A STUDY OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES

XIII. PYRAZINO[2,3-b]THIAZINES

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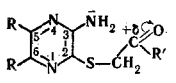
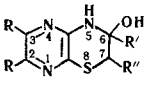
The reaction of 3-amino-2-mercaptopyrazines I and II with phenyl halides has given the 3-amino-2-phenacylthiopyrazines III-VIII. Compounds V, VI, and VIII have been converted by heating in vacuum into the the 5H-pyrazino[2,3-b]-[1,4]-thiazines XIII-XV. The reaction of I and II with chloroacetone, 3-chlorobutan-2-one, and 2-chlorocyclohexanone has given the 6-hydroxy-6,7-dihydropyrazinothiazines IX-XI.

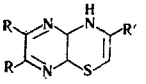
We have previously reported the synthesis of pyrimido- [2] and pyridothiazines [3] by the reaction of o-aminomercaptopyrimidines and -pyridines with halogeno ketones. In the present work, this reaction has been extended to the analogous pyrazine compounds, giving derivatives of a new heterocyclic system – pyrazino[2,3-b]-[1,4]-thiazine [4] – which are of interest as possible folic acid antagonists, and a study has been made of features in the properties of the intermediates due to the presence of a pyrazine ring and to the nature of the substituents in the carbonyl and pyrazine components. Thus, the reaction of 3-amino-2-mercaptopyrazine (I) with phenacyl bromide and its p-bromo derivative in the presence of alkali has given the 3-amino-2-phenacylthiopyrazines III and IV. In compounds III and IV, the lowering of the nucleophilicity of the amino group due to the effect of the dipole moment of the cyclic nitrogen atoms is more pronounced than in the 5-amino-6-phenacylthiopyridines, since in the first case the NH_2 group is in the α position with respect to a cyclic nitrogen. This circumstance leads to an increase in the stability of III and IV. Thus, III and IV, unlike the analogous pyridine derivatives, form hydrazones and do not cyclize on storage and on being heated with alcohols.



III-VIII



IX, XI



XII-XV

IX $R''=CH_3$; XI $R''=H$

The reaction of I with p-nitrophenacyl bromide, in which the carbonyl group is strongly activated with respect to the nucleophilic reagent because of the -M and -I effects of the NO_2 group, forms the pyrazinothiazine XII.

The introduction of two electron-donating substituents into the pyrazine ring increases the nucleophilicity of the NH_2 group and, consequently, decreases the stability of the 3-amino-2-phenacylthiopyrazines V-VIII. Thus, compounds V, VI, and VIII, obtained from 3-amino-2-mercapto-5,6-dimethylpyrazine and phenacyl halides, like the 5-amino-6-phenacylthiopyrimidines on heating in vacuum, are converted into the pyrazinothiazines XIII-XV under the conditions for the formation of hydrazones.

The reaction of I and II with aliphatic ketones (chloroacetone, 3-chlorobutanone, and 2-chlorocyclohexanone) formed the hydroxy compounds IX-XI, which did not undergo dehydration to give pyrazinothiazines.

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TABLE 1. 3-Amino-2-phenacylthiopyrazines (III-VIII), 6-Hydroxy-6,7-dihydropyrazino[2,3-b]-[1,4]-thiazines (IX-XI), and Pyrazino[2,3-b]-[1,4]-thiazines (XII-XV).

Compound	R	R′	mp, °C	Empirical formula	Found, %				Calculated, %				Yield, %
					C	H	N	S	C	H	N	S	
III	H	C_6H_5	124—125	$C_{12}H_{11}N_3OS$	58,7	4,5	16,9	13,1	58,7	4,5	17,1	3,1	87
IV	H	C_6H_4Br -p	119—120	$C_{12}H_{10}BrN_3OS$	44,7	3,5	13,2	9,9	44,4	3,1	13,0	9,9	86
V	CH_3	C_6H_5	122—123	$C_{14}H_{15}N_3OS$	61,4	5,5	15,3	11,4	61,5	5,5	15,4	11,7	97
VI	CH_3	C_6H_4Br -p	201—203	$C_{14}H_{14}BrN_3OS$†	47,5	4,0	11,6	9,0	47,7	4,0	11,9	9,1	84
VII	CH_3	$C_6H_4OCH_3$ -p	118	$C_{15}H_{17}N_3O_2S$	59,5	5,6	13,9	10,6	59.4	5,6	13,8	10,6	46
VIII	CH_3	$C_6H_4NO_2$ -p	221—222	$C_{14}H_{14}N_4O_3S$	52,6	4,3	17,7	9,9	52,8	4,4	17,6	10,1	92
IX	H	CH_3; R″ = CH	78,5—80,5	$C_8H_{11}N_3OS$	49,0	5,7	21,9	15,9	48,7	5,6	21,3	16,2	88
X	H	R′—R″ = H	120—121	$C_{10}H_{13}N_3OS$	54,0	5,7	18,8	14,4	53,8	5,9	18,8	14,4	77
XI	CH_3	CH_3, R″ = H	88—90	$C_9H_{13}N_3OS$	51,4	6,0	19,8	15,4	51,2	6,2	19,9	15,2	88
XII	H	$C_6H_4NO_2$ -p	224	$C_{12}H_8N_4O_2S$	52,9	2,9	20,2	11,6	52,9	3,0	20,6	11,8	55
XIII	CH_3	C_6H_5	129—131	$C_{14}H_{13}N_3S$	65,9	5,0	16,3	12,2	65,9	5,1	16,5	12,6	Quantitative
XIV	CH_3	C_6H_4Br-p	199—201	$C_{14}H_{12}BrN_3S$ ‡	50,6	3,6	12,3	9,7	50,3	3,6	12,6	9,6	„
XV	CH_3	$C_6H_4NO_2$-p	222—223	$C_{14}H_{12}N_4O_2S$	56,2	4,2	18,1	10,7	56,0	4,0	18,7	10,7	„

*For analysis, the substances were purified by crystallization: IV and VII from methanol; III, V, and VI from ethanol; IX from ether; VIII, X,and XV from benzene; XI and XIII from cyclohexane; and XII from toluene. XIV was purified by being boiled in ethanol. Compounds IX-XI were colorless, III, IV, and VII light yellow, V, VI, VIII and XIV yellow, XII violet, and XV brown.

† Found, %: Br 22.6. Calculated, %: Br 22.7.

‡ Found, %: Br 23.4. Calculated, %: Br 23.7.

The structures of III-XII were confirmed by their IR spectra: those of III-VIII have the absorption of CO and NH_2 groups; in the spectra of IX-XI there is no band of a CO group but the absorption of OH and NH groups is present; in the spectrum of XII there is a strong band of a NH group (at 3370 cm^{-1}). For substances XIII-XV the band of NH group is weak and is located at 3200-3250 cm^{-1}. In the PMR spectra of XII and XV there is a broadened signal of an olefinic proton which is located at 5.10 ppm for XV and is shifted upfield by 0.22 ppm for XII, which probably shows the possibility of the existence of the pyrazinothiazines in another tautomeric form – that of the 7H derivatives.

EXPERIMENTAL

3-Amino-2-mercaptopyrazine (I). a. A solution of 0.46 g (0.02 g-at.) of Na in 20 ml of anhydrous ethanol was treated with 20 ml of dimethylformamide, and the ethanol was distilled off in vacuum. The residual solution was saturated with hydrogen sulfide, 1.5 g (0.0116 mole) of 3-amino-2-chloropyrazine [5,6] was added to it, and the reaction mixture was heated at 100°C for 3 hr. The dimethylformamide was distilled off in vacuum and the residue was dissolved in ~80 ml of 5% aqueous NaOH with heating. The solution was treated with activated carbon and filtered, and the filtrate was cooled and acidified with acetic acid. The precipitate was filtered off, washed with water, and dried. Yield 1.02 g (69%), mp 260-261°C (from ethanol). According to the literature [7], yield 73%, mp 245-255°C.

b. A mixture of 2.22 g (0.02 mole) of 3-amino-2-hydroxypyrazine and 4.9 g (0.02 mole) of P_2S_5 in 80 ml of pyridine was heated at 120°C for 2 hr. The pyridine was distilled off in vacuum and the residue was dissolved in 75 ml 2 N NaOH; the insoluble part was filtered off, and alkaline solution was acidified with 10% sulfuric acid, after which the precipitate was separated off and dried. Yield 0.58 g (23%), mp 260-261°C (from ethanol). A mixture with a sample obtained by method (a) gave no depression of the melting point.

3-Amino-2-mercapto-5,6-dimethylpyrazine (II) was obtained as described previously [8]. Yield 76%, mp 259-261°C.

3-Amino-2-phenacylthiopyrazine (III). At 20-22°C with stirring, an ethanolic solution of 0.89 g (0.0045 mole) of phenacyl bromide was added to a solution of 0.63 g (0.0050 mole) of I in 15 ml of an alcohol (methanol or ethanol) containing 0.32 g of KOH. After three hours' stirring, the precipitate was separated off, washed with 5-10% aqueous alkali and then with water to neutrality, and dried. The yield was 0.96 g (87%), mp 119-120°C. Compound III exhibited the following frequencies of the vibrations of an amide C=O and of NH_2 groups, cm^{-1}: 1695; 1625; 3220; 3310; 3390.

Compounds IV-XI were obtained similarly with the difference that for IV-VIII the reaction was carried out at from -4 to -10°C and for XI at 0°C. For compounds IV-VIII the frequencies of the vibrations of the amide C=O and NH_2 groups and for compounds X and XI those of the NH and OH groups were, cm^{-1}: IV 1692; 1630; 3310; 3330; 3390; 3430; V – 1670; 1650; 3330; 3415; VI – 1683; 1660; 3320; 3420; VII – 1670; 1610; 3320; 3420; VIII – 1693; 1640; 3310; 3440; X – 3200; 3280 (broadened band); XI – 3220; 3290 (broadened band).

2,4-Dinitrophenylhydrazone of III. 0.25 g (0.001 mole) of III was added to a solution of 0.2 g (0.001 mole) of 2,4-dinitrophenylhydrazine in 10 ml of ethanol containing 6-8 drops of conc. HCl and the mixture was heated in the water bath for a few minutes, after which the solution was cooled and the resulting crystals were separated off. Yield almost quantitative. Yellow crystals, mp 200-201°C (from ethanol). Found, %: C 50.8; H 3.5; N 23.6; S 7.3. Calculated for $C_{18}H_{15}N_7O_4S$, %: C 50.8; H 3.5; N 23.0; S. 7.5.

The hydrazone of IV was obtained similarly. Yellow crystals, mp 220°C (from ethanol). Found, %: C 42.7; H 2.8; N 19.3; Br 16.0; S 6.4. Calculated for $C_{18}H_{14}BrN_7O_4S$, %: C 42.8; H 2.8; N 19.4; Br 15.8; S 6.4.

6-p-Nitrophenylpyrazino[2,3-b]-[1,4]-thiazine (XII). At 20-22°C, 2.2 g (0.009 mole) of p-nitrophenacyl bromide in 15-20 ml of $CHCl_3$ was added to a solution of 1.27 g (0.010 mole) of I in 15 ml of water containing 0.9 g of KOH. After nine hours' stirring, the precipitate was separated off, washed with 5-10% aqueous alkali and with water, and dried. Yield 1.49 g (61%), mp 219-220°C.

2,3-Dimethyl-6-phenylpyrazino[2,3-b]-[1,4]-thiazine (XIII) was obtained in quantitative yield by heating 0.5 g of V at 110-112°C over P_2O_5 in vacuum for 6 hr. Compounds XIV and XV were synthesized similarly.

The IR spectra were taken on a UR-10 instrument in the form of mulls in paraffin oil. The PMR spectra of XII and XV were taken on a JNM-4H instrument at 100 MHz in pyridine with HMSO as internal standard.

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