# THE REACTION BETWEEN QUINONES AND METALLIC ENOLATES. XXII. NITROTRIMETHYLQUINONE AND SODIOMALONIC ESTER (1)[1]

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When a quinone possessing an unsubstituted position reacts with a metallic enolate, 1,4-addition occurs and the primary product is a hydroquinone. Fully substituted quinones lack the ability to yield, by addition of an enolate, an intermediate which can aromatize to a hydroquinone. When such quinones react with enolates, they do so either (a) by replacement, in which one of the substituents of the quinone is replaced by the enolate ion or (b) by condensation at a methyl group, with formation of a coumarin. With sufficient data available, it should be possible to predict whether a fully substituted quinone, substituted by a combination of methyl and replaceable groups, will react by replacement or by condensation at a methyl group. To extend and amplify the data so far available, nitrotrimethylquinone, (I), a quinone substituted by both methyl groups and the strongly electron-attracting nitro group, has been studied with respect to its behavior toward sodiomalonic ester.
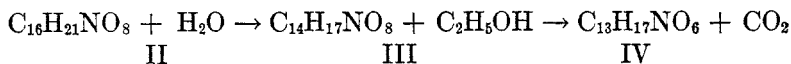

I   II R = C$_2$H$_5$ III
           VII R = CH$_3$

IV
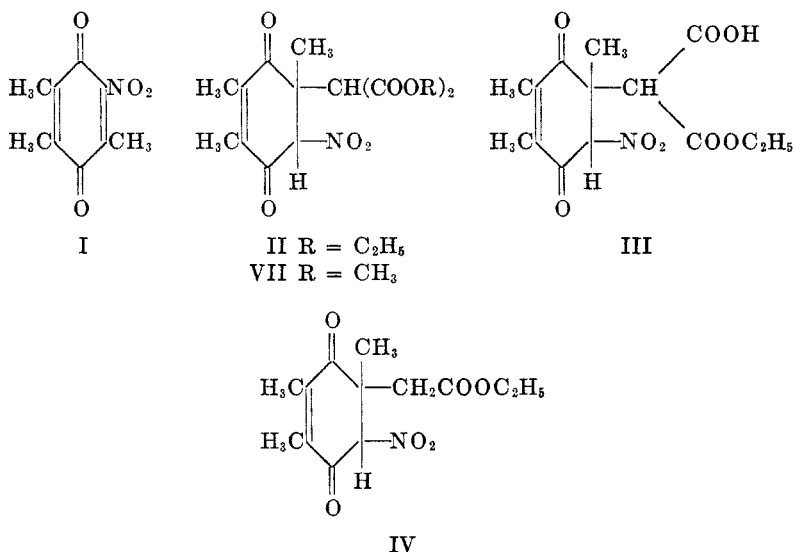
The quinone I and ethyl sodiomalonate reacted readily; a crystalline product C$_{16}$H$_{21}$NO$_8$ (II), was isolated in good yield from the reaction mixture after acidi-

fication.   The composition of the product corresponds with that required for a substance derived by direct addition of the two components.   The substance was almost white, although the crystals invariably showed a tinge of green; it decomposed on prolonged heating, but could be distilled at 190–200°/4.5 mm. with 80% recovery.   The substance appeared to exist in two forms, one melting at about 80°, and the other at about 62°.   Immediately after crystallization, the higher-melting form predominated; on standing, the solid changed, often very rapidly, until the lower-melting form predominated.   During the transition, very wide ranges in the melting point were encountered, and it was not unusual for the crystalline mass to liquefy at room temperature, after which it solidified once more.

The substance did not dissolve immediately in aqueous sodium bicarbonate, or carbonate, but after standing in contact with either of these reagents for a day, a yellow solution resulted.   In alcohol, the substance was sufficiently acidic to be titrated; one equivalent of alkali was required for neutralization.   The substance was quite sensitive toward alkalis, but fairly stable toward cold mineral acids.   When heated in ethanol or acetone, decomposition resulted.   The substance did not decolorize a solution of bromine in carbon tetrachloride, but it rapidly decolorized neutral or alkaline permanganate although no significant amounts of crystalline oxidation products could be isolated.   The substance was not a hydroquinone, for it was inert to the action of a solution of ferric sulfate; nor was there any reaction with acetic anhydride.   No carbonyl derivatives were obtained by action of either phenylhydrazine or semicarbazide.

Although the substance was an ester, it was hydrolyzed to crystalline material only under carefully controlled conditions; when dissolved in ice-cold ammonium hydroxide and subjected to the action of a cold solution of potassium hydroxide in ammonium hydroxide, there was produced a gummy solid which gradually dissolved and then the solution, after acidification, produced an acid $C_{14}H_{17}NO_8$ (III) melting at 123.5–124.5° with evolution of carbon dioxide.   The acid required two moles of alkali for neutralization; this, together with the composition of III and the behavior of II as a mono acid on titration, made it evident that hydrolysis of I had involved only one of the carbethoxyl groups.

$$C_{16}H_{21}NO_8 + H_2O \rightarrow C_{14}H_{17}NO_8 + C_2H_5OH \rightarrow C_{13}H_{17}NO_6 + CO_2$$
$$\text{II} \qquad\qquad\qquad \text{III} \qquad\qquad\qquad \text{IV}$$

When III was refluxed for a short time in xylene, decarboxylation occurred and a new acid IV, melting at 63–66°, was produced.   Acid IV was a strong acid, requiring one mole of alkali for neutralization.   The substance IV was attacked by ammoniacal potassium hydroxide solution, but the product could not be obtained pure.

When reduced by action of sodium hydrosulfite in ammonium hydroxide, II gave a white product (V) which rapidly became pink in the air and which, upon oxidation, gave a deep red quinone VI.   For comparative purposes, nitrotrimethylquinone I was subjected to the same sequence of reactions; the results were

V R = H   VI
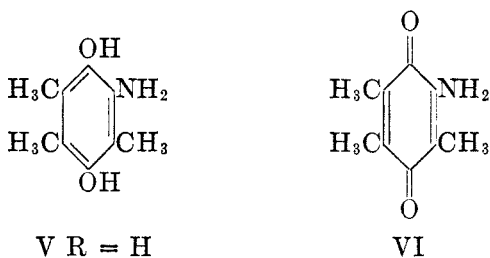
the same. The red quinone VI was obtained also by catalytic reduction of I, followed by oxidation of the hydroquinone.

When the addition product II was dissolved in ethanolic potassium hydroxide at room temperature, a bright yellow potassium salt soon separated. The analytical values given by this salt showed such a low content of carbon and hydrogen that no logical empirical formula could be deduced. The salt was readily soluble in water; acidification of the solution produced no precipitate until the solution was heated. The solid was nitrotrimethylquinone I; when the cold acidified solution of the salt was extracted with ether, only a resinous solid could be isolated from the extract. Control experiments with the quinone I paralleled the behavior of II; when I was dissolved in ethanolic potassium hydroxide, it decomposed and no I could be recovered after acidification of the solution. Likewise, when I was dissolved in ammonium hydroxide and the solution was acidified, no solid separated, nor could anything be removed from the solution by ether extraction. Yet, when the acidified solution was warmed, nitrotrimethylquinone separated.

The experimental data were sufficient to establish the structure of the addition product as II. It was apparent from the several reactions of II, in which the quinone I was formed, that II must possess the skeletal structure of I, for these reactions, in effect, constituted a reversal of the initial reaction leading to II. Malonic ester was never isolated from any of these reaction products, though the odor of it was apparent. Saponification of one ester group in II and the ready decarboxylation of the product indicated that II was a malonic ester; the stability on distillation, and the slow rate of solution in carbonate, indicated absence of a carboxyl group in II. The origin of the acidity of II did not lie in the enolizable hydrogen atom of the malonic ester group, for IV was even stronger as an acid than was II; the acidity therefore lay in the nitro group, which must be so placed in II that an *aci*-salt could be formed.

Having established that the reaction between the malonate and the quinone I was a simple addition, there were *a priori* twelve structures which could be written for such a product. Four of these were derived by addition to the quinone as an α,β-unsaturated ketone; two by addition at the carbonyl group; three by addition to a "pentad enol" involving one of the methyl groups and leading to hydroquinones; two by 1,6-addition giving mono ethers of the hydroquinone; and one nitronic ester. The second, third, and fourth of these modes of addition would all lead to hydroxyl compounds, which the addition product was not; these
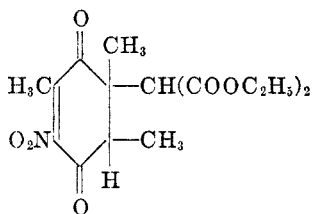
modes of addition and the resulting structures, were therefore eliminated. The fifth mode of addition would lead to a substituted methyl nitronic ester; Arndt and Rose (2) have shown that all known methyl nitronic esters decompose violently at 70–90°; the addition product II could be distilled without decomposition
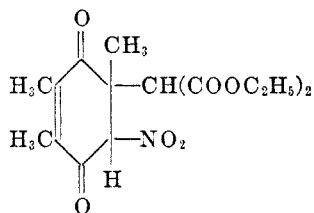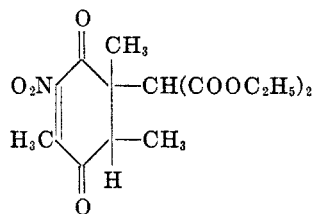

A = II
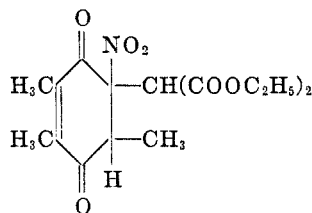
B

C

D

at 190–200°. There remained, therefore, to consider only the four structures derivable by the first mode of addition. Structures B, C, and D represent compounds which, either as such or in their enolic forms, would not be sufficiently acidic to be titratable. Structure A, however, represents the substance as a secondary nitro compound which would be quite acidic and titratable, as II was found to be. Hence, the most probable structure for II appeared to be A; using this structure, the other properties of II were readily understood. The melting point behavior of II indicated the existence of two forms, easily interconvertible. Structure A permits a *cis* and a *trans* form, easily interconvertible through the *aci* form of the secondary nitro compound. The fact that II was nearly colorless is not in disagreement with structure A, for the addition product of *p*-xyloquinone and 1,3-cyclohexadiene, having a structure very much like A, is colorless (3). The ready reversal of the reaction by which II is formed is best interpreted in terms of structure A: the acidic proton is easily removed from the carbon atom holding the nitro group, and the resulting anion would be expected to undergo readily a cleavage into nitrotrimethylquinone and the anion of malonic ester.

In its behavior toward sodiomalonic ester, the quinone I behaved as a nitro-olefin; the reaction demonstrates the strong resonance effect (electron-attracting) of the nitro group, and is completely analogous to the reaction between β-nitro-styrene and methyl sodiomalonate studied by Kohler and Engelbrecht (4), and the product of this reaction shows certain similarities with II—thus the nitro-malonic ester obtained by Kohler and Engelbrecht could not be hydrolyzed to the

corresponding acid; action of alkalis produced only oily decomposition products, and action of acids resulted in loss of the nitro group.

The behavior of nitrotrimethylquinone was studied toward three other enolates. From ethyl sodioacetoacetate, no crystalline product could be isolated and only traces of the quinone were recovered. From the bromomagnesium enolate of acetomesitylene, only oils and resins resulted. From methyl sodiomalanate, however, a crystalline addition product VII was obtained. This substance was, in its behavior, completely analogous with II.

The results of this work show that, in addition to replacement and condensation at a methyl group, a completely substituted quinone may react with an enolate by direct addition, and that steric hindrance plays a comparatively minor role in the reaction of quinones with enolates.

<div align="center">EXPERIMENTAL[2]</div>

Nitrotrimethylquinone (I). Trimethylquinone (5) (30 g.) was dissolved in a mixture of nitric acid (90 cc.) and sulfuric acid (30 cc.) and the solution was heated to 60°. After ten to twenty minutes, two layers formed; the temperature was raised to 65° for twenty minutes, when the lower layer became clear. Control of the temperature was important, for the reaction sometimes became violent, with copious evolution of oxides of nitrogen. The solution was poured into a mixture of ice (1 kg.) and water (1000 cc.). The yellow solid from three experiments was combined, pressed dry, and while still cold was dissolved in nitric acid (200 cc.) and the solution was brought to 80° for five minutes; this converted any unchanged trimethylquinone into the nitroquinone. The solution was poured into ice-water as before, and the mixture was allowed to come to room temperature. The solid was removed, allowed to stand in the air for several days until dry, and then crystallized twice from 800-cc. portions of petroleum ether (b.p. 90–100°). The bright yellow nitroquinone I weighed 70 g. (60%) and melted at 107.5–110.5°. This product was pure enough for use in the subsequent reactions; the pure quinone, m.p. 113–114°, could be obtained by adding water gradually to a warm solution of the substance in ethanol. It was important not to boil the ethanolic solution, for this resulted in production of highly colored by-products, one of which, a red compound, melted at 133.5–135.5°. The melting point of the nitroquinone, recorded in the literature, is 112–113° (6, 7). Nitrotrimethylquinone was destroyed by action of cold ethanolic potassium hydroxide or of potassium hydroxide in ammonium hydroxide. The quinone formed a yellow solution in dilute ammonium hydroxide. When this solution was acidified, no solid separated, nor could anything be removed by ether extraction, but when the yellow acidified solution was heated briefly and then cooled, nitrotrimethylquinone separated in yellow plates. Nitrotrimethylquinone could not be titrated in ethanol because of the intense colors formed as soon as any base was added.

2-Nitro-3-(dicarbethoxymethyl)-3,5,6-trimethylcyclohexene-5-dione-1,4 (II). A solution of ethyl sodiomalonate was prepared by refluxing ethyl malonate (40 g., 0.25 mole) in dry, peroxide-free dioxane (8) (80 cc.) with sodium (5.06 g., 0.22 mole) for one and three-fourths hours. The solution was cooled and added slowly to a solution of the nitroquinone I (19.5 g., 0.1 mole) in dioxane (150 cc.) maintained at 19–21°. The reaction was exothermic; twenty minutes was required for addition of the first half of the enolate, during which the color became red. As soon as half of the enolate was added, the color of the solution became an intense deep red, and no further evolution of heat occurred. The second half of the enolate was added rapidly, and the mixture was allowed to stand for sixteen hours. The solution was poured into ice and hydrochloric acid (100 cc.), the orange oil was removed and

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[2] Microanalyses by R. W. Amidon, Jay S. Buckley, J. R. Kerns, and S. A. Sundet.

dissolved in ethanol (95%, 100 cc.) at room temperature. Water was added dropwise, with occasional cooling, until crystallization was induced. The product was removed, washed with cold ethanol until nearly white, and the combined filtrates and washings were further diluted with water as before. This process was repeated several times until no further crystallization occurred. Since the product frequently liquefied on standing, all the solids were combined after a brief drying period, and crystallized from petroleum ether (200 cc., b.p. 90–100°). In this way there was obtained 26.6 g. (75%) of nearly white material, melting over various ranges within the limits 58–78°. The substance II crystallized readily from petroleum ether (b.p. 90–100°) in the form of stubby prisms terminated at each end by a pair of oblique planes; the crystals always had a faint greenish cast. Immediately after crystallization, the substance usually melted at 68–78°, occasionally as high as 81°. On standing, the crystals became translucent, and the substance was transformed into the lower-melting form. The rate of this change varied greatly with different preparations; one specimen did not change over a period of two years, another, after two weeks, melted at 61–62.5°. When the material was finely divided, the change could often be brought about by rubbing or stirring, in which case the entire mass liquefied and then resolidified to the form melting at 57–62°. Recrystallization from petroleum ether again gave the high-melting form, and the cycle could be repeated indefinitely. When crystallized from ethanol, the product changed rapidly to the lower-melting form, via the liquid. Because of this peculiar behavior, it was difficult to obtain analytical specimens free from solvent.

Anal. Calc'd for $C_{16}H_{21}NO_6$: C, 54.08; H, 5.96; N, 3.94; Mol. wt., 355.3; Neut. equiv. (one), 355.3.

Found: C, 54.48, 55.25, 56.37; H, 5.68, 5.96, 6.97; N, 3.81; Mol. wt. (benzene, cryoscopic), 332; Neut. equiv. 377, 383.

The following *variants* in procedure were tried, with no improvement and usually a decrease in yield and quality of product: reduction of the reaction time to two hours; termination of the reaction when half the enolate had been added; provision of a nitrogen atmosphere; substitution of benzene or ethanol for dioxane. Reversal of the order of adding the solutions had no effect one way or another. Substance II, regardless of its melting point, formed yellow solutions slowly (one day) in contact with aqueous sodium bicarbonate (5%) or carbonate (10%); II was readily soluble in ammonium hydroxide. In ethanol, II could be titrated to a neutral equivalent of 377–383 using phenolphthalein as the indicator. Some specimens of II became orange on prolonged standing, particularly at the point of contact of glass and sample. The substance was not stable on prolonged heating, but it could be rapidly distilled at 190–200°/4.5 mm. giving an orange distillate which, crystallized from petroleum ether, gave the solid form melting at 67–80° (80% recovery). Solutions of II in ethanol or acetone, when heated, became orange or red, and II could be recovered from these solutions only in poor yield, if at all. No acetate resulted when II was subjected to the action of acetic anhydride and sulfuric acid; from 1 g. of II, 0.6 g. was recovered, and the remainder of the product was a black tar. Oxidation of II (1.0 g.) by action of ferric sulfate produced no quinone; the only product (0.13 g.) was unchanged II. No phenylhydrazone could be isolated when II was subjected to the action of phenylhydrazine; the only product was a red oil. Nor could any semicarbazone be obtained. A solution of bromine in carbon tetrachloride did not react with II. Aqueous potassium permanganate, when added to a solution of II in acetone, was rapidly decolorized, but no oxidative degradation products could be isolated in quantity sufficient for identification. Many attempts were made to hydrolyze II under acidic conditions, but these experiments led either to unchanged material, or to intractable oils.

Potassium salt. Potassium hydroxide (15 g.) was dissolved in ethanol (95%, 100 cc.); the solution was filtered to remove carbonates and the filtrate was cooled. To it was added solid II (5 g.); the flask was stoppered and shaken until solution was complete. The yellow potassium salt soon separated; after one and one-half hours it was removed and washed with ethanol and ether. The first crop weighed 4.2 g.; the filtrate, on standing, deposited a second crop of 0.66 g. The substance was dissolved in water, the solution was

filtered, and the filtrate was poured into ethanol. The solid was removed, washed with alcohol and ether, and dried in a vacuum desiccator over calcium chloride. No logical formula could be calculated from the analytical values.

Anal. Found: C, 28.35; H, 3.41; K, 26.13, 25.89.

An aqueous solution of the salt (0.5 g.) acidified with hydrochloric acid and warmed briefly, deposited nitrotrimethylquinone (0.015 g.) on cooling. No other material could be isolated; in many experiments, the yield of quinone never exceeded 10%. If, instead of heating the acidified solution, it was extracted with ether, an amorphous resin was found in the ether extract. An aqueous solution of the resin, when heated, produced traces of nitro-trimethylquinone.

2-Nitro-3-(carboxycarbethoxymethyl)-3,5,6-trimethylcyclohexene-5-dione-1,4 (III). The addition product II (10 g.) was dissolved in concentrated ammonium hydroxide (50 cc.) and to the chilled solution there was added a cold solution of potassium hydroxide (20 g.) in ammonium hydroxide (50 cc.). An orange solid separated; this gradually redissolved. The mixture was cooled (0°) and stirred for one hour, and then poured slowly into a mixture of ice (600 g.) and hydrochloric acid (200 cc.). The solid was removed, triturated with water (75 cc.), filtered, and dried. It weighed 6.08 g. (66%) and melted at 120.5–121° (dec.). It could not be crystallized from organic solvents; for purification it was dissolved in dilute aqueous sodium bicarbonate and the solution was filtered into a well stirred mixture of ice and hydrochloric acid. This process was repeated several times, resulting in a product melting at 123.5–124.5° with darkening and evolution of gas. The gas was identified as carbon dioxide.

Anal. Calc'd for $C_{14}H_{17}NO_8$: C, 51.37; H, 5.24; Neut. equiv. (two) 163.6.

Found: C, 51.19; H, 5.25; Neut. equiv., 164, 165.

The experimental conditions as outlined above must be followed closely with respect to time, temperature, reagents and order in which the reagents were combined. When II was refluxed with aqueous sodium hydroxide (5%) the solution became very dark and only a red oil could be obtained upon acidification.

2-Nitro-3-(carbethoxymethyl)-3,5,6-trimethylcyclohexene-5-dione-1,4 (IV). Compound III (10 g.) was dissolved in hot xylene (200 cc.) and the solution was refluxed (132°) for twenty minutes. The cooled solution was extracted with six 50-cc. portions of aqueous sodium carbonate (10%), which were slowly added to ice-cold hydrochloric acid (100 cc.). The yellow solid was removed, washed with water, and dried; it weighed 4.85 g. and melted at 62–64.5°. The xylene layer was evaporated under reduced pressure and the residue was dissolved in ether and extracted with carbonate; acidification of the carbonate extracts yielded a further 1.15 g. of material melting at 62–66°. Evaporation of the ether yielded 0.06 g. of nitrotrimethylquinone. The total product (6 g., 70%) was crystallized twice from small amounts of ethanol (95%), when it formed light greenish-yellow micro-crystals melting at 63–66°.

Anal. Calc'd for $C_{14}H_{17}NO_6$: C, 55.11; H, 6.05; Neut. equiv. (one) 283.3.

Found: C, 55.32; H, 6.01; Neut. equiv., 283.

Substance IV could not be obtained from III by simple heating. At 120–130° for twelve minutes, 0.79 g. of II lost 0.082 g. in weight (theoretical, 0.107 g.). No crystalline material could be isolated from the dark residue. A sample of III was distilled under 5 mm. pressure, with a bath temperature of 195°. The only pure material isolated from the distillate was a trace of nitrotrimethylquinone. Attempts to hydrolyze IV (2.0 g.) by the procedure used for hydrolysis of II led to a yellow solid (1.85 g.) melting with decomposition at 98–139°, and from which no pure material could be isolated.

Reduction of II. A. Sodium hydrosulfite (2.9 g.) was added in small portions, with gentle warming, to a solution of II (1 g.) in ammonium hydroxide (10 cc.). Ethanol (5 cc.) and water (5–10 cc.) were added during the reduction. The solution became colorless and the white, fibrous crystals of aminotrimethylhydroquinone deposited. The mixture was cooled, the solid (0.3 g., 62%) was removed, dissolved in ethanol and the solution was

added to a solution of ferric chloride. The red solid (0.2 g.) was removed; it melted at 169–170.5° alone or when mixed with authentic aminotrimethylquinone.

B. A solution of II (6.78 g.) in benzene (20 cc., thiophene-free) was shaken with hydrogen (30 lb.) in the presence of platinum oxide catalyst (0.1 g.). The solids were removed, extracted with acetone, and the extract was added to ferric chloride as above. There resulted 0.33 g. of aminotrimethylquinone, melting at 168–170.5°.

2-Nitro-3-(dicarbomethoxymethyl)-3,5,6-trimethylcyclohexene-5-dione-1,4 (*VII*). The reaction between nitrotrimethylquinone (1.95 g.) and methyl sodiomalonate was carried out essentially as described above for the preparation of II. The product (1.1 g., 34%), recrystallized from benzene, formed prisms which softened at 105° and melted at 109–114°.

Anal. Calc'd for $C_{14}H_{17}NO_8$: C, 51.37; H, 5.24; N, 4.28.

Found: C, 51.74; 52.44; H, 5.71, 5.36; N, 4.26.

When *ethyl sodioacetoacetate* was substituted for the malonate in the above experiment, the product was a dark red oil from which a small amount of nitrotrimethylquinone could be isolated as the only solid product. A similar result was obtained when the reaction was carried out in ethanol as the solvent.

Acetomesitylene (5 g., 0.03 mole) was added to a solution of ethylmagnesium bromide (from ethyl bromide, 2.25 cc., magnesium, 0.75 g., and ether, 30 cc.). To the resulting suspension of the enolate of acetomesitylene, there was added dropwise (thirty minutes) and with stirring, a solution of nitrotrimethylquinone (2.9 g.) in ether (80 cc.). A brown solid separated; the mixture was gently refluxed for three hours and allowed to stand for a day, after which it was poured into iced hydrochloric acid (10 cc.) and extracted with ether. The combined extracts were washed with water, the solvent was removed, and the residue was extracted with petroleum ether (b.p. 28–38°) to remove acetomesitylene. There remained an amorphous, orange material (1.44 g.) from which no pure material could be obtained.

SUMMARY

In the reaction between nitrotrimethylquinone and methyl or ethyl sodiomalonate, the nitroquinone behaves as an α,β-unsaturated nitroolefin; addition of the enolate occurs directly to a double bond of the quinone without elimination of any group. This type of reaction between a fully substituted quinone and a metallic enolate is new, and the reaction demonstrates the strong resonance effect (electron attraction) of the nitro group.

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