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# SYNTHESIS OF A NOVEL RING SYSTEM: PYRIDO[3',2':4,5]ISOTHIAZOLO[2,3-a]BENZIMIDAZOLE

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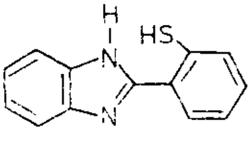
*Abstract*- Reaction between 2-mercaptonicotinic acid and *o*-phenylenediamine afforded 2-(2-mercapto-3-pyridyl)benzimidazole which underwent oxidative cyclization with bromine to give pyrido[3',2':4,5]isothiazolo[2,3-a]benzimidazole, a novel ring system.

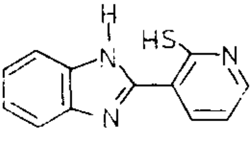
Among the various synthetic methods leading to the formation of the benzimidazole ring, that described by Phillips[1], involving the reaction between *o*-phenylenediamine and carboxylic acids or anhydrides in acidic medium, is especially noteworthy. This method appears to be generally applicable to the synthesis of 2-alkylbenzimidazoles which are obtained in good yields whereas the yields of 2-arylbenzimidazoles are frequently poor[2].

Porai-Koshits, Ginzburg and Efros[3] stated that good yields of 2-arylbenzimidazoles are achieved on heating *o*-phenylenediamine and aromatic acids in acidic medium in sealed tubes.

A careful examination of the literature showed that no data are available concerning the synthesis of 2-(2-mercaptoaryl or heteroaryl)benzimidazoles, we therefore decided to attempt the synthesis of 2-(2-mercaptophenyl)benzimidazole (Ia) and 2-(2-mercapto-3-pyridyl)benzimidazole (Ib).



Ia

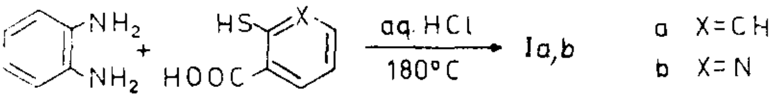


Ib

This choice was made considering our interest in the synthesis of novel heterocyclic systems having fused imidazole or benzimidazole rings[4-8]. In fact the position of the mercapto group and the imino one in Ia-b allows oxidative cyclization leading to the formation of the isothiazole ring. (scheme 1 below)

Scheme 1

The synthesis of Ia-b was accomplished by reacting *o*-phenylenediamine with 2-mercaptobenzoic acid and 2-mercaptonicotinic acid respectively:



The reactions were performed in aqueous hydrochloric acid at 180 °C in sealed tubes giving poor yields of Ia-b. Attempts to improve the yields of Ia-b were unsuccessful. As expected attempts to obtain Ia-b without employing sealed tubes also failed. By treating Ia-b with bromine in acetic acid an oxidative cyclization took place giving benzimidazo[1,2-b][1,2]benzisothiazole (IIa) and pyrido[3',2':4,5]isothia*zolo[2,3-a]benzimidazole (IIb) respectively. Compound IIa was previously obtained* by Giannola, Bajardi and Palazzo[9] as a by-product in the synthesis of 12*H*-benzimidazo[2,1-b][1,3]benzothiazin-12-one. The same authors[9] prepared this compound by reacting *o*-phenylenediamine with 3*H*-1,2-benzodithiole-3-thione.

The structure of pyrido[3',2':4,5]isothiazolo[2,3-a]benzimidazole (IIb) a hitherto unknown ring system, was confirmed by means of mass spectrometry. In fact in the mass spectrum of IIb the ions $[M]^+$ m/z 225 and $[\text{benzene-NS}]^+$ m/z 122 are detectable and this agrees with the assigned structure.

## EXPERIMENTAL

Melting points were obtained in open capillary tubes and are uncorrected. The ir spectra were measured on a Perkin-Elmer 283 spectrophotometer for potassium bromide discs. The mass spectrum of IIb was recorded with a Kratos MS 80 instrument.

### 2-(2-Mercaptophenyl)benzimidazole (Ia)

A suspension of 2-mercaptobenzoic acid (3g, 19.4mmoles) and *o*-phenylenediamine (2.1 g, 19.4mmoles) in 20% aq. HCl (40 ml) was heated at 180 °C for 45 min in a sealed tube. The dark green reaction mixture was treated with hot water and the resulting solution decolourized with charcoal, and then filtered. Compound Ia (0.52g, 12% yield) was separated out by treating the fitrate with dil. NaOH until the *p*H was 7.

Mp 241-242 °C from DMF/EtOH; ir: 3420 (cm$^{-1}$).

*Anal.* Calcd. for $C_{13}H_{10}N_2S$: C, 69.00; H, 4.45; N, 12.38. Found: C, 69.10; H, 4.39; N, 12.31.

### *2-(2-Mercapto-3-pyridyl)benzimidazole (Ib)*

This compound (Ib) was prepared starting from *o*-phenylenediamine and 2-mercaptonicotinic acid following the method described for Ia except that the reaction time was 1.5 h and 8% aq. HCl was employed. Mp 296- 297 °C from DMF (14% yield); ir: 3450 (cm$^{-1}$).

*Anal.* Calcd. for $C_{12}H_9N_3S$: C, 63.41; H, 3.99; N, 18.49. Found: C, 63.49; H, 3.88; N, 18.46.

### *Oxidative Cyclization of Ia-b*

General procedure - The theoretical amount of bromine in AcOH was slowly dropped into a well-stirred suspension of I in AcOH maintaining the temperature at 20 °C. The resulting mixture was allowed to react at room temperature for 2 h, then treated with ether and filtered. The solid product was suspended in cold 5% $NaHCO_3$ solution and then collected by filtration, washed with water, and dried.

Compound IIa was obtained in 80% yield. Mp 283-284 °C from DMF/AcOEt (reported[9] 284-286 °C). This compound was identical to an authentic specimen.

Compound IIb was obtained in 78% yield. Mp 246-247 °C from DMF/AcOEt; ir: 1420 (cm$^{-1}$), 735 (cm$^{-1}$); ms (70 eV): $[M]^+$ m/z 225, $[\text{benzene-NS}]^+$ m/z 122, $[\text{benzene-NC}]^+$ m/z 102, $[\text{benzene-N}]^+$ m/z 90.

*Anal.* Calcd. for $C_{12}H_7N_3S$: C, 63.98; H, 3.13; N, 18.65. Found: C, 63.87; H, 3.06; N, 18.60.

## ACKNOWLEDGEMENT

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