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A STUDY OF THE PRODUCTS OF THE REDUCTION OF THE ANTIBIOTIC REUMYCIN (6-METHYLPYRIMIDO[5,4-e][1,2,4]TRIAZINE-5,7-DIONE)

S. E. Esipov, N. A. Klyuev, L. A. Saburova, and V. M. Adanin

UDC 543.51+547.854

The structures of the products of the reduction of the antibiotic reumycin (I), which is a specific autooxidizable acceptor of reducing equivalents from certain flavin dehydrogenases of the respiratory chain of the mitochondria of yeast and animal tissues, have been established with the aid of physicochemical methods (UV, IR, and PMR spectroscopy and mass spectrometry). In the determination of the structures of five reduction products of reumycin effective use has been made of high-resolution mass spectrometry and a consideration of the spectra of metastable ions (the DADI technique). It has been shown that only the asym-triazine ring in the initial (I) undergoes reduction and ring-opening.

It has been shown previously [1, 2] that the anticarcinogenic activity of the antibiotic reumycin (6-methylpyrimido [5,4-e][1,2,4]triazine-5,7-dione) [3,4] is connected with its capacity for oxidizing cytoplasmatic NADH. This leads to a decrease in the reduction potentials of the tumor cells and, as a consequence, to a retardation of their pathological growth. In this process, the antibiotic is reduced, accepting reducing equivalents from flavin dehydrogenases and transferring these equivalents to oxygen. In this connection, it is of interest to model the process of reducing reumycin as one of the possible mechanisms of the biological action of the antibiotic and to determine through what possible reduced forms it takes place.

The attempts made to obtain and isolate dihydro derivatives of antibiotics of the pyrimido[5,4-e][1,2,4]triazine series directly have proved unsuccessful because of their extreme lability and rapid oxidation by atmospheric oxygen [5, 6]. We have succeeded in obtaining stable acetyl derivatives of the reduction products of the antibiotic reumycin by performing catalytic hydrogenation with hydrogen in acetic anhydride. In this way we have isolated and characterized for the first time five acetyl derivatives of the reduction products of reumycin (see the scheme of isolation).

The structures of the products (I-V) isolated were determined on the basis of UV, IR, and PMR spectroscopy and low-resolution and high-resolution mass spectrometry (HRMS). The last method was the main one.

According to the results of HRMS, the empirical composition of the isolated compound (I) is described by the formula $C_8H_8N_5O_3$ (see the experimental part). The sequence of fragmentation of M^+ and the fragmentary ions was studied precisely from the spectra of the metastable ions (the DADI technique [7]). Their empirical compositions were checked with the

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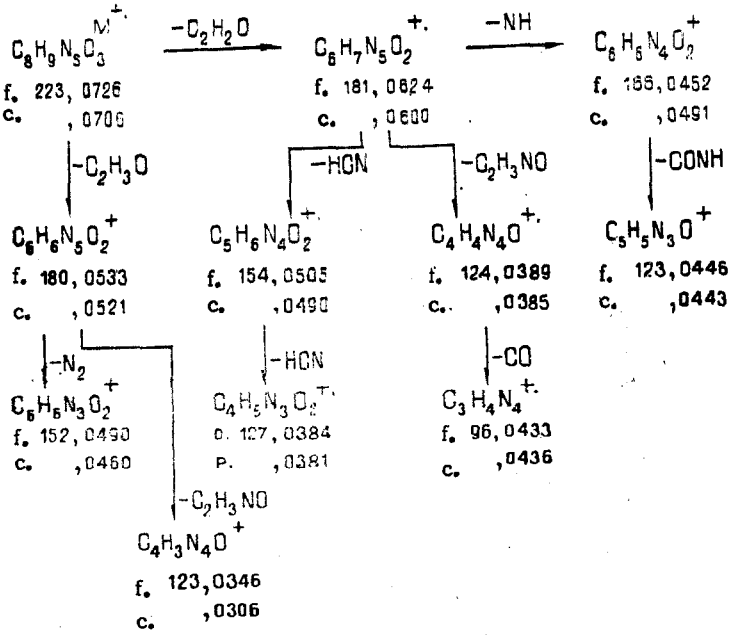
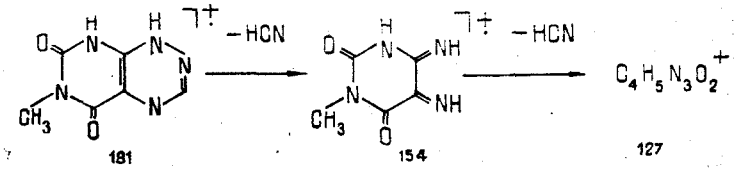
aid of HRMS. The mass spectrum of compound (I) is given in Fig. 1. As a result of the investigation performed, the pattern of dissociative ionization of M^+ of compound (I) can be represented by the following scheme:*



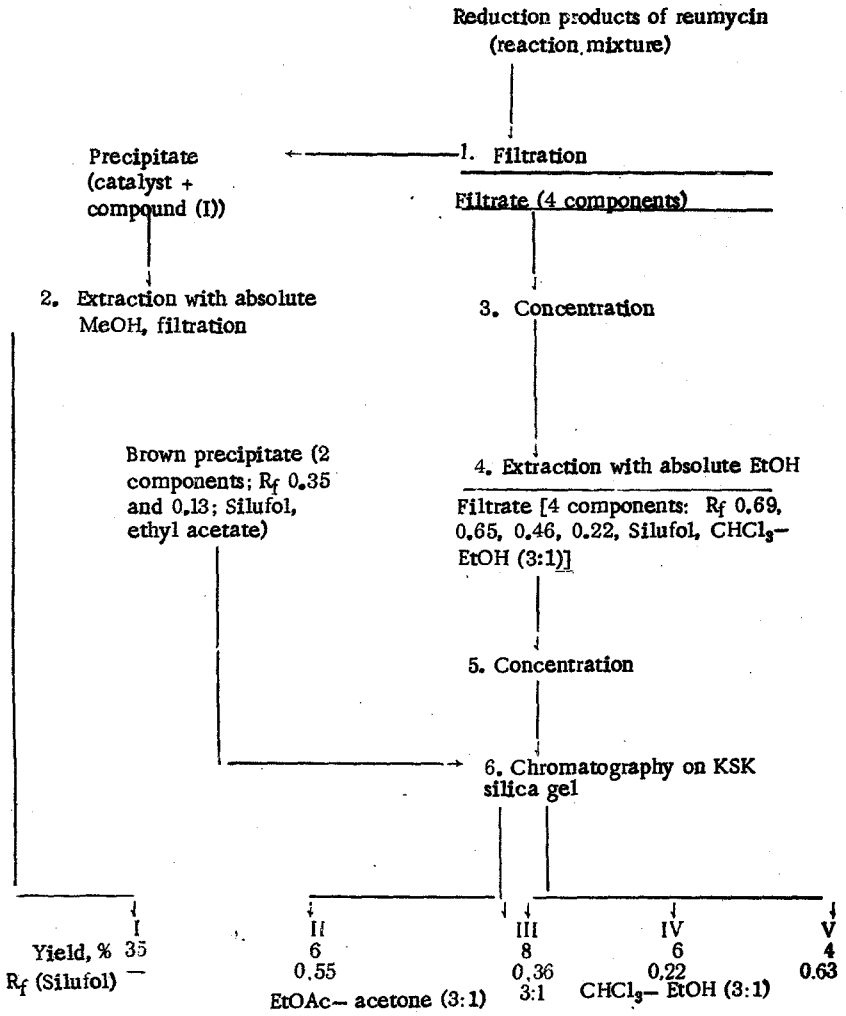
It has been shown previously [8] using a large number of examples, that the number of N-acetyl groups in a molecule can be determined from the number of ketene and acetyl particles eleminated from M^+. In our case, the (I) molecule contains only one N-acetyl group. The splitting out of the CH_3NCO particle from the fragmentary ion $(M - C_2H_2O)^+$ with m/e 124 and $(M - CH_3CO)^+$ with m/e 123 shows the retention of the uracil ring in the compound. A similar fragmentation pathway is characteristic for uracil derivatives [9, 10]. Thus, on the basis of the combination of spectral characteristics the structure of compound (I) can be described by one of the four formulas (IA-D).

The elimination of the NH particle from the pseudomolecular ion with m/e 181 shows the absence of a hydrazine fragment in the mother ion and, consequently, excludes the existence of this compound in the form of structure IB or ID [11]. This fact is confirmed by the successive processes of ejection of two HCN particles from it (the initial stage takes place by the mechanism of the retrodiene decomposition):

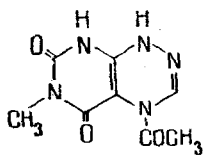


The final choice between the structures A and B for compound (I) can be made on the basis of an analysis of the decomposition of the ion with m/e 180. The splitting out of a N_2 particle from the fragmentary ion with m/e 180 is more likely when the charge in the structure of this ion is localized on the N-1 atom [12]. Thus, compound (I) has the structure of 1-acetyl-6-methyl-1,4-dihydropyrimido[5,4-e][1,2,4]triazine-5,7-dione (IC). In favor

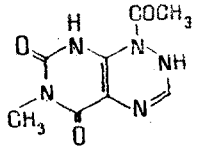
*Here and below, the figures below the formulas show the mass number (m/e) found experimentally (f) for the ion with the aid of HRMS and the accurate calculated (c) value of the mass for the given empirical composition of the ion; the arrows show the observed direction of fragmentation in the DADI spectra.



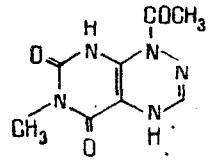
Scheme of the preparative isolation of the acetyl derivatives of reduction products of reumycin



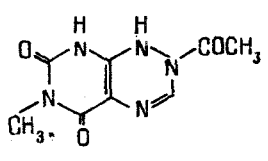
IA, IIA



IB, IIB



IC, IIC



ID, IID

of this structure is the presence in the IR spectrum of a characteristic absorption band at 3300 cm^{-1} which may be assigned to the unbound NH stretching vibration of a triazine ring, while broad bands at 3180 and 3063 cm^{-1} can be assigned to an intramolecular hydrogen bond between the carbonyl group of the acetyl substituent and the hydrogen atom of a cyclic amide, as appears in similarly substituted purines [13].

According to HRMS, the isolated substance (II) (see the scheme of isolation) has the empirical composition $C_8H_9N_3O_3$ (f. 223.0730, c. 223.0705). A comparison of the low-resolu-

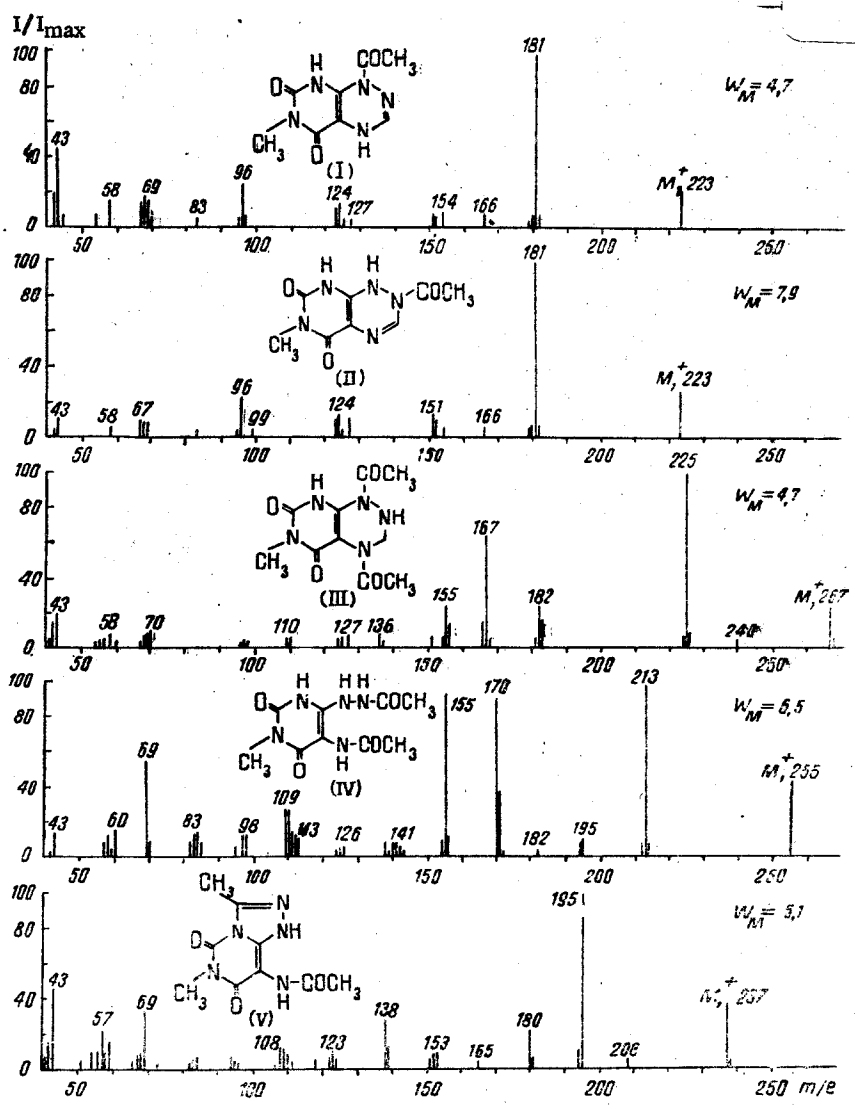
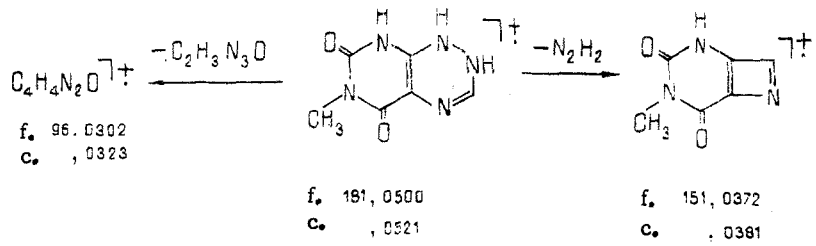


Fig. 1

tion mass spectra of compounds (I) and (II) (see Fig. 1) shows that they contain common peaks of characteristic ions. Consequently, substance (II) and (I) are isomers. The structure of substance (II) can therefore be described by one of the possible structural formulas (IIA), (IIB), and (IID). The results of IR and PMR spectroscopy confirm the presence of one acetyl grcup in the molecule. Analysis of the spectra of the metastable ions form compound (II) shows the splitting out of a $C_5H_4N_2O_2$ particle from M^+, i.e., the elimination of the uracil part of the molecule takes place. The recorded ion with m/e 99 (f. 99.0432, c. 99.0432) confirms the presence of an acetyl grouping in the triazine ring of the molecule. The interpretation of the decomposition of the pseudomolecular ion $(M - C_2H_2O)^+$ with m/e 181 of compound (II) shows that it has two fragmentation processes differing from those of the isomer (I):

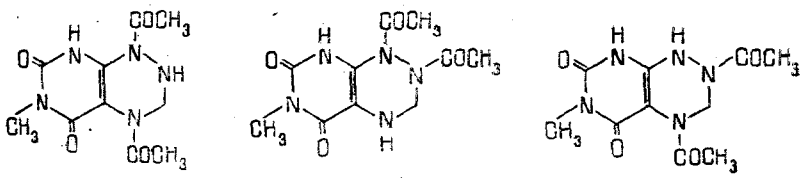
$$1)\ m/e\ 181 \xrightarrow{-N_2H_2} m/e\ 151 \text{ and } 2)\ m/e\ 181 \xrightarrow{-C_2H_3N_3O} m/e\ 96,$$

which permit compound (II) to be ascribed the structure (IIB) or (IID) [14, 15]. According to Wolkoff and Hammerum [11], structure (IID) is the more likely.



In the PMR spectrum of compound (II) the signal of the proton at C-3 is recorded in the form of a singlet (δ 7.43 ppm (1 H)), which definitively confirms the assignment that we have made. Thus, compound (II) has the structure of 2-acetyl-6-methyl-1,2-dihydropyrimido-[5,4-e][1,2,4]triazine-5,7-dione (IID).

According to the results of HRMS, the isolated compound (III) has the empirical composition $C_{10}H_{13}N_5O_4$ (f. 267.0950, c. 267.0967). The positions of the maxima of the absorption bands in the UV spectrum of compound (III) show the complete reduction of a asym-triazine ring or its opening. The PMR spectrum shows the presence of a methylene grouping in the C-3 position of the reduced triazine ring and confirms the presence of two acetyl groups in the molecule under consideration. The latter is also confirmed by the mass-spectrometric results, since under the action of electron impact the successive elimination takes place from M^+ of ketene and acetyl particles (m/e 225 and 182, respectively) [8]. In this case, the structure of compound (III) can be described by the following formulas (IIIA-C).



IIIA IIIB IIIC

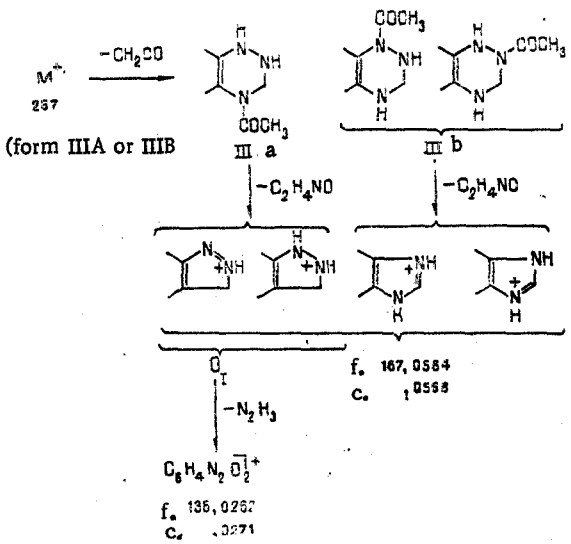
Formula (IIIC) can be excluded from consideration, since the mass spectrum of this compound includes, although with a low intensity, the peak of an ion with m/e 240, the formation of which is due to the splitting out of a HCN particle from M^+. HRMS confirms this fact, showing for it the empirical composition $C_9H_{12}N_4O_4$ (f. 240.0851, c. 240.058). For a definitive choice between the two isomeric forms (IIIA) and (IIIB) it is necessary to show the pathways of the formation of the ions with m/e 167 and 136 strictly (see Fig. 1).

Analysis of the spectra of the metastable ions shows that the ejection of a C_3H_4NO particle takes place from the pseudomolecular ion $(M - C_2H_2O)^+$. The elimination of C_2H_2NO presupposes a rearrangement which is accompanied by the migration of a hydrogen atom to the position of bond cleavage. Such a process is characteristic for cyclic amines [16, 17] and it presupposes the opening of the ring (cleavage of the β-bond in relation to the nitrogen atom on which the charge is localized.

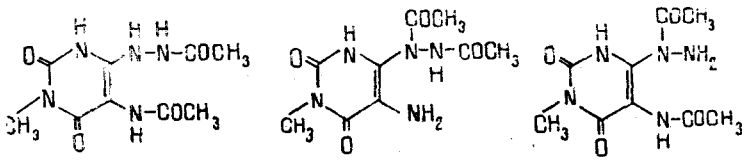
The subsequent splitting out a N_2H_3 particle can take place only from the ion Φ_1. These facts permit the isolation compound (III) to be assigned the structure of 1,4-diacetyl-methyl-1,2,3,4-tetrahydropyrimido [5,4-e][1,2,4]triazine-5,7-dione (IIIA).

In addition, using Dreiding models it was shown that the asym-triazine ring in structure (IIIB) is somewhat strained. Free rotation of the acetyl groupings is restricted both when the oxygen atoms of the carbonyl groups approach one another and when the two methyl groups approach one another, and therefore the formation of a 1,2-triacetyl derivative (for IIIB) is energetically unfavorable, which additionally confirms the correctness of the selected structure (IIIA).

A distinguishing feature of the isolated product (IV) (see the scheme of isolation) is the presence in its UV spectrum of a single absorption maximum at λ_{max}^{MeOH} 268 nm, which shows the retention unchanged of only the uracil part of the molecule. According to the results of PMR and mass spectrometry (see Fig. 1 and the experimental part), in this compound there are two acetyl groupings and it has the empirical composition $C_9H_{13}N_5O_4$ (f. 255.0957, c. 255.0967). On taking into account our observations and the information in the literature that the initial reumycin and other pyrimidotriazines [18] are not acetylated in the N-8 position

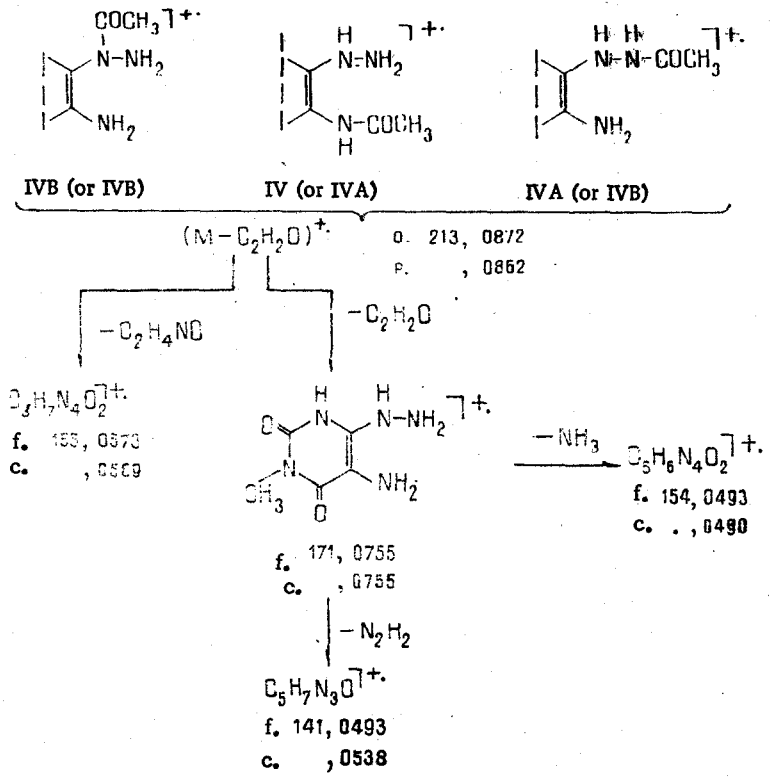


under hydrogenation conditions, it is possible to suggest three alternative structural formulas for compound (IV) — (IVA-C)



IVA IVB IVC

The process of eliminating a $C_2H_3N_2O$ particle from M^+ of compound (IV) (shown by the DADI method) excludes structure (IVB) from consideration (f. 182.0555, c. for the empirical formula $C_7H_8N_3O_3$ — 182.0562). The final choice was made on the basis of a consideration of the routes of formation of the ions with m/e 155, 154, and 141.

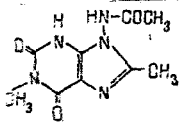


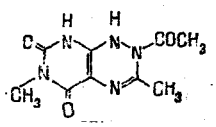
The cleavage of the N–N bond in substituted hydrazines is generally known (the energy of the N–N bond is 39 kcal/mole) [11], while the cleavage of the C–N bond (variant of fragmentation from the ions (IVb) and (IVc) requires the consumption of a considerably greater amount of energy (72.8 kcal/mole) and hardly takes place. In this case, form (IVA) becomes the only possible one for compound (IV).

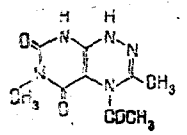
The assignment made is additionally confirmed by the processes of formation of the ions with m/e 154 and 141. The elimination of NH_3 and N_2H_2 particles is characteristic for hydrazines with an acetylated primary amino group. Thus, compound (IV) has the structure of 5-acetylamine-6-(2'-acetylhydrazino)-3-methylpyrimidine-2,4-dione (IVA).

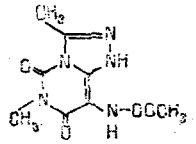
According to HRMS, the isolated compound (V) has the empirical composition $C_9H_{11}N_5O_3$ (f. 237.0861, c. 237.0862). A comparison of the mass spectra of compound (V) with that of compound (IV) considered above (see Fig. 1) shows the possibility of the formation of this compound by the dehydration of (IV).

It is known [5, 19] that the cyclization of substituted 5-amino-6-hydrazinouracils is accompanied by dehydration, leading to the formation of a triazine or triazole ring. On the basis of this hypothesis and spectral results (see the experimental part) it is possible to suggest the structure of compound (V) in the form of the following structural formulas (VA-D):

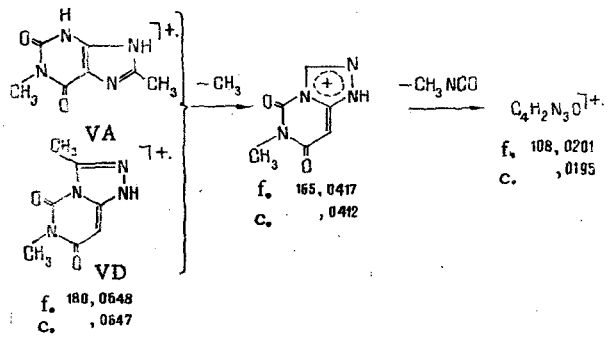

VA


VB


VC


VD

Apart from the usual splitting out of ketene (m/e 195) and an acetyl residue (m/e 194) from M^+, characterizing the presence of one acetyl grouping, the direct elimination of a C_2H_3NO particle from M^+ is observed (f. 180.0648, c. 180.0647 for the empirical composition $C_7H_8NO_2$). Such a fragmentation pathway can be dictated by the appearance of an "ortho effect," [20] and take place from forms VA and VD. The subsequent splitting out of a CH_3 radical from the ions of the possible structures (VA) and (VD) is not typical for C-methyl substituted N-heterocyclic compounds (β-cleavage relative to the hetaryl part of the molecule followed by opening of the ring is usually observed. In this case, the splitting out of a CH_3 group from the ions $(M - C_2H_3NO)^+$ is due solely to steric factors (the "peri" effect [21]), which can take place only in the case of structure (VD).



The elimination of a CH_3 group from the uracil part is excluded, since the splitting out of a CH_3NCO particle then takes place. The latter fragmentation process is charactistic for substituted uracils [9, 10]. Thus, the structure of the isolated compound (V) is described by the name 8-acetylamino-3,6-dimethyl-1,5,6,7-tetrahydro[1,2,4]triazolo[4,3-c]pyrimidine-5,7-dione (VD).

EXPERIMENTAL

UV spectra were taken on a Specord UV-VIS instrument in methanol, IR spectra on a UR-20 spectrometer (KBr tablets), and PMR spectra (δ scale) on a Varian HD-100 MHz spectrometer in solution in TFA acid or DMSO-d_6 (with TMS as standard). Low-resolution mass spectra were recorded on a Varian MAT-311A spectrometer and high-resolution mass spectra (M/M 125,000, PPA as standard) on a Varian MAT-731 instrument. In both cases the working conditions of the instrument were (we used the technique of the direct introduction of the sample into the ion source): ionizing voltage 70 eV, cathode emission current 300 μA, accelerating voltage 3 kV, temperature in the ion source 100-150°C. To determine the sequence of formation of the fragmentary ions we used the DADI technique [7].

Reduction of Reumycin. A solution of 500 mg (2.9 mmole) of reumycin in 48 ml of Ac_2O was added to a hydrogenation flask containing previously reduced PtO_2 (19 mg) and it was reduced at 20°C and atmospheric pressure until the absorption of hydrogen ceased (20 h). The amount of hydrogen consumed in hydrogenation was 100 ml (theoretically, 125 ml was necessary for the reduction of two multiple bonds). In the reduction process, the solution became decolorized and it deposited a gray precipitate, which was separated off together with the catalyst by filtration (compound (I)). To separate the catalyst, the precipitate was triturated repeatedly in absolute methanol to obtain a fine suspension, from which the particles of catalyst sedimented on to the bottom of the flask, and the suspension was separated by decantation. The substance suspended in the methanol was filtered off and dried in vacuum over P_2O_5. This gave 215 mg of compound (I). After the separation of the catalyst and the compound (I), the reaction solution was evaporated in vacuum at 35°C. This gave 420 mg of residue containing compounds (II-V).

The sequence of operations for isolating and purifying the reduced products (I-V), and their yields and chromatographic mobilities are given in the scheme.

The residue insoluble in absolute ethanol (117 mg) was chromatographed on a column (2.5 × 40 cm) in ethyl acetate–acetone (3:1), with the collection of 10-ml fractions. The process of separation was monitored by TLC on Silufol plates and the fractions similar in their component composition were combined. Fractions 11-15, after concentration and crystallization from absolute methanol, yielded 28 mg of compound (II). Fractions 21-27, by evaporation and crystallization from absolute ethanol, yielded 45 mg of compound (III).

The ethanolic extract (300 mg) was chromatographed on a column (5 ×50 cm) in the chloroform–ethanol (3:1) system, 6-ml fractions being collected. Fractions 13-24 yielded an additional 13.2 mg of compound (III), from fractions 97-118 after concentration and trituration of the residue in absolute methanol 24 mg of compound (V) was obtained, and fractions 119-128, after trituration in absolute ethanol, yielded 43 mg of compound (IV).

1-Acetyl-6-methyl-1,4-dihydropyrimido[5,4-e][1,2,4]triazine-5,7-dione (I) formed a gray substance practically insoluble in nonpolar solvents, and also in water, alcohols, and ethyl acetate, mp 211°C (yellow-colored melt). IR spectra ν_{max}, cm^{-1}: 3300 (NH of a triazine ring), 3180 (NH of an amide group bound by an intramolecular hydrogen bond with the C=O of an acetyl constituent), 3063 (arom. CH), 2905 (CH), 1735 (C=O), 1695 (amide I); M^+ 223 (f. 223.0726; c. 223.0706 for the empirical composition $C_8H_9N_5O_3$).

2-Acetyl-6-methyl-1,2-dihydropyrimido[5,4-e][1,2,4]triazine-5,7-dione (II) formed an orange crystalline powder isoluble in nonpolar solvents and sparingly soluble in ethanol, mp 232-233°C. R_f 0.55 Silufol, ethyl acetate–acetone (3:1). UV spectrum, λ_{max}^{EtOH}, nm: 229, 289, 378 (log ε 3.84, 3.92, 3.35). IR spectra $\tilde{\nu}_{max}$ 3250 and 3190 NH bound by an intramolecular hydrogen bond), 2965 and 2935 (CH), 1725, 1688, 1635 (amide I and II). PMR (TFA acid), ppm: 2.46 (3 H, s CH_3CO–N), 3.49 (3 H, s CH_3N–pyrimidine ring), 7.43 (1 H, s, C_3–H), M^+ 223 (f. 223.0730, c. for the empirical composition $C_8H_9N_5O_3$ – 223.0705).

1,4-Diacetyl-6-methyl-1,2,3,4-tetrahydropyrimido[5,4-e][1,2,4]triazine-5,7-dione (III) formed a lustrous white powder insoluble in nonpolar solvents, mp 202-203°C, R_f 0.36 [Silufol, ethyl acetate–acetone (3:1)]. UV spectrum, λ_{max}, nm: 210, 238, 310 (log ε 4.16, 3.85, 3.89). IR spectrum, ν_{max}, cm^{-1}: 3300 (NH), 2936, 2861 (CH), 1711, 1650, and 1654 (amide bands I and II). PMR spectrum (TFA acid), ppm: 2.44 and 2.47 (3 H, s, two CH_3CO–N groups), 3.50 (3H, s, CH N–pyrimidine ring), 5.98 and 4.71 (1 H each, d, J = 13.5 Hz, CH_2 group of a triazine ring); M^+ 267 (f. 267.0950; c. 267.0967 for the empirical composition $C_{10}H_{13}N_5O_4$).

5-Acetylamino-6-(2'-acetylhydrazine)-3-methylpyrimidine-2,4-dione (IV) formed colorless plates insoluble in nonpolar solvents, mp 272-273°C (decomp.) [Silufol, chloroform–ethanol (3:1)]. UV spectra, λ_{max}, nm: 205, 221, 268 (log ε 4.06, 3.72, 4.22). IR spectrum, ν_{max}, cm^{-1}: 3430 (NH), 3270 and 3210 (amide NH), 1702, 1660, and 1635 (amide bands I and II). PMR (TFA acid), ppm: 2.33 and 2.35 (3 H each, s, two CH_3CO–N groups), 3.46 (3 H, s, CH_3N–pyrimidine ring), 8.23 (1 H, s, NH in a hydrazine moiety). PMR (DMSO-d_6), ppm, 1.86 and 1.90 (3 H each, s, 2 CH_3CO–N groups), 3.07 (3 H, s, CH_3N–pyrimidine ring), 8.32 (1 H, s, NH in a hydrazine moiety), 8.51 and 9.59 (1 H each, broadened, NH of secondary amide), M^+ 255 (f. 255.0957, c. 255.0967 for the empirical composition $C_9H_{13}N_5O_4$).

8-Acetylamino-3,6-dimethyl-1,5,6,7-tetrahydro-sym-triazolo[4,3-c]pyrimidine-5,7-dione (V) formed a colorless powder insoluble in nonpolar solvents, mp 330°C (decomp.), R_f 0.63 [Silufol, chloroform–ethanol (3:1). UV spectrum, λ_{max}, nm: 205, 236, 262 (log ε 4.02, 3.91 3.85). IR spectrum, ν_{max}, cm^{-1}: 3255 and 3205 (amide NH), 2925 and 2880 (CH), 1720, 1710, 1670 (amide bands I and II), and 1590, 1520, and 1455. PMR (DMSO-d_6), ppm: 2.05 (3 H, s, CH_3CO–N group), 2.16 (3 H, s, CH_3N–pyrimidine ring), M^+ (f. 237.0861, c. 237.0862 for the empirical composition $C_9H_{11}N_5O_3$).

SUMMARY

1. The structures of the acetyl derivatives of the products of the reduction of the antibiotic reumycin {6-methylpyrimido[5,4-e][1,2,4]triazine-5,7-dione} have been established. It has been shown that the process of reduction and acetylation affects only the asym-triazine ring in the initial compound.

2. It has been shown that on the reduction of the antibiotic reumycin opening of the asym-triazine ring takes place with the formation of uracil derivatives.

3. The basic possibility of the establishment of the sequence of elimination of the N-acetyl residues from M^+ in polynitrogen heterocycles without using selectively labeled samples has been shown.

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