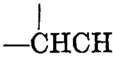
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

Preparation and Oxidation of Some Bisbenzimidazoles and Benzimidazolylhydroxypropionic Acids

KATHERINE H. TAFFS, LAILA VITTANDS PROSSER, FRANCES BAIRD WIGTON, AND MADELEINE M. JOULLIÉ[1]

Received May 31, 1960

A number of new bisbenzimidazoles and benzimidazolylhydroxypropionic acids have been prepared by a modified Phillips method. Substituents have been placed on both benzene rings of the benzimidazole nuclei and the chain linking the two benzimidazole units has been varied from simple alkane chains to hydroxylated alkane chains. The oxidation of 1,2-bis(2-benzimidazolyl)-1,2-ethandiol with potassium dichromate in sulfuric acid solution yielded a monocarbonyl compound. The same compound was also obtained by oxidation of the diol with alkaline permanganate. Benzimidazolecarboxylic acid was also obtained as a side product by varying the amount of permanganate used. The infrared spectra of some of the benzimidazolylhydroxypropionic acids showed a zwitterion structure. The oxidation products obtained from the unsubstituted benzimidazolylpropionic acid and its ester with potassium permanganate indicated that the hydroxyl group is in the *beta* position.

The antitumor effect of some bisbenzimidazoles against solid type Ehrlich ascites tumor has recently been reported by some Japanese workers.[2] As a few of the bisbenzimidazoles prepared by Wang and Joulié[3] have also shown some physiological activity in preliminary screening tests against mutant microorganisms, it seemed desirable to prepare other bisbenzimidazoles for testing purposes. It was hoped that by changing the groups in the benzene ring of the bisbenzimidazoles and by varying the connecting unit between these rings, more information could be obtained on the effect of structure on physiological activity. Bisbenzimidazoles containing methoxy, ethoxy, and dimethoxy groups, which had not been previously prepared, were made. The connecting unit was modified to include such chains as,  $-\overset{CH_3}{\overset{|}{C}}HCH_2-$, and hydroxylated chains such as $-CHOHCH_2-$, and $-(CHOH)_4-$.[4]

All of the compounds prepared in this investigation were made by Phillips' method,[5] which consists in heating the desired diamine with the appropriate dibasic acid in the presence of 4*N* hydrochloric acid for several hours or by a modification which consisted in using an additional catalytic amount of concentrated sulfuric acid.[3] Usually a refluxing period of ten hours was necessary for best yields; however, in the case of the bisbenzimidazole derived from 1,4-dimethoxy-2,3-diaminobenzene and glutaric acid a refluxing period of twenty hours was essential. In every case, the dihydrochlorides of the bisbenzimidazoles precipitated on cooling the solution. Some are more soluble than others but all may be obtained easily by regulating the amount of acid used. Some of the dihydrochlorides may be recrystallized from water or 4*N* hydrochloric acid and obtained in pure form, usually as hydrates. All of the free bases melt above 200° with decomposition.

Although the yields of 1,2-bis(2-benzimidazolyl)-ethanols were good, considerable difficulty was encountered in obtaining some of these compounds analytically pure. The product obtained by condensing *o*-phenylenediamine with malic acid was found to melt above 400°, which was rather unusual for a bisbenzimidazole. This compound was insoluble in most common organic solvents and when dissolved in high boiling solvents turned from white to yellow. This seemed to indicate that the compound was being dehydrated by heating to 1,2-bis(2-benzimidazolyl)ethylene which has been prepared by other methods and is known to be a yellow substance.[6]

Because of this difficulty, it was decided to prepare a salt of the compound, purify it and then liberate the free base from it. Both the hydrochloride and the sulfate were prepared and recrystallized easily from aqueous acid solutions. The sulfate appeared to be more stable but both salts turned yellow when heated in the solid state. Consequently they could not be dried at elevated temperatures

---

(1) To whom all inquiries should be addressed.

(2) T. Momai, H. Higurashi, M. Abe, and D. Mizuro, *J. Pharm. Soc. Japan*, **78**, 242 (1958).

(3) L. L. Wang and M. M. Joullié, *J. Am. Chem. Soc.*, **79**, 5706 (1957).

(4) A correction should be made for failing to refer to B. N. Feitelson, P. Mamalis, R. J. Maualim, V. Petrow, O. Stephenson, and B. Sturgeon, *J. Chem. Soc.*, 2389 (1952), for their prior preparation of 1,2-bis(6-nitro-2-benzimidazolyl)ethane; 1,4-bis(6-nitro-2-benzimidazolyl)butane; 1,6-bis(6-nitro-2-benzimidazolyl)hexane and 1,4-bis(6-amino-2-benzimidazolyl)butane tetrahydrochloride reported by Wang and Joullie.[3]

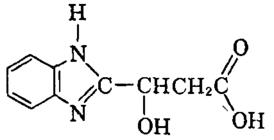
(5) M. A. Phillips, *J. Chem. Soc.*, 2393 (1928).

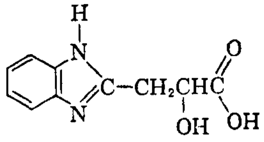
(6) (a) Soc. pour l'ind. chim. a Bale, Brit. 600, 696, April 15, 1948 [*Chem. Abstr.* **42**, 7342 (1948)]; (b) Ciba Ltda., Swiss Pat. 251,643, August 2, 1948 [*Chem. Abstr.* **44**, 667 (1950)]; (c) Ciba Ltda., Swiss pat. 240,109, March 16, 1946 [*Chem. Abstr.* **43**, 6241 (1949)]; (d) Swiss Pat. 240,112, April 1, 1946 [*Chem. Abstr.* **43**, 6241 (1949)]; (e) Ciba Ltda. Swiss Pat. 243,961, February 1, 1947 [*Chem. Abstr.* **43**, 4303 (1949)]; (f) Swiss Pat. 240,110, April 1, 1946 [*Chem. Abstr.* **43**, 6241 (1949)]; (g) Ciba Ltda., Swiss Pat. 238,148 October 1, 1945 [*Chem. Abstr.* **43**, 5217 (1949)].

even *in vacuo* and as a result they were isolated as hydrates. The sulfate was neutralized, the resulting free base was washed with water and dried at room temperature. It had a correct analysis for 1,2-bis(2-benzimidazolyl)ethanol.

The product obtained by refluxing 3-chloro-*o*-phenylenediamine with malic acid melted over a wide range even after several recrystallizations from aqueous ethanol. The product obtained did not have a correct analysis although the elemental analysis was close to that of the hydrate of the free base. To overcome this difficulty, the corresponding sulfate was prepared and it had an analysis correct for a monohydrate. From this salt the free base was obtained analytically pure, although it still exhibited a wide melting point range.

Because of the unexpected behavior of the two bisbenzimidazoles prepared from malic acid, it was decided to isolate the intermediate benzimidazolylhydroxypropionic acids to see if their formation proceeded normally. These compounds were prepared in good yields. They could have either one of two structures, (I) or (II), both of which could be converted to the same bisbenzimidazole when refluxed with more diamine in 4N hydrochloric acid.


I


II

When 3-(2-benzimidazolyl)-3-hydroxypropanoic acid was oxidized with potassium permanganate in acid solution, 2-benzimidazolecarboxylic acid was isolated. This seemed to suggest that this acid is a β-hydroxy acid.

When ethyl 3-(2-benzimidazolyl)-3-hydroxypropanoate was oxidized with potassium permanganate in acid solution, the resulting product appeared to have a β-keto structure since its infrared spectrum showed bands at 1725 cm.$^{-1}$ and 1625 cm.$^{-1}$, which are typical of β-keto esters. However, under the oxidizing conditions used, this product could not be isolated in appreciable yields and an analytically pure sample could not be obtained. Further oxidation of the enolic β-keto ester proceeds very rapidly so that benzimidazolecarboxylic acid and starting material are the only products that can be isolated. However, these results agree with the evidence obtained from the oxidation of the acid as to the position of the hydroxyl group.

When 3-(2-benzimidazolyl)-3-hydroxypropanoic acid was heated at 177° *in vacuo* it became orange brown. The product formed was found to be the corresponding unsaturated acid. This behavior is typical of β-hydroxy acids.

The infrared spectra of the benzimidazolylhydroxypropionic acids showed some interesting differences. The spectra of 3-(2-benzimidazolyl)-3-hydroxypropanoic acid and 3-(5-chloro-2-benzimidazolyl)-3-hydroxypropanoic acid exhibit bands at 1550 cm.$^{-1}$ and 1401 cm.$^{-1}$ which correspond to the asymmetric and symmetric modes of an ionized carboxyl group. Both compounds also have bands at 1325 cm.$^{-1}$ and 1326 cm.$^{-1}$, respectively. Such bands are known to be found in most amino acids and their derivatives. In contrast with these two compounds which exhibit bands characteristic of a zwitterion structure, 3-(1-benzyl-2-benzimidazolyl)-3-hydroxypropanoic acid and 3-(4,7-dimethoxy-2-benzimidazolyl)-3-hydroxypropanoic acid exhibit a sharp band at 1709 cm.$^{-1}$ characteristic of an unionized carboxyl group.

The esterification of 3-(2-benzimidazolyl)-3-hydroxypropanoic acid also seemed to indicate the zwitterion nature of this compound. This acid could be esterified directly only by using hydrogen chloride as a catalyst. This behavior is similar to that of amino acids.

The oxidation of 1,2-bis(2-benzimidazolyl)-1,2-ethanediol was carried out by using the theoretical amount of sodium dichromate to oxidize one alcohol group to a carbonyl group. The product obtained was isolated as the hydrate of a sulfate. The neutralization of this sulfate yielded a product which when recrystallized from absolute alcohol had an analysis corresponding to the hemiacetal of a monocarbonyl compound. The monocarbonyl compound was recrystallized from water also, but under these conditions it formed a stable hydrate which could only be dehydrated by heating *in vacuo* at 110° for eighty hours or more. Recrystallization from ethanol-water mixtures did not give analytically pure compounds.

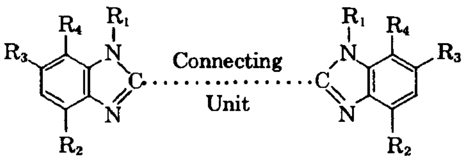
When the oxidation of 1,2-bis(2-benzimidazolyl)-1,2-ethandiol was carried out using an alkaline potassium permanganate solution in excess of the theoretical amount needed to oxidize this compound to two moles of acid, 2-benzimidazolecarboxylic acid was isolated. A similar oxidation was carried out using the theoretical amount of potassium permanganate to oxidize both hydroxyl groups to the corresponding carbonyl groups. Both benzimidazole and the monocarbonyl compound were isolated as products. When the theoretical amount of potassium permanganate to oxidize one hydroxyl group to a carbonyl group was used, the monocarbonyl compound was obtained as the only product.

1,2-Bis(2-benzimidazolyl)ethan-1-ol-2-one was oxidized with alkaline potassium premanganate to yield 2-benzimidazolecarboxylic acid in 90% yield.

When 1,2-bis(2-benzimidazolyl)ethan-1-ol-2-one was treated with an excess of diazomethane, the product formed appeared to be the hydrate of a trimethylated product. The same compound was obtained when methylation was accomplished with methyl iodide and sodium ethoxide.

TABLE I

Bisbenzimidazoles



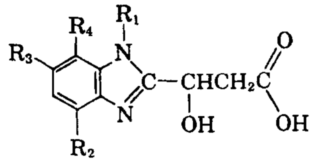
Substituents R1	R2	R3	R4	Connecting Unit	Yield, %	M.P.	Formula	Calcd. C	H	N	Cl	Found C	H	N	Cl
H	OCH_3	H	OCH_3	$(CH_2)_2$	28	310	$C_{20}H_{22}N_4O_4$	62.80	5.80	14.65	—	62.79	5.74	14.60	—
H	OCH_3	H	OCH_3	$(CH_2)_3$	29	263–264	$C_{21}H_{24}N_4O_4$	63.62	6.10	14.13	—	63.61	5.91	14.04	—
H	H	H	H	$CH(CH_3)CH_2$	60	360	$C_{17}H_{16}N_4$	73.89	5.84	20.28	—	73.68	5.64	20.49	—
H	H	Cl	H	$CH(CH_3)CH_2$	58	238–239	$C_{17}H_{14}N_4Cl_2$	59.14	4.09	16.23	20.60	59.02	4.29	16.14	20.60
H	OCH_3	H	OCH_3	$(CH_2)_4$	42	279–281	$C_{22}H_{26}N_4O_4$	64.37	6.39	13.65	—	64.25	6.46	13.65	—
H	OCH_3	H	OCH_3	$(CH_2)_6$	46	247	$C_{24}H_{30}N_4O_4$	65.74	6.90	12.78	—	65.60	6.78	12.59	—
H	OCH_3	H	OCH_3	$(CHOH)_2$	36	257	$C_{20}H_{22}N_4O_6$	57.97	5.35	13.52	—	57.80	5.23	13.55	—
H	H	OCH_3	H	$(CHOH)_2$	52	206–207	$C_{18}H_{18}N_4O_4$	61.02	5.11	15.81	—	61.02	4.98	15.67	—
H	H	Cl	H	$(CHOH)_4$	70	277	$C_{18}H_{16}N_4O_4Cl_2$	51.08	3.81	13.24	16.75	51.18	3.97	13.48	16.56
H	OCH_3	H	OCH_3	$(CHOH)_4$	22	265–266	$C_{22}H_{26}N_4O_8$	55.69	5.52	11.81	—	55.35	5.74	11.69	—
H	OCH_3	H	OCH_3	$(CH_2)_2S(CH_2)_2$	24	223	$C_{22}H_{26}N_4O_4S$	59.72	5.92	12.66	—	59.58	5.78	12.71	—
H	H	H	H	$CHOHCH_2$	85	280	$C_{16}H_{16}O_5N_4S\cdot 2\text{-}1/2H_2O$[a]	45.61	5.02	13.30	—	45.70	4.66	12.93	—
H	H	H	H	$CHOHCH_2$	75	above 400	$C_{16}H_{14}N_4O$	69.05	5.07	20.13	—	69.01	5.19	20.13	—
H	H	Cl	H	$CHOHCH_2$	89	309	$C_{16}H_{14}N_4O_5S$ $Cl_2.H_2O$[a]	41.48	3.48	12.09	—	41.29	3.54	11.87	—
H	H	Cl	H	$CHOHCH_2$	80	—	$C_{16}H_{12}N_4OCl_2$	55.34	3.49	16.14	20.42	55.22	3.57	16.12	20.29
H	H	CH_3	H	$CHOHCH_2$	70	198	$C_{18}H_{18}N_4O$	70.57	5.42	18.29	—	70.39	5.71	18.53	—
H	H	OC_2H_5	H	$CHOHCH_2$	22	—	$C_{20}H_{22}N_4O_3$	65.55	6.05	15.29	—	65.26	6.22	15.49	—
H	OCH_3	H	OCH_3	$CHOHCH_2$	38	249–250	$C_{20}H_{22}N_4O_5$	60.30	5.57	14.06	—	60.12	5.39	14.02	—
$C_6H_5CH_2$	H	H	H	$CHOHCH_2$	—	204–205	$C_{30}H_{26}N_4O$	78.57	5.72	12.21	—	78.57	5.53	12.39	—

---

[a] Sulfates.

TABLE II

3-(2-BENZIMIDAZOLYL)-3-HYDROXYPROPANOIC ACIDS



Substituents							Calcd.				Found			
R_1	R_2	R_3	R_4	Yield, %	M.P.	Formula	C	H	N	Cl	C	H	N	Cl
H	H	H	H	80	214	$C_{10}H_{10}N_2O_3$	58.25	4.88	13.59	—	58.30	5.03	13.32	—
H	H	Cl	H	89	221	$C_{10}H_9N_2O_3Cl$	49.91	3.77	11.77	14.73	50.04	3.59	11.56	14.87
H	OCH_3	H	OCH_3	40	219–220	$C_{12}H_{14}N_4O_5$	54.13	5.29	10.53	—	54.37	5.37	10.56	—
$C_6H_5CH_2$	H	H	H	43	168–173	$C_{17}H_{16}N_2O_3$	68.90	5.44	9.46	—	69.03	5.69	9.59	—

Although the infrared spectrum of the sulfate of 1,2-bis(2-benzimidazolyl)ethan-1-ol-2-one shows a strong band near 1645 cm.$^{-1}$, the infrared spectrum of the free base is very similar to the infrared spectrum of the starting material. The X-ray pictures of 1,2-bis(2-benzimidazolyl)ethanol and 1,2-bis(2-benzimidazolyl)ethan-1-ol-2-one are different.

EXPERIMENTAL

General information. All analytical samples were recrystallized four or five times from the appropriate solvent, once with the aid of decolorizing carbon. All compounds, unless otherwise noted, were dried *in vacuo* in an Abderhalden drying pistol for 24–40 hr., while heating at 80° or 110° depending on the melting point of the compound and the solvent used in its recrystallization.

The microanalyses for all compounds were performed by the Galbraith Laboratories, Knoxville, Tenn.

All of the melting points which are reported are uncorrected.

All infrared spectra were determined with a Perkin-Elmer infrared spectrophotometer Model 21. The compounds were studied in the solid state as potassium bromide disks.

Preparation of 1,2-bis(4,7-dimethoxy-2-benzimidazolyl)-ethane. This compound was prepared from 3,6-dimethoxy-*o*-phenylenediamine dihydrochloride and succinic acid. It was recrystallized from ethylene glycol monoethyl ether.

3,6-Dimethoxy-*o*-phenylenediamine dihydrochloride was obtained from the reduction of 1,4-dimethoxy-2,3-dinitrobenzene with a freshly prepared palladium on charcoal catalyst.

1,4-Dimethoxy-2,3-dinitrobenzene (15.2 g., 0.066 mole) was added to 1.5 g. of palladium on charcoal catalyst suspended in 100 ml. of absolute ethanol and the mixture hydrogenated in a Parr hydrogenation apparatus. The catalyst was removed by filtration and the solution collected in a flask containing concentrated hydrochloric acid. The yield of 3,6-dimethoxy-*o*-phenylenediamine dihydrochloride was 69%, m.p. 258° dec. This reduction has also been carried out using platinum as a catalyst and the yields obtained were similar.[7]

1,4-Dimethoxy-2,3-dinitrobenzene was prepared by the nitration of 1,4-dimethoxybenzene.[8]

Preparation of 1,3-bis(4,7-dimethoxy-2-benzimidazolyl)propane. This compound was prepared from 3,6-dimethoxy-*o*-phenylenediamine dihydrochloride and glutaric acid. A reflux period of 20 hr. was necessary to obtain this compound.

Preparation of 1,2-bisbenzimidazolylalkanes.[3] *1,2-Bis(2-benzimidazolyl)propane* was prepared from *o*-phenylenediamine and methylsuccinic acid. Methylsuccinic acid was obtained by the hydrogenation of itaconic acid over palladium on alumina. A quantitative yield of methylsuccinic acid was obtained, m.p. 113–115°, (lit. m.p. 111–112°).

1,2-Bis(6-chloro-2-benzimidazolyl)propane was prepared from 4-chloro-*o*-phenylenediamine and methylsuccinic acid.

1,4-Bis(4,7-dimethoxy-2-benzimidazolyl)butane was prepared from 3,6-methoxy-*o*-phenylenediamine dihydrochloride and adipic acid.

1,6-Bis(4,7-dimethoxy-2-benzimidazolyl)hexane was prepared from 3,6-dimethoxy-*o*-phenylenediamine dihydrochloride and suberic acid. The last four compounds were recrystallized from *N*-dimethylacetamide.

Preparation of bisbenzimidazolyl-1,2-ethanediols. 1,2-Bis-(6-methoxy-2-benzimidazolyl)-1,2-ethanediol was prepared from 4-methoxy-2-nitro-1-aminobenzene and tartaric acid without isolating the intermediate diamine. 4-Methoxy-2-nitro-1-aminobenzene (8.4 g., 0.05 mole) was dissolved in 50 ml. of 4*N* hydrochloric acid, 1 g. of 5% palladium-on-alumina added and the hydrogenation carried out in a Parr apparatus. After uptake of the theoretical amount of hydrogen, the catalyst was removed by filtration and the filtrate mixed with *d*-tartaric acid (3.75 g., 0.05 mole), 3 ml. of concd. sulfuric acid added and the reaction mixture heated for 8 hr.

1,2-Bis(4,7-dimethoxy-2-benzimidazolyl)-1,2-ethanediol was prepared from 3,6-dimethoxy-*o*-phenylenediamine dihydrochloride and *d*-tartaric acid.

1,4-Bis(6-chloro-2-benzimidazolyl)-1,2,3,4-butanetetrol was prepared from 4-chloro-*o*-phenylenediamine and mucic acid. It was recrystallized from 1:1 dimethylformamide-water solution.

1,4-Bis(4,7-dimethoxy-2-benzimidazolyl)-1,2,3,4-butanetetrol was prepared from 3,6-dimethoxy-*o*-phenylenediamine dihydrochloride and mucic acid.

2,2′-Thiodiethylenebis(4,7-dimethoxy)benzimidazole was prepared from 3,6-dimethoxy-*o*-phenylenediamine dihydrochloride and 3,3′-thiodipropionic acid.

Preparation of bisbenzimidazolylethanols. 1,2-Bis(2-benzimidazolyl)ethanol was prepared from *o*-phenylenediamine and malic acid. The dihydrochloride which formed was converted to the corresponding sulfate. This sulfate was recrystallized from 6*N* sulfuric acid and obtained analytically pure. The free base was obtained from this salt.

1,2-Bis(6-chloro-2-benzimidazolyl)ethanol was prepared from 4-chloro-*o*-phenylenediamine and malic acid. The pure

---

(7) L. Weinberger, Ph.D. thesis, University of Pennsylvania (1959).

(8) (a) J. Habermann, *Ber.*, **11**, 1037 (1878); (b) R. Nietzki and F. Rechberg, *Ber.*, **23**, 1216 (1890).

bisbenzimidazole was prepared in the same manner as described for the preparation of 1,2-bis(2-benzimidazolyl)-ethanol.

1,2-Bis(6-methyl-2-benzimidazolyl)ethanol was obtained from 4-methyl-*o*-phenylenediamine dihydrochloride and malic acid.

1,2-Bis(6-ethoxy-2-benzimidazolyl)ethanol was prepared from 4-ethoxy-2-nitro-1-aminobenzene and malic acid without isolating the intermediate diamine as described for the preparation of 1,2-bis(6-methoxy-2-benzimidazolyl)-1,2-ethanediol.

1,2-Bis(4,7-dimethoxy-2-benzimidazolyl)ethanol was obtained from 3,6-dimethoxy-*o*-phenylenediamine dihydrochloride and malic acid.

1,2-Bis(1-benzyl-2-benzimidazolyl)ethanol was prepared from *o*-nitro-*N*-benzylaniline and malic acid without isolating the intermediate diamine. The reduction was first carried out in ethanol solution using a 5% palladium-on-alumina catalyst.[9] However, it was found that the use of platinum as a catalyst is preferable since it cuts down on the amount of debenzylation which is a side reaction in this reduction.

o-Nitro-N-benzylaniline was prepared from *o*-chloronitrobenzene and benzylamine, m.p. 74° (lit.[10] m.p. 74–75°).

Preparation of 3-(2-benzimidazolyl)-3-hydroxypropanoic acids. The general procedure used for preparing these acids is illustrated in the preparation of 3-(2-benzimidazolyl)-3-hydroxypropanoic acid. Malic acid (26.8 g., 0.2 mole) was mixed with *o*-phenylenediamine (21.6 g., 0.2 mole) and the mixture dissolved in 125 ml. of 4*N* hydrochloric acid. The resulting solution was refluxed for 8 hr. and allowed to stand overnight. The precipitate which formed was removed by filtration. This precipitate proved to be 1,2-bis-(2-benzimidazolyl)ethanol, 17% yield. The solution was neutralized to *p*H 5 at which point a solid formed. It was removed by filtration and dried, yield 80%. This product was recrystallized from aqueous ethanol.

3-(6-Chloro-2-benzimidazolyl)-3-hydroxypropanoic acid was obtained from 4-chloro-*o*-phenylenediamine and malic acid.

3-(4,7-Dimethoxy-2-benzimidazolyl)-3-hydroxypropanoic acid was prepared from 3,6-dimethoxy-*o*-phenylenediamine dihydrochloride and malic acid. It was recrystallized from distilled water.

3-(1-Benzyl-2-benzimidazolyl)-3-hydroxypropanoic acid was prepared from *o*-nitro-*N*-benzylaniline and malic acid without isolating the intermediate diamine. It was precipitated at *p*H 6.

Oxidation of 3-(2-benzimidazolyl)-3-hydroxypropanoic acid. 3-(2-Benzimidazolyl)-3-hydroxypropanoic acid (5.15 g., 0.025 mole) was dissolved in 100 ml. of 10% sulfuric acid at room temperature and potassium permanganate (6.32 g., 0.04 mole) was added to the solution with stirring. After the addition of the permanganate was completed, the mixture was heated on a water bath for 20 min. Sodium bisulfite was added to the solution in order to decompose any unchanged potassium permanganate. The solution was cooled and the crystals which formed (2.75 g.) were removed by filtration. When these crystals were recrystallized from water, they yielded 1.4 g. of a compound whose infrared spectrum was identical with that of benzimidazole, m.p. 170°. Since 2-benzimidazolecarboxylic acid is known to decarboxylate readily to benzimidazole, the identity of the original crystals was proven by the formation of a derivative. Two grams of the crystals obtained from the oxidation were treated with 20 ml. of thionyl chloride and the mixture refluxed on a steam bath for 6 hr. The suspension was cooled and the precipitate which formed was removed by filtration. The crude product obtained was heated with an excess of *n*-butylamine for 30 min. The solution was cooled and water was added to precipitate a solid, yield 60%, m.p. 180°. This is the melting point of *N*-*n*-butyl-2-benzimidazolecarboxamide. This indicates that the oxidation of 3-(2-benzimidazolyl)-3-hydroxypropanoic acid yields 2-benzimidazolecarboxylic acid.

Dehydration of 3-(2-benzimidazolyl)-3-hydroxypropanoic acid. One gram of 3-(2-benzimidazolyl)-3-hydroxypropanoic acid was heated in an Abderhalden drying pistol, at 177° until the product turned dark brown. The dark solid was dissolved in dilute sodium carbonate and reprecipitated with concentrated hydrochloric acid. It was recrystallized from alcohol-water. This compound decomposes over a wide range starting at 239°.

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89. Found: C, 63.67; H, 4.49; N, 14.76.

Preparation of ethyl 3-(2-benzimidazolyl)-3-hydroxypropanoate. Twenty grams of 3-(2-benzimidazolyl)-3-hydroxypropanoic acid was dissolved in 200 ml. of absolute ethanol and the solution saturated with dry hydrogen chloride at 0°. The solution was allowed to stand for 4 days and the excess of ethanol and dry hydrogen chloride were removed under reduced pressure at room temperature. Water was added to the residue and the solution was treated with decolorizing charcoal. After removal of the charcoal it was neutralized with sodium bicarbonate. The solid formed was removed by filtration. It was recrystallized from aqueous ethanol, yield 80%, m.p. 171°.

Anal. Calcd. for $C_{12}H_{14}N_2O_3$: C, 61.54; H, 6.02; N, 11.96. Found: C, 61.54; H, 6.11; N, 11.99.

Oxidation of ethyl 3-(2-benzimidazolyl)-3-hydroxypropanoate. The oxidation of this ester was carried out several times by using potassium permanganate under acidic, basic and neutral conditions. Only in one instance, under acidic conditions, was a product obtained whose infrared spectrum appeared to be that of a β-keto ester. In all other instances, only two products could be identified, benzimidazolecarboxylic acid and the original hydroxy ester. As the results of this oxidation under varying conditions are very similar, only one example of a typical run under alkaline conditions will be described. Ethyl 3-(2-benzimidazolyl)-3-hydroxypropanoate (2.34 g., 0.01 mole) was dissolved in 400 ml. of acetone and to this solution 1.05 g. (0.066 mole) of potassium permanganate was added gradually. The solution slowly changed from purple to brown. It was warmed on a steam bath for 20 min. and allowed to stand overnight. The manganese dioxide formed was removed by filtration and neutralization of the solution yielded 1.35 g. of a product melting at 168–169°. The infrared spectrum of this compound was identical with the infrared spectrum of the starting material and a melting point determination on a mixture of both compounds showed no depression in melting point. On further evaporation of the solution a second crop of solid material (0.6 g.) was obtained. This material melted from 155–163° and appeared to be a mixture. This was confirmed by its infrared spectrum. On acidifying the solution to about *p*H 5, more solid material was obtained (0.3 g.). This solid was identified as benzimidazolecarboxylic acid through its infrared spectrum and a mixed melting point determination with an authentic sample of this compound. In addition, it was converted to its *N*-*n*-butylamide derivative as described under the oxidation of 3-(2-benzimidazolyl)-3-hydroxypropanoic acid.

Preparation of 1,2-bis(2-benzimidazolyl)-1,2-ethanediol. This compound was prepared according to the method described by Wang and Joullié.[3] The yield was 90%. It was recrystallized from water, m.p. 245° dec.

The sulfate of this compound had not been prepared before and since the sulfate was used in some of the oxidation reactions it was decided to obtain it in an analytically pure form. It was made by dissolving the free base or its hydrochloride in an excess of 6*N* sulfuric acid and cooling the resulting solution. This sulfate recrystallizes well from 6*N* sulfuric acid or hot water. It decomposes at 270°. The analytical results showed this compound to be a hydrate.

Anal. Calcd. for $C_{16}H_{18}N_4O_7S$: C, 46.82; H, 4.42; N, 13.70; S, 7.83. Found: C, 46.80; H, 4.86; N, 13.50; S, 8.05.

---

[9] S. W. Fleisher, Ph.D. thesis, University of Pennsylvania (1957).

[10] F. Kehrmann, *Ann.*, 290, 293 (1896).

Oxidation of 1,2-bis(2-benzimidazolyl)-1,2-ethanediol with potassium dichromate. 1,2-Bis(2-benzimidazolyl)-1,2-ethanediol (9.8 g., 0.03 mole) was dissolved in 400 ml. of hot 6*N* sulfuric acid. To the solution, 5.88 g. (0.02 mole) of potassium dichromate in 13 ml. of water was added. The solution turned green and was allowed to stand overnight. The crystals formed on standing were filtered with the aid of suction. They were recrystallized from 6*N* sulfuric acid, washed with water and dried. The yield was 65%, m.p. 200° dec.

The analytical results showed this compound to be a hydrate. The infrared spectrum of this compound showed a strong peak at 1625 cm.$^{-1}$

Anal. Calcd. for $C_{16}H_{16}O_7N_4S$: C, 47.10; H, 3.95; N, 13.73. Found: C, 47.15; H, 3.79; N, 13.70.

This sulfate was neutralized with sodium bicarbonate. The solid obtained was recrystallized from absolute ethanol. The infrared spectrum of this compound no longer showed a strong band at 1625 cm.$^{-1}$.

The analytical results indicate that the compound contained one mole of alcohol.

Anal. Calcd. for $C_{18}H_{18}O_3N_4$: C, 63.89; H, 5.36; N, 16.56. Found: C, 63.87; H, 5.22; N, 16.47.

When the same compound was recrystallized from water and dried for several hours at 110°, the analytical results agreed with those calculated for 1,2-bis(2-benzimidazolyl)-ethan-1-ol-2-one. The infrared spectrum of this compound still did not show a strong band at 1625 cm.$^{-1}$ This compound decomposes around 300°.

Anal. Calcd. for $C_{16}H_{12}N_4O_2$: C, 65.74; H, 4.14; N, 19.17. Found: C, 65.96; H, 4.38; N, 18.92.

Oxidation of 1,2-bis(2-benzimidazolyl)-1,2-ethandiol with potassium permanganate. This oxidation was carried out with different amounts of potassium permanganate. *A.* 1,2-Bis(2-benzimidazolyl)-1,2-ethandiol dihydrochloride (5.5 g., 0.015 mole) was dissolved in 50 ml. of boiling 10% aqueous sodium hydroxide. To this hot solution potassium permanganate (6.32 g., 0.04 mole) dissolved in a small amount of water was added slowly with vigorous shaking. The mixture was allowed to stand overnight at room temperature and the manganese dioxide removed by filtration. The *p*H of the filtrate was adjusted to 4 with concentrated hydrochloric acid. A solid was isolated in 70% yield, m.p. 163–165°. This solid was identified as benzimidazolecarboxylic acid by the same procedures as described earlier.

B. The same procedure was followed as described in A except that 3.16 g. (0.02 mole) of potassium permanganate was used instead. A solid was isolated in 60% yield and its infrared spectrum was identical with that of the 1,2-bis(2-benzimidazolyl)ethan-1-ol-2-one obtained by oxidation of 1,2-bis(2-benzimidazolyl)-1,2-ethandiol with potassium dichromate.

The solution which remained after removal of the monocarbonyl compound was acidified to *p*H 4. Another product separated and was removed by filtration. It was recrystallized from ethanol-water, m.p. 168°. A mixed melting point of this product with a known sample of benzimidazole showed no depression of melting point and the infrared spectra of these compounds were identical. This product was assumed to have been formed from the decarboxylation of benzimidazolecarboxylic acid.

C. The same oxidation procedure as in A was repeated using 1.58 g. (0.01 mole) of potassium permanganate. A solid, which was proved to be identical with the product formed by the sodium dichromate-sulfuric acid oxidation of 1,2-bis(2-benzimidazolyl)-1,2-ethandiol, was isolated in 90% yield. Acidification of the solution yielded no other product.

Oxidation of 1,2-bis(2-benzimidazolyl)ethan-1-ol-2-one with potassium permanganate. This oxidation was carried out according to the procedure described in A for the oxidation of 1,2-bis(2-benzimidazolyl)-1,2-ethandiol. Another oxidation was carried out by using 0.5 g. (0.001 mole) of the keto alcohol and 0.29 g. (0.005 mole) of potassium permanganate. In both cases benzimidazolecarboxylic acid was obtained in around 90% yields.

Methylation of 1,2-bis(2-benzimidazolyl)ethan-1-ol-2-one. The methylation was accomplished by two different methods.

A suspension of 1,2-bis(2-benzimidazolyl)ethan-1-ol-2-one (1.46 g., 0.005 mole) in 100 ml. of absolute ethanol was placed in a 500-ml. two neck flask equipped with a mechanical stirrer and water condenser. The ether-diazomethane solution (88 ml. containing diazomethane in excess of 0.02 mole) was added all at once. The temperature of the solution rose slightly and the suspended compound dissolved slowly. After some time a product separated. The solution was stirred for 10 hr. and allowed to stand overnight. The excess of diazomethane was destroyed with dilute acetic acid and an excess of water was added to the mixture to precipitate a product which was removed by filtration and recrystallized from ethanol-water, m.p. 260° dec.

The elemental analyses showed this compound to be a hydrate of a trimethyl derivative.

Anal. Calcd. for $C_{19}H_{20}N_4O_3$: C, 64.75; H, 5.72; N, 15.90. Found: C, 64.51; H, 5.74; N, 15.87.

Sodium metal (0.313 g., 0.0136 mole) was dissolved in 20 ml. of absolute ethanol. To this solution 1,2-bis(2-benzimidazolyl)ethan-1-ol-2-one (1 g., 0.0034 mole) was added, and the solution warmed on a water bath. Methyl iodide (12 ml., 0.18 mole) was added slowly with shaking and the solution was kept at 40–50° for 30 min. During this period a product separated. The solid was removed by filtration and additional material was obtained by adding water to the filtrate. Recrystallization from ethanol-water yielded a product which melted at 260° dec. and whose infrared spectrum was identical with that of the product obtained by methylation with diazomethane.

PHILADELPHIA 4, PA.