INVESTIGATION OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLIC COMPOUNDS

XXI.* PYRAZINO[2,3-b][1,4]THIAZIN-6-ONE DERIVATIVES

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The halogenation of 2,3-dimethylpyrazino[2,3-b][1,4]thiazin-6-one with bromine or 1 mole of sulfuryl chloride gives 7-bromo- and 7-chloropyrazino[2,3-b][1,4]thiazin-6-ones, while 2 moles of sulfuryl chloride give 7,7-dichloropyrazino[2,3-b][1,4]thiazin-6-one. A number of 7-amino- and 7,7-diaminopyrazino[2,3-b][1,4]thiazin-6-ones were obtained by the reaction of the appropriate halo derivatives with amines. Some of the pyrazino[2,3-b][1,4]-thiazin-6-one derivatives inhibit the growth of interweavable tumors in animals.

In the development of studies undertaken to search for biologically active substances among the two-ring condensed 1,4-thiazine systems [1, 2], we investigated the halogenation of 2,3-dimethylpyrazino[2,3-b]-[1,4]thiazin-6-one (I). The halogen atoms enter the 7 position during the action of bromine or sulfuryl chloride on I. Depending on the character of the halogenating agent and the process conditions, 2,3-dimethyl-7-halo- (II and III) and 2,3-dimethyl-7,7-dihalopyrazino[2,3-b][1,4]thiazin-6-ones (IV) are formed.

The halogen atoms in the 7 position in II-IV are labile and readily undergo nucleophilic substitution. Thus the corresponding 2,3-dimethyl-7-aminopyrazino[2,3-b][1,4]thiazin-6-ones (V-VII, X, and XI) (Table 1) are obtained by the reaction of II with 2 moles of n-butylamine dipropylamine, benzylamine, piperidine, and morpholine, or of III with morpholine in benzene at 20-22°. In the case of aniline and ethyleneimine, the reaction with III was carried out in the presence of triethylamine. In this case, 7-anilino- and 7-ethyleneiminopyrazino[2,3-b][1,4]thiazin-6-ones (VIII and IX) were obtained. The reaction of II with esters of β-phenyl-α-alanine and p-aminobenzoic acid was used to synthesize 2,3-dimethylpyrazino[2,3-b][1,4]thiazin-6-ones XII and XIII, which contain residues of the esters of the corresponding amino acids in the 7 position. 7,7-Dimorpholino- and 7,7-di(ethyleneimino)pyrazino[2,3-b][1,4]thiazin-6-ones (XIV and XV) were obtained by the reaction of 7,7-dichloropyrazino[2,3-b][1,4]thiazin-6-one (IV) with ethyleneimine and morpholine, respectively. Treatment of II with alcohol at 18-20°C yielded 2,3-dimethyl-7-ethoxypyrazino[2,3-b][1,4]thiazin-6-one (XVI).

The structures of the amines and the position of the halogen in the starting 7-halo derivatives (II and III) were confirmed in the case of 2,3-dimethyl-7-anilinopyrazino[2,3-b][1,4]thiazin-6-one (VIII) by means of PMR spectroscopy. The spectrum of a trifluoroacetic acid solution of this compound contains a signal from two CH_3 groups at 2.04 and 2.15 ppm and a signal from the proton in the 7 position with a chemical shift of 6.19 ppm, which is in agreement with the structure assigned to it and also with structures II and III.

*See [3] for communication XX.

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TABLE 1. 2,3-Dimethyl-7-aminopyrazino[2,3-b][1,4]thiazin-6-ones (V-XIII) and 2,3-Dimethyl-7,7-diaminopyrazino-[2,3-b][1,4]thiazin-6-ones (XIV, XV)

Compound	Amino group	mp, °C[a]	IR spectrum, cm^{-1}		Empirical formula	Compound	Found, %				Calc., %				Yield, %
			CO	NH			C	H	N	S	C	H	N	S	
V	NHC_4H_9	169—170	1680—1690	3200, 3270	$C_{12}H_{18}N_4OS$	V	53,9	6,9	21,3	12,2	54,1	6,8	21,0	12,0	67
VI	$N(C_2H_7)_2$	110—112	1630	3210	$C_{12}H_{22}N_4OS$	VI	57,1	7,4	19,4	11,1	57,1	7,5	19,0	10,9	49
VII	$NHCH_2C_6H_5$	191—192	1675	3200	$C_{15}H_{16}N_4OS$	VII	60,1	5,2	18,5	10,5	60,0	5,4	18,6	10,7	67
VIII	NHC_6H_5	217—218	1705	3200	$C_{14}H_{14}N_4OS$	VIII	59,0	5,2	19,8	11,1	58,7	4,9	19,6	11,2	78
IX	NC_2H_4[b]	171—173	1680—1685	3210	$C_{10}H_{12}N_4OS$	IX	50,5	5,0	23,2	13,7	50,8	5,1	23,7	13,6	40
X	NC_5H_{10}[c]	223—225	1690, 1705	3210, 3400	$C_{13}H_{18}N_4OS$	X	56,1	6,4	19,7	11,6	56,1	6,5	20,1	11,5	78
XI	NC_4H_8O[d]	246—247	1795	3220	$C_{12}H_{16}N_4OS$	XI	51,5	5,6	20,0	11,4	51,4	5,7	20,0	11,4	67
XII	$NHCHCOOC_2H_5$ | CH_3	138—140	1720—1740	3290, 3310	$C_{19}H_{22}N_4OS$	XII	58,7	5,6	14,5	8,4	59,0	5,7	14,5	8,3	72
XIII	$NHC_6H_4COOC_2H_5$-p	222—223	1710	3420	$C_{17}H_{18}N_4O_3S$	XIII	56,8	5,2	15,6	9,2	57,0	5,1	15,6	9,0	80
XIV	NC_2H_4[b]	220—221	1690	3200	$C_{12}H_{15}N_5OS$	XIV	51,7	5,7	25,0	11,9	51,9	5,5	25,3	11,6	60
XV	NC_4H_8O[d]	181—183	1680	3210	$C_{16}H_{23}N_5O_3S$	XV	52,6	6,3	19,2	8,8	52,5	6,4	19,2	8,6	66

[a]Compounds V, VI, XII, and XV were recrystallized from ether; VII was recrystallized from ethanol; VIII from benzene; IX, XIII, and IV from acetonitrile; and X, XI, and XIV from methanol. [b]Ethyleneimine group. [c]Piperidino group. [d]Morpholino group.

According to the IR spectra, V-XVI exist as lactams in the crystalline state. Their IR spectra contain absorption bands of a carbonyl group of the amide type (1670-1690 cm^{-1}) and bands of the valence vibrations of the NH group at 3100-3300 cm^{-1}.

The compounds synthesized in this study and the previously obtained 2-carboxymethylmercapto-3-amino-5,6-dimethylpyrazine [2] were subjected to a primary biological study. The toxicity for mice was determined during a single peroral introduction, and therapeutic experiments were performed on rats with interweavable Jenssen's sarcoma and mice with interweavable AK sarcoma, NK carcinoma, and La leucosis. It was found that all of the compounds studied had relatively low toxicity ($LD_{50} > 0.5$ g/kg), while 2,3-dimethylpyrazino[2,3-b][1,4]thiazin-6-one (I) and 2,3-dimethyl-7-morpholinopyrazino[2,3-b][1,4]thiazin-6-one (XI) in individual experiments on Jenssen's sarcoma and AK sarcoma induced 30-50% inhibition in the growth of the tumors.

EXPERIMENTAL

The IR spectra of mineral oil suspensions were recorded with a UR-10 spectrophotometer, and the PMR spectra were recorded with a JNM-4H-100 spectrometer with tetramethylsilane as the internal standard.

2,3-Dimethyl-7-bromopyrazino[2,3-b][1,4]thiazin-6-one (II). Bromine [0.82 g (0.0051 mole)] was added dropwise at 85-90° to 1.0 g (0.0051 mole) of 2,3-dimethylpyrazino[2,3-b][1,4]thiazin-6-one (I) in 60 ml of anhydrous chlorobenzene. At the end of the addition, the reaction mixture was held at 120° for 1 h and then cooled to 10-15°. The resulting precipitate was removed by filtration, washed with benzene, and dried to give 1.4 g (97%) of crude II. Recrystallization from ethyl acetate gave colorless crystals with mp 180-181°. Found: C 34.3; H 3.2; Br 28.8; N 15.1; S 11.5%. $C_8H_8BrN_3OS$. Calculated: C 35.1; H 2.9; Br 29.1; N 15.3; S 11.7%.

2,3-Dimethyl-7-chloropyrazino[2,3-b][1,4]thiazin-6-one (III). Sulfuryl chloride [0.9 g (0.0051 mole)] was added dropwise at 60° to 1.0 g (0.0051 mole) of I in 60 ml of anhy-

drous chlorobenzene, and the mixture was stirred at this temperature for 2 h and cooled to 10-15°. The precipitate was removed by filtration, washed with benzene, and dried to give 1.1 g (94%) of crude III with mp 163-164°. Recrystallization from ethyl acetate gave colorless crystals with mp 175-176°. Found: C 41.8; H 3.5; Cl 15.2; N 18.7; S 13.9%. $C_8H_8ClN_3OS$. Calculated: C 41.8; H 3.5; Cl 15.4; N 18.3; S 14.0%.

2,3-Dimethyl-7,7-dichloropyrazino[2,3-b][1,4]thiazin-6-one (IV). Sulfuryl chloride [1.8 g (0.010 mole)] was added dropwise at 60° to 1.0 g (0.0051 mole) of I in 50 ml of anhydrous nitrobenzene, and the mixture was stirred at this temperature for 2 h and cooled to 20°. Compound IV was precipitated by the addition of petroleum ether to give 0.74 g (55%) of crude product. Two recrystallizations from acetonitrile gave colorless crystals with mp 185-186°. Found: C 36.6; H 2.8; Cl 26.5; N 15.9; S 12.5%. $C_8H_7Cl_2N_3OS$. Calculated: C 36.3; H 2.7; Cl 26.9; N 15.9; S 12.2%.

2,3-Dimethyl-7-n-butylaminopyrazino[2,3-b][1,4]thiazin-6-one (V).* A 1.0-g (0.0036 mole) sample of II was added in small portions with vigorous stirring at 20-22° to 0.54 g (0.074 mole) of butylamine in 20 ml of anhydrous benzene. The mixture was stirred for 3 h and evaporated to dryness. The residue was triturated with water, and the solid was removed by filtration and dried in a vacuum desiccator over sulfuric acid to give 0.65 g (67%) of crude V with mp 163-165°. Recrystallization from ether gave colorless crystals with mp 169-170.5° and R_f 0.69 in ether–ethanol (36:4). Compound VI was similarly obtained.

2,3-Dimethyl-7-benzylaminopyrazino[2,3-b][1,4]thiazin-6-one (VII). A solution of 0.78 g (0.0073 mole) of benzylamine in 20 ml of anhydrous benzene was added dropwise with stirring at 20-22° to a suspension of 1.0 g (0.0036 mole) of II in 20 ml of anhydrous benzene, and the mixture was stirred for 2 h. The resulting precipitate was removed by filtration, washed with water, and dried to give 0.73 g (67%) of crude product with mp 178-180°. Recrystallization from ethanol gave colorless crystals with mp 191-192° and R_f 0.74 in ether–ethanol (32:3). Compounds X-XIII were similarly obtained.

2,3-Dimethyl-7-anilinopyrazino[2,3-b][1,4]thiazin-6-one (VIII). A 0.3-g (0.0013 mole) sample of III was added in small portions with stirring at 20-22° to 0.13 g (0.0013 mole) of triethylamine and 0.12 g (0.0013 mole) of aniline in 20 ml of anhydrous benzene, and the mixture was stirred for 3.5 h. The resulting precipitate was removed by filtration and treated with hot benzene. The benzene solution was separated from the solid residue, and the benzene was vacuum-evaporated to dryness to give 0.29 g (78%) of crude VIII with mp 215-217°. Recrystallization from benzene gave colorless crystals with mp 217-218° and R_f 0.78 in ether–ethanol (25:3).

2,3-Dimethyl-7-ethyleneiminopyrazino[2,3-b][1,4]thiazin-6-one (IX). A solution of 0.22 g (0.0052 mole) of ethyleneimine was added dropwise with stirring at 20-22° to a suspension of 0.6 g (0.0026 mole) of III in 20 ml of anhydrous benzene, and the mixture was stirred at room temperature for 2 h. The precipitate was separated and treated with hot benzene. The benzene solution was filtered away from solid and vacuum-evaporated to dryness to give 0.25 g (40%) of IX with mp 171-173°. Recrystallization from acetonitrile gave colorless crystals with mp 195-196° and R_f 0.66 in ether–ethanol (27:3). Compound XI was similarly obtained.

2,3-Dimethyl-7,7-di(ethyleneimino)pyrazino[2,3-b][1,4]thiazin-6-one (XIV). A 0.4-g (0.0015 mole) sample of IV was added in small portions with stirring at 20-22° to 0.13 g (0.003 mole) of ethyleneimine and 0.3 g (0.003 mole) of triethylamine in 20 ml of anhydrous benzene, and the mixture was stirred for 1.5 h and allowed to stand overnight. The resulting precipitate was removed by filtration and treated with hot benzene. The benzene solution was filtered away from the solid, and the solvent was vacuum-evaporated to dryness to give 0.25 g (59%) of a product with mp 184-186°. Recrystallization from methanol gave colorless crystals with mp 220-221°.

2,3-Dimethyl-7,7-dimorpholinopyrazino[2,3-b][1,4]thiazin-6-one (XV). A solution of 1.25 g (0.014 mole) of morpholine in 10 ml of anhydrous benzene was added dropwise with stirring at 20-22° to a suspension of 0.95 g (0.0036 mole) of IV in 25 ml of anhydrous benzene, and the mixture was stirred for 3 h. The precipitate was filtered away from the solution, and the solvent was vacuum-evaporated to dryness to give 0.86 g (66%) of a product with mp 154-155°. Recrystallization from acetonitrile gave colorless crystals with mp 181-183°.

* 7-Amino- and 7,7-diaminopyrazino[2,3-b][1,4]thiazin-6-ones V-XV (Table 1) are colorless, crystalline substances that are soluble in benzene and alcohols, slightly soluble in ether, and, except for V and VI, insoluble in water. Their purity was confirmed by thin-layer chromatography on Al_2O_3 with development by iodine.

2,3-Dimethyl-7-ethoxypyrazino[2,3-b][1,4]thiazin-6-one (XVI). A solution of 0.52 g of II in 50 ml of anhydrous ethanol was allowed to stand for 48 h at 20-22°. The solvent was then removed by vacuum distillation, and the residue was triturated with ether. The solid was removed by filtration, washed with water and dried to give 0.38 g (80%) of XVI with mp 139-142°. Recrystallization from ether gave colorless crystals with mp 144-145°. IR spectrum: 1690-1710 cm^{-1} (C=O), 3180, 3260 cm^{-1} (N-H). Found: C 50.2; H 5.3; N 17.9; S 13.3%. $C_{10}H_{13}N_3O_2S$. Calculated: C 50.2; H 5.5; N 17.6; S 13.4%.

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