Some Reactions of 2-Benzimidazolecarbonitrile

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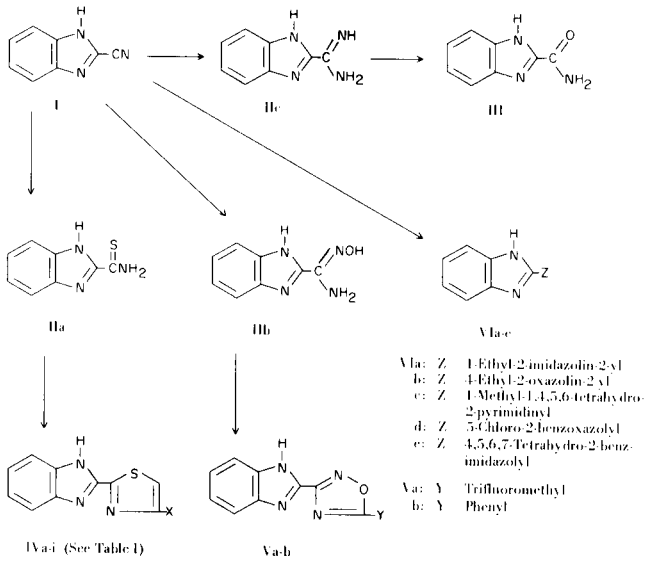
In our screening program for new anthelmintic agents, we decided to use 2-benzimidazolecarbonitrile (I) as an intermediate for the preparation of some novel benzimidazoles (2). It was hoped that I could be used to prepare the corresponding thiocarboxamide, carboxamide oxime (3) and carboxamidine (IIa-c), respectively, which in turn might be used for preparing various heterocyclic rings attached to the 2-benzimidazolyl moiety. Compounds IIa and b were readily prepared from I but IIc could not be obtained pure because of the ease with which it and ethyl 2-benzimidazolecarboximidate decomposed to 2-benzimidazolecarboxamide (III).

The formation of III was also observed in other reactions. The dehydration of 2-benzimidazolecarboxaldehyde oxime with thionyl chloride in the preparation of I, especially in the larger runs, sometimes led to substantial amounts of III which is more difficult to convert to I than the oxime. Using the conditions for preparing 2-aminoquinoxaline from 2-quinoxalinecarbonitrile and sodium hypochlorite gave III as the sole product from I instead of 2-aminobenzimidazole and carbon dioxide (4).

Several substituted thiazoles were prepared from IIa (see Table I) and two substituted 1,2,4-oxadiazoles were prepared from IIb as outlined in Scheme I. With the exception of X being a pyridyl substituent, the yields of the various thiazoles prepared were greater than 50%. Additional attempts were made to prepare IIc *via* the imidate ester when sodium methoxide was used in excess of the moles of I present. The I was recovered unchanged which was the same result previously observed when catalytic amounts of sodium methoxide were used (3).

SCHEME I



Since IIc could not be readily prepared for use in preparing heterocyclic rings in the 2-position of benzimidazole, it was thought that I might be sufficiently reactive to be used directly with difunctional nucleophiles. Indeed, it was found that I gave many heterocyclic rings of the types previously reported by Ennis, Holan and Samuel (5) besides some new variations (VIa-e) reported in this paper. The reaction of I with ethylenediamine, 1,3-diaminopropane and 1,4-diaminobutane gave 5-(imidazoline), 6-(tetrahydropyrimidine) and 7-membered (tetrahydro-1,3-diazepine) rings, respectively. The use of ethanolamine and 3-aminopropanol with I led to the formation of oxazoline and 5,6-dihydro-4*H*-1,3-oxazine rings whereas *o*-aminophenol and 2-aminobenzenethiol gave benzoxazole and benzothiazole derivatives. These compounds were previously prepared (5) using trihalomethylbenzimidazoles with the appropriate amine in solution. In our procedure, with some of the lower molecular weight difunctional amines a vigorous exothermic reaction took place after slight warming with I, while the higher melting amines were slower in reacting and were heated at a higher temperature for a longer time. The completion of the reaction was evident when ammonia evolution ceased or the liquid phase solidified. Yields for this reaction were in the range of 50% to nearly quantitative and only the preparation of derivatives (VIa-e), not previously reported is described in the experimental section.

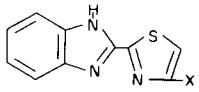
In conclusion, our work with the nitrile I shows that it is reactive and can be readily converted to a variety of ring systems using conventional reactions for nitriles. None of the derivatives prepared had significant activity as anthelmintic agents.

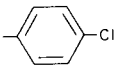
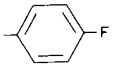
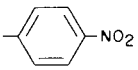
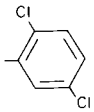
EXPERIMENTAL

Melting points were determined on a Thomas-Hoover "Unimelt" or Kofler apparatus and are uncorrected. The infrared spectra were obtained on a Beckman IR4 spectrophotometer.

TABLE I

2-(4-Substituted-2-thiazolyl)benzimidazoles (IVa-i)



Compound IV	X	Recryst. Solvent	Yield %	M.p., °C	Formula	Analyses % - Calcd. (Found) C	H	N
a		MeOH	95 (a)	195-196.5	$C_{16}H_{11}N_3S$	69.29 (69.39	4.00 3.89	15.15 15.20)
b		MeOH	69	230.5-231.5	$C_{16}H_{10}ClN_3S$	61.64 (61.77	3.23 3.06	13.48 13.58)
c		MeOH	52	209-210	$C_{16}H_{10}FN_3S$	65.07 (64.89	3.41 3.32	14.23 14.37)
d		MeOH	59	295.5-296	$C_{16}H_{10}N_4O_2S$	59.62 (59.55	3.13 3.06	17.38 17.41)
e		MeOH	54	205.5-206	$C_{16}H_9Cl_2N_3S$	55.50 (55.80	2.62 2.62	12.14 12.31)
f		EtOH	56	179-182	$C_{14}H_9N_3OS$	62.91 (63.00	3.39 3.30	15.72 15.73)
g		MeOH	57	210.5-212	$C_{14}H_9N_3S_2$	59.34 (59.05	3.20 3.06	14.83 14.56)
h		MeOH	38	278-279	$C_{15}H_{10}N_4S$	64.73 (64.95	3.62 3.64	20.13 20.20)
i		MeOH	29	287-288	$C_{15}H_{10}N_4S$	64.73 (64.64	3.62 3.48	20.13 20.09)

(a) Only the analytical sample was recrystallized from methanol in this case. All other yields are based on the recrystallized material from the specified solvent.

2-Benzimidazolethiocarboxamide (IIa).

2-Benzimidazolecarbonitrile (28.6 g., 0.2 mole) and thioacetamide (30 g., 0.4 mole) were added to dimethylformamide (200 ml.) and the stirred slurry was placed in an ice bath while dry hydrogen chloride was added for 15 minutes. The ice bath was removed and stirring continued for 30 minutes. An equal volume of ice was added and, after it had melted, the mixture was allowed to stand overnight in the refrigerator. The bright yellow solid was collected on a filter and then the wet cake was transferred to a beaker. It was cooled in an ice bath while concentrated ammonium hydroxide was added to the hydrochloride salt until the *p*H was

7-8. The solid was collected by filtration, washed with water and dried at 85° to yield 32 g. (90%) of light yellow product, m.p. 213-215°. An analytical sample was prepared by recrystallization from methanol, m.p. 216-217°; ir (potassium bromide), cm^{-1} 1305 (C-N), 1125 (C=S).

Anal. Calcd. for $C_8H_7N_3S$: C, 54.21; H, 3.98; N, 23.71. Found: C, 54.41; H, 4.04; N, 23.80.

2-(4-Phenyl-2-thiazolyl)benzimidazole (IVa).

A solution of IIa (12.4 g., 0.07 mole) and phenacyl bromide (14.3 g., 0.072 mole) in 3:1 acetic acid-water (100 ml.) was refluxed for 30 minutes. The solution was chilled and the yellow hydrobromide salt was collected on a filter. The solid was transferred to a beaker with the addition of some water and basified with ammonium hydroxide to *p*H 8-9. The slurry was heated on a steam cone and filtered while hot. The solid was washed with water and dried leaving 18.5 g. (95%) of product, m.p. 194-197°. The crystallization solvent for the analytical samples, as well as the compounds IVb-i, is recorded in Table I together with the melting points of each purified compound. All of the compounds in Table I were prepared from IIa and the appropriate bromomethyl ketone by refluxing in an acetic acid-water solution for 30-60 minutes and proceding as with IVa. The bromomethyl ketones were purchased or prepared by literature methods (6-9).

4,4′-bis[2-(2-Benzimidazolyl)thiazole] (IVj).

A hot solution of IIa (18.5 g., 0.104 mole), 1,4-dibromo-2,3-butanedione (12.7 g., 0.052 mole) and methanol (250 ml.) was filtered and then refluxed for 20 minutes. The solution was chilled in ice and the hydrobromide salt collected on a filter. Three additional crops were obtained from the mother liquor and the combined solids were recrystallized from dimethylformamide-water giving 8.5 g. (40%) of light yellow base, not melting up to 350°. An analytical sample of white solid was obtained by recrystallizing from dimethylformamide-water. It gradually darkened above 340° without melting.

Anal. Calcd. for $C_{20}H_{12}N_6S_2$: C, 59.98; H, 3.02; N, 20.99. Found: C, 59.61; H, 3.01; N, 20.75.

2-Benzimidazolecarboxamide oxime (IIb).

A modification for the preparation of this previously reported compound (3) is described. A mixture of I (28.6 g., 0.2 mole), hydroxylamine hydrochloride (15 g., 0.22 mole), and sodium acetate (20.5 g., 0.25 mole) was refluxed in 5:1 ethanol-water (600 ml.) for 30 minutes. The solution was chilled well in ice, then the white needles were collected on a filter, and washed with water. Additional solid was obtained from the filtrate so that a total of 23.3 g. (92%) was obtained, m.p. 223-225°.

2-(5-Trifluoromethyl-1,2,4-oxadiazol-3-yl)benzimidazole (Va).

To a mixture of trifluoroacetic anhydride (31.5 g., 0.15 mole) and toluene (150 ml.) was added IIb (8.8 g., 0.05 mole) which was then refluxed for 10 minutes. It was cooled and the solid collected on a filter, and washed with toluene. It was purified by crystallization from ethanol-water to obtain 5.9 g. (69%) of white solid, m.p. 172-173°; ir (potassium bromide) cm^{-1} 1620 (C=N), 1605 (C=C), 1220-1147 (CF_3), 1020 (C-O).

Anal. Calcd. for $C_{10}H_5F_3N_4O$: C, 47.26; H, 1.98; N, 22.04. Found: C, 47.14; H, 1.94; N, 22.31.

2-(5-Phenyl-1,2,4-oxadiazol-3-yl)benzimidazole (Vb).

A mixture of IIb (3.52 g., 0.02 mole) and benzoic anhydride (10.0 g., 0.044 mole) was refluxed in toluene (100 ml.) for one hour. After cooling, the solid was collected on a filter and then washed with ammonium hydroxide followed by water. Upon drying, 4.4 g. of crude product, m.p. 210-215°, was obtained. Crystallization from methanol gave white crystals, m.p. 222-223°, of the benzoate ester; ir (potassium bromide), cm^{-1} 1770 (C=O).

Anal. Calcd. for $C_{15}H_{12}N_4O_2$: C, 64.27; H, 4.32; N, 19.99. Found: C, 64.21; H, 4.19; N, 20.10.

2-Benzimidazolecarboxamide oxime benzoate (2.8 g., 0.01 mole) was heated at 225° for 2 hours and then cooled and crystallized from methanol, which gave 2.0 g. (60% yield from IIb) of Vb, m.p. 248-252°. Recrystallization from methanol gave an analytical sample of cream-colored crystals, m.p. 256-257°; ir (potassium bromide), cm^{-1} 1620 (C=N), 1605 and 1575 (C=C), 1020 (C-O).

Anal. Calcd. for $C_{15}H_{10}N_4O$: C, 68.69; H, 3.84; N, 21.37. Found: C, 68.86; H, 3.86; N, 21.46.

2-(1-Ethyl-2-imidazolin-2-yl)benzimidazole (VIa).

A mixture of 2-benzimidazolecarbonitrile (14 g., 0.1 mole) and *N*-ethyl ethylenediamine (10 g., 0.11 mole) was heated to 140° for 2 minutes when it solidified. The solid was dissolved in hot methanol (charcoal), filtered, some water added and crystallized to yield 17 g. (79%), m.p. 184-185°. An analytical sample was obtained as white crystals from methanol, m.p. 185-186°; ir (potassium bromide), cm^{-1} 1625 (C=N), 1595 (C=C).

Anal. Calcd. for $C_{12}H_{14}N_4$: C, 67.27; H, 6.59; N, 26.15. Found: C, 67.33; H, 6.63; N, 26.33.

2-(4-Ethyl-2-oxazolin-2-yl)benzimidazole (VIb).

A mixture of I (21.5 g., 0.15 mole) and 2-amino-1-butanol (16 g., 0.18 mole) was heated to 125° for 5 minutes. The tacky solid was recrystallized from methanol-water giving 19 g. (60%) of product, m.p. 218-219°. A purified sample of white crystals was obtained from methanol-water, m.p. 219-220°; ir (potassium bromide) cm^{-1} 1637 (C=N), 1600 (C=C), 1155 (C-O-C).

Anal. Calcd. for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.98; H, 6.04; N, 19.85.

2-(1-Methyl-1,4,5,6-tetrahydro-2-pyrimidinyl)benzimidazole (VIc).

A mixture of I (14.3 g., 0.1 mole) and *N*-methyl-1,3-diaminopropane (12 g., 0.14 mole) was heated to 140-150° for 15 minutes. The white solid was washed with water and dried giving 18.9 g. (88%), m.p. 216-219°. An analytical sample of white needles, m.p. 218-219°, was obtained by crystallization from methanol-water; ir (potassium bromide), cm^{-1} 2850 (N-CH_3), 1625 (C=N), 1575 (C=C).

Anal. Calcd. for $C_{12}H_{14}N_4$: C, 67.26; H, 6.59; N, 26.15. Found: C, 67.28; H, 6.56; N, 26.17.

2-(5-Chloro-2-benzoxazolyl)benzimidazole (VId).

A mixture of I (20 g., 0.14 mole) and 2-amino-4-chlorophenol (21 g., 0.15 mole) was heated to 165° for 1 hour. The solid was crystallized from dimethylformamide-water to yield 34 g. (90%), m.p. 250-252°. An analytical sample was prepared by recrystallization from dimethylformamide-water, pale tan crystals, m.p. 254-256°; ir (potassium bromide), cm^{-1} 1645 (C=N), 1595 (C=C), 1145 (C-O-C).

Anal. Calcd. for $C_{14}H_8ClN_3O$: C, 62.35; H, 2.99; N, 15.58. Found: C, 62.27; H, 3.25; N, 15.71.

2-(4,5,6,7-Tetrahydro-2-benzimidazolyl)benzimidazole (VIe).

A mixture of I (2.86 g., 0.02 mole) and 1,2-diaminocyclohexane (3.4 g., 0.021 mole) was heated to 185° for 10 minutes. A crude yield of 4.6 g. (96%) was obtained after washing the crushed solid

with methanol. An analytical sample was prepared by crystallizing twice from dimethylformamide-water, sublimes 350° without melting.

Anal. Calcd. for $C_{14}H_{16}N_4$: C, 69.96; H, 6.71; N, 23.31. Found: C, 70.01; H, 6.75; N, 23.46.

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