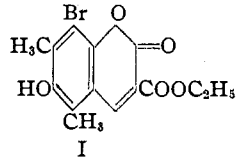
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

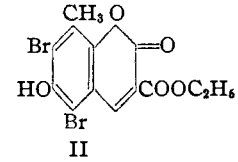
The Reaction between Quinones and Enolates. XVI. Dibromo-*o*-xyloquinone and Sodium Malonic Ester[1]

BY LEE IRVIN SMITH AND FRANKLIN L. AUSTIN[2]

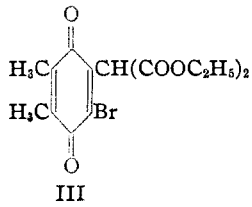
Previous work has shown that when bromotrimethylquinone[3] and dibromo-*m*-xyloquinone[4] react with sodium malonic ester, the coumarins I and II are formed, respectively. In these two



I



II

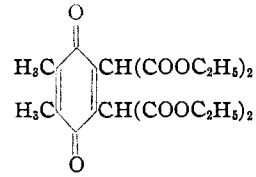


III

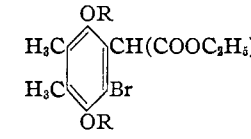
cases, a methyl group, rather than a bromine atom, reacted with the ester. Moreover, since only one of the three possible coumarins (I) was obtained from bromotrimethylquinone, it appeared that the bromine atom exerted an activating effect upon the methyl group meta to it. However, it became clear that this was not the only factor involved, for dibromo-*m*-xyloquinone, which does not contain a bromine atom meta to a methyl group, also gave a coumarin (II).

In order to study further the mutual effects of bromine atoms and methyl groups in fully substituted quinones, sodium malonic ester has now been added to dibromo-*o*-xyloquinone. In this quinone, each of the methyl groups is meta to a bromine atom, while the two pairs of like groups, bromine and methyl, are ortho to each other. Apparently no quinone having bromine and alkyl substituents with this arrangement has been studied hitherto.

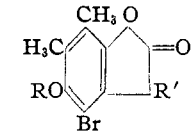
The reaction between dibromo-*o*-xyloquinone and various enolates of malonic ester proved to be extremely susceptible to slight changes in conditions. Procedures which had formerly been found to be quite satisfactory failed in this case because of the great sensitivity of the quinone toward alkali. When, however, a solution of sodium malonic ester in dry dioxane was added under an inert atmosphere to a solution of the quinone in dioxane, there was obtained a good yield of a yellow oil which had the properties of a quinone, and the composition corresponding to III. When the reaction time was prolonged, a yellow, halogen-free compound resulted; this substance (IV) was



IV



V, R = H
VI, R = Ac



VII, R = H; R′ = $COOC_2H_5$
VIII, R = R′ = H
IX, R = Ac; R′ = $COOC_2H_5$
X, R = Ac; R′ = H

formed by replacement of both bromine atoms by malonic ester groups. The behavior of dibromo-*o*-xyloquinone toward sodium malonic ester is therefore strictly analogous to that of 2,3-dibromo-α-naphthoquinone, for Liebermann found[5] that one of the bromine atoms in this quinone could be replaced rapidly by a malonic ester group, but the second halogen atom reacted only slowly. It appears, then, that in a dihalogenated dialkylquinone, the orientation of the halogen atoms with respect to each other exerts a more pronounced effect upon the course of the reaction than does the orientation of the halogen atoms with respect to the methyl groups.

The quinone malonic ester III was readily reduced to the solid hydroquinone V by sodium hydrosulfite, a property which greatly facilitated isolation and purification of the reaction product. The quinone III was readily obtained by gentle oxidation of V and, when purified in this way, III was a stable, yellow liquid which could be distilled without decomposition. The hydroquinone V formed a diacetate VI. Action of 75%

(1) Paper XV, THIS JOURNAL, **64**, 524 (1942).

(2) Abstracted from a thesis by F. L. Austin, presented to the Graduate Faculty of the University of Minnesota in partial fulfillment of the requirements for the Ph.D. degree, August, 1941.

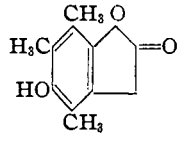
(3) Smith and Johnson, THIS JOURNAL, **59**, 673 (1937).

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

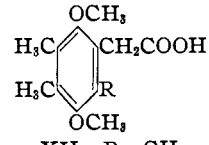
(5) Liebermann, (a) *Ber.*, **31**, 2079 (1898); (b) **33**, 566 (1900).

sulfuric acid upon V at room temperature produced the isocoumaranone VII. The isocoumaranone VII still contained an ester group, for VII was converted into VIII by action of hot acetic acid, a procedure which also converted V into VIII. The conversion of V into VIII probably involved VII as an intermediate, since VI was unaffected by boiling acetic acid, *i. e.*, cleavage of the open chained malonic ester occurred less readily than it did when a part of the malonic ester group was involved in ring formation. When VII and VIII were acetylated, the respective acetates IX and X were formed, and IX was converted into X by action of boiling acetic acid, a behavior which paralleled the conversion of VII into VIII. The successive conversion of the hydroquinone malonic ester V into the isocoumaranone ester VII and then into the isocoumaranone VIII, and the identification of these cyclic derivatives, showed that no cleavage of a carbethoxyl group had occurred during the reaction between dibromo-*o*-xyloquinone and sodium malonic ester. This chemical evidence was quite important, for the members of the acetic ester series—quinone, hydroquinone and hydroquinone diacetate (analogous to XIII)—have very nearly the same composition as the corresponding members of the malonic ester series.

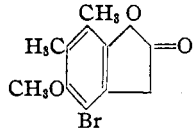
It has been shown[6] that the trimethylisocoumaranone XI, when subjected to the action of methyl sulfate and alkali, is transformed into the phenylacetic acid XII. The behavior of VIII



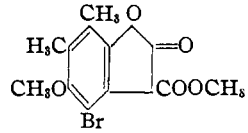
XI



XII, R = CH_3
XIII, R = Br

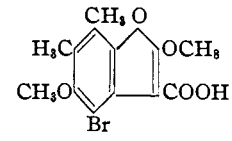


XIV

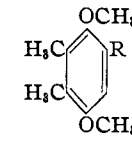


XV

under these conditions was quite analogous, for it was transformed into XIII. Methylation of the hydroquinone V, however, was more complex than was anticipated and XIII was obtained from V only by a surprisingly circuitous route. The direct methylation product of V was a substance having the composition $C_{13}H_{13}O_5Br$. This substance was readily extracted from its ether solution by sodium bicarbonate, and on steam distillation, the substance was converted into a substance insoluble in bicarbonate, namely, XIV, the methyl ether of VIII. These properties eliminated structure XV for the methylation product, and the only alternative structure for the substance was XVI, the enol methyl ether of the isocoumaranone acid corresponding to XV. This structure represents the substance as a vinylog of methyl carbonate and it expresses well the properties of the compound, particularly the instability on standing and the ready conversion to XIV on steam distillation. On methylation, XIV gave the dimethoxy acid XIII. Formation of XVI from the open chained hydroquinone V by methylation indicated that during the process cyclization had occurred, and that the process involved an intermediate such as an ester or acid derived from VII. Such an intermediate, containing a malonic acid system, could give rise to an enol ether in the presence of methyl sulfate and alkali. If such an intermediate were involved, then methylation of VII should likewise give rise to XVI. Methylation of VII gave an oil from which no solid XVI could be isolated, but that this oil contained XVI was shown by the production of XIV when the oil was steam distilled. Since XIV, when methylated, gave only the dimethoxy acid XIII, it followed that the XIV in the steam distillate from the oil must have come from XVI.



XVI



XVII, R = H
XVIII, R = CH_2Cl
XIX, R = CH_2CN
XX, R = CH_2COOH

The relationships shown among the various products are consistent with the structures assigned to them in such a way that if almost any one of the products were synthesized by an independent method, the synthesis would afford a structure proof of all the others as well. For this purpose the dimethoxyphenylacetic acid XIII was chosen, because it appeared to lend itself to synthesis more readily than any of the other compounds and also, its mode of formation from the isocoumaranone VII was in close analogy with the formation of XII from XI.[6] The route to XIII offered no particular difficulties; it involved the sequence XVII, XVIII, XIX, and XX.

(6) Smith and MacMullen, THIS JOURNAL, **58**, 629 (1936).

Bromination of XX gave XIII, identical with XIII obtained by methylation of VII or XIV.

Experimental Part[7]

o-Xyloquinone.—This was prepared from 2,3-dimethylphenol[8] by a modification of the procedure already reported.[9] This procedure is much more efficient than the direct oxidation of 2,3-dimethylaniline.[10] 2,3-Dimethylphenol (56 g.) was dissolved in water (300 cc.) containing sodium hydroxide (75 g.). Sulfanilic acid (115 g.) was diazotized and the cold mixture of the diazo salt and ice water (about 1200 cc.) was slowly stirred into the cooled phenol solution. The mixture was allowed to stand overnight, then cooled to 5° and stirred with sodium hydrosulfite (220 g.). The cooling bath was removed and the mixture was stirred for three hours. The aminophenol was filtered, washed with cold water, and dissolved by warming it with water (1000 cc.) containing sulfuric acid (60 cc.). The solution was boiled with a little Norite and filtered and the pink filtrate was added dropwise to the oxidizing agent (ferric *sulfate*, 250 g., water, 1000 cc., sulfuric acid, 30 cc.) contained in an apparatus arranged for steam distillation under reduced pressure. Steam at a pressure of 70–80 mm. was passed through the mixture continuously during the addition of the aminophenol. About four liters of distillate was collected. The distillate was cooled (0°), the solid (10 g.) was removed, and the filtrate was extracted five times with ether. The combined extracts were dried (sodium sulfate) and the solvent was removed. The residual red oil, when crystallized from petroleum ether (b. p. 28–38°), gave 28 g. of the quinone. The total yield (38 g.) was 61%, and the product melted at 56.5–57.5°. The hydroquinone (m. p. 223–224° dec.) was obtained quantitatively when an ethereal solution of the quinone was shaken with excess aqueous sodium hydrosulfite until the yellow color disappeared.

Dibromo-o-xyloquinone.[11]—o-Xyloquinone (40 g.) was dissolved in chloroform (300 cc.). Liquid bromine (96 g.) was added dropwise (three and one-half hours) to the well-stirred solution at room temperature. About half the bromine was absorbed rapidly, the remainder very slowly, and hydrogen bromide was not evolved until about half the bromine had reacted. The dibromohydroquinone was an intermediate, for it crystallized from the reaction mixture during addition of the halogen.[12] Stirring was continued for thirty-six hours, during which hydrogen bromide was slowly but steadily evolved. The yellow chloroform solution was washed successively with water, dilute bicarbonate and again with water. The solvent was removed on the steam-bath and the residue was crystallized from alcohol (1500 cc.) containing nitric acid (8 cc.). The quinone formed large yellow plates (71 g.) which melted at 151–153°. A second crop of 10 g. was obtained by concentrating the filtrate (total yield, 94%). The analytical sample was recrystallized twice from alcohol; it melted at 152.5–153°.

Anal. Calcd. for $C_8H_6O_2Br_2$: C, 32.65; H, 2.04. Found: C, 32.68; H, 1.96.

Dibromo-o-xylohydroquinone (0.26 g., 87%) was prepared by reduction of the quinone (0.3 g.) in alcohol (10 cc.) by addition of a solution of stannous chloride (2 g.) in hydrochloric acid (2 cc.). After crystallization from aqueous alcohol, the substance formed short, white needles which melted at 163–164°. Shaking an ethereal solution of the quinone with aqueous sodium hydrosulfite also gave the hydroquinone.

Anal. Calcd. for $C_8H_8O_2Br_2$: C, 32.42; H, 2.70. Found: C, 32.37; H, 2.89.

Diacetate.—The quinone (0.3 g.) was dissolved in acetic acid (5 cc.) and acetic anhydride (10 cc.). Zinc dust (0.5 g.) and a drop of sulfuric acid were added and the mixture was refluxed until it became colorless (45 min.). The acetate (0.3 g., 79%), when recrystallized from dilute acetic acid, melted at 203–206°.

Anal. Calcd. for $C_{12}H_{12}O_4Br_2$: C, 37.90; H, 3.16. Found: C, 38.19; H, 3.23.

Dibromo-o-xyloquinone and Sodium Malonic Ester.—Use of magnesium ethoxide[3] as a condensing agent in alcohol or in dry dioxane gave only gummy materials which, on acidification, led to dark oily materials from which no pure reaction products could be isolated. Sodium malonic ester in dry dioxane[4] gave only insignificant amounts of amorphous materials. Sodium malonic ester in benzene[13] toluene, or ether gave small amounts of a metallic derivative, but this, on decomposition with acid, gave mixtures which were partly amorphous and from which no pure reaction products could be obtained by crystallization or by chromatographic analysis. The fact that in most of these experiments a considerable amount of unchanged quinone was recovered indicated that the quinone was sensitive to alkaline reagents and a blank experiment showed this to be true. Sodium ethoxide in dioxane, with no malonic ester present, converted the quinone into the same sort of brown, amorphous materials. It followed that, for condensation of the quinone with an enolate, the conditions must be mild and an excess of alkali must be avoided. Best results were obtained by adding a dioxane solution of sodium malonic ester to a solution of the quinone in the same solvent. The reaction, under these conditions, was instantaneous and was accompanied by development of an intense blue color in the reaction mixture. Dioxane was an excellent solvent for the reaction; sodium malonic ester was formed readily in the hot solvent from the metal and malonic ester, thus avoiding the necessity of using sodium ethoxide in the preparation of the enolate; the enolate was completely soluble in the solvent; and the metallic derivative of the product was insoluble in dioxane and could be isolated by filtration. Temperature effects were very pronounced; at room temperature the results were entirely satisfactory, but an increase of 15–20° in temperature led to red and green by-products which were very difficult to remove. Since the reaction was exother-

(7) Microanalyses by E. E. Renfrew and C. H. Stratton.

(8) Smith and Opie, *J. Org. Chem.*, **6**, 430 (1941).

(9) Smith, Opie, Wawzonek and Prichard, *ibid.*, **4**, 318 (1939).

(10) Emerson and Smith, THIS JOURNAL, **62**, 141 (1940).

(11) The statement in *Chem. Abs.*, **32**, 4552 (1938), that Aulin and Erdtman, *Svensk. Kem. Tid.*, **49**, 208 (1937), prepared this compound, is an error. The substance actually prepared by these authors was 2,3-dimethoxy-5,6-dibromoquinone; see *Chem. Zentr.*, **108**, I, 59 (1938).

(12) Aulin and Erdtman, ref. 11, obtained only the dibromohydroquinone when 2,3-dimethoxyquinone reacted with one mole of bromine.

(13) Smith and Dobrovolny, THIS JOURNAL, **48**, 1693 (1926).

mic, some control of the temperature was necessary. This was best achieved by proper regulation of the rate at which the enolate was added to the quinone.

Ethyl 2-Bromo-4,5-dimethyl-3,6-dihydroxyphenylmalonate (V).—Ethyl malonate (20 cc., 0.125 mole) was added to a suspension of sodium (2.76 g., 0.12 gram atom) in dry dioxane (25 cc.). After the vigorous initial reaction subsided, the mixture was refluxed until all the metal was dissolved. The solution was cooled to room temperature, more dioxane (50 cc.) was added, and the solution was blown, by means of a current of dry, carbon dioxide-free air, into a dropping funnel set in one opening of a 3-necked flask. The flask in which the enolate had been prepared was rinsed twice with a little dioxane and the washings were combined with the main dioxane solution. The other openings of the 3-necked flask were fitted with a stirrer and a two-holed stopper carrying a thermometer and a calcium chloride guard tube. All the other openings to the atmosphere were likewise fitted with calcium chloride tubes. A solution of dibromo-*o*-xyloquinone (15 g., 0.05 mole) in dioxane (50 cc.) was placed in the flask and with vigorous stirring the enolate solution was added dropwise at such a rate (one hour) that the temperature did not rise appreciably. A blue color developed at once and a blue precipitate formed after a few minutes. As soon as the addition was complete, the mixture was filtered with suction in the air and the blue sodium derivative was washed with a little dioxane. The blue filtrate was acidified with acetic acid. The blue solid was dissolved in water (200 cc.) and the solution was acidified with acetic acid and shaken vigorously. A dark oil separated, which changed in color to light yellow when it was brought into intimate contact with the acid. The mixture was shaken with ether and the colorless aqueous layer was removed. The yellow ether layer was shaken with two portions of saturated sodium hydrosulfite solution, and the (now colorless) ether solution was washed twice with water and filtered through sodium sulfate. The filtrate was concentrated to a small volume and petroleum ether (b. p. 28–38°) was added. The hydroquinone V (12.23 g.) precipitated as a colorless solid which melted at 127–128°. The acidified filtrate from the metallic derivative was diluted with an equal volume of water, and was filtered to remove a small amount of unchanged dibromoxyloquinone. The filtrate was extracted with ether and the extract was shaken with sodium hydrosulfite. The hydroquinone V from this solution contained a green impurity which was removed by repeated crystallization from petroleum ether (b. p. 60–68°) followed by one crystallization from ether. It weighed 2.42 g. and melted at 126–127°. The combined solids (14.65 g.) represented a yield of 78%.

Anal. Calcd. for $C_{15}H_{19}O_6Br$: C, 48.00; H, 5.08. Found: C, 48.02, 48.12; H, 5.36, 5.33.

3-Bromo-2-dicarbethoxymethyl-5,6-dimethylbenzoquinone (III).—Ferric chloride (3 g.) was added in small portions and with shaking to a solution of the hydroquinone V (0.8 g.) in alcohol (15 cc.). The greenish solution was diluted with water and extracted with benzene. The benzene extract was dried over sodium sulfate, the solvent was removed and the residue was distilled. It boiled at 115–120° under 1 mm. pressure and formed a viscous, yellow oil.

Anal. Calcd. for $C_{15}H_{17}O_6Br$: C, 48.25; H, 4.56. Found: C, 48.04; H, 4.65.

This yellow oil, on reduction with sodium hydrosulfite, gave the hydroquinone V, m. p. and mixed m. p. 125–127°.

2,3-Bis-(dicarbethoxymethyl)-5,6-dimethylbenzoquinone (IV).—Dibromo-*o*-xyloquinone (2 g.) was treated with two equivalents of sodium malonic ester as described above, and the reaction mixture was allowed to stand overnight. An equal volume of water was added and the mixture was acidified with acetic acid and extracted with ether. The ether was removed and replaced by petroleum ether (b. p. 28–38°) and the solution was set aside in a refrigerator for several weeks. The solid was removed and crystallized several times from petroleum ether. It formed hard yellow crystals which melted at 83–84° and which were free from halogen.

Anal. Calcd. for $C_{22}H_{28}O_{10}$: C, 58.41; H, 6.19. Found: C, 58.19; H, 6.20.

Diacetate, VI.—The hydroquinone V (0.22 g.) was dissolved in acetic anhydride (5 cc.) containing a drop of sulfuric acid, and the solution was set aside overnight. Water (50 cc.) was added, and after decomposition of the acetic anhydride was complete, the mixture was extracted with ether. The ether extract was washed with sodium bicarbonate (10%) and then with water, and was dried (sodium sulfate). The solvent was removed and the residue was crystallized twice from ether–petroleum ether (b. p. 28–38°). The product weighed 0.24 g. (89%) and melted at 92–93°. It was unaffected when its solution in acetic acid was refluxed for thirty minutes.

Anal. Calcd. for $C_{19}H_{23}O_8Br$: C, 49.67; H, 5.02. Found: C, 49.70; H, 5.21.

3-Carbethoxy-4-bromo-6,7-dimethyl-5-hydroxyisocoumaranone (VII).—The hydroquinone V (2.19 g.) in chloroform (50 cc.) was shaken twice with sulfuric acid (75%, 30 cc. each time). The chloroform solution was washed with water and the solvent was evaporated, the last traces under reduced pressure. The residue was moistened with petroleum ether (b. p. 60–68°) and the solid (1.82 g., 95%) was filtered and recrystallized several times from benzene–petroleum ether. The isocoumaranone apparently separated with benzene of crystallization, for the crystalline solid rapidly crumbled to a powder in the air. The sample for analysis was dried *in vacuo* at 78° for three hours; it melted at 109–110°.

Anal. Calcd. for $C_{13}H_{13}O_5Br$: C, 47.42; H, 3.95. Found: C, 47.62; H, 3.96.

When the above procedure was followed using 65% sulfuric acid, a mixture of the isocoumaranone and starting material resulted. When the hydroquinone was dissolved in concd. sulfuric acid and the yellow solution was poured over ice, a mixture of white, red and green material was formed.

Acetate IX.—The isocoumaranone ester VII (0.4 g.) was warmed for ten minutes on the steam-bath with acetic anhydride (10 cc.) and a drop of sulfuric acid. The product was crystallized twice from alcohol, when it formed colorless needles melting at 117–118°. It gave a pronounced depression in melting point when mixed with the diacetate V.

Anal. Calcd. for $C_{15}H_{16}O_6Br$: C, 48.52; H, 4.04. Found: C, 48.87; H, 4.15.

4-Bromo-6,7-dimethyl-5-hydroxyisocoumaranone (VIII).—A. The diacetate VI (0.35 g.) was refluxed for fifteen minutes in acetic acid (5 cc.) containing hydrochloric acid (5 cc.). The red solution was poured into water and the solid was removed and dried. After crystallization from ether–petroleum ether, the substance melted at 146–150°. B. The isocoumaranone ester VII (0.15 g.) was refluxed in acetic acid for forty-five minutes. The product melted at 154–155°. C. The hydroquinone V (1.5 g.) was refluxed for forty-five minutes in acetic acid (15 cc.) containing a pinch of granulated zinc. The isocoumaranone VIII (0.90 g., 88%) melted at 155–156° after crystallization from ether–petroleum ether. The products from A, B, and C gave no depression in melting point when mixed.

Anal. Calcd. for $C_{10}H_9O_3Br$: C, 46.69; H, 3.50. Found: C, 46.91; H, 3.75.

Acetate X.—A. The acetate IX was refluxed for thirty minutes in acetic acid. The product melted at 194–197°. B. The isocoumaranone VIII (0.2 g.) was dissolved in acetic anhydride (5 cc.) containing a drop of sulfuric acid, and the solution was allowed to stand for six hours at room temperature. The product (0.2 g., 86%) was crystallized from alcohol–acetone (3:1). It then melted at 195–197°. The products from A and B were identical.

Anal. Calcd. for $C_{12}H_{11}O_4Br$: C, 48.16; H, 3.68. Found: C, 48.16; H, 3.81.

4-Bromo-3-carboxy-2,5-dimethoxy-6,7-dimethylcoumarone, XVI.—The hydroquinonemalonic ester V (1.5 g.) was dissolved in methanol (15 cc.) containing methyl sulfate (15 cc., freshly distilled). The solution was heated to the boiling point and was vigorously stirred while a solution of potassium hydroxide (15 g.) in methanol (90 cc.) was added as rapidly as possible. The mixture was refluxed for one and one-half hours and was then diluted with thrice its volume of water and extracted with ether. The alkaline aqueous layer was acidified with hydrochloric acid, and the mixture was chilled in an ice-bath until the precipitated oil solidified. The solid (0.74 g., 56%) was removed and crystallized twice from methanol and once from ether–petroleum ether (b. p. 28–38°). The substance melted at 141–143° and was soluble in 10% sodium bicarbonate solution.

Anal. Calcd. for $C_{13}H_{13}O_5Br$: C, 47.72; H, 3.95. Found: C, 47.61; H, 4.04.

4-Bromo-6,7-dimethyl-5-methoxyisocoumaranone, XIV.—A. The coumarone acid XVI (0.2 g.) was steam distilled. The product, present in both the distillate (0.08 g.) and in the residue, was removed and crystallized from petroleum ether. It melted at 113–113.5°. B. The isocoumaranone ester VII (0.93 g.) was dissolved in methanol (9 cc.) containing methyl sulfate (9 cc.). The hot solution was stirred while a solution of potassium hydroxide (9 g.) in methanol (55 cc.) was added rapidly. After the solution was refluxed for thirty minutes, it was diluted with water and extracted with ether. Acidification of the aqueous layer produced an oil which could not be crystallized. When this oil was steam distilled, XIV was isolated from the distillate. It melted at 108–110° after crystallization from petroleum ether. When mixed with the product from A above, the substance melted at 109–111°. This substance was insoluble in sodium bicarbonate or in sodium carbonate.

Anal. Calcd. for $C_{11}H_{11}O_3Br$: C, 48.71; H, 4.06. Found (sample from A): C, 48.89; H, 4.27.

***o*-Xylohydroquinone Dimethyl Ether (XVII).**—*o*-Xylohydroquinone (9.5 g.) was dissolved in methanol (75 cc.) containing methyl sulfate (75 cc.). The solution was heated and vigorously stirred while a solution of potassium hydroxide (95 g.) in methanol (475 cc.) was added as rapidly as possible. The mixture was refluxed for one hour and then was steam distilled. The solid (11 g., 96%) in the distillate was removed, dried *in vacuo*, and recrystallized from dilute methanol. It melted at 78°.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.29; H, 8.43. Found: C, 72.03; H, 8.51.

2,5-Dimethoxy-3,4-dimethylbenzyl Chloride (XVIII).—The dimethyl ether XVII (7 g.) was suspended in a mixture of hydrochloric acid (25 cc.) and formalin (40%, 5 cc.). The suspension was rapidly stirred while a current of hydrogen chloride was passed through it. The temperature rose and the solid melted. After an hour, the temperature fell and the suspension solidified. The mixture was then warmed gently on the steam-bath for one and one-half hours. The cooled reaction mixture was extracted with ether and the extract was washed with water until the wash water remained neutral (litmus). The ether solution was dried (sodium sulfate), the solvent was removed and the residue was distilled. The benzyl chloride XVIII (4.7 g., 52%) boiled at 162–163° under 25 mm. After crystallization from petroleum ether (b. p., 60–68°), the substance melted at 67–68°.

Anal. Calcd. for $C_{11}H_{14}O_2Cl$: C, 61.54; H, 6.99. Found: C, 61.72; H, 7.24.

The residue left in the distilling flask after removal of XVIII solidified on cooling. It was probably the di-(chloromethyl) compound, but it was not investigated.

The dimethyl ether XVII (3.0 g.) failed to undergo a Mannich reaction when it was stirred for eighteen hours on the steam-bath with morpholine (3.3 cc.), formalin (2 cc.) and alcohol (10 cc.). The starting material (2.9 g., 97%) was recovered. Apparently a free hydroxyl group is necessary for a Mannich reaction to occur with phenol or hydroquinone derivatives.[14]

2,5-Dimethoxy-3,4-dimethylbenzyl Cyanide (XIX).—The chloride XVIII (3.5 g.) was dissolved in alcohol (100 cc.) and the solution was added dropwise over a period of one hour to a well-stirred solution of potassium cyanide (1.4 g.) in water (1.3 cc.) on the steam-bath. After refluxing for four hours, the mixture was cooled, the potassium chloride was removed and the filtrate was concentrated to about one-half of its original volume. Water was added, and the precipitate (1.83 g., 55%) was removed and crystallized twice from petroleum ether (b. p. 60–68°) and twice from dilute alcohol. The benzyl cyanide formed long, colorless needles which melted at 95–96°.

Anal. Calcd. for $C_{12}H_{15}O_2N$: C, 70.25; H, 7.32. Found: C, 70.36; H, 7.35.

2,5-Dimethoxy-3,4-dimethylphenylacetic Acid (XX).—The benzyl cyanide XIX (1.6 g.) was refluxed for one and

(14) Decombe, *Compt. rend.*, **197**, 258 (1933).

one-half hours with acetic acid (5 cc.), sulfuric acid (5 cc.) and water (5 cc.). The red solution was poured over ice and the brown solid was removed by ether extraction. The ether layer was extracted twice with sodium carbonate solution (10%, 35 cc. each time). The carbonate extract was warmed to expel ether, then cooled and acidified. The solid was removed and crystallized from ether–petroleum ether (b. p. 60–68°), followed by crystallization from petroleum ether alone. The acid XX (0.77 g., 44%) formed colorless needles which melted at 120–121°.

Anal. Calcd. for $C_{12}H_{16}O_4$: C, 64.29; H, 7.14. Found: C, 64.54; H, 7.30.

2,5-Dimethoxy-3,4-dimethyl-6-bromophenylacetic Acid (XIII).—A. The acid XX (0.25 g.) in chloroform (10 cc.) was brominated by addition of a solution of bromine (0.2 g.) in chloroform (3 cc.). The solution was stirred at room temperature overnight. The solvent was evaporated and the residue was washed with a little cold benzene and then recrystallized from benzene–petroleum ether (b. p. 60–68°). The acid melted at 151–153.5°. B. The methoxyisocoumaranone XIV (0.26 g.) was dissolved in methanol (4 cc.) containing methyl sulfate (4 cc.). The solution was refluxed while a solution of potassium hydroxide (4 g.) in methanol (20 cc.) was added. The mixture was refluxed for an hour and was then diluted with water and acidified with hydrochloric acid. The solution, on standing in the refrigerator overnight, deposited 0.16 g. (57%) of the phenylacetic acid XIII which melted at 151–154°. C. The isocoumaranone VIII (1.1 g.) in methanol (15 cc.) was treated with potassium hydroxide (13 g.) in methanol (65 cc.) as described under B. The alkaline solution was diluted with water, extracted once with ether, and then warmed to expel ether. The cooled solution was acidified and the precipitate was removed and crystallized once from dilute methanol and twice from benzene–petroleum ether (b. p. 60–68°). The pure acid XIII (0.81 g., 63%) formed white needles which melted at 154–155°. The products from A, B, and C were identical, as shown by mixed melting point determination. Large depressions in the melting point resulted when the acid was mixed with VIII (m. p. 155–156°) or with XVI (m. p. 141–143°).

Anal. Calcd. for $C_{12}H_{15}O_4Br$: C, 47.52; H, 4.95. Found: (sample from C) C, 47.68; H, 4.99.

Summary

1. Dibromo-*o*-xyloquinone and sodium malonic ester react in cold dioxane to give a substitution product, 3-bromo-2-dicarbethoxymethyl-5,6-dimethylbenzoquinone (III). If the reaction time is prolonged, both bromine atoms of the quinone are replaced by malonic ester groups.

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. This behavior of the quinone is in contrast with that of the isomeric dibromo-*m*-xyloquinone, in which the bromine atoms are inert and the only attack by sodium malonic ester is at a methyl group.

3. Many derivatives of the hydroquinone-malonic ester V have been prepared, and the substances obtained from it by ring closure have been studied.

4. One of the degradation products of V, namely, 2,5-dimethoxy-3,4-dimethyl-6-bromophenylacetic acid (XIII) was synthesized by an independent method starting with *o*-xylohydroquinone.

5. Improved procedures are given for preparation of *o*-xyloquinone and some of its derivatives.

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α,β-Dialkylphenethylamines. Alkylation of Phenylacetone

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Although numerous substituted phenethylamines have been prepared since the discovery of the physiological activity associated with the $C_6H_5C—C—N$ structure, compounds having alkyl groups attached to both the *alpha* and *beta* carbons have not been reported. In the present investigation several amines with the general formula $C_6H_5CHRCHNH_2CH_3$, one such compound with a methyl on the nitrogen, and also one amine with two alkyls on the beta carbon, $C_6H_5C(CH_3)_2CHNH_2CH_3$, have been synthesized from the corresponding ketones and some data on their physiological action have been obtained.

A number of alkylations of phenylacetone and similar ketones in the presence of sodium ethoxide have been described by Tiffeneau and co-workers.[2] In the present work it was found that the reaction of methyl iodide with phenylacetone in the presence of one equivalent of sodium ethoxide gave a mixture in which unreacted phenylacetone predominated. It seemed probable that this re-

(1) Sharp and Dohme Research Associate, 1938–1940.

(2) Tiffeneau and Lévy, *Bull. soc. chim.*, [4] **33**, 759 (1923); Lévy and Jullien, *ibid.*, **45**, 941 (1929).