INVESTIGATION OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES

XXIV.* SYNTHESIS OF PYRIMIDO[5,4-b][1,4]-7-OXAZINONES

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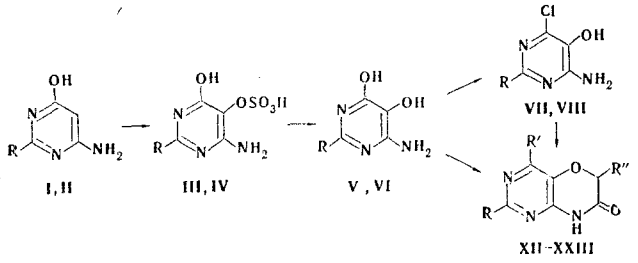
A number of derivatives of a new heterocyclic system – pyrimido[5,4-b][1,4]-7-oxazinone – were obtained by the reaction of substituted 5-hydroxy-6-aminopyrimidines with ethyl esters of α-halocarboxylic acids.

Pyrido[3,2-b][1,4]oxazine [2], pyrimido[4,5-b][1,4]oxazine [3-5], and pyrono[3,2-b][1,4]oxazine [6] derivatives are described in the literature. However, up until now there has been no information regarding methods for the preparation and properties of the pyrimido[5,4-b][1,4]oxazine system.

In a continuation of our research [7] to find biologically active substances, we developed a general method for the preparation of 7-oxo derivatives of pyrimido[5,4-b][1,4]oxazine by the reaction of 5-hydroxy-6-aminopyrimidines with ethyl esters of α-halocarboxylic acids.

The necessary 5-hydroxy-6-aminopyrimidines (VI-VIII) were obtained from 4-hydroxy-6-amino- (I) and 2-methyl-4-hydroxy-6-aminopyrimidines (II).



I, III, V, VII R=H;
II, IV, VI, VIII R=CH_3;
XII R=CH_3, R′=OH, R″=H; XIII R=CH_3, R′=Cl, R″=H;
XIV R=R″=H, R′=Cl; XV R=NH_2, R′=CH_3, R″=H;
XVI R=R″=CH_3, R′=OH; XVII R=CH_3, R′=OH, R″=C_2H_5;
XVIII R=R″=CH_3, R′=Cl; XIX R=CH_3, R′=Cl, R″=C_2H_5;
XX R=NH_2, R′=R″=CH_3; XXI R=NH_2, R′=CH_3, R″=C_2H_5;
XXII R=CH_3CONH, R′=R″=CH_3; XXIII R=CH_3CONH, R′=CH_3, R″=H.

The reaction of I and II with ammonium persulfate via the method in [8] gave 4-hydroxy-6-amino-5-pyrimidyl hydrosulfates (III, IV), which were saponified with hydrochloric acid to the corresponding 4,5-dihydroxy-6-aminopyrimidines (V, VI). It was shown that V and VI react with phosphorus oxychloride to give 4-chloro-6-hydroxy-6-aminopyrimidines (VII, VIII); i.e., the hydroxyl group in the 4 position of the pyrimidine ring is replaced by a chlorine atom.

*See [1] for communication XXIII.

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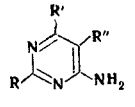
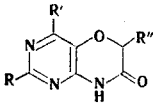
TABLE 1



III–XI



XII–XXIII

Comp.	R	R′	R″	mp, °C (crystallization solvent)	Empirical formula	Found, %				Calculated, %				Yield, %
						C	H	Cl (S)	N	C	H	Cl (S)	N	
III	H	OH	OSO_3H	270* (water)	$C_4H_5N_3O_5S \cdot H_2O$	21,5	3,5	(14,2)	—	21,3	3,1	(14,2)	—	55
IV	CH_3	OH	OSO_3H	253* (water)	$C_5H_7N_3O_5S$	27,0	3,4	(14,6)	19,2	27,2	3,2	(14,5)	19,0	42
V	H	OH	OH	>300 (water)	$C_4H_5N_3O_2$	38,0	3,8	—	33,5	37,8	4,0	—	33,1	78
VI	CH_3	OH	OH	>300 (water)	$C_5H_7N_3O_2$	42,9	5,2	—	30,0	42,6	5,0	—	29,8	88
VII	H	Cl	OH	191—193* (water)	$C_4H_4ClN_3O$	32,7	2,9	24,1	28,7	33,0	2,8	24,4	28,9	70
VIII	CH_3	Cl	OH	208—210* (water)	$C_5H_6ClN_3O$	37,8	3,9	22,3	26,4	37,6	3,8	22,2	26,3	62
X	CH_3	CH_3	OSO_3H	173—174* (water)	$C_6H_9N_3O_4S$	33,0	4,4	(14,5)	19,4	32,9	4,1	(14,6)	19,2	40
XI	CH_3	CH_3	Cl	163—164† (water)	$C_6H_8ClN_3$	45,7	5,3	22,1	—	45,7	5,1	22,5	—	62
XII	CH_3	OH	H	>350 (water)	$C_7H_7N_3O_3$	46,4	3,8	—	22,7	46,4	3,9	—	23,2	63
XIII	CH_3	Cl	H	175,5—176 (ether)	$C_7H_6ClN_3O_2$	42,4	3,2	17,6	20,8	42,1	3,0	17,8	21,1	76
XIV	H	Cl	H	222—224(ethyl acetate)	$C_6H_4ClN_3O_2$	39,0	2,1	18,9	22,7	38,8	2,2	19,0	22,7	56
XV	NH_2	CH_3	H	>345 (acetic acid)	$C_7H_8N_4O_2$	46,4	4,5	—	30,9	46,7	4,5	—	31,1	89
XVI	CH_3	OH	CH_3	>300 (water)	$C_8H_9N_3O_3$	49,1	4,8	—	—	49,2	4,7	—	—	71
XVII	CH_3	OH	C_2H_5	>300 (water)	$C_9H_{11}N_3O_3$	51,9	5,1	—	19,8	51,7	5,3	—	20,1	66
XVIII	CH_3	Cl	CH_3	169,5—170,5(ether)	$C_8H_8ClN_3O_2$	45,1	3,8	16,6	19,3	45,0	3,8	16,6	19,7	84
XIX	CH_3	Cl	C_2H_5	155—155.5 (ether)	$C_9H_{10}ClN_3O_2$	47,6	4,4	15,7	18,8	47,5	4,4	15,6	18,5	77
XX	NH_2	CH_3	CH_3	>300 (acetic acid)	$C_8H_{10}N_4O_2$	49,3	5,6	—	28,7	49,5	5,2	—	28,9	76
XXI	NH_2	CH_3	C_2H_5	>300 (acetic acid)	$C_9H_{12}N_4O_2$	51,6	5,7	—	27,0	51,9	5,8	—	27,0	65
XXII	$CH_3CO—NH$	CH_3	CH_3	225—227 (alcohol)	$C_{10}H_{12}N_4O_3$	50,6	5,0	—	23,8	50,8	5,1	—	23,7	45
XXIII	$CH_3CO—NH$	CH_3	H	245—246 (water)	$C_9H_{10}N_4O_3$	—	—	—	25,4	—	—	—	25,2	45

*Decomposition.

†According to [9], mp 165°.

2,4-Dimethyl-6-aminopyrimidine (IX) reacts with ammonium persulfate to give 2,4-dimethyl-6-amino-5-pyrimidyl hydrosulfate (X), which is hydrolyzed by hydrochloric acid to give 2,4-dimethyl-5-chloro-6-aminopyrimidine (XI) instead of the expected 2,4-dimethyl-5-hydroxy-6-aminopyrimidine.

Like phenols, the 5-hydroxypyrimidines give an intense blue coloration with $FeCl_3$ solution.

The corresponding 6,7-dihydro-8H-pyrimido[5,4-b][1,4]-7-oxazinones (XII-XXI) are obtained in 60-90% yields by the reaction of VI-VIII and 2,6-diamino-5-methyl-5-hydroxypyrimidine [8] with ethyl esters of α-halocarboxylic acids (monochloroacetic, α-bromopropionic, and α-bromosuccinic acids) in alcohol in the presence of sodium ethoxide or triethylamine.

2-Acetamido derivatives (XXII, XXIII) are formed smoothly by reaction of acetic anhydride on 2-amino-4,6-dialkylpyrimido-7-oxazinones (XX, XXI).

The data from the IR and UV spectra of the pyrimido-7-oxazinones (XII-XXI) show that these compounds have the lactam structure in the solid state and in solution. Absorption bands characteristic for the amide CO group at 1690-1720 cm^{-1} and amide NH group at 3120-3170 cm^{-1} are observed in the IR spectra of mineral oil suspensions of the compounds. The same maximum (λ_{max} 292 nm) is observed in the UV spectra of XIII and XIX in alcohol and dioxane, while this maximum is found at 294 nm in the spectra of aqueous or aqueous alcohol solutions. Protons of the 2-CH_3 group (singlet, 3H, 2.66 ppm) and of the CH_2 group (singlet, 2H, 4.83 ppm) are observed in the PMR spectra of a chloroform solution of XIII.

EXPERIMENTAL

2-Methyl-4-hydroxy-6-amino-5-pyrimidyl Hydrosulfate (IV). A solution of 96 g (0.42 mole) of ammonium persulfate in 180 ml of water was added at 5-10° in the course of 4 h to a solution of 40 g (0.32 mole) of II in 630 ml of 3 N NaOH, and the mixture was stirred at room temperature for 2 h and allowed to stand until the following day. The solution was acidified to pH 2 with concentrated HCl, and the mixture was allowed to stand overnight in a refrigerator. The precipitate was separated and washed with water to give IV. 4-Amino-6-hydroxy-5-pyrimidyl hydrosulfate (III) was similarly obtained.

2-Methyl-4,5-dihydroxy-6-aminopyrimidine (VI). A suspension of 31.2 g of IV in 700 ml of 5 N HCl was refluxed for 1 h and cooled. The precipitate was separated to give 21.9 g (88%) of the hydrochloride of VI. The base was isolated by neutralization of a suspension of the hydrochloride of VI in water with solid $NaHCO_3$ or by crystallization of the hydrochloride of VI from water. 4,5-Dihydroxy-6-aminopyrimidine (V) was similarly obtained.

2-Methyl-4-chloro-5-hydroxy-6-aminopyrimidine (VIII). A suspension of 22.5 g of VI and 170 ml of $POCl_3$ was refluxed for 7 h. The excess phosphorus oxychloride was removed by vacuum distillation, and the residue was decomposed with ice. The reaction mass was held at room temperature for 2 h and then heated to 90°. It was then cooled and neutralized with concentrated NH_4OH to pH 3-4 and stored in a refrigerator overnight. The precipitated VIII was separated and washed with water. An additional amount of VIII was obtained by extracting the mother liquor with ether.

4-Chloro-5-hydroxy-6-aminopyrimidine (VII). A suspension of 10 g of V in 12 ml of phosphorus oxychloride was heated in an autoclave for 11 h at a bath temperature of 130°. The mass was then decomposed by pouring over 100 g of ice. Compound VII was then isolated by the method used to obtain VIII.

2,4-Dimethyl-6-amino-5-pyrimidyl Hydrosulfate (X). This compound was obtained by the method used to prepare 2,6-diamino-4-methyl-5-pyrimidyl hydrosulfate [8].

2,4-Dimethyl-5-chloro-6-aminopyrimidine (XI). A suspension of 5.56 g of X and 16 ml of 5 N HCl was refluxed for 25 min, cooled, and neutralized with $NaHCO_3$. The precipitated XI was removed by filtration.

2-Methyl-4-hydroxy-6,7-dihydro-8H-pyrimido[5,4-b][1,4]-7-oxazinone (XII). A 0.01-mole sample of the hydrochloride of VI and 0.01 mole of ethyl monochloroacetate were added to sodium ethoxide, obtained from 0.02 g-atom of sodium and 30 ml of absolute alcohol, and the mixture was refluxed for 3 h. The alcohol was removed by distillation, and water was added to the residue. The aqueous mixture was acidified to pH 5-6 with acetic acid or dilute (1 : 4) HCl and allowed to stand until the next day. The precipitated XII was separated and washed with water. Compounds XV-XVII, XX, and XXI were similarly obtained.

2-Methyl-4-chloro-6,7-dihydro-8H-pyrimido[5,4-b][1,4]-7-oxazinone (XIII). A. A 0.02-mole sample of VIII and 0.028 mole of ethyl monochloroacetate were added successively to sodium ethoxide, obtained

from 0.02 g-atom of sodium and 60 ml of absolute alcohol, and the mixture was refluxed for 3 h. The alcohol was removed by distillation, and 10 ml of water was added to the residue; the resulting oily residue was converted to crystalline XIII on standing. Compounds XIV, XVIII, and XIX were similarly obtained.

B. A solution of 0.02 mole of VIII, 0.028 mole of ethyl monochloroacetate, and 0.02 mole of triethylamine in 60 ml of absolute alcohol was refluxed for 3 h. Another 0.01 mole of acid ester and 0.01 mole of triethylamine were added, and the mixture was again refluxed for 2 h. The alcohol was then removed by distillation, and water was added to the residue to give XIII in 78% yield. Compound XIV was similarly obtained in 65% yield.

2-Acetamido-4,6-dimethyl-6,7-dihydro-8H-pyrimido[5,4-b][1,4]-7-oxazinone (XXII). A 0.38-g sample of XX was refluxed in 10 ml of acetic anhydride for 1.5 h, and the mixture was then evaporated to dryness. The residual XXII was washed with 5 ml of alcohol. Compound XXIII was similarly obtained. The pyrimidooxazinones were colorless crystalline substances that were quite soluble in alkalis. Compounds with NH_2 and OH groups in the pyrimidine ring were only slightly soluble in organic solvents. The remaining compounds were more soluble. The IR spectra were recorded with a UR-10 spectrophotometer, the UV spectra were recorded with an SF-4 spectrophotometer, and the PMR spectra were recorded with a JNM-4H-100 spectrometer (with tetramethylsilane as the internal standard).

LITERATURE CITED

1. T. S. Safonova, M. P. Nemeryuk, L. A. Myshkina, and N. I. Traven', Khim. Geterotsikl. Soedin., 944 (1972).
2. H. Heide and G. Olsen, Acta Chem. Scand., 23, 2322 (1969).
3. P. B. Russel, G. B. Elion, and G. H. Hitchings, J. Am. Chem. Soc., 71, 474 (1949).
4. G. Elion and G. H. Hitchings, J. Am. Chem. Soc., 74, 3877 (1952).
5. J. Mirza, W.Pfleiderer, A. Brewer, A. Stuert, and H. Wood, J. Chem. Soc., C, 437 (1970).
6. F. Eiden and J. Plückhan, Arch. Pharm., 302, 628 (1969).
7. T. S. Safonova, M. P. Nemeryuk, V. A. Chernov, N. A. Andreeva, A. S. Sokolova, N. A. Ryabokon', A. F. Keremov, and T. P. Lapshina, Routes to the Synthesis and Investigation of Antitumorigenic Preparations [in Russian], No. 3, Zinatne, Riga (1970), p. 91.
8. R. Hull, J. Chem. Soc., 2033 (1956).
9. A. G. Bayer, Ber., 4, 176 (1871).