eral recrystallizations from petroleum ether, fine white needles were obtained, m.p. 128.5–130.5° (from 100°).

*Anal.* Calcd. for $C_{21}H_{22}O_4NBr$: C, 58.34; H, 5.13; N, 3.24. Found: C, 57.62; H, 5.08; N, 3.20.

Qualitative analysis indicated the presence of bromine, but the compound did not immediately oxidize potassium iodide in aqueous solution, as did the starting material.

**Methanolysis of α-Bromo-β-morpholino-p-nitrobenzylacetophenone (Form B) (Vb).**—A solution of 4.0 g. of the adduct Vb in 100 ml. of methanol was refluxed for 2.5 hours. After removal of the solvent under reduced pressure, there was left 3.8 g. of light-yellow granules. The residue was readily soluble in methanol and methanolic ether, but was insoluble in ether, petroleum ether, and benzene; it did not oxidize an acidified solution of potassium iodide. Upon insertion in a block preheated to 170°, a sample appeared to evolve a gas; raising the temperature caused decomposition at 178–183°.

The product was treated with sodium bicarbonate and extracted with ether. The ether extract was washed with water, dried over magnesium sulfate, and evaporated to give a glassy solid which melted immediately when immersed in a block heated to 60°. Crystallization from petroleum ether (b.p. 65–110°) gave crops of solid, melting over wide ranges between the limits of 78–153°, which consisted of small yellow granules about which were clustered fine yellow needles. No homogeneous material could be isolated. Qualitative analysis of fractions melting at 117–153° and 78–118° indicated the presence of nitrogen and a small amount of halogen.

**Acknowledgment.**—We are indebted to Dr. Allan K. Colter for helpful comment in connection with the discussion of the solvolysis and rearrangement reactions.

PITTSBURGH 13, PENNA.

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[CONTRIBUTION FROM THE MERCK, SHARP AND DOHME RESEARCH LABORATORIES, DIVISION OF MERCK AND CO., INC.]

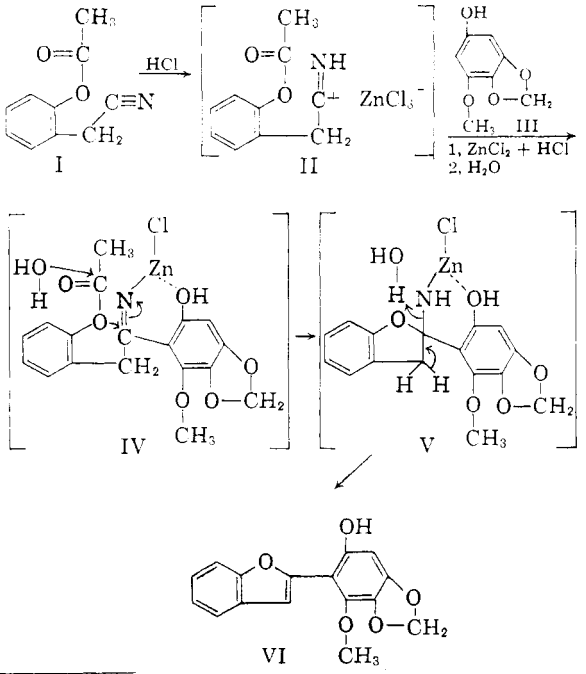
# The Synthesis of 2-(6-Hydroxy-2-methoxy-3,4-methylenedioxyphenyl)-benzofuran, A New Compound from Yeast

BY ARTHUR F. WAGNER, ANDREW N. WILSON AND KARL FOLKERS

RECEIVED MAY 11, 1959

2-(6-Hydroxy-2-methoxy-3,4-methylenedioxyphenyl)-benzofuran (VI), was synthesized by the condensation of *o*-acetoxyphenylacetonitrile (I) with 3-methoxy-4,5-methylenedioxyphenol (III). The deoxy-analog, 2-(2-methoxy-3,4-methylenedioxyphenyl)-benzofuran (XIV), was synthesized from methyl *o*-benzyloxyphenylacetate (IX) and methyl 2-methoxy-3,4-methylenedioxybenzoate (X). Nitration of the deoxy-analog XIV gave 2-(2-methoxy-3,4-methylenedioxyphenyl)-3-nitrobenzofuran (XV).

Forbes, Zilliken, Roberts and György[1] isolated and characterized a new crystalline compound from yeast which *in vitro* protects the red blood cells of vitamin E deficient rats from hemolysis by dialuric acid. From a series of degradation studies[2] this compound was shown to be 2-(6-hydroxy-2-methoxy-3,4-methylenedioxyphenyl)-benzofuran (VI).




We now describe the synthesis of VI and its 6-deoxy analog, 2-(2-methoxy-3,4-methylenedioxyphenyl)-benzofuran (XIV).

2-(6-Hydroxy-2-methoxy-3,4-methylenedioxyphenyl)-benzofuran (VI) was synthesized in about 10% yield by the condensation of *o*-acetoxyphenylacetonitrile (I) with 3-methoxy-4,5-methylenedioxyphenol[3] (III) under the conditions of the Hoesch synthesis.[4] *o*-Acetoxyphenylacetonitrile was converted *in situ* to the intermediate II which in turn condensed with 3-methoxy-4,5-methylenedioxyphenol in ether solution in the presence of anhydrous zinc chloride and hydrogen chloride. After several days, an aqueous extract of the reaction mixture was heated yielding a mixture of products from which *o*-hydroxyphenylacetic acid and 2-(6-hydroxy-2-methoxy-3,4-methylenedioxyphenyl)-benzofuran (VI) were isolated. The isolation of the benzofuran derivative at this stage of the reaction sequence would not be predicted in view of the relatively drastic conditions necessary to cyclize the related derritols[5,6] and especially in the light of the well-documented studies of Whalley and Lloyd[7] with hydroxy-deoxybenzoins. They demonstrated the spontaneous cyclization of 2′-hydroxy-deoxybenzoins to benzofurans, but in contrast encountered an increased stability in the

(1) M. Forbes, F. Zilliken, G. Roberts and P. György, THIS JOURNAL, **80**, 385 (1958).

(2) M. A. P. Meisinger, F. A. Kuehl, Jr., E. L. Rickes, N. G. Brink and K. Folkers; M. Forbes, F. Zilliken and P. György, *ibid.*, **81**, 4979 (1959).

(3) A. F. Wagner, E. Walton, A. N. Wilson, J. O. Rodin, F. W. Holly, N. G. Brink and K. Folkers, *ibid.*, **81**, 4983 (1959).

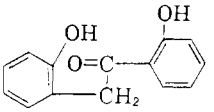
(4) P. E. Spoerri and A. S. DuBois, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1949, Vol. V, p. 387.

(5) A. Butenandt, *Ann.*, **464**, 253 (1928).

(6) L. E. Smith and F. B. La Forge, THIS JOURNAL, **54**, 2997 (1932).

(7) W. B. Whalley and G. Lloyd, *J. Chem. Soc.*, 3213 (1956).

2,2′-dihydroxydeoxybenzoins (VII) which could be sublimed unchanged. The contrasting facile cy-



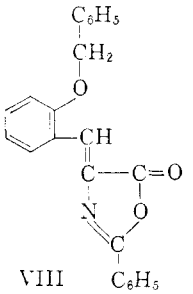
VII

clization observed in this instance is most likely due to an acid-induced transformation proceeding through intermediates such as IV and V during the hydrolysis of the intermediate condensation product.

*o*-Hydroxyphenylacetic acid was separated from the reaction mixture by sublimation; 2-(6-hydroxy-2-methoxy-3,4-methylenedioxyphenyl)-benzofuran was isolated from the sublimation residue by chromatography on Florisil. Elution of the Florisil column with benzene–petroleum ether gave 2-(6-hydroxy-2-methoxy-3,4-methylenedioxyphenyl)-benzofuran (VI). The identity of the synthetic product and the substance from yeast, assigned the structure 2-(6-hydroxy-2-methoxy-3,4-methylenedioxyphenyl)-benzofuran, was established by mixed melting point, comparative paper chromatography and infrared spectra.

The 6-deoxy-analog, 2-(2-methoxy-3,4-methylenedioxyphenyl)-benzofuran (XIV), was synthesized in about 25% yield starting with methyl *o*-benzyloxyphenylacetate (IX) and methyl 2-methoxy-3,4-methylenedioxybenzoate (methyl croweacate) as the key intermediates.

Methyl *o*-benzyloxyphenylacetate was synthesized from 2-phenyl-4-(2-benzyloxybenzylidene)-5-oxazolone[8] (VIII). Alkaline hydrolysis of VIII



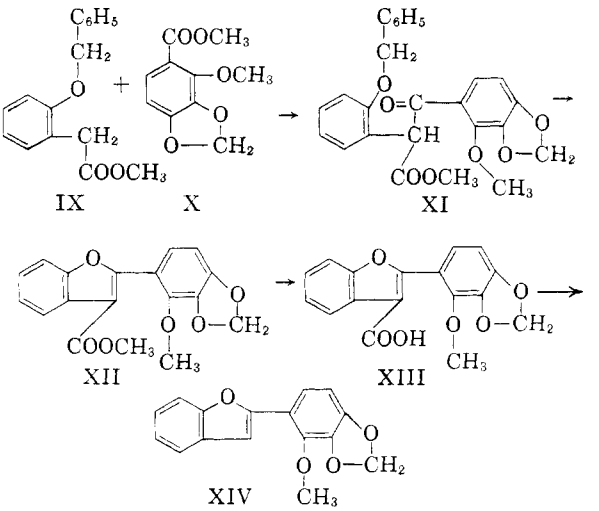
VIII

followed by oxidation with hydrogen peroxide in alkaline solution yielded *o*-benzyloxyphenylacetic acid, which after esterification with diazomethane gave methyl *o*-benzyloxyphenylacetate (IX). Methyl 2-methoxy-3,4-methylenedioxybenzoate (X) was prepared by the esterification of 2-methoxy-3,4-methylenedioxybenzoic acid[3,9] with diazomethane.

When methyl *o*-benzyloxyphenylacetate and methyl 2-methoxy-3,4-methylenedioxybenzoate were condensed in the presence of sodium hydride, the keto ester, α-(2-benzyloxyphenyl)-α-carbomethoxy-2′-methoxy-3′,4′-methylenedioxyacetophenone (XI), was isolated in about 30% yield. When XI was treated with a mixture of

(8) F. Bergel, J. W. Haworth, A. L. Morrison and H. Rinderknecht, *J. Chem. Soc.*, 261 (1944).

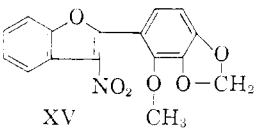
(9) A. R. Penfold, G. R. Ramage and J. L. Simonsen, *ibid.*, 756 (1938).



IX X XI XII XIII XIV

glacial acetic acid and concentrated hydrochloric acid at 60–70° for one hour, the benzyl group was cleaved and cyclization occurred; methyl 2-(2-methoxy-3,4-methylenedioxyphenyl)-benzofuran-3-carboxylate (XII) was obtained in about 60% yield. Alkaline hydrolysis of the ester XII gave 2-(2-methoxy-3,4-methylenedioxyphenyl)-benzofuran-3-carboxylic acid (XIII) which readily decarboxylated to 2-(2-methoxy-3,4-methylenedioxyphenyl)-benzofuran (XIV) in refluxing acetic acid–hydrochloric acid.

When 2-(2-methoxy-3,4-methylenedioxyphenyl)-benzofuran (XIV) was nitrated with concentrated nitric acid in acetic acid solution, 2-(2-methoxy-3,4-methylenedioxyphenyl)-3-nitrobenzofuran (XV) was isolated in 66% yield. The structure of the nitro compound (XV) was based on the isolation of 2-methoxy-3,4-methylenedioxybenzoic acid from the potassium permanganate oxidation of XV and the isolation of salicylic acid from the alkaline fusion of XV.



XV

**Acknowledgments.**—We are indebted to Dr. N. R. Trenner and Mr. R. W. Walker for infrared spectral data and to Mr. R. N. Boos and associates for microanalyses.

## Experimental

**o-Acetoxyphenylacetonitrile (I).**—Five and one-half grams of *o*-hydroxyphenylacetonitrile[10] was dissolved in 10 ml. of pyridine and 10 ml. of acetic anhydride was added. After being allowed to stand at room temperature overnight, the reaction mixture was poured onto a mixture of ice and dilute hydrochloric acid. The product was extracted with ether. The ether solution was dried and concentrated and the residual oil (6.2 g.) was purified by distillation *in vacuo* at 105–110°; $\lambda_{max}^{neat}$ 4.49, 5.7, 6.24 and 8.3 μ.

*Anal.* Calcd. for $C_{10}H_9NO_2$ (175.18): C, 68.56; H, 5.18; N, 8.00. Found: C, 68.80; H, 5.27; N, 8.00.

**2-(6-Hydroxy-2-methoxy-3,4-methylenedioxyphenyl)-benzofuran (VI).**—A mixture of 1.0 g. (6 mmoles of 3-methoxy-4,5-methylenedioxyphenol (III), 1.05 g. (6 mmoles) of *o*-acetoxyphenylacetonitrile (I) and 0.8 g. of freshly fused zinc

(10) A. Robertson, *ibid.*, 489 (1933).

chloride in 60 ml. of anhydrous ether was cooled in an ice–salt mixture. While being stirred, the reaction mixture was saturated with anhydrous hydrogen chloride. The reaction mixture was stirred for 65 hours at about 5°.

At the end of the reaction period, the supernatant ether solution was decanted, the ether-insoluble residue was dissolved in 50 ml. of water, and the aqueous solution was heated on the steam-bath for one hour. After the aqueous mixture had cooled to room temperature, the product was isolated by extraction with ether. Concentration of the ether extract gave a 1.1-g. residue.

The residue was treated at room temperature with a mixture of 10 ml. of 1 *N* sodium hydroxide and 10 ml. of methanol for 20 minutes. After the alkaline mixture was acidified, it was extracted with ether. The product (1.05 g.), obtained by concentration of the ether extract, was purified by distilling the accompanying *o*-hydroxyphenylacetic acid at 110–120° *in vacuo*.

The residue (0.45 g.) was dissolved in about 5 ml. of chloroform and the solution was chromatographed on acid-washed alumina (30 g.). The column was eluted with chloroform and the product (0.25 g.) was isolated from the first 60 ml. of eluate. This fraction was then dissolved in benzene–petroleum ether (1:1) and was further purified by chromatography on 30 g. of Florisil. Elution of the column with benzene–petroleum ether (1:1) gave about 170 mg. of 2-(6-hydroxy-2-methoxy-3,4-methylenedioxyphenyl)-benzofuran, m.p. 118.0–118.5°. There was no depression in melting point on admixture of the product with a specimen of the substance obtained by isolation from yeast.[1] Both the synthetic and naturally derived products had *Rf* 0.83 after paper chromatography on Whatman No. 1 paper using the system water–ethanol–concentrated ammonium hydroxide (37:5:8), and both gave red color on spraying with the Emmerie-Engel reagents[11] (0.2% $\alpha,\alpha$-dipyridyl and 0.5% ferric chloride in ethanol). The infrared spectra of both the synthetic and naturally derived products were identical.

*Anal.* Calcd. for $C_{16}H_{12}O_6$ (284.26): C, 67.60; H, 4.26. Found: C, 67.46; H, 4.50.

**o-Benzyloxyphenylacetic Acid.**—A solution of 20 g. of 2-phenyl-4-(2-benzyloxybenzylidene)-5-oxazolone[8] (VIII) in 200 ml. of 10% sodium hydroxide was boiled for 5 hours. The mixture was diluted to 500 ml. with water, cooled to 10° and saturated with sulfur dioxide. The precipitated benzoic acid was removed by filtration. The filtrate was acidified with 35 ml. of concentrated hydrochloric acid and then heated on the steam-bath until the evolution of sulfur dioxide was complete (about 10–15 minutes). The mixture was cooled and made alkaline by the addition of 12 g. of sodium hydroxide.

Ten milliliters of 30% hydrogen peroxide was added to the above solution. After about 1 hour, the solution was acidified to congo red paper by the addition of hydrochloric acid and then extracted three times with ether. The combined ether extracts were concentrated and 12 g. (88%) of *o*-benzyloxyphenylacetic acid, m.p. 87–90°, was obtained. After recrystallization from a mixture of alcohol and water, the product melted at 96–97°.

*Anal.* Calcd. for $C_{15}H_{14}O_3$ (242.26): C, 74.36; H, 5.82. Found: C, 74.44; H, 5.61.

**Methyl *o*-Benzyloxyphenylacetate (IX).**—Twelve grams of *o*-benzyloxyphenylacetic acid was dissolved in 100 ml. of ether and 170 mg. of diazomethane in 100 ml. of ether was added. The residual acid was removed by extraction with aqueous sodium bicarbonate solution, and the ether solution was concentrated. Distillation of the residue at reduced pressure gave 7.3 g. (58%) of methyl *o*-benzyloxyphenylacetate, b.p. 155–160° (0.3 mm.), m.p. 43–44°.

*Anal.* Calcd. for $C_{16}H_{16}O_3$ (256.29): C, 74.98; H, 6.29. Found: C, 74.49; H, 6.51.

**Methyl 2-Methoxy-3,4-methylenedioxybenzoate (Methyl Croweacate) (X).**—A solution of diazomethane in ether was added to a solution of 5.2 g. of 2-methoxy-3,4-methylenedioxybenzoic acid (croweacic acid)[8,9] in methanol. The excess of diazomethane was decomposed by the addition of acetic acid. The ether solution was washed with aqueous sodium bicarbonate and then concentrated. Distillation of the residue at reduced pressure gave 2.7 g. (49%) of methyl 2-methoxy-3,4-methylenedioxybenzoate, b.p. 120–125° (0.2 mm.), $n^{26}D$ 1.5450.

*Anal.* Calcd. for $C_{10}H_{10}O_5$ (210.18): C, 57.14; H, 4.80. Found: C, 57.45; H, 5.10.

**$\alpha$-(2-Benzyloxyphenyl)-$\alpha$-carbomethoxy-2'-methoxy-3',4'-methylenedioxyacetophenone (XI).**—A mixture of 1 g. of methyl *o*-benzyloxyphenylacetate (IX), 0.8 g. of methyl 2-methoxy-3,4-methylenedioxybenzoate (X) and 0.2 g. of sodium hydride in 20 ml. of dry benzene was stirred and refluxed for 18 hours. The reaction mixture was poured onto ice and the layers were separated. The aqueous phase was extracted three times with ether, and the combined ethereal solution was dried and concentrated.

The residue was digested at room temperature with 7–8 ml. of ether, and the colorless, solid residue was removed by filtration. The yield of $\alpha$-(2-benzyloxyphenyl)-$\alpha$-carbomethoxy-2'-methoxy-3',4'-methylenedioxyacetophenone was 0.5 g. (28%), m.p. 122–128°. On recrystallization from methanol, the product melted at 130–131°; $\lambda_{max}^{methanol}$ 2820 ($\epsilon$ 10,400), 2380 Å. ($\epsilon$ 13,800).

*Anal.* Calcd. for $C_{25}H_{22}O_7$ (434.43): C, 69.11; H, 5.11. Found: C, 69.11; H, 5.12.

**2-(2-Methoxy-3,4-methylenedioxyphenyl)-benzofuran-3-carboxylic Acid (XIII).**—A mixture of 320 mg. of $\alpha$-(2-benzyloxyphenyl)-$\alpha$-carbomethoxy-2'-methoxy-3',4'-methylenedioxyacetophenone (XI), 10 ml. of glacial acetic acid and 5 ml. of concentrated hydrochloric acid was heated at 60–70° for one hour. The mixture was diluted with water and extracted twice with ether. Concentration of the combined ether extracts gave 200 mg. of a viscous oil. The residue was taken up in a mixture of 1 ml. of ether and 15 ml. of petroleum ether, and 50 mg. of starting material was recovered. On evaporation of the liquor, 150 mg. (62%) of methyl 2-(2-methoxy-3,4-methylenedioxyphenyl)-benzofuran-3-carboxylate (XII) was obtained.

This ester was dissolved in 10 ml. of ethanol and a solution of 125 mg. of potassium hydroxide in 10 ml. of water was added. The mixture was refluxed for 4 hours. It was diluted with water and the solution was extracted with ether. The aqueous phase was acidified to *p*H 2 with hydrochloric acid, and 70 mg. of 2-(2-methoxy-3,4-methylenedioxyphenyl)-benzofuran-3-carboxylic acid, m.p. 170–185°, precipitated. On recrystallization from alcohol–water, the product melted at 188–191°.

*Anal.* Calcd. for $C_{17}H_{12}O_6$ (312.27): C, 65.38; H, 3.88. Found: C, 65.21; H, 3.85.

**2-(2-Methoxy-3,4-methylenedioxyphenyl)-benzofuran-3-carboxylic Acid (XIII) and 2-(2-Methoxy-3,4-methylenedioxyphenyl)-benzofuran (XIV).**—A mixture of 2 g. of $\alpha$-(2-benzyloxyphenyl)-$\alpha$-carbomethoxy-2'-methoxy-3',4'-methylenedioxyacetophenone (XI), 40 ml. of glacial acetic acid and 15 ml. of concentrated hydrochloric acid was heated at 90–100° for one hour. The reaction mixture was diluted with water and extracted twice with ether. The ether extract on concentration gave a 1.5-g. residue which was heated with a mixture of 1.5 g. of potassium hydroxide, 40 ml. of ethanol and 20 ml. of water for 2–3 hours. The alcohol was removed by concentration, and the residue was extracted four times with ether. The aqueous phase was acidified to *p*H 1, and 0.5 g. (35%) of 2-(2-methoxy-3,4-methylenedioxyphenyl)-benzofuran-3-carboxylic acid, m.p. 186–189°, was obtained.

The ether phase was concentrated and 0.6 g. (49%) of 2-(2-methoxy-3,4-methylenedioxyphenyl)-benzofuran, m.p. 84–90°, was obtained. After sublimation and recrystallization from isopropyl alcohol, the compound melted at 95–97°; $\lambda_{max}^{methanol}$ 3080 ($\epsilon$ 34,400), 3220 Å. ($\epsilon$ 28,300).

*Anal.* Calcd. for $C_{16}H_{12}O_4$ (268.26): C, 71.63; H, 4.51. Found: C, 71.50; H, 4.78.

**2-(2-Methoxy-3,4-methylenedioxyphenyl)-benzofuran (XIV).**—A mixture of 1.62 g. of 2-(2-methoxy-3,4-methylenedioxyphenyl)-benzofuran-3-carboxylic acid (XIII), 30 ml. of glacial acetic acid and 11 ml. of concentrated hydrochloric acid was refluxed for one hour. The solution was concentrated to dryness. The residue was dissolved in water and the mixture was extracted twice with ether. Concentration of the ether extract gave 1.34 g. (96%) of 2-(2-methoxy-3,4-methylenedioxyphenyl)-benzofuran, m.p. 85–90°.

**2-(2-Methoxy-3,4-methylenedioxyphenyl)-3-nitrobenzofuran (XV).**—A solution of 1 g. of 2-(2-methoxy-3,4-methyl-

(11) A. Emmerie and C. Engel, *Rec. trav. chim. Pays-Bas*, **57**, 1351 (1938).

enedioxyphenyl)-benzofuran (XIV) in 25 ml. of glacial acetic acid was cooled and treated with 0.5 ml. of concentrated nitric acid. The solution was stirred at room temperature for 0.5 hour and then diluted with 60 ml. of water. The precipitate (1.1 g.) was removed by filtration and dried. It was dissolved in 10 ml. of a 1:1 mixture of benzene and petroleum ether and was chromatographed on 100 g. (2 × 37 cm.) of acid-washed alumina using the same solvent mixture. The developing solvent was then changed to benzene and about 200 ml. of the eluate was collected. On concentration of the eluate, 711 mg. (66%) of 2-(2-methoxy-3,4-methylenedioxyphenyl)-3-nitrobenzofuran, m.p. 143–149°, was obtained. After one recrystallization from methano and one from cyclohexane, the product melted at 152–153°.

*Anal.* Calcd. for $C_{16}H_{11}NO_6$ (313.26): C, 61.34; H, 3.54; N, 4.47. Found: C, 61.65; H, 3.71; N, 4.98.

**Permanganate Oxidation of 2-(2-Methoxy-3,4-methylenedioxyphenyl)-3-nitrobenzofuran (XV).**—A mixture of 50 mg. of 2-(2-methoxy-3,4-methylenedioxyphenyl)-3-nitrobenzofuran (XV), 15 ml. of acetone, 120 mg. of potassium permanganate and 2 ml. of water was refluxed for one hour. The acetone was removed by distillation, and the residue was taken up in water. An aqueous solution of sodium bisulfite was added until the manganese dioxide had dissolved. An excess of solid potassium bicarbonate was added, and the solution was extracted twice with ether. On concentration of the ether extract, 29 mg. of a yellow oil was obtained. The aqueous phase was acidified and extracted four times with ether, and on concentration of the ether extract 16 mg. of a solid remained. The material, on recrystallization from alcohol–water, melted at 154–160°; there was no depression in the melting point of this compound on admixture with an authentic specimen of croweacic acid. The identity was also confirmed by paper chromatography, and by ultraviolet and infrared absorption spectra.

**Alkaline Fusion of α-(2-Methoxy-3,4-methylenedioxyphenyl)-3-nitrobenzofuran (XV).**—A mixture of 16 mg. of 2-(2-methoxy-3,4-methylenedioxyphenyl)-3-nitrobenzofuran (XV) 125 mg. of potassium hydroxide, and two drops of water was heated in a gold crucible at 230° for 10–15 minutes. The melt was dissolved in water, and the solution was acidified and extracted with ether. The ether solution was extracted with aqueous bicarbonate solution; the bicarbonate extract was acidified and then extracted with ether. Concentration of the ether solution gave a 4.8-mg. residue which was purified by sublimation at 60–80° (0.3 mm.). The sublimate melted at 154° (micro-sub-stage); there was no depression in the melting point of this compound on admixture with an authentic sample of salicylic acid.

RAHWAY, N. J.

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[CONTRIBUTION FROM THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY, THE JOHNS HOPKINS SCHOOL OF MEDICINE]

# Imidazole Catalysis. VI.[1] The Intramolecular Nucleophilic Catalysis of the Hydrolysis of an Acyl Thiol. The Hydrolysis of n-Propyl γ-(4-Imidazolyl)-thiolbutyrate

BY THOMAS C. BRUICE

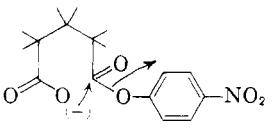
RECEIVED APRIL 11, 1959

The intramolecular catalysis of the hydrolysis of the thiol-acyl bond of *n*-propyl γ-(4-imidazolyl)-thiolbutyrate (IV) has been studied. With the intramolecular assistance of the imidazolyl group this ester at *p*H values near neutrality undergoes solvolysis at between $10^6$ and $10^7$ times as fast as a normal thiol-ester. The possible relationship of this finding to the mechanism of action of acyl-thiolases is pointed out. The mechanism of the intramolecular catalysis has been shown to be similar to that for the hydrolysis of the phenyl esters of γ-(4-imidazolyl)-butyric acid which proceed *via* formation of a lactam intermediate.

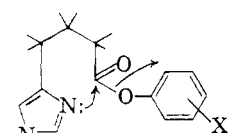
## Introduction

It was pointed out a few years ago that intramolecular reactions might serve as worthwhile models for enzymatic processes.[2] Since this suggestion a number of studies involving intramolecular participation in the hydrolysis of ester and amide bonds have been reported in the literature (*cf.* ref. 1 for a detailed account). According to the present concepts of intramolecular catalysis, the large enhancement in rate of an intramolecular reaction as contrasted to a bimolecular reaction is due to a much less negative entropy of activation, the latter factor probably reflecting a smaller loss of translational entropy.[1,3]

To date two intramolecular models appear to be of particular interest since they show a surprising kinetic similarity to the solvolysis of the enzyme ester complex. These are the mono-glutarate ester of *p*-nitrophenol[4] (I) and the phenyl esters of γ-(4-imidazolyl)-butyric acid (II).[1] The hydrolysis of I has been shown to proceed with anchimeric participation of the carboxyl anion, the rate constant being in the range of esteratic rates and about $10^2$ slower than IIa. For the model IIa



I



IIa, X = *p*-$NO_2$
b, X = *m*-$NO_2$
c, X = *p*-Cl
d, X = H

the rate and its *p*H dependence curve are almost identical to that for the hydrolysis of the *p*-nitrophenyl acetate – chymotrypsin complex[5]—which also involves participation of an imidazolyl group. For the phenyl esters II the rate decreases as the substituents on the phenolic portion become more electron releasing but all the rates fall in the range of enzymic catalyzed hydrolytic reactions, the slowest studied (IId) having a rate constant larger than that for the hydrolysis of the phenyl acetate–wheat germ lipase complex.[6]

(1) For the previous paper in this series see: T. C. Bruice and J. M. Sturtevant, THIS JOURNAL, **81**, 2860 (1959).

(2) H. Morawetz and E. W. Westhead, *J. Polymer Sci.*, **16**, 273 (1955).

(3) M. L. Bender and M. C. Neveu, THIS JOURNAL, **80**, 5388 (1958).

(4) P. E. Zimmering, E. W. Westhead and H. Morawetz, *Biochem. Biophys. Acta*, **25**, 376 (1957).

(5) T. Spencer and J. M. Sturtevant, THIS JOURNAL, **81**, in press (1959).

(6) O. Gawron, C. J. Grelecki and M. Duggan, *Arch. Biochem. Biophys.*, **44**, 455 (1953).