128–129° and it mix-melts at the same temperature with the substance prepared according to the method of Pond and Shoffstall.

**3-*p*-Methoxyphenyl-5-phenylisoxazole (X).**—A solution of 2.5 g. of the enol in 25 cc. of hot methanol was treated with 2 g. of hydroxylamine hydrochloride in 5 cc. of water. The solution was refluxed for three hours, and finally allowed to cool. On chilling, a colorless solid separated. It was filtered and recrystallized from methanol, melting and mix-melting at 119° with the substance obtained according to Pond and Shoffstall. The yield was 1.25 g.

A solution of 5 g. of benzal-*p*-methoxyacetophenone dibromide in 100 cc. of boiling ethanol was treated with 1.75 g. of hydroxylamine hydrochloride in 2.5 cc. of water. While still hot, this solution was treated with 4.25 g. of potassium hydroxide in 5 cc. of water. The colorless solution gradually became yellow, and a colorless solid (KBr) separated. The mixture was allowed to stand for ten minutes and filtered. Upon cooling, colorless needles separated. This material was filtered, and recrystallized from ethanol, producing a colorless solid, melting and mix-melting with the above described materials at 119°.

## Summary

1. We have prepared the enolic modification of *p*-methoxydibenzoylmethane by a series of reactions different from that by which it has been prepared previously, and have shown that the products of the two series of reactions are identical.

2. We have shown that this enolic modification reacts as 1-phenyl-3-*p*-methoxyphenylpropene-one-3-ol-1 (V) in that this enolic modification as well as benzal-*p*-methoxyacetophenone dibromide gives rise to the isoxazole (X).

WASHINGTON, D. C. RECEIVED JANUARY 23, 1943

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

# The Preparation and Reactions of 2-Benzimidazolecarboxylic Acid and 2-Benzimidazoleacetic Acid

BY RALPH A. B. COPELAND[1] AND ALLAN R. DAY

Of the acids in the 2-substituted benzimidazole series, only 2-benzimidazolecarboxylic acid and β-2-benzimidazole-propionic acid have been reported previously. The former was prepared by Bistrzycki and Przeworski,[2] but no derivatives other than the barium salt have been reported. The benzimidazole-propionic acid together with the amide and the methyl and ethyl esters have been prepared by Meyer and Luders,[3] and more recently by Chatterjee.[4]

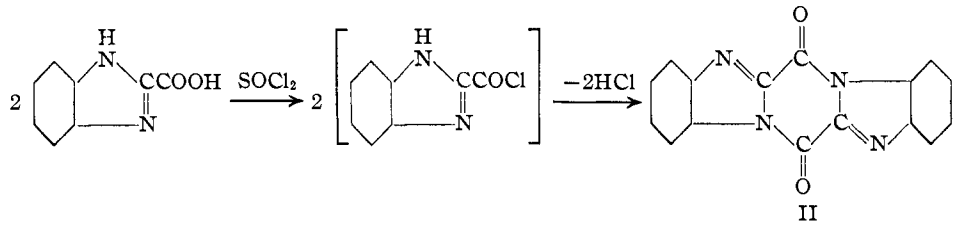
The fact that these acids are bifunctional compounds, resembling the amino acids in that they contain acidic and basic groups, suggested that a study of their reactions might be of interest. Furthermore, similarities between these acids and heterocyclic acids of known physiological activity may also be worthy of attention.

2-Benzimidazolecarboxylic acid (I) was prepared by the permanganate oxidation of 2-hydroxymethylbenzimidazole.[2] Attempts to prepare the acid chloride by the action of phosphorus chlorides or thionyl chloride on the acid were unsuccessful. Refluxing the acid with a large excess of thionyl chloride gave a yellow compound which contained no chlorine. Analyses and equivalent weight determinations indicated this product to be dibenzimidazo-(1,2-a,1′,2′-d)-tetrahydropyrazine-6,13-dione (II). This compound may be regarded as a cyclic diamide or as a substituted diketopiperazine.

The reactions of II fully substantiate the proposed structure. Prolonged refluxing with dilute hydrochloric acid has little effect on the molecule. Concentrated hydrochloric acid gradually dissolves the compound on heating with the formation of 2-benzimidazolecarboxylic acid. Dilute sodium hydroxide solution hydrolyzes the compound readily to the soluble sodium salt of 2-benzimidazolecarboxylic acid. Aqueous ammonia and primary and secondary amines react to form the amide or substituted amides. The use of dilute aqueous solutions of the amine results in lower yields of the amides, due to the competitive reaction of hydrolysis and subsequent salt formation.

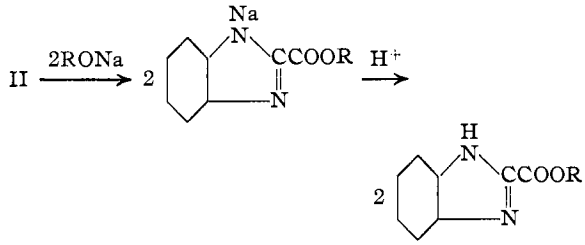
Esters of 2-benzimidazolecarboxylic acid were likewise prepared from the cyclic diamide (II). The esters may be prepared by refluxing the diamide with a dry alcoholic solution of hydrogen chloride or by treating the diamide with an alcoholic solution of the corresponding sodium alk-

(1) Present address, Agfa Film Corporation, Binghamton, N. Y.
(2) Bistrzycki and Przeworski, *Ber.*, **45**, 3483 (1912).
(3) Meyer and Luders, *Ann.*, **416**, 29 (1918).
(4) Chatterjee, *J. Chem. Soc.*, 2965 (1929).



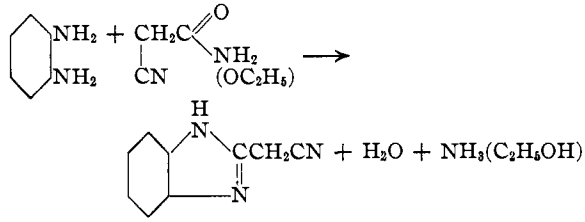
II

oxide. A sodium derivative is formed, which on being treated with acetic acid yields the ester. The reaction may be represented as



No reaction takes place when II is refluxed with sodium methoxide in dry benzene, but the addition of methyl alcohol to the reaction mixture results in immediate cleavage. This would indicate that the reaction is essentially alcoholysis catalyzed by the sodium alkoxide.

2-Benzimidazoleacetic acid was prepared by the acid or alkaline hydrolysis of 2-cyanomethylbenzimidazole. The 2-cyanomethyl compound was obtained by heating *o*-phenylenediamine with cyanoacetamide or ethyl cyanoacetate



Attempts to prepare the acid chloride of 2-benzimidazoleacetic acid were unsuccessful. Only a dark brown, amorphous material was obtained, which failed to respond as either the acid chloride or as a cyclic or linear amide. Esters of 2-benzimidazoleacetic acid are conveniently prepared by the action of dry alcoholic hydrogen chloride on the cyano derivative. The amides in this series were prepared by the ammonolysis or aminolysis of the ethyl ester.

## Experimental

**Preparation of 2-Hydroxymethylbenzimidazole.**—It was prepared from *o*-phenylenediamine and glycolic acid according to Phillips' procedure[5]; yield, 61%; m. p. 171–172°. (All melting points are corrected values.)

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

*Anal.* Calcd. for $C_8H_8N_2O$: N, 18.92. Found: N, 18.80.

**Preparation of 2-Benzimidazolecarboxylic Acid.**—The method of Bistrzycki and Przeworski[2] (potassium permanganate oxidation of the hydroxymethyl compound) was used for this preparation; yield, 71%; m. p. 169–171° with decarboxylation. The acid crystallizes with two molecules of water, which may be removed by heating at 80–90°. Prolonged heating at this temperature slowly decarboxylates the acid. When recrystallized from boiling water, some decarboxylation occurs as shown by high nitrogen values. A fairly pure product can be obtained by recrystallization from alcohol.

*Anal.* Calcd. for $C_8H_6N_2O_2$: N, 17.28. Found: N, 17.39.

**Preparation of Dibenzimidazo-(1,2-a,1′,2′-d)-tetrahydropyrazine-6,13-dione.**—Twenty grams (0.124 mole) of anhydrous 2-benzimidazolecarboxylic acid was powdered and added slowly to 125 cc. of thionyl chloride. After the first vigorous evolution of hydrogen chloride and sulfur dioxide had subsided, the mixture was heated for six hours on a water-bath. The suspended acid changed from a white, fluffy material to a dense, yellow, crystalline compound. After cooling, the product was removed by filtration; yield, 86%; m. p. above 300°. The hydrated acid gave similar results. The crude product was used in most cases for the hydrolysis, ammonolysis and alcoholysis studies.

To prepare a pure sample for analysis, the following procedure was used. Five grams of the product was heated to boiling in 100 cc. of water, filtered and the residue dried. The loss in weight of 0.35 g. was shown to be due to benzimidazole, which was recovered from the water filtrate; m. p. 171–172°. The residue was refluxed with 100 cc. of acetone for forty-five minutes and filtered. The residue, 4.22 g., was extracted with acetone, in an apparatus arranged for continuous hot extraction, over a period of two weeks. In this way 4 g. of small, rhombic crystals of the pure product was obtained.

*Anal.* Calcd. for $C_{16}H_8N_4O_2$: C, 66.66; H, 2.80; N, 19.45. Found: C, 66.56; H, 2.79; N, 19.39.

Molecular weight determinations were impossible because of the insolubility of the compound. Its equivalent weight was determined by measuring the quantity of standard sodium hydroxide consumed in its hydrolysis. *Equiv. Wt.* Calcd. for $C_{16}H_8N_4O_2$: 144.1. Found: 143.2, 143.7.

**Reactions of Dibenzimidazo-(1,2-a,1′,2′-d)-tetrahydropyrazine-6,13-dione (II). Acid Hydrolysis.**—Two grams of II was refluxed with concentrated hydrochloric acid for eight hours or until all of the sample dissolved. On cooling, colorless needles of 2-benzimidazolecarboxylic separated; yield, 1.5 g. (67%); m. p. 170° with decarboxylation.

TABLE I

N-SUBSTITUTED 2-BENZIMIDAZOLECARBOXAMIDES

| Amine used | Yield, % | M. p., °C. | Carbon, Hydrogen, Nitrogen, % Calcd. C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|
| Methylamine | 70 | 246.5 | 61.70 | 5.18 | 23.99 | 61.58 | 5.08 | 23.89 |
| Ethylamine | 43 | 210–211 | 63.47 | 5.86 | 22.21 | 63.32 | 5.96 | 22.06 |
| Ethanolamine | 86 | 219–220 | 58.53 | 5.40 | 20.49 | 58.55 | 5.35 | 20.53 |
| β-Methoxyethylamine | 86 | 138 | 60.26 | 5.98 | 19.17 | 60.23 | 5.92 | 19.06 |
| *n*-Butylamine | 85 | 180.5–181.5 | 66.33 | 6.96 | 19.34 | 66.46 | 6.89 | 19.33 |
| Benzylamine | 70 | 172.4 | 71.70 | 5.21 | 16.73 | 71.63 | 5.03 | 16.65 |
| Cyclohexylamine | 58 | 269.5 | 69.11 | 7.04 | 17.28 | 69.14 | 7.12 | 17.18 |
| Dimethylamine | 50 | 223–224 | 63.47 | 5.86 | 22.21 | 63.39 | 5.79 | 22.16 |
| Diethylamine | 57 | 124.5 | 66.33 | 6.96 | 19.36 | 66.27 | 6.76 | 19.37 |
| Di-*n*-butylamine | 51 | 101.2 | 70.29 | 8.48 | 15.37 | 70.14 | 8.42 | 15.33 |
| Morpholine | 58 | 181.2 | 62.32 | 5.67 | 18.18 | 62.12 | 5.69 | 18.08 |

**Basic Hydrolysis.**—Two and six-tenths grams of II was heated with 25 cc. of 1 *N* sodium hydroxide solution. It dissolved readily to a pale yellow solution, from which on acidification with acetic acid, 2-benzimidazolecarboxylic acid separated; yield, 3 g. (84%); m. p. 169° with decarboxylation.

**Aminolysis. Preparation of Amides of 2-Benzimidazolecarboxylic Acid.**—In general 3 g. (0.0104 mole) of II was heated with an aqueous solution of the amine until the yellow crystals dissolved or until they were converted to colorless crystals. The solutions or suspensions were cooled, diluted with water when necessary, and the amides removed by filtration. In cases where the pure amine was used, complete solution was effected and the amide was precipitated by the addition of water.

**2-Benzimidazolecarboxamide.**—Twenty-five cc. of concentrated ammonium hydroxide was used and the mixture refluxed for twenty minutes. The crude product was dissolved in hydrochloric acid, decolorized with Norite and reprecipitated with ammonium hydroxide; yield, 2.7 g. (78%); m. p. above 300°. A sample recrystallized from ethyl alcohol yielded colorless needles.

*Anal.* Calcd. for $C_8H_7N_3O$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.46; H, 4.40; N, 25.90.

The ease with which these reactions can be carried out in either aqueous or non-aqueous media suggested the possibility of applying them to the identification of amines and consequently a series of amines were used. The results are recorded in Table I.

**Alcoholysis. Preparation of Ethyl 2-Benzimidazolecarboxylate**

**(1) Use of Alcoholic Hydrogen Chloride.**—Two grams of the cyclic diamide (II) was refluxed for twelve hours in 50 cc. of 10% alcoholic hydrogen chloride or until the starting compound had completely dissolved. The solution was neutralized with solid sodium bicarbonate, filtered and the filtrate evaporated to dryness. The residue was recrystallized from alcohol and water; colorless needles, m. p. 212.7–213.7° (228–230° on Fisher-Johns block); yield, 83%.

*Anal.* Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.30; N, 14.77. Found: C, 63.11; H, 5.36; N, 14.76.

**(2) Use of Sodium Ethoxide.**—Sodium (0.40 g., 0.017 mole) was dissolved in 40 cc. of dry alcohol and 2.5 g. (0.0087 mole) of the cyclic diamide (II) added. The yellow crystals dissolved and the colorless sodio compound precipitated. Partial evaporation of the alcohol brought the yield of sodio derivative to 95% (3.5 g.). Due to difficulties encountered in attempts to purify the derivative, the crude sample was used for analysis.

*Anal.* Calcd. for $C_{10}H_9N_2O_2Na$: N, 13.21. Found: N, 12.76.

Three grams of the above sodio compound was added to 10 cc. of 1:1 acetic acid and stirred. After a few minutes the solid was removed and recrystallized from alcohol and water; yield, 2.1 g. (79%); m. p. 212.7–213.7°.

When the sodio compound is dissolved in warm water, a basic solution results which yields colorless needles of 2-benzimidazolecarboxylic acid when neutralized with acetic acid; m. p. 169–171°.

**Preparation of Methyl 2-Benzimidazolecarboxylate, Use of Sodium Methoxide.**—Sodium (0.40 g., 0.017 mole) was dissolved in 40 cc. of dry methyl alcohol and 2.5 g. (0.0087 mole) of the cyclic diamide added. A yellow solution was formed from which the sodio compound did not precipitate. A slight excess of acetic acid was added and the solution evaporated. The residue was dissolved in water and neutralized with sodium bicarbonate. The precipitate, so obtained, was recrystallized from alcohol and water with the aid of Norite; yield, 92%; m. p. 187.3°.

*Anal.* Calcd. for $C_9H_8N_2O_2$: C, 61.35; H, 4.58; N, 15.91. Found: C, 61.38; H, 4.35; N, 15.83.

**2-Benzimidazoleacetic Acid Series. Preparation of 2-Cyanomethylbenzimidazole.**—*o*-Phenylenediamine (10.8 g., 0.10 mole) and 17 g. (0.15 mole) of ethyl cyanoacetate were placed in the reaction tube and heated in boiling aniline for twenty minutes. After cooling, the residue was broken up and extracted with ether. The residue was recrystallized from hot water with the aid of Norite and finally from alcohol and water; yield, 11 g. (70%); m. p. 209.7–210.7°.

*Anal.* Calcd. for $C_9H_7N_3$: C, 68.78; H, 4.49; N, 26.75. Found: C, 68.66; H, 4.37; N, 26.68.

*o*-Phenylenediamine (10.8 g., 0.10 mole) and 16.8 g. (0.20 mole) of cyanoacetamide were heated in a nitrobenzene bath. At 165–170° the melt began to effervesce, with vigorous bubbling from 170–190°. At 209° (six minutes after the bubbling had begun) the bubbling had practically stopped. The heating at 200° was continued for nine minutes, and the mixture then cooled. The

brown mass was extracted with ether and the residue recrystallized from water with the aid of Norite; yield, 9.9 g. (63%); m. p. 210°.

In the preparation of 2-cyanomethylbenzimidazole, only intractable gums are obtained if too high a temperature is used or if the heating period is too long.

**Preparation of 2-Benzimidazoleacetic Acid. (1) Acid Hydrolysis of 2-Cyanomethylbenzimidazole.**—Five grams (0.032 mole) of the cyano compound was refluxed for two hours in 50 cc. of 1:1 sulfuric acid. On cooling, colorless needles of the sulfate separated. The sulfate was dissolved in water, made basic with ammonium hydroxide and then acidified with acetic acid. Small, colorless needles of 2-benzimidazoleacetic acid separated; yield, 4.8 g. (88%); m. p. 116° with decarboxylation, solidification and remelting at 176° (2-methylbenzimidazole).

*Anal.* Calcd. for $C_9H_8N_2O_2$: C, 61.35; H, 4.58; N, 15.91. Found: C, 61.24; H, 4.64; N, 15.98.

**(2) Alkaline Hydrolysis of 2-Cyanomethylbenzimidazole.**—2-Cyanomethylbenzimidazole (1.57 g., 0.01 mole) was added to 20 cc. of a water solution containing 1.2 g. of sodium hydroxide and 3 cc. of ethyl alcohol and refluxed for two hours or until no more ammonia was evolved. The solution was then acidified with acetic acid; yield, 1.65 g. (94%); m. p. 116° with decarboxylation.

**Reaction of 2-Benzimidazoleacetic Acid with Thionyl Chloride.**—This reaction produced only highly insoluble, amorphous solids which could not be identified.

**Preparation of Ethyl 2-Benzimidazoleacetate.**—Five grams (0.032 mole) of the cyano derivative was added to 75 cc. of 9% alcoholic hydrogen chloride and refluxed for ninety minutes. The solution was filtered and the filtrate evaporated. The residue was treated with bicarbonate solution and recrystallized from alcohol with the aid of Norite. Colorless crystals were obtained by slow evaporation of the solution; yield, 4.8 g., (74%); m. p. 128.5–129.5°.

*Anal.* Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.73. Found: C, 64.49; H, 6.03; N, 13.60.

**Preparation of 2-Benzimidazoleacetamide.**—One gram of the ethyl ester was refluxed for ten minutes with 20 cc. of concentrated ammonium hydroxide. On cooling a 70% yield of the amide separated. Colorless crystals were obtained by recrystallization from alcohol with the aid of Norite; m. p. 244–247° dec.

*Anal.* Calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.19; N, 24.00. Found: C, 61.63; H, 5.20; N, 23.93.

N-Methyl-2-benzimidazoleacetamide (m. p. 214–216.5° decomp.), N-*n*-butyl-2-benzimidazoleacetamide (m. p. 209.5–212.5 decomp.), and N-(β-methoxyethyl)-2-benzimidazoleacetamide (m. p. 183.5–185° dec.) were also prepared by similar methods.

## Summary

1. 2-Benzimidazolecarboxylic and 2-benzimidazoleacetic acids have been prepared and their reactions studied.

2. 2-Benzimidazolecarboxylic acid is shown to form a diketopiperazine derivative when treated with thionyl chloride. The cleavage of this compound has been studied as a method for the preparation of derivatives of 2-benzimidazolecarboxylic acid.

3. Derivatives of 2-benzimidazoleacetic acid were prepared from the corresponding 2-cyanomethylbenzimidazole and from the ethyl ester of the acid.

PHILADELPHIA, PENNA. RECEIVED JANUARY 22, 1943

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

# The Synthesis of a Pyridine Analog of Hydnocarpic Acid and of a Lower Homolog

BY FREDERICK BRODY AND MARSTON TAYLOR BOGERT

Although there seems to be a considerable difference of opinion as to the curative value of chaulmoogric and hydnocarpic acids and their numerous derivatives in the treatment of leprosy, the fact remains that no drug has yet been discovered which is any more effective in combating this dread disease.

We have, therefore, undertaken the synthesis of compounds of analogous constitution, in which the cyclopentene nucleus of hydnocarpic and chaulmoogric acid has been replaced by various heterocyclic nuclei, and this first paper describes the synthesis of a pyridine analog (VIII). A later paper will report similar experiments leading to a thiazole analog. Pharmacological tests with the pyridine compound on rat leprosy are now being carried out at the National Institute of Health, Bethesda, Md., and the results will appear elsewhere.

Since both leprosy and tuberculosis are due to acid-fast bacteria, the discovery of curative drugs for the one may point the way to the synthesis of remedial medicinals for the other.

α-Picoline (II) was selected as source material because of the reactivity of its methyl group with alkali amides in liquid ammonia solution resulting in the formation of metallic derivatives which in turn react with halides, in a manner somewhat resembling the acetoacetic ester synthesis