benzene[6]—To a warm solution of 0.040 g. of VII in 2 ml. of 95% ethanol was added a warm solution of 0.040 g. of 1,3,5-trinitrobenzene in 2 ml. of 95% ethanol. The reaction mixture was allowed to stand at room temperature for 0.5 hr. The yellow crystalline product was collected and dried: yield 0.050 g. (68.5%); m.p. 162–162.5°. Crystallization from 95% ethanol gave the trinitrobenzene complex of VII as yellow stout needles. m.p. 162.5–163°, $[\alpha]^{26}D$ −15°, lit.[5] m.p. 158–163.

Anal. Calcd. for $C_{26}H_{23}N_9O_6$: C, 65.95; H, 4.90; N, 8.88. Found: C, 66.12; H, 5.04; N, 8.54.

Novel Preparation of Benzimidazoles from N-Arylamidines. New Synthesis of Thiabendazole[1]

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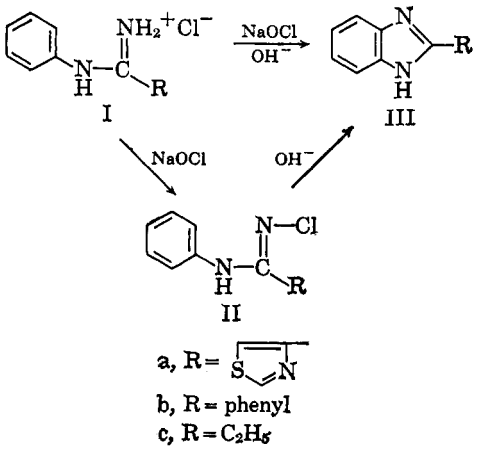
A new, efficient procedure for the conversion of N-arylamidines with hypochlorite and base to benzimidazoles has been devised. Using this technique, a new synthesis of thiabendazole has been realized.

Because of the increasing importance of benzimidazoles in recent chemical literature,[2] we felt that a simpler approach to the synthesis of these heterocyclics other than that described by Brown, *et al.*,[2] would be of great value. The procedure for preparing benzimidazoles usually involves the condensation of *o*-phenylenediamine or *o*-nitroaniline with a carboxylic acid derivative.[3] In each case, the cyclization directly involves a coupling at the *o*-phenylene nitrogens.

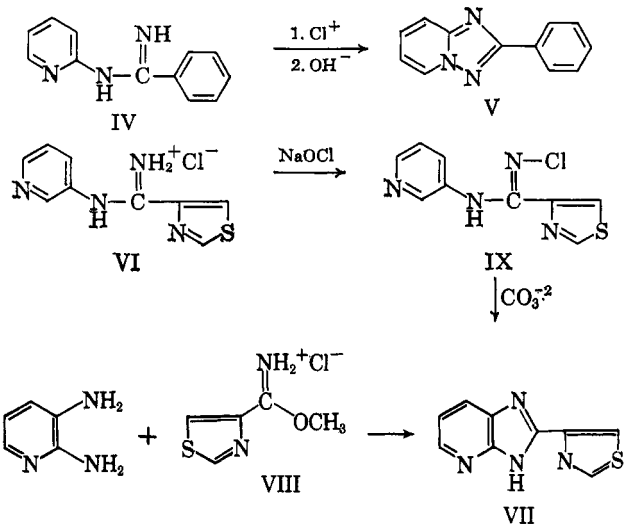
Since N-arylamidines are available[4] by the reaction of an aromatic amine with a nitrile or imidate, it appeared that substituted amidines I were potential precursors for benzimidazoles if they could be induced to cyclize by some oxidative process. A previous method[5] for the conversion of some amidines to benzimidazoles required the preparation of N-hydroxyamidines from amidines and hydroxylamine with the subsequent benzimidazole formation after treatment with benzenesulfonyl chloride and pyridine.

It was found that the N-arylamidine hydrochlorides I could, indeed, be transformed to benzimidazoles with 1 mole of sodium hypochlorite and base in excellent yields under mild conditions. The N-chloroamidine II might be isolated as a discrete intermediate, if desired prior to the addition of base. For example, in the preparation of 2-(4-thiazolyl)benzimidazole (IIIa, generic name thiabendazole),[1] an aqueous methanolic solution of N′-phenyl-4-thiazolecarboxamidine hydrochloride (Ia) was treated with 1 mole of sodium hypochlorite to form the crystalline N-chloroamidine IIa which could be isolated or processed directly with 1 equiv. of base in refluxing aqueous methanol to the benzimidazole IIIa in 98% yield. The benzimidazole formation could be followed by the disappearance of the positive halogen with potassium iodide–starch paper.



In a similar manner, N-phenylbenzamidine[5] (Ib) and N-phenylpropionamidine[6] (Ic) yielded 2-phenylbenzimidazole (IIIb, 94% yield) and 2-ethylbenzimidazole[7] (IIIc, 70% yield), respectively.

In order to extend our oxidative cyclization process to the preparation of azabenzimidazoles, we synthesized N-(2-pyridyl)benzamidine[8] (IV) and N′-(3-pyridyl)-4-thiazolecarboxamidine (VI). The amidines IV and VI were converted as hydrochlorides to their N-chloroamidines, respectively, and cyclized upon treatment with caustic. It is interesting to note that in the case of N-(2-pyridyl)benzamidine (IV) cyclization occurred at the pyridine nitrogen to produce 2-phenyl-1,3,3a-tri-



(1) United States Accepted Nomenclature approved generic name. The registered trade-mark of Merck & Co., Inc., for this anthelmintic is Thibenzole®.

(2) H. D. Brown, A. R. Matzuk, I. R. Ilves, L. H. Peterson, S. A. Harris, L. H. Sarett, J. R. Egerton, J. J. Yakstis, W. C. Campel, and A. C. Cuckler, *J. Am. Chem. Soc.*, **83**, 1764 (1961).

(3) E. S. Schipper and A. R. Day, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p. 267.

(4) R. L. Shriner and F. W. Neumann, *Chem. Rev.*, **35**, 351 (1944).

(5) M. W. Partridge and H. A. Turner, *J. Chem. Soc.*, 2086 (1958).

(6) R. Scholl and E. Bertsch, *Monatsh*, **39**, 238 (1918).

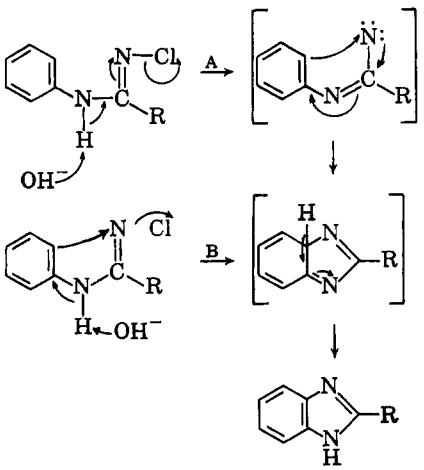
(7) E. L. Holljes, Jr., and E. C. Wagner, *J. Org. Chem.*, **9**, 31 (1944).

(8) P. Oxley, M. W. Partridge, and W. F. Short, *J. Chem. Soc.*, 1110 (1947).

azaindene[9] (V). The structure of the compound isolated from the cyclization of VI was demonstrated to be 2-(4-thiazolyl)-4-azabenzimidazole (VII, 23% yield) by comparison with an authentic sample obtained from the reaction of 2,3-diaminopyridine and methyl thiazolyl-4-carboximidate hydrochloride (VIII).

In the examples cited above, the amidines were prepared by treating aniline or 2-aminopyridine with a nitrile in the presence of aluminum chloride[8] or hydrogen chloride.[6] N-(3-Pyridyl)-4-thiazolecarboxamidine hydrochloride (VI) was obtained from the imino ether[10] hydrochloride (VIII) of 4-cyanothiazole[11] and 3-aminopyridine.

Although the complications of ring-chlorinated side products might be anticipated after treating N-arylamidines with hypochlorite, this difficulty was not observed in the examples cited. Mechanistic interpretations of the described conversions of N-chloroamidines to benzimidazole suggest either an imine radical intermediate (path A) or a bond-making–bond-breaking participation sequence (path B).



Experimental[12]

N'-Phenyl-4-thiazolecarboxamidine Hydrochloride (Ia).—To a solution of 5.00 g. (45.5 mmoles) of 4-cyanothiazole[11] and 4.23 g. (45.4 mmoles) of aniline in 18 ml. of *sym*-tetrachloroethane there was added rapidly with stirring 6.06 g. (45.4 mmoles) of anhydrous aluminum chloride. The temperature increased spontaneously to 80° during addition and thereafter the reaction was refluxed for 20 min., during which time the aluminum chloride complex separated as a viscous oil. The mixture was cooled to room temperature and excess 5 *N* sodium hydroxide was added to decompose the complex and dissolve the precipitated aluminum hydroxide. The organic layer was separated and the aqueous layer was extracted with three 5-ml. portions of methylene chloride. The combined organic layers were washed with water, dried over anhydrous potassium carbonate, and filtered. Addition of dry hydrogen chloride to the filtrate yielded Ia, 9.07 g. (83%), m.p. 258–260° dec. Concentration of the mother liquors afforded a second crop (1.50 g.) which required recrystallization from ethanol: 0.78 g. (7%), m.p. 256–259° dec. An analytical sample was obtained from isopropyl alcohol–ethyl acetate, m.p. 258–260° dec.

Anal. Calcd. for $C_{10}H_{10}ClN_3S$: C, 50.10; H, 4.20; Cl, 14.79; N, 17.53; S, 13.38. Found: C, 50.12; H, 4.46; Cl, 14.71; N, 17.54; S, 13.65.

2-(4-Thiazolyl)benzimidazole (IIIa).—To a stirred solution of 10 g. (41.7 mmoles) of N-phenyl-4-thiazolecarboxamidine hydrochloride (Ia) in 120 ml. of 50% aqueous methanol there was added at room temperature 14.5 ml. of 2.88 *M* sodium hypochlorite[13] (41.7 mmoles) to yield a suspension of the intermediate N-chloro compound IIa. After about 5 min. of continued stirring, 5.75 g. (54.3 mmoles) of sodium carbonate was added as a saturated solution and the mixture refluxed for 20 min. The suspension was cooled to room temprature, collected by filtration, and washed well with water. After drying *in vacuo*, the product weighed 8.20 g. (98%): m.p. 296–297°, equiv. wt. 205 (calcd. 201). Recrystallization by dissolving the product in hot dilute hydrochloric acid and adjusting the pH of the hot solution to 6 with dilute ammonium hydroxide yielded a 93% recovery: m.p. 301–302° (lit.[2] m.p. 304–305°), $\lambda_{max}^{0.1\,N\,HCl}$ 301 mμ (ε 25,500), 241 mμ (ε 13,270).

Anal. Calcd. for $C_{10}H_7N_3S$: C, 59.68; H, 3.51; N, 20.88; S, 15.93. Found: C, 59.74; H, 3.62; N, 20.57; S, 15.99.

The intermediate N-chloro-N'-phenyl-4-thiazolecarboxamidine (IIa) may be isolated prior to carbonate addition by filtration. A better method for the preparation of IIa was the addition of hypochlorite to amidine hydrochloride Ia in a system of methylene chloride–water. The N-chloroamidine IIa was extracted into the methylene chloride layer, dried over sodium sulfate, and concentrated to a crystalline solid (98%), m.p. 93–96.5°.

Anal. Calcd.: Cl, 14.92; mol. wt., 238. Found: Cl, 15.20; mol. wt. (iodometry of positive halogen concentration), 236.

Recrystallization from methylene chloride–cyclohexane yielded an analytical sample, m.p. 97–99°.

Anal. Calcd. for $C_{10}H_8ClN_3S$: C, 50.53; H, 3.39; Cl, 14.92; N, 17.68; S, 13.49. Found: C, 50.75; H, 3.41; Cl, 14.64; N, 17.47; S, 13.69.

Conversion of the N-Chloro Intermediate IIa to IIIa.—A stirred suspension of 10 g. (42.1 mmoles) of N-chloro-N'-phenyl-4-thiazolecarboxamidine (IIa) in 120 ml. of 50% aqueous methanol was treated with 1.77 g. (44.2 mmoles) of sodium hydroxide in 3 ml. of water. The mixture was refluxed for 15 min., then cooled to room temperature, (negative potassium iodide–starch paper test), and the pH was adjusted to 6 with dilute hydrochloric acid. The crystalline product was collected on a funnel, washed well with water, and air dried to yield 8.15 g. (96%) of IIIa, m.p. 300–302°. Recrystallization from hot dilute hydrochloric as described above resulted in a pure product, m.p. 300–301.5° (95% recovery), which was identical with compound IIIa as obtained above by infrared, ultraviolet, and paper chromatographic analysis (R_f 0.61, 0.1 *N* HCl–capryl alcohol).

2-Phenylbenzimidazole (IIIb).—To a stirred solution of 3.92 g. (20 mmoles) of N-phenylbenzamidine[5] in 40 ml. of methanol containing 20 ml. of 1 *N* hydrochloric acid there was added at room temperature 13.5 ml. of 1.56 *M* sodium hypochlorite[13] (21 mmoles). After about 5 min. of stirring, 2.76 g. (26 mmoles) of sodium carbonate was added as a saturated aqueous solution and the mixture refluxed for 30 min. The reaction was cooled to room temperature and the product was collected by filtration and washed with 50% aqueous methanol followed by water until carbonate free. After drying *in vacuo*, the product weighed 3.65 g. (94%): m.p. 290–292° (lit.[5] m.p. 288°), λ_{max}^{MeOH} 302 mμ (ε 24,000).

Anal. Calcd. for $C_{13}H_{10}N_2$: C, 80.38; H, 5.19; equiv. wt., 194. Found: C, 80.12; H, 5.33; equiv. wt., 198.

The intermediate N-chloro compound IIb may be prepared as described for IIa: m.p. 130–131.5° (from methylene chloride–petroleum ether), 85% yield.

Anal. Calcd. for $C_{13}H_{11}ClN_2$: C, 67.67; H, 4.81; Cl, 15.37; N, 12.14. Found: C, 67.94; H, 4.92; Cl, 15.46; N, 11.87.

2-Ethylbenzimidazole (IIIc).—A solution of 7.40 g. (50 mmoles) of N-phenylpropionamidine[6] in 150 ml. of 50% aqueous methanol was treated with 4.27 ml. (50 mmoles) of concentrated hydrochloric acid at 10°. With stirring, 37.5 ml. of 1.40 *M* sodium hypochlorite[13] was added, followed in 5 min. by a solution of 2.10 g.

(9) J. D. Bower and G. R. Ramage, *J. Chem. Soc.*, 4506 (1957); J. D. Bower, *ibid.*, 4510 (1957).

(10) F. C. Schaefer and G. A. Peters, *J. Org. Chem.*, **26**, 412 (1961).

(11) P. Brookes, R. J. Clark, A. T. Fuller, M. P. V. Mijovic, and J. Walker, *J. Chem. Soc.*, 916 (1960).

(12) Melting points are uncorrected. We are indebted to R. W. Walker and N. Allen for infrared spectra, to A. Kalowsky for ultraviolet spectra, to J. P. Gilbert and associates for equivalent weight determinations, to R. N. Boos and associates for elemental analyses, to N. R. Trenner and B. Arison for n.m.r. spectra, and especially to W. Ding for technical assistance.

(13) M. S. Newman and H. L. Holmes, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 429; to obtain 2.8–3.0 *M* sodium hypochlorite we have found it convenient to employ 80 g. of sodium hydroxide in 270 ml. of water at 0–5° and introduce 70 g. of chlorine gas with stirring and cooling.

(52.5 mmoles) of sodium hydroxide in 5 ml. of water. The reaction was refluxed for 30 min. (until positive halogen concentration diminished), then cooled to room temperature to yield a crystalline mass. The product was collected on a funnel, washed with methanol–water, and dried *in vacuo:* weight 4.3 g. (59%), m.p. 167–172°. An additional crop was obtained by removing much of the methanol *in vacuo:* 1.9 g. (26%), m.p. 161–167°. The combined crops (6.2 g.) were recrystallized from 400 ml. of boiling water to yield 5.1 g. (70%): m.p. 166–170° (lit.[7] m.p. 172°), λ_{max}^{MeOH} 281 mμ (ε 8,220).

Anal. Calcd. for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N, 19.16. Found: C, 73.58; H, 6.58; N, 19.45.

Methyl Thiazolyl-4-carboximidate Hydrochloride (VIII).—To a solution of 100 g. (0.908 mole) of 4-cyanothiazole[11] in 300 ml. of anhydrous methanol there was added with stirring a solution of 5.47 g. (0.101 mole) of sodium methoxide in 100 ml. of methanol. The solution was stirred for 17 hr. at room temperature, after which the catalyst was neutralized by the addition of 6.08 g. (0.101 mole) of glacial acetic acid. The reaction mixture was concentrated *in vacuo* to a crystalline mass and the product free base was extracted from sodium acetate with methylene chloride. The hydrochloride VIII was crystallized from 1 l. of methylene chloride by the addition of 99 ml. of 8.96 *N* methanolic hydrogen chloride: yield 148 g. (92%), m.p. 151–154° dec. Recrystallization from methanol–ether produces an analytical sample, m.p. 151–154° dec.

Anal. Calcd. for $C_5H_7ClN_2OS$: C, 33.62; H, 3.95; N, 15.68. Found: C, 33.54; H, 3.95; N, 15.81.

N′-(3-Pyridyl)-4-thiazolecarboxamidine Hydrochloride (VI).—A mixture of 20 g. (0.112 mole) of VIII and 10.5 g. (0.112 mole) of 3-aminopyridine in 50 ml. of ethanol was stirred at room temperature for 17 hr., after which the crystalline product was collected on a funnel, washed with ethanol, and dried *in vacuo*. The yield of crude product was 17.2 g. (64%), m.p. 214–217° dec. Recrystallization from methanol–ether produced 12.2 g. of pure product, m.p. 223–225°.

Anal. Calcd. for $C_9H_9ClN_4S$: C, 44.90; H, 3.77; Cl, 14.73; N, 23.28; S, 13.32; equiv. wt., 241. Found: C, 44.71; H, 3.83; Cl, 14.73; N, 23.79; S, 13.62; equiv. wt., 241.

N-Chloro-N′-(3-pyridyl)-4-thiazolecarboxamidine (IX).—A solution of 5.00 g. (20.8 mmoles) of VI in a mixture of 40 ml. of water and 40 ml. of methylene chloride was stirred at room temperature with 7.30 ml. of 2.85 *M* sodium hypochlorite[13] (20.8 mmoles) for 15 min. The organic layer was separated and the aqueous phase was extracted with two small portions of methylene chloride. After drying over sodium sulfate and removing the drying agent by filtration, the filtrate was concentrated to a small volume and the product was crystallized by the addition of petroleum ether: 4.42 g. (89%), m.p. 143–144° dec. Recrystallization from ethyl acetate yielded an analytical sample, m.p. 146–147°.

Anal. Calcd. for $C_9H_7ClN_4S$: C, 45.28; H, 2.96; Cl, 14.85; N, 23.47. Found: C, 45.47; H, 2.78; Cl, 14.83; N, 23.46.

2-(4-Thiazolyl)-4-azabenzimidazole (VII).—To a stirred suspension of 2.00 g. (8.38 mmoles) of IX in 24 ml. of 50% aqueous methanol there was added 0.98 g. (9.22 mmoles) of sodium carbonate as a saturated aqueous solution. The mixture was refluxed until the positive halogen test on potassium iodide–starch paper was negative (20 min.), after which it was cooled to room temperature, filtered, and washed with cold 50% aqueous methanol, then water to yield 0.39 g. (23%) of product, m.p. 304–307°. Recrystallization from methanol produced a sample melting 310–311°, $\lambda_{max}^{0.1\ N\ HCl}$ 321 mμ (ε 29,600), which was identical with the imidazole VII obtained by condensing 2,3-diaminopyridine and VIII by infrared, ultraviolet and n.m.r. analysis.

Anal. Calcd. for $C_9H_6N_4S$: C, 53.45; H, 2.99; N, 27.70. Found: C, 53.50; H, 2.70; N, 27.57.

Compound VII from 2,3-Diaminopyridine.—A suspension of 2,3-diaminopyridine (15 g., 0.137 mole) and 24.5 g. (0.137 mole) of VIII in 63 ml. of ethanol was stirred at room temperature for 18 hr., after which the crystalline product was collected and washed with ethanol (25 ml.) and water. After drying *in vacuo*, the product weighed 4.36 g., m.p. 308–309°. The mother liquors deposited an additional sample weighing 6.30 g., m.p. 290–292°. Recrystallization from methanol yielded a sample: m.p. 310–312.5°, $\lambda_{max}^{0.1\ N\ HCl}$ 320 mμ (ε 30,200). The product was identical with VII obtained from compound IX by infrared, ultraviolet, n.m.r., and microchemical analysis.

2-Phenyl-1,3,3a-triazaindene (V).—To a solution of 10 g. (50.7 mmoles) of N′-(2-pyridyl)benzamidine[8] (IV) in a mixture of 50 ml. of methylene chloride and 50 ml. of water at 5° there was added with stirring 50.7 ml. of 1 *N* hydrochloric acid followed by 18.1 ml. of 2.81 *M* sodium hypochlorite[13] (50.7 mmoles). After stirring 30 min. at 10°, the organic layer was removed and the aqueous layer was extracted with three 5-ml. portions of methylene chloride. The combined organic layers were washed with water and then dried over anhydrous sodium sulfate. Filtration and concentration yielded a crystalline N-chloro intermediate which was washed with ethanol and dried *in vacuo:* 9.43 g., m.p. 85–87°. Five grams (21.6 mmoles) of the intermediate was suspended in 60 ml. of 50% aqueous methanol and treated with 2.75 g. (25.9 mmoles) of sodium carbonate in the usual manner. The product weighed 3.90 g. (74%) based on starting amidine IV: m.p. 135–137.5°. Recrystallization from acetone produced a sample: m.p. 138–139° (lit.[9] m.p. 141°); picrate m.p. 164–166° (lit.[9] m.p. 168°). The ultraviolet spectrum of V in cyclohexane was identical with reported values.

Anal. Calcd. for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.52; H, 4.41; N, 21.39.

Allene Chemistry. III.[1] Free-Radical Addition of Hydrogen Sulfide to Allene

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Hydrogen sulfide and allene have been allowed to react in varying relative ratios under typical free-radical conditions in the liquid phase at −70°. The reactions occurred selectively by terminal attack of the sulfhydryl radicals on allene. 3-Propenethiol was formed as the primary reaction product. If hydrogen sulfide was used in an excess, 3-propenethiol reacted further to form 1,3-propanedithiol in good yield. When allene was used in excess, diallyl sulfide was formed in moderate yield, along with oligomers of 3-propanethiol and other by-products.

The first definitely free-radical addition of hydrogen sulfide to an olefinic double bond was reported by Vaughan and Rust[3] in 1942. They found that under the influence of ultraviolet light addition occurred very rapidly even at −78° and was highly selective yielding "anti-Markownikoff" products. Based on their results and the similar course of thiol–olefin additions,[4] they proposed the following mechanism for the reaction.

$$(H_2S \longrightarrow) HS\cdot + CH_2{=}CHR \longrightarrow$$

$$HSCH_2\dot{C}HR \xrightarrow{H_2S} HSCH_2CH_2R + HS\cdot$$

The generality of this mechanism has subsequently been confirmed by the similar course of the free-radical

(1) Allene Chemistry II: K. Griesbaum, A. A. Oswald, and D. N. Hall, *J. Org. Chem.*, **29**, 2404 (1964).

(2) Author to whom correspondence should be addressed.

(3) W. E. Vaughan and F. F. Rust, *J. Org. Chem.*, **7**, 472 (1942); U. S. Patents 2,398,479 (1946) and 2,392,295 (1946).

(4) M. S. Kharasch, A. T. Read, and F. R. Mayo, *Chem. Ind.* (London), **57**, 752 (1938).