xanthone, m. p. 249–250°. Ullmann and Wagner[10] report 243°.

o-Phenoxy-p-hydroxybenzoic Acid.—Demethylation of *o*-phenoxy-*p*-methoxybenzoic acid with aluminum chloride in benzene gave 54% of the hydroxy acid which melted at 163–164° after vacuum sublimation and crystallization from water.

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.84; H, 4.27. Found: C, 67.64; H, 4.54.

p-Phenoxy-o-hydroxybenzoic Acid.—The acid mixture resulting from the oxidation of the 3-methoxy aldehydes was demethylated with aluminum chloride in benzene. The product melted at 162–167°, yield 76%. Vacuum sublimation at 150–170° of 0.126 g. of this product gave 0.122 g. melting at 167–168°. Crystallization from benzene–petroleum ether raised the melting point to 180.8–181.4°. Mixed with an authentic specimen of *p*-phenoxy-*o*-hydroxybenzoic acid (182.4–183°) the melting point was 180.4–181.2°.

Synthesis of p-Phenoxy-o-hydroxybenzoic Acid: 2-Amino-4-chlorotoluene.—2-Nitro-4-chlorotoluene (100 g.) in 100 cc. of methanol was reduced in the presence of 3 g. of Raney nickel at 60° (2000 lb.). The pure amine boiled at 120–125° (40 mm.), yield 83%.

4-Chloro-2-hydroxytoluene.—Diazotization and hydrolysis of the above amine according to the procedure described for 3-bromo-4-hydroxytoluene (above) gave 85% of the chlorocresol melting at 67–68°. Methylation with dimethyl sulfate[7] gave 80% of 4-chloro-2-methoxytoluene boiling at 104–106° (25 mm.).

p-Methoxy-o-methoxytoluene.—A mixture of potassium phenoxide (4.3 g.), 5.0 g. of 4-chloro-2-methoxytoluene and 0.1 g. of copper powder was heated for two and one-half hours at 250–270°. The products were taken up in ether and vacuum distilled. The desired diphenyl ether boiled at 275–276°, yield 10%. It was oxidized to the methoxy acid without further purification.

p-Phenoxy-o-hydroxybenzoic Acid.—The above compound was oxidized with permanganate in aqueous pyridine. The crude acid melted at 74–75°, yield 31%; it was used without further purification for the preparation of the hydroxy acid, which was obtained by demethylation with hydriodic acid in acetic acid. The pure acid, crystallized from benzene–petroleum ether, melted at 182.4–183.0°.

Anal. Calcd. for $C_{13}H_{10}O_4$: C, 67.84; H, 4.27. Found: C, 67.54; H, 3.93.

3-Hydroxydiphenyl Ether.—Demethylation of 3-methoxydiphenyl ether with potassium hydroxide in ethylene glycol gave a 76% yield of the hydroxydiphenyl ether. A 70% yield was obtained by demethylation with hydriodic acid (sp. gr. 1.5) in acetic acid. The liquid product was used without special purification.

The aryloxyacetic acid formed from this ether melted at 67–67.4° (from petroleum ether (86–100°)).

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.80; H, 4.95. Found: C, 68.91; H, 4.65.

Demethylation of the aldehyde mixture (2 g.) from 3-methoxydiphenyl ether with aluminum chloride (6 g.) in benzene (60 cc.) gave 0.4 g. of alkali-soluble material which was found to be 3-hydroxydiphenyl ether by conversion to its aryloxyacetic acid, m. p. 65–66°, mixed with an authentic specimen (67–67.4°), m. p. 66–67°.

Summary

1. The Gattermann aldehyde synthesis applied to the three mono methoxydiphenyl ethers gives good yields of aldehydes with the 2- and 3-isomers but not with the 4-isomer.

2. 2-Methoxydiphenyl ether yields a mixture of approximately equal amounts of the 5- and 4′-aldehydes. The structures of these aldehydes have been established by two independent methods.

3. The aldehydes from 3-methoxydiphenyl ether consist of a mixture of the 4- and 6-isomers in which the 4-isomer predominates.

COLUMBIA, MISSOURI RECEIVED MAY 8, 1943

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Reaction between Quinones and Metallic Enolates. XVII. Dibromo-*p*-xyloquinone and Sodiomalonic Ester[1]

BY LEE IRVIN SMITH AND JOSEPH NICHOLS[2]

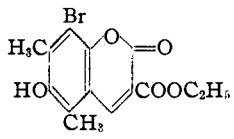
Previous work[1,3,4] has shown that a brominated methylquinone may react with a metallic enolate to produce either a coumarin derivative by reaction at a methyl group, or a quinonemalonic ester by direct replacement of a bromine atom. Thus, trimethylbromoquinone is converted by action of sodiomalonic ester into the coumarin I; in this case, no replacement of the bromine atom occurs, and the reaction is confined entirely to the methyl group which is in the meta position to the bromine atom. In a similar fashion, dibromo-*m*-xyloquinone is converted into the coumarin II, and no product could be isolated which was derived by replacement of a bromine atom. However, dibromo-*o*-xyloquinone reacts entirely by replacement of a bromine atom, and the primary

(1) XVI. Smith and Austin, THIS JOURNAL, **64**, 528 (1942).

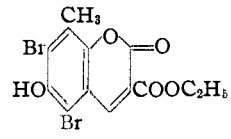
(2) Abstracted from a thesis by Joseph Nichols, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, February, 1943.

(3) Smith and Byers, *ibid.*, **63**, 612 (1941).

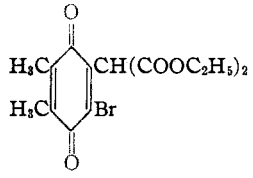
(4) Smith and Johnson, *ibid.*, **59**, 673 (1937).



I



II

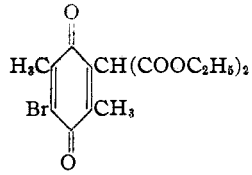


III

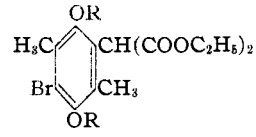
product is a yellow quinone III; when an excess of the enolate is used, both bromine atoms can be replaced, but there is no evidence of any reaction involving a methyl group. In order to complete the studies on the dibromodimethylquinones, the reaction between sodiomalonic ester and dibromo-*p*-xyloquinone has now been investigated.

This quinone proved to possess a halogen atom which was extremely active toward sodiomalonic ester, but the reaction between the quinone and the enolate was quite susceptible to changes in conditions, particularly changes in the nature of the solvent; the best yield of product (84%) was obtained by operating in dry dioxane which was free from peroxides. No trace of any coumarin derivative could be found in the reaction product, and it thus appeared that dibromo-*p*-xyloquinone paralleled completely in behavior the ortho isomer, which likewise failed to yield any detectable amount of a coumarin derivative.

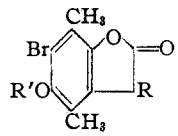
The product IV was a yellow solid which had the properties of a quinone. It was readily reduced, either catalytically or by action of sodium hydrosulfite, to a white hydroquinone V. The action of mild oxidizing agents upon V gave the quinone IV, and showed that, in the reduction of IV, no changes had occurred other than simple reduction. The hydroquinone V readily formed a diacetate, VI. When the hydroquinone V was subjected to the action of diluted sulfuric acid (75%) at room temperature, cyclization occurred and the isocoumaranone ester VII was formed. Less concentrated acid (60%) produced a mixture of VII and unchanged V, whereas the action of concentrated sulfuric acid resulted in partial elimination of the carbethoxyl group and produced a mixture of VII and the isocoumaranone VIII. The ester VII was easily hydrolyzed and decarboxylated when its solution in acetic acid was warmed, and the product was the isocoumaranone VIII. The quinone IV was converted, by reduction with zinc and acetic acid, directly into the isocoumaranone VIII, and VIII was also obtained when the solution of diacetate VI in acetic and hydrochloric acids was heated. The isocoumaranones VII and VIII gave, respectively, the acetates IX and X when they were dissolved in acetic anhydride containing a few drops of sulfuric acid and allowed to stand overnight at room temperatures, and action of dilute acetic acid upon the acetate IX converted it into the acetate X. All of these transformations are in complete analogy with the results obtained in the previous study of the behavior of the compounds derived from dibromo-*o*-xyloquinone.



IV
IVA, H instead of Br

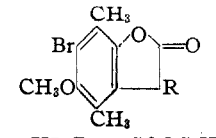


V, R = H
VA, H instead of Br
VI, R = Ac

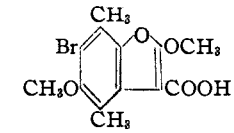


VII, R = $COOC_2H_5$; R′ = H
VIIA, H instead of Br
VIII, R = R′ = H
VIIIA, H instead of Br
IX, R = $COOC_2H_5$; R′ = Ac
X, R = H; R′ = Ac

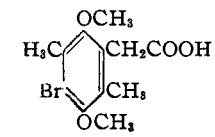
The action of methyl sulfate and alkali upon the hydroquinone V, or upon the isocoumaranone ester VII, led to a mixture of two products. The chief product was a substance XI, $C_{14}H_{15}O_5Br$, which melted at 96–97°, and was insoluble in sodium carbonate solution. The other methylation product, XII, formed in small amounts only, melted at 210–211° and had the composition $C_{13}H_{13}O_5Br$.



XI, R = $COOC_2H_5$
XIII, R = H



XII



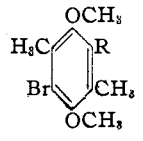
XIV

Both XI and XII, when subjected to the action of acetic acid, gave the methoxyisocoumaranone XIII. Further methylation of XIII gave the phenylacetic acid derivative XIV, and XIV was also the product resulting from the action of methyl sulfate and alkali upon the isocoumaranone VIII.

The fact that the products XI and XII were produced by methylation of both V and VII indicated that the first step in the methylation reaction involved a ring closure of the hydroquinone V rather than a ring cleavage of VII. The conversion, by methylation, of XI and XII first into XIII and then into XIV, as well as the formation of XIV directly from VIII by methylation, also indicated that methylation of V involved, as a first step, ring closure to VII.

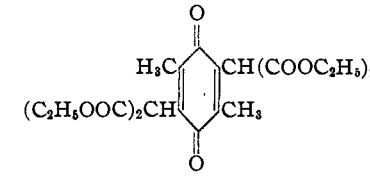
Substance XII, soluble in carbonate and hence possessing a carboxyl group, was, therefore, correctly represented as the enol ether of an isocoumaranonecarboxylic acid; a similar transformation of an isocoumaranone ester into the enol ether of an isocoumaranone acid by methylation has been observed previously.[1] The methylation product XI was insoluble in carbonate or aqueous potassium hydroxide. It therefore possessed no carboxyl group; nevertheless this substance could not be extracted with ether from the alkaline mixture resulting from the methylation reaction until after the mixture was acidified. Moreover, when the alkaline mixture was poured into water, a white sodium (or potassium) derivative precipitated. This white metallic derivative was insoluble in ether, left a residue when it was burned, and gave XI when it reacted with acid. The insoluble metallic derivative was therefore an enolate, from which it followed that XI was an isocoumaranone ester. It is, however, difficult to understand why methylation of VIII, which gave XIV directly, should not have led to XIII, whereas both V and VII could be converted into XIII without cleavage of the hetero ring.

Although there was little doubt as to the structure of the quinone IV or of the many products derived from it, an independent synthesis of one of these derivatives was undertaken. The phenylacetic acid XIV was selected as the most suitable of these products for synthesis, and the first plan of attack involved, as the initial step, chloromethylation of *p*-xylohydroquinone dimethyl ether. But the chloromethylation could not be confined to the introduction of one chloromethyl group, and the resulting mixture of products could not be separated. On the other hand, bromination of the hydroquinone ether was readily controlled to give good yields of the mono bromo compound XV, which in turn was readily chloromethylated to XVI. Action of potassium cyanide upon XVI gave the nitrile XVII, which was hydrolyzed to the acid XIV, identical with the phenylacetic acid obtained by methylation of V, VII or VIII.

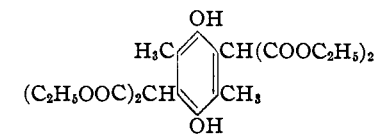


XV, R = H
XVI, R = CH_2Cl
XVII, R = CH_2CN

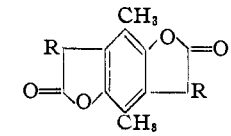
Although the product IV was obtained from dibromo-*p*-xyloquinone and sodiomalonic ester with great ease, replacement of the second bromine atom by a malonic ester residue proceeded with great difficulty and the disubstitution product could be obtained only in poor yields. In order to obtain the halogen-free compound XVIII, it was necessary to add the monosubstitution product IV to a solution of three moles of sodiomalonic ester in boiling dioxane, and to reflux the mixture for an hour. The disodium derivative of XVIII was filtered and decomposed with acid; the yield of XVIII was but 16%, and most of the product was a viscous red oil which could not be crystallized. A series of transformation



XVIII



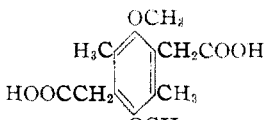
XIX



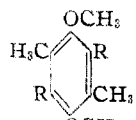
XX, R = $COOC_2H_5$
XXI, R = H

products analogous to those obtained from IV was prepared from XVIII in essentially the same manner. Reduction of XVIII gave the hydroquinone XIX; cyclization of XIX was accomplished by

action of diluted (75%) sulfuric acid, and the product was the difuranoid compound XX. When a solution of XX in acetic acid was warmed, the substance was hydrolyzed and decarboxylated to XXI, which could also be obtained directly from the quinone XVIII by action of zinc and acetic acid. Methylation of XXI by action of methyl sulfate and alkali led to cleavage of both hetero rings and formation of the benzene-*p*-diacetic acid XXII. The diacetic acid was synthe-



XXII



XXIII

sized from *p*-xylohydroquinone dimethyl ether XXIII, by a sequence of reactions exactly paralleling the synthesis of XIV—*i. e.*, a series represented by XXIII in which both R groups are successively CH_2Cl, CH_2CN and CH_2COOH. The synthetic product was identical with XXII obtained from dibromo-*p*-xyloquinone and sodiomalonic ester.

The reaction between dibromo-*p*-xyloquinone and sodiomalonic ester led to the *quinones* IV and XVIII. No hydroquinones or cyclic products were obtained until the primary products were reduced. In contrast to this behavior, when *p*-xyloquinone with two nuclear hydrogen atoms reacted with sodiomalonic ester, the chief product was the cyclic isocoumaranone VIIA, which could only have been formed *via* the hydroquinone VA. Hence, in this case, a *hydroquinone* was the direct product of the reaction, and no reducing agent was required to produce it. Along with VIIA, there was formed a small amount of the double isocoumaranone XX, which resulted via the sequence VA, IVA, and XIX. Action of *p*-xyloquinone upon VA produced *p*-xylohydroquinone and IVA and the latter then reacted with the enolate by 1,4-addition, followed by a tautomeric shift to give XIX.

The difuranoid compounds XX and XXI are of some interest in connection with the Mills–Nixon effect, for the three ring system in these compounds of necessity requires that a double bond be held in common by adjoining five- and six-membered rings. Such a system is strained, according to the Mills–Nixon theory of the fixation of double bonds in polynuclear systems. Yet XX and XXI were obtained in excellent yields and under mild reaction conditions from the open-chained hydroquinone XIX. These and other similar examples of ring closures already in the literature indicate that in ring closures of this type the Mills–Nixon effect, though doubtless of some importance, is certainly not a controlling factor.

Experimental Part[5]

***p*-Xyloquinone** (81 g., 80.8%) m. p. 122–124°, was prepared from *p*-xylenol (90 g.) by the general method described previously.[6]

***p*-Xylohydroquinone.**—A solution of the quinone (30 g.) in ether (400 cc.) was shaken with three 200-cc. portions of freshly prepared saturated aqueous sodium hydrosulfite. The colorless ether solution was washed with water and dried (sodium sulfate). Removal of the solvent left a residue of 28.6 g. (94.1%) of the white hydroquinone. After it was washed with a little petroleum ether (b. p. 28–38°), the substance melted at 208–213°.[7] Reduction of the quinone by action of zinc and acetic acid likewise gave the hydroquinone. Although the product, when prepared this way, had a sharper m. p. (softened at 205°, melted at 212–213°), the yield was lower (80%).

Dibromo-*p*-xyloquinone.—Preparation of this substance by action of nitric acid upon tribromo-*p*-xylenol[8] was abandoned because complete bromination of *p*-xylenol to the tribromo derivative could be accomplished only with considerable difficulty. Direct bromination of *p*-xyloquinone gave the dibromoquinone (59.6%), but complete bromination required forcing conditions. On the other hand, *p*-xylohydroquinone reacted smoothly with bromine at room temperature and was converted into the dibromoquinone in excellent yield. The primary product, obtained by bromination of either the quinone or the hydroquinone, was a red quinhydrone; this was converted completely into the quinone by action of a little nitric acid.

Bromine (68 g., 0.425 mole) was added dropwise and with stirring to a solution of *p*-xylohydroquinone (27 g., 0.196 mole) in acetic acid (1200 cc.). The solution was then stirred at room temperature for an additional three hours and poured into water. The red quinhydrone (55 g.) was removed and dissolved in ethanol (2500 cc.). Nitric acid (25 cc.) was added, and the solution was warmed on the steam-bath until the color became yellow. When cooled, the solution deposited 50.8 g. (88.3%) of golden-yellow leaflets of the dibromoquinone. The quinone, after successive recrystallization from alcohol and petroleum ether (b. p. 77–115°), softened at 178° and melted at 183–184°. The recorded m. p. is 184°,[7a] but repeated crystallization did not give a product with a higher or sharper m. p.

(5) Microanalyses by Stanley T. Rolfson.

(6) Smith, Opie, Wawzonek and Prichard, *J. Org. Chem.*, **4**, 318 (1939).

(7) The melting points reported in the literature vary from 208 to 213°: (a) Carstaujen, *J. prakt. Chem.*, [2] **23**, 421 (1881); (b) Nietzski, *Ann.*, **215**, 125 (1882); (c) Sabatier and Mailhe, *Ann. chim. phys.*, [8] **16**, 70 (1909); (d) Conant and Fieser, THIS JOURNAL, **45**, 2194 (1923).

(8) (a) v. Auwers and Rapp, *Ann.*, **302**, 153 (1898); (b) v. Auwers, *Ber.*, **32**, 17 (1899).

Anal. Calcd. for $C_8H_6O_2Br_2$: C, 32.68; H, 2.06. Found: C, 32.75; H, 2.19.

The behavior exhibited by dibromo-*p*-xyloquinone on melting appeared to be characteristic of the compound itself, for even when it was prepared from *p*-xylenol (m. p. 75–76°) that had been recrystallized eight times from petroleum ether (b. p. 60–68°), the dibromoquinone still softened at 176–178° and melted at 183°.

Dibromo-*p*-xylohydroquinone.—The dibromoquinone (1.1 g.) was dissolved in acetic acid (50 cc., 60%) and the solution was refluxed with zinc (10 g., 20 mesh) for fifteen minutes. The colorless solution was filtered and the filtrate was diluted with water (200 cc.). The hydroquinone was removed from the cooled mixture and was dried and recrystallized from ether–petroleum ether (b. p. 28–38°). The product melted at 174.5–175.5° after preliminary softening.[9]

5-Bromo-2-dicarbethoxymethyl-3,6-dimethyl-*p*-benzoquinone (IV).—For good results in the condensation of dibromo-*p*-xyloquinone and sodiomalonic ester, it was necessary to operate at room temperature in purified, dry dioxane, free from peroxides and, because the product IV was a stronger acid than malonic ester, to use two moles of sodiomalonic ester per mole of bromoquinone. A yield of only 44% of IV was obtained when only one mole of sodiomalonic ester was used per mole of quinone; when the dioxane was not purified, the yield of IV was but 21%; if the reaction mixture was heated, even when purified dioxane was used, the product was almost entirely a black, viscous tar; and with alcohol as a solvent, only red oils resulted. When benzene was used as the solvent, IV was obtained, but only in yields of about 55%. In many instances in which dioxane was used as the solvent, there was deposited from the purple reaction mixture a small amount (1–6%) of an insoluble black sodium compound. Action of hydrochloric acid upon this substance converted it into a fine red powder (m. p. 165–169°) which was the quinhydrone of dibromo-*p*-xyloquinone.[10] The reduction of some of the quinone to hydroquinone in this reaction is difficult to explain, since no coumarin derivative was ever obtained.

A solution of malonic ester (21 g., 0.132 mole) in dry dioxane (100 cc., free from peroxides)[11] was protected from moisture and refluxed with sodium (2.53 g., 0.11 gram atom) until all the metal dissolved (two to three hours). The light yellow solution was cooled to room temperature and then quickly added to a well-stirred solution of dibromo-*p*-xyloquinone (15.0 g., 0.051 mole) in pure dioxane (500 cc.). The solution, which assumed a momentary brown color that quickly changed to dark purple, was stirred at room temperature for five hours and then filtered. Only a trace of insoluble material usually was formed. The filtrate was acidified with dilute hydrochloric acid, and the solution, now yellow, was diluted with water (2000 cc.) and extracted with ether (800 cc. in portions). The combined extracts were washed with water and the solvent was removed. The residual oil was dissolved in aqueous ethanol (400 cc., 50%) and set aside overnight at −20°. The orange solid was removed and crystallized twice from 200-cc. portions of aqueous ethanol (70%) at a final temperature of −20°. The yellow quinone IV weighed 15.9 g. (83.7%) and melted at 65–66°.

Anal. Calcd. for $C_{15}H_{17}O_6Br$: C, 48.25; H, 4.59. Found: C, 48.29; H, 4.55.

Ethyl 4-Bromo-2,5-dimethyl-3,6-dihydroxyphenylmalonate (V).—The quinone IV (15 g.), dissolved in pure dry ether (200 cc.) was shaken with two 100-cc. portions of saturated, freshly prepared aqueous sodium hydrosulfite. The colorless ether solution was washed once with water, poured through a mat of sodium sulfate, concentrated by distillation to a volume of 25 cc., and diluted with petroleum ether (100 cc., b. p. 28–38°). The cooled mixture deposited 14.5 g. (96%) of the white hydroquinone, which after repeated crystallization from petroleum ether (b. p. 60–68°) softened at 108° and melted at 111–112°. The same product V was obtained by rapid (thirty minutes) catalytic reduction (platinum oxide) of a petroleum ether (b. p. 60–68°) solution of IV under low (40 lb.) pressure.

Anal. Calcd. for $C_{15}H_{19}O_6Br$: C, 48.01; H, 5.10. Found: C, 48.34; H, 5.25.

The quinone IV was readily obtained by action of ferric sulfate upon an alcoholic solution of the hydroquinone V.

Ethyl 4-Bromo-2,5-dimethyl-3,6-diacetoxyphenylmalonate (VI).—The hydroquinone V (0.5 g.) was dissolved in acetic anhydride (10 cc.), sulfuric acid (2 drops) was added, and the solution was set aside overnight at room temperature. Water was added, the mixture was warmed gently (steam-bath) to destroy excess acetic anhydride, and then extracted with ether. The ether layer was washed with carbonate (10%) and dried (sodium sulfate). The ether was removed and the residue was recrystallized from petroleum ether (b. p. 60–68°). The product melted sharply at 110–111°; when mixed with V (also melting at 111°) the substance melted at 93–100°.

Anal. Calcd. for $C_{19}H_{23}O_8Br$: C, 49.68; H, 5.05; Br, 17.40. Found: C, 49.38; H, 5.10; Br, 17.25, 17.79.

3-Carbethoxy-4,7-dimethyl-6-bromo-5-hydroxyisocoumaranone (VII).—The hydroquinone V (3 g.) in chloroform (100 cc.) was shaken with two 50-cc. portions of sulfuric acid (75%) for five-minute periods. The chloroform solution was washed with water and dried (sodium sulfate). The solvent was removed under reduced pressure, and the residual oil solidified when it was rubbed with a little petroleum ether (b. p. 60–68°). Recrystallization from this solvent gave 2.4 g. (91.2%) of the isocoumaranone VII, which melted at 117–118.5°.

Anal. Calcd. for $C_{13}H_{13}O_5Br$: C, 47.43; H, 3.98. Found: C, 47.54; H, 4.11.

The acetate (IX) was prepared from 1 g. of VII by the procedure described for preparation of VI above, except that the excess acetic anhydride was hydrolyzed by allowing the mixture to stand in the cold. The product (1.10 g., 97.3%) melted at 120–122° after it had been repeatedly crystallized from petroleum ether (b. p. 60–68°).

Anal. Calcd. for $C_{15}H_{15}O_6Br$: C, 48.56; H, 4.07. Found: C, 48.53; H, 4.07.

4,7-Dimethyl-6-bromo-5-hydroxyisocoumaranone (VIII).—A. From the quinone IV: A solution of IV (3 g.) in aqueous acetic acid (60 cc., 60%) was refluxed with zinc

(9) Teichner, *Ber.*, **35**, 2303 (1902), reports the m. p. as 174–175°.

(10) Teichner, ref. 9, gives the m. p. as 169°.

(11) Fieser, "Experiments in Organic Chemistry," D. C. Heath & Co., New York, N. Y., 2nd Ed., 1941, p. 369.

(10 g., 20 mesh) for twenty minutes. The filtered solution was diluted with water (300 cc.) and cooled. The white needles (1.5 g., 72.5%) were removed and crystallized from alcohol; the substance then melted at 200–201° with decomposition. **B.** From the carbethoxyisocoumaranone VII: A solution of VII (0.5 g.) in acetic acid (30 cc., 60%) was refluxed for fifteen minutes. The solution was diluted with water and the product (0.33 g., 84.6%) was isolated as described above. It melted at 198–201° with decomposition. **C.** From the diacetate IX: A solution of IX (0.5 g.) in a mixture of acetic acid (10 cc.) and hydrochloric acid (10 cc.), was refluxed for fifteen minutes. The product (0.17 g.), isolated as described above, melted at 199–201° with decomposition. Mixtures of VIII prepared by these three methods showed no depression in m. p.

Anal. Calcd. for $C_{10}H_9O_3Br$: C, 46.72; H, 3.53. Found: C, 46.80; H, 3.62.

The **acetate X** was prepared by acetylation of VIII in acetic anhydride by the procedure described above, or by refluxing the carbethoxyisocoumaranone IX in acetic acid for twenty minutes. The yield by the second method was 93.8%. The acetate X melted at 166–168° after crystallization from petroleum ether (b. p. 77–115°).

Anal. Calcd. for $C_{12}H_{11}O_4Br$: C, 48.18; H, 3.71. Found: C, 48.47; H, 3.77.

3-Carbethoxy-6-bromo-4,7-dimethyl-5-methoxyisocoumaranone (XI) and 3-Carboxy-6-bromo-4,7-dimethyl-2,5-dimethoxycoumarone (XII).—A. From the hydroquinone V: A well-stirred solution of V (5 g.) in a mixture of methanol (50 cc.) and methyl sulfate (35 cc.) was heated to the boiling point. The source of heat was removed, and a solution of potassium hydroxide (35 g.) in methanol (150 cc.) was added as rapidly as the vigorous reaction permitted. The red mixture was refluxed for thirty minutes, then was cooled, diluted with water (300 cc.), acidified with hydrochloric acid, and thoroughly extracted with ether. The ether solution was washed with water, dried (sodium sulfate), and evaporated. The residual orange oil was dissolved in ethanol (300 cc.) and cooled. The solution deposited 1.9 g. of colorless needles melting at 85–87°. This material was warmed with petroleum ether (30 cc., b. p. 60–68°) and the small amount of insoluble material (0.08 g., m. p. 200–205°) was removed. The cooled filtrate deposited a solid which was removed and crystallized repeatedly and successively from ethanol and petroleum ether (b. p. 60–68°). The product, XI, then melted at 96–97°. It was insoluble in aqueous sodium carbonate or potassium hydroxide.

Anal. Calcd. for $C_{14}H_{15}O_5Br$: C, 49.00; H, 4.41. Found: C, 49.10, 49.07; H, 4.42, 4.68.

The high-melting material, insoluble in petroleum ether, was XII. It was recrystallized twice from acetone, when it melted at 210–211° (bath pre-heated to 200°) with decomposition. This substance was soluble in aqueous sodium carbonate.

Anal. Calcd. for $C_{12}H_{13}O_5Br$: C, 47.43; H, 3.98. Found: C, 47.40; H, 3.93.

B. From the carbethoxyisocoumaranone VII: A well-stirred solution of VII (5.25 g.) in a mixture of methanol (50 cc.) and methyl sulfate (35 cc.) was subjected as described above to the action of sodium hydroxide (35 g.) in methanol (200 cc.). The mixture, processed as described above, gave a residual orange oil which, when dissolved in ethanol (40 cc.) and cooled, yielded 2.77 g. (50.8%) of material that melted at 91–93.5°. About 10 mg. of the high-melting XII was removed by treatment with petroleum ether; the remainder of the material was XI.

6-Bromo-4,7-dimethyl-5-methoxyisocoumaranone (XIII).—A. From the methoxycarbethoxyisocoumaranone XI: A solution of XI (0.5 g.) in aqueous acetic acid (15 cc., 70%) was refluxed for fifteen minutes. The mixture was diluted with water (100 cc.) and the solid (0.36 g., 91%) was removed, dried, and crystallized from petroleum ether (b. p. 60–68°). This substance (XIII) formed needles which melted at 165–166°; the material was insoluble in aqueous carbonate. **B.** From the coumarone XII: The coumarone XII (10 mg.) in acetic acid (2 cc., 80%) was subjected to the same treatment as that just described. The product XIII melted at 165–166°, alone or when mixed with XIII prepared from XI.

Anal. Calcd. for $C_{11}H_{11}O_3Br$: C, 48.73; H, 4.09; Br, 29.48. Found: C, 48.99; H, 4.04; Br, 29.91.

The methoxyisocoumaranone XIII (0.15 g.) was dissolved in alcoholic potassium hydroxide (10 cc., 20%), water (3 cc.) was added, and the solution was refluxed for two hours. The cooled solution, when acidified with dilute hydrochloric acid, slowly deposited unchanged XIII.

4-Bromo-3,6-dimethoxy-2,5-dimethylphenylacetic Acid (XIV).—A. From the hydroxyisocoumaranone VIII: A solution of potassium hydroxide (10 g.) in methanol (60 cc.) was added, as rapidly as possible, to a well-stirred, warm solution of VIII (0.75 g.) in a mixture of methanol (20 cc.) and methyl sulfate (10 cc.). The mixture was refluxed for one hour, then was diluted with water (300 cc.) and acidified with hydrochloric acid. The white solid (m. p. 156–157°, 0.76 g., 81.7%) was removed and crystallized four times from petroleum ether (b. p. 77–115°). The acid XIV then melted at 158–159°. **B.** From the methoxyisocoumaranone XIII: A solution of XIII (0.3 g.) in methanol (10 cc.) and methyl sulfate (6 cc.) was subjected to the action of potassium hydroxide (6 g.) in methanol (60 cc.) as described under A. The product XIV (0.21 g., 62.7%) melted at 157–158.5° after crystallization from petroleum ether.

Anal. Calcd. for $C_{12}H_{15}O_4Br$: C, 47.54; H, 4.99. Found: C, 47.81; H, 4.90.

***p*-Xylohydroquinone Dimethyl Ether.**—A mixture of the hydroquinone (11.4 g.), methyl sulfate (45 cc.), and methanol (60 cc.) was heated to the boiling point and potassium hydroxide (45 g.) in methanol (300 cc.) was added as rapidly as possible. The mixture was refluxed for one hour, and then was steam distilled. The white solid in the distillate was removed; it weighed 13.2 g. (96.4%) and melted at 107–108°.[12]

3,6-Dimethoxy-2,5-dimethylbromobenzene (XV).—A solution of the hydroquinone dimethyl ether (6.9 g.) in acetic acid (125 cc.) was stirred and brominated by dropwise addition of bromine (2.3 cc.). The solution was stirred at room temperature for three hours, then was poured into water and extracted with ether. The extract

(12) Noelting and Werner, *Ber.*, **23**, 3246 (1890), give the m. p. as 108°.

was washed with water, dried (sodium sulfate), and the solvent was removed. The residual red oil was dissolved in ethanol (200 cc.) and the solution was passed through a two-foot chromatograph tube packed with a 1:1 mixture of Norite A and Hyflo. The colorless filtrate was concentrated to a volume of 75 cc. by distillation and then diluted with water (50 cc.) and cooled. The solid (7.73 g., 75.8%) melted at 52–54°; after three recrystallizations from ethanol, it melted at 57–59°.

Anal. Calcd. for $C_{10}H_{13}O_2Br$: C, 49.00; H, 5.35. Found: C, 48.80; H, 5.43.

3,6-Dimethoxy-4-bromo-2,5-dimethylbenzyl Chloride (XVI).—The bromo compound XV (5 g.) was dissolved in a mixture of acetic acid (50 cc.), hydrochloric acid (50 cc.), and formalin (20 cc., 40%). This solution was stirred and maintained at 60–70° for four hours while a rapid stream of hydrogen chloride was passed into it. The mixture of liquid and white solid was poured into water (500 cc.) and the solid was removed and crystallized twice from aqueous ethanol (85%). The product weighed 4.65 g. (77.8%) and formed feathery needles which melted at 94–95°.

Anal. Calcd. for $C_{11}H_{14}O_2BrCl$: C, 45.00; H, 4.81. Found: C, 45.07; H, 4.98.

3,6-Dimethoxy-4-bromo-2,5-dimethylbenzyl Cyanide (XVII).—A solution of the chloride XVI (2.5 g.) in ethanol (100 cc.) was added dropwise and with stirring to a warm (steam bath) solution of potassium cyanide (1.5 g.) in water (5 cc.). The mixture was refluxed for five hours, then about half the ethanol was removed by distillation and the residue was poured into water (400 cc.). The solid was removed and crystallized from petroleum ether (b. p. 60–68°). It then weighed 1.85 g. (77.8%) and melted at 114–115°. Another crystallization gave a product which melted at 115–116°.

Anal. Calcd. for $C_{12}H_{14}O_2NBr$: C, 50.72; H, 4.97. Found: C, 50.97; H, 5.07.

This cyanide XVII (0.5 g.) was dissolved in a mixture of acetic acid (10 cc.), sulfuric acid (8 cc.), and water (10 cc.), and the solution was refluxed for one and one-half hours. Water (300 cc.) was added and the solution was extracted with ether. The ether solution was washed with water and then extracted with two 40-cc. portions of aqueous sodium carbonate (10%). The combined carbonate solutions were acidified with hydrochloric acid, and the precipitate was removed, dried, and crystallized from petroleum ether (b. p. 77–115°). The product (0.38 g., 71%) was the phenylacetic acid XIV, which melted at 158–159° alone or when mixed with XIV prepared by methylation of VIII or of XIII.

2,5-Bis-(dicarbethoxymethyl)-3,6-dimethyl-*p*-benzoquinone (XVIII).—To a boiling solution of sodiomalonic ester (from 10 cc. of malonic ester and 0.92 g. of sodium) in pure dioxane (50 cc.), there was added, dropwise and with stirring, a solution of the quinone malonic ester IV (5 g.) in pure dioxane (80 cc.). The reaction mixture was refluxed for an hour, during which it became dark brown and deposited a dark precipitate of a sodium compound. The mixture was cooled and the solid was removed by filtration and washed with a little dioxane. The solid and the filtrate were separately decomposed with hydrochloric acid. From the filtrate, nothing but a viscous red oil was obtained. The acidified solid was extracted with ether, the ethereal solution was washed with water and dried (sodium sulfate), and the solvent was evaporated. The residual red oil was dissolved in hot petroleum ether (150 cc., b. p. 60–68°) and the solution was boiled with a little charcoal and filtered. The clear yellow filtrate was concentrated by distillation to a volume of 20 cc. and cooled. The yellow quinone diacid XVIII (0.95 g., 15.7%) was removed and crystallized from ethanol. It melted at 74–76°.

Anal. Calcd. for $C_{22}H_{28}O_{10}$: C, 58.41; H, 6.24. Found: C, 58.60; H, 6.40.

No XVIII could be obtained directly, at room temperature, from dibromo-*p*-xyloquinone and sodiomalonic ester even when four equivalents of the latter and a reaction time of eighteen hours were used. Nor could any XVIII be obtained from IV unless the reaction mixture was heated—only unchanged IV was obtained in the cold. When only two equivalents of sodiomalonic ester per equivalent of IV was used, the yield of XVIII was but 6–7%.

2,5-Bis-(dicarbethoxymethyl)-3,6-dimethylbenzohydroquinone (XIX).—The quinone XVIII (0.75 g.) was dissolved in ether (30 cc.) and shaken with two portions of saturated aqueous sodium hydrosulfite. The colorless ether solution was washed with water, dried (sodium sulfate), concentrated to a volume of 10 cc., and diluted with petroleum ether (50 cc., b. p. 28–38°). The cooled mixture deposited 0.6 g. (80%) of a white solid which melted at 151–154° after repeated crystallization from methanol.

Anal. Calcd. for $C_{22}H_{30}O_{10}$: C, 58.14; H, 6.65. Found: C, 58.14; H, 6.78.

2,6-Diketo-4,8-dimethyl-3,7-dicarbethoxybenzo-(1,2-b,-4,5-b')-tetrahydrodifuran (XX).[13]—The hydroquinone XIX (0.3 g.) was dissolved in chloroform (15 cc.) and shaken with sulfuric acid (30 cc., 75%). The chloroform solution was washed with water, dried (sodium sulfate), and evaporated. The residual solid, after crystallization from ethanol, weighed 0.15 g. (62.5%) and melted at 128–130°. After this was recrystallized from petroleum ether (b. p. 60–68°), it melted at 129–131°.

Anal. Calcd. for $C_{18}H_{18}O_8$: C, 59.66; H, 5.01. Found: C, 59.65; H, 5.08.

2,6-Diketo-4,8-dimethylbenzo-(1,2-b,4,5-b')-tetrahydrodifuran (XXI).[13]—**A.** From the difuran XX: A solution of XX (25 mg.) in aqueous acetic acid (5 cc., 80%) was refluxed for twenty minutes. The cooled solution deposited 14 mg. (92.7%) of white XXI which decomposed at 337–340°. **B.** From the quinone XVIII: A solution of XVIII (0.75 g.) in aqueous acetic acid (25 cc., 70%) was refluxed with zinc (5 g., 20-mesh) for thirty minutes. The mixture was filtered; the cooled filtrate deposited 0.33 g. (91.7%) of a grayish-white material which decomposed at 330°. After repeated crystallization from acetic acid, the product formed needles which decomposed at 335–337°.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.14; H, 4.85.

3,6-Dimethoxy-2,5-dimethyl-1,4-di-(carboxymethyl)-benzene (XXII).—The difuran XXI (0.2 g.) was dissolved in a mixture of methanol (10 cc.) and methyl sulfate (10

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cc.). The solution was heated to the boiling point, and to it was added, quickly and with stirring, a solution of potassium hydroxide (10 g.) in methanol (45 cc.). The mixture was refluxed for thirty minutes, then was diluted with water (200 cc.), acidified with hydrochloric acid, and extracted with ether. The ether solution was extracted with aqueous sodium carbonate and the carbonate extract was acidified with hydrochloric acid and cooled. The precipitate was removed and crystallized from acetic acid. The product weighed 0.09 g. (34.6%) and melted with decomposition at 265–270°. A further crystallization from acetic acid gave a product which melted with decomposition at 267–271°.

Anal. Calcd. for $C_{14}H_{18}O_6$: C, 59.56; H, 6.43. Found: C, 59.38; H, 6.29.

3,6-Dimethoxy-2,5-dimethyl-1,4-di-(chloromethyl)-benzene; 3,6-Dimethoxy-α^1,α^4-dichlorodurene (XXIII, R = CH_2Cl).—*p*-Xylohydroquinone dimethyl ether (11.0 g.) and paraformaldehyde (15 g.) were suspended in hydrochloric acid (150 cc.), and a rapid stream of hydrogen chloride was passed through the well-stirred mixture for four hours. The mixture was then stirred at room temperature for five hours, after which it was allowed to stand overnight. The mixture was poured into water (1000 cc.), and the white solid was removed and crystallized from ethanol. It weighed 15.5 g. (89%) and melted at 164–166°. This product, after further crystallization successively from petroleum ether (b. p. 77–115°) and from ethanol, melted at 165.5–166°.

Anal. Calcd. for $C_{12}H_{16}O_2Cl_2$: C, 54.76; H, 6.13. Found: C, 54.94; H, 5.98.

3,6-Dimethoxy-2,5-dimethyl-1,4-di-(cyanomethyl)-benzene; 3,6-Dimethoxy-α^1,α^4-dicyanodurene (XXIII, R = CH_2CN).—A hot solution of the above dichloro compound (5 g.) in a mixture of ethanol and acetone (300 cc., 1:3) was added dropwise to a stirred and warmed (steam-bath) solution of potassium cyanide (6 g.) in water (20 cc.). The mixture was refluxed for six hours and then poured into water (1000 cc.). The white solid was removed and crystallized from ethanol (400 cc.). It then weighed 4.2 g. (91.3%) and melted at 205–206°. A second crystallization from ethanol gave material which melted at 207–207.5°.

Anal. Calcd. for $C_{14}H_{16}O_2N_2$: C, 68.83; H, 6.60. Found: C, 69.13; H, 6.41.

A solution of this dicyanide (2.0 g.) in a mixture of acetic acid (50 cc.), sulfuric acid (25 cc.), and water (25 cc.) was refluxed for three hours and then diluted with water (400 cc.). The cooled mixture deposited a white solid which was removed and dissolved in ether. The ethereal solution was extracted with aqueous sodium carbonate (100 cc., 10%) and the alkaline extract was acidified with hydrochloric acid and cooled. The solid (XXII) was removed and crystallized twice from acetic acid. The product (0.8 g., 35%) melted with decomposition at 270–271°, alone or when mixed with a specimen of XXII prepared by methylation of XXVI.

***p*-Xyloquinone and Sodiomalonic Ester.**—A cooled solution of sodiomalonic ester (from malonic ester, 30 g., 0.19 mole, and sodium, 3.45 g., 0.15 gram atom) in dry, peroxide-free dioxane (75 cc.) was added dropwise and with stirring to a solution of the quinone (5 g., 0.037 mole) in the same solvent (100 cc.). The mixture immediately became deep purple, and while it was stirred (twenty hours) at room temperature, the color gradually changed to brown and a solid (disodium derivative of XX) separated. The solid was removed, washed with a small amount of dioxane and added to dilute hydrochloric acid. The resulting solution was extracted with ether and the extract was washed with water and dried (sodium sulfate). The solvent was removed and the residual solid was crystallized from alcohol. It then weighed 0.5 g. (3.8%) and melted at 125–128°; after crystallization again from alcohol, it melted at 128–131°, alone or when mixed with a specimen of XX prepared from dibromo-*p*-xyloquinone. When this substance (0.1 g.) was refluxed for ten minutes in acetic acid (10 cc., 80%), it was converted into XXI, m. p. 325–335°.

4,7-Dimethyl-5-hydroxyisocoumaranone (VIIIA).—The filtrate and washings obtained when the above disodium derivative was removed were acidified with dilute hydrochloric acid, diluted with water (300 cc.), and extracted with ether. The extract was washed with water, dried (sodium sulfate), and the solvent was removed. The residual material (VIIA) was contaminated with a red oil and was very difficult to purify by crystallization. The mixture was subjected to distillation with steam; this process removed excess malonic ester and simultaneously hydrolyzed and decarboxylated VIIA to VIIIA, which remained in the distillation flask as a solid. It was removed and crystallized from alcohol; it weighed 2.7 g. (41.5%) and melted at 214–216°.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.40; H, 5.66. Found: C, 67.66; H, 5.86.

Summary

1. Dibromo-*p*-xyloquinone and sodiomalonic ester react in dioxane at room temperature to give a substitution product, 5-bromo-2-dicarbethoxymethyl-3,6-dimethyl-*p*-benzoquinone IV. When a large excess of sodiomalonic ester is used under forcing conditions, both bromine atoms of the quinone are replaced by malonic ester groups, and the product is the bis derivative XVIII.

2. The reaction is confined entirely to the bromine atoms; no trace was found of a coumarin formed by attack of the reagent upon a methyl group of the quinone. The behavior of this quinone toward sodiomalonic ester thus parallels that of dibromo-*o*-xyloquinone, but is in contrast with the behavior of dibromo-*m*-xyloquinone, in which the bromine atoms are inert and the only attack of sodiomalonic ester is at a methyl group to give a coumarin.

3. The hydroquinones V and XIX, corresponding, respectively, to the mono- and di-substitution products IV and XVIII, have been transformed into various heterocyclic derivatives, and the products obtained by methylation of some of

these derivatives have been studied. One of the degradation products of IV, namely, 3,6-dimethoxy-4-bromo-2,5-dimethylphenylacetic acid XIV, and one of the degradation products of XVIII, namely, the bis-acetic acid XXII, have been synthesized by independent methods starting with *p*-xylohydroquinone.

4. When *p*-xyloquinone reacts with sodiomalonic ester, the chief product is the cyclic isocoumaranone VIIA; this is accompanied by a small amount of the double isocoumaranone XX. These products are derived from *hydroquinones*, which are the primary products of the reaction; when the bromoquinone reacts with the enolate, the primary products are *quinones*.

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[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

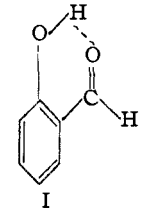
The Polymerization of the Free Radicals of the Wurster Dye Type: the Dimeric Resonance Bond

BY L. MICHAELIS AND S. GRANICK

1. Introduction: the α- and β-Forms of Wurster Dyes

The univalent oxidation products of aromatic paradiamines, or Wurster dyes, exist in dilute solution as free radicals and have been, as such, exhaustively discussed in a preceding paper.[1] In solutions of higher concentration, or at low temperature, and also in the crystalline state, most of them form polymers which differ in color from the free radical. The free radicals represent what Piccard[2] had designated as the α-forms, the polymerized compounds are Piccard's β-forms. Whereas the radicals all show two distinct absorption bands in the visible spectrum, separated by about 300 Å., in various regions of the spectrum according to the degree of methylation of the amino groups, the β-forms are all deep green-blue in the crystalline state, macroscopically almost black; microscopically, observed through a polarizer, dichroitic, usually blue and yellow. Whether or not a radical polymerizes under proper conditions of concentration, temperature, or in the solid state, is easy to recognize by the difference in color whenever the radical is yellow or red, but this is practically impossible when the radical is blue, as in the tetramethyl compound. Piccard came to the conclusion that the unmethylated, the monomethyl, and the dimethyl compounds in the crystalline state are entirely in the β-form, the trimethyl and the tetramethyl compounds in the crystalline state are α-forms (which we can confirm only for the tetramethyl compound). Magnetic measurements for the crystalline state by Katz,[3] and Katz and Kuhn,[4] and furthermore by Rumpf and Trombe,[5] revealed that the crystalline form of the dimethyl compound (Wurster's red) is diamagnetic and consequently a polymer, whereas the crystalline form of the tetramethyl compound (Wurster's blue) is paramagnetic, and so a free radical.

No structural formula has been proposed as yet for the polymers. A closer investigation into the matter has shown that this process of polymerization of free radicals discloses a type of chemical bond which depends on a special type of resonance, combined with a kind of hydrogen bond. In general, a hydrogen bond is established by a shared proton. In addition, it has been recognized that a hydrogen bond may cause a resonance in a conjugated bond structure so that, in addition to the shared proton, a pair of electrons is shared. For instance, in salicylic aldehyde, a resonance will be established with the limiting structures I and



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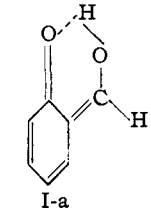

I-a

I-a. This scheme does not take into consideration that structure I is also in resonance with another structure in which the Kekulé structure of the ring is reversed, whereas in I-a no such reversal is possible. Very likely, the resonance of the two

(1) L. Michaelis, M. P. Schubert and S. Granick, THIS JOURNAL, **61**, 1981 (1939).

(2) (a) J. Piccard, *Ann.*, **381**, 351 (1916); (b) J. Piccard, *Ber.*, **59**, 1438 (1926).

(3) H. Katz, *Z. Physik*, **87**, 238 (1933).

(4) R. Kuhn and H. Katz, *Z. angew. Chem.*, **46**, 478 (1933).

(5) P. Rumpf and F. Trombe, *J. Chim. Phys.*, **35**, 110 (1938).