5-H_e), 2.00 (s, $CH_3C(=O)-$), 3.24 (m, 6-H_a), 3.62 (m, 6-H_e), 4.20 (q, CH_3CH_2O), 4.30 (s, 2H), and 4.48 ppm (q, 3H). Found %: C 53.8; H 7.6; N 5.7. $C_{11}H_{19}NO_5$. Calculated %: C 53.8; H 7.8; N 5.7.

1-Ethoxycarbonyl-3,4-diacetoxy-4-methylpiperidine (IV). A 1.08-g sample of acetyl chloride and 1.41 g of acetic anhydride were added to a solution of 1.4 g (6.9 mmole) of IId in 50 ml of benzene, and the mixture was refluxed for 4 h. It was then cooled to room temperature, and the solvent was removed by distillation. The residue was vacuum distilled to give 1.64 g (82%) of IV with bp 112-125°C (0.4 mm), n_D^{20} 1.4632, and R_f 0.68. IR spectrum (thin layer): 1740 (ester C=O) and 1710 cm^{-1} (amide C=O). Found %: C 54.2; H 7.5; N 4.9. $C_{13}H_{21}NO_6$. Calculated %: C 54.3; H 7.4; N 4.9.

LITERATURE CITED

1. J. Strogl, M. Janda, J. Stibor, and J. Kucera, Collect. Czech. Chem. Commun., 38, 455 (1973).
2. L. G. Efremenko and A. M. Korolev, Izv. Akad. Nauk SSSR, No. 1, 147 (1970).
3. K. B. Wiberg and K. A. Saegebarth, J. Am. Chem. Soc., 79, 2822 (1957).
4. J. E. Coleman, C. Ricciuti, and D. Swern, J. Am. Chem. Soc., 78, 5344 (1956).
5. V. B. Mochalin and A. N. Kornilov, Zh. Obshch. Khim., 44, 2334 (1974).
6. K. B. Sharpless and D. R. William, Tetrahedron Lett., No. 35, 3045 (1975).
7. O. Meth-Cohn and H. Suschitzky, Chem. Ind., No. 5, 433 (1969).
8. L. S. Stanishevskii, I. G. Tishchenko, A. S. Puzikov, A. M. Zvonkov, and A. A. Zil'manovich, Zh. Org. Khim., 11, 643 (1975).
9. P. L. Kuhn, J. Am. Chem. Soc., 74, 2492 (1952).
10. A. R. U. Cole and G. T. A. Muller, J. Chem. Soc., No. 3, 1224 (1959).

INVESTIGATION OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES. 38.* REACTIONS OF 2-MERCAPTO-3-UREIDOPYRIDINES WITH HALO β-DIKETONES

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The reaction of 2-mercapto-3-ureido-6-chloropyridine with chlorodibenzoylmethane in the presence of alkali leads to 2-(benzoylmethylthio)-3-benzamido-6-chloropyridine, whereas the reaction in the absence of alkali leads to 2-chloro-6-phenyl-7-benzoylpyrido[2,3-b][1,4]thiazine. Under similar conditions 2-(diacetylmethylthio)-3-ureido-6-chloropyridine, 2-(acetylmethylthio)-3-ureido-6-chloropyridine, and 2-chloro-6-methyl-7-acetylpyrido[2,3-b][1,4]thiazine were obtained from 2-mercapto-3-ureido-6-chloropyridine and chloroacetylacetone. Treatment of 2-(diacetylmethylthio)-3-ureido-6-chloropyridine with alcoholic alkali leads to 2-(acetylmethylthio)-3-ureido-6-chloropyridine. 2-Chloro-6-phenyl-7-acetylpyrido-[2,3-b][1,4]thiazine and 2-(benzoylmethylthio)-3-ureido-6-chloropyridine are formed in the reaction of 2-mercapto-3-ureido-6-chloropyridine with chlorobenzoylacetone in the presence of an equimolar amount of alkali, while 2-(benzoylmethylthio)-3-acetamido-6-chloropyridine is formed when excess alkali is used.

*See [1] for communication 37.

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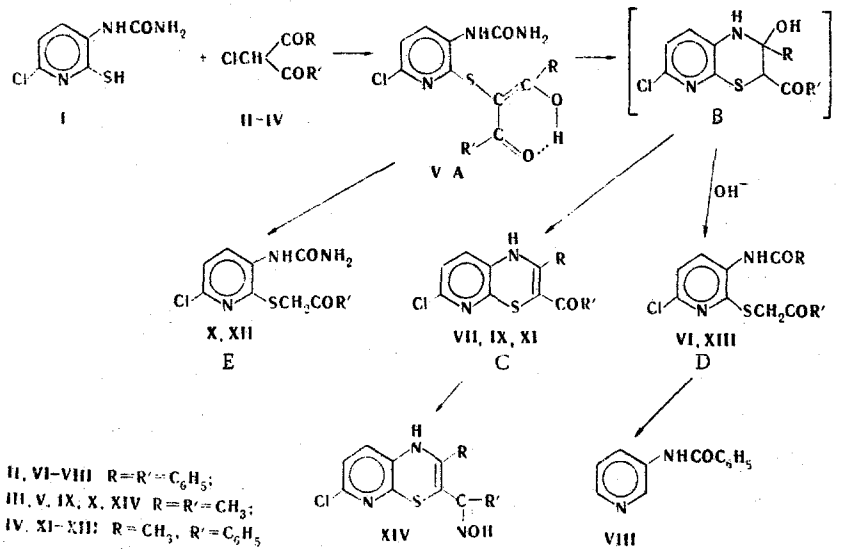
It has been observed that pyrimido[4,5-b][1,4]thiazines that contain carbonyl groups in the thiazine ring have antitumorigenic activity and inhibit folic exchange enzymes [2, 3]. In a continuation of our earlier research [2, 3] we undertook the synthesis of analogous derivatives in the pyrido[2,3-b][1,4]thiazine series. For this, we investigated the reaction of 2-mercapto-3-ureido-6-chloropyridine (I) with halo β-diketones, viz., chlorodibenzoylmethane (II), chloroacetylacetone (III), and chlorobenzoylacetone (IV). The reaction of I with chloro ketone II in the presence of equimolar amounts of basic agents (KOH and K_2CO_3) or in pyridine leads to 2-(benzoylmethylthio)-3-benzamido-6-chloropyridine (VI). 6-Phenyl-7-benzoylpyridothiazine (VII) was obtained from the same starting compounds when alkali was absent.

The structure of VI was confirmed by the presence in the IR spectrum of NH (3260 cm^{-1}), amide CO (1650 cm^{-1}), and ketone CO (1690 cm^{-1}) absorption bands and by the signal of a CH_2 group (4.69 ppm) and signals of aromatic protons in the PMR spectrum. In addition, its structure was proved by conversion to the known 3-benzamidopyridine (VIII). According to the data from the IR and PMR spectra, VII has the 5-H structure (from the presence of an NH band at 3450 cm^{-1} and the absence of a signal from a proton attached to C_7).



An S-alkylation product (V) and a pyridothiazine (IX) were isolated in the reaction of pyridine I with chloroacetylacetone (III) in the presence of alkali. An oxime (XIV) was obtained from IX. Compound V exists in the enol form, which is stabilized by an intramolecular hydrogen bond, as confirmed by the presence in the PMR spectrum of signals of two equivalent CH_3 groups (2.2 ppm) and the absence of a methylidyne proton. The IR spectrum of IX contains an NH bond (3290 cm^{-1}), whereas a 7-H signal is not observed in the PMR spectrum, and this constitutes evidence for a 5-H rather than a 7-H structure.

The reaction of pyridine I with chlorobenzoylacetone IV in the presence of an equimolar amount of NaOH gives pyridothiazine XI and XII. Compound XIII is isolated when excess alkali is used. Only XI is obtained when pyridine I is heated with chloro ketone IV in the absence of basic agents.

The reaction of pyridine I and chloro ketone III in the presence of excess alkali gives X. The latter was isolated by treatment of diketone V with alcoholic alkali and is the product of acid cleavage of the β-diketone fragment of the V molecule.

On the basis of the data obtained it may be assumed that several competitive reactions may occur under the indicated conditions. One of them is acid cleavage of the initially formed S-acetylthio derivative A to E as in the case of derivatives of β-dicarbonyl compounds [4, 5]. In addition to this, A undergoes cyclization to hydroxy amino compound B, which is accompanied by splitting out of a carbamide residue. Compound B is dehydrated to C in a medium that is close to neutral or in an acidic medium, whereas it undergoes destructive changes with cleavage of the C_6—C_7 bond under the influence of basic agents, as a result of which compounds with open structure D are formed. Similar processes have been noted in the reaction of I with chlorooxalacetic ester [6].

TABLE 1. Characteristics of the Compounds Obtained

Compound	mp, deg C[a]	IR spectrum, cm^{-1}		UV spectrum, λ_{max}, nm (log ε)	Found, %					Empirical formula	Calc., %					Yield, %
		NH	Amide CO, ketone CO		C	H	Cl	N	S		C	H	Cl	N	S	
V	192–193	3290	1670	260 (4,14)	43,9	3,7	11,5	14,1	10,9	$C_{11}H_{12}ClN_3O_2S$	43,8	4,0	11,7	13,9	10,6	40
VI	189–190	3260	1650, 1690	—	62,6	3,7	9,1	7,2	8,6	$C_{20}H_{15}ClN_2O_2S$	62,7	3,9	9,2	7,3	8,4	80
VII	178–180	3210	—	264 (3,81)	66,1	3,8	9,5	8,0	8,9	$C_{20}H_{13}ClN_2O_2S$	65,8	3,6	9,7	7,7	8,7	67
VIII	116–117	3200	1680	—	72,7	4,9	—	13,9	—	$C_{12}H_{10}N_2O$	72,8	5,1	—	14,1	—	90
IX	204–205	3290	—	290 (3,8), 367 (3,8)	49,8	3,8	14,6	11,6	13,3	$C_{10}H_{10}ClN_2OS$	49,9	3,7	14,8	11,6	13,3	—
X	179–180	3340	1660, 1710	259 (4,005), 309 (3,84)	42,0	4,0	13,5	16,3	12,3	$C_9H_{10}ClN_3O_2S$	41,8	3,9	13,6	16,2	12,3	50
XI	245–247	3260	—	—	59,2	3,7	11,6	9,3	10,7	$C_{15}H_{11}ClN_2OS$	59,5	3,6	11,8	9,2	10,6	54
XII	213–215[b]	3350	1660, 1720	—	52,4	3,9	10,7	12,8	10,2	$C_{14}H_{12}ClN_3O_2S$	52,3	3,7	11,0	13,0	10,0	42
XIII	148–150[c]	3270	1670, 1700	253 (4,33), 302 (3,81)	56,2	4,1	11,0	10,0	8,7	$C_{15}H_{13}ClN_2OS$	56,2	4,3	10,9	10,3	8,6	10
XIV	180–181	3270			46,9	3,7	13,9	—	12,8	$C_{10}H_{10}ClN_3OS$	46,9	3,9	13,8	—	12,5	80

[a]The compounds were crystallized: V-VII and IX-XIII from ethanol, VIII from water, and XIV from benzene. [b]According to [7], this compound had mp 225-226°C [7]. [c]According to [7], this compound had mp 148-149°C.

EXPERIMENTAL

The IR spectra were recorded with a double-beam UR-10 spectrometer and with a Perkin-Elmer spectrometer at 400-4000 nm. The PMR spectra were obtained with a JNM-411-11 spectrometer with hexamethyldisiloxane as the internal standard. Information on the synthesized compounds and their spectral chracteristics are presented in Table 1.

2-(Benzoylmethylthio)-3-benzamido-6-chloropyridine (VI). A) A solution of 0.64 g (2.5 mmole) of II in 10 ml of ethanol was added at −10°C to a solution of 0.5 g (2.5 mmole) of I in 20 ml of ethanol containing 0.14 g (2.5 mmole) of KOH, and the mixture was stirred at −5°C for 1 h and at 20°C for 2 h. The precipitate was removed by filtration and dried to give 0.35 g of VI. The mother liquor was evaporated to dryness in vacuo, and the residue was triturated with ether. The solid material was removed by filtration to give another 0.3 g of VI.

B) A solution of 0.64 g (2.5 mmole) of II in 5 ml of pyridine was added to a solution of 0.5 g (2.5 mmole) of I in 5 ml of pyridine at 0°C in the course of an hour. After stirring at 0°C for 0.5 h, the mixture was poured into water, and the precipitate was removed by filtration, washed with water, and dried to give 0.75 g of VI.

C) A suspension of 0.5 g (2.5 mmole) of I in 40 ml of acetone containing 0.17 g (1.2 mmole) of K_2CO_3 was added to a solution of 0.64 g (2.5 mmole) of II in 10 ml of acetone at 0°C, and the mixture was stirred at 0°C for 1 h. The precipitate was removed by filtration and washed with acetone. The acetone mother liquor was evaporated to dryness in vacuo, and the residue was extracted with ethyl acetate. The ethyl acetate was removed by vacuum evaporation, and the solid residue was triturated with petroleum ether, and the solid material was removed by filtration to give 0.9 g of VI, which was crystallized from ethanol.

2-Chloro-6-phenyl-7-benzoylpyrido[2,3-b][1,4]thiazine (VII). A mixture of 0.5 g (2.5 mmole) of I and 0.64 g (2.5 mmole) of II was refluxed in 100 ml of acetone for 3 h, after which the acetone was removed in vacuo, and the dry residue was extracted with ethyl acetate. The ethyl acetate was removed in vacuo, and the dry residue was triturated with ether to give 0.6 g of VII, which was crystallized from ethanol.

3-Benzamidopyridine (VIII). A mixture of 0.5 g (1.3 mmole) of VII and 5 g of a Raney nickel catalyst in 40 ml of ethanol was refluxed for 2 h, after which the hot mixture was filtered, and the ethanol was removed from the filtrate by vacuum distillation. The residue was triturated with water, and the solid material was removed by filtration and washed with ether to give 0.23 g of VIII, which was crystallized from water.

2-Chloro-6-methyl-7-acetylpyrido[2,3-b][1,4]thiazine (IX) and 2-(Diacetylmethylthio)-3-ureido-6-chloropyridine (V). A solution of 0.335 g (2.5 mmole) of III in 5 ml of ethanol was added at 0°C in the course of 15 min to a solution of 0.5 g (2.5 mmole) of I in 20 ml of ethanol containing 0.14 g (2.5 mmole) of KOH, and the mixture was stirred at 0°C for 30 min and at 20°C for 2 h. The resulting precipitate was removed by filtration to give 0.3 g of V. The ethanol mother liquor that remained after separation of V was evaporated to dryness in vacuo, and the residue was triturated with water. The solid material was removed by filtration and dried to give 0.5 g of IX, which was crystallized from ethanol.

2-(Acetylmethylthio)-3-ureido-6-chloropyridine (X) and V. A) A solution of 0.33 g (2.5 mmole) of III in 10 ml of alcohol was added in the course of 15 min to a solution of 0.5 g (2.5 mmole) of I in 20 ml of ethanol containing 0.28 g (5 mmole) of KOH, and the mixture was stirred for 4 h. The ethanol was then removed by vacuum distillation, and the residue was triturated with water. The solid material was removed by filtration and dried to give 0.32 g of X. The aqueous alkaline mother liquor obtained from the separation of X was acidified with CH_3COOH, and the precipitate was removed by filtration to give 0.15 g of V.

B) A mixture of 0.8 g (2.6 mmole) of V and 50 ml of ethanol containing 0.145 g (2.6 mmole) of KOH was refluxed for 1.5 h, after which the ethanol was removed by vacuum distillation, and the dry residue was triturated with water. The solid material was removed by filtration to give 0.45 g of X, which was crystallized from ethanol.

2-Chloro-6-methyl-7-benzoylpyrido[2,3-b][1,4]thiazine (XI). A mixture of 0.5 g (2.5 mmole) of I and 0.48 g (2.5 mmole) of IV in 100 ml of acetone was refluxed for 2 h, after which the acetone was removed in vacuo, and the dry residue was triturated with water and extracted with ethyl acetate. The ethyl acetate was removed by vacuum distillation, and the residue was triturated with ether. The solid material was removed by filtration to give 0.4 g of XI, which was crystallized from ethanol.

2-(Benzoylmethylthio)-3-ureido-6-chloropyridine (XII). A solution of 0.96 g (5 mmole) of IV in 10 ml of ethanol was added to 0°C to a solution of 1 g (5 mmole) of I in 20 ml of ethanol containing 0.28 g (5 mmole) of KOH, and the mixture was stirred for 3 h. The substance that was liberated was removed by filtration, washed with alcohol and water, and dried to give 0.3 g of XI. The alcohol mother liquor after separation of XI was evaporated in vacuo, and the dry solid residue was triturated with acetone. The solid material was removed by filtration and dried to give 0.3 g of XII. The acetone mother liquor from the separation of XII was evaporated in vacuo to give an additional 0.45 g of XI.

2-(Benzoylmethylthio)-3-acetamido-6-chloropyridine (XIII). A solution of 0.96 g (5 mmole) of IV in 10 ml of ethanol was added at 0°C to a solution of 1 g (5 mmole) of I in 20 ml of ethanol containing 0.56 g (10 mmole) of KOH, and the mixture was stirred at the same temperature for 2 h. The precipitate was removed by filtration and washed with alcohol and water to give 0.2 g of XIII. The ethanol mother liquor from the separation of XIII was evaporated in vacuo, and the residue was triturated with a mixture of ether and alcohol. The solid material was removed by filtration to give 0.8 g of XII, which was crystallized from ethanol.

2-Chloro-6-methyl-7-acetylpyrido[2,3-b][1,4]thiazine (XIV). A mixture of 0.5 g (2.5 mmole) of IX and 0.15 g (2.5 mmole) of hydroxylamine in 5 ml of pyridine and 20 ml of ethanol was refluxed for 2 h, after which the ethanol was removed by vacuum distillation, and the residue was poured into water. The solid material was removed by filtration and dried to give 0.42 g of XIV, which was crystallized from ethanol.

LITERATURE CITED

1. L. G. Levkovskaya, I. E. Mamaeva, O. S. Anisimova, and T. S. Safonova, Khim. Geterotsikl. Soedin., No. 2, 250 (1979).
2. T. S. Safonova, M. P. Nemeryuk, V. A. Chernov, K. A. Andreeva, A. S. Sokolova, I. A. Ryabokon', A. F. Keremov, and T. P. Lapshina, in: Methods for the Synthesis and Search for Antitumorigenic Preparations [in Russian], Riga (1970), p. 91.
3. N. A. Ryabokon', N. I. Andreeva, M. P. Nemeryuk, A. F. Keremov, V. A. Chernov, and T. S. Safonova, Khim.-Farm. Zh., No. 4, 15 (1975).
4. J. Barnikow, H. Kunzer, and D. Richter, Ann., 49, 695 (1966).
5. T. S. Safonova and I. E. Mamaeva, Khim. Geterotsikl. Soedin., No. 1, 120 (1973).
6. T. S. Safonova and L. G. Levkovskaya, Khim. Geterotsikl. Soedin., No. 1, 78 (1971).
7. L. G. Levkovskaya, Master's Dissertation, Moscow (1968).