2], or *as*-triazine [3] as a result of the nucleophilic attack of their pyrimidotriazine nucleus with formamide at C-8a, with HO ion at C-5, and with primary amines at C-7, respectively. It was also reported that fervenulin and its 3-substituted derivatives reacted with indole under the conditions of acid catalysis with the formation of 4a-indolyl derivatives [4]. On heating in aqueous – alcohol solutions in the presence of hydrochloric acid, fervenulin-4-oxide (I) decomposed to yield 1,3-dimethyl-5-nitroso-6-hydrazinouracyl [5].

In this work, it was found that passing gaseous chlorine through a solution of fervenulin-4-oxide [6] in aqueous hydrochloric acid led to the formation of 6,8-dimethyl-3,5,7-trioxo-2,3,5,6,7,8-hexahydropyrimido[5,4-e][1,2,4]-triazine-(fervenulin-3-one-4-oxide, II).



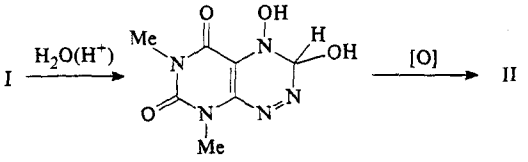
The ^1H NMR spectrum of compound II in deuterodimethylsulfoxide contained only the signals at 3.13 and 3.30 ppm, attributed to the NCH_3 groups. The IR spectrum of crystalline compound II, suspended in vaseline oil, exhibits three intense absorption bands (1670, 1715, and 1770 cm^{-1}) due to carbonyl groups. The bands at 1670 and 1715 cm^{-1} apparently can be assigned to the vibrations of 5-oxo and 7-oxo groups of the uracyl fragment, because similar absorption bands are observed at 1680 and 1724 cm^{-1} in the spectrum of the initial fervenulin-4-oxide. Therefore, the band at 1770 cm^{-1} is due to the vibrations of 3-oxo group. Besides this, the IR spectrum of product II contains wide absorption bands at 3180 and 3270 cm^{-1}, which confirm the presence of a bound NH group in the molecule.

The value of $\nu_{C_3=O}$ in compound II, which is markedly higher compared to that in the spectrum of fervenulone III unoxidized at the N_4 atom (1670, 1715, 1725 cm^{-1}), apparently can be explained by the presence of two close-lying dipoles of the $N_4 \rightarrow O$ and $C_3=O$ groups.



The mutual influence of the dipoles (the field effect) results in a lower polarization of bonds and the corresponding increase in the $\nu_{C_3=O}$ frequency.

The formation of fervenulin-3-one-4-oxide can be represented as a result of two sequential stages: (i) nucleophilic addition of water to fervenulin-4-oxide I under the conditions o acid catalysis and (ii) oxidation of the adduct to the fina product II.



Heating compound II in dimethylformamide leads to de oxidation with the formation 45% of 6,8-dimethyl-3,5,7-tri oxo-2,3,5,6,7,8-hexahydropyrimido[5,4-e][1,2,4]triazine identical with a compound described in [4]. This simpl method for the synthesis of fervenulin-3-one-4-oxide is th

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first case of nucleophilic substitution of the H-3 hydrogen atom with conservation of the N-oxide function in the series of 1,2,4-triazine-4-N-oxides. Moreover, the above-described conversions offer a new pathway to obtaining one of the pyrimidotriazine antibiotics (2-methylfervenul-3-one, MSD-92) [6], thus opening the way to the synthesis of its 4-N-oxide derivatives.

EXPERIMENTAL PART

The ^{1}H NMR spectra were recorded on a Perkin-Elmer R-12B spectrometer operated at 60 MHz. The chemical shifts are given according to the δ scale (ppm) referenced to tetramethylsilane (TMS). The IR spectra were measured on an UR-20 spectrophotometer using samples prepared as nujol mulls. The results of elemental analyses agreed with analytical calculations.

6,8-Dimethyl-3,5,7-trioxo-2,3,5,6,7,8-hexahydropyrimido[5,4-e][1,2,4]triazine-4-oxide (II). Gaseous chlorine was passed at 15 – 20°C for 1 h through a suspension of 0.2 g (1.0 mmole) of 6,8-dimethyl-3,5,7-trioxo-2,3,5,6,7,8-hexahydropyrimido[5,4-e][1,2,4]-triazine-4-oxide (fervenulin-4-oxide, I) in 3 ml of 80% aqueous acetic acid. The precipitate of compound II was filtered and recrystallized from acetic acid. Yield of compound II, 75%; m.p., 220 – 221°C; $C_7H_7N_5O_4$; ^{1}H NMR spectrum, DMSO-d_6 (δ, ppm): 3.13 (s, NCH_3), 3.30 (s, NCH_3); IR spectrum (ν_{max}, cm^{-1}): 1670, 1715, 1770 (CO).

6,8-Dimethyl-3,5,7-trioxo-2,3,5,6,7,8-hexahydropyrimido[5,4-e][1,2,4]triazine (III). A mixture of 0.22 g (1.0 mmole) of 6,8-dimethyl-3,5,7-trioxo-2,3,5,6,7,8-hexahydropyrimido[5,4-e][1,2,4]-triazine-4-oxide (II) with 2 ml dimethylformamide was boiled for 20 min. The solution was evaporated in vacuum and the residue was treated with 2 ml ethanol. The precipitate of fervenul-3-one III was filtered and recrystallized from ethanol. Yield of compound III, 45%; IR spectrum (ν_{max}, cm^{-1}): 1670, 1715, 1725 (CO).

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