During the course of a study of the metabolism of propionic acid, an effort was made to use the dichromate method in the degradation of propionic acid. $CH_3C^{14}H_2COOH$ and $C^{14}H_3C^{13}H_2$-COOH, prepared by established synthetic methods essentially as outlined elsewhere,[3] were degraded. The partition coefficient[4] for the isotopic acids agreed with theory within experimental error. The distribution of isotope in the latter compound was verified by conversion to lactate, *via* α-bromination, and stepwise degradation of the lactate by established procedures.[5,6]

TABLE I

DEGRADATION OF SYNTHETIC ISOTOPIC PROPIONIC ACID

Type of propionic acid	Type of isotope	Isotope concentration in the degradation fractions[a] CO₂ ("carboxyl" carbon of propionate)	BaCO₃ (α-carbon of propionate)	CHI₃ (β-carbon of propionate)
$CH_3C^{14}H_2COOH$	C^{14}	61	184	0
$C^{14}H_3C^{13}H_2COOH$	C^{13}	0.12	0.58	0
	C^{14}	152	0	494

[a] C^{13} values are given in atom per cent. excess and C^{14} values in counts/min./mg. of carbon.

Conversion of the isotopic propionic acids to carbon dioxide and acetic acid was accomplished using the dichromate oxidation of Carson, *et al.*[2] Titrable acid and carbon dioxide could be obtained in equivalent yields, but the carbon dioxide, as shown in Table I, contained isotope from both the α- and β-carbons of the propionate. The acid fraction from the dichromate oxidation was removed from the reaction mixture by steam distillation. A small aliquot of the free acid, when fractionated by silica gel chromatography,[7] was found to have at least two components.[8] The remainder was neutralized with barium hydroxide, evaporated to dryness, and further degraded by pyrolysis[9] and sodium hypoiodite.[10] The reactions undergone by the acetic acid present in this fraction may be summarized

$$Ba(COOCH_3)_2 \xrightarrow[\text{vacuum}]{500\text{–}520°} BaCO_3 + CH_3COCH_3$$

$$CH_3COCH_3 \xrightarrow{NaOI} CHI_3 + CH_3COOH$$

The barium carbonate arises from the carboxyl group of the acetic acid and should correspond to the α-carbon of the original propionic acid. The iodoform is formed from the methyl group of the acetic acid and should correspond to the β-carbon of the propionic acid. The distribution of isotope in these fractions, shown in Table I, is in line with these expectations. It should be pointed out that the carboxyl group of any unreacted propionic acid would be converted to barium carbonate during the pyrolysis.

From the foregoing data the following conclusions may be drawn: (a) The carbon dioxide arising from the dichromate oxidation of propionic acid described by Carson, *et al.*,[2] does not come solely from the carboxyl group of the acid, as supposed by these authors, but contains appreciable carbon from the α- and β-positions of the propionic acid. (b) The equivalence which may be obtained between carbon dioxide and titrable acid produced in the reaction is fortuitous. (c) The acetic acid produced in the reaction appears to arise from the α- and β-carbons of propionic acid, as proposed by Carson, *et al.*[2]

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(3) H. G. Wood, "Cold Spring Harbor Symposia on Quantitative Biology," **13**, 201 (1948).

(4) O. L. Osburn, H. G. Wood and C. H. Werkman, *Ind. Eng. Chem., Anal. Ed.*, **8**, 270 (1936).

(5) H. G. Wood, N. Lifson and V. Lorber, *J. Biol. Chem.*, **159**, 475 (1945).

(6) N. Lifson, V. Lorber, W. Sakami and H. G. Wood, *ibid.*, **176**, 1263 (1948).

(7) S. R. Elsden, *Biochem. J.*, **40**, 252 (1946).

(8) The two components which were eluted from the silica gel column migrated at rates comparable to those observed for acetic and propionic acids. The conditions of the test, however, were not well enough standardized to render the results acceptable for purposes of identification. The faster component, presumed to be unreacted propionic acid, made up about 20%, by titration, of the total acid eluted in the two fractions.

(9) A. V. Grosse and S. Weinhouse, *Science*, **104**, 402 (1946).

(10) L. F. Goodwin, THIS JOURNAL, **42**, 39 (1920).

The Reaction of Hydroquinone with Ethyl Chloroacetate

BY CARL M. MOSER

In an attempt to find a more convenient synthesis of homogentisic acid (hydroquinone-2-acetic acid), the boron fluoride catalyzed alkylation of hydroquinone with ethyl chloroacetate was investigated in the hope that C-alkylation might predominate. A survey of the literature did not reveal any previous alkylation of phenolic compounds with alkyl halides catalyzed by boron fluoride. Hennion and Kurtz[1] investigated the boron fluoride catalyzed alkylation of benzene and toluene with alkyl halides and found that reaction at atmospheric pressure proceeds only in the presence of small quantities of polar catalysts, and the highest yields are obtained with tertiary and benzyl halides.

From the boron fluoride catalyzed alkylation of hydroquinone with ethyl chloroacetate an oily mixture was obtained. After alkaline hydrolysis of the oily mixture, two acids of m. p. 248° and 150° were obtained. The higher-melting acid could be esterified with ethanol in the presence of boron fluoride–ether complex as catalyst, and this ester proved to be identical with diethyl hydroquinone-O-diacetate (III) previously synthesized by Carter and Lawrence.[2] The higher melting acid was thus proved to be I. The melting point of the lower melting acid was in close proximity to that reported for both homo-

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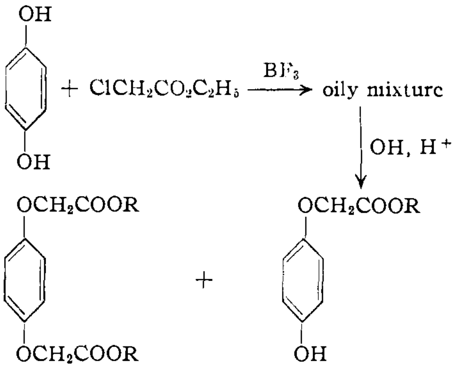
(1) Hennion and Kurtz, THIS JOURNAL, **65**, 1001 (1943).

(2) Carter and Lawrence, *J. Chem. Soc.*, **77**, 1226 (1900).



I, R = H
III, R = C_2H_5

II, R = H
IV, R = C_2H_5

gentisic acid[3] and *p*-hydroxyphenoxyacetic acid.[2] That this acid was the latter compound was determined by means of a mixed melting point determination.

From the reaction of disodium hydroquinoxide with two moles of ethyl bromoacetate in alcoholic solution, Carter and Lawrence reported the isolation of both the diester III and the acid II in unspecified yield. The reaction was repeated using ethyl chloroacetate rather than ethyl bromoacetate and the results are somewhat different from those reported by Carter and Lawrence.

When the reaction conditions followed the directions given by Carter and Lawrence, the diester III and diacid I were isolated, in 38 and 36% yield, respectively; none of the acid II could be isolated. When disodium hydroquinoxide was treated with one mole of ethyl chloroacetate, 23% of the desired acid II was isolated along with 18% of diacid I and 13% of diester III. In addition, a small quantity of an oily solid was isolated, but in insufficient quantity for purification. When hydroquinone was treated with one mole of sodium ethoxide and one mole of ethyl chloroacetate, the acid II was isolated in only 7% yield and, in addition, the ester IV was obtained in 23% yield.

While the hydrolysis of esters to acids does not ordinarily take place in alcoholic solution, the isolation of the free acid both in the previous and in the present investigation can probably be accounted for by the small amount of water present in commercial "absolute" alcohol as well as some that may have been absorbed from the atmosphere.

The next method to be investigated as a possible route to homogentisic acid was the use of the morpholine modification[4] of the Willgerodt reaction[5] on 2,5-dihydroxyacetophenone. When a mixture of 2,5-dihydroxyacetophenone, morpholine and sulfur are refluxed in the usual apparatus exposed to the air, a dark, tough resin formed that was only sparingly soluble in boiling acetone. When the reaction was carried out under nitrogen, the product was still dark and tarry in character, and no crystalline material could be isolated, nor was any isolated after treatment of the resinous products with alkali. The use of other minor modifications was without effect. The failure of this reaction was probably due to the sensitivity of the dihydroxyacetophenone to the oxidizing action of the reagent.

The 2,5-dihydroxyacetophenone used in the present investigation was prepared by the boron fluoride catalyzed acylation of hydroquinone with acetic acid. If boron fluoride-ether complex was used as catalyst rather than gaseous boron fluoride, only hydroquinone diacetate was isolated.

Experimental[6]

The Reaction of Ethyl Chloroacetate with Hydroquinone and Boron Fluoride (a) Hydroquinone-O,O-diacetic Acid.—To a mixture of 55 g. of hydroquinone, 50 g. of ethyl chloroacetate, 2 g. of glacial acetic acid and 1 g. of water in a 250 cc. Erlenmeyer flask cooled in an ice–salt-bath, boron fluoride gas was bubbled in under the surface until 50 g. had been absorbed. The flask was removed from the ice-bath and allowed to warm up to room temperature over the course of an hour. Then the flask was heated on the steam-bath with occasional swirling for forty-five minutes, after which all the hydroquinone had dissolved and the solution was dark red. The mixture was filtered and the white precipitate washed with a little cold water. After crystallization from ether and chloroform, 25 g. of small white needles were obtained, m. p. 171–172°, mixed m. p. with hydroquinone, 171–172°. The filtrate obtained after the separation of hydroquinone was in two layers, which were separated, and the aqueous layer was extracted once with 75 cc. ether. The ether was evaporated in a blast of air and the oily residue combined with the oily layer. The oily product was hydrolyzed by boiling with 500 cc. of 10% sodium hydroxide under nitrogen for forty-five minutes, the mixture was allowed to cool under nitrogen and then acidified. The precipitate that formed was filtered and dried, and after recrystallization from a mixture of alcohol and water (Norite) 5 g. of small needles, m. p. 246–248° (dec.), were obtained. The reported[2] melting point for hydroquinone-O,O-diacetic acid is 251°.

The ethyl ester was prepared in the usual manner with the use of boron fluoride–ether complex. The ester was obtained as short white needles from dilute ethanol, m. p. 70–71°. On admixture of an authentic sample, the m. p. was 70–71°.

(b) *p*-Hydroxyphenoxyacetic Acid.—The filtrate obtained after the removal of hydroquinone-O,O-diacetic acid was extracted five times with 100-cc. portions of ether. The ether extracts were combined, washed with saturated salt solution, and dried over anhydrous sodium sulfate. The ethereal solution was concentrated to a volume of about 100 cc., treated with a small amount of charcoal, filtered and then the reddish solution was concentrated about 25 cc. more. An equal volume of chloroform was added and the mixture was placed in the ice-box for several hours. The precipitate was collected, dried and crystallized from a mixture of ethyl acetate and chloroform. The acid was obtained as small, tan prisms, m. p. 148–150°. The mixed m. p. with an authentic sample was 146–148°.

Reaction of Hydroquinone with Ethyl Chloroacetate in Presence of Sodium Ethoxide.—To a solution of 9.2 g. (0.4 mole) of sodium dissolved in 500 cc. of commercial "absolute" alcohol, 22 g. (0.2 mole) of hydroquinone was added. The mixture was refluxed for five minutes and then cooled. To the suspension of hydroquinoxide 48.8 g.

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(3) Hahn and Stenner, *Z. physiol. Chem.*, **181**, 88 (1929).

(4) Schwenk and Bloch, THIS JOURNAL, **64**, 3051 (1942).

(5) A recent review of the Willgerodt reactions may be found in a chapter of the same name by Carmack and Spielman, "Organic Reactions," III, 83 (1946).

(6) All melting points were taken on the Fischer–Johns apparatus.

(0.4 mole) of ethyl chloroacetate was added all at once, and the resulting mixture was refluxed for five hours. The mixture was cooled, the *p*H adjusted to *ca.* 3 with a few drops of concentrated hydrochloric acid, distributed between water and ether, and the layers separated. The ether layer was washed twice with 10% sodium carbonate solution, and the alkali wash was added to the aqueous layer. The ether layer was dried over anhydrous sodium sulfate, and then the ether was evaporated. The residue (22.5 g.) was the diester III, m. p. 64–68°. Crystallization from dilute ethanol gave 21.4 g. (38%) of white needles, m. p. 70–71° (reported[2] m. p. 72°). The aqueous layer was acidified and filtered. The slightly tan solid obtained after drying melted at 240–245°. After two recrystallizations from dilute ethanol (Norite), the acid I (16.2 g., 36%) was obtained in the form of short white needles, m. p. 248–249° (reported[2] m. p. 251°). The ethyl ester of this acid could be prepared in the usual manner with boron fluoride-etherate as catalyst. After crystallization from dilute ethanol the ester melted at 70–71°, and there was no depression on admixture of the ester described above. The aqueous filtrate remaining after removing the acid was exhaustively extracted with ether. The ether extract was washed with saturated salt solution and dried over anhydrous sodium sulfate. The residue remaining after evaporation of the ether consisted of about 2 g. of a dark, viscous oil, which could not be induced to crystallize and was not further investigated. When the reaction was carried out with the use of one mole of ethyl chloroacetate and two moles of base, diester III (13%) and diacid I (18%) were isolated as described above. From the aqueous filtrate there was obtained by ether extraction 23% of the acid II, which was obtained as faintly yellow prisms, m. p. 149–150.5° (reported[2] m. p. 152°), after crystallization from a mixture of ethyl acetate and chloroform. When one mole of ethyl chloroacetate and one mole of base were used, 7% of the acid II and 23% of the ester IV were isolated. The ester crystallized from very dilute ethanol as white needles, m. p. 125–126°.

Anal.[7] Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.25; H, 6.23.

Reaction of 2,5-Dihydroxyacetophenone with Morpholine and Sulfur.—The following experiment is typical of many carried out. A mixture of 5 g. of 2,5-dihydroxyacetophenone, 7.8 g. of morpholine and 1.0 g. of sulfur was refluxed for two hours. At the end of that time the reaction mixture was nearly black. On cooling, the product of the reaction was found to be a dark, tough resin that was insoluble in all boiling organic solvents except acetone, and the resin was only slightly soluble in that reagent. If the reaction was carried out under conditions that carefully excluded air, the dark reaction mixture on cooling deposited a dark tarry product that was soluble in boiling alcohol, insoluble in boiling chloroform, but no crystalline product could be isolated. If the reaction was carried out under nitrogen for only fifteen minutes, about 20% of the starting ketone could be recovered in rather an impure state. Attempts to hydrolyze the tarry product with 10% sodium hydroxide were fruitless.

2,5-Dihydroxyacetophenone.—To a suspension of 44 g. of hydroquinone in 36 g. of glacial acetic acid well cooled in an ice–salt-bath, boron fluoride gas was bubbled in until 25 g. had been absorbed. The mixture was gently heated on the steam-bath for an hour, at which time all the hydroquinone had dissolved and the solution was colored a deep cherry red. After standing for twelve hours at room temperature, the mixture was decomposed by pouring it into a solution of 25 g. of sodium acetate dissolved in 150 cc. of water. The solid that separated was collected and the filtrate was extracted two times with 200-cc. portions of ether. The ether was evaporated and the residue added to the precipitate previously collected. The combined solid material was refluxed for fifteen minutes with a solution of 20 g. of sodium hydroxide dissolved in 200 cc. of water. The mixture was cooled, acidified; the precipitate was collected, washed. After crystallization from a mixture of ethanol and water, 16 g. (67% based on unrecovered hydroquinone) of yellow-green needles were obtained, m. p. 203–204° (reported[8] 202–203°). From the filtrate 26 g. of hydroquinone of good quality, m. p. 171–172°, could be isolated.

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[7] Analysis performed by William R. Ruby of these Laboratories.

[8] Amin and Shah, "Organic Syntheses," **28**, 42 (1948). A bibliography of the various methods used in the preparation of the ketone is given here.

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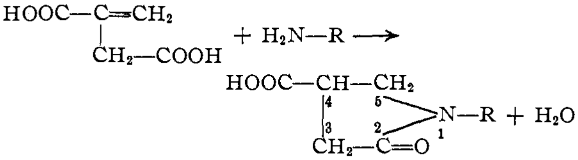
The Reaction of Itaconic Acid with Primary Amines

BY PETER L. PAYTASH, EDWARD SPARROW AND JOSEPH C. GATHE

The condensation of primary amines with methylenesuccinic acid (itaconic acid) to give carboxypyrrolidones has apparently been studied in the case of only four amines, aniline, *p*-toluidine, phenylhydrazine and α-naphthylamine.[1] The probable mechanism of type reaction of pyrrolidonation is[2]



In the present report, forty-five amines have been investigated in the hope of establishing the limits of this type of reaction. Four of these amines condensed with itaconic acid in the presence of water, the medium used by the earlier investigators. A modification of the original method, fusion of the reactants, was required to bring about reaction in thirty-two cases. The results are summarized in Table I.

The nine amines which failed to react by either method were 2,4,6-trichloroaniline, 2,4,6-tribromoaniline, 2-nitroaniline, 2,4-dinitroaniline, 2,5-dimethoxyaniline, 2,5-diethoxyaniline, 2-carboxyaniline, sulfathiazole and sulfanilic acid. The reaction therefore appears to be limited both by the nature and the position of the substituents in the amine.

Experimental[3]

A mixture of itaconic acid, the amine and water (in the ratio of one acid molecule to each amino group) was refluxed for forty-five to sixty minutes

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[1] Gottlieb, *Ann.*, **77**, 284 (1851); Michael and Palmer, *Am. Chem. J.*, **9**, 199 (1887); Scharfenberg, *Ann.*, **254**, 149 (1889); Anschütz and Reuter, *ibid.*, **254**, 129 (1889).

[2] The numbering of the ring positions is that used in *Chemical Abstracts* 1-R-4-carboxy-2-pyrrolidones, rather than that appearing in Beilstein and the earlier papers, 1-R-3-carboxy-5-pyrrolidones.

[3] Technical grade itaconic acid, generously supplied by the Pfizer Co. and melting at 165–171°, was used throughout since carefully purified acid, melting at 167.5–168.5°, gave the same results. All of the amines were purified. All melting points are uncorrected; melting points below 300° were determined with a Fisher–Johns heating block, those above 300° with a Thiele tube by the capillary method.