DERIVATIVES OF CONDENSED PYRIMIDINE, PYRAZINE, AND PYRIDINE SYSTEMS. XXXII.* SYNTHESIS AND PROPERTIES OF PYRAZINO-[2,3-b][1,4]THIAZIN-6-ONES

L. A. Myshkina and T. S. Safonov

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Reaction of 2-mercapto-3-amino-5,6-dimethyl- and 2-mercapto-3-amino-5,6-diphenylpyrazines with α-halo acid esters gave 2-carbethoxy-3-aminopyrazines, which are converted by the action of sodium ethoxide to 5,6-dimethyl- and 5,6-diphenylpyrazino[2,3-b]-[1,4]thiazin-6-ones. The latter are more conveniently obtained from 2-chloro-3-amino-5,6-dimethyl- and 2-chloro-3-amino-5,6-diphenylpyrazines and thioglycolic acid. 5,6-Dihydropyrazinothiazine is formed by reduction of 5,6-dimethyl pyrazino[2,3-b][1,4]thiazin-6-one, whereas the 2,3-dimethyl-5-amino-6-sulfonic acid and its N-oxide are formed by oxidation.

In a continuation of our earlier research, which was undertaken to search for anticancer, substances, we investigated the reaction of 2-mercapto-3-amino-5,6-dimethyl- (I) and 2-mercapto-3-amino-5,6-diphenylpyrazines (II) with ethyl chloroacetate. As a result, we obtained 2-carbethoxymethylthio-3-aminopyrazines (III and IV), the structure of which was confirmed by the presence of absorption bands of an amino group and a ester CO group in the IR spectra. In contrast to 2-carboxymethylthio-3-aminopyrazines [3], III and IV are converted to pyrazino[2,3-b][1,4]thiazin-6-ones (V and VI) under the influence of alkaline but not acidic agents. Compound V was isolated in an attempt to obtain the corresponding amide from III (by bubbling ammonia into an alcohol solution of thioether III).

However, pyrazinothiazin-6-ones are more conveniently obtained by reaction of 2-chloro-3-amino-5,6-dimethylpyrazine (X) and 2-chloro-3-amino-5,6-diphenylpyrazine (XI) with thioglycolic acid in aqueous alkaline media. The primary products of the reaction are 2-carboxymethylthio-3-aminopyrazines (XII and XIII), which are cyclized to pyrazinothiazin-6-ones (V and VI) when they are heated with hydrochloric acid. This method for the preparation of V and VI has an advantage over the above-described methods with respect to the number of steps (the necessity for replacement of the chlorine atom by an SH group is excluded) and with respect to the yields of final products. 2-Dicarbethoxymethylthio-3-aminopyrazines (VII and VIII) are formed by reaction of I and II with bromomalonic ester in the presence of 1 mole of alkali. 2-Dicarbethoxymethylthio-3-amino-5,6-dimethylpyrazine hydrobromide (IX) was isolated when the reaction of I with bromomalonic ester was carried out in the absence of alkali. Absorption bands of ester CO and NH_2 groups are observed in the IR spectra of VII-IX, and the spectrum of hydrobromide IX additionally contains a broad band at 2630-2700 cm^{-1}, which is related to vibrations of the NH_3^+ group.

Attempts to convert 2-dicarbethoxymethylthio-3-aminopyrazines VII and VIII to the corresponding pyrazinothiazinones were unsuccessful: the starting materials were recovered when they were heated in the presence of sodium ethoxide, whereas destructive changes occurred under more severe conditions.

* See [1] for communication XXXI.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow.
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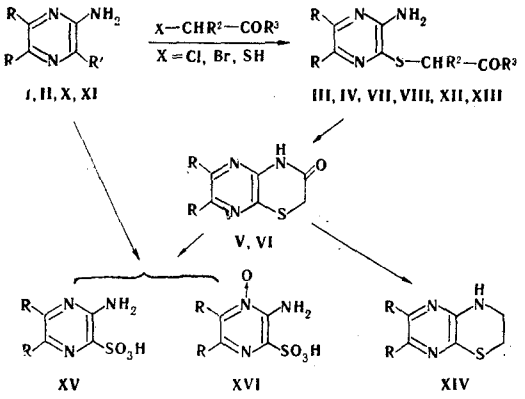

I R=CH_3, R^1=SH; II R=C_6H_5, R^1=SH; X R=CH_3, R^1=Cl; XI R=C_6H_5, R^1=Cl; III R=CH_3, R^2=H, R^3=OC_2H_5; IV R=C_6H_5, R^2=H, R^3=OC_2H_5; VII R=CH_3, R^2=$CO_2C_2H_5$, R^3=OC_2H_5; VIII R=C_6H_5, R^2=$CO_2C_2H_5$, R^3=OC_2H_5; XII R=CH_3, R^2=H, R^3=OH; XIII R=C_6H_5, R^2=H, R^3=OH; V, XIV, XV, XVI R=CH_3; VI R=C_6H_5

In order to further study the properties of pyrazinothiazin-6-one [4] we investigated the reduction of its 2,3-dimethyl derivative (V) with lithium aluminum hydride in tetrahydrofuran (THF). In this case, 5,6-dihydropyrazino[2,3-b][1,4]thiazine (XIV) is formed. The structure of the latter was confirmed by the absence of lactam ring absorption bands in its IR spectrum.

In order to convert the pyrazinothiazin-6-ones to the corresponding sulfoxides and sulfones, which are of interest for biological study, we investigated the action of hydrogen peroxide on 2,3-dimethylpyrazino[2,3-b][1,4]thiazin-6-one (V). As a result of the reaction, the sulfur is oxidized, the thiazine ring is opened, and the pyrazine ring nitrogen atom is oxidized to give 2,3-dimethyl-5-amino-6-sulfonic acid XV and its N_4-oxide (XVI). The structures of XV and XVI were confirmed by the presence in their IR spectra of absorption bands of NH_2 and SO_2 groups and also by comparison with authentic samples obtained by oxidation of 2-mercapto-3-amino-5,6-dimethylpyrazine (I). The presence of an oxide group in XVI at N_4 rather than at N_1 was proved by means of a qualitative reaction with $FeCl_3$. The appearance of a blue coloration attests to location of the N→O group in the α position with respect to the amino group of the pyrazine ring.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were obtained with a UR-10 spectrometer.

The starting 2-mercapto-3-amino-5,6-dimethyl- (I), 2-mercapto-3-amino-5,6-diphenyl- (II) 2-chloro-3-amino-5,6-dimethyl- (X), and 2-chloro-3-amino-5,6-diphenylpyrazines (XI) were synthesized by the method in [3].

2-Carbethoxymethylthio-3-amino-5,6-dimethylpyrazine (III). An alcohol solution of 0.72 g (0.058 mole) of ethyl chloroacetate was added dropwise at 20-22° to a solution of 1.0 g (0.065 mole) of I in 50 ml of ethanol containing 0.36 g of KOH. The mixture was stirred for 3.5 h, after which the KCl was separated, the alcohol solution was evaporated to dryness in vacuo, and the residue was triturated with water. The resulting solid was removed by filtration, washed with water, and dried to give 0.95 g (67.2%) of white crystals with mp 73-74° (from water). IR spectrum: 1740 (ester CO), 1640, 3300, and 3430 (NH_2) cm^{-1}. Found: C 49.5; H 6.3; N 17.7; S 13.3%. $C_{10}H_{15}N_3O_2S$. Calculated: C 49.8; H 6.3; N 17.4; S 13.3%.

2-Carbethoxymethylthio-3-amino-5,6-diphenylpyrazine (IV). A similar method was used to obtain this compound in 57.5% yield. The yellow crystals had mp 123-124.5° (from ethanol). IR spectrum: 1745 (ester CO), 1635, 3310, and 3450 (NH_2) cm^{-1}. Found: C 65.7; H 5.4; N 11.3; S 8.5%. $C_{20}H_{19}N_3O_2S$. Calculated: C 65.7; H 5.2; N 11.5; S 8.8%.

2-Carboxymethylthio-3-amino-5,6-dimethylpyrazine (XII). A 1.0-g (0.026 mole) sample of pyrazine X was added to a solution of 2.64 ml [3.5 g (0.038 mole)] of thioglycolic acid in 20 ml of water containing 4.3 g (0.032 mole) of KOH, and the mixture was heated at 90-95° for 1 h, after which it was cooled to 15-18° and acidified with CH_3COOH. Workup gave 3.98 g (73.8%) of white crystals with mp 172-173° (from methanol). The product was identical to the compound previously obtained by the method in [3].

2-Carboxymethylthio-3-amino-5,6-diphenylpyrazine (XIII) [3]. This compound was similarly obtained from XI and thioglycolic acid in 90.1% yield. The yellow crystals had mp 235° (from butanol).

2-Dicarbethoxymethylthio-3-amino-5,6-dimethylpyrazine (VII). An alcohol solution of 1.54 g (0.064 mole) of diethyl bromomalonate was added dropwise at 60-65° to a solution of 1.0 g (0.065 mole) of I in 50 ml of ethanol containing 0.36 g of KOH. The mixture was stirred at the same temperature for 3.5 h, after which the KBr was separated, and the mother liquor was vacuum evaporated to dryness. The residue was triturated with water and dried to give 1.18 g (75.4%) of yellow crystals with mp 90-91° (from alcohol). IR spectrum: 1725, 1740 (ester CO), 1645, 3210, 3330, and 3430 (NH_2) cm^{-1}. Found: C 50.1; H 6.0; N 13.2; S 10.4%. $C_{13}H_{19}N_3O_4S$. Calculated: C 49.8; H 6.1; N 13.4; S 10.2%.

2-Dicarbethoxymethylthio-3-amino-5,6-dimethylpyrazine Hydrobromide (IX). A suspension of 0.5 g of I in 50 ml of ethanol and 0.78 g of diethyl bromomalonate was refluxed on a water bath for 2.5-3 h. The solvent was then removed by vacuum distillation, the residue was triturated with ether, and the solid was removed by filtration and dried to give 0.96 g (75.7%) of white crystals with mp 162-163° (from alcohol). IR spectrum: 1730 (ester CO), 1655, 3300, 3350 (NH_2), and 2630-2700 (NH_3^+) cm^{-1}. Found: Br 20.3; S 7.9%. $C_{13}H_{19}N_3O_4S \cdot HBr$. Calculated: Br 20.2; S 8.1%.

Dry ammonia was bubbled into a suspension of hydrobromide IX in ether. The resulting NH_4Br was separated, and the ether was evaporated to give a yellow crystalline substance with mp 90-91°. No melting-point depression was observed for a mixture of this product with the VII obtained above.

2-Dicarbethoxymethylthio-3-amino-5,6-diphenylpyrazine (VIII). This compound was similarly obtained from II and ethyl bromomalonate in 75.4% yield. The yellow crystals had mp 99-100.5° (from cyclohexane). IR spectrum: 1750, 1765 (ester CO), 1640, 3290, and 3460 (NH_2) cm^{-1}. Found: C 63.4; H 5.3; N 9.5; S 7.2%. $C_{23}H_{23}N_3O_4S$. Calculated: C 63.2, H 5.3; N 9.2; S 7.2%.

2,3-Dimethylpyrazino[2,3-b][1,4]thiazin-6-one (V). A) A 1.0-g (0.063 mole) sample of X was added to a solution of 2.64 ml [3.5 g (0.029 mole)] of thioglycolic acid in 20 ml of water containing 4.3 g of KOH, and the mixture was then heated at 90-95° for 1 h, after which 100 ml of 8% aqueous hydrochloric acid was added. The mixture was held at this temperature and neutralized with sodium acetate. The resulting precipitate was removed by filtration, washed with water, and dried to give 3.82 g (68.3%) of white crystals with mp 186-187° (from water). The compound was identical to the substance obtained by the method in [3].

B) A mixture of sodium ethoxide (0.23 g of Na in 20 ml of absolute ethanol) and 0.5 g of III was held at 20-22° for 24 h, after which the solvent was removed by vacuum distillation, and the residue was triturated with water and dried to give 0.28 g (69.2% based on III or 57.2% based on X). The compounds obtained by methods A and B were identical.

2,3-Diphenylpyrazino[2,3-b][1,4]thiazin-6-one (VI). This compound was similarly obtained in 77% yield as yellow crystals with mp 253-255° (from alcohol).

2,3-Dimethyl-5,6-dihydropyrazino[2,3-b][1,4]thiazine (XIV). A solution of 1.5 g (0.078 mole) of V in THF was added dropwise with vigorous stirring in the course of 1 h at 50° to a suspension of 1.16 g (0.306 mole) of $LiAlH_4$ in 100 ml of dry THF, after which the reaction mixture was held at this temperature for 4.5 h. Water (7 ml) was then added dropwise at 40° in the course of 30 min, and the mixture was refluxed for 1.5 h. The precipitate was removed by filtration, the THF solution was dried with sodium sulfate, and the solvent was removed by vacuum distillation. The residue was triturated with ether, and the solid product was removed by filtration and dried to give 0.87 g (62.5%) of white crystals with mp 145-146° (from ether). Found: C 53.1; H 6.2; N 23.4; S 17.6%. $C_8H_{11}N_3S$. Calculated: C 53.0; H 6.1; N 23.2; S 17.7%.

2,3-Dimethyl-5-aminopyrazine-6-sulfonic Acid (XV) and 2,3-Dimethyl-5-aminopyrazine-6-sulfonic Acid 4-Oxide (XVI). A 2.3-ml sample of 30% H_2O_2 was added dropwise at 20-22° with stirring to a suspension of 1.0 g of V and 4.2 ml of glacial acetic acid, and the mixture was stirred for 2.5 h, during which the solid dissolved completely. The reaction mixture was allowed to stand at this temperature for 2 days. The resulting precipitate was removed by filtration, washed with ether, and dried. The yield of sulfonic acid XV, with mp 272° (from ethanol), was 0.1 g (10.3%). IR spectrum: 1660, 3350 (NH_2), 1210-1240 (SO_2) cm^{-1}. Found: C 35.3; H 4.7; S 15.7%. $C_8H_9N_3O_3S$. Calculated: C 35.5; H 4.5; S 15.8%.

The acetic acid mother liquor was vacuum evaporated to dryness to give 0.68 g (60.5%) of oxide XVI. The white crystals melted above 300°. IR spectrum: 1635, 3250, 3370 (NH_2), 1070-1090 (broad bands), and 1285-1295 (SO_2, N→O) cm^{-1}. Found: C 32.7; H 4.1; N 19.0; S 14.8%. $C_6H_9N_3O_4S$. Calculated: C 32.9; H 4.1; N 19.2; S 14.6%.

B) A 1-ml sample of 30% H_2O_2 was added dropwise at 20-22° to a suspension of 0.2 g of I in 10 ml of CH_3COOH, and the reaction mixture was allowed to stand at this temperature for 2 days. The resulting

precipitate was removed by filtration and dried to give 0.1 g of acid XV with mp 272°. Evaporation of the acetic acid mother liquor gave 0.03 g of oxide XVI with mp >300°. The two compounds were identical to those obtained by method A.

LITERATURE CITED

1. V. M. Nesterov, S. K. Elagina, and T. S. Safonova, Khim. Geterotsikl. Soedin., 1280 (1974).
2. T. S. Safonova, Zh. Vsesoyuzn. Khim. Obshchestva im. D. I. Mendeleeva, 18, 6 (1973).
3. T. S. Safonova and L. A. Myshkina, Khim. Geterotsikl. Soedin., No. 3, 230 (1971).
4. T. S. Safonova, L. A. Myshkina, V. A. Chernov, and A. S. Sokolova, Khim. Geterotsikl. Soedin., 1498 (1971).