Benzimidazoles. I. 2-(Heterocyclic Substituted)benzimidazoles

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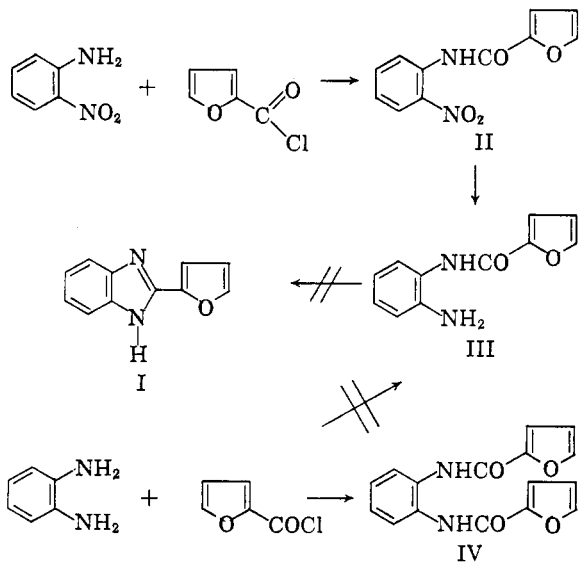
The syntheses and properties of benzimidazoles substituted in the 2-position with various heterocyclic moieties are described and discussed.

In view of the general interest in heterocyclic compounds in our laboratories and also the increasing interest[1-3] in certain benzimidazole derivatives described here, it seemed appropriate to record our experiences with syntheses in this series.

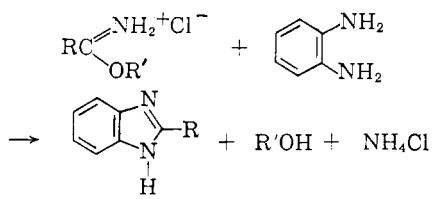
In this study, the synthesis of the model, 2-(2-furyl)benzimidazole (I), was considered in detail, since the furan intermediates were more readily available and were probably the least stable of the series. Furthermore, syntheses of I have already been the subject of considerable discussion.[1,2,4,5]

That this synthesis is not a straightforward problem is attested by the observations that the classic Phillips synthesis[6] failed to produce I, a modification[6] of the Phillips synthesis using a sealed tube served only to carbonize the starting materials, and polyphosphoric acid did likewise. Further attempts to utilize furan acid intermediates were unsuccessful when it was found that *o*-phenylenediamine gave only the bisacylated product (IV) upon treatment with furoyl chloride in pyridine. When III finally was obtained through reduction of II, it could not be converted to I, even by heating at reflux in xylene in the presence of *p*-toluenesulfonic acid.



On the other hand, 2-furaldehyde with *o*-phenylenediamine in the presence of certain oxidizing agents readily gave I in good yields.[1,2,4] The Weidenhagen synthesis[4]—*i.e.*, in which cupric acetate is the oxidizing agent—was also employed in this study, with generally good results, to produce several of the new benzimidazoles listed in Table I. It also was noticed that air can act as the oxidizing agent in this method, although the possibility was not investigated further.

It was of considerable interest to us to develop a method involving very mild conditions with few side reactions and other possible sources of contamination. The little-studied benzimidazole synthesis utilizing imido esters[7] provided such a method. Several of the derivatives in Table I were produced in good yields under the extremely mild conditions of this reaction. It was found possible to use higher homologs of *o*-phenylenediamine successfully. Similar attempts with 4-chloro- and 4-nitro-*o*-phenylenediamine and 2,3-diaminopyridine failed. The imido ester method of benzimidazole synthesis will be the subject of a subsequent paper in this series.

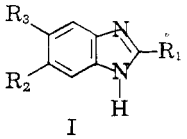


The spectral data of Table II serve to establish the structures assigned to these benzimidazoles. It is difficult to derive any further information regarding the nature of the compounds from these spectra than has already been given in a pertinent discussion in footnote *c* of Table II.

(1) D. Jerchel, H. Fischer, and M. Kracht, *Ann.*, **575**, 162 (1952).
(2) D. Jerchel, M. Kracht, and K. Krucker, *ibid.*, **590**, 232 (1954).
(3) 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. Campbell, and A. C. Cuckler, *J. Am. Chem. Soc.*, **83**, 1764 (1961); *Chem. and Eng. News*, p. 39, May 1, 1961.
(4) R. Weidenhagen, *Ber.*, **69**, 2263 (1936).
(5) C. F. Huebner, R. Lohmar, R. J. Dimler, S. Moore, and K. P. Link, *J. Biol. Chem.*, **159**, 503 (1945).
(6) For discussion and leading references, see: K. Hofmann, "Part I. Imidazole and Its Derivatives" in "The Chemistry of Heterocyclic Compounds," A. Weissberger, ed., Interscience Publishers, Inc., New York, 1953, p. 261.
(7) For a recent general review, and leading references, see R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 179 (1961).

TABLE I

DATA ON SYNTHESES OF SUBSTITUTED BENZIMIDAZOLES



I

		Yield, %	M.P., °C.[c]	Recrystallizing Solvent	Calcd. N	Calcd. Other	Found N	Found Other
i	R_1 = —C:CHCH:CHO, R_2 = R_3 = H	25[a] 80[b]	290–292 uncorr.	50% aq. C_2H_5OH	15.2	C, 71.8; H, 4.4	14.6	C, 71.3 H, 4.6
ii	R_1 = —C:CHCH:CHO, R_2 = —CH_3, R_3 = H	86.5[a] 63[b]	196.0–197.0	Cyclohexane	14.1		14.2	
iii	R_1 = —C:CHCH:CHO, R_2 = R_3 = —CH_3	62.5[b]	224.0–225.0[e]	Benzene	13.2		13.3	
iv	R_1 = —C:CHCH:CHO, R_2 = Cl, R_3 = H	76.3[a]	178.5–179.0	Dil. C_2H_5OH	12.8	Cl, 16.3	12.5	Cl, 15.9
v	R_1 = —C:CHCH:CHO, R_2 = NO_2, R_3 = H	87[a]	227.0–227.5	Dil. C_2H_5OH; toluene	18.3		18.2	
vi	R_1 = —$CH(CH_2)_3O$, R_2 = R_3 = H	66[a]	212.5–214.5	Dil. C_2H_5OH	14.9		14.9	
vii	R_1 = —$CH(CH_2)_4O$, R_2 = R_3 = H	18[a,f]	263.0–265.5 uncorr.	Dil. C_2H_5OH	13.9		14.1	
viii	R_1 = —C:CHCH:CHS, R_2 = R_3 = H	10[d] 80[b]	Decompd. >290	Acetic acid; vac.-sublim.	14.0	S, 16.0	13.9	S, 15.7
ix	R_1 = —C:CHCH:CHNH, R_2 = R_3 = H	50[a]	278.0–280.5 uncorr.	Dil. C_2H_5OH; vac.-sublim.	23.0		23.3	
x	R_1 = —C:CHCH:CHO R_2 = R_3 = H 4-Aza-derivative	37[a]	237.0	Toluene; vac.-sublim.	22.7	C, 64.8; H, 3.8	22.2	C, 64.8 H, 3.7

[a] By the method of Weidenhagen. [b] By the imido ester method. [c] Melting points were observed on a Fisher-Johns block and are corrected unless otherwise noted. [d] By a modified Phillips procedure. [e] Melting point, 209–211° reported in ref. 2. [f] Low yield, probably due to instability of starting material.

TABLE II

ULTRAVIOLET ABSORPTION SPECTRA OF SUBSTITUTED BENZIMIDAZOLES[a,e]

Compound[b]	λ_{max}, mμ	$\log_{10}\epsilon_{max}$	Compound	λ_{max}, mμ	$\log_{10}\epsilon_{max}$
Ii	249	4.09	2-Phenyl-	241	4.15
	305	4.60	benzimidazole[c]	303–304	4.37
Iviii	247	3.97	2-Methoxy-	244	3.81
	313	4.37	benzimidazole[d]	274	3.86
				281	3.82
Iix	251	3.98	Ivi	243	3.81
	309	4.61		273	3.91
				281	3.89
Ix	249	3.89	Ivii	243	3.81
	315	4.63		274	3.90
				281	3.91

[a] In methanol. [b] Compare numbers with structures of Table I. [c] Data from G. Leandri, A. Mangini, F. Montanari, and R. Passerini, *Gazz. chim. ital.*, **85**, 769 (1955). [d] Prepared by R. E. Sticker, of these Laboratories, as described by G. K. Hughes and F. Lions, *J. Proc. Roy. Soc. N.S. Wales*, **71**, 209 (1938); *Chem. Abstr.*, **32**, 5830 (1938). [e] The author is indebted to Raymond Dumlao of these laboratories for obtaining these measurements.

Experimental

Weidenhagen's Benzimidazole Synthesis[4] as Adapted.—A mixture of 0.18 mole of an *o*-phenylenediamine, 500 ml. of methanol, and 80 g. (0.40 mole) of cupric acetate in 1 l. of water, and 0.23 mole of an aldehyde (prepared in that order) was heated at reflux for 2 hr. and allowed to stand overnight (16 hr.) at room temperature. The copper salt was collected by filtration (occasionally in Celite), washed with water, and suspended in 1 l. of 50% ethanol. The suspension was stirred while a slow stream of hydrogen sulfide was introduced over a 2.5-hr. period, heated to boiling, and filtered rapidly through Celite in a steam-heated Büchner funnel. More product could be obtained by rinsing the filter cake with hot ethanol. A relatively pure product crystallized from the filtrate. In general, one recrystallization from a suitable solvent system using Norit gave analytically pure material.

The Imido Ester Benzimidazole Synthesis[7] as Adapted.—To a stirred solution of 0.03 mole of an *o*-phenylenediamine in 25 ml. of anhydrous ethanol was added, all at once, 0.03 mole of the imido ester hydrochloride.[8] The reactions were only slightly exothermic. After the mixture had been stirred for 1 hr., 50 ml. of water was added, which caused dissolution of the precipitated ammonium chloride and precipitation of the product in an almost analytically pure form. Large-scale runs gave similar results.

***N,N'*-Bis(2-furoyl)-*o*-phenylenediamine (IV).**—To a solution of 21.6 g. (0.2 mole) of *o*-phenylenediamine in 300 ml. of benzene and 100 ml. of pyridine was added 26.1 g. (0.2 mole) of 2-furoyl chloride, gradually and with stirring. Stirring was continued for 1 hr. and water (50 ml.) was added. A solid precipitated (18.2 g., 62%) which was collected by filtration and recrystallized from ethanol–water as tiny colorless plates, m.p. 221.5° (uncorr.).

(8) Harold Krehm kindly supplied the ethyl 2-furimidate hydrochloride.

Anal. Calcd. for $C_{16}H_{12}N_2O_4$: C, 64.9; H, 4.1. Found: C, 64.8; H, 4.3.

N-(**2-Furoyl**)-*o*-**nitroaniline** (**II**).—This was prepared essentially according to the preceding directions. A 0.2-molar run gave 25.67 g. (55.3%; mother liquors not treated) of product. Recrystallization from benzene–ligroin with Norit yielded the product as brilliant yellow needles, m.p. 115.0–117.0° (corr.).

Anal. Calcd. for $C_{11}H_8N_2O_4$: N, 12.1. Found: N, 12.9.

N-(**2-Furoyl**)-*o*-**phenylenediamine** (**III**).—In the usual manner,[9] 11.6 g. (0.05 mole) of *N*-(2-furoyl)-*o*-nitroaniline was hydrogenated in 200 ml. of ethanol with Raney nickel at 60 p.s.i. of hydrogen and room temperature in 0.5 hr. Isolation yielded 4.50 g. (44.5%) of product which recrystallized from cyclohexane with Norit as colorless tiny needles, m.p. 91.5–92.0° (corr.).

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.3; H, 5.0; N, 13.9. Found: C, 64.7; H, 5.2; N, 13.6.

Benzimidazoles. II. Synthesis of *N*-Heterocyclic Ring Systems Containing 1,2-Fused Benzimidazole Moieties

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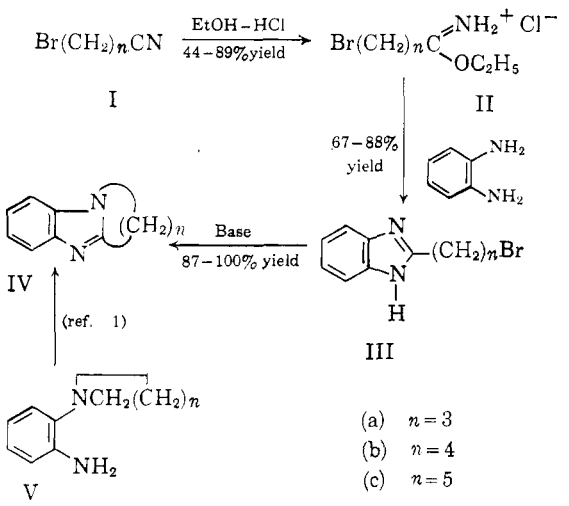
A new synthesis of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole, 1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole, and 7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]benzimidazole is described and discussed.

Saunders[1a] and Nair and Adams[1b] have recently described elegant techniques for the preparation of certain 1,2-fused benzimidazoles. In their methods, the *N*-(*o*-aminophenyl) heterocyclics, Vb and Vc, were converted by two different types of oxidative ring closures to 1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole[2a,3–5] (IVb) and 7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]benzimidazole[2b] (IVc), respectively. Only Nair and Adams have reported the preparation of the next lower homolog of this series, *i.e.*, 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]-benzimidazole[2c,6] (IVa), by this oxidative type of cyclization. Furthermore, a variety of derivatives containing substituents in the benzene rings of the benzimidazole nuclei of IV are described in both treatments.[1]

In the present paper, a practical alternative and complementary approach to this interesting series of compounds, including all three members, is presented.

Discussion

Although imido ester hydrochlorides,[7] and certainly ω-halo bases,[8] have been employed for heterocyclic ring syntheses, the combination of these provides a novel and practical approach in the series under consideration.



The preparations of several ω-haloalkanimidates have been described in the literature.[9–12] It was the experience of this author that the conversion of the ω-bromoalkanonitriles, I, to the corresponding imido ester salts, II, could be effected readily and in good yield. Obtaining the salts, II, in a crystalline state was attended by some difficulty and was finally accomplished consistently as described in detail in the Experimental. Although these salts were analyzed very shortly after isolation and in the crude state owing to general instability of imido ester salts,[7] the results were surprisingly good. Furthermore, the salts did not seem to be hygroscopic and could be stored under refrigeration without decomposition for at least several weeks. However, IIb and IIc did show

(1)(a) K. H. Saunders, *J. Chem. Soc.*, 3275 (1955). (b) M. D. Nair and R. Adams, *J. Am. Chem. Soc.*, **83**, 3518 (1961).

(2)(a) A. M. Patterson, L. T. Capell, and D. F. Walker, "The Ring Index," 2nd ed., American Chemical Society, Washington, D.C., 1960, No. 2578; (2b) *ibid.*, No. 3146; (2c) *ibid.*, No. 2387.

(3) G. Morgan and J. Stewart, *J. Chem. Soc.*, 1292 (1938).

(4) R. Huisgen and H. Rist, *Ann.*, **594**, 159 (1955).

(5) W. L. Mosby, *J. Org. Chem.*, **24**, 419 (1959).

(6) W. Reppe and co-workers, *Ann.*, **596**, 209 (1955).

(7) For a discussion and leading references, see R. Rogers and D. G. Neilson, *Chem. Rev.*, **61**, 179 (1961).

(8) Consult any standard reference on heterocyclic chemistry, *i.e.*, volumes in the series, "The Chemistry of Heterocyclic Compounds," A. Weissberger, ed., Interscience Publishers, New York, N. Y.

(9) F. E. King, R. M. Acheson, and P. C. Spensley, *J. Chem. Soc.*, 1401 (1949).

(10) W. Klarer and E. Urech, *Helv. Chim. Acta*, **27**, 1762 (1944).

(11) C. A. MacKenzie, G. A. Schmidt, and L. R. Webb, *J. Am. Chem. Soc.*, **73**, 4990 (1951).

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