1*H*-Imidazo[4,5-*b*]pyrazines. III. 2-Thiols and Derivatives (1,2)

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1*H*-Imidazo[4,5-*b*]pyrazine-2-thiols were prepared. Their chlorination, alkylation and cyclization reactions are discussed.

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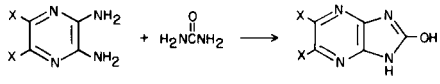
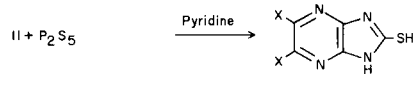
Many methods are available to convert *o*-phenylenediamine into benzimidazole-2-thiol, as summarized by Hofmann (3). When 2,3-diamino pyrazines (I) were caused to react with either carbon disulfide in the presence of base or *S*-methylthiouronium sulfate, no 1*H*-imidazo[4,5-*b*]pyrazine-2-thiol was isolated. They were prepared *via* the hydroxyl compounds which had been prepared by a modified procedure of Schipper and Day (4). 2,3-Diaminopyrazines (I) were fused with urea in diphenyl ether to give 1*H*-imidazo[4,5-*b*]pyrazin-2-ols (II). Reaction of II with phosphorus pentasulfide in pyridine, according to the procedure of Martin and Tarasiejska (5), gave the corresponding thiols (III).



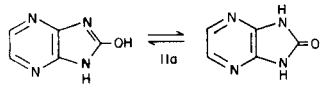
Ia X = H
b X = Cl

II (a and b)



IIIa, X = H
b, X = Cl

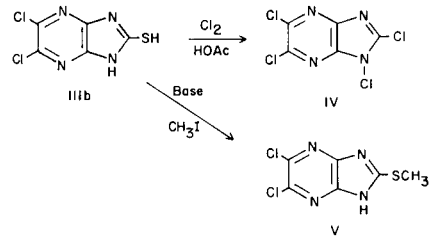
Mason (6) studied the tautomerism of enol-one forms of 1*H*-imidazo[4,5-*b*]-pyrazin-2-ol (IIa) and concluded that it possessed the amide form. The same is probably true for the thiol-thione III. In this article, the enol and thiol forms



IIa

are used for the simplicity of presentation, with the understanding that they probably exist in the ketone form in the unalkylated compounds II and III.

Chlorination of 5,6-dichloro-1*H*-imidazo[4,5-*b*]pyrazine-2-thiol (IIIb) gave 1,2,5,6-tetrachloro-1*H*-imidazo[4,5-*b*]-pyrazine, IV, which loses chlorine on standing. Alkylation of IIIb with iodomethane in the presence of a base gave V.

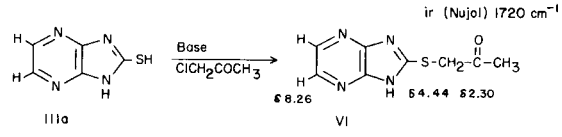


IIIb

IV

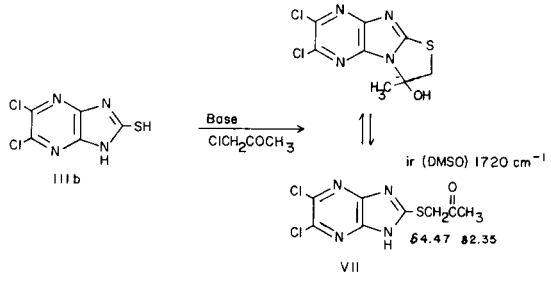
V

The alkylation products of IIIa and b with chloroacetone exhibited different characteristics. From IIIa, the thioacetone existed in its normal form, with spectral data as indicated. From IIIb, the same reaction gave a product that existed in the thioacetone form VII in solution (DMSO) only. When the ir was recorded in solid state (Nujol), no carbonyl absorption was observed. Instead a hydroxyl absorption was observed, indicating the existence of a hemiketal.



IIIa

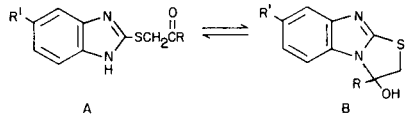
VI



IIIb

VII

Alper, *et al.* (7), reported the ring-chain tautomerism of the benzimidazole system. The equilibria were effected by



A

B

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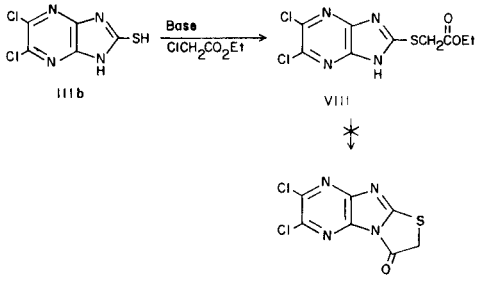
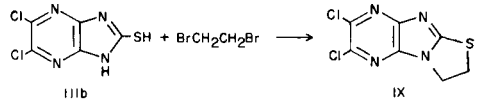
the size and inductive effect of R and the inductive effect of R'. When R = CH_3 and R' = H, the cyclic structure B existed in solid state. In solution, about 65% of the chain form A was present. When R = CH_3 and R' = NO_2, the compound again existed in its cyclic structure B in the solid state. In solution, the chain form increased to 79%.

The different structures of VI and VII in the solid state could not be explained.

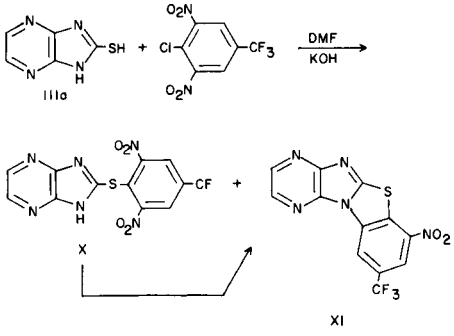
When ethyl chloroacetate was used in place of chloroacetone in the reaction with IIIb, the open chain form VIII was observed in both solid and solution. No lactam was obtained.



When 2 moles of the thiol IIIb, in the presence of 2 moles of base, was caused to react with 1 mole of 1,2-dibromoethane, the bis-thioethane was not obtained. Instead an intramolecular cyclization was favored to give IX.



Compound IIIa reacted with 4-chloro-3,5-dinitrobenzoyltrifluoride in dimethylformamide to form both the normal (X) and ring closure (XI) compounds similar to the case of benzimidazole-2-thiol reactions reported by D'Amico, Tung and Dahl (8). When X was heated in DMF, it was converted to XI.



EXPERIMENTAL

5,6-Dichloro-1*H*-imidazo[4,5-*b*]pyrazin-2-ol (IIb).

A mixture of 50 ml. of diphenyl ether, 9.0 g. (0.05 mole) of 2,3-diamino-5,6-dichloropyrazine and 3.5 g. (0.05 mole) of urea was heated to 240° for 5 hours. After cooling, the reaction mixture was poured into 500 ml. of hexane, stirred well and filtered. The solid was dissolved in 150 ml. of 1*N* sodium hydroxide treated with charcoal and filtered. The filtrate was acidified with acetic acid and the precipitate collected by filtration. The solid was then placed in a Soxhlet extractor and extracted with ethanol for 3 days. From the ethanol solution, 3.9 g. of product was obtained (38%), m.p. 350-353°.

Anal. Calcd. for $C_5H_2Cl_2N_4O$: C, 29.30; H, 0.98; N, 27.33. Found: C, 29.56; H, 1.34; N, 27.05.

1*H*-Imidazo[4,5-*b*]pyrazin-2-ol (IIa).

By the same procedure as given above, IIa was prepared in 57% yield, m.p. 338-340°.

Anal. Calcd. for $C_5H_4N_4O$: C, 44.1; H, 3.0; N, 41.1. Found: C, 44.5; H, 2.9; N, 41.5.

5,6-Dichloro-1*H*-imidazo[4,5-*b*]pyrazine-2-thiol (IIIb).

A mixture of 10.3 g. (0.05 mole) of 5,6-dichloro-2-hydroxy-1*H*-imidazo-[4,5-*b*]pyrazine and 40 g. (0.18 mole) of phosphorus pentasulfide in 200 ml. xylene, was heated under reflux for 24 hours. After removal of xylene analysis of the crude mixture indicated that it was a mixture of the desired product and starting material. The mixture was added to 200 ml. of dry pyridine and an additional 40 g. of phosphorus pentasulfide was added in small portions. After the addition was complete, the reaction mixture was heated under reflux for 24 hours. The solvent was removed under reduced pressure, and the solid residue stirred in 400 ml. of water for 4 hours. The product was collected on a filter, and then partially dissolved in 300 ml. of 1*N* sodium hydroxide and refiltered. The filtrate, upon acidification with acetic acid, afforded a yellow precipitate. This material was recrystallized from 200 ml. of 85:15 ethanol:water to give 4.5 g. (41%) of 5,6-dichloro-1*H*-imidazo[4,5-*b*]pyrazine-2-thiol.

Anal. Calcd. for $C_5H_2Cl_2N_4S$: C, 27.15; H, 0.91; Cl, 32.08; N, 25.33; S, 14.51. Found: C, 27.24; H, 0.82; Cl, 32.20; N, 25.30; S, 14.38.

1*H*-Imidazo[4,5-*b*]pyrazine-2-thiol (IIIa).

By the same procedure as given above, IIIa was prepared in 47% yield.

Anal. Calcd. for $C_5H_4N_4S$: C, 39.46; H, 2.65; N, 36.82. Found: C, 39.63; H, 2.85; N, 37.10.

1,2,5,6-Tetrachloro-1*H*-imidazo[4,5-*b*]pyrazine (IV).

5,6-Dichloro-1*H*-imidazo[4,5-*b*]pyrazine-2-thiol, (23 g., 0.103 mole), was suspended in 1000 ml. of 30% acetic acid. The reaction mixture was cooled to 0° while chlorine was bubbled in under a Dewar condenser filled with dry ice. The rate was adjusted so a gentle refluxing of chlorine was observed. The reaction was allowed to proceed for 2 hours then the condenser was removed and excess chlorine evaporated. The reaction mixture was then stirred into 1 kg. of ice and filtered. The solid was recrystallized from dichloromethane to yield 7.4 g. (29%) of product, m.p. > 330°.

Anal. Calcd. for $C_5Cl_4N_4$: C, 23.27; Cl, 55.10; N, 21.63. Found: C, 23.53; Cl, 54.86; N, 21.82.

5,6-Dichloro-2-methylthio-1*H*-imidazo[4,5-*b*]pyrazine (V).

In 100 ml. of methanol was mixed 11.0 g. (0.05 mole) of 5,6-dichloro-1*H*-imidazo[4,5-*b*]pyrazine-2-thiol and 10 ml. of iodomethane. To this mixture under a Dewar condenser was added slowly 4 g. (0.1 equivalents) of sodium hydroxide in 50 ml. of water. The temperature rose to 45°. The reaction mixture was stirred at room temperature for ½ hour, diluted with 200 ml. of water and filtered. The alkaline solution was acidified with acetic acid and the product was collected by filtration. Recrystallization from 50 ml. THF and 200 ml. of methanol yielded 4.5 g. (38%) of product; nmr (DMSO-d_6): showed a singlet at 2.64 ppm.

Anal. Calcd. for $C_6H_4Cl_2N_4S$: C, 30.63; H, 1.71; N, 23.84. Found: C, 30.73; H, 2.01; N, 23.66.

1-[(1*H*-Imidazo[4,5-*b*]pyrazin-2-yl)thiol]-2-propanone (VI).

In a mixture of 150 ml. of methanol and 30 ml. of water was dissolved

2.8 g. (0.07 mole) of sodium hydroxide. To this solution was added 10.7 g. (0.07 mole) of 1*H*-imidazo[4,5-*b*]pyrazine-2-thiol. The mixture was stirred at room temperature for 0.5 hour. Chloroacetone, 6.5 g. (0.07 mole) was added and the whole stirred at room temperature overnight. Methanol was removed under reduced pressure, and the residue was diluted with 100 ml. of water and filtered. The filtrate was acidified with acetic acid and more solid separated. It was collected by filtration. The solids were combined and recrystallized from THF to give 5.6 g. of product, m.p. 212-213; ir (Nujol): (C=O) 1720 cm^{-1}; nmr (DMSO-d_6): δ 2.30 (s, 3H), 4.44 (s, 2H), and 8.26 (s, 2H).

Anal. Calcd. for $C_8H_8N_4OS$: C, 46.14; H, 3.87; N, 26.91. Found: C, 46.22; H, 3.98; N, 26.78.

1-[(5,6-Dichloro-1*H*-imidazo[4,5-*b*]pyrazin-2-yl)thiol]-2-propanone (VII).

A solution of base was prepared by dissolving 2 g. (0.05 equivalents) of sodium hydroxide in 20 ml. of water and 100 ml. of methanol. To this solution was added 11.0 g. (0.05 mole) of 5,6-dichloro-1*H*-imidazo[4,5-*b*]-pyrazine-2-thiol which was partially soluble. To this dark red solution was added 4.6 g. (0.05 mole) of chloroacetone. The color lightened as the reaction proceeded. After 3 hours at room temperature, the reaction mixture was evaporated to dryness. The residue was dissolved in 250 ml. of 1*N* sodium hydroxide and 500 ml. of water and filtered. The filtrate was acidified to give 11.5 g. of solid with very weak C=O adsorption in the ir. Crystallization from THF-hexane gave a product which showed no carbonyl absorption in a Nujol mull. A C=O absorption was observed at 1720 cm^{-1} when the ir spectrum was taken in DMSO solution. The nmr (DMSO-d_6) showed singlets at 2.35 (3H) and 4.47 (2H), yield 5.6 g. (41%) m.p. 186-187°.

Anal. Calcd. for $C_8H_6Cl_2N_4OS$: C, 34.67; H, 2.18; N, 20.22. Found: C, 34.62; H, 2.27; N, 20.42.

Ethyl (5,6-Dichloro-1*H*-imidazo[4,5-*b*]pyrazin-2-yl)thioacetate (VIII).

A base solution was prepared by dissolving 2 g. (0.05 equivalents) of sodium hydroxide in 50 ml. ethanol and 50 ml. of water. To this solution was added 11.0 g. (0.05 mole) of 5,6-dichloro-1*H*-imidazo[4,5-*b*]pyrazine-2-thiol, followed by 6.1 g. (0.05 mole) of ethyl chloroacetate. The whole was heated to boiling under reflux for 4 hours, cooled to room temperature and filtered. The solid was recrystallized from 100 ml. of 2B alcohol to give 5.9 g. (39%) of product; nmr (deuteriochloroform + DMSO-d_6): δ 4.15 (s, 2H); 3.78 (q, 2H) 1.13 (t, 3H); ir (Nujol): (C=O) 1720 cm^{-1}.

Anal. Calcd. for $C_9H_8Cl_2N_4O_2S$: C, 35.19; H, 2.62; N, 18.24. Found: C, 34.08; H, 2.76; N, 17.96.

6,7-Dichloro-2,3-dihydrothiazolo[3',2':1,2]imidazo[4,5-*b*]pyrazine (IX).

In 25 ml. of water was dissolved 2.4 g. (0.06 equivalents) of sodium hydroxide. To this solution was added 13.2 g. (0.06 mole) of 5,6-dichloro-1*H*-imidazo[4,5-*b*]pyrazine-2-thiol, 120 ml. of methanol and 5.6 g. (0.03 mole) of 1,2-dibromomethane. The reaction mixture was stirred at room temperature for 20 hours. It was then diluted with 500 ml. of water and acifified with acetic acid, and filtered. The solid was washed with 600 ml. of ether. From the ether solution was recovered 5.1 g. (0.023 mole) of starting thiol. The ether insoluble material, 6.8 g., 92%, was purified by Soxhlet extraction with acetone.

Anal. Calcd. for $C_7H_4Cl_2N_4S$: C, 34.02; H, 1.63, Cl, 28.70; N, 22.67; S, 12.98. Found: C, 34.24; H, 1.71; Cl, 28.50; N, 22.46; S, 12.98.

7-Nitro-9-trifluoromethylbenzothiazolo[3',2'-1,2]imidazo[4,5-*b*]pyrazine (XI).

In a reaction flask were placed 25.8 g. (0.095 mole) of 4-chloro-3,5-dinitrobenzoyl trifluoride, 14.4 g. (0.095 mole) of 1*H*-imidazo[4,5-*b*]-pyrazine-2-thiol, 100 ml. of DMF, 10 ml. of water and 6.3 g. (85%, 0.095 equivalents) of potassium hydroxide. The whole was heated to 90°, and gas evolution was observed. Heating was continued for 2 hours until evolution ceased. The reaction mixture was cooled to room temperature, diluted with 300 ml. of water, chilled and filtered. The solid was washed with water, followed by methanol and dried. It was then washed with dichloromethane until the washings became colorless. The dichloromethane solution was concentrated and the residue recrystallized from chloroform to give 2.5 g. (7.8%) of the product (XI), m.p. 208-209°.

Anal. Calcd. for $C_{12}H_4F_3N_5O_2S$: C, 42.48; H, 1.19; N, 20.64. Found: C, 42.07; H, 1.45; N, 20.36.

The dichloromethane insoluble material was stirred in 400 ml. 0.5*N* sodium hydroxide and filtered. The filtrate was acidified with acetic acid to give 16.2 g. (44%) of yellow precipitate, compound X, m.p. 213 dec.

Anal. Calcd. for $C_{12}H_5F_3N_6O_4S$: C, 37.31; H, 1.30; N, 21.76. Found: C, 36.94; H, 1.44; N, 21.87.

REFERENCES AND NOTES

(1) This work was partially supported by the National Cancer Institute under Contract No. NOI-CM-12313.

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