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

Ricardo Bossio, Stefano Marcaccini, Valerio Parrini, and Roberto Pepino
CNR, Centro di studio sulla chimica e la struttura dei composti esteroaligi e loro applicazioni, Dipartimento di Chimica Organica, Università di Firenze, via G.Capponi 9, 50121 Firenze, Italy

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 Phillips¹, 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 poor².

Porai-Koshits, Ginzburg and Efros³ 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).

This choice was made considering our interest in the synthesis of novel heterocyclic systems having fused imidazole or benzimidazole rings⁴⁻⁸. 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

\[ \text{Ilb} \xrightarrow{\text{Ox}} \text{IIb} \]

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

\[ \text{NH}_2 \text{NH}_2 + \text{CH}=\text{CH} \overset{\text{aq HCl, 180°C}}{\rightarrow} \text{Ia,b} \quad \text{a} \quad X=\text{CH} \quad \text{b} \quad X=\text{N} \]

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]isothiazolo[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\(^\beta\)-benzimidazo[2,1-b][1,3]benzothiazin-12-one. The same authors\(^9\) prepared this compound by reacting o-phenylenediamine with 3\(^\beta\)-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 filtrate with dil. NaOH until the pH was 7.
Mp 241-242 °C from DMF/EtOH; ir: 3420 (cm\(^{-1}\)).


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

This compound (Ib) was prepared starting from o-phenylenediamine and 2-mercaptanonicotinic 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\(_9\)N\(_3\)S: 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 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, [benzene-NS]\(^+\) m/z 122, [benzene-NC]\(^+\) m/z 102, [benzene-N]\(^+\) m/z 90.

Anal. Calcd. for C\(_{12}\)H\(_9\)N\(_3\)S: C, 63.98; H, 3.13; N, 18.65. Found: C, 63.87; H, 3.06; N, 18.60.

**ACKNOWLEDGEMENT**

The authors are grateful to Mrs. Brunella Innocenti for elemental analyses.

**REFERENCES AND NOTES**

* Author to whom correspondence should be addressed.


Received, 17th July, 1985