[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

Syntheses of Dimethoxybenzimidazoles, Dihydroxybenzimidazoles and Imidazo-*p*-benzoquinones

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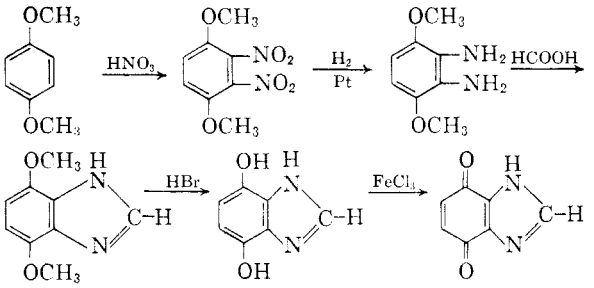
The syntheses of a number of 4,7- and 5,6-dimethoxybenzimidazoles and of the corresponding dihydroxy derivatives are reported. Several of the 4,7-dihydroxy compounds have been converted to quinones.

Imidazole derivatives of 1,4-naphthoquinone[1] have been demonstrated to possess antimetabolite activity against vitamin B_{12}-requiring *E. coli* 113-3, folic acid-requiring *L. casei* and purine-requiring *E. coli B* 96.[2] These activities have prompted us to extend this work to imidazo-*p*-benzoquinones and related compounds. This paper describes some of this work.

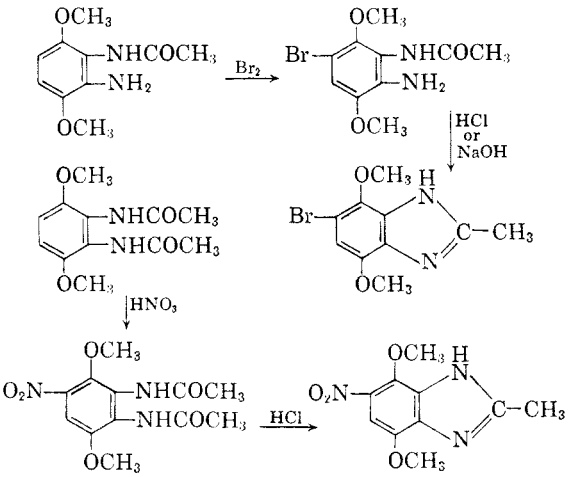
An obvious approach to the syntheses of such compounds is through the preparation of suitable dimethoxybenzimidazoles. 1,4-Dimethoxybenzene and 1,2-dimethoxybenzene were the starting materials for these preparations. For example:



1,2-Dimethoxybenzene was treated in a similar manner.

The nitration of 1,4-dimethoxybenzene was carried out by the methods of Habermann[3] and of Nietzki and Rechberg.[4] The 2,3-diamino-1,4-dimethoxybenzene oxidized rapidly in air and it was found necessary to convert it to the hydrochloride as soon as possible. The diamine was converted to 4,7-dimethoxybenzimidazole by Phillips' procedure.[5] A number of 2-substituted 4,7-dimethoxybenzimidazoles were prepared by using other acids in place of formic acid (see Table I). 2-Carboxyethyl-4,7-dimethoxybenzimidazole was prepared from the diamine and succinic anhydride by the method of Chatterjee.[6] The corresponding methyl ester and hydrazide were also prepared.

To introduce other substituents into the benzene ring, it was found most convenient to introduce them before ring closure to the imidazole. For example:



It is interesting to note that the diacetamido derivative could not be brominated whereas the monoacetamido compound undergoes bromination under mild conditions. Nitration of the diacetamido derivative proceeded normally. The nitro group may also be introduced by direct nitration of the benzimidazole. For example, 4,7-dimethoxybenzimidazole was nitrated to form 5-nitro-4,7-dimethoxybenzimidazole. The latter was reduced to the corresponding amino compound which was isolated as its hydrochloride.

4,7-Dimethoxybenzimidazole was converted to the corresponding dihydroxy derivative by heating with 48% hydrobromic acid. When the 2-position is alkylated, the ether linkages are not cleaved, under similar conditions, due to the insolubility of the compound to be cleaved. In these cases, cleavage was effected by heating with concentrated hydrochloric acid in sealed tubes. In general, the hydroquinones could not be isolated as the free bases. Their hydrohalides were obtained in solid form but only in two cases were analytically pure samples obtained. The impure hydrohalides may be oxidized directly to the corresponding quinones (Table II).

1,2-Dimethoxybenzene, the starting material for 5,6-dimethoxybenzimidazole, was nitrated in two

(1) J. R. E. Hoover and A. R. Day, *J. Am. Chem. Soc.*, **76**, 4148 (1954).

(2) D. B. McNair Scott, Dept. of Physiology, Medical School of the University of Pennsylvania, private communication.

(3) J. Habermann, *Ber.*, **11**, 1037 (1878).

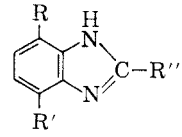
(4) R. Nietzki and F. Rechberg, *Ber.*, **23**, 1216 (1890).

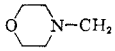
(5) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).

(6) B. Chatterjee, *J. Chem. Soc.*, 2965 (1929).

TABLE I

4,7-DISUBSTITUTED BENZIMIDAZOLES

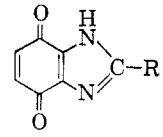


R	R′	R″	Yield, %	M.P. °C (dec.)	Formula	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
OCH_3	OCH_3	H	88	218–222	$C_9H_{10}N_2O_2$	60.66	60.54	5.66	5.44	15.72	15.89
OCH_3	OCH_3	CH_3	90[e]	224–226	$C_{10}H_{12}N_2O_2$	62.49	62.51	6.30	6.42	14.58	14.55
OCH_3	OCH_3	C_2H_5	57[f]	190–193	$C_{11}H_{14}N_2O_2$	64.05	63.91	6.84	6.98	13.58	13.42
OCH_3	OCH_3	n-C_3H_7	50[g]	183–189	$C_{12}H_{16}N_2O_2$	65.43	65.59	7.33	7.25	12.72	12.55
OCH_3	OCH_3	i-C_5H_{11}	23[e]	157–160	$C_{14}H_{20}N_2O_2$	67.71	67.57	8.12	8.39	11.28	11.37
OCH_3	OCH_3	CH_3OCH_2	69[h]	154–157	$C_{11}H_{14}N_2O_3$	59.44	59.26	6.35	6.48	12.61	12.47
OCH_3	OCH_3	$HOCH_2$	72[h]	200–202	$C_{10}H_{12}N_2O_3$	57.63	57.42	5.81	5.71	13.45	13.26
OCH_3	OCH_3		90	178–180	$C_{14}H_{19}N_3O_3$	60.63	60.42	6.91	7.08	15.15	15.21
OCH_3	OCH_3	$(CH_2)_2COOH$	40[a]	[d]	$C_{12}H_{15}N_2O_4Cl$	50.26	50.24	5.27	5.36	9.77	9.79
OCH_3	OCH_3	$(CH_2)_2COOCH_3$	65	154–157	$C_{13}H_{16}N_2O_4$	59.08	58.98	6.10	5.87	10.60	10.54
OCH_3	OCH_3	$(CH_2)_2CONHNH_2$	87	188–196	$C_{12}H_{16}N_4O_3$	54.53	54.34	6.10	6.13	21.20	21.18
OH	OH	H	100[b]	285–325	$C_7H_7N_2O_2Br$	36.38	36.59	3.01	3.24	12.12	12.07
OH	OH	CH_3	60[c]	297–299	$C_8H_9N_2O_2Cl$	47.89	48.08	4.52	4.54	13.97	13.86
OH	OH	$(CH_2)_2COOCH_3$	90	213–219	$C_{11}H_{12}N_2O_4$	55.96	55.93	5.12	5.12	11.82	11.86

[a] As hydrochloride. Chlorine calcd., 12.37; Found, 12.17. [b] As hydrobromide. Bromine calcd., 34.58; Found, 34.60. [c] As hydrochloride. Chlorine calcd., 17.67; Found, 17.50. [d] No definite melting point. [e] Recrystallized from aqueous ethanol. [f] Recrystallized from ethanol. [g] Recrystallized from aqueous ethanol and from chloroform-ethylacetate. [h] Recrystallized from water.

TABLE II

IMIDAZO-*p*-BENZOQUINONES



R	Yield, %	M.P. °C (dec.)	Formula	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
H	92	>340	$C_7H_4N_2O_2$	56.76	56.76	2.72	2.83	18.92	18.97
CH_3	79	250	$C_8H_6N_2O_2$	59.25	59.41	3.73	3.59	17.28	17.26
n-C_3H_7	36	>300	$C_{10}H_{10}N_2O_2$	63.10	63.33	5.27	5.28	14.73	14.64
i-C_5H_{11}	29	164	$C_{12}H_{14}N_2O_2$	66.04	66.21	6.46	6.28	12.84	12.73

steps. The mono nitro derivative was prepared according to the procedure of Cardwell and Robinson.[7] The second nitro group was introduced by using fuming nitric acid.[8] The dinitro compound may be reduced to the corresponding diamine with tin and hydrochloric acid or catalytically over palladium. It had been claimed earlier that only one nitro group was reduced by hydrogen in the presence of palladium.[9] We found no evidence for this observation in the present study.

The 1,2-diamino-4,5-dimethoxybenzene was converted to 5,6-dimethoxybenzimidazole and 2-methyl-5,6-dimethoxybenzimidazole by Phillips' procedure.[5] Both of these compounds are water soluble. Attempts to prepare 2-ethyl- and 2-propyl-5,6-dimethoxybenzimidazoles, by Phillips' method, failed. Extensive decomposition occurred. Similar results were obtained when the diamine was treated with propionyl chloride in pyridine solution. The reaction of the diamine with glycolic acid, by Phillips' method, gave the expected 2-hydroxymethyl-5,6-dimethoxybenzimidazole. The latter compound was converted to the corresponding 2-chloromethyl compound by thionyl chloride. The 2-chloromethyl derivative could not be obtained by treating the diamine with chloroacetic acid.

2-Chloromethyl-5,6-dimethoxybenzimidazole was

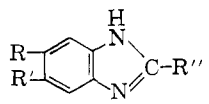
(7) D. Cardwell and R. J. Robinson, *J. Chem. Soc.*, **107**, 256 (1915).

(8) H. Vermeulen, *Rec. trav. chim.*, **48**, 969 (1929).

(9) K. Frisch and M. T. Bogert, *J. Org. Chem.*, **8**, 331 (1943).

TABLE III

5,6-DISUBSTITUTED BENZIMIDAZOLES



R	R′	R″	Yield %	M.P. °C (dec.)	Formula	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
OCH_3	OCH_3	H	93	179–183	$C_9H_{10}N_2O_2$	60.66	60.41	5.66	5.59	15.72	15.79
OCH_3	OCH_3	CH_3	65[e]	168–172	$C_{10}H_{12}N_2O_2$	62.49	62.49	6.30	6.21	14.58	14.40
OCH_3	OCH_3	CH_2OH	78[f]	240–241	$C_{10}H_{12}N_2O_3$	57.69	57.54	5.81	5.72	13.46	13.21
OCH_3	OCH_3	CH_2Cl[a]	62	[d]	$C_{10}H_{12}N_2O_2Cl_2$	45.64	45.67	4.60	4.38	10.65	10.49
OCH_3	OCH_3	$CH_2N(C_4H_9)_2$	60	95–97	$C_{18}H_{29}N_3O_2$	67.68	67.59	9.15	8.91	13.15	13.06
OCH_3	OCH_3	$CH_2N(CH_2CH_2Cl)_2$[b]	56	182	$C_{14}H_{20}N_3O_2Cl_3$	45.56	45.46	5.44	5.36	11.39	11.61
OH	OH	H[c]	98	>300	$C_7H_7N_2O_2Br$	36.38	36.50	3.05	2.90	12.13	12.31

[a] As hydrochloride. Chlorine calcd. 26.95; Found 26.73. [b] As hydrochloride. Chlorine calcd. 28.90; Found 28.61. [c] As hydrobromide. Bromine calcd. 34.58; Found 34.31. [d] No definite melting point. [e] Recrystallized from chloroform–petroleum ether and dioxane. [f] Recrystallized from dioxane.

condensed with dibutylamine, morpholine, and diethanolamine, respectively, to form the corresponding 2-aminomethyl compounds. 2-Di(2-hydroxyethyl)aminomethyl - 5,6 - dimethoxybenzimidazole was converted to the corresponding nitrogen mustard by treatment with thionyl chloride. The imidazoles prepared from 1,2-diamino-4,5-dimethoxybenzene are listed in Table III.

EXPERIMENTAL

2,3-Dinitro-1,4-dimethoxybenzene was prepared by a previously described method.[3,4] The crude product was recrystallized from acetic acid.

2,3-Diamino-1,4-dimethoxybenzene. A solution of 22.8 g. (0.135 mole) of 2,3-dinitro-1,4-dimethoxybenzene in 125 ml. of ethanol was hydrogenated with platinum oxide as the catalyst. After removing the catalyst, the filtrate was made strongly acidic by adding concentrated hydrochloric acid. The crude hydrochloride of the product was removed by filtration. The salt was dissolved in water. The solution was made alkaline with sodium hydroxide solution and extracted with chloroform. The extract was reduced to small volume and the product precipitated by the addition of petroleum ether. The product was then recrystallized from water, with the aid of decolorizing carbon and sodium bisulfite, and finally from chloroform and petroleum ether. The yield was 40%, m.p. 85–87°.

Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.14; H, 7.20; N, 16.66. Found: C, 57.01; H, 7.37; N, 16.51.

4,7-Dimethoxybenzimidazole. A solution of 27.4 g. (0.133 mole) of 2,3-diamino-1,4-dimethoxybenzene hydrochloride in 200 ml. of 98% formic acid was refluxed for 2 hr. The solution was cooled and made basic with ammonium hydroxide. The light brown precipitate was removed, recrystallized from ethanol-water with the aid of decolorizing carbon and finally recrystallized from ethanol and chloroform.

2-Alkyl-4,7-dimethoxybenzimidazoles. These compounds were prepared from the corresponding diamine and organic acids by Phillips' method.[5]

2-Chloromethyl-4,7-dimethoxybenzimidazole. 2-Hydroxymethyl-4,7-dimethoxybenzimidazole (9.6 g., 0.046 mole) was refluxed for 2 hr. with 12 ml. of thionyl chloride in 125 ml. of chloroform. The solution was chilled and the hydrochloride of the product precipitated by the addition of ether, yield 11.9 g. (95%), m.p. 228–232°.[10]

2-Morpholinomethyl-4,7-dimethoxybenzimidazole. A solution of 2.63 g. (0.01 mole) of 2-chloromethyl-4,7-dimethoxybenzimidazole and 4.77 g. (0.03 mole) of morpholine in 50 ml. of ethanol was refluxed for 4 hr. The ethanol was removed by distillation and the residue extracted with chloroform. The chloroform extract was treated with decolorizing carbon and dried over magnesium sulfate. The addition of dry hydrogen chloride precipitated the hydrochloride of the product, yield 2.96 g. (95%). The salt was dissolved in water, the solution neutralized with sodium bicarbonate and the free base then extracted with chloroform. Most of the chloroform was removed and petroleum ether added to precipitate the free base.

2-Carboxyethyl-4,7-dimethoxybenzimidazole hydrochloride. A solution of 9.85 g. (0.0586 mole) of 2,3-diamino-4,7-dimethoxybenzene and 11.7 g. (0.117 mole) of succinic anhydride in 110 ml. of xylene was refluxed for 3 hr. The hot xylene was decanted immediately and the residue extracted with hot 4*N* hydrochloric acid. On cooling the extract, the hydrochloride of the product precipitated. It was removed, washed with hot acetone and then recrystallized from 4*N* hydrochloric acid.

The methyl ester was prepared by the usual method used for the esterification of amino acids.

Hydrazide of 2-carboxyethyl-4,7-dimethoxybenzimidazole. Hydrazine hydrate (4.6 g., 0.091 mole) and 1.5 g. (0.0057 mole) of the methyl ester of 2-carboxyethyl-4,7-dimethoxybenzimidazole were dissolved in 10 ml. of methanol and the solution was refluxed for 1 hr. The mixture was poured into ice water to precipitate the hydrazide. The latter was recrystallized from water with the aid of decolorizing carbon.

4,7-Dihydroxybenzimidazole hydrobromide. 4,7-Dimethoxybenzimidazole (3.4 g., 0.019 mole) was refluxed for 1 hr. with 35 ml. of 48% hydrobromic acid. On cooling, the hydrobromide of the dihydroxy compound separated in quantitative yield. The product was purified by recrystallization from ethanol-ether.

2-Methyl-4,7-dihydroxybenzimidazole hydrochloride. 2-Methyl-4,7-dimethoxybenzimidazole (2.7 g., 0.01 mole) and 15 ml. of concentrated hydrochloric acid were heated in a sealed Pyrex tube for 20 hr. at 100°. After cooling, the tube was opened and the contents filtered. The hydrochloride

(10) J. M. Cohen, Doctoral Dissertation, University of Pennsylvania, 1958.

was recrystallized from ethanol-ether, with the aid of decolorizing carbon.

Methyl ester of 2-carboxyethyl-4,7-dihydroxybenzimidazole. 2-Carboxyethyl-4,7-dimethoxybenzimidazole (5.04 g., 0.0202 mole) was heated in a sealed Pyrex tube with 25 ml. of concentrated hydrochloric acid for 24 hr. at 100°. A 66% yield of the crude hydrochloride was obtained. Since we were not successful in purifying the product, we converted it to its methyl ester. The hydrochloride of the latter was obtained in quantitative yield. It was dissolved in water and the solution neutralized with sodium bicarbonate to precipitate the free base. The latter was recrystallized from dioxane–petroleum ether.

2-Acetamido-3-amino-1,4-dimethoxybenzene. 2,3-Diamino-1,4-dimethoxybenzene (13.2 g., 0.064 mole) was dissolved in 170 ml. of water at 35°. The solution was treated with charcoal and filtered. To this solution was added 6.2 ml. (0.065 mole) of acetic anhydride followed by the addition of 5.3 g. (0.065 mole) of sodium acetate in 30 ml. of water. The acetamido derivative separated on standing. It was recrystallized from ethanol with the aid of decolorizing carbon, yield 53%, m.p. 143–145°.

Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.12; H, 6.71; N, 13.13. Found: C, 57.28; H, 6.63; N, 13.30.

2,3-Diacetamido-1,4-dimethoxybenzene. Acetic anhydride (2.28 ml., 0.0242 mole) was added to 2.43 g. (0.0119 mole) of 2,3-diamino-1,4-dimethoxybenzene in 50 ml. of water, followed by the addition of 1.96 g. (0.024 mole) of sodium acetate in 15 ml. of water. The diacetamido derivative separated on standing. It was recrystallized from ethanol, yield 37%, m.p. 203–213° dec.

Anal. Calcd. for $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.11. Found: C, 56.96; H, 6.61; N, 11.30.

2-Acetamido-3-amino-6-bromo-1,4-dimethoxybenzene. 2-Acetamido-3-amino-1,4-dimethoxybenzene (2.1 g., 0.01 mole) was dissolved in 75 ml. of dioxane and a solution of 1.6 g. (0.01 mole) of bromine in 16 ml. of dioxane was slowly added. The hydrobromide of the bromo compound separated from the reaction mixture. The crystals were dissolved in water and the solution treated with sodium bicarbonate. The precipitate which formed was removed, dried, and recrystallized from chloroform–petroleum ether, yield 70%, m.p. 164–167°.

Anal. Calcd. for $C_{10}H_{13}N_2O_3Br$: C, 41.54; H, 4.53; N, 9.69; Br, 27.64. Found: C, 41.35; H, 4.35; N, 9.89; Br, 27.85.

2,3-Diacetamido-6-nitro-1,4-dimethoxybenzene. 2,3-Diacetamido-1,4-dimethoxybenzene (2.52 g., 0.01 mole) was dissolved in 15 ml. of acetic acid and 25 ml. of concentrated sulfuric acid was slowly added. This solution was cooled to 5° and 0.9 g. (0.01 mole) of concentrated nitric acid in 0.7 g. of concentrated sulfuric acid was added, keeping the temperature between 0–10°. After standing for 1 hr., the solution was poured into ice water and neutralized to *p*H 7. The precipitate which formed was removed and recrystallized from ethanol, yield 66%, m.p. 265–268 dec.

Anal. Calcd. for $C_{12}H_{15}N_3O_6$: C, 48.49; H, 5.09; N, 14.14. Found: C, 48.46; H, 4.98; N, 14.29.

2-Methyl-5-bromo-4,7-dimethoxybenzimidazole. This compound was prepared from 2-acetamido-3-amino-6-bromo-1,4-dimethoxybenzene by Phillips' method.[5] The product was recrystallized from benzene and from chloroform–petroleum ether, yield 89%, m.p. 177–181°.

Anal. Calcd. for $C_{10}H_{11}N_2O_2Br$: C, 44.30; H, 4.09; N, 10.33; Br, 29.47. Found: C, 44.27; H, 4.10; N, 10.24; Br, 29.60.

This compound was also obtained when the 2-acetamido-3-amino compound was heated with 10% sodium hydroxide in aqueous ethanol.

2-Methyl-5-nitro-4,7-dimethoxybenzimidazole. 2,3-Diacetamido-5-nitro-1,4-dimethoxybenzene (6.2 g., 0.0208 mole) was dissolved in 100 ml. of 4*N* hydrochloric acid and refluxed for 2 hr. The cooled solution was made slightly basic. The precipitate which formed was removed, dried, and extracted with chloroform. The extracted product was recrystallized from benzene and from dioxane–petroleum ether, yield 80%, m.p. 204–205°.

Anal. Calcd. for $C_{10}H_{11}N_3O_4$: C, 50.63; H, 4.67; N, 17.71. Found: C, 50.44; H, 4.55; N, 17.63.

5-Nitro-4,7-dimethoxybenzimidazole. 4,7-Dimethoxybenzimidazole (1.78 g., 0.01 mole) was suspended in 15 ml. of acetic acid and 25 ml. of concentrated sulfuric acid was gradually added, keeping the temperature below 40°. The solution was cooled to 0–10° and a mixture of 0.9 g. (0.01 mole) of concentrated nitric acid and 0.7 g. of concentrated sulfuric acid was added. After 0.5 hr. the solution was allowed to come to room temperature and then poured into ice water and the *p*H adjusted to 5. The precipitate which formed was recrystallized from ethanol and ethanol-water, yield 86%, m.p. 210°.

Anal. Calcd. for $C_9H_9N_3O_4$: C, 48.43; H, 4.06; N, 18.82. Found: C, 48.60; H, 4.22; N, 19.04.

5-Amino-4,7-dimethoxybenzimidazole dihydrochloride. 5-Nitro-4,7-dimethoxybenzimidazole in ethanol was hydrogenated in the presence of a palladium-charcoal catalyst. The catalyst was removed and concentrated hydrochloric acid added to the filtrate to precipitate the product as its dihydrochloride. The latter was recrystallized from ethanol-water with the aid of decolorizing carbon, yield 95%, m.p. 230–231°.

Anal. Calcd. for $C_9H_{13}N_3O_2Cl_2$: C, 40.62; H, 4.93; N, 15.79; Cl, 26.65. Found: C, 40.80; H, 4.73; N, 15.68; Cl, 26.50.

Imidazo-p-benzoquinone. 4,7-Dihydoxybenzimidazole hydrobromide (3.7 g., 0.016 mole) was dissolved in water and an excess of ferric chloride added. After standing for 2 hr., the yellow product was collected by filtration and recrystallized from dimethylformamide.

2-Methylimidazo-p-benzoquinone. 2-Methyl-4,7-dihydroxybenzimidazole (1.15 g., 0.0057 mole) was dissolved in 30 ml. of water and 0.63 g. (0.0063 mole) of chromic anhydride in 5 ml. of water was added to the solution. After standing for 2 hr., the yellow product was removed by filtration. It was recrystallized from acetic acid, with the aid of decolorizing carbon, and twice from ethylene glycol monomethyl ether.

2-Propylimidazo-p-benzoquinone. This compound was prepared from crude 2-propyl-4,7-dihydroxybenzimidazole hydrochloride by oxidation with chromic anhydride. The crude quinone was extracted with benzene and finally recrystallized from benzene.

2-Isoamylimidazo-p-benzoquinone. Crude 2-isoamyl-4,7-dihydroxybenzimidazole hydrochloride was used for this preparation and chromic anhydride was the oxidizing agent. The yellow product was recrystallized from dioxane–petroleum ether.

4-Nitro-1,2-dimethoxybenzene. 1,2-Dimethoxybenzene (23 g., 0.018 mole) was added dropwise to a mixture of 10 ml. of concentrated nitric acid and 20 ml. of water, between 15–30°. After 15 min., the mixture was poured into ice water. The precipitate was removed, washed and dried, yield 100%, m.p. 96–99° (crude product).

4,5-Dinitro-1,2-dimethoxybenzene. 4-Nitro-1,2-dimethoxybenzene (33 g., 0.14 mole) was added to 115 ml. of fuming nitric acid, keeping the temperature at 0°. After 0.5 hr., the mixture was poured into ice water. The precipitate was removed, washed and dried, yield 38.9 g. (95%), m.p. 125–132° (crude product).[11]

4,5-Diamino-1,2-dimethoxybenzene. The corresponding dinitro compound was hydrogenated, in the presence of a palladium-on-carbon catalyst, in ethanol solution. After removing the catalyst, the diamine was obtained by removing the ethanol *in vacuo*, m.p. 131°.[9]

5,6-Dimethoxybenzimidazole. 4,5-Diamino-1,2-dimethoxybenzene was treated with 98% formic acid as in the prep-

(11) The preparations of the last two compounds are included because difficulties were encountered with the previously described preparations.

aration of 5,7-dimethoxybenzimidazole. The product was recrystallized from dioxane with the aid of decolorizing carbon.

2-Methyl-5,6-dimethoxybenzimidazole and 2-hydroxymethyl-5,6-dimethoxybenzimidazole were prepared by Phillips' method.[5]

2-Chloromethyl-5,6-dimethoxybenzimidazole hydrochloride. A mixture of 8.19 g. (0.0393 mole) of 2-hydroxymethyl-5,6-dimethoxybenzimidazole and 15 ml. of thionyl chloride was refluxed for 4 hr. The mixture was cooled and the solid removed and washed with chloroform. It was recrystallized from ethanol with the aid of decolorizing carbon.

2-Di-n-butylaminomethyl-5,6-dimethoxybenzimidazole. A solution of 2.63 g. (0.01 mole) of 2-chloromethyl-5,6-dimethoxybenzimidazole hydrochloride and 3.78 g. (0.03 mole) of di-*n*-butylamine in 5 ml. of ethanol was refluxed for 3 hr. The alcohol was removed by evaporation and the residue treated with water. The water solution was extracted with chloroform. The chloroform was removed and the residue dissolved in ether. The addition of petroleum ether precipitated an oil which solidified on cooling. This product was purified by forming its hydrochloride in carbon tetrachloride solution. The salt was recrystallized from ethanol and then converted to the base by treatment with sodium carbonate solution. The free base was recrystallized from carbon tetrachloride–petroleum ether.

2-Di(β-chloroethyl) aminomethyl-5,6-dimethoxybenzimidazole. 2-Chloromethyl-5,6-dimethoxybenzimidazole hydrochloride (3.22 g., 0.0123 mole) and 3.9 g. (0.070 mole) of diethanolamine were dissolved in 40 ml. of ethanol and the solution was refluxed for 3 hr. The ethanol was removed *in vacuo* and 100 ml. of chloroform added. A small upper layer formed and was discarded. Ten ml. of thionyl chloride was added to the chloroform layer and the solution was refluxed for 1 hr. After cooling, the precipitate was removed by filtration. It was recrystallized from ethanol with the aid of decolorizing carbon.

5,6-Dihydroxybenzimidazole Hydrobromide. 5,6-Dimethoxybenzimidazole (1 g., 0.0056 mole) was dissolved in 25 ml. of 48% hydrobromic acid and the solution was refluxed for 1 hr. On cooling, the product crystallized. It was recrystallized from ethanol–petroleum ether.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

Preparation of Pyrido-(2,3)-pyrazines, Pyrido-(3,4)-pyrazines and Imidazo-(b)-pyridines

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A number of imidazopyridines and pyridopyrazines have been prepared. Imidazo-(b)-pyridines having methyl groups and/or halogen were converted to mono *N*-oxides by the action of 1.2 *M* peracetic acid. Electron attracting substituents prevented *N*-oxidation. The pyridopyrazines failed to give *N*-oxides under a variety of conditions.

A number of benzimidazoles and quinoxaline derivatives have been found to possess antimetabolite or bactericidal activity. The activity of these compounds is somewhat dependent on the nature and positions of substituent groups. Much less is known about the imidazopyridines and pyridopyrazines. It seemed desirable to prepare a number of substituted imidazopyridines and pyridopyrazines for testing purposes. Diaminopyridines were the starting materials for these preparations.[2]

2-Amino-5-chloropyridine was nitrated to form 2-amino-3-nitro-5-chloropyridine. The latter was reduced most efficiently with sodium dithionate to the corresponding 2,3-diamino compound. The diamine was converted to 6-chloroimidazo-(b)-pyridine by refluxing with formic acid and to 7-chloropyrido-(2,3)-pyrazine and 2,3-dimethyl-7-chloropyrido-(1,3)-pyrazine by treatment with glyoxal and diacetyl respectively. The diphenyl derivative was made from the diamine and benzil.

When 2-amino-3-nitro-5-chloropyridine was reduced with stannous chloride in concentrated hydrochloric acid, a dichlorinated diamine was isolated. This product was assumed to be 5,6-dichloro-2,3-diaminopyridine. It was converted to the corresponding pyridopyrazines with glyoxal and diacetyl.

2-Amino-4-methylpyridine was brominated in alcohol solution to give 2-amino-4-methyl-5-bromopyridine. The latter was nitrated to the corresponding 3-nitro compound which was then reduced with stannous chloride to 2,3-diamino-4-methyl-5-bromopyridine. The diamine was converted to 2-hydroxy-6-bromo-7-methylimidazo-(b)-pyridine by fusion with urea and to 2-mercapto-6-bromo-7-methylimidazo-(b)-pyridine by treatment with carbon disulfide in alcoholic potassium hydroxide solution. 6-Bromo-7-methylimidazo-(b)-pyridine was obtained from the diamine by heating with formic acid. This imidazo compound was oxidized to 6-bromo-7-imidazo-(b)-pyridinecarboxylic acid. 2,3-Diamino-4-methyl-5-bromopyridine was also treated with glyoxal, diacetyl and benzil, respectively, to obtain the corresponding pyridopyrazines.

The preparation of 2,3-diamino-5-bromo-6-methylpyridine from 2-amino-6-methylpyridine was completely analogous to that just described for the 4-methyl isomer. The 2,3-diamino-5-bromo-6-methylpyridine was converted to the corresponding

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(2) The new compounds that were prepared during this investigation are being tested at the University of Pennsylvania. The results will be reported later.