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SYNTHESIS OF 6-OXO-6,7,8,9-TETRAHYDRO-10H-PYRIMIDO-[5,4-b][1,4]BENZOXAZINES AND 6-OXO-6,7,8,9-TETRA-HYDROPYRIMIDO[4,5-b][1,4]BENZODIOXANES

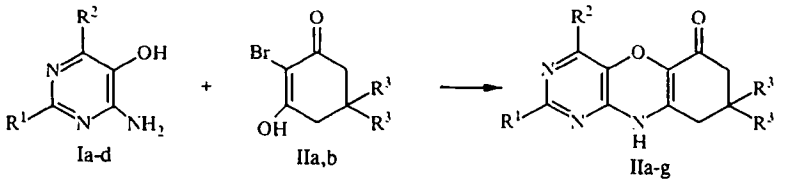
N. V. Sazonov, I. E. Mamaeva, and T. S. Safonova

Reaction of 5-hydroxy-6-aminopyrimidines with 2-bromohydroresorcinol and bromodimedone in DMF in the presence of sodium hydride gave 6,7,8,9-tetrahydro-10H-pyrimido[5,4-b][1,4]benzoxazines. When 4-chloro-5-hydroxy-6-aminopyrimidine was treated with bromodimedone the principal products were 6,7,8,9-tetrahydro-pyrimido[4,5-b][1,4]benzodioxanes. The nucleophilic substitution of the chlorine atom in position 4 of the tetrahydropyrimidobenzoxazines by amines, sodium alkanoates, and thiourea has been studied and the corresponding amines and alkoxy- and thio derivatives of this tricyclic system obtained.

Preparative methods and properties for 9-oxo-6,7,8,9-tetrahydro- and 9-amino-7,8-dihydropyrimido[4,5-b][1,4]benzothiazines have been reported in previous publications [1-4]. Among these, compounds have been discovered which inhibit the dihydrofolate reductase enzyme of folate exchange and show antitumor and neurotropic activity.

In continuation of this work we have undertaken the synthesis of derivatives of 6,7,8,9-tetrahydro-10H-pyrimido[5,4-b][1,4]benzoxazines not reported before in the literature. With this in view, we have investigated the reaction of the 5-hydroxy-6-aminopyrimidines (Ia-d) with bromodihydroresorcinol (IIa) and bromodimedone (IIb).

It was found that treatment of the pyrimidines Ia-d with bromoketones IIa,b in DMF in the presence of an equimolar amount of sodium hydride at 55-70°C gave 6-oxo-6,7,8,9-tetrahydro-10H-pyrimido[5,4-b][1,4]benzoxazines (IIIa-f) in 42-67% yield.



Ia,d,IIIa,d,f,g R^1 = H; Ib,c IIIb,c,eR^1 = Me;
Ic,d, IIIc-f R^2 = H; Ia,b IIIa,b,g R^2 = Cl;
IIa, IIIa-d R^3 = H; IIb IIIe-g R^3 = Me

Different results were obtained upon treating the bromodimedone IIb with 4-chloro-5-hydroxy-6-aminopyrimidines Ia, b. Hence, when Ia was treated with bromodimedone in the conditions indicated above, the corresponding 6-oxopyrimidobenzoxazine IIIg was isolated in 17% yield. Carrying out this reaction at a higher temperature (85-90°C) led to the preparation of the novel heterocyclic system 6,7,8,9-tetraydropyrimido[4,5-b][1,4]benzodioxane (IVa). The presence of IIIg in the reaction mixture was only revealed by chromatography of the reaction product.

The reaction of 2-methyl-4-chloro-5-hydroxy-6-aminopyrimidine (Ib) with bromodimedone in DMF with one or two moles of sodium hydride at 80-90°C gave the 4-aminopyrimidobenzodioxane IVb in 42% yield.

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TABLE 1. Parameters for Compounds Synthesized IIIa-g, IVa,b, Va-g

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Crystallization solvent	R_f	IR spectrum, ν, cm^{-1}		Yield, %
		C	H	N				CO	NH	
1	2	3	4	5	6	7	8	9	10	11
IIIa	$C_{10}H_8ClN_3O_2$*[2]	50,19 / 50,54	3,40 / 3,39	18,01 / 17,68	261...262	DMF–acetone (1:10)	0,50	1640	3110, 3190	59
IIIb	$C_{11}H_{10}ClN_3O_2$*[3]	52,61 / 52,49	4,11 / 4,00	17,08 / 16,69	281...282	Ethanol	0,48	1618	3230	67
IIIc	$C_{11}H_{11}N_3O_2$	60,95 / 60,82	5,05 / 5,10	19,29 / 19,35	283...284	Ethanol		1645	3410	54
IIId	$C_{10}H_9N_3O_2$	59,12 / 59,11	4,19 / 4,47	20,99 / 20,68	273...274	Isopropanol		1640	3190	43
IIIe	$C_{13}H_{15}N_3O_2$	63,43 / 63,66	6,08 / 6,16	16,94 / 17,13	250...251	Ethanol		1645	3140	59
IIIf	$C_{12}H_{13}N_3O_2$	62,74 / 62,32	5,64 / 5,67	18,41 / 18,17	255...257	Isopropanol	0,40	1645	3410	42
IIIg	$C_{12}H_{12}ClN_3O_2$*[4]	54,12 / 54,24	4,77 / 4,55		252...253	H_2O– ethanol (3 : 1)	0,52	1650	3410	17
IVa	$C_{12}H_{13}N_3O_2$	58,16 / 58,29	5,33 / 5,30	17,08 / 17,00	275...276	Ethanol	0,57	1670	3130, 3320	39
IVb	$C_{13}H_{15}N_3O_2$	59,70 / 59,76	5,89 / 5,79	16,40 / 16,08	265...266	Ethanol	0,61	1670	3165, 3375	42
Va	$C_{14}H_{16}N_4O_3$	58,3 / 58,32	5,82 / 5,59	19,22 / 19,44	270...271	Ethanol	0,40	1635	3120	96
Vb	$C_{15}H_{18}N_4O_2$	62,79 / 62,92	6,60 / 6,34	19,39 / 19,57	261...262	H_2O–ethanol (1 : 3)	0,37	1655	3120	86
Vc	$C_{15}H_{19}N_5O_2$	59,79 / 59,78	6,50 / 6,36	23,32 / 23,24	249...251	Ethanol		1638	3130	77
Vd	$C_{19}H_{20}N_4O_2$	68,00 / 67,83	6,08 / 5,99	16,55 / 16,62	262...263	Ethanol				62
Ve	$C_{11}H_{11}N_3O_3$	56,63 / 56,65	4,81 / 4,75	18,09 / 18,02	266...267	H_2O– methanol		1645	3405	87
Vf	$C_{13}H_{15}N_3O_3$	59,52 / 59,76	5,92 / 5,79	16,13 / 16,08	238...240	H_2O– ethanol		1640	3400	73
Vg	$C_{11}H_{11}N_3O_2S$*[5]	52,72 / 52,99	4,68 / 4,45	16,80 / 16,86	296...298	H_2O–CH_3COOH				90

*IR spectra for IIIc,e-g, Ve,f recorded in $CHCl_3$, the rest in Vaseline oil.

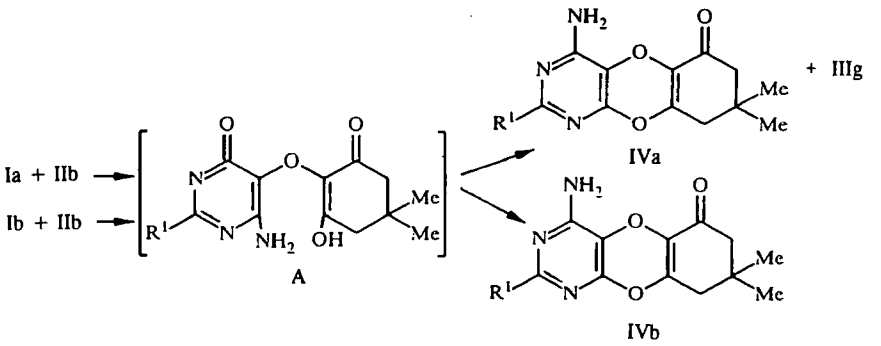
*[2]Found, %: Cl 14.65. Calculated, %: Cl 14.92.

*[3]Found, %: Cl 14.29. Calculated, %: Cl 14.09.

*[4]Found, %: Cl 13.26. Calculated, %: Cl 13.55.

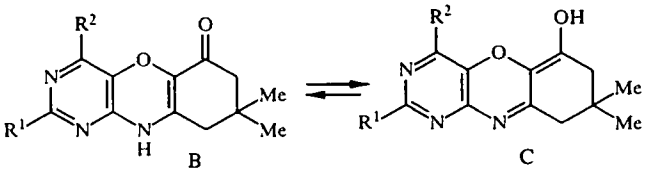
*[5]Found, %: S 12.76. Calculated, %: S 12.86.

Evidently there initially occurs a reaction of the hydroxyl group in the pyrimidine ring with the bromine atom of the bromodimedone to form the intermediate ether A. Then, thanks to the presence in the pyrimidine fragment of ether A of the amino group and the chlorine atom, there can occur two concurrent processes. The enolic hydroxyl in the dimedone residue can react both with the amino group and the chlorine atom and this can lead to closing of the oxazine or the dioxane rings to form the tricyclic systems IIIg and IVa, b.



Ia, IIIg, IVa R^1 = H; Ib, IVb R^1 = Me

The tetrahydrobenzoxazines IIIa-g, like the analogous tetrahydrobenzothiazines [3], can have an enamine (B) or an amine (C) like structure.



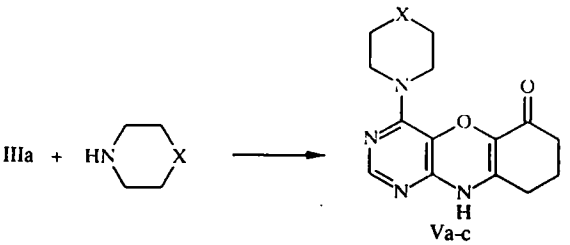
The choice between these structures in favor of structure B was made by us on the basis of IR and PMR spectra. Hence in the IR spectra of IIIa-g there are absorption bands for the NH group at 3210-3110 cm^{-1} (in crystals) and 3400 cm^{-1} (in $CHCl_3$ solution) and bands characteristic for CO group stretching at 1655-1645 cm^{-1}. The PMR spectra of these compounds show a signal for the N_{10} proton at 9.22-9.55 ppm.

The structures of the 6-oxotetrahydropyrimidobenzodioxanes IVa, b were confirmed by the appearance in their IR spectra of absorption bands for the CO and NH groups at 1670 and 3130-3375 cm^{-1} respectively.

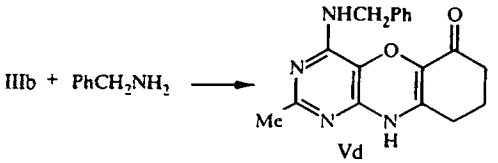
The reactions of 4-chloro-6-oxopyrimidobenzoxazines IIIa,b with nucleophilic reagents were investigated. It was found that refluxing 4-chloropyrimidobenzoxazine IIIa in n-butanol with morpholine, piperidine, and N-methylpiperazine and IIIb with benzylamine gave the corresponding 4-amino derivatives Va-d in 62-96% yields. Treatment of IIIa, b with sodium methylate and ethylate gave the 4-alkoxy substituted Ve,f and reaction of IIIb with thiourea led to the 4-thio derivative Vg.

The structures of Va-c, e, f were confirmed by the presence in their IR spectra of absorption bands for the CO and NH groups at 1635-1655 and 3120-3130 cm^{-1} respectively.

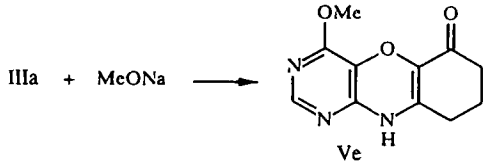
The action of a series of tetrahydropyrimidobenzoxazines IIIa-f, Va-g on the activity of dihydrofolate reductase isolated from rat liver [5] has been studied. It was found that these compounds, in contrast to analogous tetrahydropyrimidobenzothiazines [1, 2], do not inhibit enzyme activity. 2-Methyl-4-ethoxytetrahydropyrimidobenzoxazine Vf and 4-aminotetrahydropyrimidobenzodioxane IVa *in vitro* suppress the growth of tuberculous bacilli at concentrations of 1 and 0.5 μg/ml and 2-methyl-4-aminotetrahydropyrimidobenzodioxane IVb and 2-methyl-4-thiotetrahydropyrimidobenzoxazine Vg at a concentration of 3.9 μg/ml.



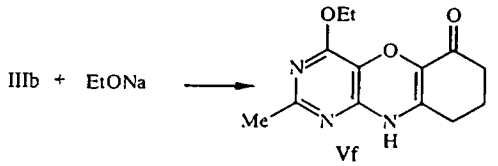
Va X = O, Vb X = CH_2, Vc X = NMe



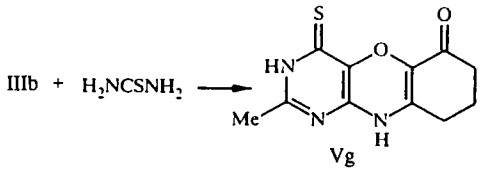
Vd



Ve



Vf



Vg

EXPERIMENTAL

IR spectra were taken on a Perkin-Elmer spectrophotometer as a suspension in Vaseline oil and in $CHCl_3$ solution. PMR spectra were recorded on an INM-100 spectrometer using $CDCl_3$ and TMS internal standard. Monitoring of the reaction course and the purity of the substances was carried out by TLC on Silufol UV-254 plates in benzene–ethyl acetate–ethanol (5:5.1:1.5) with UV visualization.

Elemental analytical data and physicochemical parameters for the compounds prepared are given in Table 1.

The starting 4-chloro-5-hydroxy-6-aminopyrimidine (Ia) and 2-methyl-4-chloro-5-hydroxy-6-aminopyrimidine (Ib) were synthesized according to method [6].

2-Methyl-5-hydroxy-6-aminopyrimidine (Ic). A suspension of compound Ib (8.25 g, 51.8 mmole) in water (100 ml) and Pd/C (5%, 1 g) was hydrogenated for 12 h in an autoclave at 70°C and 30 atmospheres. It was cooled, the catalyst filtered off, the filtrate evaporated to 50 ml, neutralized using sodium bicarbonate, and the precipitate filtered, washed with water, and dried. Yield of Ic 5.0 g (78%), mp 290-291°C (with decomp., from water). Found, %: C 47.80; H 5.30; N 33.50. $C_5H_7N_3O$. Calculated, %: C 48.00; H 5.60; N 33.60.

5-Hydroxy-6-aminopyrimidine (Id) was prepared similarly from Ia, mp 250°C (from water). According to [7], mp 250°C.

4-Chloro-6-oxo-6,7,8,9-tetrahydro-10H-pyrimido[5,4-b][1,4]benzoxazine (IIIa). Compound Ia (2.92 g, 20 mmole) was added to a suspension of sodium hydride (0.48 g, 20 mmole) in anhydrous DMF (30 ml). The mixture was stirred for 10 min, 2-bromodihydroresorcinol (IIa, 3.82 g, 20 mmole) was added, and the product was heated to 55°C, held at 55-63°C for 12 h, and cooled. The precipitated IIIa was filtered off, washed with water, and dried. Evaporation of the mother liquor and the precipitate water wash gave an additional amount of IIIa.

Similarly, the derivatives of pyrimidine Ib-f and bromoketone IIa or bromodimedone IIb gave compounds IIIb-f with the difference that, in the synthesis of IIIc,d the reaction mixture was heated at 70°C, for IIIe 2 h at 60-65°C and 4.5 h at 95-100°C, and for the synthesis of IIIf 6 h at 100-110°C. Compounds IIId,f were obtained from the reaction mixture after dilution with water by extraction with chloroform.

4-Chloro-6-oxo-8,8-dimethyl-6,7,8,9-tetrahydropyrimido[5,4-b][1,4]benzoxazine (IIIg). Compound Ia (1.0 g, 6.87 mmole) was added to a suspension of sodium hydride (0.16 g, 6.87 mmole) in DMF (20 ml). The mixture was stirred for 10 min, bromodimedone IIb (1.5 g, 6.87 mmole) added, and the reaction mixture was held for 14 h at 55-60°C. After cooling, it was evaporated to dryness, the residue dissolved in methanol (5 ml), the solution passed through an aluminium oxide column (Brockmann grade II activity, 10 g), and eluted with ether. The eluate was evaporated and the residue was dissolved in methanol (5 ml), water added (10 ml), and the precipitate filtered off and dried.

Compounds IIIa-g are yellow-green, crystalline, high melting materials, soluble on heating in the lowest alcohols and insoluble in water.

4-Amino-6-oxo-8,8-dimethyl-6,7,8,9-tetrahydropyrimido[4,5-b][1,4]benzodioxane (IVa). Compound Ia (1.45 g, 10 mmole) was added to a suspension of sodium hydride (0.48 g, 20 mmole) in DMF (20 ml). The mixture was stirred for 10 min, bromoketone IIb (2.19 g, 10 mmole) added, stirring continued for 20 min at 20°C and then 16 h at 85-90°C, cooled, and poured into water (80 ml). The precipitate was filtered off, washed with water, and dried.

IVb was prepared similarly from Ib and IIb with the difference that the reaction mixture was heated for 12 h, the DMF distilled off *in vacuo* and the residue suspended in water, neutralized with acetic acid, filtered, washed with water, and dried.

Compounds IVa, b are colorless, high melting, crystalline substances, insoluble in water, but soluble with heating in most organic solvents.

4-Morpholino-6-oxo-6,7,8,9-tetrahydro-10H-pyrimido[5,4-b][1,4]benzoxazine (Va). A suspension of compound IIIa (0.5 g, 2.11 mmole) and morpholine (0.55 g, 6.33 mmole) in a mixture of n-butanol (20 ml) and DMF (3 ml) was refluxed for 4.5 h, evaporated to dryness, the residue diluted with water (10 ml), and the precipitate filtered, washed with water and dried.

Compound Vb-d were prepared similarly with the difference that the reaction of IIIa with piperidine and N-methylpiperazine and of compound IIIb with benzylamine was carried out in n-butanol (4 h refluxing). Compound Vc was separated after distillation of solvent by extraction with chloroform.

4-Methoxy-6-oxo-6,7,8,9-tetrahydro-10H-pyrimido[5,4-b][1,4]benzoxazine (Ve). Compound IIIa (0.6 g, 2.5 mmole) was added to a solution of sodium methylate prepared from sodium (0.12 g, 0.005 g atom) in anhydrous methanol (20 ml). The mixture was heated for 6 h in an autoclave at 105-110°C, evaporated to dryness, water (20 ml) added to the residue, and the product neutralized with acetic acid, extracted with chloroform (3 × 50 ml), and the extract dried over sodium sulfate and evaporated.

Compound Vf was prepared similarly from IIIb with the difference that the reaction was carried in anhydrous ethanol (5 h reflux).

2-methyl-4-thio-6-oxo-6,7,8,9-tetrahydro-3H,10H-pyrimido[5,4-b][1,4]benzoxazine (Vg). A mixture of compound IIIb (1.28 g, 5.4 mmole) and thiourea (1.28 g, 1.68 mmole) in ethanol (50 ml) was refluxed for 14 h, cooled, and the precipitate filtered and dried.

The biological investigation was carried out by N. A. Ryabokon' (preparation of the dihydrofolate reductase) and by L. I. Shcherbakova (the tuberculous bacilli).

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