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

ROY C. DE SELMS

Communication No. 2259, Kodak Research Laboratories, Eastman Kodak Co., Rochester 4, N. Y.

Received January 30, 1962

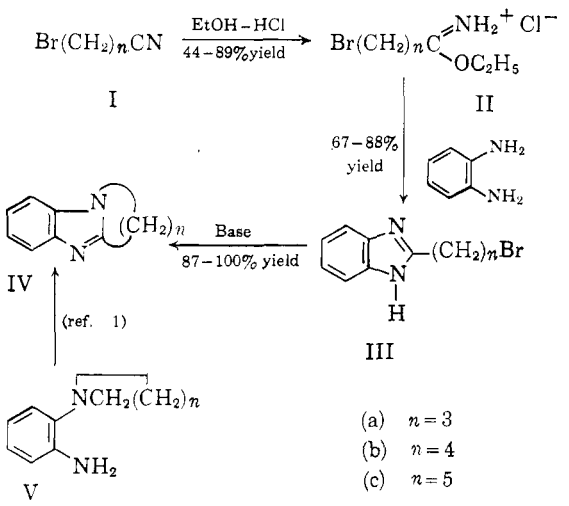
A new synthesis of 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]benzimidazole, 1,2,3,4-tetrahydropyrido[1,2-*a*]benzimidazole, and 7,8,9,10-tetrahydro-6*H*-azepino[1,2-*a*]benzimidazole is described and discussed.

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).

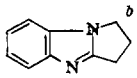
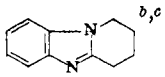
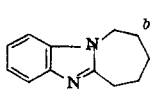
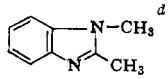
noticeable decomposition after storage for several weeks at room temperature.

The benzimidazoles, III, were formed readily and in good yield. It should be noted that just above their melting points, IIIa and IIIb resolidified, presumably to the hydrobromides of IVa and IVb or to corresponding polymers which melted at much higher temperatures. Indeed, IIIb could not be recrystallized without inter- or intramolecular salt formation. It is more likely that this is an intramolecular process since IIIc, which would undergo formation of a seven-membered ring yielding the hydrobromide salt of IVc, did not exhibit these properties. Furthermore, a high-dilution technique was required to form IVc from IIIc, although IVa and IVb were formed readily from IIIa and IIIb under conditions of high concentration.

As can be seen from Table I, the ultraviolet absorption spectra of IVa, IVb, and IVc are almost identical with the spectrum of 1,2-dimethylbenzimidazole. In fact, they are so nearly identical that any comments attributing differences to effects of "strain" by the various sizes of fused rings would be meaningless. These data, together with molecular-weight determinations and mode of formation, serve to establish conclusively the structures of the compounds represented by IV. It should be noted that earlier workers, with the notable exception of Huisgen and Rist,[4] did not present spectral and molecular-weight data together in support of their assignments of structure. The present work serves also to confirm the previous findings.

TABLE I

PHYSICAL PROPERTIES OF 1,2-FUSED BENZIMIDAZOLES

Compound	λ_{max}, mμ	$\log_{10}\epsilon$ (CH_3OH)	λ_{max}, mμ	$\log_{10}\epsilon$ (0.01 *N* HCl)	Melting Points: Compound	Melting Points: Picrate[a]
 IVa	247	3.74	237	3.65	114.5–116.5	222.0–222.5
	274	3.75	269	3.86		
	282	3.80	275	3.92		
 IVb	253	3.83	239	3.65	101.0–102.0	228.0–229.0
	275	3.81	269	3.90		229–230[14a]
	282	3.83	276	3.98		
 IVc	252	3.84	241	3.65	123.5–125.0	223.0–224.0
	276	3.79	270	3.93		
	283	3.85	277	4.00		
			240	3.69		
			269	3.90		
			275	3.97		

[a] These are probably all monopicrates; *cf.* ref. 1. [b] Compare data of ref. 1b. [c] Compare data of ref. 4 and 5. [d] Data from G. H. Beaven, E. R. Holiday, and E. A. Johnson, *Spectrochimica Acta*, 4, 338 (1951).

It can be seen from the flow diagram that the methods of Saunders[1a] and Nair and Adams[1b] (*i.e.*, V→IV) can yield derivatives of IV unambiguously substituted in the benzene ring of the benzimidazole moiety. This can be done by merely starting with the correspondingly substituted derivatives of V. On the other hand, unsymmetrically situated substituents in the heterocyclic ring of V would be expected to give rise to mixtures of ambiguously substituted products. It is in this respect that the present method complements those of the earlier workers.[1] Thus, by starting with a halonitrile of known structure, the structure of the derivative of IV ultimately obtained would be unambiguously substituted in the saturated heterocyclic moiety.

Experimental[13]

Ethyl γ-Bromobutyrimidate Hydrochloride (IIa).—A mixture of 44.4 g. (0.30 mole) of γ-bromobutyronitrile (Eastman Kodak Co. No. 5625), 13.8 g. (0.30 mole) of absolute ethanol and 150 ml. of anhydrous ether was cooled to −10° and a slow stream of hydrogen chloride was passed through the mixture over a period of 3 hr., the temperature being kept between 0 and −10°. The mixture was poured cautiously (dissolved hydrogen chloride gas causes frothing) into a large evaporating dish in a good hood. When enough solvent had evaporated so that most of the crystalline product separated, the mixture was triturated with anhydrous ether, the product was collected by filtration in a sintered-glass funnel, washed with ether, and air-dried for a short period. There was obtained 61.5 g. (89%) of product as colorless platelets, m.p. 101.5–102.5° dec.

Anal. Calcd. for $C_6H_{13}BrClNO$: C, 31.2; H, 5.6; N, 6.1. Found: C, 30.8; H, 5.6; N, 6.1.

When this substance was allowed to stand at 10° for 3 weeks, dried at room temperature for 1 day, and again analyzed, the following results were obtained: C, 30.4; H, 5.5.

Ethyl δ-Bromovalerimidate Hydrochloride (IIb).—This was prepared by the method described in the previous example. From 48.6 g. (0.30 mole) of δ-bromovaleronitrile (Aldrich Chemical Co.) there was obtained 55.5 g. (76%) of product as colorless platelets, m.p. 74–78° (dec.) (softened at 69°).

Anal. Calcd. for $C_7H_{15}BrClNO$: C, 34.4; H, 6.1; N, 5.7. Found: C, 33.7; H, 6.1; N, 5.7.

Ethyl ε-Bromocaprimidate Hydrochloride (IIc).—This was prepared by the method described in the previous example. From 52.8 g. (0.30 mole) of ε-bromocapronitrile (Sapon Chemical Co.), there was obtained 34.0 g. (44%) of product as colorless waxy platelets, m.p. 74–78° dec. (softened at 66°).

Anal. Calcd. for $C_8H_{17}BrClNO$: C, 37.2; H, 6.6; N, 5.4. Found: C, 36.8; H, 6.7; N, 5.7.

2-(3-Bromopropyl)benzimidazole (IIIa).—A mixture of 1.08 g. (0.01 mole) of *o*-phenylenediamine, 2.31 g. (0.01 mole) of ethyl γ-bromobutyrimidate hydrochloride, and 10 ml. of absolute ethanol was stirred for 1 hr.; by the end of this time much presumed ammonium chloride had precipitated. When 20 ml. of water was added, the ammonium chloride dissolved and the product precipitated. The product was collected by filtration and washed with water. There was obtained 2.00 g. (83%) as colorless platelets, m.p. 93.5–94.5° (resolidified and remelted at 223–243°

(13) Melting points were taken on a Fisher-Johns block and are corrected unless otherwise noted. Molecular weights were determined in benzene by a microebullioscopic technique.

uncorr.). Recrystallization from benzene–ligroin gave colorless prisms which oiled out before crystallizing, m.p. 89–91° (resolidified by 100° and remelted at 160–243°, depending upon the rate of heating).

Anal. Calcd. for $C_{10}H_{11}BrN_2$: Br, 33.5; N, 11.7. Found: Br, 33.9; N, 11.6.

2-(4-Bromobutyl)benzimidazole (IIIb).—This was prepared by the method described in the previous example, but on a tenfold scale. From 24.5 g. (0.10 mole) of ethyl δ-bromovalerimidate hydrochloride there was obtained 17.0 g. (67%) of product as colorless platelets, m.p. 79.0–80.5° (resolidified at 82–84° and remelted at 235–265° uncorr.). This product could not be recrystallized without apparent ring closure. Thus, the attempt to recrystallize it using ligroin gave a colorless, microcrystalline solid in low yield which was assumed to be the hydrobromide salt of IVb, m.p. 275–285° (uncorr.).

Anal. Calcd. for $C_{11}H_{13}BrN_2$: Br, 31.6; N, 11.1. M.p., 275–285°. Found: Br, 31.7; N, 10.9. M.p., 79.0–80.5°. Found: Br, 31.2; N, 10.8.

2-(5-Bromopentyl)benzimidazole (IIIc).—This was prepared by the method described in the first example, but on a ten-fold scale. From 25.9 g. (0.10 mole) of ethyl ε-bromocaprimidate hydrochloride, there was obtained 23.5 g. (88%) of product as colorless platelets, m.p. 103.0–104.0°; it did not resolidify below 200°. Recrystallization from benzene–ligroin did not change the crystal form or the melting point.

Anal. Calcd. for $C_{12}H_{15}BrN_2$: Br, 30.0; N, 10.5. Found: Br, 29.6; N, 10.6.

2,3-Dihydro-1*H*-pyrrolo[1,2-a]benzimidazole (IVa).—A mixture of 3.00 g. (0.054 mole) of potassium hydroxide and 25 ml. of ethanol was stirred for 15 min. and 12.00 g. (0.050 mole) of crude 2-(3-bromopropyl)benzimidazole was then added all at once. The resulting mixture was stirred for 20 min. (by the end of which time much presumed potassium bromide had separated) and then diluted with 150 ml. of water, extracted with ether, the ether extract was washed with brine, dried over anhydrous sodium sulfate, and the solvent removed in a vacuum, leaving 6.0 g. (76%) of product as an oil which crystallized very slowly. The crude product was extracted with hot benzene, the benzene extract was treated with Norit, filtered, and evaporated in a vacuum, leaving 3.40 g. (43% of product as colorless granules), m.p. 112.0–114.0°. Recrystallization from *n*-heptane using Norit yielded colorless prisms, m.p. 114.5–116.5° (lit.,[6] m.p. 115°).

Anal. Calcd. for $C_{10}H_{10}N$: C, 76.0; H, 6.4; N, 17.7; mol. wt., 158. Found: C, 76.6; H, 6.7; N, 17.5; mol. wt., 171.

Picrate.—The picrate was prepared in ethyl acetate and recrystallized from 2-methoxyethanol in the form of yellow needles, m.p. 222.0–222.5°.

IVa was obtained in quantitative yield when higher dilution and sodium ethoxide as the base were employed.

1,2,3,4-Tetrahydropyrido[1,2-a]benzimidazole (IVb).—This was prepared by the first method described in the previous example. From 12.7 g. (0.05 mole) of 2-(4-bromobutyl)benzimidazole there was obtained 7.5 g. (87%) of crude product, after extraction with benzene, as colorless granules, m.p. 96.0–110.5°. Recrystallization twice from ligroin using Norit yielded colorless granules, m.p. 101.0–102.0° (lit.,[1,3,10] m.p. 101–102° and 107°).

Anal. Calcd. for $C_{11}H_{12}N_2$: N, 16.3; mol. wt., 172. Found: N, 16.0; mol. wt., 173.

Picrate.—The monopicrate was prepared as described in ref. 1; the product was obtained as yellow needles, m.p. 228.0–229.0° (lit.,[1] m.p. 229–230°).

7,8,9,10-Tetrahydro-6*H*-azepino[1,2-a]benzimidazole (IVc).—The method used in the previous examples gave only high-melting, apparently polymeric, materials that were not further investigated.

To a 500-ml. flask containing a solution of 0.23 g. (0.01 g.-atom) of sodium in 250 ml. of absolute ethanol was attached a 100-ml. Soxhlet extractor, and above that a condenser, and a dropping funnel containing a solution of 2.67 g. (0.01 mole) of 2-(5-bromopentyl)benzimidazole in 50 ml. of absolute ethanol. The solution containing the benzimidazole was dropped slowly into the Soxhlet extractor which drained at 15-min. intervals over a total period of 30 hr. The reaction mixture was heated at reflux for an additional 64 hr., the solvent was removed at reduced pressure, and the residue extracted with hot benzene. The solvent was removed from the extract at reduced pressure, leaving 1.75 g. (94%) of product as colorless irregular crystals, m.p. 117.5–123.0°. Treatment of the product in benzene with Norit, followed by recrystallization from refluxing ligroin, yielded colorless irregular prisms, m.p. 123.5–125.0° (lit.,[1] m.p. 124–125°).

Anal. Calcd. for $C_{12}H_{14}N_2$: N, 15.0; mol. wt., 186. Found: N, 15.3; mol. wt., 190.

Picrate.—The picrate was prepared in ethyl acetate and recrystallized from 2-methoxyethanol, giving yellow needles, m.p. 223.0–224.0°.

Acknowledgment.—The author wishes to express his appreciation for very informative conversations on this subject with Dr. L. G. S. Brooker, of these laboratories, and for the technical assistance of Messrs. D. F. Ketchum, R. H. Barrett, and R. Dumlao, also of these laboratories, in making the analyses.