

which did not form nicotinic acid when subjected to acid or to alkaline hydrolysis.

Nitrous acid treatments³ did not effect demethylation. Trigonelline is apparently stable toward boiling nitric acid, even in the presence of oxidizing catalysts. Concentrated sulfuric acid at 300° and 65% oleum at 125°, with or without mercury as catalyst, also do not alter trigonelline. Chlorates, bromates, chromates and hypochlorites were also tried under a variety of conditions, without the formation of nicotinic acid.

Aniline hydrochloride was substituted for pyridine hydrochloride in the above outlined experiment with negative result. When quinoline hydrochloride was used,

pyridine was produced which indicated demethylation with accompanying decarboxylation. Betaine N-methyl- α -picolinic acid reacts with pyridine hydrochloride already at 140° with formation of pyridine.

Summary

Pyridine hydrochloride effects the cleavage of methyl betaines of pyridinecarboxylic acids. With trigonelline the products are nicotinic acid and N-methylpyridinium chloride.

RAHWAY, N. J.

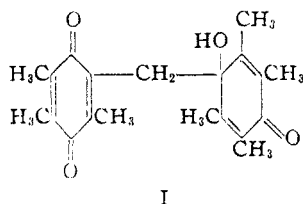
RECEIVED MAY 10, 1944

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

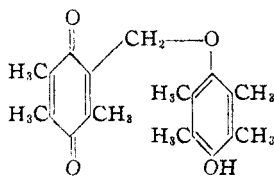
The Reaction between Quinones and Metallic Enolates. XIX.¹ The Structure of Diduroquinone

BY LEE IRVIN SMITH, ROY W. H. TESS AND GLENN E. ULLYOT

Duroquinone, in the presence of alkaline reagents in polar solvents, is converted into an orange dimer, diduroquinone.^{2,3} The dimer was shown by Rugheimer and Hänkel³ to contain a hydroxyl group, to yield durohydroquinone upon reduction, and to give duroquinone upon pyrolysis. These properties were considered to support structure I for the substance, rather than structure II, even though the compound could not be dehydrated.



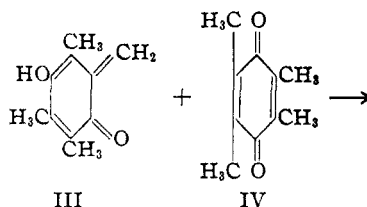
I



II

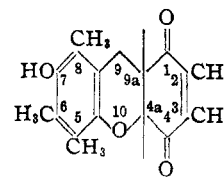
Diduroquinone was encountered very early in the work described in this series of papers⁴ and although it was felt that neither structure I nor II adequately represented the substance, no clue to a more satisfactory structure for the dimer was found until recently. Through considerations advanced in connection with the mechanism whereby methylated quinones are converted into coumarins⁵ it appeared that the structure of di-

duroquinone might be V, formed as a result of a diene reaction between duroquinone IV and its tautomer III, as shown.



III

IV



V

The properties of diduroquinone described in the present paper support the structure V, which represents the substance as a *p*-hydroxychroman of a special type. The similarity of the adsorption spectrum of diduroquinone (Fig. 1)⁶ to those of hydroduroquinone, its monoethers, various 5-hydroxycoumarans, and 6-hydroxychromans, all of which show absorption maxima between 280 and 300 μ ,⁷ indicates the presence in the dimer of a benzenoid ring carrying a hydroxyl group and an ether group para to each other. Chemical evidence that diduroquinone is a *p*-hydroxychroman is supplied by the fact that the substance can be oxidized to a quinone VI, which can be reduced to an orange hydroquinone VII. The hydroquinone VII can be dehydrated, regenerating diduroquinone.

(1) XVIII, THIS JOURNAL, **66**, 2131 (1943).

(2) v. Pechmann, *Ber.*, **21**, 1417 (1888); **22**, 2115 (1889).

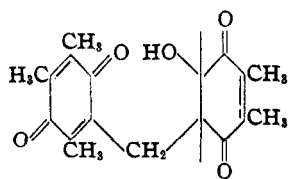
(3) Rugheimer and Hänkel, *ibid.*, **29**, 2176 (1896).

(4) (a) Smith and Dobrovolsky, THIS JOURNAL, **48**, 1420 (1926); (b) **48**, 1693 (1926).

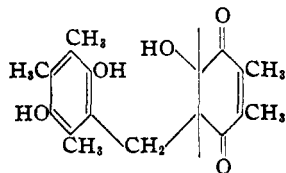
(5) Smith, Arnold and Nichols, *ibid.*, **65**, 2131 (1943).

(6) A Beckman Quartz Spectrophotometer was used.

(7) (a) Morton, "The Application of Absorption Spectra to the Study of Vitamins, Hormones, and Coenzymes," Adam Hilger, Ltd. 1942, 2nd ed., pp. 108-115. (b) Webb, Smith, *et al.*, *J. Org. Chem.*, **4**, 389 (1939).



VI

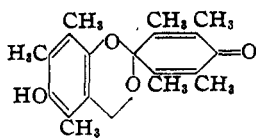


VII

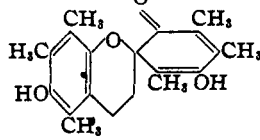
This sequence of reactions leading from V to VI, then VII, and back to V, is characteristic of *p*-hydroxy-coumarans and -chromans,⁸ and serves to identify these substances as a class. Diduroquinone, therefore, is a *p*-hydroxy-chroman.

It is obvious that other courses than the one leading to V may be taken by a diene reaction between two molecules of duroquinone, leading also to *p*-hydroxychromans, for example, structures VIII, IX and X. Structures such as VIII, which contain the ketal linkage, are inherently improbable and may be dismissed from consideration. The ketal linkage would rupture when such compounds are oxidized and no product analogous to VII, containing all the carbon atoms of diduroquinone, could be obtained on oxidation.

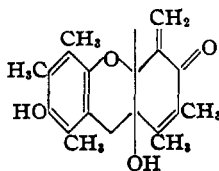
Diduroquinone reacts with 2.86 equivalents of methylmagnesium iodide, 0.81 equivalent of gas is evolved, and 2.05 equivalents of Grignard reagent are added. These values are in good agreement with the requirements of structure V, and not at all with the



VIII



IX



X

requirements of VIII, IX, X, or any of the other possible *p*-hydroxychromans derived from the two molecules of duroquinone, unless some of these structures (*e. g.*, IX) are written in tautomeric forms. The results of the Grignard analysis, however, must be interpreted with some caution, for although the ethyl ether of diduroquinone adds 1.84 equivalents of methylmagnesium iodide, as required for an ether of V, it also yields 0.52 equivalent of gas—a behavior which cannot be explained at the present time.

When the structures for all the possible *p*-hydroxychromans derivable from two molecules of diduroquinone are considered in the light of the evidence from the Grignard analysis and in the light of the known behavior of quinones as dienophiles, structure V becomes the most logical one.

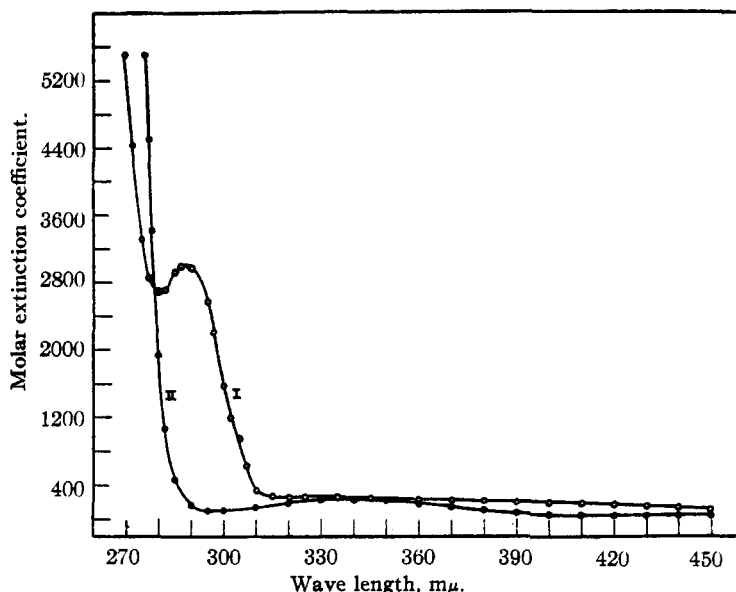


Fig. 1.—Absorption spectra: Curve I, O, diduroquinone in 95% alcohol; Curve II, ●, duroquinone in 95% alcohol.

Diduroquinone, therefore, is certainly a *p*-hydroxychroman, and most probably is V, 1,4-diketo-2,3,4a,5,6,8,9a-heptamethyl-7-hydroxy-1,4,4a,9a-tetrahydroxanthene.⁹

Experimental Part

Diduroquinone (V).—Aqueous potassium hydroxide (6 drops, 15%) was added to a solution of duroquinone (5 g.) in ethanol (95%, 70–75 cc.) at room temperature. The orange solution became violet, then brown, and after half an hour the dimer began to separate. After four hours, the mixture was cooled (0°), and the solid was removed and washed with a little ethanol. The product weighed 4.7 g. (94%) and melted at 204–206°. After three crystallizations from ethanol the substance melted at 207.5–208°. The same percentage yield is obtained when four times these quantities of materials are employed; for the larger amounts, it is more convenient to crystallize the product from acetic acid, as it is not very soluble in ethanol, even at the boiling point.

Anal. Calcd. for C₂₈H₂₄O₄: C, 73.17; H, 7.32. Found:

(8) (a) John, Dietzel and Emte, *Z. physiol. Chem.*, **287**, 173 (1938); (b) Smith, Ruoff and Wawzonek, *J. Org. Chem.*, **6**, 236 (1941).

(9) Ring Index No. 2000.

C, 73.2, 73.2; H, 7.63, 7.87. Millimole of sample, 0.349; millimole of gas, 0.281; millimole added reagent, 0.716. Calcd. active H, 1.0; carbonyl, 2.0. Found: active H, 0.81; carbonyl, 2.05.

Ethyl Ether of Diduroquinone.—A solution of potassium hydroxide (0.4 g.) in ethanol (13 cc.) was added to a solution of diduroquinone (0.96 g., 0.003 mole) in ethanol (15 cc.) containing ethyl bromide (5 cc.). The mixture was refluxed for two hours and then poured into water. The product was removed and crystallized from dilute ethanol. It then formed light yellowish crystals (0.85 g., 82%) which melted at 129–130°. Two more crystallizations gave a pale yellow, almost colorless, solid which melted at 130–131°.

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.15; H, 7.86. Found: C, 74.0; H, 8.04. Millimole of sample, 0.353, 0.329; millimole of gas, 0.204, 0.170; millimole added reagent, 0.690, 0.570. Calcd.: active H, 0; carbonyl, 2.0. Found: active H, 0.58, 0.51; carbonyl, 1.95, 1.73.

Acetyl Derivative of Diduroquinone.—The dimer (4 g.) was refluxed for three hours with an excess of acetic anhydride. The cooled solution was diluted with water, the solid was removed and crystallized from ethanol. It weighed 3.5 g. (77%) and melted at 132–133°. The substance does not have a sharp melting point until after it has been dried on a steam-bath; apparently the substance crystallizes from alcohol with solvent of crystallization.³

2-(3',6'-Diketo-2'-hydroxy-1',2',4',5'-tetramethyl-1',2',3',6'-tetrahydrobenzyl)-3,5,6-trimethyl-1,4-benzoquinone (VI).—A solution of ferric chloride (1.5 g., 0.09 mole) in ethanol (30 cc.) was added to a hot solution of diduroquinone (0.99 g., 0.03 mole) in ethanol (80 cc.), and the solution was heated on the steam-bath for one hour and fifty minutes. The solution was poured into water and extracted several times with ether. The yellow ethereal solution was washed successively with water, aqueous sodium bicarbonate (5%), and water, then dried (sodium sulfate), evaporated to about 5 cc., and cooled. The yellow crystals (0.83 g., 80%) were removed and washed with a little cold ethanol. Crystallization from petroleum ether (b. p. 60–68°) gave a product (0.74 g.) which melted at 132–138°. Repeated crystallization gave a product with approximately the same melting point; the analytical sample melted at 128–137°.¹⁰

Anal. Calcd. for $C_{26}H_{24}O_5$: C, 69.75; H, 7.02. Found: C, 69.74; H, 7.16.

2-(3',6'-Diketo-2'-hydroxy-1',2',4',5'-tetramethyl-1',2',3',6'-tetrahydrobenzyl)-3,5,6-trimethylhydroquinone (VII).—A solution of the quinone VI (0.50 g.) in ether (40 cc.) was shaken for forty-five minutes with a solution of sodium hydrosulfite (2 g.) in water (40 cc.). The ether layer was removed and washed successively with water, aqueous sodium bicarbonate (5%), and water, then dried (sodium sulfate), and evaporated, finally under reduced pressure. The residue, after crystallization from ligroin (b. p. 60–68°), formed orange crystals (0.33 g., 66%) which melted at 144–149°. Repeated crystallization did not give a product with a higher or sharper melting point; the analytical sample melted at 141–148°.¹⁰

Anal. Calcd. for $C_{26}H_{28}O_5$: C, 69.34; H, 7.57. Found: C, 69.26; H, 7.83.

(10) The quinone VI and the hydroquinone VII invariably appeared as compounds with rather wide ranges in melting point, and repeated crystallizations failed to produce substances with sharp melting points. This behavior is believed to be due to decomposition at the melting points. Structure V shows two asymmetric carbon atoms, 4a and 9a, but only one (racemic) form is possible because a *trans* relationship of the rings joined by these atoms is impossible. But when the hetero ring of V is opened, as in VI and VII, the two asymmetric carbon atoms 4a and 9a are no longer restricted in configuration and two racemates are possible. Although VI and VII are believed to be stereochemically homogeneous, it is possible that, at the melting points, partial inversion occurs at atoms 4a and 9a in these compounds. If so, this would account for the wide ranges in the melting points. When the hetero ring in VII was closed, the resulting diduroquinone V melted sharply.

Cyclization to Diduroquinone (V).—The hydroquinone VII (110 mg.) was added to a solution of sulfuric acid (1 cc.) in cold methanol (12 cc.). After standing for one day at room temperature, the solution began to deposit crystals; after three days, the solution was cooled, and the precipitate was removed and washed with cold methanol. The orange product (75 mg., 72%) melted at 203–206°, alone or when mixed with authentic diduroquinone (m. p. 205–206°).

Miscellaneous Experiments upon Diduroquinone. A.—An excess of thionyl chloride was warmed on the steam-bath for three hours with diduroquinone (2 g.). Removal of the thionyl chloride left a viscous oil, which was dissolved in a benzene-ligroin mixture. The solution, after standing for four days, deposited a tan solid (1.8 g.). Crystallization of this material from ethanol gave two solids in amounts too small to be investigated: one, yellow needles, melted at 153–155°; the other, orange, melted at 136–138°.

B.—Diduroquinone (1.0 g.) in ethanol (100 cc.) was warmed for thirty minutes with 2,4-dinitrophenylhydrazine (1.8 g.) and hydrochloric acid (3 cc.). The solution, when cooled, deposited a red solid from which only diduroquinone and the hydrazine could be isolated by crystallization. No phenylhydrazone was found.

C.—A solution of diduroquinone (1.0 g.) in ethanol (100 cc.) containing hydroxylamine hydrochloride (0.64 g.), was refluxed for one and one-half hours. The solution, on cooling, deposited diduroquinone. This was redissolved by warming the mixture, and a solution of sodium acetate (1 g.) in water (1 cc.) and ethanol (4 cc.) was added. The solution was refluxed for four hours and then cooled. Diduroquinone (0.9 g.) was deposited.

D.—A small amount of diduroquinone, refluxed for several hours with a solution (15%) of potassium hydroxide in ethanol and then acidified, was converted into a dark greenish yellow substance of indefinite melting point. No diduroquinone was recovered. Diduroquinone was unchanged when its solution in acetic acid was boiled for four hours while a current of hydrogen chloride was passed through the solution. Similarly, the substance was unchanged when refluxed for three hours in acetic acid containing hydrobromic acid. When refluxed in acetic acid containing hydriodic acid, diduroquinone was converted into hydrodicroquinone, m. p. 220–230°. Diduroquinone dissolved in cold sulfuric acid and was recovered unchanged when the solution was diluted with water. The substance underwent charring in sulfuric acid when the temperature was raised to 60–65°.

E. Various Reduction Experiments upon Diduroquinone and its Derivatives.—Diduroquinone was unaffected by sodium hydrosulfite even after several hours. Reduction of diduroquinone in alcohol under high pressures of hydrogen, and in the presence of a copper chromite catalyst, gave hydrodicroquinone. Reduction by action of zinc and acetic acid gave hydrodicroquinone; reduction in alcohol by action of zinc and hydrochloric acid also gave hydrodicroquinone. Reduction by action of sodium amalgam and alcohol gave a very small amount of a white solid melting at 199–213°, probably the hydroquinone. Reduction of the ethyl derivative of diduroquinone by low pressure catalytic hydrogenation, or by action of sodium amalgam and alcohol gave oily solids with wide ranges in melting point and which could not be purified. Reduction of the acetyl derivative of diduroquinone by action of zinc and acetic acid gave hydrodicroquinone.

Summary

1. It has been shown that diduroquinone, the dimer of duroquinone, is a *p*-hydroxychroman, for the substance, on mild oxidation, gives a *p*-quinone which is reducible to a hydroquinone and this, in turn, can be cyclized to diduroquinone. This is the typical behavior of *p*-hydroxychromans.

2. Diduroquinone is formed by a diene synthesis involving the double bond of one molecule of the quinone and the conjugated system of the pentad-enolic form of a second molecule of quinone.

3. The absorption spectrum of diduroquinone has been determined.

4. The chemical behavior of diduroquinone is discussed.

MINNEAPOLIS 14, MINNESOTA RECEIVED MAY 12, 1944

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

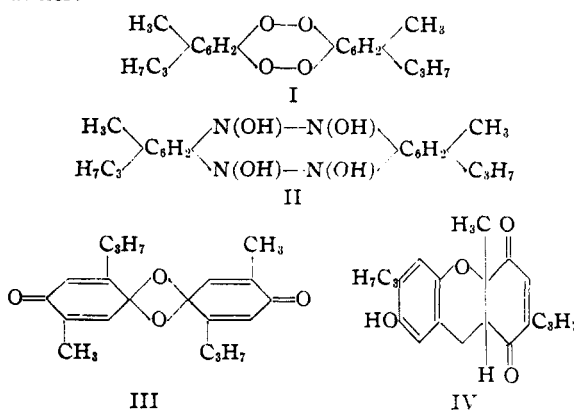
Dithymoquinone

BY LEE IRVIN SMITH AND ROY W. H. TESS

Having established that diduroquinone is a *p*-hydroxychroman¹ it was decided to investigate another quinone dimer, dithymoquinone, to determine whether or not it was also a *p*-hydroxychroman, analogous to diduroquinone. The results of this study show that dithymoquinone is quite different from diduroquinone, and that the two substances cannot be structurally similar.

Dithymoquinone was first discovered by Lallemand in 1857 and called by him "oxythymoile."² The first significant work on the substance was done by Liebermann and Ilinski,³ though it remained for Lagodzinski and Mateescu⁴ to establish that the polymer was a dimer. The significant facts about the chemistry of dithymoquinone, as established by the previous workers in the field, may be summed up as follows: The substance was prepared by the action of light upon thin layers of thymoquinone; when crystallized from ethanol, it formed long, light yellow needles melting at 200–201° and resembling anthraquinone in appearance. The substance was quite stable, and was sparingly soluble in all the usual solvents. Reduction, by a variety of methods, gave thymohydroquinone. Cold sulfuric acid, bromine in acetic acid or water, sulfurous acid, acetic anhydride, and even hot nitric acid, were all without action upon the substance. When quickly heated, the dimer could be distilled at 232° (the boiling point of the monomer), and the distillate contained thymoquinone. Curiously enough, the substance reacted with various carbonyl reagents; a diphenylhydrazine, a dioxime and a tetraoxime⁵ have been reported. The dioxime, on reduction, gave *p*-aminothymol, whereas the tetraoxime, on reduction, gave *p*-diaminocymene. Reaction with phenylhydrazine converted dithymoquinone into benzeneazothymol, along with the diphenylhydrazine; reaction of thymoquinone with phenylhydrazine produced thymohydroquinone and nitrogen. Liebermann and Ilinski, on the basis of their work,

proposed structures I and II, respectively, for dithymoquinone and its tetraoxime; Lagodzinski and Mateescu proposed structure III for the dimer.



A structure such as IV for dithymoquinone, representing it as a *p*-hydroxychroman, analogous to the structure established for diduroquinone, appears to be impossible. Dithymoquinone could not be prepared by action of alkali upon thymoquinone; only dark solutions resulted, from which the amount of unchanged quinone that could be isolated decreased steadily as the time of contact increased. The only method found for preparation of the quinone was the original one—illumination of thin layers of the monomer, when the dimer resulted in 76% yields. With excess methylmagnesium iodide, dithymoquinone gave 1.84 moles of gas and added 1.81 moles of the reagent. All attempts to prepare hydroxyl derivatives of the dimer were unsuccessful; acetic anhydride, acetyl chloride, and phosphorus trichloride were without action, nor could a methyl ether be prepared. These facts indicate that the substance probably contains no hydroxyl group; certainly, if one is present, it must be tertiary.

Reduction of dithymoquinone by sodium hydro-sulfite gave thymohydroquinone, but only slowly—thirty to forty minutes as compared with thirty seconds for thymoquinone itself, and the reduction of the dimer occurred with equal difficulty in bright summer sunlight or under artificial light. Action of hydrobromic acid in acetic acid led to rapid darkening of the dimer, and no new product

(1) Smith, Tess and Ulliot, *THIS JOURNAL*, **66**, 1320 (1944).

(2) Lallemand, *Ann. chim. phys.*, [3] **49**, 167 (1857).

(3) (a) Liebermann, *Ber.*, **10**, 613, 2177 (1877); (b) Liebermann and Ilinski, *ibid.*, **18**, 3193 (1885).

(4) Lagodzinski and Mateescu, *ibid.*, **27**, 958 (1894).

(5) Kehrman and Messinger, *ibid.*, **28**, 3558 (1891), showed that this tetraoxime, m. p. 290°, was not the same as the dioxime of thymoquinone, which they found to melt at 235°.