1-Aryl-2-phenacyl-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4-ones (IIf-h). The solution of 0.01 mole of Ia, d, e with 3 g (0.02 mole) of benzoyl chloride in 10 ml of pyridine was heated at 140°C for 3 h after which it was poured into water, and the resulting precipitate was crystallized from ethanol.

1-Phenyl-2-phenacyl-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4-one (IIf). A solution of 2.9 g (0.01 mole) of Ia, 1.1 g (0.01 mole) of methylbenzoate, and 0.54 g (0.01 mole) of sodium methoxide in 10 ml of dry methanol was refluxed for 10 h, after which it was cooled and diluted with water, and the resulting precipitate was removed by filtration and crystallized to give 1.45 g (50%) of a product with mp 252-253°C. No melting-point depression was observed for a mixture of this product with a sample of IIf obtained in the preceding experiment.

1-Phenyl-2-(N-phenylcarbamoylmethyl)-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4-one (III). A solution of 2.9 g (0.01 mole) of Ia and 1.2 g (0.01 mole) of phenyl isocyanate in 20 ml of dry benzene was refluxed for 30 min, after which the solvent was removed by distillation, and the residue was crystallized from ethanol.

1-Phenyl-2-styryl-6,7,8,9-tetrahydropyrimido[4,5-b]quinolin-4-one (IV). A solution of 2.9 g (0.01 mole) of Ia, 3.2 g (0.03 mole) of benzaldehyde, and 0.43 g (0.005 mole) of piperidine in 15 ml of ethanol was refluxed for 10 h, after which the solvent and volatile impurities were removed by steam distillation, and the residue was crystallized from ethyl acetate.

LITERATURE CITED

1. N. I. Shramm and M. E. Konshin, Khim. Geterotsikl. Soedin., No. 1, 114 (1985).
2. M. Yu. Gavrilov and M. E. Konshin, Khim. Geterotsikl. Soedin., No. 1, 43 (1988).

STRUCTURES OF THE COVALENT HYDRATES AND PRODUCTS OF ACIDIC HYDROLYSIS OF RHEUMYCIN AND FERVENULIN

S. V. Shorshnev, G. G. Aleksandrov, S. E. Esipov, N. A. Klyuev, and A. I. Chernyshev

UDC 547.859'873:542.934'946:543.422.25

It is shown that pyrimido[5,4-e]-1,2,4-triazinediones are hydrated at the $N_{(4)}$–$C_{(4a)}$ bond in aqueous acidic media. The equilibrium constants of these processes were measured by PMR spectroscopy. The structure of the covalent adduct of fervenulin was established by x-ray diffraction analysis. Formic, 5-diazo-3-methylbarbituric, and methylparabanic acids were identified among the products of destruction of the hydrates in acidic media.

It has been shown that pyrimido[5,4-e]-1,2,4-triazines (7-azapteridines) in neutral aqueous and alcohol solutions form covalent adducts due to the addition of water or alcohol to the $C_{(5)}$–$N_{(6)}$ bond [1, 2]. The three-dimensional structures of these products have not been established. A study of the behavior of 6-methyl- [rheumycin (Ia)] and 6,8-dimethyl- [fervenulin (Ib)] pyrimido[5,4-e]-1,2,4-triazine-5,7(6H,8H)-diones in aqueous media provides evidence for the chemical stability of these compounds over a wide range of pH values (1-9) [3]. The stability of 7-azalumazines Ia, b as compared with 7-azapteridine under the indicated conditions can be explained by the saturated character of the pyrimidine ring. At pH > 9 one observes the addition of water to Ia, b at the $C_{(5)}$–$N_{(6)}$ bond with its subsequent cleavage and cyclization of the ureido group to give an imidazolidine ring [4]. An investi-

All-Union Scientific-Research Institute of Antibiotics, Moscow 113105. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1654-1660, December, 1988. Original article submitted May 14, 1987.

0009-3122/88/2412-1367$12.50

TABLE 1. ^1H and ^{13}C NMR Spectra of Pyrimidotriazinediones I and Their Covalent Hydrates II

Compound	^1H NMR spectrum, δ*, ppm			^{13}C NMR spectrum, δ †, ppm (SSCC, Hz)						
	3-H	$N_{(6)}CH_3$	$N_{(8)}CH_3$	$C_{(3)}$, d	$C_{(4a)}$, d	$C_{(5)}$, q	$C_{(7)}$	$C_{(8a)}$	$N_{(6)}CH_3$, q	$N_{(8)}CH_3$, q
Ia	9,67	3,34	—	155,1 (^1J=213,3)	133,5 (^3J=8,8)	161,8 (^3J=2,9)	150,8 q (^3J=2,9)	152,9 s —	29,0 (^1J=142,7)	—
IIa	8,64	3,13	—	145,0 (^1J=209,6)	67,1 (^3J=5,9)	164,3 (^3J=3,8)	150,4 q (^3J=3,2)	145,3 d (^4J=1,6)	29,2 (^1J=143,7)	—
Ib	9,69	3.39	3.71	154.7 (^1J=212,5)	134,3 (^3J=8,1)	160,9 (^3J=3,0)	151.0 m —	152.6 q (^3J=2,9)	29.7 (^1J=142,6)	30.2 (^1J=142.7)
IIb	8,65	3,16	3,27	143,5 (^1J=209,6)	66,4 (^3J=4,9)	162,9 (^3J=3,2)	149,6 m —	145,8 q.d (^3J=3,2, ^4J=1,4)	29,0 (^1J=143,7)	30,3 (^1J=143,7)

*The solvents were D_2O for Ia, b and DCl/D_2O for IIIa, b.
†In connection with the low solubility of pyrimidotriazinediones Ia, b in water (~1%) the spectra of these compounds were recorded from solutions in d_6-DMSO; DCl/D_2O was used for IIa, b.

gation of the protonation of rheumycin and fervenulin in anhydrous media by ^1H and ^{13}C NMR spectroscopy showed that the preferred center of cation formation of these compounds is the $N_{(2)}$ atom of the triazine ring [5]. It is assumed that the presence of a positive charge should activate the formation of covalent hydrates of Ia, b in an acidic medium due to the addition of water to the triazene heterocyclic system. The present research is devoted to an investigation of the hydration process and the identification and study of the structures of the covalent adducts of rheumycin and fervenulin and the products of their chemical transformations in acidic media.

The PMR spectra of aqueous (D_2O) and acidified [with 1 N hydrochloric acid (DCl)] solutions of pyrimidotriazines Ia or Ib constitutes evidence for the formation, in an acidic medium, of covalent hydrates IIa, b. In the spectra of solutions of Ia, b at pD < 1 the corresponding signals of hydrate IIa, b, which are shifted to strong field (Table 1), are recorded in addition to the signals of the protons of the starting compounds. The formation of the covalent hydrates is a slow (on the PMR time scale) equilibrium process. The addition of a solution of sodium hydroxide (NaOD) or hydrochloric acid to the reaction mixtures leads, respectively, to an increase or decrease in the ratios of the Ia, b and IIa, b concentrations in solution. This is manifested in an increase or decrease in the relative intensities of the signals of Ia, b and IIa, b in the spectra. The decrease in the intensity of the yellow color of their solutions also constitutes evidence for the addition of water and acid to Ia, b. The presence in the PMR spectra of the reaction mixtures of individual intense signals of the $CH_3N_{(6)}$ protons of starting Ia, b and hydration products IIa, b made it possible to calculate the equilibrium constants of these reactions $K(a) = (10.2 \pm 1.4)\cdot10^{-3}$ and $K(b) = (13.9 \pm 2.2)\cdot10^{-3}$ liter^2/mole^2, which virtually coincide. The centers of hydration of rheumycin and fervenulin in acidic media were established by ^{13}C NMR spectroscopy in analogy with the structure of the σ adducts of pteridine with water and ammonia [6]. According to the ^{13}C NMR spectra of Ia, b and IIa, b (Table 1), the addition of water takes place at the $N_{(4)}$–$C_{(4a)}$ bond of the triazine ring. In the ^{13}C NMR spectra without decoupling of the spin–spin coupling (SSC) with the protons of solutions of IIa, b doublet signals of $C_{(4a)}$ atoms with characteristic $^3J_{C(4a),3\text{-}H}$ constants are recorded at stronger field as compared with the signals of the analogous C atoms of rheumycin and fervenulin. The shifts of these signals are 66.4 ($\delta_{Ia} - \delta_{IIa}$), and 67.9 ppm ($\delta_{Ib} - \delta_{IIb}$). The remaining signals of the spectra with the corresponding multiplicities and SSC constants are shifted to a considerably smaller extent. The chemical shifts of the terminal carbon atoms of the uracilotriazine systems IIa, b constitute evidence that the C_{4a} atoms have sp^3 hybridization, while the remaining shifts constitute evidence for sp^2 hybridization. These facts indicate the addition of water to the $N_{(4)}$–$C_{(4a)}$ bonds and are in good agreement with data on the hydration of 1,2,4-triazine to the $N_{(4)}$–$C_{(5)}$ bond [7, 8] (see scheme on following page).

The three-dimensional structure of the hydration products was established in the case of the covalent hydrate IIb of fervenulin by means of x-ray diffraction analysis. In connection with the existence of a chemical equilibrium in the reaction involving the formation of adduct IIb this compound was isolated by crystallization at a low temperature (−4°C)

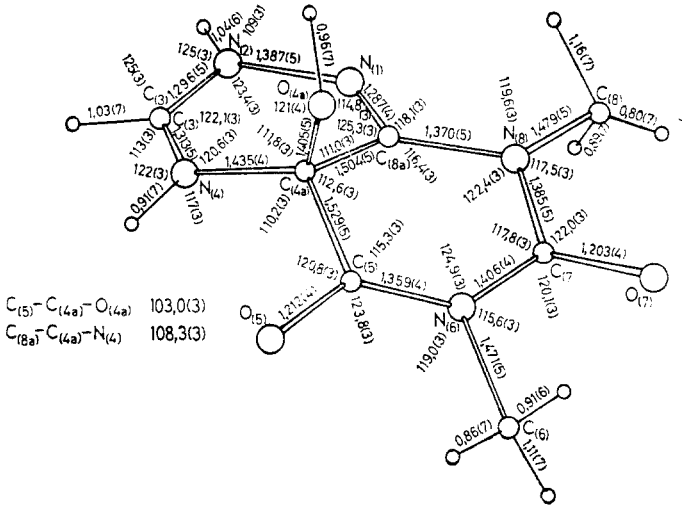
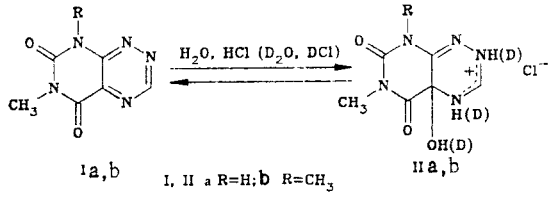


Fig. 1. Structure of the covalent hydrate IIb molecule.



from solution in concentrated hydrochloric acid (HCl). The crystals, after washing with concentrated HCl and rapid drying in vacuo, were investigated by x-ray diffraction analysis.

The hydrate IIb crystals ($C_7H_9N_5O_3 \cdot HCl$) were rhombic and had the following parameters: a = 12.984(6) Å, b = 22.262(9) Å, c = 7.142(4) Å, z = 8, and space group Pbca. The structure was decoded by the direct method and was refined by the method of least squares within the complete-matrix anisotropic approximation up to R = 0.049 (R_w = 0.052) for 1080 reflections with $F^2 \geq 3\sigma$. The hydrogen atoms, which were revealed by differential synthesis, were refined within the isotropic approximation. The coordinates of the atoms are presented in Table 2. The structure of the IIb molecule and the bond lengths and bond angles are shown in Fig. 1. The structure consists of $C_7H_{10}N_5O_3^+$ organic cations and Cl^- anions that are linked together in the crystal by hydrogen bonds and interionic and van der Waals interactions. The cation of IIb consists of two heterorings – pyrimidine and 1,2,4-triazine – fused at the $C_{(4a)}$–$C_{(8a)}$ bond and is the product of the addition of an OH group and two protons to fervenulin. In contrast to fervenulin (Ib), which has a planar structure [9], the planarity of the IIb cation, because of the addition of an OH group to the nodal $C_{(4a)}$ atom, which converts it to a tetrahedral configuration, is disrupted substantially. In addition, one observes lengthening of the C–C and C–N bonds with the participation of the $C_{(4a)}$ atom; this is in complete agreement with the difference in the radii of the carbon atoms (sp^2 and sp^3 hybridization) in Ib and IIb, respectively. The lengths of the remaining bonds in the pyrimidine fragment of the IIb cation virtually coincide with those found for Ib. In the triazine ring the lengths of the $N_{(2)}$–$C_{(3)}$ and $C_{(3)}$–$N_{(4)}$ bonds differ substantially from those found in fervenulin (Ib), evidently due to localization on the $N_{(2)}$–$C_{(3)}$–$N_{(4)}$ fragment of the positive charge. This assumption is confirmed by the close values of the lengths of the $N_{(2)}$–$C_{(3)}$ and $C_{(3)}$–$N_{(4)}$ bonds [1.296(5) and 1.313(5) Å, respectively], as well as by the participation of both the $HN_{(2)}$ and $HN_{(4)}$ protons in hydrogen bonds with the chloride anion; in addition to these atoms, the proton of the hydroxy group also participates in a hydrogen bond with the anion (Table 3). The results of the investigation showed that the product of covalent hydration of fervenulin Ib in the presence of hydrochloric acid is 4a-hydroxy-4,4a-dihydro-6,8-dimethylpyrimido[5,4-e]-1,2,4-triazine-5,7(6H,8H)-dione (IIb). The stability of the covalent hydrates of rheumycin and fervenulin only in an acidic medium can be explained by the formation of the thermodynamically more favorable protonated form, the stability of which is ensured by amidinium resonance.

TABLE 2. Coordinates* of the Atoms ($\cdot 10^4$; $\cdot 10^{-3}$ for H) in the Structure of Covalent Hydrate IIb

Atom	x	y	z	Atom	x	y	z
Cl	5679(1)	930(1)	2840(1)	$C_{(8a)}$	5685(2)	3619(2)	2337(5)
$O_{(4a)}$	4375(2)	4016(1)	4353(4)	$C(N_{(6)})$	2949(3)	3403(2)	−776(7)
$O_{(5)}$	3496(2)	4490(1)	800(4)	$C(N_{(8)})$	6034(5)	2538(2)	1955(9)
$O_{(7)}$	4118(2)	2491(1)	415(5)	$H_{(3)}$	659(4)	517(3)	294(6)
$N_{(1)}$	6655(2)	3685(2)	2641(5)	$H(O_{(4a)})$	476(5)	395(2)	549(9)
$N_{(2)}$	6959(2)	4270(1)	3017(5)	$H(N_{(2)})$	776(5)	429(3)	299(8)
$N_{(4)}$	5366(2)	4671(1)	2501(4)	$H(N_{(4)})$	504(4)	501(3)	775(8)
$N_{(6)}$	3792(2)	3488(1)	574(4)	$H(1CN_{(6)})$	255(5)	316(3)	−7(9)
$N_{(8)}$	5338(2)	3062(1)	1815(5)	$H(2CN_{(6)})$	263(4)	374(2)	−85(7)
$C_{(3)}$	6355(3)	4730(2)	2836(6)	$H(3CN_{(6)})$	323(4)	321(2)	−211(7)
$C_{(4a)}$	4878(3)	4094(1)	2628(5)	$H(1CN_{(8)})$	652(5)	266(3)	116(9)
$C_{(5)}$	3998(3)	4051(1)	1213(5)	$H(2CN_{(8)})$	651(5)	264(3)	330(9)
$C_{(7)}$	4399(3)	2978(2)	932(6)	$H(3CN_{(8)})$	567(5)	227(4)	164(9)

*The temperature factors of the atoms can be obtained from the authors of this paper.

TABLE 3. Hydrogen Bonds in the Structure of Covalent Hydrate IIb

Atom	d Cl···H, Å	d Cl···(N, O), Å	Cl—H—(N, O), °
Cl···H—$N_{(2)}$ (3/2−x, 1/2−y, z)	2,09(5)	3,101(2)	163(3)
Cl···H—$N_{(4)}$ (x, 1/2−y, 1/2+z)	2,25(5)	3,124(2)	161(3)
Cl···H—$O_{(4a)}$ (x, 1/2−y, −1/2+z)	2,08(5)	3,014(2)	164(3)

TABLE 4. Coordinates of the Atoms ($\cdot 10^4$) in the Diazobarbiturate III Crystal

Atom	x	y	z	Atom	x	y	z
$O_{(2)}$	3933(6)	3180(18)	4175(8)	$N_{(8)}$	4020(13)	−3574(22)	9133(15)
$O_{(4)}$	2658(6)	−3805(19)	6293(8)	$C_{(2)}$	3974(9)	1836(25)	5122(11)
$O_{(6)}$	5457(7)	1685(21)	8196(8)	$C_{(4)}$	3280(9)	−1909(26)	6293(12)
$N_{(1)}$	4691(7)	2411(20)	6199(9)	$C_{(5)}$	4059(8)	−1104(23)	7284(10)
$N_{(3)}$	3259(8)	−342(22)	5169(10)	$C_{(6)}$	4788(9)	1003(26)	7310(12)
$N_{(7)}$	4051(9)	−2457(30)	8311(13)	$C(N_{(3)})$	2453(10)	−1136(28)	4018(12)

Covalent hydrates IIa, b decompose under more severe conditions (6 N hydrochloric acid at 95-100°C). According to the ^1H and ^{13}C NMR spectral data, formic acid [$\delta_{(^1H)}$ 8.17, $\delta_{(^{13}C)}$ 165.5 ppm, $^1J_{^1H,^{13}C}$ = 219.8 Hz [10]] was identified among the products of transformation of hydrates IIa, b. Other products of the acidic hydrolysis of IIa are 5-diazo-3-methylbarbituric acid (III) and methylparabanic acid (IVa). The structure of methylimidazolinetrione IVa, which was previously synthesized by oxidative decomposition of methyluric acid [14] and by acidic hydrolysis of methylalloxane [12], was confirmed by data from UV and PMR spectroscopy and high-resolution mass spectrometry. The structure of product III was established by x-ray diffraction analysis.

The III crystals are monoclinic and have the following parameter: a = 13.144(6), b = 4.803(2), c = 11.053(8) Å, β = 101.92(4)°, V = 682.8(8) Å^3, Z = 4, and space group $P2_1/n$. The structure was decoded by the direct method and was refined by the method of least squares within the completely matrix anisotropic approximation up to R = 0.092 for 670 reflections with $F^2 \geq 3\sigma$. The final coordinates of the atoms are presented in Table 4. The III molecule is virtually planar and is characterized by the geometrical parameters that one usually finds for pyrimidine systems (Fig. 2); the lengths of the chemically equivalent bonds are virtually identical: $C_{(2)}$—$N_{(1)}$ and $C_{(6)}$—$N_{(1)}$ 1.39(1), $C_{(4)}$—$N_{(3)}$ and $C_{(2)}$—$N_{(3)}$ 1.45(1) and 1.41(1), $C_{(4)}$—$C_{(5)}$ and $C_{(5)}$—$C_{(6)}$ 139(1) Å. The lengths of all of the C=O bonds coincide [1.22(1) Å]. The diazo group is virtually linear, angle $C_{(5)}N_{(7)}N_{(8)}$ is 178(2)°, and the lengths of the $C_{(5)}$—$N_{(7)}$ and $N_{(7)}$—$N_{(8)}$ bonds are 131(2) and 1.06(2) Å, respectively. In the crystal the III molecules are linked together by means of $N_{(1)}$—H...$O_{(2)}$ intermolecular hydrogen bonds [$N_{(1)}$...$O_{(2)}$ 2.87 Å] and form centrosymmetric hydrogen-bonded dimers.

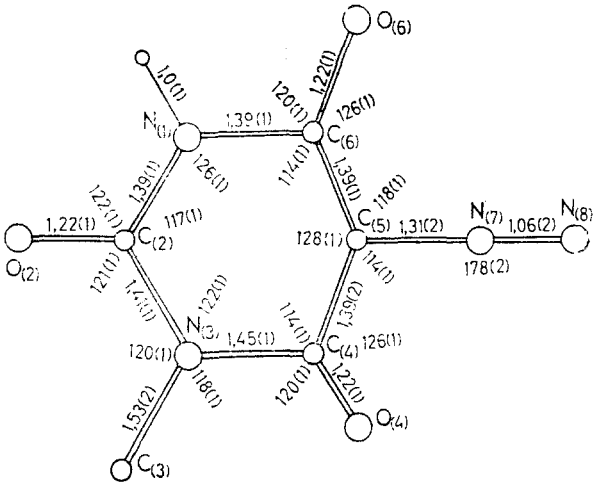
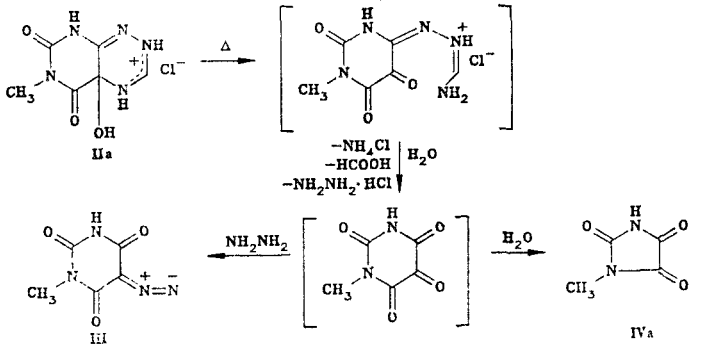


Fig. 2. Structure of the 5-diazo-3-methylbarbituric acid (III) molecule.

The destruction of hydrate IIa to III and IVa can be explained by a number of successive transformations.



Nucleophilic attack by the hydroxide anion at the $C_{(3)}$ and $C_{(8a)}$ atoms leads to cleavage of the $N_{(2)}$–$C_{(3)}$ and $N_{(1)}$–$C_{(8a)}$ bonds with subsequent splitting out of hydrazone and formamide. The latter is hydrolyzed to formic acid. The transhydrazination of methylalloxane at the $C_{(5)}$ atom, which was described in [11], and the oxidation of the hydrazone lead to diazobarbiturate III. Methylparabanic acid (IVa) is evidently formed from methylalloxane through ring contraction [12, 13].

Covalent hydrate IIb of fervenulin is converted in an acidic medium to dimethylparabanic acid (IVb), which was previously described in [12, 13]. Its structure was established in analogy with IVa on the basis of data from the high-resolution mass spectra and the UV and PMR spectra.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra of ~5% solutions of the investigated substances in D_2O were recorded at 40°C with a Bruker WH-90 spectrometer (West Germany) at 90 (^1H) and 22.62 MHz (^{13}C). The chemical shifts on the δ scale were measured relative to the signal of dioxane as the internal standard: 3.65 (^1H) and 67.40 ppm (^{13}C). The accuracy in the measurement of the chemical shifts as determined by digital resolution was 0.005 for ^1H and 0.02 ppm for ^{13}C.

The mass spectra were obtained with a Varian MAT-311A spectrometer (Swiss). In the case of III and IVa, b the spectra were recorded with direct introduction of the samples into the ion source at an accelerating voltage of 3.0 kV, an ionizing voltage of 70 eV, a cathode-emission current of 1.0 mA, and an ionization-chamber temperature of 150°C. In the case of hydrates IIa, b the spectra were obtained by the method of bombardment with fast atoms (BFA) of xenon in a glycerol matrix.

X-ray diffraction analysis of IIa and III was carried out with a Syntex-P1 automatic diffractometer (USA); λ_{CuK_α}, Ni filter, $\theta/2\theta$ scanning, $3° \leq 2\theta \leq 120°$.

The UV spectra were recorded with a pye-Unicam SP 8-100 spectrophotometer (Great Britain). The melting points were determined with a Boetius heating stage (East Germany). The purity of the substances were monitored by TLC on Silufol UV-254 plates; the spots were detected in UV light at λ 254 nm.

The equilibrium constants of the covalent hydration of rheumycin (Ia) and fervenulin (Ib) were calculated from the equation

$$K=\alpha/\left[\left(B_0-\frac{\alpha A_0}{1+\alpha}\right)\left(C_0-\frac{\alpha A_0}{1+\alpha}\right)\right],$$

which was obtained from the expression of the law of mass action K = D/(ABC) taking into account the equation of material balance $A_0 = A + D$, $B_0 = B + D$, $C_0 = C + D$, where A_0 and A, B_0 and B, and C_0 and C are the starting and equilibrium concentrations, respectively, of pyrimidotriazines Ia, b, water, and hydrochloric acid, respectively, D is the equilibrium concentration of covalent hydrates IIa, b, and $\alpha = D/A$ is the ratio of the equilibrium concentrations of covalent hydrates IIa, b and the corresponding pyrimidotriazines Ia, b measured from the integral intensities of the $CH_3N_{(6)}$ signals in the PMR spectra of the reaction mixtures. In the measurement of the equilibrium constants the concentrations of pyrimidotriazines Ia, b and hydrogen chloride ranged from $A_0 = (3.31\text{-}5.62)\cdot10^{-2}$, C_0 = 0.62-4.89 moles/liter; the water concentration was kept constant at B_0 = 53.5 moles/liter; the ratios of the equilibrium concentrations of covalent hydrates IIa, b and pyrimidotriazines Ia, b were α = 0.84-4.39.

4-Hydroxy-4,4a-dihydro-6-methylpyrimido[5,4-e]-1,2,4-triazine-5,7(6H,8H)-dione Hydrochloride (IIa). A 1-ml sample of 6 N HCl was added to 18 mg (0.1 mmole) of rheumycin (Ia), and the solution was evaporated in the vacuum created by an oil pump to give 22 mg (96%) of IIa in the form of a straw-colored substance with mp 160-239°C (dec., from 6 N HCl). UV spectrum (6 N HCl), λ_{max} (log ε): 226 (sh, 3.95), 287 (3.55), 332 nm (sh, 3.08). Mass spectrum:* 198 $[(M - HCl) + H]^+$.

4a-Hydroxy-4,4a-dihydro-6,8-dimethylpyrimido[5,4-e]-1,2,4-triazine-5,7(6H,8H)-dione Hydrochloride (IIb). This compound was similarly obtained in 93% yield and had mp 120-173°C (dec., from 6 N HCl). UV spectrum (6 N HCl), λ_{max} (log ε): 228 (3.81), 286 (3.50), 341 nm (2.88). Mass spectrum: 212 $[(M - HCl) + H]^+$.

Acidic Hydrolysis of 6-Methylpyrimido[5,4-e]-1,2,4-triazine-5,7(6H,8H)-dione (Ia). A 1-ml sample of 6 N HCl solution was added to a solution of 90 mg (0.50 mmole) of rheumycin (Ia) in 4 ml of water, and the mixture was heated for 1 h at 95-100°C. The cooled solution was lyophilized twice, and the residue was subjected to preparative chromatography on 20 × 20 cm glass plates (Silpearl) in BN chambers by elution with chloroform–acetone (39:1) admitted into the stream. A 15-mg (17.8%) sample of 5-diazo-3-methylpyrimidinetrione (III), with mp 195-197°C (from chloroform), was extracted from the zone with R_S = 1 (path length 12.2-13.0 cm). UV spectrum (water), λ_{max} (log ε): 262 (3.94), 205 nm (4.12). PMR spectrum (D_2O): 3.32 ppm (s, 3-CH_3). Mass spectrum: 168 (57.8), 140 (24.5), 111 (15.4), 97 (41.4). High-resolution mass spectrum: 168.0296 (M^+), calculated 168.0283 ($C_5H_4N_4O_3$); 140.0222 ($[M - N_2]^+$), calculated 140.0222 ($C_5H_4N_2O_3$); 97.0168 ($[M - CHN_3O]^+$), calculated 97.0164 ($C_4H_3NO_2$). Extraction from the zone with R_S = 0.75-0.84 gave 17 mg (26.4%) of methylparabanic acid (IVa) with mp 150-152°C (from methanol) (mp 149.5°C [14]). UV spectrum (water), λ_{max} (log ε) 256 (3.03), 212 nm (4.02). PMR spectrum (D_2O): 3.21 ppm (s, 3-CH_3). Mass spectrum: 128 (100.0), 100 (78.8), 72 (23.6), 57 (68.4). High-resolution mass spectrum: 128.0225 (M^+), calculated 128.0221 ($C_4H_4N_2O_3$): 100.0257 ($[M - CO]^+$), calculated 100.0273 ($C_3H_4N_2O_2$).

Acidic Hydrolysis of 6,8-Dimethylpyrimido[5,4-e]-1,2,4-triazine-5,7(6H,8H)-dione (Ib). A 4-ml sample of 6 N HCl solution was added to a suspension of 96 mg (0.50 mmole) of fervenulin (Ib) in 4 ml of water and the solution was heated at 95-100°C for 15 h. After cooling, a solution of 67 mg (0.80 mmole) of $NaHCO_3$ in 3 ml of water was added to the reaction mixture, and it was lyophilized. The residue was treated with 50 ml of chloroform (ten 5-ml portions), and the extract was chromatographed with a column (the ratio of the height

*Here and subsequently, the m/z values are presented (relative intensity, %).

to the diameter was 10:1) packed with L 40/100 silica gel. Elution with chloroform (20 ml) with subsequent removal of it by distillation gave 14 mg (20.0%) of dimethylparabanic acid (IVb) with mp 103-105°C (from chloroform). UV spectrum (water), λ_{max} (log ε): 261 (3.16), 216 nm (3.96). PMR spectrum ($CDCl_3$): 3.18 ppm (s, NCH_3). Mass spectrum: 142 (87.0), 114 (16.8), 86 (5.7), 57 (55.0). High-resolution mass spectrum: 142.0382 (M^+), calculated 142.0379 ($C_5H_6N_2O_3$); 114.0428 ($[M - CO]^+$), calculated ($C_4H_6N_2O_2$); 86.0475 ($[M - C_2O_2]^+$), calculated 86.0480 ($C_3H_6N_2O$).

LITERATURE CITED

1. M. E. C. Biffin, D. J. Brown, and T. Sugimoto, J. Chem. Soc., C, No. 1, 139 (1970).
2. J. Clark and F. S. Yates, J. Chem. Soc., C, No. 13, 2475 (1971).
3. S. E. Esipov, A. I. Chernyshev, S. V. Shorshnev, N. I. Yakushkina, and V. L. Antonovskii, Antibiot. Med. Biotekhnol., No. 2, 122 (1985).
4. S. V. Shorshnev, S. E. Esipov, N. I. Yakushkina, N. A. Klyuev, V. G. Zhil'nikov, and A. I. Chernyshev, Khim. Geterotsikl. Soedin., No. 9, 1252 (1987).
5. S. V. Shorshnev, S. E. Esipov, and A. V. Chernyshev, Khim. Geterotsikl. Soedin., No. 11, 1532 (1988).
6. J. P. Geerts, A. Nagel, and H. C. Van der Plas, Org. Magn. Reson., 8, 637 (1976).
7. W. W. Paudler and T.-K. Chen, J. Heterocycl. Chem., 7, 767 (1970).
8. A. Albert, Advances in Heterocyclic Chemistry, Vol. 20, A. R. Katritzky and A. J. Boulton (eds.), Academic Press, New York (1976), p. 117.
9. G. G. Aleksandrov and S. E. Esipov, Antibiot. Med. Biotekhnol., No. 3, 181 (1986).
10. E. Breitmaier and W. Voelter, ^{13}C NMR Spectroscopy, Verlag Chemie, Weinheim—New York (1978), pp. 97, 193.
11. O. Kühling, Berichte, 24, 4140 (1891).
12. H. Kwart, R. W. Spayd, and C. J. Collins, J. Am. Chem. Soc., 83, 2579 (1961).
13. E. Fischer, Berichte, 14, 1905 (1881).
14. H. B. Hill, Berichte, 9, 1090 (1876).

NUCLEOPHILIC SUBSTITUTION IN HYDROXYISOXAZOLIDINES

I. A. Motorina, L. A. Sviridova, G. A. Golubeva, K. N. Zelenin, I. P. Bezhan, A. Yu. Ershov, and Yu. G. Bundel'

UDC 547.786.1:541.623:542.958.3:543.422.25

Nucleophilic substitution of the hydroxy-group in 3- (or 5-)hydroxyisoxazolidines affords the aryl(alkyl)amino-, alkoxy-, and hydrazino-compounds. 5-Dimethylhydrazinooxazolidines exist preferentially in the linear form.

Functional derivatives of isoxazolidine are of particular interest as potentially physiologically active compounds, since they include antitumor [1] and antibacterial drugs [2], antidepressants [3], and fungicides [4]. The introduction of functional groups into the isoxazolidine ring was an important but difficult task, only the 5-alkoxy derivatives being available until recently [5]. In a previous communication [6], we reported a promising method for the synthesis of 3- and 5-hydroxyisoxazolidines. Bearing in mind the hemiaminal nature of the hydroxy-group in these compounds, and its tendency to undergo nucleophilic exchange, we developed a method for the synthesis of other 3- and 5-functionalized isoxazolidines from the hydroxyisoxazolidines. The nucleophilic reactants used were alcohols, aliphatic and aromatic amines, N-substituted hydrazones and hydrazides:

M. V. Lomonosov Moscow State University, Moscow 119899. S. M. Korov Academy of Military Medicine, Leningrad 194175.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1661-1665, December, 1988. Original article submitted June 29, 1987.