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

THE REACTION BETWEEN QUINONES AND METALLIC ENOLATES. XXIII. AMINOTRIMETHYLQUINONE AND SODIOMALONIC ESTER (1)[1]

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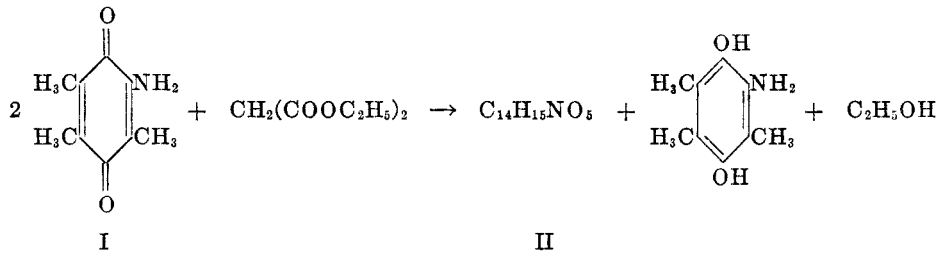
In the previous paper (1) the behavior of nitrotrimethylquinone toward sodiomalonic ester was described. In this paper, a similar study of aminotrimethylquinone is presented; the study was undertaken because of the strongly contrasting electronic character of the nitro and amino groups in the two quinones, and in order to extend the data regarding the several reactions which may occur between a quinone and a metallic enolate.

The quinone I and sodiomalonic ester reacted in dioxane to form a deep red solid which, when acidified, produced an orange solid $C_{14}H_{15}NO_5$ (II). The composition of II corresponded to a product formed from one mole each of II and ethyl malonate, with elimination of ethanol and two hydrogen atoms, and indicated strongly that II was a coumarin derivative. Neither the quinone I nor its hydroquinone was isolated by steam-distillation of the dioxane filtrates; the only material isolated from the steam-distillate was a small amount of hydroxytrimethylquinone. In a control experiment, it was found that the quinone I, when steam-distilled from dilute acid, was largely converted into hydroxytrimethylquinone. It thus appeared that the reaction was analogous to that between duroquinone and sodiomalonic ester (2) and that the enolate anion had attacked the quinone I at a methyl group.

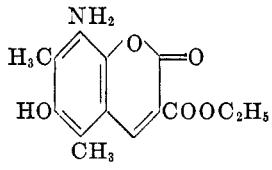


I II

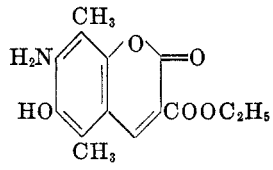
Three coumarins, A, B, and C, were possible products of this reaction, depending upon which of the three methyl groups in I had been attacked. In addition, attack at the methyl group *ortho* to the amino group could give rise to the carbostyril D by a cyclization involving the amino group.

The substance II was soluble in concentrated acid, but insoluble in dilute acid; the Folin (phenol) test was positive, and action of ferric chloride produced colored oxidation products. These properties indicated that II was a 6-hydroxy-

[1] Abstracted from a thesis by Frank A. Cutler, Jr., presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, April, 1948.



A



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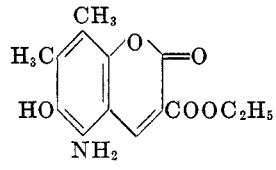

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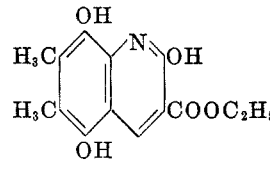
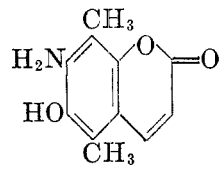


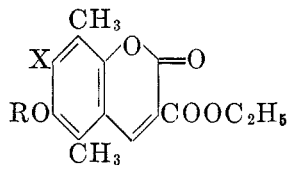
D

coumarin; when it was found that II could be diazotized, the presence of an amino group was demonstrated and structure D, the carbostyril, was eliminated as a possibility.

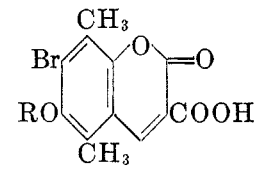
The coumarin II formed a monoacetyl derivative (III) and a colorless diacetyl derivative (IV). The monoacetyl derivative III gave a positive Folin test; III was therefore the N-acetyl derivative. The diacetyl derivative IV gave no Folin test; it was therefore the O,N-diacetyl compound. When II was refluxed in hydrochloric acid, hydrolysis and decarboxylation occurred; the initial product separating from the acid solution appeared to be an amine hydrochloride but this was readily hydrolyzed in water to give V. The rather easy decarboxylation of the coumarin II was unusual, for the other 3-carboxycoumarins studied so far in this series undergo decarboxylation only under severe conditions. For this reason, it is probable that decarboxylation of II involved opening of the heterocyclic ring, with decarboxylation followed by recyclization.



V



VI X = Br; R = H
VII X = Cl; R = H
VIII X = Br; R = Ac



IX R = H
X R = Ac

Two of the three bromine analogs of A, B, and C (NH_2 replaced by Br) namely, the analogs of A and C, were known (3). The simplest proof of structure of II was to convert II into the bromine analog *via* the Sandmeyer reaction. In this way, II was converted, in 80% yield, into a bromocoumarin VI and in 65% yield into a chlorocoumarin VII. The bromocoumarin VI was obtained in three polymorphic forms, melting at 151–153°, 158–159.5°, and 160.5–162°, respectively; it formed an acetate VIII, melting at 160–161°. Hydrolysis of the bromocoumarin ester VI yielded an acid IX, melting at 250.5–251.5° (dec.) which

formed an acetate X melting at 219.5–220.5°. It was obvious that II did not possess structure A; although the melting points of the respective bromo derivatives of C and II were quite different, the melting points of the other derivatives were close. However, the mixed melting points of the derivatives of C and II were in every case depressed and it became apparent that II must be represented by structure B and that the bromo analog derived from II must have the analogous structure, namely, 3-carbethoxy-5,8-dimethyl-6-hydroxy-7-bromocoumarin VI.

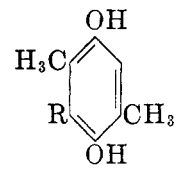
This was confirmed by an independent synthesis of VI. *p*-Xylohydroquinone XI was converted by bromination into the monobromohydroquinone XII and the latter was chloromethylated to form the benzyl chloride XIII. When XIII was subjected to the action of ethyl sodiomalonate, alkylation, cyclization and dehydrogenation occurred, producing VI. This specimen of VI showed the same triple melting point as the specimen obtained from II; the ester acetate, acid,

TABLE I

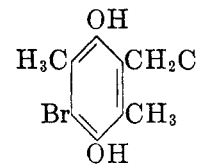
MELTING POINTS OF BROMINE ANALOGS °C.

RELATED AMINE	COUMARIN ESTER	ACETATE OF ESTER	COUMARIN ACID	ACETATE OF ACID
A	206–207			
C	200	160–161	250	223
II Trimorphic	151–153	160–161	250.5–251.5	219.5–220.5
	158–159.5			
	160.5–162			

and acid acetate all had the same melting points as those derived from II; melting points of mixtures of the respective derivatives were not depressed.



XI R = H
XII R = Br



XIII

Hence, when aminotrimethylquinone reacts with sodiomalonic ester, the product is a coumarin (B) resulting from attack of the enolate ion at the methyl group *para* to the amino group. As the yield of II (97.4% or 48.7% conversion) was high, it is unlikely that any other reaction occurred. The course of this reaction is interesting; it reflects the strong resonance effect (electron release) of the amino group. This reaction is in contrast with the behavior of bromotrimethylquinone—although the bromoquinone is converted into a coumarin, it is the methyl group *ortho* to the bromine atom which is involved.

EXPERIMENTAL[2]

Aminotrimethylquinone I. Nitrotrimethylquinone (1) (10 g.) dissolved in acetic acid (60 cc.) was shaken for three hours with hydrogen (30 lbs.) in the presence of platinum oxide catalyst (0.15 g.). The solution was filtered, acetic acid (50 cc.) was added to the filtrate, and air was drawn through the solution for two hours. The intensely red solution was chilled and neutralized with ammonium hydroxide, and the red solid was removed, washed with cold water, and dried. The dried product from two such experiments was extracted with benzene (175 cc.) in a Soxhlet extractor; from the extract, on cooling, there separated 12.32 g. (73%) of the aminoquinone melting at 166.5–170.5°. This was pure enough for condensation with malonic ester. A specimen, recrystallized from benzene, melted at 169.5–171.5°.

Anal. Calc'd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48.
Found: C, 65.51; H, 6.76; N, 8.33.

Aminotrimethylhydroquinone. The nitroquinone (1 g.), dissolved in acetone (10 cc.) and water (10 cc.), was heated and sodium hydrosulfite (4.2 g.) was added in small portions. As the acetone evaporated from the solution, water was added to keep the volume constant. The mixture was cooled and the white solid (0.61 g., 71%) was removed and dried. The hydroquinone melted with decomposition. When the melting point was determined in the ordinary way, the substance became red and melted at about 170°, the melting point of the quinone. In a bath preheated to 206°, the hydroquinone melted slowly; in a bath at 210°, it melted rapidly—hence the melting point was about 206–210°. The substance could be recrystallized from large volumes of hot water if sodium hydrosulfite was added. On exposure to air, the white solid soon became red; under nitrogen, it appeared to be stable. The hydroquinone (0.61 g.), dissolved in aqueous acetone, was oxidized by action of ferric chloride to the quinone, m.p., 166–171°. *Acetylaminotrimethylhydroquinone diacetate* was prepared from the crude hydroquinone by action of acetic anhydride containing a little sulfuric acid. Crystallized from ethanol (Norit), it was white and melted at 131–132.5°.

Anal. Calc'd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53.
Found: C, 61.22; H, 6.44.

Hydroxytrimethylhydroquinone. The aminoquinone I (0.37 g.) was dissolved in hydrochloric acid (10 cc.), the solution was diluted with water and the resulting suspension of aminoquinone was steam-distilled. From the cooled distillate (200 cc.), the hydroxyquinone (0.21 g., 57%) separated as orange needles melting at 94–95°.

Anal. Calc'd for $C_9H_{10}O_3$: C, 65.05; H, 6.07.
Found: C, 65.10; H, 6.19.

3-Carbethoxy-5,8-dimethyl-6-hydroxy-7-aminocoumarin (II = B). Ethyl malonate (29.9 g., 0.187 mole) in dry, peroxide-free dioxane (60 cc.) was refluxed with sodium (3.78 g., 0.164 g. atom) for one hour and the cooled solution of the enolate was added to aminotrimethylquinone (12.32 g., 0.75 mole) in dioxane (180 cc.). The mixture was protected from moisture by a calcium chloride tube, was stirred for seven hours, and then was allowed to stand for sixteen hours. The deep red solid was removed, washed with a little dioxane, and added to hydrochloric acid (1.2 *N.*, 500 cc.). The yellow solid was removed and crystallized from ethanol (95%, 450 cc.), when it formed orange prisms (10.1 g., 97.4%) melting at 228–229°.

Anal. Calc'd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05.
Found: C, 60.50; H, 5.50; N, 5.41.

The filtrate from the dark solid, exposed to air for two months, deposited a further amount of dark solid which was converted, by action of hydrochloric acid, into additional II (1.31 g.). Steam-distillation of the filtrate yielded a small amount of hydroxytrimethylquinone, m.p. and mixed m.p. 93.5–95°. The aminocoumarin ester II was sparingly soluble

[2] Microanalyses by R. W. Amidon and Jay S. Buckley, Jr.

in hot benzene; the solution in benzene or acetone showed a strong blue fluorescence. The compound was insoluble in 1.2 *N* hydrochloric acid, but dissolved in 6 *N* acid. Action of alkalis gave rise or orange or deep red colors which were not discharged when the solutions were shaken with sodium hydrosulfite. The Folin test was positive, and the substance was oxidized by permanganate. Action of ferric chloride upon an acetone solution of II (0.5 g.) gave rise to a deep red solution from which two solids were isolated: one of these was yellow (0.1 g.) and melted with decomposition at 300–325°; the other (0.05 g.) was dark red and decomposed at 187–191°. These substances were not investigated further.

3-Carbethoxy-5,8-dimethyl-6-hydroxy-7-acetylaminocoumarin (III). The aminocoumarin II (0.1 g.) was suspended in acetic anhydride (5 cc.). Sulfuric acid (2 drops) was added; the solid rapidly dissolved. The solution was allowed to stand for ten minutes, then was poured into water (20 cc.), neutralized with ammonium hydroxide, and the solid was removed and crystallized from ethanol (95%, 15 cc.). It weighed 0.097 g. (84%), melted at 256° (dec.) (bath preheated to 250°), and gave a positive Folin test.

Anal. Calc'd for $C_{16}H_{17}NO_6$: C, 60.18; H, 5.37; N, 4.39.
Found: C, 59.71; H, 5.60; N, 4.26.

3-Carbethoxy-5,8-dimethyl-6-acetoxy-7-acetylaminocoumarin (IV). Acetylation of II was carried out as above, except that the solution was allowed to stand for a week at room temperature before the product was isolated. The solid was dissolved in petroleum ether (150 cc., b.p. 90–100°), the solution was filtered to remove a small amount of III and the filtrate was cooled. The white solid (0.1 g., 76%) melted at 130.5–131.5° after it was crystallized twice from petroleum ether. The Folin test was negative.

Anal. Calc'd for $C_{18}H_{19}NO_7$: C, 59.83; H, 5.30.
Found: C, 59.87; H, 5.53.

5,8-Dimethyl-6-hydroxy-7-aminocoumarin (V). The coumarin ester II (2 g.) was refluxed for two hours in hydrochloric acid (6 *N*, 80 cc.). The mixture was cooled and the solid was removed and dried in a vacuum desiccator over potassium hydroxide. The material then weighed 1.62 g. (theoretical for $C_{11}H_{11}NO_3 \cdot HCl$, 1.74 g.) and did not melt below 265°. When added to water, the solid became bright greenish-yellow and the water contained chloride ion; the solution decomposed sodium bicarbonate with effervescence. This hydrochloride (from 0.5 g. of II) was dissolved in boiling water (300 cc.) and the solution was cooled. The solid (0.262 g., 71%) was dissolved in wet acetone and reprecipitated by addition of water, when it melted at 261° with decomposition. The substance was insoluble in aqueous sodium bicarbonate (5%).

Anal. Calc'd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40.
Found: C, 64.71; H, 5.68.

3-Carbethoxy-5,8-dimethyl-6-hydroxy-7-chlorocoumarin (VII). The aminocoumarin II (0.5 g., 0.002 mole) was dissolved in hydrochloric acid (10 cc.) and the cold solution was diazotized by dropwise addition of a solution of sodium nitrite (0.13 g., 0.002 mole) in water (5 cc.). A solution of cupric sulfate (2 g.) in water (10 cc.) was added and the mixture was heated on the steam-bath. The tan solid (0.35 g., 65%, m.p. 166–168°) was removed and crystallized three times from aqueous ethanol. It formed greenish needles which sintered at 166.5° and melted to a brown liquid at 171.5–173°.

Anal. Calc'd for $C_{14}H_{13}ClO_5$: C, 56.67; H, 4.41.
Found: C, 56.87; H, 4.70.

3-Carbethoxy-5,8-dimethyl-6-hydroxy-7-bromocoumarin (VI). The aminocoumarin VI (2 g., 0.007 mole) dissolved in hydrobromic acid (40 cc., 34%) was cooled (1°) and diazotized by dropwise addition (twenty minutes) of a solution of sodium nitrite (0.51 g., 97%, 0.007 mole) in water (10 cc.). Cuprous bromide (from 38.8 g. of cupric sulfate) was dissolved in hydrobromic acid (38 cc., 34%); the solution was cooled (1°) and added to the diazonium solution. The black solution was warmed gradually (thirty minutes) to 52°; the solid was removed, and the filtrate was heated to 75°. The combined solids were dissolved in ethanol (65 cc., 95%), the solution was filtered, the hot filtrate was diluted gradually with water (35 cc.) until solid began to separate, and cooled. The crude product (2 g., 81%) melted

partially at 148–152° and completely at 160–161°. The material, crystallized three times from dilute ethanol, as above, and dried at 100°, melted at 151–153°; the cooled melt remelted at 151–153°, 158–159.5°, or at 160.5–162°, depending upon whichever crystalline form first appeared when the melt was cooled. The melting points were distinct and reproducible. The low-melting form of VI occurred as stubby prisms; the form with intermediate melting point occurred as coarse needles, and the high-melting form occurred as fine fibres. The trimorphism was encountered in all specimens of VI.

Anal. Calc'd for $C_{14}H_{13}BrO_5$: C, 49.27; H, 3.84.
Found: C, 49.50; H, 3.89.

3-Carbethoxy-5,8-dimethyl-6-acetoxy-7-bromocoumarin (VIII). The bromocoumarin VI (0.1 g.) was warmed for thirty minutes in acetic anhydride (6 cc.) containing a drop of sulfuric acid. Water was added, the solid (0.096 g., 87%, m.p. 159–161°) was removed and crystallized three times from aqueous ethanol (50%), when it was white and melted at 160–161°.

Anal. Calc'd for $C_{16}H_{15}BrO_6$: C, 50.15; H, 3.95.
Found: C, 50.36; H, 3.90.

A mixture of VIII and 3-carbethoxy-6-acetoxy-7,8-dimethyl-5-bromocoumarin, m.p. 159–160° (3), melted at 154–156°.

3-Carboxy-5,8-dimethyl-6-hydroxy-7-bromocoumarin (IX). The bromocoumarin II (0.5 g.), heated on the steam-bath with hydrochloric acid (45 cc.) for one and three-fourths hours, gradually dissolved and then the solution deposited a solid. The product was removed from the cooled suspension and crystallized from benzene (130 cc.) when it formed dark yellow crystals (0.34 g., 74%) melting at 247.5–250.5° with decomposition (bath preheated to 244°). Recrystallized from benzene (Norit), the substance softened at 247° and melted at 250.5–251.5° (dec.) (bath preheated to 244°). The substance was readily soluble in aqueous sodium bicarbonate (5%).

Anal. Calc'd for $C_{12}H_9BrO_5$: C, 46.03; H, 2.90.
Found: C, 46.52; H, 2.90.

3-Carboxy-5,8-dimethyl-6-acetoxy-7-bromocoumarin (X). The coumarin IX (0.136 g.) was acetylated as described for VI. The product (0.135 g., 88%), crystallized three times from aqueous ethanol (Norit), was white and melted at 219.5–220.5°.

Anal. Calc'd for $C_{14}H_{11}BrO_6$: C, 47.34; H, 3.12.
Found: C, 47.28; H, 3.18.

A mixture of X and 3-carboxy-6-acetoxy-7,8-dimethyl-5-bromocoumarin, m.p. 220–225° (3) melted at 196–206°.

p-Xyloquinone was prepared from *p*-xylenol (4, 5) and reduced to the *hydroquinone XI* by the method of Smith and Johnson (6). The hydroquinone melted at 210–213.5°.

Bromo-p-xylohydroquinone (XII). A solution of *p*-xylohydroquinone XI (6.35 g., 0.046 mole) in acetic acid (330 cc.) was stirred and brominated at room temperature by gradual (one hour) addition of a solution of bromine (7.2 g., 0.045 mole) in acetic acid (20 cc.). The mixture was stirred for three hours, allowed to stand for seventeen hours; then concentrated to 25 cc. under reduced pressure and with exclusion of air. The solution was diluted to 100 cc. by dropwise addition of water; the mixture was chilled and the solid was removed and crystallized from petroleum ether (450 cc., b.p., 90–100°). The white needles (6.5 g., 66%) melted at 123–126.5° with darkening.

Anal. Calc'd for $C_8H_9BrO_2$: C, 44.26; H, 4.18.
Found: C, 44.61; H, 4.60.

The *diacetate*, prepared in the usual way and crystallized from aqueous ethanol, melted at 107.5–109°.

Anal. Calc'd for $C_{12}H_{13}BrO_4$: C, 47.86; H, 4.35.
Found: C, 47.72; H, 4.50.

2,5-Dimethyl-3,6-dihydroxy-4-bromobenzyl chloride (XIII). The hydroquinone XII (3 g.) was dissolved in acetic acid (60 cc.) containing formalin (6 cc., 40%), and the solution was maintained at 5–15° while a brisk stream of hydrogen chloride was passed into it for three

and one-half hours. The solid was removed, washed with cold water, dried, and crystallized from benzene (35 cc.). It was cream-colored, weighed 1.75 g. (50%), and melted at 147–150°. The analytical specimen, crystallized three times from benzene, was white and melted at 147.5–150°.

Anal. Calc'd for $C_9H_{10}BrClO_2$: C, 40.71; H, 3.80.
Found: C, 40.90; H, 3.95.

A solution of the benzoyl chloride XIII (0.8 g., 0.003 mole) in dry, peroxide-free dioxane (10 cc.) was added, dropwise (twenty minutes), and with stirring, to a solution of sodiomalonic ester (from sodium, 0.21 g., ethyl malonate, 1.82 cc.) in dioxane (5 cc.). The mixture was stirred for seven hours and then allowed to stand for seventeen hours. The deep red solid was removed, washed with a little dioxane, and added to hydrochloric acid (1.2 *N.*, 10 cc.). The yellow solid, crystallized from aqueous ethanol, weighed 0.22 g. (22%) and melted at 148–151.5° with sintering at 145.5°. Recrystallized from dilute ethanol and dried at 100°, the solid sintered at 150° and melted at 151–153°. The cooled melt remelted at 151–153°, 158–159.5°, and 160.5–162°. A mixture of this material and the bromocoumarin obtained from the aminocoumarin II showed the same melting points. Acetylation of this product gave an acetyl derivative melting at 159–161°, alone or when mixed with VIII; hydrolysis of the product by action of hydrochloric acid gave an acid melting at 247.5–250.5°, alone or when mixed with IX; acetylation of the acid gave an acetyl derivative melting at 214–217°, alone or when mixed with X.

SUMMARY

1. Aminotrimethylquinone has been synthesized.

2. This quinone reacts with sodiomalonic ester to form 3-carbethoxy-5,8-dimethyl-6-hydroxy-7-aminocoumarin (II = B) by attack of the enolate anion at the methyl group of the quinone *para* to the amino group, demonstrating the strong resonance effect (electron release) of the amino group in this quinone.

3. The chemical properties of the aminocoumarin have been investigated and several derivatives of it have been prepared.

4. The structure of the aminocoumarin (II = B) has been proved by an independent synthesis starting with *p*-xylohydroquinone.

MINNEAPOLIS 14, MINNESOTA

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