(62.3%) of Vb, with mp 251-253°C, and 0.16 g (29.6%) of VIb with mp 221-222°C. IR spectrum: 1670 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 224 (4.38), 226 (4.37), and 340 nm (4.47). Molecular weight 274. According to the data in [3], this compound had mp 219-220°C.

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DERIVATIVES OF CONDENSED PYRIMIDINE, PYRAZINE, AND PYRIDINE SYSTEMS. 39.* SYNTHESIS AND STRUCTURES OF 9-OXO-5H-6,7,8,9-TETRAHYDRO-PYRIMIDO[4,5-b][1,4]THIAZINES

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UDC 547.859'869.2.07

A number of 9-oxo-5H-6,7,8,9-tetrahydropyrimido[4,5-b][1,4]benzothiazines were synthesized by the reaction of 5-amino-6-mercaptopyrimidines with 2-halo-substituted cyclohexane-1,3-diones. It is demonstrated by means of the IR and UV spectra that these compounds exist primarily in the enamino ketone form.

Substances that display both antibacterial and pharmacological activity are found among pyrimido[5,4-b][1,4]benzothiazines and the isomeric pyrimido[4,5-b][1,4]benzothiazines [2-4]. No information regarding the synthesis and biological properties of pyrimidobenzothiazines that contain a partially or completely saturated benzene ring is available; in particular, no data on 6,7,8,9-tetrahydropyrimido[4,5-b][1,4]benzothiazines (I) are available.

In a continuation of our research [5] on the synthesis of pyrimido[4,5-b][1,4]thiazine derivatives we have shown that the reaction of 5-amino-6-mercaptopyrimidines (II) with 2-halo-substituted cyclohexane-1,3-diones (III) is a convenient method for the preparation of I [6]. The inertness of halogen in the 2 position of cyclohexane-1,3-diones, which are capable of enolization, is well known [7, 8]. In addition, it has been observed that the reaction of pyrimidine derivatives IIa-d, which contain substituents such as Cl, OCH_3, and $N(CH_3)_2$ in the 4 position, with 2-bromodimedone and 2-bromodihydroresorcinol proceeds under mild conditions and leads to the production of Ia-f in satisfactory yields (Table 1). We were unable to isolate any intermediates in this case. However, intermediate sulfide IV was obtained in the reaction of pyrimidine IIe with 2-bromodimedone under the conditions of the synthesis of Ia-f.

*See [1] for communication 38.

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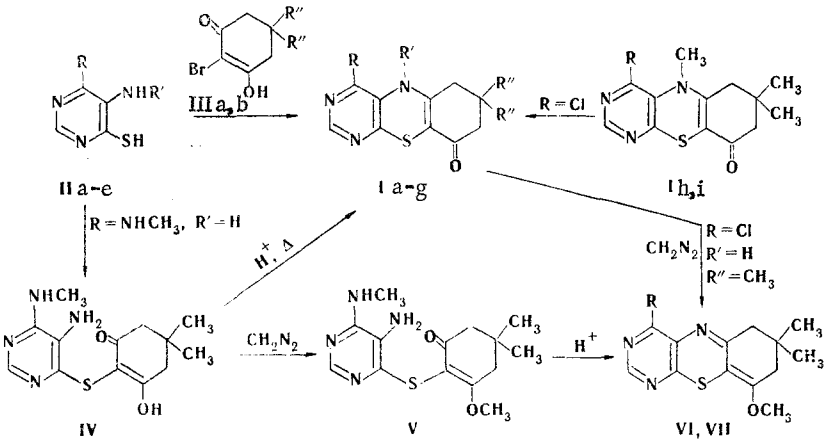
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 755-760, June, 1980. Original article submitted March 15, 1979; revision submitted January 22, 1980.

0009-3122/80/1606-0580$07.50

TABLE 1. 9-Oxo-6,7,8,9-tetrahydropyrimidino[4,5-b][1,4]benzothiazines (Ia-i)

Compound	R	R′	R″	mp, °C*	Found, %					Empirical formula	Calc., %					Yield, %
					C	H	Cl	N	S		C	H	Cl	N	S	
Ia	OCH_3	H	CH_3	240—242	56,2	5,2	—	15,1	11,7	$C_{13}H_{14}N_3O_2S$	56,5	5,1	—	15,2	11,6	67
Ib	Cl	H	H	251—252	47,2	3,3	14,2	16,5	—	$C_{10}H_8ClN_3OS$	47,3	3,2	14,0	16,6	—	69
Ic	Cl	CH_3	H	198—200	49,3	3,6	—	16,0	—	$C_{11}H_{10}ClN_3OS$	49,3	3,8	—	15,8	—	62
Id	Cl	H	CH_3	228—229	50,9	4,2	11,9	14,8	11,6	$C_{12}H_{12}ClN_3OS$	51,1	4,3	11,6	14,9	11,4	80
Ie	Cl	CH_3	CH_3	148—150	52,5	4,7	11,9	14,2	11,1	$C_{13}H_{14}ClN_3OS$	52,8	4,8	12,0	14,2	10,8	59
If	$N(CH_3)_2$	H	CH_3	224—226	57,7	6,2	—	19,5	—	$C_{14}H_{18}N_4OS$	57,9	6,2	—	19,3	—	57
Ig	$NHCH_3$	H	CH_3	295	56,2	6,0	—	19,8	11,9	$C_{13}H_{16}N_4OS$	56,5	5,9	—	20,3	11,6	85
Ih	OCH_3	CH_3	CH_3	168—169	58,0	5,9	—	—	—	$C_{14}H_{17}N_3O_2S$	57,7	5,9	—	—	—	90
Ii	$N(CH_3)_2$	CH_3	CH_3	204	59,4	6,2	—	18,7	—	$C_{15}H_{20}N_4OS$	59,2	6,6	—	18,4	—	87

*The compounds were recrystallized: Ia, c-g from ethanol, Ib from aqueous DMF, Ih from methanol, and Ii from aqueous ethanol.



II a $R=OCH_3$, $R'=H$; b $R=Cl$, $R'=H$; c $R=Cl$, $R'=CH_3$; d $R=N(CH_3)_2$, $R'=H$; e $R=NHCH_3$, $R'=H$; III a $R''=H$; b $R''=CH_3$; I a $R=OCH_3$, $R'=H$, $R''=CH_3$; b $R=Cl$, $R'=R''=H$; c $R=Cl$, $R'=CH_3$, $R''=H$; d $R=Cl$, $R'=H$, $R''=CH_3$; e $R=Cl$, $R'=R''=CH_3$; f $R=N(CH_3)_2$, $R'=H$, $R''=CH_3$; g $R=NHCH_3$, $R'=H$, $R''=CH_3$; h $R=OCH_3$, i $R=N(CH_3)_2$; VI $R=NHCH_3$; VII $R=Cl$

Compound IV is unstable and readily undergoes cyclization to 4-methylamino-9-oxo-6,7,8,9-tetrahydropyrimido[4,5-b][1,4]benzothiazine (Ig) when it is heated above 100°C or treated with mineral acids. The thermally stable methyl ether V was obtained by treatment of IV with diazomethane. The spectral characteristics of this compound indicate that it has a sulfide structure rather than a cyclic carbinol amine structure. Thus, the ^{13}C spectrum of V contains the signal of the carbon atom of a carbonyl group at 188.1 ppm (the cyclic carbinol amine does not contain a carbonyl group). A signal of a lone proton at 9.9 ppm, which undergoes slow exchange with deuterium under the influence of deuteromethanol, is observed in the PMR spectrum of V. It was shown by the double-resonance method that this proton is attached to the nitrogen atom of the $NHCH_3$ group. This constitutes evidence for the existence of an intramolecular hydrogen bond between the $NHCH_3$ group and the carbonyl group in the carbocyclic part of the V molecule. The same hydrogen bond should also exist in IV, and this leads to an increase in its stability as compared with the analogous compounds that contain substituents such as Cl, OCH_3, or $N(CH_3)_2$ in the 4 position.

Thus, the data obtained indicate that sulfides of the IV type, which subsequently undergo intramolecular cyclization, are formed in the first step of the reaction of 5-amino-6-mercaptopyrimidines with 2-halo-substituted cyclohexane-1,5-diones. Thus 4-methylamino-7,7-dimethyl-9-methoxy-6H-7,8-dihydropyrimido[4,5-b][1,4]benzothiazine, which was isolated in the form of the hydrochloride (VI), was obtained by the action of hydrochloric acid on methyl ether V. In this case the cyclization occurs through reaction of the 5-NH_2 group of the pyrimidine component of sulfide V with the carbonyl group of the carbocyclic part of the molecule. However, the participation of the enol hydroxy group that is present in sulfides of the IV type, which may occur in the formation of Ia-f or in the case of thermal dehydration

TABLE 2. Data from the IR and UV Spectra of 9-Oxotetrahydropyrimidobenzothiazines (Ia, c-f, h, i) and VII

Compound	R	R′	R″	IR spectra, cm^{-1}						UV spectra	
				Crystals			$CHCl_3$				
				ν_{CO}	$\nu_{C=C}$, $\nu_{C=N}$, δ_{NH}	ν_{NH}	ν_{CO}	$\nu_{C=C}$, $\nu_{C=N}$, δ_{NH}	ν_{NH}	λ, nm	ε
Ia	OCH_3	H	CH_3	1621 ms	1586 vs 1540 m	3260 s	1642 m	1605 s 1582 ms 1545 w	3425 s	217 255 293 333 464	16980 16240 7980 9500 2068
Ic	Cl	CH_3	H	1620 s	1578 vs 1500 s – 1525 sh	—	1647 s	1589 s 1503 s 1525 sh		222 247 300 356	14520 7800 7700 5600
Id	Cl	H	CH_3	1633 m	1589 vs, br 1545 m 1520 m	3255 s	1648 m	1618 s 1545 m 1523 w	3412 m	218 249 290 368 440 br sh	18320 15400 8800 9060 1476
Ie	Cl	CH_3	CH_3	1650 s	1594 s 1524 m 1510 ms	—	1650	1597 s 1510 s	—	221 248 358	16980 8840 7020
If	$N(CH_3)_2$	H	CH_3	1620 m	1570 vs br	3230	1640 m	1603 s 1564 m	3395 m 3270 w br	224 261 298 348	18320 10300 10900 11360
Ih	OCH_3	CH_3	CH_3	1635 s	1590 s 1552 s 1533 s	—	1635 s	1583 s 1543 s 1523 s	—	224 255 323 425	21180 12780 10200 1995
Ii	$N(CH_3)_2$	CH_3	CH_3	1622 s	1570 s 1540 s	—	1637 m br	1584 m 1543 vs	—	252 290 sh 334 421	15240 8600 1400 2526
VII	Cl	—	CH_3	—	1595 s 1566 s 1522 w 1507 w	—	—	1595 s 1575 1500 1513 m	—	223 254—260 275 sh 352 420 br sh	17960 15180—14800 9600 9300 3250

of IV, is not excluded. Thus, it was observed that pyrimidobenzothiazine Ia is formed in the reaction of IIa not only with bromodimedone but also with its methyl ether (in 60% yield), and this constitutes evidence for the participation of the OCH_3 group in the intramolecular cyclization.

The 9-oxo-6,7,8,9-tetrahydropyrimido[4,5-b][1,4]benzothiazines (Ia-g) are crystalline, high-melting, orange substances that are readily soluble in aqueous alkalis. These compounds are weak acids (pK_a of Ia in 50% alcohol = 11.27, and pK_a of Id in 50% alcohol = 9.38). On the other hand, VI, which differs from Ia-g with respect to the position of the double bonds, displays basic properties and exists in the form of a stable hydrochloride. The halogen atom in the 4 position of these compounds is readily replaced under the influence of nucleophilic agents. Thus, the corresponding Ih and Ii derivatives were obtained by treatment of Ie with sodium methoxide or dimethylamine. 2,4-Dinitrophenylhydrazones VIII and IX are formed in the reaction of Ic and Id with 2,4-dinitrophenylhydrazine, while the reaction of Id with diazomethane leads to methyl ester VII in low yield.

An examination of the IR spectra of Ia, d, f and the model compounds 5-N-methyl derivatives Ic, e, h, i and 9-O-methyl derivative VII indicates that Ia, d, f exist primarily in the enamino ketone form. On the basis of the data obtained (Table 2) and the literature data for enamino ketones [9, 10] the absorption bands at 1640-1650 and 1545-1615 cm^{-1} (in $CHCl_3$) in the spectra of Ia, d, f were assigned to the stretching vibrations of the carbonyl group and the C=Cand C=N bonds, respectively.

An effect of steric interaction between the methyl group and the substituent in the 4 position of the molecule is observed in the UV spectra of 5-N-methyl derivatives Ic, e, h, i. The impossibility of the placement of these substituents in a single plane because of overlapping of the van der Waals radii leads to disruption of the conjugation of the free electron pair of the nitrogen atom in the 5 position of the molecule with the π-electron of the pyrimidine ring and the 5a–9a double bond. This leads to a decrease in the intensity and, in individual cases, to the absence of some of the absorption maxima in the spectra of the 5-N-methyl derivatives as compared with the corresponding compounds that have a hydrogen atom in the 5 position (Table 2).

EXPERIMENTAL

The PMR spectra of the compounds were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard. The IR spectra of mineral oil pastes or solutions of the compounds in chloroform were recorded with a Perkin-Elmer-457 Spectrometer. The UV spectra of the compounds in 95% alcohol were obtained with an EPS-3 recording spectrophotometer.

9-Oxo-6,7,8,9-tetrahydropyrimido[4,5-b][1,4]benzothiazines (Ia-g). A solution of 6.4 mmole of bromo ketone IIIa, b in 20 ml of alcohol was added to a solution of 6.5 mmole of the corresponding 5-amino-6-mercaptopyrimidine IIa-e in 20 ml of alcohol containing 0.6 g of KOH, and the mixture was stirred for 6 h. The solvent was then removed by vacuum distillation, and the residue was treated with water. The aqueous mixture was acidified with hydrochloric acid, and the precipitate was removed by filtration and washed with water to give Ia-g (Table 1).

2-(4-Methylamino-5-amino-6-pyrimidinylmercapto)-3-hydroxy-5,5-dimethylcyclohexen-2-one (IV). A solution of 1.3 g (6.8 mmole) of bromodimedone in 10 ml of methanol was added to a solution of 6.4 mmole of mercaptopyrimidine Id in 20 ml of methanol containing 0.8 g (14.2 mmole) of KOH. After 12 h, the solvent was removed by vacuum distillation, and the residue was dissolved in water. The solution was filtered, and the filtrate was acidified with acetic acid to give 1.7 g (90%) of IV as a light-cream-colored substance with mp 294°C (after reprecipitation from solution in aqueous KOH solution by the addition of acetic acid). PMR spectrum (in d_6-DMSO): 1.07 s, 6H (CH_3 group attached to the cyclohexene ring), 2.15 (s, 4H, cyclohexene ring CH_2 groups), 2.96 (s, 3H, $NHCH_3$), and 7.73 ppm (s, 1H, pyrimidine proton). Found %: C 53.0; H 6.4. $C_{13}H_{15}N_4O_2S$. Calculated %: C 53.0; H 6.2.

2-(4-Methylamino-5-amino-6-pyrimidinylmercapto)-3-methoxy-5,5-dimethylcyclohexen-2-one (V). A solution of CH_2N_2, obtained from 6.3 g of nitrosomethylurea in 50 ml of dioxane, was added to a solution of 1 g (3.4 mmole) of IV in 250 ml of DMF, and the reaction mixture was allowed to stand at 20°C for 12 h. The solvent was removed by vacuum distillation almost to dryness, and the solid material was separated and crystallized from methanol to give 0.6 g (46%) of V with mp 234-235°C. IR spectrum of the crystals: 3390, 3520, 3200, and 1660 cm^{-1}

(NH, NH_2). PMR spectrum (in $CDCl_3$): 0.93 (s, 6H, CH_3 group attached to the cyclohexene ring), 2.21 (s, 4H, cyclohexene ring CH_2 groups), and 9.9 ppm (s, 1H, $NHCH_3$ proton). Found %: C 54.5; H 6.7; N 18.0. $C_{14}H_{20}N_4O_2S$. Calculated %: C 54.5; H 6.5; N 18.2.

4-Methylamino-7,7-dimethyl-9-methoxy-6H-7,8-dihydropyrimido[4,5-b][1,4]benzothiazine (VI) Hydrochloride. Two drops of concentrated HCl were added to a solution of 0.2 g of V in 10 ml of methanol. After 3 h, the solvent was removed by vacuum distillation to dryness, and the residue was recrystallized from methanol to give 0.18 g (85%) of VI as a red crystalline substance with mp 253°C. PMR spectrum (in $CDCl_3$): 1.03 (s, 6H, CH_3 group attached to the cyclohexene ring), 2.19 (s, 4H, cyclohexane ring CH_2 groups), 3.05 (s, 3H, CH_3, $NHCH_3$), 3.62 (s, 3H, OCH_3), and 7.8 ppm (s, 1H, pyrimidine proton). Found %: C 51.4; H 5.9; N 9.8. $C_{14}H_{19}ClN_4OS$. Calculated %: C 51.4; H 5.9; N 9.8.

4-Chloro-7,7-dimethyl-9-methoxy-6H-7,8-dihydropyrimido[4,5-b][1,4]benzothiazine (VII). A solution of CH_2N_2 in dioxane, obtained from 5 g of nitrosomethylurea, was added to a solution of 0.7 g of Ib in dioxane. After 12 h, the solvent was removed by vacuum distillation, and the residue was dissolved in ether. The ether solution was passed through a column filled with Al_2O_3, and the ether eluates were evaporated to give 0.16 g of VII as a yellow crystalline substance with mp 168-170°C (from cyclohexane). Found %: C 52.6; H 4.3; Cl 12.2. $C_{13}H_{14}ClN_3OS$. Calculated %: C 52.8; H 4.8; Cl 12.0.

4-Chloro-7,7-dimethyl-9-oxo-6,7,8,9-tetrahydropyrimido[4,5-b][1,4]benzothiazine Dinitrophenylhydrazone (VIII). A solution of 0.4 g (2 mmole) of 2,4-dinitrophenylhydrazine in 20 ml of ethanol containing a few drops of concentrated HCl was added to a solution of 0.5 g (1.8 mmole) of Ib in 20 ml of ethanol. After 24 h, the resulting precipitate was separated to give 0.4 g (49%) of hydrazone VIII as a dark-red crystalline substance with mp 258-259°C (from DMF). Found %: Cl 7.1; N 21.1; S 7.0. $C_{18}H_{16}ClN_7O_4S$. Calculated %: Cl 7.7; N 21.1; S 6.9.

4-Chloro-5,7,7,-trimethyl-9-oxo-6,7,8,9-tetrahydropyrimido[4,5-b][1,4]benzothiazine 2,4-Dinitrophenylhydrazone (IX). This compound was obtained in 50% yield under the conditions in the preceding experiment by treatment of Id with 2,4-dinitrophenylhydrazine. Workup gave a dark-red substance with mp 226-228°C (from ethanol). Found %: Cl 7.4; N 20.6; S 6.7. $C_{19}H_{18}ClN_7O_4S$. Calculated %: Cl 7.4; N 20.5; S 6.7.

4-Methoxy-5,7,7-trimethyl-9-oxo-6,7,8,9-tetrahydropyrimido[4,5-b][1,4]benzothiazine (Ih). A solution of sodium methoxide in methanol, obtained from 0.1 g of sodium (a twofold excess), was added to a solution of 0.5 g of Id in 20 ml of methanol, and the reaction mixture was stirred at room temperature for 12 h. The solvent was removed by distillation, the residue was treated with water, and the solid was removed by filtration (Table 1).

4-Dimethylamino-5,7,7-trimethyl-9-oxo-6,7,8,9-tetrahydropyrimido[4,5-b][1,4]benzothiazine (Ii). A 3-ml sample of a 33% aqueous solution of dimethylamine was added at 50°C to a solution of 1 g of Id in alcohol, after which the mixture was maintained at this temperature for 2 h and allowed to stand at room temperature for another 6 h. The solvent was removed by distillation, the residue was treated with water, and the solid material was removed by filtration (Table 1).

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