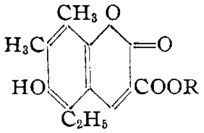
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

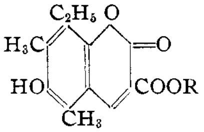
The Reaction between Quinones and Metallic Enolates. XIV. Synthesis of the Three 3-Carboxy-6-hydroxy-bz-dimethyl Ethylcoumarins and their Ethyl Esters[1]

BY LEE IRVIN SMITH AND J. W. OPIE[2]

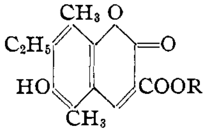
In the previous paper[1] it was shown that the reaction between trimethylethylquinone and sodium malonic ester produced an inseparable mixture of isomers which contained all three of the coumarin esters derivable from this quinone by reaction of the enolate at one of the methyl groups. This was demonstrated by thermal analysis of the products and for this purpose it was necessary to synthesize the three coumarin acids I, II, III and their ethyl esters IV, V, VI.



I, R = H
IV, R = C_2H_5

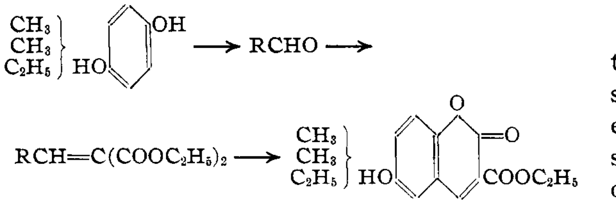


II, R = H
V, R = C_2H_5

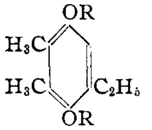


III, R = H
VI, R = C_2H_5

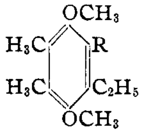
The syntheses started with the corresponding dimethylethylquinones, the preparation of which has been described recently.[3] It was originally planned to synthesize the coumarins from the hydroquinones via the following sequence of compounds



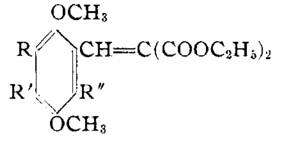
but the yields of hydroquinone aldehydes obtained in the model experiments were very poor and the aldehydes were extremely difficult to separate from unchanged hydroquinones. Nor were much better results obtained by subjecting the hydroquinone dimethyl ethers to the Gattermann reaction. Although the dimethoxyaldehydes doubtless would have formed, they could not be separated from unchanged starting material except by distillation[4] and the small amounts of material available made this impracticable. Finally, in the chloromethylation of the hydroquinone dimethyl ethers a process was found by means of which a good yield of product could be obtained; moreover, this product was either a solid which could be readily purified or, if not, one of the later intermediates (particularly the benzyl alcohols) was a fairly high melting solid which could be obtained in a state of high purity. The sequence of reactions which led to the coumarin esters started with the three dimethylethylquinones and included, in succession



VII, R = H
VIII, R = Ac
IX, R = CH_3



X, R = CH_2Cl
XI, R = CH_2OAc
XII, R = CH_2OH
XIII, R = CHO



XIV A, R = CH_3; R' = CH_3; R'' = C_2H_5
B, R = C_2H_5; R' = CH_3; R'' = CH_3
C, R = CH_3; R' = C_2H_5; R'' = CH_3

the intermediates VII to XIV (illustrated for one series only—that derived from 2,3-dimethyl-5-ethylquinone). In this sequence of reactions, the steps from the quinones to VIII are conventional ones and require little comment. It was found very advantageous, however, to prepare the hydroquinone dimethyl ethers IX via the acetates VIII rather than directly from the hydroquinones. The yields of IX were not only better, but a much purer product resulted. The chloromethylation of IX was a smooth reaction and offered no difficulty, but conversion of the chloromethyl compounds X to the alcohols XII by direct hydrolysis resulted in very poor yields of XII. However, the indirect conversion of X to XII via the ace-

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(1) Paper XIII, THIS JOURNAL, **63**, 932 (1941).

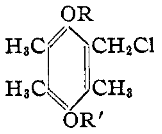
(2) Abstracted from a thesis by Joseph W. Opie, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, July, 1940.

(3) Smith and Opie, *J. Org. Chem.*, **6**, in press (1941).

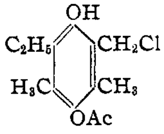
(4) Smith, THIS JOURNAL, **56**, 472 (1934).

tates XI proceeded well and in good yields.[5] The alcohols XII were oxidized to the aldehydes XIII by chromic acid in acetic acid. It was difficult to crystallize the aldehydes, and it was not possible in every case to obtain these substances as solids. However, the steps from XIII to the coumarin acids could be carried out using the crude reaction products, from each previous step, postponing purification until the coumarin acids I, II, III were formed. In this way much time and material were saved. The benzalmalonic esters XIV were converted into the coumarin acids by action of hydrobromic acid in acetic acid, according to the procedure of John and Günther.[6] In this process, the ether and ester groups were cleaved and simultaneously the coumarin ring was closed. Finally, the coumarin acids I, II, III were converted into their ethyl esters IV, V, VI by esterification with ethanol in the presence of a little sulfuric acid.

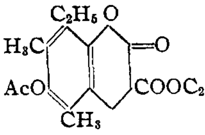
A shorter route from the quinones to the coumarins was not found. The discovery[7] that chloromethylation of trimethylhydroquinone diacetate was accompanied by loss of one of the acetyl groups, giving a monoacetoxy derivative (presumably XV) instead of the diacetoxy derivative (XVI) previously reported[5] appeared at first to open the way to a much less laborious synthesis of the coumarins than that actually used. In the initial experiments, performed upon the diacetate of 2,6-dimethyl-3-ethylhydroquinone, the chloromethylation product (XVI) was used to alkylate ethyl malonate. Ring closure occurred simultaneously, and the product was the acetate (XVIII) of the dihydrocoumarin ester related to II. The dihydrocoumarins were not available for comparison, however, and model experiments performed on the trimethyl analog of XVIII, and on the corresponding trimethylhydroxy coumarin ester[8] showed that these hydrocoumarins could not be dehydrogenated to coumarins by the procedure which Smith and Horner[9] had found quite successful in connection with a dihydrocoumarin derived from naphthalene.



XV, R=H; R′=Ac
XVI, R=R′=Ac



XVII



XVIII

Experimental Part[10]

In this section, the series of compounds derived from ethyl-*o*-xyloquinone, and leading to coumarin I, will be designated as A; those derived from ethyl-*m*-xyloquinone and leading to coumarin II, as B; and those derived from ethyl-*p*-xyloquinone and leading to coumarin III, as C.

Hydroquinone, VII.—The quinone (14 g.) was dissolved in acetic acid (60 cc.). Water (45 cc.) and excess zinc (20 mesh) were added, and the mixture was refluxed until it was colorless. Boiling water (60 cc.) was added, and the hot solution was immediately decanted from the zinc. The zinc was washed once with boiling water (60 cc.) which was decanted into the main solution. The solution was allowed to cool to room temperature, and was then chilled in an ice-bath and the product was filtered off. A small specimen (0.5 g.) was crystallized once from benzene to provide an analytical sample.

2,3-Dimethyl-5-ethylhydroquinone, VIIA, melted at 160–160.5°; the yield was 85%.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.28; H, 8.43. Found: C, 72.84; H, 8.46.

2,6-Dimethyl-3-ethylhydroquinone, VIIB, melted at 158–158.5°; the yield was 74%.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.28; H, 8.43. Found: C, 72.13; H, 8.61.

2,5-Dimethyl-3-ethylhydroquinone, VIIC, melted at 158–159°; the yield was 92%.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.28; H, 8.43. Found: C, 72.38; H, 8.80.

Diacetates VIII.—The hydroquinone (13 g.) was suspended in acetic anhydride (50 cc.), a drop of sulfuric acid was added and the mixture was refluxed for fifteen minutes. The solution was poured over ice, made basic with ammonium hydroxide and the product was removed and crystallized from petroleum ether.

The Acetate VIIIA, of VIIA, melted at 90–91°; the yield was 98%.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.20; H, 7.20. Found: C, 67.55; H, 7.32.

The Acetate VIIIB, of VIIB, melted at 65–66°; the yield was 100%.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.20; H, 7.20. Found: C, 67.01; H, 6.80.

The Acetate VIIIC, of VIIC, melted at 74.5–75.5°; the yield was 64%.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.20; H, 7.20. Found: C, 66.97; H, 7.20.

The Dimethyl Ethers IX.—The diacetate VIII (24.6 g.) was dissolved in methanol (200 cc.) and methyl sulfate

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(5) Smith, Ungnade, Opie, Prichard, Carlin and Kaiser, *J. Org. Chem.*, **4**, 323 (1939).

(6) John and Günther, *Ber.*, **72**, 1649 (1939).

(7) By Mr. R. B. Carlin, in this Laboratory.

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

(9) Smith and Horner, *ibid.*, **60**, 676 (1938).

(10) Microanalyses by E. E. Renfrew and E. E. Hardy.

(100 cc.) was added. To the vigorously stirred and refluxing solution, a solution of potassium hydroxide (120 g.) in methanol (600 cc.) was added slowly until the mixture was strongly basic. Methyl sulfate (30 cc.) was then slowly added, followed by the basic solution, then more methyl sulfate (50 cc.) and again more base. The basic solution was steam distilled, and the distillate was diluted with much water and extracted eight times with ether. The combined ether extractions were washed thoroughly with water and the ether was removed. The ethers were all oils which were not purified further. The yields were: IXA, 90%; IXB, 26%; IXC, 88%.

The Chloromethylation Products X.—The dimethyl ether IX (13.6 g.) was mixed with formalin (50 cc.) and hydrochloric acid (60 cc.) in a 3-necked flask equipped with a stirrer and an efficient reflux condenser. The mixture was stirred vigorously while a rapid stream of hydrogen chloride was passed through. The mixture became quite hot, but after one hour the temperature began to fall, and at this point the flask was immersed in a water-bath at 50–60°. The product began to precipitate after two and one-half hours, and the reaction was complete after three and one-half hours. The product was removed and crystallized from ligroin.

2,5-Dimethoxy-3,4-dimethyl-6-ethylbenzyl Chloride XA, melted at 61–62°; the yield was 99%.

Anal. Calcd. for $C_{13}H_{19}O_2Cl$: C, 64.46; H, 7.84. Found: C, 64.15; H, 7.60.

2,5-Dimethoxy-4,6-dimethyl-3-ethylbenzyl Chloride XB, melted at 60–62°; the yield was 100%.

Anal. Calcd. for $C_{13}H_{19}O_2Cl$: C, 64.46; H, 7.84. Found: C, 64.37; H, 7.84.

2,5-Dimethoxy-3,6-dimethyl-4-ethylbenzyl Chloride XC, melted at 81–82°, the yield was 100%.

Anal. Calcd. for $C_{13}H_{19}O_2Cl$: C, 64.46; H, 7.84. Found: C, 64.35; H, 7.96.

The Benzyl Acetates XI.—The chloride X (16.5 g.) was dissolved in acetic acid (250 cc.). Potassium acetate (40 g.) was added and the mixture was refluxed for one hour. The mixture was poured over ice and the product was removed by ether extraction. The acetates were very difficult to handle and only one of them was obtained pure enough for analysis. XIA (yield 85%) was a waxy solid melting at 30–40°; XIB (yield 91%) was oily; but XIC (yield 91%) was obtained as a solid melting at 54.5–56.5° after crystallization from petroleum ether.

2,5-Dimethoxy-3,6-dimethyl-4-ethylbenzyl Acetate XIC.

Anal. Calcd. for $C_{15}H_{23}O_3$: C, 67.60; H, 8.26. Found: C, 67.52; H, 8.19.

The Benzyl Alcohols XII.—The acetate XI (15.5 g.) was dissolved in ethanol (150 cc.). Aqueous potassium hydroxide (225 cc., 20%) was added and the mixture was refluxed for one hour and poured over ice. The product was removed and crystallized from ligroin.

2,5-Dimethoxy-3,4-dimethyl-6-ethylbenzyl alcohol XIIA, melted at 116.5–118°; the yield was 100%.

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.64; H, 8.92. Found: C, 70.12; H, 9.02.

2,5-Dimethoxy-4,6-dimethyl-3-ethylbenzyl alcohol XIIB, melted at 107–108°; the yield was 80%.

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.64; H, 8.92. Found: C, 69.83; H, 9.05.

2,5-Dimethoxy-3,6-dimethyl-4-ethylbenzyl alcohol XIIC, was not obtained pure. The product, melting at 78.5–80°, yield 63%, was a mixture of XIIC and the corresponding dibenzyl ether. The ether could be isolated from the mixture; it melted at 127.5–128.5° after several crystallizations from petroleum ether.

Anal. Calcd. for $C_{26}H_{38}O_5$: C, 72.56; H, 8.84. Found: C, 72.29, 72.36; H, 8.92, 9.06.[11]

The Benzaldehydes XIII.—The benzyl alcohol XII (6.7 g.) was dissolved in acetic acid (90 cc.) containing water (10 cc.). A solution of chromic acid (2.4 g.) dissolved in acetic acid (90 cc.) and water (10 cc.) was slowly added with vigorous stirring, keeping the temperature below 50°. The mixture was poured over ice (total volume 1000 cc.) and extracted twice with ether. The ether extractions were washed four times with water, once with sodium hydroxide (10%), and then filtered. The solvent was removed and the residue was crystallized from ligroin.

2,5-Dimethoxy-3,4-dimethyl-6-ethylbenzaldehyde, XIIIA, melted at 53–54°; the yield was 90%.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.27; H, 8.10. Found: C, 70.38; H, 8.30.

2,5-Dimethoxy-4,6-dimethyl-3-ethylbenzaldehyde XIIIB was obtained as an oil which could not be crystallized. The yield was 35%.

2,5-Dimethoxy-3,6-dimethyl-4-ethylbenzaldehyde XIIIC, was also obtained as an oil by oxidation of the mixture of the benzyl alcohol XIIC and the corresponding benzyl ether. The yield was 70%.

3-Carboxy-6-hydroxy-7,8-dimethyl-5-ethylcoumarin I.—Ethyl malonate (9 cc.) was added to a solution of sodium (1.3 g.) in dry ethanol (100 cc.). The mixture was cooled to 0°, the benzaldehyde XIIIA (6 g.) was added and the mixture was allowed to stand at room temperature for fifty-six hours. The solution was poured over ice, acidified with hydrochloric acid and extracted twice with ether. Removal of the ether left a yellow oil (9 g.) which was dissolved in acetic acid (180 cc.). Hydrobromic acid (48%, 120 cc.) was added and the solution was refluxed for thirty minutes. Water was added and the mixture was extracted thoroughly with ether. The ether solution was washed with water until free of acid and was then extracted twice with sodium carbonate (10%, 100 cc. each time). Acidification of the carbonate solution produced a yellow precipitate which melted at 223–224° after it was crystallized twice from acetic acid.

Anal. Calcd. for $C_{14}H_{14}O_5$: C, 64.12; H, 5.34. Found: C, 64.19; H, 5.73.

3-Carbethoxy-6-hydroxy-7,8-dimethyl-5-ethylcoumarin IV.—The above acid (I) was dissolved in dry ethanol (100 cc.), sulfuric acid (0.5 cc.) was added and the solution was refluxed for forty-eight hours. The product, precipitated by addition of water, was removed and crystallized from petroleum ether. It then melted at 178–179.5°. It was taken up in ether and the solution was poured through a tube filled with alumina (Brockmann).

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(11) The authors are indebted to Mr. D. Hayman, of the Merck Laboratories, for this analysis.

The yellow filtrate, when evaporated, left the ester IV which melted at 180°.

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.21; H, 6.20. Found: C, 66.12; H, 6.05.

3 - Carboxy - 6 - hydroxy - 5,7 - dimethyl - 8 - ethylcoumarin II.—Ethyl malonate (3 cc.) was added to a solution of sodium (0.4 g.) in dry ethanol (25 cc.). The mixture was cooled to 0° and the benzaldehyde XIIIB (colorless oil, 1 g.) in alcohol (20 cc.) was added. The mixture was allowed to stand for four days at room temperature and was then processed as for I above. The yellow oil (2 g.) was demethylated and cyclized by boiling it for twenty minutes in acetic acid (45 cc.) containing hydrobromic acid (48%, 30 cc.). Addition of water precipitated a yellow solid which was removed and crystallized from acetic acid (16 cc.). It melted at 232–234°.

Anal. Calcd. for $C_{14}H_{15}O_5$: C, 64.12; H, 5.34. Found: C, 64.33; H, 5.57.

The filtrate from this crystallization was combined with that obtained when the crude coumarin acid was precipitated, and steam distilled to remove acetic acid. The cooled residue in the distillation flask was extracted with ether, and the ether, in turn, was extracted with sodium carbonate (20%, 200 cc.). Acidification of the carbonate produced a sticky yellow solid which was removed, dissolved in acetic acid and demethylated with hydrobromic acid as described above. The resulting product melted at 225–227°.

3 - Carbethoxy - 6 - hydroxy - 5,7 - dimethyl - 8 - ethylcoumarin V.—The above material melting at 225–227° was dissolved in dry ethanol (50 cc.). Sulfuric acid (10 drops) was added and the mixture was refluxed for twenty-four hours. The product, isolated as described for IV and crystallized once from ligroin, melted at 173–174.5°.

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.21; H, 6.20. Found: C, 66.34; H, 6.05.

3 - Carboxy - 6 - hydroxy - 5,8 - dimethyl - 7 - ethylcoumarin III.—Ethyl malonate (4 cc.) was added to a solution of sodium (0.54 g.) in dry ethanol (50 cc.). The solution was cooled to 0° and the benzaldehyde XIIIC (yellow oil, 2.8 g.) in alcohol (25 cc.) was added. After standing for three days at room temperature the mixture was processed as above and the resulting yellow oil was refluxed for thirty minutes in acetic acid (120 cc.) containing hydrobromic acid (48%, 80 cc.). Dilution with water produced a yellow precipitate (1.3 g.) which, after crystallization three times from acetic acid, melted at 250°.

Anal. Calcd. for $C_{14}H_{14}O_5$: C, 64.12; H, 5.34. Found: C, 64.09; H, 5.70.

3 - Carbethoxy - 6 - hydroxy - 5,8 - dimethyl - 7 - ethylcoumarin VI.—The above acid (0.3 g.) was dissolved in dry ethanol (15 cc.). Sulfuric acid (0.3 cc.) was added and the solution was refluxed for eighteen hours. The mixture was poured over ice and the solid (0.3 g.) was removed and crystallized from ethanol. It melted at 199–201°.

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.21; H, 6.20. Found: C, 66.50; H, 6.38.[11]

2 - Hydroxy - 4,6 - dimethyl - 3 - ethyl - 5 - acetoxybenzyl Chloride XVII.—The diacetate VIIIB (0.91 g.) was suspended in formalin (10 cc.) and hydrochloric acid (15 cc.). The solution was vigorously stirred while a rapid current of hydrogen chloride was passed through. A cooling-bath was used to prevent the temperature rising above 40°. After ninety minutes, the mixture was poured over ice and the solid was removed, washed thoroughly with water and dried. After crystallization from ligroin it weighed 0.32 g. (33%) and melted at 144.5–146°.

Anal. Calcd. for $C_{13}H_{17}O_3Cl$: C, 60.94; H, 6.64. Found: C, 60.85; H, 6.88.

3 - Carbethoxy - 6 - acetoxy - 5,7 - dimethyl - 8 - ethyl-3,4-dihydrocoumarin XVIII.—Ethyl malonate (2 cc.) was added to a vigorously stirred suspension of sodium (0.04 g.) in dry ether (10 cc.). The mixture was stirred and refluxed until the metal had reacted completely, then the benzyl chloride XVII (0.3 g.) in dry ether was added. Sodium chloride precipitated at once; after a few minutes, the ether solution was washed with water, dried (Drierite) and the ether was evaporated. The remaining yellow oil crystallized when its solution in petroleum ether was chilled. The white product melted at 128.5–129.5°.

Anal. Calcd. for $C_{18}H_{22}O_6$: C, 64.64; H, 6.58. Found: C, 63.95; H, 6.68.

Summary

1. This paper contains a description of the syntheses of the three 3-carboxy-6-hydroxy-bz-dimethylethylcoumarins I, II and III, and their ethyl esters IV, V and VI. The syntheses started in each case with the corresponding dimethylethylquinone, and were designed so that the structures of the resulting coumarins are unequivocal.

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