

## Summary

The preparation of seven new basically-substituted isoalloxazine compounds and the intermedi-

ates used in their preparation has been described.

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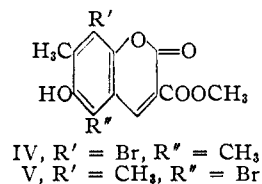
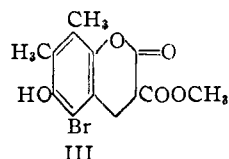
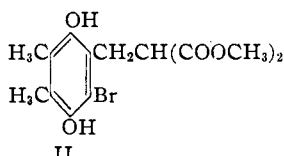
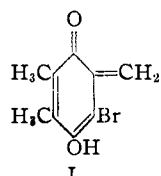
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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

## The Reaction between Quinones and Metallic Enolates. XX.<sup>1</sup> Second Paper on Bromotrimethylquinone and Sodio Malonic Esters

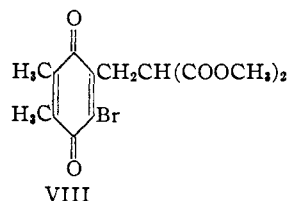
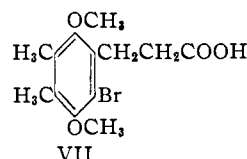
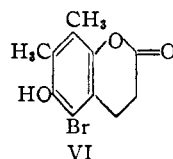
BY LEE IRVIN SMITH AND PAUL F. WILEY<sup>2</sup>

The reaction between methylated quinones and metallic enolates, leading to coumarins, has been pictured as involving four steps: (a) a "pentadenolization" of the quinone to give a methylene quinone, such as I; (b) a Michael reaction, involving addition of the metallic enolate (or of its ions) to the new conjugated system in I, producing the hydroquinone II; (c) cyclization of II to a hydrocoumarin III; and (d) dehydrogenation of the hydrocoumarin to the coumarin V. The end result of this series of reactions will depend upon a number of factors such as the relative velocities of competitive (or consecutive) reactions, solubilities of the intermediates, oxidizing power of the quinone (or its tautomer), presence or absence of air or other oxidizing agent, etc. Theoretically it is possible, therefore, for the reaction between a methylated quinone and a metallic enolate to produce either a coumarin or a hydrocoumarin. Although the products have been coumarins in all cases heretofore observed, it has now been found that the reaction between bromotrimethylquinone and methyl malonate in the presence of magnesium methoxide produced not the coumarin V, but the hydrocoumarin III.



The product of this reaction (obtained in a yield of 69%) formed a diacetate and gave a dimethyl ether by reaction with diazomethane, which eliminated structure V for it. The presence of an ester grouping in III was shown by hydrolysis of the substance to carbon dioxide and

a non-acidic substance VI, although the properties of VI were somewhat peculiar for a compound of this structure. It was not possible to convert III into VII by action of potassium hydroxide and methyl sulfate according to the method of Smith and Denyes.<sup>3</sup> Since the condensation between



alkylated quinones and metallic enolates, leading to coumarins, involves dehydrogenation at some step, it appeared possible that III could be dehydrogenated to V. This reaction was achieved. When III was refluxed with trimethylbromoquinone in methanol or dioxane, V was formed in a yield of 20%; in the first case, trimethylbromohydroquinone was isolated from the reaction mixture. The product V, as well as its acetate, was identified by comparison with authentic samples.

In previous papers<sup>4</sup> reports have been made of successful dehydrogenations of dihydrocoumarins by action of ferric chloride. When the hydrocoumarin III was subjected to the action of ferric chloride in methanol, the quinone VIII was formed in a yield of 90%. This quinone was reduced readily to the hydroquinone II, which on oxidation regenerated VIII. The hydroquinone II, when hydrolyzed by action of hydrochloric acid, gave the same substance VI as was obtained by similar hydrolysis of the hydrocoumarin III. This indirect conversion of III to VI *via* VIII and II afforded added evidence that the substance was not a coumarin, V, and it also eliminated II as a possible structure for this product (the com-

(1) Paper XIX, *THIS JOURNAL*, **66**, 1320 (1944).

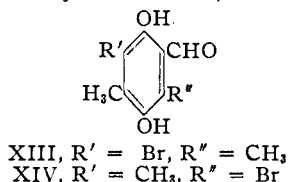
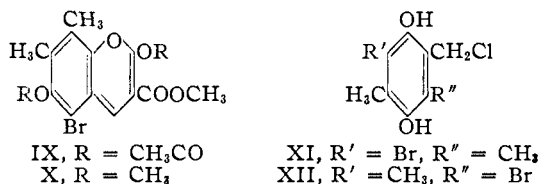
(2) Abstracted from a thesis by Paul F. Wiley, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, July, 1944.

(3) Smith and Denyes, *THIS JOURNAL*, **58**, 304 (1936).

(4) (a) Smith and Horner, *THIS JOURNAL*, **60**, 676 (1938); (b) Smith and Johnson, *ibid.*, **59**, 673 (1937).

positions of III and II, as well as of their derivatives, are nearly the same).

Granted that structure III is correct, then the diacetate and dimethyl ether of this substance must be derived from the enolic form of III and must be represented by IX and X, respectively.



No compounds of this sort are known, although several enol derivatives of analogous five membered ring structures—*isocoumaranones*—are known.<sup>5</sup>

The hydrocoumarin VI was a difficult substance to purify, and concordant analytical values could not be obtained for it. Nor could it be converted into the quinone propionic acid (corresponding to VIII) by the method previously used<sup>3</sup> for such transformations of hydrocoumarins. Nevertheless, in view of the formation of VI by action of hydrochloric acid upon both III and II, there can be little doubt of the structure of VI.

This work provides the first example of a reaction between an alkylated quinone and a metallic enolate in which the reaction conditions are such that a dihydrocoumarin can be isolated. From the mother liquors remaining after III was removed, there was isolated a very small amount of a yellow solid melting around 200°, which was most likely the coumarin V (m. p. 241°), although the amount was insufficient for purification and identification. That slight changes in conditions, etc., may exert a considerable effect upon the nature of the product is shown by the fact that when the magnesium enolate of *ethyl* malonate is used, the main product is the coumarin V.

Coumarins IV and V were formed when the substituted benzyl chlorides XI and XII, respectively, were used to alkylate sodio methyl malonate; a coumarin was also produced when XI was used to alkylate sodio ethyl malonate. These results are in contrast to those obtained in a previous study of pseudophenol halides<sup>6</sup> which gave benzylmalonic esters or hydrocoumarins, rather than coumarins. Since the only difference in procedure used in handling these two pseudophenol halides and the one previously studied<sup>6</sup> involved a change in the solvent (dioxane in place

of ether), the difference between the products in the two cases must be due to differences in the relative rates of the competing reactions. With regard to the last two steps, cyclization and dehydrogenation, it cannot be said with certainty which occurs first. What evidence there is, however, indicates that cyclization precedes dehydrogenation, for it has been possible to dehydrogenate the hydrocoumarin III to the coumarin V by action of a quinone, whereas no such dehydrogenation of benzylmalonic esters such as II to benzalmalonic esters has been observed.

Coumarin IV was prepared not only from the benzyl chloride XI, but also from the aldehyde XIII. This coumarin, however, was *not* identical with the carbomethoxycoumarin previously reported<sup>4b</sup> as obtained from trimethylbromoquinone. Nor was the carbomethoxycoumarin synthesized from XI identical with the carbomethoxycoumarin previously reported<sup>4b</sup> as obtained from trimethylbromoquinone and sodio ethyl malonate. Therefore the structure IV, previously reported for these products, is in error. However, the coumarin V derived from the benzyl chloride XII as well as from the bromoaldehyde XIV and methyl malonate was identical in all respects with the corresponding coumarin ester previously obtained from bromotrimethylquinone and metallic enolates of malonic esters. It follows that all the basic structures reported by Smith and Johnson,<sup>4b</sup> with meta orientations of the methyl groups, must be replaced by structures analogous to V with ortho orientations of the methyl groups.

In order to make certain of the identity of the various specimens of V, and to avoid any error due to a possible failure of the mixed melting point tests, X-ray powder diagrams were determined of four samples of 3-carbomethoxy-5-bromo-6-hydroxy-7,8-dimethylcoumarin, V. The four specimens of V were as follows, and the diagrams are shown in Fig. 1.<sup>7</sup> It is obvious, from the diagrams, that all four samples are identical.

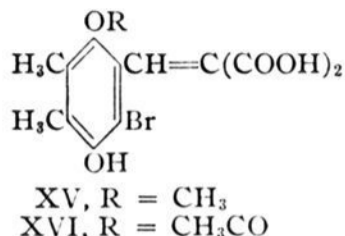
In the earlier paper<sup>4b</sup> it was shown that trimethylbromoquinone and magnesium ethyl malonate reacted to give an excellent yield of a magnesium derivative, which was converted by action of hydrochloric acid into the coumarin ester corresponding to V. However, this magnesium derivative, by action of methyl sulfate or of acetyl chloride, was converted into products closely related to, but different from, the methyl ether and

(5) (a) Smith and Nichols, *ibid.*, **65**, 1739 (1943); (b) Wilds, *ibid.*, **64**, 1421 (1942); (c) Wilds and Johnson, *ibid.*, **67**, 286 (1945).

(6) Smith and Carlin, *ibid.*, **64**, 524 (1942).

(7) The authors wish to acknowledge their indebtedness to Dr. Harold P. Klug of this Laboratory, who prepared the diagrams. Sample 1 was passed through a 250-mesh sieve; the others were ground, but not sieved. The samples were mounted as a sheet of powder between Scotch tape and were photographed on sextants of a flat, circular film using Cu-K $\alpha$  radiation at approximately 30,000 volts and 20 milliamperes. Exposure two hours; distance from sample to film approximately 5 cm.; 0.025 inch pinhole slits. The sample was oscillated and the camera was rotated at 1 r.p.m. during the exposure.

acetate of V (ethyl ester), respectively. These compounds were tentatively assigned structures XV and XVI. These substances have now been



found to have the same basic structures as V and its derivatives; the substance previously regarded as XV is in reality the carbomethoxycoumarin V, whereas the acetate, previously regarded as XVI, is actually not an acetate at all, but is the carboxycoumarin corresponding to V. The colorless acetylation product derived from the supposed XV, and for which no structure was written, is actually the acetate of V.

### Experimental<sup>8</sup>

**Magnesium Methoxide.**—Magnesium (5 g.) was refluxed for one and one-half hours with dry methanol (150 cc.) containing a crystal of iodine. It was occasionally necessary to remove the source of heat in order to control the extremely vigorous reaction. The large granular crystals (9.8 g., 57%) of the methoxide were removed from the cooled mixture and dried in a vacuum desiccator.

**Magnesium Ethoxide.**—Magnesium (10 g.) was covered with a mixture of dry ethanol (128 cc.) and xylene (20 cc.). Iodine (1 g.) was added, and the mixture was stirred and refluxed for six hours while protected from moisture (calcium chloride tube). Dry ethanol (100 cc.) was added, the mixture was cooled, and the solid (44 g., 93%) was removed, dried in a vacuum desiccator, passed through a 40-mesh sieve, and stored in a tightly stoppered bottle.

**Bromotrimethylquinone.**—Trimethylhydroquinone<sup>9,10</sup> (47.5 g., 0.3 mole) was dissolved in acetic acid (950 cc.) containing a crystal of iodine. A solution of bromine (54.4 g., 0.34 mole) in acetic acid (190 cc.) was added dropwise and with stirring. The mixture was stirred at room temperature for five hours and poured into water (2300 cc.). The solid was removed, mixed with a solution of ferric sulfate (700 g., 1.25 moles) in water (1900 cc.) and hydrochloric acid (190 cc.), and the mixture was steam distilled. The distillate was cooled and filtered, and the filtrate was extracted with ether until the extracts were colorless. The combined extracts were dried, the ether was removed and the residue was combined with the solid previously obtained from the steam distillate. The product weighed 50.2 g. (68%) and melted at 79–80°.

**3-Carbomethoxy-3,4-dihydro-5-bromo-6-hydroxy-7,8-dimethylcoumarin, III.**—A solution of methyl malonate (11.5 g., 0.087 mole) in dry methanol (1000 cc.) was refluxed for one hour with finely powdered magnesium methoxide (7.5 g., 0.087 mole). A solution of bromotrimethylquinone (10 g., 0.044 mole) in dry methanol (100 cc.) was added dropwise (one hour) to the refluxing solution. The mixture was stirred and refluxed for an additional thirteen hours. The light gray solid (13 g.) was removed from the cooled mixture, washed with dry ether, and carefully mixed with hydrochloric acid (10%, 80 cc.), whereupon there was evolution of considerable heat and the color of the mixture became yellow. The mixture was cooled and

(8) Microanalyses by S. T. Rolfsen, R. W. King and P. Morgan, except for those marked with an asterisk, which were carried out in the laboratories of Merck and Co., Inc., through the courtesy of Dr. R. T. Major.

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

(10) Smith, *THIS JOURNAL*, **56**, 472 (1934).

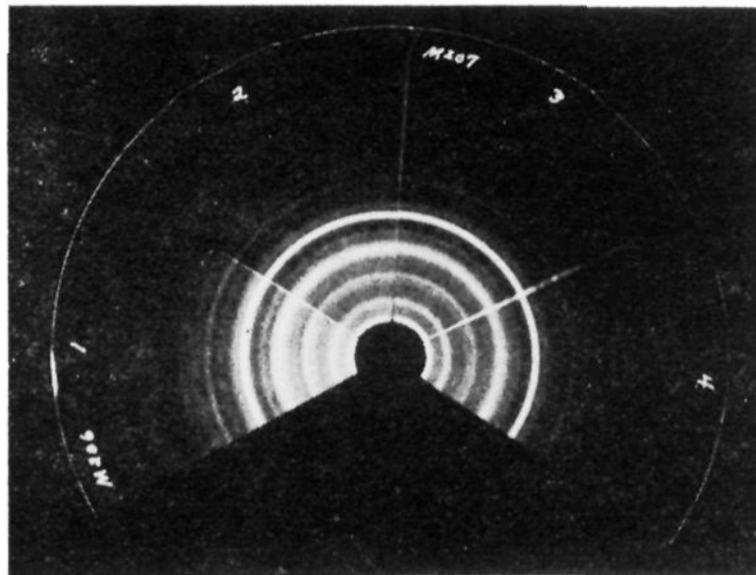


Fig. 1.—M 206, no. 1, by hydrolysis and subsequent esterification with methyl alcohol of a specimen of 3-carbomethoxy-5-bromo-6-hydroxy-7,8-dimethylcoumarin obtained from trimethylbromoquinone and sodio ethyl malonate; M 206, no. 2, from XI and methyl malonate; M 206, no. 3, by action of methyl sulfate upon the magnesium derivative produced from trimethylbromoquinone, ethyl malonate, and magnesium ethoxide; M 206, no. 4, the original product of Smith and Johnson, prepared by them by the method used for no. 3.

the solid (9.9 g., 69%, m. p. 142–146°) was removed. After one crystallization from methanol, the product weighed 7.1 g. and melted at 149–150°; repeated crystallization gave a white, microcrystalline solid melting at 152–153°.

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{13}\text{O}_5\text{Br}$ : C, 47.41; H, 3.95; Br, 24.31; mol. wt., 329. Found: C, 47.52; H, 4.20; Br, 24.28, 24.44; mol. wt., 329, 333 (calcd. from the values for Br); 357 (cryoscopic). Calcd. for  $\text{C}_{14}\text{H}_{17}\text{O}_6\text{Br}$  (II): C, 46.53; H, 4.71.

The dihydrocoumarin III (0.3 g.) was dissolved in methyl sulfate (5 cc.) and a solution of potassium hydroxide (20%) was added dropwise and with stirring until the mixture was just alkaline. Methyl sulfate (2 cc.) was added, followed by more alkali until the solution was again alkaline, then by methyl sulfate until the alkali was neutralized. The mixture was poured into water (60 cc.). A semi-solid material resulted, but no pure crystalline material could be isolated.

The dihydrocoumarin III (0.1 g.) in ethanol (95%, 100 cc.) was shaken for four hours with hydrogen (42 lb.) in the presence of palladium-barium carbonate catalyst (0.1 g.). The catalyst was removed and the solution was concentrated to a volume of 5 cc. by distillation. When water (10 cc.) was added, an oil separated, but this could not be induced to crystallize.

**2,6-Diacetoxy-3-carbomethoxy-5-bromo-7,8-dimethyl-1,4-chromene, IX.**—The hydrocoumarin III (1 g.) was warmed for ten minutes on the steam-bath with acetic anhydride (2 cc.) and sulfuric acid (1 drop). The cooled solution was cautiously diluted with water until precipitation began, then thoroughly chilled and the solid was removed and crystallized from methanol. It was white, weighed 0.08 g. and melted at 169–169.5°.

*Anal.* Calcd. for  $\text{C}_{17}\text{H}_{17}\text{O}_7\text{Br}$ : C, 49.39; H, 4.11. Found: C, 49.45; H, 4.25. Calcd. for  $\text{C}_{18}\text{H}_{21}\text{O}_8\text{Br}$  (diacetate of II): C, 48.54; H, 4.72.

**2,6-Dimethoxy-3-carbomethoxy-5-bromo-7,8-dimethyl-1,4-chromene, X.**—A solution of diazomethane (from 2 g. of nitrosomethylurea) in ether (20 cc.) was added to a cold solution of the hydrocoumarin III (0.33 g., 0.001 mole) in ether (85 cc.). The solution was allowed to stand overnight at room temperature; it was then filtered and the

filtrate was concentrated until solid began to separate. The cooled solution then deposited 0.16 g. of white solid melting at 163–167°. This was crystallized several times from a 1:2 mixture of benzene and petroleum ether (b. p., 90–100°), when it melted at 168–169°.

*Anal.* Calcd. for  $C_{18}H_{17}O_4Br$ : C, 50.42; H, 4.76. Found: C, 50.68; H, 4.87. Calcd. for  $C_{18}H_{21}O_4Br$  (dimethyl ether of II): C, 49.34; H, 5.40.

**3,4-Dihydro-5-bromo-6-hydroxy-7,8-dimethylcoumarin, VI.**—The hydrocoumarin ester III (4 g.) was dissolved in acetone (400 cc.), water (200 cc.), and hydrochloric acid (200 cc.) and the solution was refluxed for three and one-half hours. Acetone was removed by evaporation at 45° under reduced pressure; during this process, a tarry material was first deposited on the walls of the flask, followed by deposition of a solid. The mixture was cooled and the light brown solid (1.7 g.) was removed, dissolved in methanol, and the solution was boiled with charcoal. The charcoal was removed and the filtrate was concentrated to a volume of 15 cc. and cooled. There resulted 0.47 g. of white needles which melted at 171–172°. Concordant analytical values could not be obtained for this compound, although different samples of the substance were analyzed, and by several different analysts.

*Anal.* Calcd. for  $C_{11}H_{11}O_3Br$ : C, 48.71; H, 4.06; Br, 29.52; mol. wt., 271. Found: C, 50.97, 51.89, 53.79, 53.55, 56.29; H, 4.73, 4.21, 5.08, 4.87, 4.40; mol. wt. (cryoscopic), 264.

The above hydrolysis was repeated (using 0.6 g. of III and proportionate amounts of the other reagents) in an apparatus arranged so that the gases could be swept out with a current of nitrogen and passed through barium hydroxide solution. A copious precipitate of barium carbonate was obtained; the organic product (VI) weighed 0.05 g. and melted at 162–166°.

A solution of VI (0.5 g.) in benzene (10 cc.) was refluxed for thirty minutes with 10 cc. of an alkaline solution prepared from sodium (0.7 g.), methanol (15 cc.) and water (5 cc.). The aqueous layer quickly became red and the benzene layer lost its color. The benzene layer was removed and the aqueous layer, after extraction with ether, was acidified and again extracted with ether. The second ether extract was in turn extracted with aqueous sodium bicarbonate (5%, 20 cc.). The ether solution was evaporated; the residue (0.06 g.) was starting material melting at 163–166°. The bicarbonate solution was acidified (litmus) and extracted with ether. Evaporation of this extract under reduced pressure left a residue of dark red oil which could not be crystallized. A portion of this oil, dissolved in ether, was shaken with aqueous sodium hydrosulfite; the dark red solution quickly became almost colorless. Evaporation of the ether left a light yellow, semi-solid residue, from which no pure material could be obtained by crystallization.

**Dehydrogenation of III to the Coumarin V.**—A. The dihydrocoumarin, III (0.33 g., 0.001 mole) and trimethylbromoquinone (0.23 g., 0.001 mole) were refluxed for fifty hours in dioxane (15 cc.). The solution was concentrated to 5 cc. and diluted with water (10 cc.). The yellow solid (0.065 g., 20%) was removed and crystallized from methanol. It melted at 240°, alone or when mixed with an authentic sample of V. The acetate, prepared in the usual way, melted at 189° alone or when mixed with an authentic specimen of the acetate of V.

B. The dihydrocoumarin III (0.33 g., 0.001 mole) and bromotrimethylquinone (0.46 g., 0.002 mole) were refluxed in methanol (50 cc.) for forty-two hours. The solution was concentrated to 25 cc. and cooled. The yellow solid (16 mg., m. p. and mixed m. p. with V, 235–238°) was removed and the filtrate was concentrated to 5 cc. and cooled. The black crystalline quinhydrone (0.15 g., 33%) melted at 144–146°. The filtrate from the quinhydrone was steam distilled in the presence of manganese dioxide (0.1 g.) and the solid remaining in the distillation

flask was removed and extracted with methanol. The methanol solution was evaporated to 2 cc. and cooled; there resulted 0.026 g. of the coumarin V, m. p. 233–236°.

The coumarin V (0.4 g.) in acetic acid (200 cc.) was shaken with hydrogen under atmospheric pressure in the presence of palladium-barium carbonate catalyst (0.4 g.). Almost no hydrogen was absorbed in one and one-half hours; the solution yielded 0.36 g. of unchanged V.

**2-( $\beta,\beta$ -Dicarbomethoxyethyl)-3-bromo-5,6-dimethylbenzoquinone, VIII.**—A solution of the hydrocoumarin III (0.1 g.) and ferric chloride hexahydrate (0.3 g.) in methanol (15 cc.) containing hydrochloric acid (0.6 cc.) was allowed to stand at room temperature for twelve hours. Water (30 cc.) was added and the solution was cooled. The yellow needles (0.097 g., 89%, m. p., 95–97°) were removed and crystallized from methanol, when they melted at 97–98°.

*Anal.* Calcd. for  $C_{14}H_{13}O_6Br$ : C, 46.80; H, 4.18; Br, 22.29. Found: C, 47.09; H, 4.58; Br, 22.92.

**2-( $\beta,\beta$ -Dicarbomethoxyethyl)-3-bromo-5,6-dimethylhydroquinone, II.**—The quinone VIII (50 mg.) in ether (10 cc.) was shaken with aqueous sodium hydrosulfite (10%, 5 cc.). The ether layer was removed, dried (sodium sulfate), and evaporated under reduced pressure. The residue, a white solid, melted at 109–112°. Action of ferric chloride upon this hydroquinone in methanol converted it into the quinone VIII, m. p. and mixed m. p., 95–97°.

A solution of the quinone VIII (0.097 g.) in ether (40 cc.) was shaken with aqueous sodium hydrosulfite (0.5 g. in 20 cc.) until the color disappeared. The ether solution was removed and evaporated on the steam-bath. The white residue was dissolved in acetone (5 cc.), water (5 cc.) and hydrochloric acid (5 cc.), and the solution was refluxed for three and one-half hours. The acetone was removed by evaporation under reduced pressure and the remaining solution was cooled. The brown solid was removed and crystallized from methanol. It weighed 8 mg., and was the hydrocoumarin VI, m. p. and mixed m. p., 162–165°.

*m*-Xyloquinone, m. p. 74–75°, was prepared from 3,5-dimethylphenol as previously described.<sup>9</sup>

*m*-Xylohydroquinone was prepared by reduction of the quinone by action of stannous chloride in hydrochloric acid. The yield was 92% and the product melted at 151–153°. It is important that the quinone be pure, otherwise the reduction product is very difficult to purify.

**Bromo-*m*-xylohydroquinone.**—A solution of bromine (6.69 g., 0.041 mole) in acetic acid (20 cc.) was added dropwise and with stirring to a solution of *m*-xylohydroquinone (6 g., 0.043 mole) in acetic acid (120 cc.). The mixture was stirred for five hours, and then the acetic acid was removed by rapid (fifteen–twenty minutes) evaporation on the steam-bath under reduced pressure. The residue was crystallized from dilute ethanol (40%, 60 cc.). The product (7.1 g., 75%) melted at 145–146°; after several crystallizations from aqueous ethanol, a specimen melted at 148–149°.

*Anal.* Calcd. for  $C_8H_9O_2Br$ : C, 44.24; H, 4.15. Found: C, 44.17; H, 3.58.

This hydroquinone gave no aldehyde when it reacted with zinc cyanide, hydrochloric acid, and aluminum chloride. The product was a high melting brown solid, insoluble in aqueous bisulfite, which appeared to be polymeric.

**Bromo-*m*-xylohydroquinone Dimethyl Ether.**—A solution of bromo-*m*-xylohydroquinone (4 g., 0.02 mole) in methanol (110 cc.) and methyl sulfate (25.5 g., 0.2 mole) was heated to the boiling point, the flame was removed and, with vigorous stirring, a solution of potassium hydroxide (49 g., 0.85 mole) in methanol (200 cc.) was added at such a rate that refluxing was maintained. Refluxing was then continued for thirty minutes, water (600 cc.) was added and the solution was cooled. The solid (3.2 g., 71%) was removed and crystallized several times from methanol. The substance melted at 53–54°.

*Anal.* Calcd. for  $C_{10}H_{13}O_2Br$ : C, 48.98; H, 5.31. Found: C, 48.21; H, 5.12.

(11) K. C. Johnson, Ph.D. Thesis, University of Minnesota, 1937, reported this compound to melt at 148°.

No aldehyde could be obtained from this ether by reaction with zinc cyanide, hydrochloric acid, and aluminum chloride according to the procedure of Tess<sup>12</sup>; the product was a black, viscous tar, insoluble in aqueous sodium bisulfite, and from which no crystalline material could be isolated. Although the ether reacted with formaldehyde and hydrochloric acid, the product was not a simple chloromethyl derivative. The ether (3.2 g.) was dissolved in acetic acid (32 cc.) containing hydrochloric acid (32 cc.) and formalin (40%, 12.8 cc.). The solution was stirred and maintained at 60–70° while a current of hydrogen chloride was passed through it for four hours. The mixture was poured into water (250 cc.) and the solid (2.8 g.) was removed; it melted at 75–95°. After several crystallizations from petroleum ether (b. p. 90–100°) the substance (0.11 g.) melted at 138–139.5°, but this product was not the chloromethyl derivative.

*Anal.* Calcd. for  $C_{11}H_{14}O_2ClBr$ : C, 44.97; H, 4.77. Found: C, 56.19; H, 7.15.

**2,4-Dimethyl-3,6-dihydroxy-5-bromobenzyl Chloride, XI.**—Bromo-*m*-xylohydroquinone (1 g.) was dissolved in a mixture of formalin (2 cc., 40%) and acetic acid (17 cc.). Hydrogen chloride was bubbled into the well-stirred solution for two and one-half hours while the temperature was maintained at 5–15°. Deposition of solid began after one hour. The mixture was cooled and the gray, powdery solid (0.63 g., 51%, m. p. 151–153° dec.) was removed and crystallized several times from a 1:1 mixture of ether and petroleum ether (b. p. 90–100°). The substance formed glistening white needles which melted at 158–159° (dec.), but the melting point varied somewhat with the rate of heating. Slight variations in the procedure affect the yields very much, for these varied from 35 to 65% under apparently identical conditions.

*Anal.* Calcd. for  $C_9H_{10}O_2ClBr$ : C, 40.67; H, 3.76. Found: C, 40.85; H, 4.24.

When acetic anhydride, followed by water, was added to the original filtrate after removal of XI, there resulted the diacetate of XI in yields amounting to 20–40%.

**2,4-Dimethyl-3,6-diacetoxy-5-bromobenzyl Chloride.**—The chloride XI (0.4 g.) was dissolved in acetic anhydride (3 cc.) containing a trace of sulfuric acid. The solution was heated to the boiling point and then cooled. The solid (0.35 g., 66%, m. p., 148–150°) was removed and crystallized several times from a 1:5 mixture of benzene and petroleum ether (b. p. 98–100°) when it melted at 153–153.5°.

*Anal.* Calcd. for  $C_{13}H_{14}O_4ClBr$ : C, 44.51; H, 3.99. Found: C, 44.12; H, 3.94.

This diacetate could not be obtained by chloromethylation of the diacetate of bromo-*m*-xylohydroquinone. In contrast with the chloride XI, this diacetate was extremely unreactive. Thus, when 1.05 g. of the diacetate was refluxed for six hours with a solution of sodio methyl malonate (from 0.79 g. of methyl malonate and 0.138 g. of sodium) in dioxane (25 cc.), no alkylation occurred and 0.9 g. of the diacetate was recovered.

**2,4-Dimethyl-3,6-dihydroxybenzaldehyde.**—*m*-Xylohydroquinone (1.2 g.) in benzene was converted to the aldehyde by action of zinc cyanide, aluminum chloride and hydrochloric acid. The yield was poor and the product was difficult to purify. The yellow aldehyde (0.11 g., 7.7%) melted at 143–145° after crystallization from water. The aldehyde could not be prepared from the hydroquinone and *N*-methylformanilide according to the procedure of Fieser and Hartwell<sup>13</sup>; most of the hydroquinone was recovered unchanged.

In duplicate experiments, this aldehyde (0.1 g.) and malonic acid (0.1 g.) were dissolved in ethanol containing piperidine (3 drops) and the solution was allowed to stand at room temperature for three days. It was poured into hydrochloric acid (8%, 10 cc.) and cooled; the solid (a) 0.065 g., (b) 0.062 g. was unchanged aldehyde (m. p., 145–146°). No other material could be isolated from the re-

action mixture; no coumarin, as claimed by Smith and Johnson<sup>4b</sup> to be the product of this reaction, could be obtained.

**2,4-Dimethyl-3,6-dihydroxy-5-bromobenzaldehyde, XIII.**—A cold solution of the above aldehyde (0.2 g., 0.0012 mole) in carbon tetrachloride (100 cc.) containing a crystal of iodine was stirred and brominated by dropwise addition of a solution of bromine (0.19 g., 0.0012 mole) in carbon tetrachloride (20 cc.). The mixture was stirred and cooled for four hours, during which a yellow solid (0.31 g.) deposited. The solid was removed and crystallized from aqueous methanol (90%); the product weighed 0.15 g. (51%) and melted at 176–178°. After repeated crystallization the substance melted at 185–186°.

*Anal.* \*Calcd. for  $C_9H_9O_3Br$ : C, 44.08; H, 3.67. Found: C, 44.28; H, 3.68.

**Bromo-*o*-xylohydroquinone.**—Bromine (3.2 g., 0.14 mole) in acetic acid was added dropwise and with stirring to a solution of *o*-xylohydroquinone<sup>12</sup> (2 g., 0.15 mole) in acetic acid (145 cc.) at room temperature. Stirring was continued for four hours and the solvent was removed by rapid evaporation under reduced pressure on the steam-bath. The residue, crystallized from aqueous ethanol (40%, 15 cc.) weighed 2.4 g. (80%) and melted at 120–122°. A specimen, crystallized several times from benzene, melted at 123–124°.

*Anal.* Calcd. for  $C_8H_9O_2Br$ : C, 44.24; H, 4.15. Found: C, 44.33; H, 4.43.

**4,5-Dimethyl-3,6-dihydroxy-2-bromobenzyl Chloride, XII.**—A solution of bromo-*o*-xylohydroquinone (1 g., 0.005 mole) in acetic acid (8 cc.) containing formalin (40%, 2 cc.) was stirred and cooled (10–15°) while a current of hydrogen chloride was passed through it for two and one-half hours. The red reaction mixture was cooled and the light gray powder (1 g., 83%) was removed. This material was very unstable and decomposed with formation of a red substance when attempts were made to crystallize it. The crude product was analyzed.

*Anal.* Calcd. for  $C_9H_{10}O_2ClBr$ : C, 40.67; H, 3.76. Found: C, 41.03; H, 3.76.

**2,5-Dihydroxy-3,4-dimethylbenzaldehyde.**—A solution of 2,5-dimethoxy-3,4-dimethylbenzaldehyde<sup>12</sup> (0.6 g., 0.003 mole) in acetic acid (6 cc.) containing hydrobromic acid (48%, 6 cc.) was refluxed for two hours. The black solution was poured over ice (20 g.), the ice was allowed to melt, and the mixture was steam distilled to remove acetic acid and unchanged dimethoxyaldehyde. The hot residue was filtered and the filtrate was concentrated to a volume of 15–20 cc. This mixture was cooled until the tar began to solidify, and was then filtered and the filtrate was cooled. The large yellow crystals (0.19 g., 37%) melted at 148–150°; a specimen, recrystallized from dilute methanol (30%), melted at 149–150°.

*Anal.* Calcd. for  $C_9H_{10}O_3$ : C, 65.06; H, 6.02. Found: C, 65.01, 64.79; H, 6.12, 5.97.

**2-Bromo-3,6-dihydroxy-4,5-dimethylbenzaldehyde, XIV.**—A solution of bromine (0.19 g., 0.0012 mole) in carbon tetrachloride (20 cc.) was added dropwise and with stirring to a cooled solution of the above aldehyde (0.2 g., 0.0012 mole) in carbon tetrachloride (130 cc.) containing a crystal of iodine. The mixture was stirred for three and one-half hours and the solvent was removed by evaporation on the steam-bath. The residue (0.26 g., 88%) melted at 114–118°; after several crystallizations from methanol the substance formed fine, yellow needles melting at 124–125°.

*Anal.* Calcd. for  $C_9H_9O_3Br$ : C, 44.08; H, 3.67. Found: C, 44.62; H, 3.94.

**3-Carbomethoxy-5,7-dimethyl-6-hydroxy-8-bromocoumarin, IV. A.** A solution of methyl malonate (1.32 g., 0.01 mole) in dry, peroxide-free dioxane (25 cc.) was stirred at room temperature with sodium (0.21 g., 0.009 mole) until the metal dissolved (ten hours). A solution of the benzyl chloride XI (0.8 g., 0.003 mole) in dry, peroxide free dioxane (25 cc.) was added dropwise and with stir-

(12) Smith and Tess, *THIS JOURNAL*, **66**, 1528 (1944).

(13) Fieser and Hartwell, *THIS JOURNAL*, **60**, 2555 (1938).

ring. The mixture was stirred for twenty-four hours, during which the color became green, then purple, and finally brown. Hydrochloric acid (0.5 cc.) was added, the red solution was diluted with water (100 cc.), cooled, and the solid (0.35 g., 35%) was removed and crystallized from methanol. The yellow needles melted at 263–264°, alone or when mixed with an authentic sample prepared from the aldehyde XIII.

*Anal.* \*Calcd. for  $C_{13}H_{11}O_5Br$ : C, 47.70; H, 3.36. Found: C, 47.92; H, 3.57.

**B.** The aldehyde XIII (0.1 g.) and methyl malonate (0.1 g.) were dissolved in methanol (5 cc.) containing piperidine (3 drops). The solution, after standing at room temperature for sixteen hours, contained a deposit of yellow crystals (0.03 g., m. p., 256–258°) which were removed and crystallized twice from methanol. The solid then melted at 263–264° (dec.).

*Anal.* Calcd. for  $C_{13}H_{11}O_5Br$ : C, 47.70; H, 3.36. Found: C, 47.98; H, 3.03.

**3-Carboethoxy-5,7-dimethyl-6-hydroxy-8-bromocoumarin.**—The benzyl chloride XI was used to alkylate ethyl malonate, exactly as described above for the alkylation of methyl malonate except that ethyl malonate (1.92 g., 0.012 mole) was used in place of the methyl ester. The product, after crystallization from 95% ethanol, weighed 0.21 g. (20%) and melted at 206–207°.

*Anal.* \*Calcd. for  $C_{14}H_{13}O_5Br$ : C, 49.26; H, 3.84. Found: C, 48.86; H, 4.06.

**3-Carboethoxy-3,4-dihydro-5,7-dimethyl-6-hydroxycoumarin.**—A solution of the above bromocoumarin (80 mg.) in ethanol (95%, 40 cc.) was shaken for three hours with hydrogen (45 lb.) in the presence of palladium-barium carbonate catalyst (80 mg.). The catalyst was removed and the solvent was evaporated at 30–35° under reduced pressure. The residue was crystallized from ethanol (80%, 1 cc.). The hydrocoumarin (42 mg.) melted at 122–126°; recrystallization gave a specimen melting at 130–132°. Smith and Johnson<sup>4b</sup> reported 142–143° as the melting point of the product they supposed to have this structure.

*Anal.* Calcd. for  $C_{14}H_{16}O_5$ : C, 63.61; H, 6.06. Found: C, 63.75; H, 6.14.

A mixture of this hydrocoumarin and 3-carboethoxy-3,4-dihydro-7,8-dimethyl-6-hydroxycoumarin (m. p., 140–142°) melted at 108–117°.

**3-Carbomethoxy-7,8-dimethyl-6-hydroxy-5-bromocoumarin, V.**—A. A solution of sodio methyl malonate in dry, peroxide-free dioxane (25 cc.) was prepared from sodium (0.21 g., 0.009 mole) and methyl malonate (1.32 g., 0.01 mole). To this was added, dropwise and with stirring, the benzyl chloride XII (0.8 g., 0.003 mole) in dioxane (25 cc.). The mixture was stirred for twenty-four hours, then made acidic with hydrochloric acid (1 cc.), diluted with water (100 cc.), cooled and filtered. The dark, amorphous solid was dissolved in methanol and the solution was boiled with charcoal. The solution was filtered, the filtrate was concentrated until crystallization began, and then cooled. The product (0.13 g., 13%) melted at 241–242° after it was crystallized from methanol. When mixed with a specimen of V prepared from the aldehyde XIV, there was no depression in melting point. The acetate of V, prepared in the usual manner, melted at 191° alone or when mixed with an authentic specimen.

**B.** A solution of the aldehyde XIV (0.2 g., 0.008 mole), methyl malonate (0.2 g., 0.0015 mole) and triethylamine (3 drops) in methanol (10 cc.) was allowed to stand for three days at room temperature. The solid (0.02 g., 8%) was removed and crystallized from methanol, when it melted at 239–240°.

**C.** From **3-Carboxy-7,8-dimethyl-6-hydroxy-5-bromocoumarin.**—The coumarin acid (20 mg.) was refluxed for twenty-four hours in dry methanol (10 cc.) containing sulfuric acid (1 drop). The solution was concentrated to about 3 cc. and carefully diluted with water until a solid began to deposit. The solid was removed from the cooled mixture and recrystallized from methanol; the product

melted at 240–242°. The acetate melted at 191°. Specimens A, B and C of V were identical, showing no depression in melting point when they were mixed in any combination. Likewise, the acetates of these products were identical.

**3-Carboethoxy-7,8-dimethyl-6-hydroxy-5-bromocoumarin.**—A solution of bromotrimethylquinone (5.75 g., 0.025 mole) in dry ethanol (50 cc.) was added dropwise (thirty-five minutes) at room temperature to a well-stirred solution of ethyl malonate (4 g., 0.025 mole, freshly distilled) and sodium (0.75 g., 0.033 gram atom) in dry ethanol (25 cc.). The mixture was allowed to stand for thirty minutes and was then poured into a mixture of ice (250 g.) and hydrochloric acid (25 cc.). After the ice melted, the solid was removed and crystallized twice from ethanol. It weighed 2.4 g. (28%) and melted at 198–200°. Smith and Johnson<sup>4b</sup> reported 200°. This coumarin (m. p. 200°) when mixed with 3-carboethoxy-5,7-dimethyl-6-hydroxy-8-bromocoumarin (m. p. 206–207°) melted at 178–187°.

**3-Carboethoxy-3,4-dihydro-7,8-dimethyl-6-hydroxycoumarin.**—The above coumarin ethyl ester (0.2 g.) in ethanol (95%, 100 cc.) was shaken for three hours with hydrogen (42 lb.) in the presence of palladium-barium carbonate catalyst (0.2 g.). The catalyst was removed, the filtrate was concentrated to 10 cc. and diluted with water (15 cc.). The cooled solution deposited 0.11 g. (72%) of the white hydrocoumarin, which melted at 141–143°. Smith and Johnson<sup>4b</sup> gave 142–143° as the melting point of this product, which they supposed had the methyl groups meta to each other. It was not possible to dehydrogenate this compound to the coumarin by action of ferric chloride, although several attempts were made to do so. A typical experiment is described: the hydrocoumarin (0.13 g.) in ethanol (95%, 20 cc.) was refluxed for one hour with a solution of ferric chloride hexahydrate (0.4 g.) in water (7 cc.). Water (20 cc.) was added and the solution was cooled, but no solid was deposited. Addition of more water (10 cc.) followed by removal of the ethanol also failed to produce a solid, only a small amount of yellow oil separated when the solution was cooled. Evaporation of the solution to 5 cc. caused the separation of a black, amorphous solid.

**3-Carboxy-7,8-dimethyl-6-hydroxy-5-bromocoumarin.**—Either coumarin ester, V or the ethyl ester (1 g.) when refluxed for four hours in acetone (75 cc.), water (50 cc.) and hydrochloric acid (50 cc.) gave the acid in about 75% yield. After crystallization from methanol, the substance melted at 245–247°. Esterified with methanol, this acid gave the ester V; esterified with ethanol, the product was the ethyl ester.

**The Magnesium Derivative.**—Magnesium ethoxide (12 g., 0.1 mole) was refluxed for two hours with ethyl malonate (12 g., 0.075 mole, freshly distilled) in dry ethanol (500 cc.) while the mixture was protected from moisture by a calcium chloride guard tube. Then, while a slow current of dry air was passed through the refluxing mixture, a solution of bromotrimethylquinone (16 g., 0.07 mole) in dry ethanol (250 cc.) was added dropwise. Passage of the air current and refluxing were continued for twelve hours. The mixture was cooled and the solid was removed, washed twice with small portions of dry ether, and dried in a vacuum desiccator. The tan solid weighed 24.3 g. This magnesium derivative (21.3 g.) was refluxed with methanol (225 cc.) containing methyl sulfate (56 g.). The solid soon (twelve to fifteen minutes) dissolved; after the mixture was refluxed for one hour, it was cooled (0°). The yellow solid (3.4 g., m. p. 140–150°) was removed and crystallized repeatedly from acetic acid, when it melted at 241–242°. It was the carbomethoxycoumarin V.

*Anal.* Calcd. for  $C_{13}H_{11}O_5Br$ : C, 47.70; H, 3.36. Found: C, 47.73; H, 3.61.

Smith and Johnson<sup>4b</sup> who tentatively regarded this substance as XV, reported it to melt at 240–241°. Better yields were obtained when the magnesium derivative was processed in smaller lots (2–3 g.); the yield also varied with different samples of the magnesium derivative. This carbomethoxycoumarin V, m. p. and mixed m. p., 240–242°

also resulted when the corresponding coumarin acid was esterified with methanol.

**3-Carbomethoxy-7,8-dimethyl-6-methoxy-5-bromocoumarin.**—The combined mother liquors from the recrystallization of V (3.4 g., from the magnesium derivative above) were heated and diluted with water to incipient turbidity. The cooled solution deposited 1.4 g. of the methyl ether-ester, melting at 158–160°. After several crystallizations from ethanol, the product formed light yellow needles which melted at 170–171°.

*Anal.* Calcd. for  $C_{14}H_{13}O_3Br$ : C, 49.27; H, 3.81; Br, 23.46;  $OCH_3$  (two), 13.2; mol. wt., 345. Found: C, 49.28, 48.99; H, 3.74, 3.96; Br, 23.12, 22.98;  $OCH_3$ , 17.9; mol. wt. (calcd. from the values for Br), 341, 348.

This methoxycoumarin ester (0.5 g.) was recovered unchanged after it was heated on the steam-bath for fifteen minutes with acetic anhydride (15 cc.) and sulfuric acid (1 drop).

**3-Carboxy-7,8-dimethyl-6-methoxy-5-bromocoumarin.**—The above methoxy ester (0.1 g.) was refluxed for thirty minutes in acetic acid (10 cc.) containing hydrochloric acid (10%, 5 cc.). The hot solution was diluted with water to incipient crystallization, and then cooled. The solid was removed and crystallized from methanol. It weighed 40 mg. and melted at 205–207°, alone or when mixed with an authentic specimen prepared by methylation of the coumarin acid: Smith and Johnson<sup>4b</sup> report 210–211° as the melting point of this compound. When the methoxy acid (35 mg.) was refluxed for twelve hours in methanol (15 cc.) containing sulfuric acid (1 drop), the product (20 mg.) was the ether-ester, m. p. and mixed m. p., 158–161°.

**3-Carbomethoxy-7,8-dimethyl-6-acetoxy-5-bromocoumarin.**—The coumarin ester V (0.71 g., from the magnesium derivative) was heated for fifteen minutes on the steam-bath with acetic anhydride (16 cc.) and sulfuric acid (2 drops). The cold solution was diluted with water and the solid was removed and crystallized from methanol. The white acetate (0.63 g., 79%) melted at 191–192°. Smith and Johnson<sup>4b</sup> reported their "white acetyl derivative" to melt at 187–188°.

*Anal.* Calcd. for  $C_{15}H_{13}O_6Br$ : C, 48.78; H, 3.52; Br, 21.68; mol. wt., 369. Found: C, 49.22; H, 3.77; Br, 21.78, 21.56; mol. wt., 361 (cryoscopic), 367, 371 (calcd. from the values for Br).

A sample of the coumarin ester V, prepared by esterification of the acid, gave the same acetate, m. p. and mixed m. p. 191–192°.

*Anal.* Found: C, 49.07; H, 3.67.

**3-Carboxy-7,8-dimethyl-6-hydroxy-5-bromocoumarin.**—The above acetate (0.1 g.) was refluxed for forty-five minutes in acetic acid (5 cc.) containing hydrobromic acid (48%, 1 cc.). The hot solution was diluted with water to incipient precipitation, then cooled and filtered. The acid (52 mg.) melted at 245–246°, alone or when mixed with an authentic specimen obtained by hydrolysis of the ethyl ester. The methyl ester V (38 mg.), m. p. and mixed m. p., 240–241°, was obtained by hydrolysis of the above acetate (0.1 g.) by action of methanolic potassium hydroxide at room temperature for twenty minutes. The ester V (0.7 g.) was refluxed for three hours in acetic acid (21 cc.) containing hydrobromic acid (48%, 7 cc.). When the solution was diluted with water, there resulted 0.5 g. of the coumarin acid, m. p. 244–246°. A solution of the coumarin acid (0.25 g.), methanol (100 cc.) containing sulfuric acid (3 drops) was refluxed for sixty-six hours. The solution was concentrated to 30 cc. and cooled. The product (0.21 g.) was the ester V, m. p. and mixed m. p., 241–242°.

The magnesium derivative (2 g.) was refluxed for ten minutes with acetyl chloride (20 cc., freshly distilled).

The solution was diluted with water and the solid was removed and crystallized several times from acetic acid. The product (43 mg.) obtained in this way was 3-carboxy-7,8-dimethyl-6-hydroxy-5-bromocoumarin, m. p. and mixed m. p., 244–246°. Smith and Johnson<sup>4b</sup> tentatively regarded this compound as XVI and reported it to melt at 231–232°.

**3-Carboxy-7,8-dimethyl-6-acetoxy-5-bromocoumarin.**—The above coumarin acid (from the magnesium derivative) was warmed with acetic anhydride containing a trace of sulfuric acid. The solution was poured into water and the solid was removed. The crude solid melted at 218–220°, alone or when mixed with a specimen of this acetate (m. p. 223–224°) which had been prepared by Smith and Johnson.

**3-Carbomethoxy-3,4-dihydro-7,8-dimethyl-6-acetoxy-coumarin.**—The acetate of coumarin ester V (0.1 g.) was dissolved in ethanol (95%, 50 cc.) and subjected for three hours to the action of hydrogen (42 lb.) in the presence of palladium-calcium carbonate catalyst (0.1 g.). After removal of the catalyst, the solution was concentrated to 10 cc., diluted with water (30 cc.), and cooled. The product (74 mg.) was removed and crystallized from ethanol, when it melted at 131.5–132°.

*Anal.* Calcd. for  $C_{15}H_{16}O_6$ : C, 61.64; H, 5.15. Found: C, 61.35; H, 4.91.

### Summary

1. Bromotrimethylquinone reacts with methyl malonate in the presence of magnesium methoxide to form the hydrocoumarin III rather than the coumarin, V, in contrast to the reaction of this quinone with ethyl malonate in the presence of magnesium ethoxide, whereby a coumarin is formed. This is the first example of the isolation of a dihydrocoumarin as the product of a reaction between an alkylated quinone and a metallic enolate.

2. The hydrocoumarin III is dehydrogenated to the coumarin V by action of trimethylbromquinone—the first example of such a direct dehydrogenation of a hydrocoumarin to a coumarin by action of a quinone.

3. Three examples are given of the formation of coumarins, rather than hydrocoumarins, from chloromethylhydroquinones and malonic esters.

4. It is shown that the product of the reaction between trimethylbromoquinone and sodio malonic esters, previously reported to possess structure IV and to be a derivative of *m*-xyloquinone, does not have this structure. The structure is actually V, and the substance is a derivative of *o*-xyloquinone.

5. Both coumarins, IV and V, have been synthesized by unequivocal methods.

6. It is shown that malonic ester enolates react with bromotrimethylquinone to produce compounds of the same type irrespective of whether the metal is sodium or magnesium.

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