

Synthesis of Polycyclic Fused Benzimidazole Derivatives

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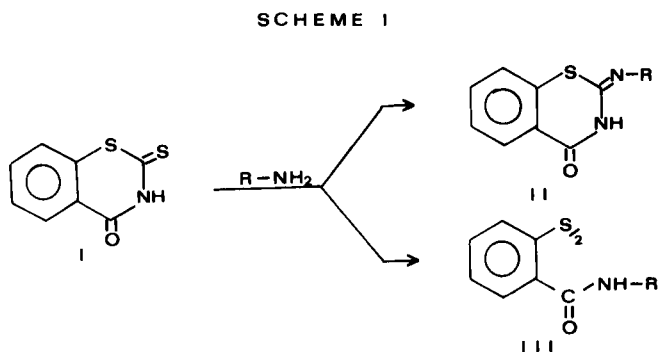
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An easy method for the synthesis of tetracyclic systems containing an imidazole and an isothiazole or an imidazole and a thiazine ring, by reacting 2*H*-1,3-benzothiazine-2-thion-4(3*H*)one with aromatic primary diamines is reported. The structures were assigned based upon mass spectra and modes of cleavage of the compounds. The most important fragments are described.

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Earlier reports from this laboratory (1-2) have described the syntheses and chemical transformations of several 2-substituted-1,3-benzothiazines. In particular the reaction of 2*H*-1,3-benzothiazine-2-thion-4(3*H*)one (I) with primary amines lead to the formation of 2-substituted 2*H*-1,3-benzothiazin-4(3*H*)ones (II) or either amides of dithiosalicylic acid (III) (Scheme I).



We now wish to report the facile synthesis of the tetracyclic system IV by reacting compound I with aromatic primary *o*-diamines. In this way a benzimidazole nucleus was fused to the 1,3-benzothiazine ring structure in order to study the biological properties of the resulting compounds. Pharmacological action is under examination.

The reaction proceeded with hydrogen sulfide elimination and cyclisation culminating with extrusion of ammonia, affording compound IV. According to the findings of Wagner and Richter (3) and to our studies (1-2), 1,3-thiazines in alkaline medium are converted into 3*H*-1,2-benzodithiole-3-thione (V). Therefore, the latter reacts with the excess amine (4) to yield benzisothiazolone derivatives (VI) as is shown in Scheme II.

We have confirmed the formation of VI by allowing

diamines to react with V under the same experimental conditions.

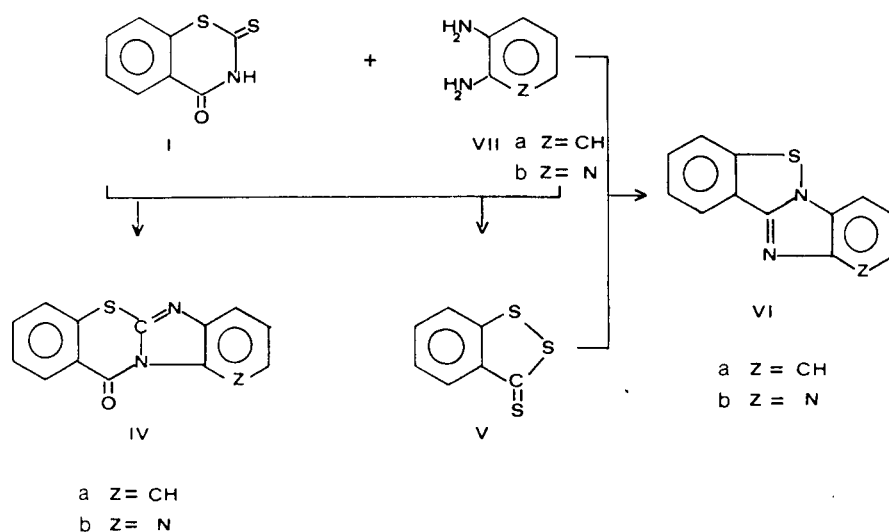
The structures of the products were assigned, based upon their mass spectra which showed a typical fragmentation. These data allow an unequivocal assignment of the structures. Fragments of importance from the standpoint of structural confirmation are found with *m/e* 224 (225), 220 (221), 136, 116, 108, 90 (91), corresponding to the modes of cleavage shown in Scheme III. Fragments with *m/e* 136 and 108 are very typical for a benzothiazine structure according to our previous findings (5) and to Lown and Ma who determined the mass spectra of non-fused thiazinones (6). Furthermore, the assignment of thiirane structure to the fragment with *m/e* 108 is in alignment with the studies of Clarke (7).

Characteristic mass spectra peaks of compounds IV are reported in Tables I and II. All main peaks indicated have a relative abundance of $\geq 2\%$ of the base peak. For those ions which contained sulfur, as indicated by peak measurements, appropriate lines corresponding to the ³⁴S isotope peak were visible at 2 mass units higher. We do not include "simple" fragmentation that have minimal interest.

EXPERIMENTAL

Microanalyses were performed by Dr. Kurt Eder, Geneva, Switzerland. Melting points were determined on a Büchi-Tottoli capillary apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer model 157 infrared spectrometer as nujol mulls. The mass spectra were measured by a J. E. O. L. JMS-01SG-2 mass spectrometer. Heating temperature of the samples was around 120-200° operating at 75 eV. Thin layer chromatography utilizing 0.25 mm silica gel Merck plates with fluorescent indicator and a solvent system consisting of ethyl acetate 7 parts to benzene 3 parts was utilized for chromatographic confirmation of the purity of compounds.

SCHEME II



SCHEME III

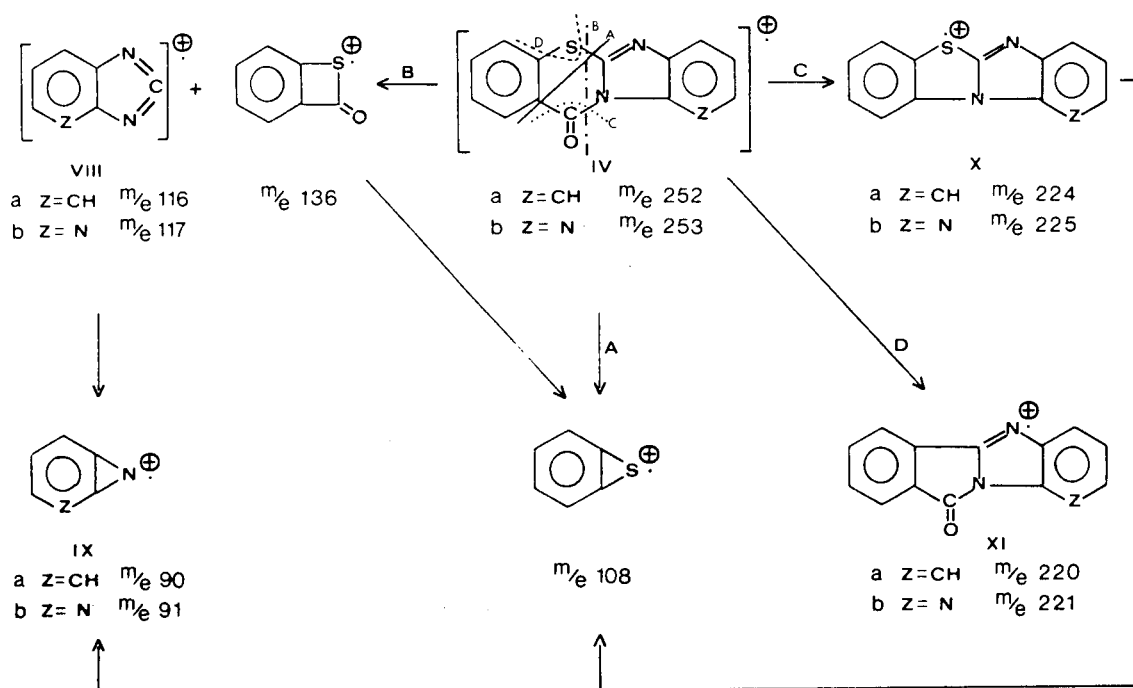


TABLE I

Characteristic Mass Spectra Peaks of Imidazobenzothiazines

Compound	Molecular ion	Common fragmentations					90	Z = CH
		M-28	M-32	138	136	108		
IVa	m/e	252	224	220			90	Z = CH
	%	100	25	5	2	11	16	23
IVb	m/e	253	225	221			91	Z = N
	%	100	9	6	2	11	10	5

TABLE II

Mass Spectra of Imidazobenzothiazines

Compound	m/e (%)	Mass Spectra
Compound IVa	m/e (%)	254 (5), 253 (18), 252 (100), 224 (25), 223 (10), 220 (5), 192 (6), 191 (3), 179 (5), 166 (6), 162 (4), 148 (4), 138 (2), 136 (11), 134 (7), 125 (5), 121 (6), 120 (11), 116 (3), 108 (16), 107 (4), 105 (9), 104 (5), 102 (4), 96 (7), 95 (4), 90 (23), 77 (12), 76 (19), 75 (11), 74 (7), 70 (7), 69 (18), 64 (14), 63 (22), 62 (7), 51 (8), 50 (19), 39 (15).
Compound IVb	m/e (%)	255 (7), 254 (18), 253 (100), 225 (9), 221 (5), 209 (8), 136 (11), 134 (5), 130 (6), 126.5 (4) (M ⁺⁺), 116 (3), 108 (10), 91 (5), 76 (6), 69 (6), 50 (5), 29 (20).

12*H*-Benzimidazo[2,1-*b*][1,3]benzothiazin-12-one (IVa).

2*H*-1,3-Benzothiazine-2-thion-4(3*H*)one (I) (2 g., 0.01 mole) and 1,2-diaminobenzene (1.3 g., 0.012 mole) were heated with stirring for five minutes, during which time hydrogen sulfide and ammonia were evolved. After cooling, the dark brown mixture was extracted with 50 ml. of ethanol from which a product separated. The crude solid precipitate (2.2 g.) (66%) was collected, washed, dried and recrystallized twice from ethanol using charcoal. White needles m.p. 222-224°; ir: 1675 cm⁻¹ (C=O); mass spectral data are shown in Table II.

Anal. Calcd. for C₁₄H₈N₂OS: C, 66.66; H, 3.17; N, 11.11; S, 12.69. Found: C, 66.74; H, 3.08; N, 11.13; S, 12.81.

Benzimidazo[1,2-*b*][1,2]benzothiazole (VIa).

(i) This compound was obtained as byproduct of the above reaction as an amorphous homogeneous powder as described for compound IVa. After removal of 12*H*-benzimidazo[2,1-*b*][1,3]-benzothiazin-12-one (IVa), the ethanolic mother liquor was poured into 200 ml. of water. The resulting precipitate was collected, washed with 100 ml. of water, dried and recrystallized from ethyl acetate affording 0.2 g. (6%) of product m.p. 285-287°; mass spectrum (characteristic peaks): m/e (relative intensity) 224 (100), 198 (6) (M-CN), 192 (6) (M-S), 134 (20), 112 (30) (M/2⁺⁺).

Anal. Calcd. for C₁₃H₈N₂S: C, 69.64; H, 3.57; N, 12.50; S, 14.28. Found: C, 69.72; H, 3.22; N, 12.24; S, 14.54.

(ii) 3*H*-1,2-Benzodithiole-3-thione (V) (1.84 g., 0.01 mole) and 1.3 g. (0.012 mole) of 1,2-diaminobenzene, were heated for eight minutes. The reaction proceeded with hydrogen sulfide elimination. After cooling the reaction mixture was extracted with 60 ml. of acetic acid. Dilution with 60 ml. of water afforded a yellow product (1.2 g.) (38.2%) which when dried and recrystallized twice from ethyl acetate using charcoal melted at 284-286° undepressed with a sample of VIa. The infrared spectra of the two samples were identical.

11*H*-Pyrido[3',2':4,5]imidazo[2,1-*b*][1,3]benzothiazin-11-one (IVb).

Condensation of 2*H*-1,3-benzothiazine-2-thion-4(3*H*)one (2 g., 0.01 mole) with 2,3-diaminopyridine (1.3 g., 0.012 mole) as described for IVa afforded a deep brown reaction mixture which, after extraction with 50 ml. of ethanol, gave 2.4 g. (72%) of IVb. After recrystallization from benzene, the product as pale yellow

crystals melted at 197-198°; ir: 1690 cm⁻¹ (C=O). Mass spectral data are shown in Table II.

Anal. Calcd. for C₁₃H₇N₃OS: C, 61.66; H, 2.76; N, 16.60; S, 12.64. Found: C, 61.72; H, 2.54; N, 16.68; S, 12.83.

Pyrido[3',2':4,5]imidazo[1,2-*b*][1,2]benzothiazole (VIb).

(i) From the ethanolic mother liquor of compound IVb, after dilution with 50 ml. of water, a yellow amorphous powder separated (0.1 g.) (3%). The product, washed with 50 ml. of water, dried and recrystallized from methanol melted at 293-294°; mass spectrum: (characteristic peaks), m/e (relative intensity) 225 (100), 199 (6) (M-CN), 193 (6) (M-S), 134 (40), 112.5 (30) (M/2⁺⁺).

Anal. Calcd. for C₁₂H₇N₃S: C, 64.00; H, 3.11; N, 18.66; S, 14.22. Found: C, 64.21; H, 2.89; N, 18.72; S, 14.36.

(ii) 3*H*-1,2-Benzodithiole-3-thione (V) (1.84 g., 0.01 mole) was heated for five minutes with 2,3-diaminopyridine (1.3 g., 0.012 mole). After cooling, the dark brown reaction mixture was extracted portionwise with 50 ml. of boiling ethanol. The combined ethanolic extracts were concentrated to give 0.8 g. (25%) of crude. An analytical sample, m.p. 292-293° was obtained by crystallizing twice from methanol using charcoal. The infrared spectrum of the sample was identical to that of VIb.

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REFERENCES AND NOTES

- (1) S. Palazzo, L. I. Giannola, S. Caronna, M. Neri, *Atti Accad. Sci. Lett. Arti Palermo*, IV, XXXIII, 411 (1974).
- (2) S. Palazzo, L. I. Giannola and M. Neri, *J. Heterocyclic Chem.*, 12, 1077 (1975).
- (3) G. Wagner and P. Richter, *Z. Chem.*, 6, 185 (1966).
- (4) E. W. McClelland, L. A. Warren and J. H. Jackson, *J. Chem. Soc.*, 1582 (1929).
- (5) Work in progress.
- (6) J. W. Lown and J. C. N. Ma, *Can. J. Chem.*, 45, 939 (1967).
- (7) G. M. Clarke, R. Grigg and D. H. Williams, *J. Chem. Soc. (B)*, 339 (1966).