The epoxide **44** (4.7 g, 0.02 mole), 6.2 ml of *i*-PrNH$_2$ and 11 ml of MeOH, left 64 hr at room temp and worked up, gave 4.35 g of **32**, mp 77.5–78.0° from Et$_2$O. *Anal.* ($C_{16}H_{26}N_2O_3$) C, H, N. 1-(2-Morpholinophenoxy)-3-*tert*-butylaminopropan-2-ol (**33**) was similarly prepd and isolated in 56.2% yield as the monophosphate monoethanolate, mp 175–176°. *Anal.* ($C_{17}H_{28}N_2O_2 \cdot H_3PO_4 \cdot C_2H_6O$) C, H, N, P. Similarly prepd were 1-(4-morpholinophenoxy)-3-isopropylamino-2-propanol, mp 98.5–99.5° (*i*-PrOH) [*Anal.* ($C_{16}H_{26}N_2O_3$) C, H, N] and 1-(3-morpholinophenoxy)-3-isopropylamino-2-propanol, isolated as the oxalate, mp 165–167.5° (EtOH) [*Anal.* ($C_{16}H_{26}N_2O_3 \cdot C_2H_2O_4$) C, H, N, O]. The last 2 compds were much less active in the β-adrenergic blocking screens than **32** and **33**.

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Bisbenzimidazoles. Potent Inhibitors of Rhinoviruses[1]

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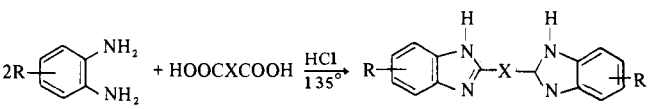
(*S*,*S*)-1,2-Bis(5-methoxy-2-benzimidazolyl)-1,2-ethanediol (**11**, Abbott 36683), reported in the literature as active against poliovirus type 1, was found in our laboratories to be a potent inhibitor of rhinoviruses in cell culture. A series of 27 bisbenzimidazoles and 11 related monobenzimidazoles were synthesized by the method of Phillips, namely, condensation of a substituted *o*-phenylenediamine with a carboxylic acid in 5 *N* HCl at 135°. None of the monobenzimidazoles was active against rhinoviruses. Eight bisbenzimidazoles in addition to **11** were active. Structural features of the bisbenzimidazoles essential for antiviral activity were: (1) no substituent in the 1 position of the benzimidazole; (2) a 5-methoxy or 5-ethoxy substituent; and (3) a two-carbon chain, unsubstituted or substituted by hydroxyl, connecting the two benzimidazoles.

Numerous derivatives of benzimidazole have been tested for antiviral activity.[2] In 1958, 2-(α-hydroxybenzyl)benzimidazole or HBB was reported to inhibit poliovirus type 1 in monkey kidney and HeLa cell cultures.[3] HBB has been extensively studied by Tamm and coworkers[4] and by others[2] and has been shown to inhibit several types of enteroviruses. More recently HBB has been found to inhibit rhinoviruses, although at relatively high concentrations.[5] In our laboratories HBB has been found to have weak activity against only a few serotypes of rhinovirus.

In 1963, O'Sullivan and Wallis[6] reported the antipoliovirus activity of 1,2-bis(2-benzimidazolyl)-1,2-ethanediol (**8**), an analog of HBB, and, in 1968, Akihama, *et al.*,[7] reported the synthesis and antipolio activity of three derivatives (**9**, **10**, **11**) of this compound which are substituted in the 5 position of the benzimidazole ring system. The percentage inhibitions of plaques of poliovirus type 1 by **8–11** at 10^{-5} *M* were 38, 33, 32, and 100, respectively. The minimal inhibitory concentration of the methoxy derivative **11** was 2×10^{-7} *M* compared with 10^{-4} *M* for HBB.

In our laboratories, Schleicher and coworkers[8] have found the methoxy derivative **11** to be a potent inhibitor of rhinoviruses in WI-38 cell culture: at a concentration of 0.1 μg/ml, **11** produced 100% inhibition of the cytopathic effect

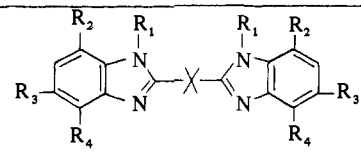


(CPE). The chloro derivative **10** was inactive, but its hydrochloride salt was slightly active. The other two compounds (**8** and **9**), as well as their salts, were inactive. The potency and broad spectrum of inhibition of rhinoviruses by **11** encouraged us to synthesize a series of bisbenzimidazoles and some related monobenzimidazoles.

Results and Discussion

Chemistry. The benzimidazoles were synthesized by the method of Phillips,[9] namely, acid-catalyzed condensation of a substituted *o*-phenylenediamine with a carboxylic acid. The 27 bisbenzimidazoles synthesized are listed in Table I. All of the bisbenzimidazoles prepared in this study were symmetrically substituted, *i. e.*, with the same substituent on both benzimidazole moieties. Compound 3 was obtained by demethylation of **4**; we were unable to demethylate **11**. Compound **20** was obtained from an attempted oxidation of **11** with the use of nitric acid. Hydrochloride salts of

Table I. Bisbenzimidazoles



No.	Formula[a]	Configuration	R_1	R_2	R_3	R_4	X	Yield, %	Mp, °C
1	$C_{15}H_{12}N_4$		H	H	H	H	CH_2	20	>270
2	$C_{17}H_{16}N_4O_2 \cdot 0.5H_2O$		H	H	OCH_3	H	CH_2	40	>285
3	$C_{16}H_{14}N_4O_2 \cdot 0.5H_2O$[b]		H	H	OH	H	$(CH_2)_2$	60	185-189
4	$C_{18}H_{18}N_4O_2$		H	H	OCH_3	H	$(CH_2)_2$	63	255-257
5	$C_{19}H_{20}N_4O_2$		H	H	OCH_3	H	$(CH_2)_3$	15	105-108
6	$C_{16}H_{14}N_4O$	*S*	H	H	H	H	$CH_2CH(OH)$	41	>290[c]
7	$C_{18}H_{18}N_4O_3 \cdot 2HCl \cdot 0.5H_2O$	*S*	H	H	OCH_3	H	$CH_2CH(OH)$	7	280 dec
8	$C_{16}H_{14}N_4O_2$	*S,S*	H	H	H	H	$(CHOH)_2$	77	265 dec[d]
9	$C_{18}H_{18}N_4O_2 \cdot H_2O$	*S,S*	H	H	CH_3	H	$(CHOH)_2$	16	230-231 dec[e]
10	$C_{16}H_{12}Cl_2N_4O_2$	*S,S*	H	H	Cl	H	$(CHOH)_2$	24	225-227[f]
11	$C_{18}H_{18}N_4O_4$	*S,S*	H	H	OCH_3	H	$(CHOH)_2$	70	221-223 dec[g]
12	$C_{18}H_{18}N_4O_4$	*R,R*	H	H	OCH_3	H	$(CHOH)_2$	54	221-222 dec
13	$C_{18}H_{18}N_4O_4$	*R,S*	H	H	OCH_3	H	$(CHOH)_2$	34	260 dec
14	$C_{20}H_{22}N_4O_4$	*S,S*	H	H	OCH_2CH_3	H	$(CHOH)_2$	31	232-233 dec
15	$C_{22}H_{26}N_4O_4$	*S,S*	H	H	$OCH_2CH_2CH_3$	H	$(CHOH)_2$	18	230 dec
16	$C_{18}H_{14}N_4O_6 \cdot 1.5H_2O$[h]	*S,S*	H	H	COOH	H	$(CHOH)_2$	11	>260
17	$C_{24}H_{30}N_4O_4 \cdot 0.5H_2O$	*S,S*	n-C_3H_7	H	OCH_3	H	$(CHOH)_2$	7	220-221
18	$C_{18}H_{18}N_4O_4 \cdot H_2O$	*S,S*	H	OCH_3	H	H	$(CHOH)_2$	60	145 dec
19	$C_{20}H_{22}N_4O_6$	*S,S*	H	OCH_3	H	OCH_3	$(CHOH)_2$	24	251-252 dec[i]
20	$C_{18}H_{16}N_6O_8 \cdot 0.5H_2O$	*S,S*	H	H	OCH_3	NO_2[j]	$(CHOH)_2$	96	247-252 dec
21	$C_{22}H_{22}N_4O_6$	*S,S*	H	H	OCH_3	H	$(CHOCOCH_3)_2$	55	204 dec
22	$C_{20}H_{22}N_4O_2$	*k*	H	H	OCH_3	H	$(CHCH_3)_2$	30	283-285
23	$C_{20}H_{22}N_4O_2$		H	H	OCH_3	H	$CH_2C(CH_3)_2$	32	218-223
24	$C_{22}H_{26}N_4O_2$		H	H	OCH_3	H	$[C(CH_3)_2]_2$	2	295-298
25	$C_{20}H_{20}N_4O_2$	*R,S* cis	H	H	OCH_3	H	-CH-CH- (CH2-CH2)	17	184-196
26	$C_{20}H_{20}N_4O_2$	*RS,RS* trans	H	H	OCH_3	H	-CH-CH- (CH2-CH2)	24	138-144
27	$C_{20}H_{22}N_4O_6$	Galacto[l]	H	H	OCH_3	H	$(CHOH)_4$	28	283-285 dec

[a] All compds were analyzed for C, H, N. [b] N: Calcd 18.48, found 19.04. [c] Lit.[17] mp > 400°. [d] Lit.[6] mp 268-269° dec. [e] Lit.[7] mp 230-231°. [f] Lit.[7] mp 219-220°. [g] Lit.[17] mp 206-207°,[1] and lit.[7] mp 213-214°. [h] C: Calcd 52.81, found 52.37. [i] Lit.[17] mp 257°. [j] Nmr (see Experimental Section) indicated a mixture of the 5-methoxy-4-nitro derivative (the structure given for 20) and the 5-methoxy-6-nitro isomer in 2:1 ratio. [k] Mixture of stereoisomers, prepared from commercial mixture of DL and *meso*-2,3-dimethylsuccinic acid. [l] Prepared from mucic acid.

several bisbenzimidazoles were prepared, but in only one instance, the 5-chloro derivative **10**, was the salt of an inactive base found to be active.†

The 11 monobenzimidazoles synthesized are listed in Table II. The monobenzimidazoles having a carboxylic acid group on the 2 substituent were obtained as by-products in the preparation of bisbenzimidazoles or by the use of 1 mole of diamine per mole of dicarboxylic acid.

Biological Activity. The antiviral activity of the benzimidazoles was determined against rhinoviruses 1A and 42, selected as representative serotypes, in WI-38 cell culture at concentrations of 10-1000 μg/ml by Schleicher and coworkers.[8] A compound was considered active only if it produced 100% inhibition of virus-induced cytopathic effect at a concentration of 100 μg/ml or less. Because the criterion for activity at a given concentration was 100% inhibition of CPE, rather than 50 or 75%, the experimental variation in the minimum active concentration determined for a compound was large. Hence it generally was not possible to distinguish small differences in activity.

None of the monobenzimidazoles inhibited the test rhinoviruses, although compounds **30** and **31** have been reported to inhibit poliovirus.[10] Nine of the bisbenzimidazoles were active, in each case against both 1A and 42 serotypes. The minimal inhibitory concentrations were: 10 μg/ml for **4**, **7**, **11-14**, and **21**; 100 μg/ml for the hydrochloride salt of **10**; and 320 μg/ml for **19**. None of the compounds was more active than **11**. Compounds **11** and **14** were tested at lower concentrations and found to be active as low as 0.1 and 1 μg/ml, respectively.‡

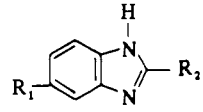
Bisbenzimidazole **11** (Abbott 36683) was chosen for further studies. In cell cultures, **11** inhibits the replication of several picorna viruses: all 55 recognized serotypes of rhinovirus at 10 μg/ml; all three types of poliovirus at 10 μg/ml; and both of the representative types of Coxsackie virus tested (A-9 at 10 μg/ml and B-3 at 100 μg/ml).[8] Evidence for activity of **11** *in vivo* has also been obtained. When chimpanzees were experimentally infected with rhinovirus 30 and medicated orally with **11** at 100 mg/kg for four days, no rhinovirus could be isolated from throat swabs on days 1-8 post infection, whereas virus was isolated from control chimpanzees for approximately 10 days.[11]

Structure-Activity Relations. (a) Substitution on the Benzene Ring. The effect of substitution on the benzene ring was determined from a group of compounds all of which had 1,2-ethanediol as the connecting chain. With no substituent (**8**), 5-methyl (**9**), or 5-carboxyl (**16**), the bis-

†It is possible that the observed activities reflect, at least in part, the solubilities attained in the buffered medium employed in the cell cultures. This could account for the slight activity of the HCl salt of 10 whereas 10 itself appeared inactive since the salt would reach a saturated solution at a faster rate.

‡Owing to discontinuation of this study before its completion, it was not possible to test at lower concentrations the other compounds active at 10 μg/ml.

Table II. Monobenzimidazoles



No.	Formula[a]	Configuration	R_1	R_2	Yield, %	Mp, °C
28	$C_8H_8N_2O \cdot HCl$		OCH_3	H	73	123-125[b]
29	$C_9H_{10}N_2O_2$		OCH_3	CH_2OH	50	198-200[c]
30	$C_{10}H_{12}N_2O_2$	*RS*	OCH_3	$CH(OH)CH_3$	42	156-158[d]
31	$C_{15}H_{14}N_2O_2$	*RS*	OCH_3	$CH(OH)C_6H_5$	5	169-171[e]
32	$C_{11}H_{12}N_2O_3$		OCH_3	CH_2CH_2COOH	43	152-160
33	$C_{10}H_{10}N_2O_3$	*S*	H	$CH(OH)CH_2COOH$	(10)[f]	221-223 dec[g]
34	$C_{10}H_{10}N_2O_4$[h]	2*R*,3*S*[i]	H	$(CHOH)_2COOH$	(12)[f]	117-119 dec
35	$C_{11}H_{12}N_2O_5 \cdot 1.5H_2O$	2*R*,3*S*[i]	OCH_3	$(CHOH)_2COOH$	40	155-165 dec
36	$C_{12}H_{14}N_2O_5 \cdot 0.5H_2O$[j]	2*R*,3*S*[i]	OC_2H_5	$(CHOH)_2COOH$	5	160-170 dec
37	$C_{12}H_{16}N_2O_5$	D-gluco[k]	H	$(CHOH)_4CH_2OH$	62	217-218 dec[l]
38	$C_{13}H_{18}N_2O_6$	D-gluco[k]	OCH_3	$(CHOH)_4CH_2OH$	29	193-195 dec

[a] All compds were analyzed for C, H, N. [b] Ochiai and Katada[19] report mp 123°. [c] Grimaldi and Day[20] report mp 190-191°. [d] Rabiger and Joullié[21] report mp 160-161°. [e] Wagner, *et al.*,[22] report mp 165-166°. [f] Isolated as a by-product from synthesis of the related bisbenzimidazole. [g] Lit.[17] mp 214°. [h] H: Calcd 4.54, found 5.03. [i] The side chain is numbered starting with the carboxylic acid group. Prepared from (*R,R*)-tartaric acid. [j] N: Calcd 10.18, found 10.63. [k] Prepared from D-gluconic acid. [l] Moore and Link[23] report mp 215°.

benzimidazole was inactive. The 5-chloro derivative (**10**) was slightly active as the hydrochloride salt. The 5-methoxy derivative (**11**) was active, with the 5-ethoxy derivative (**14**) slightly less active, and the 5-propoxy derivative (**15**) inactive. The isomeric 4-methoxy compound (**18**) was inactive; surprisingly, the 4,7-dimethoxy derivative (**19**) was slightly active. Since we were unable to synthesize the 5-hydroxy derivative in which the connecting chain is 1,2-ethanediol, we prepared the 5-hydroxy analog **3** in which the connecting chain is unsubstituted. This compound was inactive, whereas the 5-methoxy analog **4** was active.

(b) Substitution on the Imidazole Ring. Only one variation was attempted. The 1-propyl analog (**17**) of the most active bisbenzimidazole (**11**) was synthesized and found to be inactive. Propyl was selected, rather than methyl or ethyl, because the 1-propyl derivative of HBB has been reported as the most active member in a series of 1-alkyl derivatives of HBB.[6]

(c) **Variations of the Connecting Chain.** The effect of variation in the connecting chain was determined from a group of compounds all of which contained the 5-methoxybenzimidazole moiety. The chain connecting the two benzimidazoles must be two carbons; both one- and three-carbon saturated chains were inactive (**2** and **5** *vs.* **4**). Alkyl substitution on the chain destroyed activity (**22-26**). Substitution by hydroxyl on one carbon atom (**7**) or on both carbon atoms (**11-13**) retained activity. Esterification of both hydroxyl groups retained activity (**21**), although it is possible that the observed activity is actually that of **11** formed by hydrolysis in the test system.

(d) **Stereochemistry.** Surprisingly, all three stereoisomers (**11**, **12**, **13**) of the most active structure were active.

Comparison with HBB Derivatives. The structure-activity relations for bisbenzimidazoles active against rhinoviruses can be compared with the structure-activity relations for HBB derivatives active against enteroviruses.[12,13]

(a) Whereas substitution at the 1 position of HBB by small alkyl groups increased activity, this change in the bisbenzimidazole series (**17**) destroyed activity in the one case studied.

(b) In the HBB series methyl substituion on the α-carbon of the 2 substituent markedly increased activity toward echovirus 6[13] but decreased activity toward poliovirus type 2.[6] In the bisbenzimidazoles this change destroyed the activity toward rhinoviruses (**22-26**).

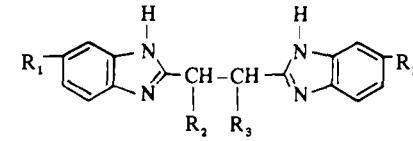
(c) The α-hydroxyl group is very important in both series. Thus, 2-benzylbenzimidazole is much less active than HBB, and seven of the active bisbenzimidazoles have α-hydroxyl groups.

(d) Electron-donating substituents in the 5 position of the benzimidazole ring of HBB increase cytotoxicity with little effect on antiviral activity. In the bisbenzimidazole series seven of the active compounds have a 5-methoxy or 5-ethoxy substituent; the electron-donating property cannot be the only important characteristic of the substituent, however, since the 5-hydroxy and 5-propoxy analogs (**3** and **15**, respectively) are inactive.

(e) The D isomer of HBB is reported to be 2.5-3 times as active as the L isomer.[14] The three stereoisomers of 1,2-bis(5-methoxy-2-benzimidazolyl)-1,2-ethanediol (**11**, **12**, **13**) were all active at 10 μg/ml. As mentioned above, whether there was a small difference in activity among these isomers was not determined.

Conclusion

The structural features of the bisbenzimidazoles which appear to be essential for inhibitory activity *vs.* rhinoviruses are summarized by the following formula



where $R_1 = OCH_3, OC_2H_5$
R_2 and R_3 = H, OH, $OCCH_3$ (O)

The bisbenzimidazoles constitute a significant advance in the search for antiviral agents in that they are the first class of compounds reported to inhibit all known serotypes of rhinovirus in cell culture. In addition to their broad spectrum, these compounds are active at very low concentrations *in vitro*, and one member has been shown to prevent an experimental rhinovirus infection in animals. Thus, the bisbenzimidazoles provide evidence that the development of synthetic drugs for the prevention of rhinovirus infections is possible.

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer. Nmr spectra were obtained on Varian A-60 or HA-100 spectrometers. Melting points were determined on a Thomas-Hoover capillary mp apparatus or a Fisher-Johns block and are uncorrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for the elements are within ±0.4% of the theoretical values.

Many of the benzimidazoles formed stable hydrates. All samples were dried at 80°, which generally removed H_2O of hydration. In those instances in which this temp failed to remove the H_2O of hydration, the compounds were analyzed as hydrates; satisfactory analyses could not be obtained for a few compds. Many of the benzimidazoles, especially those with OH groups in the connecting chain, did not melt sharply but rather decomposed.

Starting Materials. All of the carboxylic acids and *o*-phenylenediamine, 4-chloro-*o*-phenylenediamine, 3,4-diaminotoluene, and 3,4-diaminobenzoic acid were obtained commercially. 4-Methoxy-2-nitroaniline and 4-ethoxy-2-nitroaniline were obtained commercially and catalytically reduced to the diamines by use of 2% by wt of 5% Pd on charcoal in abs EtOH. Literature procedures were used for the preparation of 4-propoxy-*o*-phenylenediamine,[15] 3-methoxy-*o*-phenylenediamine,[16] 3,6-dimethoxy-*o*-phenylenediamine,[17] and 4-methoxy-N^1-propyl-*o*-phenylenediamine.[18]

General Procedure for the Synthesis of Benzimidazoles. A. Optimum Reaction Conditions. To determine the optimum reaction conditions for the synthesis of bisbenzimidazoles, the condensation of *o*-phenylenediamine with L-tartaric acid was studied. Each of 5 reaction parameters was varied in order to determine its effect on yield, other parameters being held constant. The parameters, variations, and per cent yields of bisbenzimidazole were: reaction time: 3, 6, 17 hr (29, 40, 53%); temp: 80, 135° (32, 71%); effect of O_2: air, N_2 (31, 32%); molar ratio of HCl to diamine: 1:1, 2:1 (53, 71%); molar ratio of diamine to dicarboxylic acid: 2:1, 3:1 (71, 77%). The best conditions were: 17 hr, 135°, under N_2, with a molar ratio of HCl–diamine–dicarboxylic acid of 4:2:1. (Although the reaction run under N_2 did not give a higher yield, the product was easier to purify.)

B. Bisbenzimidazoles. A mixt of 0.1 mole of the *o*-phenylenediamine, 0.05 mole of the dicarboxylic acid, and 40 ml of 5 *N* HCl (0.2 mole) was heated in an oil bath at 135° under N_2 for approx 18 hr. The mixt was cooled in an ice bath to ppt the HCl salts of the bisbenzimidazole and any monobenzimidazole. The solid was collected, washed with cold H_2O, and dissolved in a minimum amount of hot H_2O. The soln was treated with Darco and filtered. The filtrate was cooled and basified with concd NH_4OH. The ppt of bisbenzimidazole was collected, washed, and crystd from alcohol or aqueous alcohol. Some bisbenzimidazoles, owing to their limited solubilities, could not be crystd. Acidification of the ammoniacal filtrate with AcOH sometimes gave a small amount of the corresponding monobenzimidazole.

C. Monobenzimidazoles. The ratio of reactants was 0.05 mole of the *o*-phenylenediamine, 0.05 mole of the carboxylic acid, and 20 ml of 5 *N* HCl (0.1 mole). Procedure was the same as in B. When a monocarboxylic acid was used, the product was isolated on basification with NH_4OH. When a dicarboxylic acid was used, some bisbenzimidazole was obtained, and after it was removed, the product was isolated by acidification with AcOH.

(*S,S*)-1,2-Bis(5-methoxy-2-benzimidazolyl)-1,2-ethanediol Diacetate (21). A soln of 19.8 g (0.51 mole) of 11 in 135 ml of Ac_2O was prepared, keeping temp at room temp or lower, and allowed to stand overnight. The yellow soln was evapd at 40–50° *in vacuo*, leaving a viscous green-yellow oil. The oil was dissolved in a small amount of MeOH, and the soln was poured into aqueous $NaHCO_3$. A yellow semisolid formed and solidified on standing. Crystn from abs EtOH–C_6H_6 gave colorless crysts of 21: 12.3 g (55%); dec at *ca.* 200°.

Nitration of 11 to Produce 20. A mixt of 5.0 g (0.12 mole) of 11 and 50 ml of concd HNO_3 (sp gr 1.42) was heated on the steam bath for 2 hr. The mixt was poured onto crushed ice, and the resulting soln was basified with concd NH_4OH. The ppt was collected, washed with H_2O, and dried to give 6.0 g (96%) of crude **20** melting at 247–252°. Because of limited solubility, purification was not feasible. The product was shown to be a mixt by 2 MeO absorptions at δ 3.94 and 3.95 ppm in the nmr (obtained on a soln in DMSO-d_6 at 90° on a Varian HA-100). The absorptions of the aromatic protons indicated a mixt of 4-nitro isomer (H-6 at δ 7.15, d, J = 9.5 Hz; H-7 at 7.75, d, J = 9.5 Hz) and 6-nitro isomer (H-4 at δ 7.30, s; H-7 at 8.03, s) in a ratio of approx 2:1. (The possibility of a nonsymmetrical molecule containing 4-nitro in one benzimidazole and 6-nitro in the other could not be excluded.)

1,2-Bis(5-hydroxy-2-benzimidazolyl)ethane (3). A mixt of 4.83 g (0.015 mole) of 4 and 34.7 g (0.3 mole) of pyridine·HCl was heated in an oil bath at 210° for 4 hr. The resultant soln was poured onto ice, and the yellow HCl salt of 3 was collected and washed with H_2O. The solid was dissolved in hot H_2O, treated with Darco, filtered, and the filtrate was basified with NH_4OH. The ppt was collected, dissolved in aqueous HCl, and the purification was repeated. The ppt was washed with H_2O and dried *in vacuo* at 80° to give 2.75 g (60%) of 3 (off-white); mp 185–189°.

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