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Base Catalyzed Acylative Decarboxylation. Part III. (1) Acylation of Homophthalic Acid (2,3)

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Homophthalic acid (I) reacts with acetic anhydride in the presence of base to form the expected product, *o*-carboxyphenylacetone (III). Besides III, three other new products were formed, namely, 3-methyl-4-carboxyisocoumarin (II), 4-acetyl-3-methylisocoumarin (IV) and 8-acetyl-7-methylnaphtho[1,2-*c*]isocoumarin. A mechanism for the formation of these compounds is presented. The presence of 3-methyl-4-carboxyisocoumarin (II) supports an earlier suggestion (1) that acylation can occur prior to and without decarboxylation, which has been a point of concern in this reaction.

Arylacetic acids condense with aliphatic anhydrides in the presence of base yielding ketones and carbon dioxide (1,4,5). The mechanism of this decarboxylation-condensation reaction has been of interest for some time since Dakin and West (4) published their first paper using amino acids. Some workers have proposed that with acylacetic acids the decarboxylation precedes the acylation (6-8) while others have preferred a quasi six-membered ring intermediate in which the decarboxylation and acylation occur simultaneously (9). In an earlier paper we presented arguments, based on kinetic isotope effect data, that acylation occurred prior to decarboxylation (1). In this paper we demonstrate that acylation can indeed occur without decarboxylation.

When homophthalic acid (I) (Scheme A) was allowed to react with acetic acid and pyridine in addition to the expected *o*-carboxyphenylacetone (III) three other products were formed one of which was an acylative product which has not yet been decarboxylated, 3-methyl-4-carboxyisocoumarin (II). We believe that the isolation of this product further substantiates the acylative-decarboxylation mechanism in which acylation occurs prior to decarboxylation.

The formation of the diacylation products, IV and V, is no doubt a result of the enhanced reactivity resulting from the *o*-carboxyl group. Compound V is an interesting product which results from two acylative decarboxylation reactions followed by an aldol-Knoevenagel condensation-

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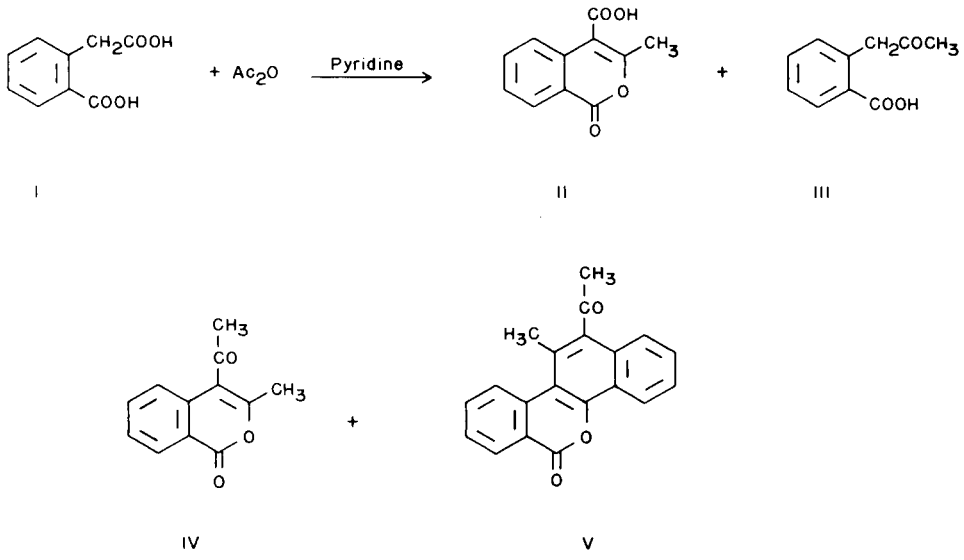
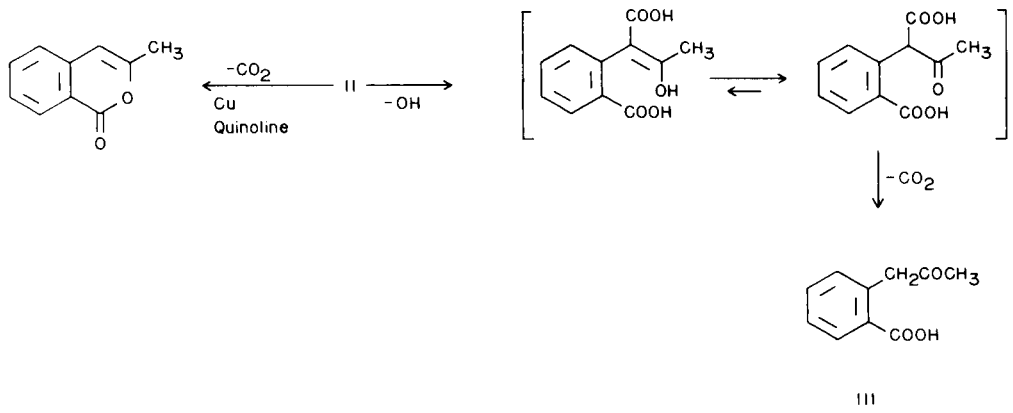
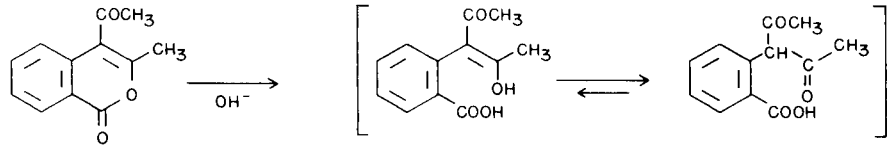


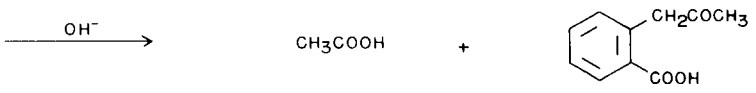
SCHEME B



III

SCHEME C





III

cyclization reaction likely made possible by the stabilization resulting through aromatic ring formation.

The separation of the products was not difficult but the proof of their structures was more challenging, particularly for compound V, until X-ray crystallographic analyses were applied.

The separation of the products was achieved by solvent extraction. The two acids were separated from the neutral portion by sodium bicarbonate extraction. Petroleum ether-benzene treatment separated II from III, and water extraction brought about the separation of IV from V.

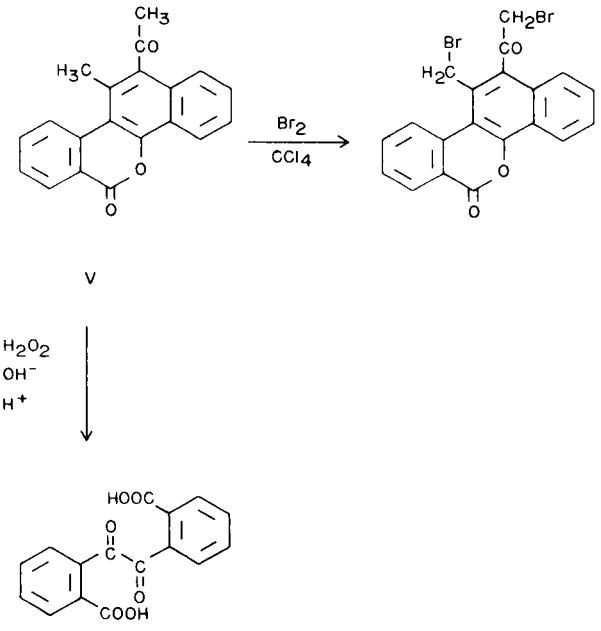
Compound II was found to be a monocarboxylic acid with a molecular formula $C_{11}H_8O_4$. It did not produce an oxime or 2,4-dinitrophenylhydrazone, indicating the absence of a keto or aldehydic group. The CO stretching at 5.95 μ and the OH stretching at 3.4 μ in the infrared spectrum indicated an α,β-unsaturated or arylcarboxylic acid. Another carbonyl group was noted by a peak at 5.75 μ which implied the presence of an ester or lactone functional group for the remaining oxygen atom. N.m.r. studies showed only two types of protons, the aromatics appearing as multiplets between τ 2.2-3.2 and a singlet at τ 8.0 which was likely a methyl group attached to a double bond or to an aromatic system. (The acidic proton was masked by the solvent peak, trifluoroacetic acid. Alkaline hydrolysis of II (Scheme B) gave *o*-carboxyphenylacetone, III, with a loss of carbon dioxide.

Decarboxylation of II (Scheme B) by heating with copper powder in diethylene glycol monomethylether solution yielded 3-methylisocoumarin. On this evidence the structure of II was established to be 3-methylisocoumarin-4-carboxylic acid.

Compound III was identified as *o*-carboxyphenylacetone, a known compound (10), by its spectral data, melting point and the melting point of its 2,4-dinitrophenylhydrazone derivative.

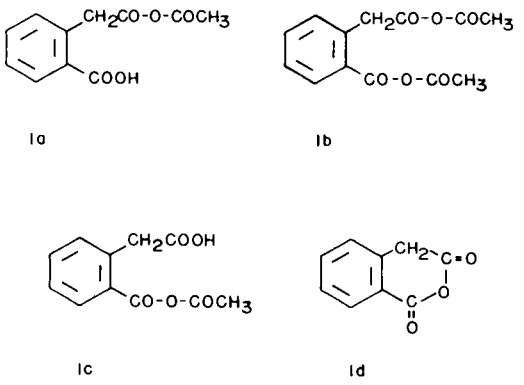
Compound IV, $C_{12}H_{11}O_3$, showed two carbonyl bands in the infrared spectrum at 5.75 and 5.93 μ, produced

SCHEME D



SCHEME E

Possible Reactive Intermediates



iodoform with hypoiodite, and gave a violet coloration with *m*-dinitrobenzene and sodium hydroxide demonstrating the presence of an acetyl group in this molecule. N.m.r. studies showed only three types of protons. A multiplet centered at τ 2.5 indicating aromatic protons, singlets at τ 7.55 and τ 7.75 implying the presence of $-COCH_3$ protons and a methyl group attached to a double bond or an aromatic system, respectively. Alkaline hydrolysis and a retrograde aldol of IV gave *o*-carboxyphenylacetone, III (Scheme C). Based on this evidence compound IV has been shown to be 4-acetyl-3-methylisocoumarin.

Compound V, $C_{20}H_{14}O_3$, showed two carbonyl absorption bands at 5.8 and 5.9 μ. It gave positive iodoform tests and coloration with *m*-dinitrobenzene and sodium hydroxide, showing the presence of an acetyl group in the molecule. Its n.m.r. spectrum showed aromatic protons centered at τ 2.15 and 3.0 and methyl signals at τ 7.65 and 7.7. Mild oxidation of V with alkaline peroxide at 60° gave diphthalic acid, showing that two *ortho* substituted phenylene groups are connected together by a two carbon atom bridge (Scheme D). These evidences and X-ray crystallography of its dibromide, which was formed when V was treated with bromine in carbon tetrachloride, has demonstrated that compound V is 8-acetyl-7-methylnaphtho[1,2-*c*]isocoumarin.

DISCUSSION

A logical explanation for the formation of compounds II-V is as follows: homophthalic acid (I) in the presence of acetic anhydride forms any or all of the mixed anhydrides shown (Ia-Id) (Scheme E). They are likely in equilibrium one with another. One of these anhydrides (and perhaps more than one) underwent on acylative decarboxylation in the presence of acetic anhydride and

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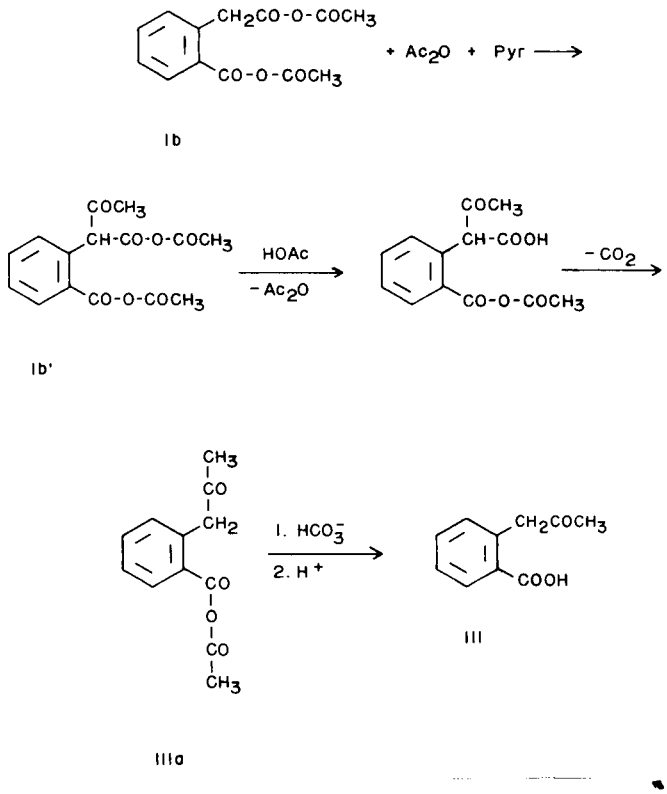
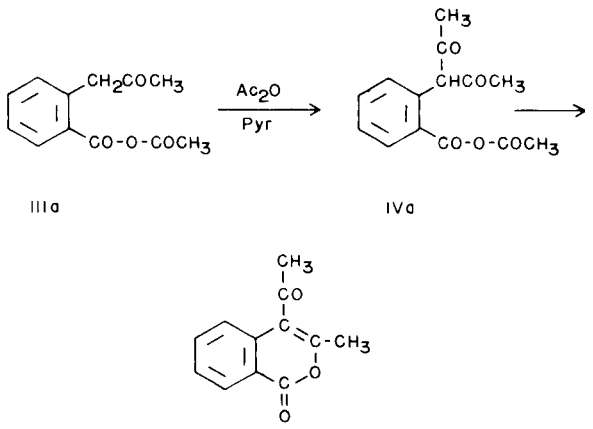


SCHEME G



IIIa IVa

IV

pyridine to form *o*-carboxyphenylacetone (III). The mechanism for this transformation is discussed in detail in reference 1, and is briefly described here using Ib as the starting mixed anhydride (Scheme F); starting with the cyclic anhydride Id would be an equally good choice as similar reactions could be written using this anhydride.

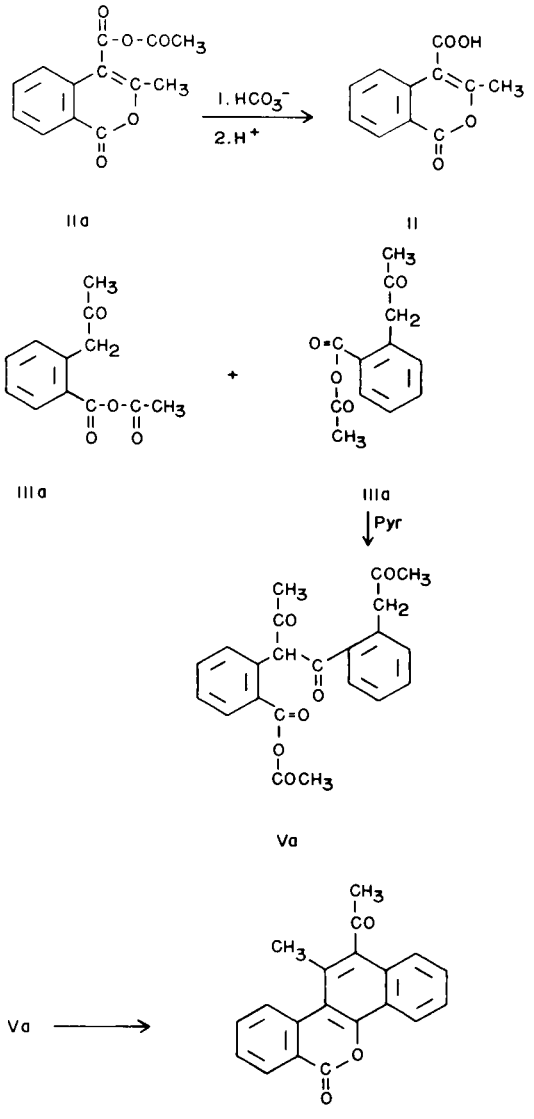
The anhydride, IIIa, was further acylated with acetic anhydride and base (pyridine) to the diacyl derivative (IVa) which can readily be cyclized to form the lactone, 3-methyl-4-acetylisocoumarin (IV) (Scheme G). 3-Methyl-4-carboxyisocoumarin (II) could have conceivably been formed by enolization and cyclization of the *C*-acylated double mixed anhydride Ib′ to produce IIa, which produced upon mild treatment with bicarbonate solution and then acid the acid, II (Scheme H). The isocoumarin ring structure was very stable and although it could have been cleaved with base, it was reformed when the mixture was reacidified.

The first three compounds discussed (II, III, IV) were therefore, essentially prepared by acylative decarboxylation reactions of the appropriate anhydride, enolization, cyclization, and finally, where necessary, hydrolysis of the anhydride to the acid.

The formation of 8-acetyl-7-methylnaphtho[1,2-c]-isocoumarin (V) included, in addition to these reactions, an aldol-Knoevenagel type condensation with active ketones, which may normally not occur under such mild conditions. However, in this instance the condensation reaction had enough added driving force that the condensation results in the formation of a naphthenoid aromatic ring and this additional stabilization shifted the equilibrium toward the product. Therefore, it is proposed that V was produced through dimerization of IIIa by an acylative decarboxylation reaction, and the resultant triketoanhydride intermediate (Va) continued to react via an aldol-Knoevenagel type reaction forming the new aromatic ring system which provided the necessary driving force (Scheme H). Finally, either stepwise or simultaneously the keto anhydride enolyzed and lactonization occurred to form the isocoumarin ring (Scheme H).

Compound V rather surprisingly brominated to a dibromide rather easily with bromine in carbon tetrachloride, one bromide substituting on the methyl ketone and the other on the methyl group of the ring. The position of the two bromine atoms was unequivocally established by X-ray crystallography, which completely

SCHEME H



IIa II

IIIa IIIa

Va

Va

established the entire structure of V. A detailed discussion of the X-ray crystallography is being published elsewhere by R. E. Davis.

EXPERIMENTAL

Melting points were taken by the capillary method using a Mel-temp apparatus. The microanalyses were performed by Drs. G. Weiler and F. B. Strauss, Oxford, England and Dr. H. W. Galbraith, Microanalytical Laboratories, Knoxville, Tennessee. Infrared spectra were recorded on a Beckman IR-8 spectrometer with potassium bromide pellet and ultraviolet spectra were determined with a Cary 15 instrument. N.m.r. spectra were recorded by a Varian A-60 spectrometer, using trifluoroacetic acid as a solvent and tetramethylsilane as an internal or external standard. The mass spectrum of V was determined by Dr. W. M. Schubert at the University of Washington and the X-ray analyses by Dr. R. E. Davis at the University of Texas (11, 12).

Materials.

Reagent grade acetic anhydride was used. Analytical reagent grade pyridine was dried and distilled over potassium hydroxide. Homophthalic acid was prepared by the chromic acid oxidation of indene (13) and purified by repeated crystallization from water.

Condensation of Homophthalic Acid with Acetic Anhydride.

Homophthalic acid (I), acetic anhydride and pyridine (1:10:5 moles) were refluxed for eight hours under anhydrous conditions, in an atmosphere of nitrogen and kept over night. Excess of acetic anhydride and pyridine were removed under reduced pressure to produce a brown, semi-solid material as the mixture of products.

3-Methyl-4-carboxyisocoumarin (II).

The above mixture was dissolved in chloroform and washed with 5% sodium bicarbonate solution several times until no precipitate was formed upon acidification of the washings. The sodium bicarbonate extracts were collected, concentrated to half their original volume and acidified by 1:3 hydrochloric acid which precipitated compounds II and III. The mixture was thoroughly dried and treated with a 1:1 petroleum ether (30-60°)-benzene mixture. The residue was crystallized from 50% ethanol to give white crystals of II m.p. 224° in small amounts (3.2%).

Anal. Calcd. for $C_{11}H_8O_4$: C, 64.75; H, 3.94. Found: C, 64.91; H, 4.12.

The infrared spectrum shows two strong carbonyl bands at 5.75 and 5.95 μ; a hydroxy band at 3.3-3.4 μ, a series of sharp bands at 6.2 6.8, 7.00, 7.58, 8.4, 9.4, 12.6, 13.2, 14.5 μ and other smaller bands in a potassium bromide pellet. The n.m.r. spectrum gave a singlet at τ 8.00 and a multiplet centered at τ 2.6.

Amide of II.

A solution of 1.0 g. of II and 5.0 ml. of thionyl chloride was refluxed for 15 minutes and the reaction mixture poured into 15 ml. of cold concentrated ammonium hydroxide solution. A white precipitate was formed which crystallized from 50% ethanol and melted at 274-275°.

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.04; H, 4.47; N, 6.90. Found: C, 64.71; H, 4.63; N, 6.65.

Decarboxylation of (II).

A 2 g. sample of II was refluxed with 100 ml. of diethylene glycol monomethyl ether containing 1 g. of copper powder for two hours. The mixture was poured over ice to give a white solid which crystallized from ether and melted at 74-75°. Melting point previously reported (14) for 3-methyl isocoumarin is 73-74°.

o-Carboxyphenylacetone (III).

The petroleum ether-benzene extract of the acidic portion of the acylation product on evaporation gave III in 20% yield. This material was crystallized from a minimum amount of 1:1 petroleum ether-benzene mixture to give a white crystalline product m.p. 120°. Melting point reported (15) for o-carboxyphenylacetone is 118-119°. The oxime of III melted at 159-160.5° (lit. m.p. 162°) (15). The 2,4-dinitrophenylhydrazone of o-carboxyphenylacetone (previously unreported), melted at 193-194°.

Anal. Calcd. for $C_{16}H_{14}N_4O_6$: C, 53.63; H, 3.94; N, 15.64. Found: C, 53.73; H, 3.94; N, 15.51.

4-Acetyl-3-methylisocoumarin (IV).

After removing all the acidic components, by washing with 7% sodium bicarbonate solutions, the chloroform solutions containing the acylation products were evaporated and the residue was extracted five to seven times with hot water. The hot water extracts were then combined, concentrated to half their original volume and cooled in an ice bath for four to five hours, when a white solid (IV) was separated out. Recrystallization of the material gave white needles of IV m.p. 99° in 9.4% yield.

Anal. Calcd. for $C_{12}H_{10}O_3$: C, 71.28; H, 4.98. Found: C, 71.24; H, 5.12.

The infrared spectrum of IV showed two strong carbonyl bands at 5.75 and 5.93 μ, a series of sharp bands at 6.7, 7.4, 7.6, 8.4, 9.3, 9.65, 10.3, 12.95, 14.4, 14.9 μ and other smaller bands. The n.m.r. spectrum of IV gave two singlets at τ 7.75 and 7.55 and a multiplet centered at τ 2.5.

Saponification of 0.110 g. of IV gave 0.082 g. of III (90% yield). Mixed melting points of the product of saponification and an authentic sample of III, and their respective 2,4 dinitrophenylhydrazone derivatives, did not show any depression.

8-Acetyl-7-methylnaphtho[1,2-c]isocoumarin (V).

The residue remaining after hot water extraction of the non-acidic portion (see above) melted at 130-140°. After thirteen recrystallizations from acetone this crude product produced white crystals of V, m.p. 190° in 9% yield.

Anal. Calcd. for $C_{20}H_{14}O_3$: C, 79.45; H, 4.67. Found: C, 79.35; H, 4.78.

The infrared spectrum of V showed a strong twin band at 5.8 and 5.9 μ, a series of sharp bands at 6.2, 6.7, 7.0, 7.2, 7.4, 7.6, 7.8, 8.03, 8.33, 9.0, 13.2, 14.4, 14.75, 15.0 and other smaller bands. The n.m.r. spectrum of V gave two slightly overlapping singlets at τ 7.67 and 7.7 and two multiplets centered at τ 2.15 and 3.0. The ultraviolet spectrum gave λ maximum at 272 mμ in ethanol solution. The mass spectrum gave a mass peak at 302, base peak at 287, peaks at 259 and 231 and other smaller peaks.

Mild Oxidation of V.

A mixture of 2 g. of V and 1.53 g. of potassium hydroxide in 15 ml. of water was added to a solution of 5.2 g. of potassium permanganate in 65 ml. of water with vigorous stirring. Stirring was continued for 30-50 minutes, until a test portion added to water showed no permanganate color. A rise in temperature (up to 60°) and frothing were observed during the reaction. Manganese dioxide was filtered off and the filtrate was acidified with concentrated hydrochloric acid which gave 0.5 g. of white crystals melting at 257-258° after crystallization from 1:1 methanol acetone mixture. The oxidation product was identified as diphthalic acid by comparison of the infrared spectrum with that of an authentic sample and by a mixed melting point determination.

Bromination of V.

To a 1.0 g. sample of V dissolved in 100 ml. of carbon tetra-

chloride was added a solution of bromine in carbon tetrachloride until a yellow color persisted. The resulting solution was kept overnight and the total volume was reduced to 50 ml. by air distillation by passing in a stream of nitrogen. This caused a white crystalline product to form which was crystallized from acetone, m.p. 216.5-217.5°.

Anal. Calcd. for $C_{20}H_{12}Br_2O_3$: C, 52.20; H, 2.62; Br, 34.73. Found: C, 53.48; H, 2.67; Br, 34.46.

REFERENCES

(1) G. G. Smith and D. H. Fahey, *J. Am. Chem. Soc.*, 81, 3391 (1959).

(2) This work was supported in part by a grant from the National Science Foundation, No. GP6006, and by the University Research Councils, Washington State University and Utah State University.

(3) A portion of this work was presented to the Graduate School, Washington State University, in partial fulfillment for a Masters degree by Carol Witte (DeLong). This work was reported in part as an Abstract of Papers, Division of Organic Chemistry, 132nd Meeting of the American Chemical Society, New York, N. Y., Sept. 9, 1957, p. 19p.

(4) H. D. Dakin and R. West, *J. Biol. Chem.*, 78, 91 (1928).

(5) J. A. King and F. H. McMillan, *J. Am. Chem. Soc.*, 73, 4911 (1951).

(6) R. H. Wiley and O. H. Borum, *ibid.*, 72, 1626 (1950).

(7) R. H. Wiley, *Science*, 111, 259 (1950).

(8) R. H. Wiley, *ibid.*, 114, 448 (1951).

(9) J. A. King and F. H. McMillan, *J. Am. Chem. Soc.*, 77, 2814 (1955).

(10) J. Grottlief, *Ber.*, 32, 965 (1899).

(11) The X-ray crystallography was performed by Dr. R. E. Davis, University of Texas, Austin, Texas.

(12) The mass spectrum was taken by Dr. W. M. Schubert, University of Washington, Seattle Washington.

(13) *Org. Syntheses*, Coll. Vol. III, p. 249.

(14) H. Nogauri, *J. Pharm. Soc. Japan*, 61, 46 (1941).

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