Department of Chemistry, University of Pennsylvania

Synthesis of Bridgehead Nitrogen Compounds which Contain the Benzimidazole Moiety. 2,3-Dihydro-1*H*-pyrrolo[1,2-a]benzimidazoles.

Allan R. Freedman, Delbert S. Payne and Allan R. Day

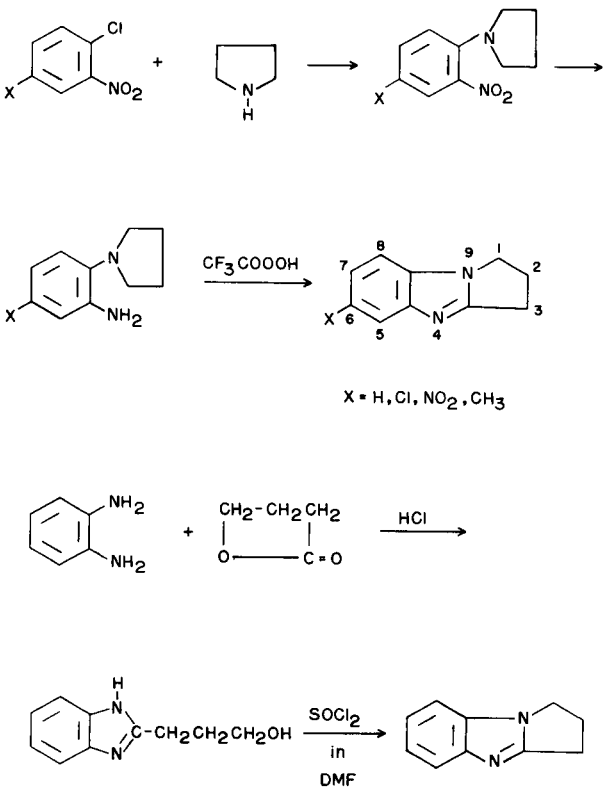
An improved synthetic procedure has been developed for the preparation of 2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazoles. Of the monosubstituted derivatives, only the chloro 2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazole was shown to be a mixture of the 6- and 7-isomers.

The first synthesis of 2,3-dihydro-1*H*-pyrrolo-[1,2-a]benzimidazole was reported in 1955 by Reppe (1), who obtained it by heating *o*-phenylenediamine with γ-butyrolactone at 270°. During the course of the present investigation two other papers were published. Nair and Adams (2) prepared four 2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazoles. DeSelms (3) prepared the parent compound from *o*-phenylenediamine and ethyl γ-bromobutyrimidate hydrochloride.

An improved method which proved general for the synthesis of this ring system consisted of heating 2-(γ-hydroxypropyl)benzimidazoles with thionyl chloride in dimethylformamide. Under these conditions the hydroxyl group is replaced by chlorine and subsequent ring closure gives the 2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazoles. The 2-(γ-hydroxypropyl)benzimidazoles were prepared from *o*-phenylenediamines and γ-butyrolactone under Phillips' conditions (4). Two of these compounds, 2-(γ-hydroxypropyl) benzimidazole and 2-(γ-hydroxypropyl)-5(6)-methylbenzimidazole have been previously reported (1). The 2-(γ-hydroxypropyl)-benzimidazoles which were prepared are listed in Table I.

The products in Table I separated as solids or oils which solidified on cooling and stirring. The 2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazoles which were prepared are listed in Table II.

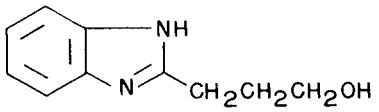
Due to the tautomeric nature of the imidazole ring, the monosubstituted 2,3-dihydro-1*H*-pyrrolo-[1,2-a]benzimidazoles could form either or both of two possible isomeric forms depending on the direction of ring closure. The first three compounds in Table II were purified by thin layer and column chromatographic methods in an effort to separate isomeric forms. Thin layer chromatography showed 6(7)-chloro-2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazole to be a mixture of the 6- and 7-chloro isomers. To obtain working quantities of the two components, a 2.5% methanol in chloroform solution of the mixture was run through a column of silica gel. Column chromatography yielded two products;



(A) m.p. 96-98° and (B) m.p. 133-134°. Their analyses were the same and their infrared and ultraviolet spectra were nearly identical. Isomer B had the same melting point as that reported by Nair and Adams (2) for 6-chloro-2,3-dihydro-1*H*-

TABLE I

2-(γ-Hydroxypropyl)benzimidazoles

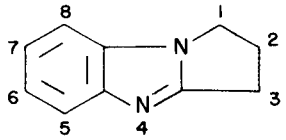


Subst.	Yield %	M.p. °C	Formula	Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found	Nitrogen % Calcd.	Nitrogen % Found
-	84	158-160 (b)	$C_{10}H_{12}N_2O$	-	-	-	-	-	-
5(6)-CH_3	95	130-131 (c)	$C_{11}H_{14}N_2O$	69.45	69.31	7.41	7.42	14.72	14.47
5(6)-Cl	65	160-164	$C_{10}H_{11}ClN_2O$ (d)	57.00	57.09	5.27	5.36	13.29	13.20
5(6)-NO_2	80	160-162	$C_{10}H_{11}N_3O_3$	54.29	54.13	5.02	5.03	18.99	19.07
5(6)-NH_2 (a)	90	239.5-242	$C_{10}H_{15}Cl_2N_3O$ (e)	45.45	45.25	5.72	5.74	15.91	15.76
5,6-CH_3	84	163-165	$C_{12}H_{16}N_2O$	70.57	70.50	7.88	7.76	13.71	13.81
5,6-CH_3O	55	167-169	$C_{12}H_{16}N_2O_3$	61.02	61.25	6.78	7.01	11.86	11.92
4,7-CH_3O	78	116-118	$C_{12}H_{16}N_2O_3$	61.02	60.87	6.78	6.63	11.86	11.80

(a) As dihydrochloride. (b) Lit. m.p. 161-163° (1). (c) Lit. m.p. 137° (1). (d) Chlorine %; Calcd. 16.85. Found: 16.77. (e) Chlorine %; Calcd. 26.86. Found: 26.81.

TABLE II

2,3-Dihydro-1*H*-pyrrolo[1,2-a]benzimidazoles



Subst.	Yield %	M.p. °C	Formula	Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found	Nitrogen % Calcd.	Nitrogen % Found
-	44	115 (a)	$C_{10}H_{10}N_2$	-	-	-	-	-	-
6-CH_3	43	144-145 (b)	$C_{11}H_{12}N_2$	76.71	76.50	7.03	7.19	16.26	16.42
6(7)-Cl	63	99-108 (c)	$C_{10}H_9N_2Cl$ (d)	62.32	62.51	4.72	4.54	14.53	14.59
6-Cl	48	96-98	$C_{10}H_9ClN_2$	62.32	62.24	4.72	4.62	14.53	14.47
7-Cl	49	133-134	$C_{10}H_9ClN_2$	62.32	62.30	4.72	4.71	14.53	14.53
6-NO_2	60	209-210 (e)	$C_{10}H_9N_3O_2$	59.11	59.29	4.48	4.49	20.69	20.85
6-NH_2 (f)	31	294-297	$C_{10}H_{13}Cl_2N_3$	48.80	48.69	5.32	5.36	17.07	17.20
6,7-CH_3	61	177-179 (g)	$C_{12}H_{14}N_2$	77.39	77.23	7.57	7.53	15.04	15.14
6,7-CH_3O	50	194-196 (h)	$C_{12}H_{14}N_2O_2$	66.06	66.20	6.42	6.67	12.84	13.09
5,8-CH_3O	45	133-135 (i)	$C_{12}H_{14}N_2O_2$	66.06	66.15	6.42	6.51	12.84	12.74
5,8-OH (j,n)	50	305-306	$C_{10}H_{11}ClO_2N_2$ (k)	53.00	53.13	4.90	4.78	12.36	12.56
quinone	45	144.5-145 (l)	$C_{10}H_8N_2O_2$	63.82	63.99	4.30	4.41	14.88	14.69
6,7-OH (j)	64	266-268	$C_{10}H_{11}ClN_2O_2$ (m)	53.00	52.89	4.90	5.04	12.36	12.17

(a) Taken up in ethyl acetate rather than ether, recrystallized from ethyl acetate, lit. m.p. 115° (1). (b) Recrystallized from ether-hexane, lit. m.p. 144° (2). (c) Recrystallized from ether-hexane, lit. m.p. 133-134° (2). (d) Chlorine %; Calcd. 18.40. Found: 18.25. (e) Taken up in ethyl acetate, recrystallized from ethyl acetate, lit. m.p. 209-210° (2). (f) As dihydrochloride, recrystallized from ethanol-hexane. (g) Recrystallized from ethyl acetate. (h) Taken up in ethyl acetate and recrystallized from ethyl acetate. (i) Taken up in benzene and recrystallized from benzene. (j) As hydrochloride. (k) Chlorine %; Calcd. 15.67. Found: 15.37. (l) Recrystallized from chloroform-hexane. (m) Chlorine %; Calcd. 15.62. Found: 15.47. (n) Demethylation of 5,8-dimethoxy-2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazole was effected by heating with concentrated hydrochloric acid under pressure at 100°. The resulting 5,8-dihydroxy compound was oxidized with chromic acid to 2,3-dihydro-1*H*-pyrrolo[1,2-a]imidazobenzoquinone.

pyrrolo[1,2-a]benzimidazole which they had prepared by an unequivocal method. It was concluded therefore that compound (A) was 7-chloro-2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazole.

A similar examination of the nitro-2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazole showed this to be a pure product. Film chromatography showed just one spot and column chromatography produced just one band. The recovered material had the same melting point of 209-210°. This is the melting point reported by Nair and Adams for 6-nitro-2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazole which they had prepared by an unequivocal method. The electron-withdrawing nitro group favors ring closure with the nitrogen which is *para* to it rather than with the nitrogen which is *meta* to it. The nitro compound was converted to the corresponding chloro compound by hydrogenation and diazotization followed by a Sandmeyer reaction. The chloro compound melted at 133-134°.

Chromatographic examination of the methyl-2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazole also showed only one isomer to be present. The material recovered from the single band on the column melted at 144-145°. This value was identical with the melting point reported by Nair and Adams for 6-methyl-2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazole.

It would appear that the presence of a *m*-directing or *o,p*-directing group in the benzene ring strongly favors ring closure with the nitrogen atom *para* to it. The chloro group through its dual nature, exerting both an inductive and a resonance effect, promotes ring closure at both nitrogen atoms.

EXPERIMENTAL

2-(γ-Hydroxypropyl)benzimidazoles (Table I).

The appropriate *o*-phenylenediamine (0.05 mole) and 0.05 mole of γ-butyrolactone were dissolved in 50 ml. of 4 *N* hydrochloric acid and refluxed for 18 hours in a nitrogen atmosphere and a final 15 minutes with decolorizing carbon. The mixture was filtered hot, and the cooled filtrate was neutralized with ammonium hydroxide. The product usually separated as an oil which solidified on further cooling and stirring. The products were recrystallized from ethanol-water or from dioxane. The 6-amino compound was obtained from the corresponding nitro compound by catalytic (Pt) hydrogenation in ethanol. It was converted to its dihydrochloride by treating with dry hydrogen chloride in ethanol-ether solution. The salt was recrystallized from ethanol.

2,3-Dihydro-1*H*-pyrrolo[1,2-a]benzimidazoles. (Table II).

A solution of a 2-(γ-hydroxypropyl)benzimidazole (0.010 mole) was dissolved in 50 ml. of dimethylformamide. Thionyl chloride (0.010 mole) was slowly added to the cooled solution and the solution refluxed for 45 minutes. It was refluxed for an additional 5 minutes with decolorizing carbon, filtered and the filtrate evaporated to dryness *in vacuo*. The residue was dissolved in water and the solution neutralized (sodium bicarbonate) to precipitate the free base. The latter was taken up in ether, decolorized with decolorizing carbon and the solvent removed *in vacuo*. The product was then recrystallized from a suitable solvent (see Table II).

5,8-Dihydroxy-2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazole was obtained as its hydrochloride by heating the 5,8-dimethoxy compound with concentrated hydrochloric acid at 100° under pressure. It was recrystallized from ethanol.

2,3-Dihydro-1*H*-pyrrolo[1,2-a]imidazobenzoquinone.

This compound was obtained as follows: 5,8-Dihydroxy-2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazole hydrochloride (2.6 g.) was dissolved in 50 ml. of water and 1.8 g. of chromic anhydride in 40 ml. of water was slowly added with stirring. The solution was slowly warmed to 60°, cooled and extracted with benzene. The benzene extract was dried (magnesium sulfate) and evaporated.

Thin Layer and Column Chromatography.

The plates (20 cm. x 20 cm.) were coated with silica gel (Kieselgel D-5) or Alumina (Fluka Type DU) to a thickness of 300 μ. The plates were air dried and activated by heating at several temperatures for varying periods of time. The best results were obtained from plates coated with silica gel and heated at 50° for 2 hours. The compound was dissolved in methanol and applied to the plate about 2.5 cm. from the edge. The spot was thoroughly dried and then inserted in the developing solvent. Many developing solvent mixtures were tried but 2.5% methanol in chloroform gave optimum migration and separation. The spots fluoresced brightly under ultraviolet light (366 mμ). For the chloro 2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazole, two spots separated with RF = 0.525 (A) and RF = 0.825 (B).

The same material, Kieselgel Fluka D-5, was used for the column chromatography. The small particle size of the material made it difficult to pack the column. When the column was packed with dry silica gel, it could not be wetted in the conventional manner. Consequently a slurry of the silica gel, free from air bubbles, in chloroform was carefully added to the column and allowed to completely drain. The column was rinsed with a small amount of solvent before chromatographic separation was started. A solution of the chloro-2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazole in 2.5% methanol in chloroform was then added. The separation of 2 bands was slow, requiring about 15 hours. At this point, 2 bands had separated (about 6.5 cm. apart). The upper band (A) fluoresced yellow in U. V. (366 mμ) and the lower band fluoresced blue under the U. V. of the same wavelength. After complete drainage, the column was carefully extruded, the two bands cut out and each was extracted with chloroform. The extract from section (A), on evaporation, yielded pure 7-chloro-2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazole, m.p. 96-98° and the extract from section (B) gave pure 6-chloro-2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazole, m.p. 133-134° (5). A large number of solvent systems was used for the above separation, but 2.5% methanol in chloroform gave the best results.

Chromatographic examination of the nitro-2,3-dihydro-1*H*-pyrrolo-[1,2-a]benzimidazole and methyl-2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazole showed no separation of spots or bands. Only one isomer was isolated in each case. The melting points were identical with those reported for 6-nitro-2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazole and 6-methyl-2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazole (2).

6-Chloro-2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazole from 6-nitro-2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazole.

6-Nitro-2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazole was hydrogenated over platinum in ethanol solution. The yield was practically quantitative. The 6-amino-2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazole (14.1 g., 0.067 mole) was suspended in a mixture of 10 ml. of water and 14 ml. of concentrated hydrochloric acid. The suspension was cooled to 0°. A solution of 4.59 g. (0.067 mole) of sodium nitrite in 14 ml. of water, which had been cooled to 0°, was slowly added to the suspension with stirring. A clear, dark brown solution was obtained. The cold solution was added slowly to a solution of cuprous chloride (2 equivalents) in concentrated hydrochloric acid. A precipitate of the cuprous salt of 6-chloro-2,3-dihydro-1*H*-pyrrolo[1,2-a]-benzimidazole formed with an evolution of nitrogen. The mixture was allowed to come to room temperature and the precipitate removed. The precipitate was suspended in 4 *N* hydrochloric acid, treated with hydrogen sulfide for 1 hour and the copper sulfide removed by filtration. The filtrate was cooled and neutralized with ammonium hydroxide. The resulting precipitate was removed, washed with water and dried. It was dissolved in hot benzene and petroleum ether (30-60°) added to incipient cloudiness. On cooling, 6-chloro-2,3-dihydro-1*H*-pyrrolo[1,2-a]benzimidazole crystallized, yield 30%, m.p. 133-134°.

REFERENCES

(1) W. Reppe, *et al.*, *Ann.*, 596, 176, 209 (1955).

(2) M. D. Nair and R. Adams, *J. Am. Chem. Soc.*, 83, 3518 (1961).

(3) R. C. DeSelms, *J. Org. Chem.*, 27, 2165 (1962).

(4) M. A. Phillips, *J. Chem. Soc.*, 2328 (1928).

(5) This agrees with the melting point reported by Nair and Adams for the 6-chloro isomer.

Received February 11, 1966 Philadelphia, Pennsylvania 19104