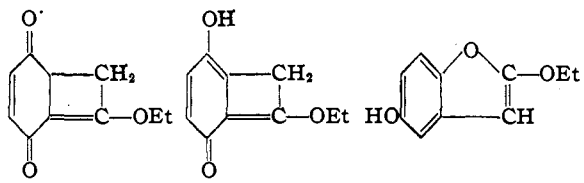
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Ketene Acetals. XIV. The Reactions of Ketene Acetal with Quinones

BY S. M. MCELVAIN AND EDWARD L. ENGELHARDT

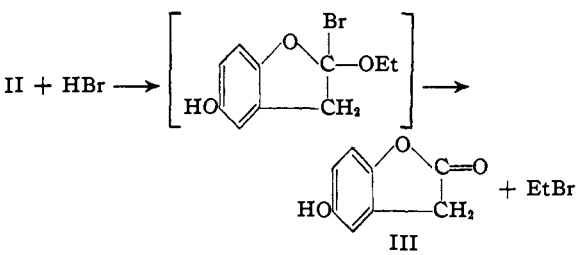
In the eighth paper of this series[1] the reactions between ketene diethylacetal and a variety of α,β-unsaturated carbonyl compounds were reported. One of these unsaturated carbonyl compounds was *p*-benzoquinone which was found to react with ketene acetal readily in refluxing benzene to give a white crystalline product, m. p. 94–95°, that was converted to hydroquinone-acetic (homogentisic) acid by hydrolysis in acid solution. This reaction product had a molecular formula $C_{10}H_{10}O_3$ and the structure I was assigned to it.



I Ia II

This structure (I), which is the vinylog of an ester, was then considered preferable to the isomeric 2-ethoxy-5-hydroxycoumarone (II) because the latter possesses a ketene acetal structure in the five membered ring and this structure seemed incompatible with the fact that the compound did not show any tendency to form a polyorthoester through intermolecular condensation of the phenolic hydroxyl group with the ketene acetal portion of the molecule. Also, from the ease with which ketene acetal reacts with phenol[2] it seemed unlikely that the phenol II would be isolated from a reaction mixture in which an excess of ketene acetal was present. However, a study of the reactions of ketene acetal with other quinones, which is the subject of the present report, has led to the conclusion that the structure I which was assigned to the product obtained from benzoquinone is incorrect. For example, it seemed highly improbable, in view of the failure of dimethylmaleic anhydride to react with ketene acetal,[1] that such a quinone as *m*-xyloquinone, which is now found to yield a product analogous to that obtained from benzoquinone and ketene acetal, could form a compound with the four-membered ring structure of I. This dimethylquinone, however, could form the enol ether (VI) analogous to II. Consequently, it was necessary to re-examine the product obtained from benzoquinone to establish its structure with certainty.

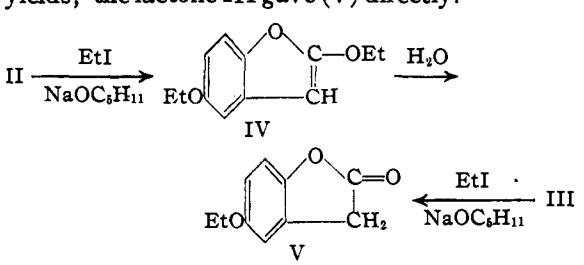
This compound is now found to contain one hydroxyl group as shown by the formation of a monoacetate with acetic anhydride and by its reaction in the Grignard machine. However, it is not inconceivable that the enolic form (Ia) of I would be responsible for these reactions. But the compound does not *add* the Grignard reagent, and this is evidence in favor of structure II since structures I and Ia, as vinylogs of esters, would be expected to add this reagent. Good evidence for structure II is found in the reaction of the compound with dry hydrogen bromide in dioxane. This reagent converts the compound into 5-hydroxycoumaranone-2[2a] (homogentisic lactone, III) and ethyl bromide in the same manner that other ketene acetals are converted into the corresponding esters and ethyl bromide.



III

It should be noted, however, that about ten hours are required to complete the reaction with the ethoxycoumarone II, whereas the simple ketene acetals react instantaneously with this reagent.

The coumarone II was finally shown to be the correct structure for the compound obtained from the reaction between benzoquinone and ketene acetal by its conversion into 5-ethoxycoumaranone (V). While neither II nor the lactone III could be directly ethylated by either ketene acetal or diazoethane, the sodium salts of II and III in isoamyl alcohol were successfully alkylated with ethyl iodide. The coumarone II gave V after hydrolysis of the oily intermediate (IV) in 28% yields; the lactone III gave (V) directly.



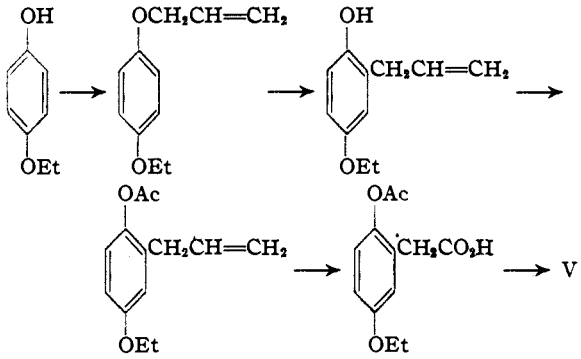
IV V

5-Ethoxycoumaranone (V) was also prepared from 4-ethoxyphenol through the sequence of reactions

(1) McElvain and Cohen, THIS JOURNAL, **64**, 260 (1942).

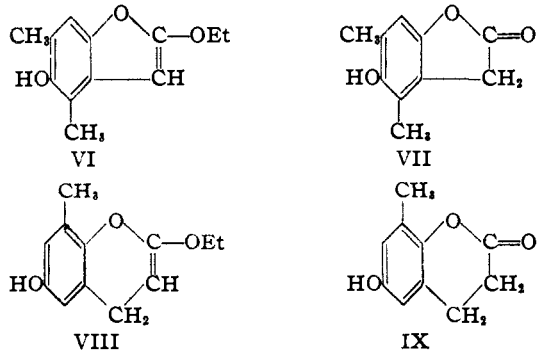
(2) Barnes, Knudiger and McElvain, *ibid.*, **62**, 1281 (1940).

(2a) The lactones of the *o*-hydroxyphenylacetic acids described in this paper are named as keto derivatives (coumaranones) of coumaran 2,3-dihydro-benzo[b]furan (no. 841 in "The Ring Index," Patterson and Capell, A. C. S. Monograph Series, no. 84). Thus the lactone III is a coumaranone-2. Traditionally this structure has been designated as an isocoumaranone, but the term isocoumaran is assigned to the 1,3-dihydro form of benzo[c]furan (no. 843) by "The Ring Index."

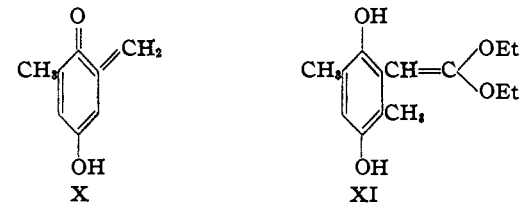


It is apparent that structure Ia could not give the coumaranone V. The fact that this ethoxylactone is obtained from the above three starting materials establishes the structure II for the product of the condensation of ketene acetal with benzoquinone.

m-Xyloquinone reacts much more slowly with ketene acetal than does benzoquinone. A temperature of 150° is necessary to cause reaction and under these conditions the reaction product is a viscous black tar from which a white crystalline compound $C_{12}H_{14}O_3$, m. p. 100–101°, was isolated in 7% yields. These more drastic conditions—benzoquinone condenses with ketene acetal in boiling benzene—are the probable cause of the high yield of polymeric material and the low yield of the desired product from *m*-xyloquinone. This product was shown to be 2-ethoxy-5-hydroxy-4,6-dimethylcoumarone (VI) by reactions analogous to those applied to II. The isomeric 2-ethoxy-6-hydroxy-8-methyl-chromene-2 (VIII), which conceivably might have been formed from the addition of ketene acetal to the methylene-quinoid form of *m*-xyloquinone (X), was eliminated as a possible structure of the reaction product by comparison of the lactones VII and IX,[3] the hydrolysis products of VI and VIII.



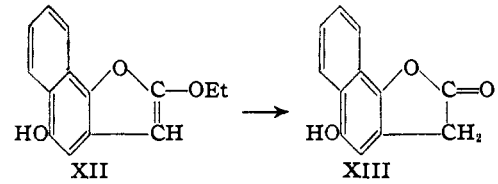
The reaction between *p*-xyloquinone and ketene acetal requires the same drastic conditions that were necessary for the reaction with *m*-xyloquinone. However, the only product that could be obtained from the reaction tar was a small amount of *p*-xylohydroquinone. This hydroquinone may come from the reduction of some unreacted *p*-xyloquinone by the intermediate hydroquinone-ketene acetal XI, before this latter compound loses alcohol to form a coumarone. The large amounts of tar formed in this and the *m*-xyloquinone reaction may be due to the polymerization of intermediates corresponding to XI.



The coumarones II and VI are hydrolyzed in neutral 75% alcohol to the ethyl esters of the corresponding hydroquinone-acetic acids. Hydrolysis in dilute aqueous acid solution converts II and VI to the lactones III and VII.

Duroquinone does not react with ketene acetal under the conditions that produce complete reaction with *m* and *p*-xyloquinone. The fact that most of the duroquinone is recovered unchanged is a further indication that methylene-quinoid forms such as X either are not present under the conditions of this reaction or are not effective reactants.

1,4-Naphthoquinone, in contrast to the xyloquinones, reacts with ketene acetal at 90°. But like the xyloquinone reactions the main product is a tar from which only a small (2%) yield of 2-ethoxy-5-hydroxy-6,7-benzocoumarone (XII) could be obtained. In contrast to the corresponding coumarones II and VI, XII yields the lactone XIII directly on hydrolysis in neutral 75% alcohol.



Bromo-quinones have reactive cationoid centers at the carbon holding the bromine substituent as well as at the unsubstituted positions in the ring. Since ketene acetal has been shown to react with active halogen compounds, RX (R is benzyl, acetyl, and benzoyl), to give substituted acetic esters, RCH_2COOEt and the ethyl halide,[4] it seemed of interest to determine the manner of reaction of ketene acetal with some representative bromoquinones.

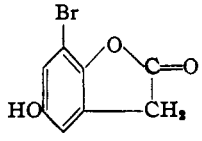
Ketene acetal reacts readily in refluxing benzene at one of the unsubstituted carbons of bromobenzoquinone to yield a bromocoumarone. This coumarone was not isolated, but the corresponding coumaranone was obtained in 27% yields by hydrolyzing the crude reaction mixture in 75%

(3) The lactone IX has been described by Smith and Byers, THIS JOURNAL, **63**, 612 (1941), as melting at 149–150°. The lactone VII melts at 143–144°; a mixture of VII and IX melted at 108–112°.

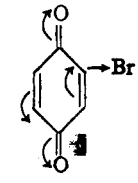
(4) McElvain and Kundiger, *ibid.*, **64**, 254 (1942).

alcohol. The ethyl bromide produced during this reaction amounted to 10% of the theoretical, but no quinone resulting from the replacement of bromine could be isolated. The bromocoumaranone isolated from this reaction is believed to have the structure XIV. The polarization of 2-bromobenzoquinone shown in XV indicates that the most reactive unsubstituted cationoid center should be at the 6-position, since the inductive effect of the 2-bromo substituent causes the 4-carbonyl to concentrate the catio-enoid polarization it produces at this 6-position while the effect of the 1-carbonyl is distributed between the 3- and 5-positions. The attack of the anionoid ketene acetal at the 6-position of XV would produce XIV. Smith and Johnson[5] have shown that the bromine of 2-bromo-3,5,6-trimethylbenzoquinone (bromopseudocumoquinone, XVI) has a similar effect and causes the exclusive reaction of the 6-methyl group with sodio-malonic ester.

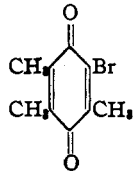
In an effort to determine the position of the bromine in the coumaranone XIV it was converted to the corresponding dimethyl ether of the bromohomogentisic acid (XVII), but all attempts to oxidize this acid to a dimethoxybromobenzoic acid were unsuccessful.



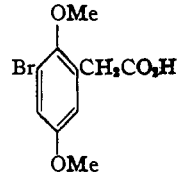
XIV



XV



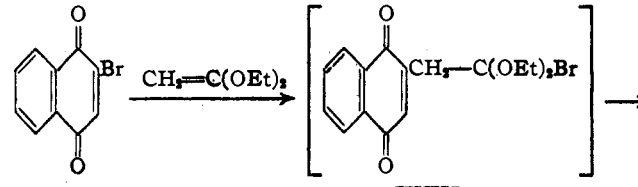
XVI



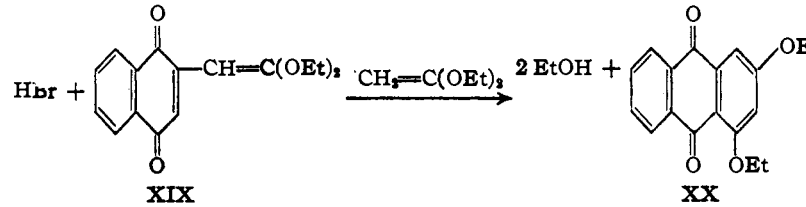
XVII

2,5-Dibromobenzoquinone also reacts at an unsubstituted carbon with ketene acetal in refluxing benzene to form a coumarone. This product was not isolated but hydrolyzed in 75% alcohol to ethyl 2,5-dibromo-3,6-dihydroxyphenylacetate which was obtained in 40% yields. The more reactive 2,6-dibromobenzoquinone reacts readily with the acetal in ether solution at room temperature, but the reaction product was a tar from which no definite product could be isolated. However, no ethyl bromide was formed during this reaction showing that neither of the bromine substituents was replaced.

2-Bromonaphthoquinone requires a temperature of 125° in the absence of a solvent to react with ketene acetal. Ethyl bromide was evolved and from the reaction mixture xanthopurpurin diethyl ether (XX) was isolated in 21% yields. In this reaction the carbon holding the bromine substituent is the point of attack. The primary addition product (XVIII) presumably loses hydrogen bromide (*cf.* the formation of disubstituted acetic esters from ketene acetal and benzyl bromide[4]) to form the quinoneketene acetal (XIX) which then condenses with another molecule of ketene acetal and cyclizes with the loss of two molecules of alcohol to yield XX.

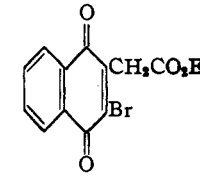


XVIII



XIX XX

2,3-Dibromonaphthoquinone, which has no unsubstituted cationoid center, reacts with ketene acetal in refluxing benzene to give ethyl 3-bromo-1,4-naphthoquinon-2-ylacetate (XXI) in 58% yields.



XXI

2-Bromo-3-methyl-1,4-naphthoquinone requires a temperature of 125° to react with ketene acetal. About one-fourth of the theoretical amount of ethyl bromide was evolved over a period of 24 hours, but it was not possible to isolate any crystalline product from the reaction tar either by distillation or hydrolysis.

From the results described above it is apparent that the reactivities of quinones with ketene acetal as well as the nature of the reaction products are greatly influenced by substituents in the quinone molecules. Methyl substituents appear to lower the cationoid reactivity of a quinone to the point where the conditions that are necessary to produce reaction also cause quite complete polymerization of the initial condensation product.

(5) Smith and Johnson, THIS JOURNAL, **59**, 673 (1937).

The benzo substituent of 1,4-naphthoquinone has a similar effect. The fact that the completely methylated duroquinone remains unchanged in the presence of ketene acetal shows that this reagent attacks only the cationoid ring carbons of a quinone.

Bromo-substituents activate the quinone for reaction with ketene acetal and in most cases the necessary conditions are sufficiently mild that fair yields of condensation products may be isolated from these reactions. Bromobenzoquinones react preferentially at an *unsubstituted* cationoid carbon while the bromonaphthoquinones react at the carbon carrying the bromine substituent even when an unsubstituted carbon is exposed (*cf.* 2-bromo-1,4-naphthoquinone). The higher reactivities of the bromoquinones as compared to the methyl substituted quinones is undoubtedly due to the higher polarizations of the quinone molecules that are induced by the bromine substituents in contrast to the neutralizing actions of the opposite inductive effects of the methyl groups.

Some unsuccessful attempts were made to determine the course of the reaction between ketene acetal and ortho quinones. These highly reactive compounds yielded tars from which no definite compound could be isolated. 1,2-Benzoquinone reacts in ether solution at room temperature. On partial evaporation of the ether a white solid was obtained which did not have a melting point. Hydrolysis of the reaction product in the presence of sulfur dioxide gave a small quantity of catechol and an intractable tar. 1,2-Naphthoquinone also reacts in ether at room temperature, but in this case also it was not possible to isolate any definite reaction product.

The authors are indebted to Professor Lee I. Smith of the University of Minnesota for a sample of 6-hydroxy-8-methyl-3,4-dihydrocoumarin (IX) for comparison with the lactone VII; and also for a generous supply of duroquinone for a study of its reaction with ketene acetal.

Experimental

Preparation of Starting Materials.—*m*-Xyloquinone and *p*-xyloquinone were prepared from 3,5-dimethylphenol and 2,5-dimethylphenol, respectively, by the method of Smith, *et al.*,[6] with the following modifications which were suggested by Professor L. I. Smith in a private communication:

(1) The coupling reaction mixture was allowed to stand for twenty-four hours; (2) sodium hydrosulfite was used to reduce the azo compound instead of stannous chloride; (3) ferric sulfate was used to oxidize the aminophenol in the case of the *p*-isomer; potassium dichromate had to be used for the *m*-isomer.

Bromobenzoquinone was prepared by the following modification of the method of Sarauw.[7] Benzoquinone (66 g.) was dissolved in 3 kg. of chloroform and dry hydrogen bromide passed in until the black precipitate of the quinhydrone became white. The precipitate, consisting of a mixture of bromohydroquinone and 2,5-dibromohydroquinone was dried in air, then oxidized by stirring for 12 hours at room temperature with a solution of 36.6 g. of potassium bromate and 30 ml. of 1 *N* sulfuric acid in 1200 ml. of water. The mixture then was cooled to 0° and the precipitate filtered and dried. The dry quinone, which contains about 10% of the dibromoquinone,[7] was distilled in a 125-ml. von Braun flask at 20 mm. The distillate which still contained considerable 2,5-dibromobenzoquinone was placed in a glass funnel, the stem of which held a loose plug of glass wool, and was surrounded by a water-bath held at 57–60°. The filtrate was recrystallized from petroleum ether (40–60°) and yielded 25.1 g. of bromobenzoquinone, m. p. 52–55°. Another recrystallization gave 19.2 g. (17%) of pure product, m. p. 54–55°.

2,5-Dibromobenzoquinone was prepared by dissolving bromobenzoquinone in chloroform and passing in dry hydrogen bromide until the precipitate was white. The precipitate (dibromohydroquinone) was filtered off and dried. The 2,5-dibromohydroquinone (51.0 g.) was stirred with a suspension of 0.25 g. of vanadium pentoxide in a solution of 11.6 g. of potassium bromate and 11 ml. of 1 *N* sulfuric acid in 1500 ml. of water for twelve hours at room temperature. The quinone was filtered, washed with 200 ml. of cold water, and dried. The crude product was recrystallized twice from glacial acetic acid and gave 33.0 g. (65%) of pure 2,5-dibromobenzoquinone, m. p. 189–190°.

2-Bromonaphthoquinone was prepared by the following modification of the method of Zincke and Schmidt.[8] Naphthoquinone (10 g.) was dissolved in 200 ml. of glacial acetic acid and the solution cooled to incipient crystallization. The solution was protected from light, and 4.0 ml. of bromine added from a pipet. The mixture was allowed to stand in the dark for four hours, and a stream of carbon dioxide then was passed through for an hour in order to sweep out the excess bromine. Fused sodium acetate (20 g.) was added and the mixture stirred until the salt dissolved. The solution then was allowed to stand for twenty-four hours at room temperature after which time it was poured into 2 liters of cold water. The product was collected and dried. Two vacuum sublimations at 120° and 1 mm. gave 8.44 g. (56%) of product, m. p. 128–130°. Another sublimation raised the melting point to 130–131°.

2,3-Dibromonaphthoquinone was prepared by the following modification of the method of Zincke and Schmidt.[8] Naphthoquinone (5.0 g.) was dissolved in 100 ml. of glacial acetic acid, 20 g. of fused sodium acetate and 4.0 ml. of bromine added, the mixture allowed to stand for 24 hours at room temperature and then poured into 400 ml. of water. The precipitate was collected, dried, and recrystallized twice from glacial acetic acid. The weight of product, m. p. 216–218°, was 6.64 g. (66%).

4-Ethoxyphenol.—Hydroquinone (109 g.) was dissolved in a solution of 59 g. of potassium hydroxide in 400 ml. of 95% ethyl alcohol. The mixture was heated to refluxing, the steam-bath removed, and 135 ml. of diethyl sulfate added through a dropping funnel at a rate that kept the solution boiling gently. The solution was refluxed with stirring for one hour after the addition was complete. The mixture then was transferred to a steam distillation apparatus, and a solution of 45 g. of sodium hydroxide in 400 ml. of water added. The mixture was steam distilled until the volume of the distillate was two liters, in order to remove the hydroquinone diethyl ether. The residue was acidified with dilute sulfuric acid and the steam distillation resumed until the volume of the second portion of distillate was three liters. This distillate was extracted with a mixture of equal parts of ether and petroleum ether, the extract dried over anhydrous calcium sulfate, and the solvent distilled off. The weight of 4-ethoxyphenol, m. p., 66–68°, was 25.8 g. (20.6%). It was used without further purification.

Reactions of 2-Ethoxy-5-hydroxycoumarone (II). A. Hydrolysis in 75% Alcohol.—Instead of isolating the coumarone, the residue from the reaction of 27 g. of benzoquinone with 60 g. of ketene acetal, after removal of the benzene and the ethyl orthoacetate,[1] was dissolved in 200 ml. of 75% alcohol. The solution was evaporated to dry-

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

(7) Sarauw, *Ann.*, **209**, 99 (1881).

(8) Zincke and Schmidt, *Ber.*, **27**, 2758 (1894).

ness on a steam-bath; the residue solidified on cooling. On vacuum sublimation at 115° and 1 mm., 20.9 g. (47%) of ethyl hydroquinone-acetate was obtained which melted at 118–119°. Analytically pure material prepared by recrystallization from chloroform melted at 119–120°. The dibenzoate, prepared by treating a small quantity of the ester with excess benzoyl chloride in pyridine, melted at 128–130°.[9] Ethyl hydroquinone-acetate (3.05 g.) was refluxed for four and one-half hours with 50 ml. of 10% hydrochloric acid. The aqueous acid was distilled off on a steam-bath under reduced presure. Sublimation of the residue at 150° and 1 mm. gave 2.23 g. (95%) of crude **5-hydroxycoumaranone-2**, m. p. 180–185°. Pure material, prepared by recrystallization from water, melted at 189–190°.

B. With Dry Hydrogen Bromide.—2-Ethoxy-5-hydroxycoumarone[1] (II) (0.50 g.) was dissolved in 5 ml. of dry dioxane and 16 ml. of a solution of 0.182 *N* hydrogen bromide in dry dioxane was added. Periodic titrations of 1-ml. aliquots of this solution showed that about ten hours of standing at room temperature was necessary for one equivalent of the acid to disappear. A similar reaction mixture was made up and allowed to stand for twenty-four hours. The solution then was concentrated at 40° under reduced pressure until the volume was 1–2 ml., and the residue taken up in 15 ml. of cold water. The precipitate was filtered off and dried. It weighed 0.33 g. and melted at 185–189°. A recrystallization from water gave 0.28 g. (67%) of product, m. p. 189–191°, which did not depress the melting point of an authentic sample of 5-hydroxycoumaranone (III).

C. With Methylmagnesium Iodide.—The coumarone (II) was treated with a measured excess of methylmagnesium iodide in the Grignard machine by the method of Kohler, Stone and Fuson[10]; 1.12 millimoles of II evolved 1.10 millimoles of methane. There was no significant amount of addition of the Grignard reagent. Under the same conditions, 1.03 millimoles of methyl salicylate evolved 1.01 millimoles of methane, and when water was added to the remaining reaction mixture the methane evolved showed that 1.88 millimoles of the Grignard reagent had added to the ester.

5-Ethoxycoumaranone-2 (V). A. From the Coumarone (II).—To 30 ml. of dry isoamyl alcohol containing 0.009 mole of sodium isoamyl oxide and 2 ml. of ethyl iodide, was added 1.6 g. of 2-ethoxy-5-hydroxycoumarone (II), and the solution refluxed for eight hours. The isoamyl alcohol then was distilled from the dark brown reaction mixture under reduced pressure and the residue extracted with dry benzene. The benzene extract after evaporation on a steam-bath, left a brown oil. This oil was dissolved in a minimum quantity of 80% dioxane, 6 drops of concentrated hydrochloric acid added, and the solution evaporated to dryness on a steam-bath. Sublimation of the residue at 130° and 1 mm. gave crystals that were mixed with a yellow oil. The crystals were pressed dry on filter paper, recrystallized from a mixture of benzene and petroleum ether, and resublimed. The yield of product, m. p. 85–88°, was 0.54 g. Recrystallization from an alcohol–water mixture gave 0.49 g. (28%) of 5-ethoxycoumaranone-2 (V), m. p. 89–90°.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.4; H, 5.66; OC_2H_5, 25.2. Found: C, 67.3; H, 5.71; OC_2H_5, 25.1.

B. From 5-Hydroxycoumaranone (III).—The coumaranone (0.57 g.) was subjected to exactly the same ethylation procedure as the coumarone II in A. The yield of 5-ethoxycoumaranone-2, m. p. 89–90°, was 0.04 g.

C. From 4-Ethoxyphenol.—4-Ethoxyphenol (17.5 g.) was dissolved in 150 ml. of dry acetone, 15.4 g. of allyl bromide and 18.3 g. of anhydrous potassium carbonate were added, and the reaction mixture heated on a steam-bath with mechanical stirring for four hours. The acetone then was evaporated on a steam-bath and the residue extracted with 200 ml. of a mixture of equal parts of ether and petroleum ether (60–68°). The extract was washed with a 10% sodium hydroxide solution, then with water, and dried over anhydrous calcium sulfate. On evaporation of the solvent the residue crystallized. The yield of **hydroquinone allyl ethyl ether**, m. p. 38–39°, was 18.1 g. (80%). An analytical sample prepared by recrystallization from an alcohol–water mixture and sublimation at 110° and atmospheric pressure, melted at 39–40°.

Anal. Calcd. for $C_{11}H_{10}O_2$: C, 74.1; H, 7.91. Found: C, 74.2; H, 7.69.

A mixture 23.0 g. of hydroquinone allyl ethyl ether and 12.5 g. of diethylaniline was heated to refluxing. The temperature of the boiling liquid rose from 205° to 245° over a period of three hours, and remained constant at the latter value. The reaction mixture then was cooled, dissolved in petroleum ether (60–68°) and extracted twice with 10% sulfuric acid to remove the diethylaniline. The phenol then was extracted with 10% sodium hydroxide, the alkaline extract acidified, and extracted with a mixture of equal parts of ether and petroleum ether (60–68°), the extract dried over anhydrous calcium sulfate, and the solvent distilled off. The residue was a brown liquid. It was distilled through a 6 cm. Vigreux column and the material boiling from 184–185° (50 mm.) collected. The yield of **2-allyl-4-ethoxy-phenol**, $n^{24}D$ 1.5379, d^{20}_4 1.057, was 20.6 g. (89.5%).

Anal. Calcd. for $C_{11}H_{10}O_2$: C, 74.1; H, 7.91. Found: C, 73.7; H, 7.72.

A mixture of 20.6 g. of the phenol and 16 g. of acetic anhydride, previously distilled from fused sodium acetate, was heated on a steam-bath for two hours and then, after cooling, dissolved in a mixture of equal parts of ether and petroleum ether (60–68°). The ether solution was washed twice with 10% sodium hydroxide and with water and, after drying over anhydrous calcium sulfate, the solvent was distilled off. The residue, a pale yellow liquid, was distilled through a 6-cm. Vigreux column. The yield of **2-allyl-4-ethoxyphenyl acetate**, boiling at 161–162°, (1.5 mm.) $n^{20}D$, 1.5122, d^{20}_4 1.055, was 22.4 g. (88%). It was colorless but darkened slowly on standing.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.8; H, 7.31. Found: C, 70.6; H, 7.07.

Three grams of the acetate was dissolved in 25 ml. of glacial acetic acid and one equivalent of ozone passed into the solution at room temperature. The solution gave a positive starch–iodide test at the conclusion of the ozonolysis. The solution was diluted with 5 ml. of water and 2.9 g. (two equivalents) of 30% hydrogen peroxide solution added. The mixture, after evaporation on a steam-bath, left a dark brown oily residue. Water was added to the residue and the mixture re-evaporated. No odor of acetic acid was noticeable at the end of the second evaporation. The oily residue was dissolved in 50 ml. of 95% alcohol, treated with a solution of 2.4 g. of sodium ethoxide in 50 ml. of absolute alcohol, and the mixture refluxed for four hours. The alcohol then was distilled off and 50 ml. of water added to the tarry residue. The mixture was saturated with carbon dioxide and extracted with two 50-ml. portions of ether. The water layer was made just acid to congo red with 10% hydrochloric acid and a 2-ml. excess added. Evaporation of the solution gave a gummy black residue which on sublimation at 120° and 1 mm. gave 0.41 g. of crude product, m. p. 81–84°. Recrystallization from an alcohol–water mixture gave 0.35 g. (14.5%) of pure 5-ethoxycoumaranone-2 (V), m. p. 89–90°. This material did not depress the melting point of the coumaranones prepared in A and B.

Reaction of *m*-Xyloquinone with Ketene Acetal. 2-Ethoxy-4,6-dimethyl-5-hydroxycoumarone (VI).—Preliminary experiments showed that *m*-xyloquinone did not react with ketene acetal when the reactants were heated together at 125° in the absence of a solvent or in refluxing xylene. A mixture of 7 g. of *m*-xyloquinone and 13.1 g. of ketene acetal was heated to 150° for 12 hours in a steel bomb fitted with a Pyrex liner. At the conclusion of the heating period the reaction mixture was a viscous black oil. Unchanged ketene acetal (1.5 g.) and ethyl orthoacetate (6.6 g.) were removed by distillation through a 15-cm.

(9) *Cf.* Hahn and Stenner, *Z. physiol. Chem.*, **181**, 100 (1929).

(10) Kohler, Stone and Fuson, THIS JOURNAL, **49**, 3181 (1927).

modified Widmer column at 200 mm. The residue that boiled above 100° (200 mm.) was distilled in a 50 ml. Claisen flask and the following fractions collected: (1) 3.8 g., b. p. below 120° (0.3 mm.); (2) 2.0 g., b. p. 120–139° (0.3 mm.); (3) 4.3 g., residue. Fraction (2) solidified on standing and 1.22 g. of an oily solid was obtained on recrystallization from a benzene–petroleum ether (60–68°) mixture. Vacuum sublimation of this material gave 0.70 g. (7%) of product, m. p. 99–101°. Another sublimation gave pure material, m. p. 100–101°.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.9; H, 6.83. Found: C, 69.8; H, 7.04. Analysis on the Grignard machine showed that 0.815 millimole of VI evolved 0.793 millimole of methane, and did not add a significant quantity of the reagent when treated with an excess of methylmagnesium iodide.

Ethyl 2,4-Dimethyl-3,6-dihydroxyphenylacetate.—A mixture of 7.0 g. of *m*-xyloquinone and 20 g. of ketene acetal was heated to 150° for twelve hours as before. The residue, after removal of the excess ketene acetal and the ethyl orthoacetate, was distilled in a 50-ml. Claisen flask and the following fractions collected at 0.4 mm. pressure: (1) 2.3 g., 95–120°; (2) 2.6 g., 120–135°; (3) 2.3 g., 135–150°; (4) 1.9 g., 150–178°; (5) 3.4 g., residue. Fractions (1) through (4) were dissolved separately in 75% alcohol and evaporated to dryness. Fraction (3) solidified immediately on cooling and gave 0.49 g. of light brown crystals, m. p. 144–146° on recrystallization from chloroform. Another recrystallization and a vacuum sublimation at 140° and 1 mm. gave 0.45 g. of product, m. p. 145–147°. Fractions (2) and (4) solidified on standing for two days. They were combined and yielded 0.60 g. of the same material on recrystallization from a mixture of benzene and petroleum ether (60–68°) and vacuum sublimation. An analytical sample prepared by another recrystallization melted at 147–148°.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.3; H, 7.18; OC_2H_5, 20.1. Found: C, 64.1; H, 7.16; OC_2H_5, 19.9.

4,6-Dimethyl-5-hydroxycoumaranone-2 (VII).—Ethyl 2,4-dimethyl-3,6-dihydroxyphenylacetate (0.23 g.) was refluxed with 35 ml. of 25% hydrochloric acid for three hours. The solution was evaporated to dryness and the residue sublimed at 115° and 1 mm. The crude sublimate weighed 0.16 g. and melted at 142–144°. Recrystallization from water and resublimation gave 0.11 g. (56%) of 4,6-dimethyl-5-hydroxycoumaranone, m. p. 143–144°. The melting point was not changed by another recrystallization and resublimation.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.4; H, 5.66. Found: C, 67.2; H, 5.38.

Attempted Reaction of Duroquinone with Ketene Acetal.—A mixture of 5.0 g. of duroquinone and 7.75 g. of ketene acetal was heated to 150° for 12 hours. On cooling, the reaction mixture set to an orange crystalline mass. The mixture was washed into a 500-ml. Claisen flask and steam distilled until no more quinone came over. The insoluble quinone was filtered off from the distillate and the filtrate was extracted with ether. The total recovery of duroquinone from the filtration and the ether extract amounted to 4.68 g. of a product, m. p., 108–110°.

Reaction of *p*-Xyloquinone with Ketene Acetal.—A mixture of 7.05 g. of *p*-xyloquinone and 20 g. of ketene acetal was heated in a bomb (Pyrex liner) to 150° for twelve hours. The excess ketene acetal and the ethyl orthoacetate were removed under diminished pressure, and the residue distilled in a 50-ml. Claisen flask at 0.35 mm. Only 1.93 g. of solid material was distilled below a temperature of 150°. Recrystallization from a mixture of benzene and petroleum ether (60–68°) and vacuum sublimation gave 0.77 g. of *p*-xylohydroquinone, m. p. 205–208°, which was identified by oxidation to *p*-xyloquinone.

Reaction of 1,4-Naphthoquinone with Ketene Acetal. 2-Ethoxy-5-hydroxy-6,7-benzocoumarone (XII).—A mixture of 13.5 g. of naphthoquinone[11] and 20 g. of ketene acetal was heated at 100° for twelve hours. The ethyl orthoacetate was removed, and the residue subjected to vacuum distillation in a 50-ml. Claisen flask. The fraction boiling from 160–190° at 1.0 mm. was collected. After recrystallization from a mixture of benzene and petroleum ether (60–68°) followed by a vacuum sublimation, 0.60 g. of a white solid, which was slightly discolored by a yellow impurity, was obtained. Resublimation removed the color and gave 0.45 g. (2%) of product, m. p. 106–108°.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.7; H, 5.30. Found: C, 73.4; H, 5.23. When treated with methylmagnesium iodide in the Grignard machine, 0.619 millimole of XII evolved 0.678 millimole of methane, and did not add a significant quantity of reagent.

5-Hydroxy-6,7-benzocoumaranone-2 (XIII).—A mixture of 27.0 g. of naphthoquinone and 40 g. of ketene acetal reacted as described above. The reaction mixture was hydrolyzed in 75% alcohol by the usual method. The residue from the evaporation of the alcohol weighed 40.5 g. When this residue was subjected to vacuum distillation in a 125-ml. von Braun flask the following fractions were collected: (1) 1.2 g., b. p. 150–160° (0.3 mm.); (2) 3.4 g., b. p. 165–190° (0.6 mm.). Fraction (2) solidified on cooling and gave 0.94 g. of a yellow solid, m. p. 197–200°, on recrystallization from benzene. Two more recrystallizations gave 0.63 g. (2%) of the coumaranone (XIII), m. p., 204–205°.

Anal. Calcd. for $C_{12}H_8O_3$: C, 72.0; H, 4.05. Found: C, 72.0; H, 4.27.

Reaction of Bromobenzoquinone with Ketene Acetal. 5-Hydroxy-(7?)-bromocoumaranone-2 (XIV).—Bromobenzoquinone (7.80 g.) was dissolved in 50 ml. of sodium-dried benzene and 9.68 g. (2 equivalents) of ketene acetal added. The reaction mixture was refluxed for twenty-four hours. The benzene and ethyl orthoacetate were distilled off under reduced pressure, the residual tar dissolved in 75% alcohol, and the solution evaporated to dryness. Sublimation of the residue at 170° and 1 mm. and recrystallization of the sublimate from chloroform gave 3.03 g. of the crude coumaranone, m. p. 198–202°. Another recrystallization from chloroform gave 2.53 g. (26.5%) of product, m. p. 201–204°, with decomposition. An analytical sample prepared by two more recrystallizations from 95% ethanol melted at 202–204°.

Anal. Calcd. for $C_8H_5O_3Br$: Br, 34.90. Found: Br, 35.08.

The coumaranone (XIV) (0.42 g.) was methylated by the method of Smith and Nichols.[12] The product, 3,6-dimethoxy-(5?)-bromophenylacetic acid (XVII), was purified by recrystallization from a mixture of methanol and water, a vacuum sublimation at 130° and 1 mm., followed by another recrystallization. It weighed 0.26 g. and melted at 194–195°.

Anal. Calcd. for $C_{10}H_{11}O_4Br$: OCH_3, 22.5; neut. equiv., 275. Found: OCH_3, 21.9; neut. equiv., 286.

It was thought that the acid (XVII) should be oxidized readily by basic permanganate to the corresponding substituted benzoic acid. However, conditions under which the benzoic acid could be isolated were not found. At room temperature XVII was not attacked. Refluxing XVII with an excess of basic permanganate yielded a resin from which no crystalline product could be isolated. At 70°, 2.6 equivalents of permanganate was used up without completely oxidizing the product; some of the starting material and some resin were the only products which could be isolated from the reaction mixture.

Reaction of 2,5-Dibromobenzoquinone with Ketene Acetal.—2,5-Dibromobenzoquinone (5.0 g.) was refluxed with 4.4 g. (2 equivalents) of ketene acetal in 75 ml. of benzene for twelve hours. After removal of the benzene and ethyl orthoacetate, the residue was subjected to vacuum sublimation at 160° and 1 mm. The sublimate was dissolved in 75% alcohol, and the solution evaporated to dryness. The residue was recrystallized from benzene and

(11) Fieser, "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 383.

(12) Smith and Nichols, THIS JOURNAL, **65**, 1744 (1943).

yielded 2.21 g. of **ethyl 2,5-dibromo-3,6-dihydroxyphenylacetate**, m. p. 125–126°. A second crop of this product weighing 0.39 g. and melting at 123–125° was obtained from the mother liquor. The total yield amounted to 40%. An analytical sample prepared by another recrystallization of the first crop melted at 126–127°.

Anal. Calcd. for $C_{10}H_{10}O_4Br$: Br, 45.17; OC_2H_5, 12.7. Found: Br, 45.03; OC_2H_5, 12.6.

Reaction of 2,6-Dibromobenzoquinone with Ketene Acetal.—When this quonone was heated with ketene acetal in dry xylene, only a trace of ethyl bromide was evolved, showing that the reaction does not proceed by replacement of bromine.

The quinone[13] (5.00 g.) was refluxed with 4.40 g. (2 equivalents) of ketene acetal in 100 ml. of dry benzene for twelve hours. Removal of the benzene and ethyl orthoacetate left a dark red resin. Vacuum sublimation of this resin at 170° and 1 mm. gave 0.75 g. of a light brown oil which failed to crystallize. It was hydrolyzed in 75% alcohol, and yielded an oily residue which also failed to crystallize. This residue was dissolved in 10 ml. of dioxane, 0.5 ml. of concentrated hydrochloric acid added and the solution evaporated to dryness. The residue was a black tar from which nothing could be sublimed at 1 mm. and below 190°.

Reaction of 2-Bromonaphthoquinone with Ketene Acetal. Xanthopurpurin Diethyl Ether (XX).—A mixture of 10.1 g. of 2-bromonaphthoquinone and 20.2 g. of ketene acetal was heated to 125° for sixteen hours. The ethyl bromide eliminated in this reaction amounted to 40% of the theoretical. On cooling the reaction mixture a solid separated which was filtered off and washed with 50 ml. of cold 95% alcohol. The dark green crystals which were somewhat gummy were recrystallized from 95% alcohol and gave 3.11 g. of yellow-green crystals. These were dissolved in 150 ml. of dry benzene and boiled with 0.1 g. of norite. The solution was filtered, evaporated to a volume of 25 ml. and allowed to crystallize. The yield of the bright yellow xanthopurpurin diethyl ether, m. p. 169–170°, was 2.24 g. A second crop of 0.36 g. of this compound having the same melting point was obtained from the mother liquor. The yield of the combined crops amounted to 20.6%. Lower yields (14%) were obtained when 5 equivalents of ketene acetal were used. The compound had the correct carbon, hydrogen, and ethoxyl content for xanthopurpurin diethyl ether. The melting point of a mixture of this product with an authentic sample of xanthopurpurin diethyl ether prepared by the method of Plath[14] from xanthopurpurin[15] was 169–170°.

Reaction of 2,3-Dibromonaphthoquinone with Ketene Acetal. Ethyl 3-Bromonaphthoquinon-2-ylacetate (XXI).—A solution of 5.0 g. of 2,3-dibromonaphthoquinone and 6.0 g. of ketene acetal in 100 ml. of benzene was refluxed for twelve hours. When solvent was distilled off, a crystalline residue, which was somewhat oily, remained. This residue was washed with a little cold alcohol and sublimed at 150° and 1 mm. The sublimate was recrystallized from a mixture of alcohol and water and gave 2.47 g. of ethyl 3-bromo-1,4-naphthoquinon-2-ylacetate, m. p. 122–123°. A second crop of crystals of this product weighing 0.49 g. and melting from 120–122° was obtained from the mother liquor. The combined yield was 57.6%. Analytically pure material, prepared by another vacuum sublimation of the first crop, melted at 124–125°.

Anal. Calcd. for $C_{14}H_{11}O_4Br$: Br, 24.7; OC_2H_5, 13.9. Found: Br, 25.0; OC_2H_5, 13.9.

(13) Heinichen, *Ann.*, **253**, 285 (1889).

(14) Plath, *Ber.*, **9**, 1205 (1876).

Summary

The condensation product from ketene acetal and benzoquinone is shown to be 2-ethoxy-5-hydroxycoumarone instead of 7-ethoxy-2,5-diketobicyclo[4,2,0]octadiene-3,6 as previously reported.

Xyloquinones and 1,4-naphthoquinone are much less reactive than benzoquinone toward ketene acetal. The temperatures necessary to produce reaction appear to polymerize most of the initial reaction products so that only small yields of coumarones corresponding to the one obtained with benzoquinone are isolated. Duroquinone does not react with ketene acetal.

Bromoquinones are much more reactive toward the acetal than are the methyl-substituted quinones. With bromobenzoquinones the reaction takes place at one of the unsubstituted ring carbons. With the bromonaphthoquinones a bromine substituent is replaced with the evolution of ethyl bromide; 2-bromonaphthoquinone yields xanthopurpurin diethyl ether and 2,3-dibromonaphthoquinone yields ethyl 3-bromo-1,4-naphthoquinon-2-ylacetate.

(15) Friedlander, "Fortschritte der Teerfarbenfabrikation," Vol. 9, p. 691, Julius Springer, Berlin, 1911.

MADISON, WISCONSIN RECEIVED APRIL 20, 1944

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF MERCK & CO., INC.]

Erythrina Alkaloids. XIV. Isolation and Characterization of Erysothiovine and Erysothiopine, New Alkaloids Containing Sulfur[1a]

BY KARL FOLKERS, FRANK KONIUSZY AND JOHN SHAVEL, JR.

The new alkaloids,[1b] erythramine, erythraline and erythratine, which were isolated from seeds of various species of *Erythrina* have been designated free alkaloids because they appear to exist in the seeds as free organic ammonium bases or salts, as indicated by the technique used in their isolation. These free alkaloids correspond to the well-known alkaloids isolated from many different families of plants. It is characteristic of many such alkaloids that they can be extracted from alkaline aqueous concentrates by certain immiscible organic solvents.

During the study and extraction[2] of the crude free alkaloidal fractions from *Erythrina glauca* Willd. and *Erythrina berteroana* Urb., it was found that after these fractions had been removed completely, the residual aqueous extracts were still very potent, as shown by the biological assays with frogs for curare-like action. For these two

(1a) Original manuscript received November 8, 1943.

(1b) Folkers and Koniuszy, THIS JOURNAL, **61**, 1232 (1939); *ibid.*, **62**, 436 (1940).

(2) Folkers and Koniuszy, *ibid.*, **62**, 1677 (1940).