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

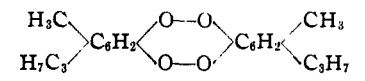
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Dithymoquinone

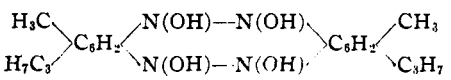
BY LEE IRVIN SMITH AND ROY W. H. TESS

Having established that diduroquinone is a *p*-hydroxychroman[1] 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.

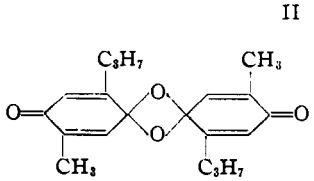
Dithymoquinone was first discovered by Lallemand in 1857 and called by him "oxythymoile."[2] The first significant work on the substance was done by Liebermann and Ilinski,[3] though it remained for Lagodzinski and Mateescu[4] to establish that the polymer was a dimer. The significant facts about the 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 diphenylhydrazone, a dioxime and a tetraoxime[5] 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 diphenylhydrazone; 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.



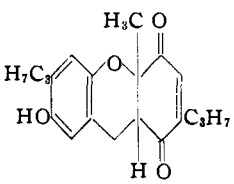
I



II



III



IV

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 hydrosulfite 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 Ullyot, 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) Kehrmann and Messinger, *ibid.*, **23**, 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°.

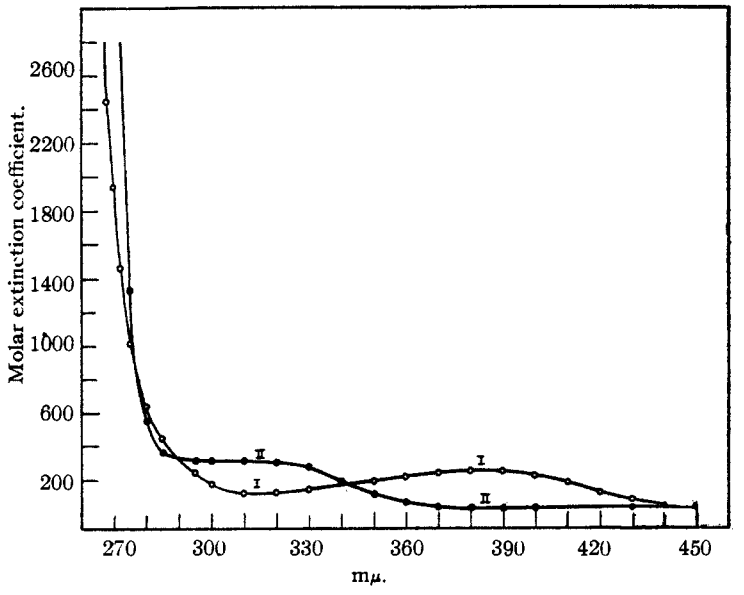
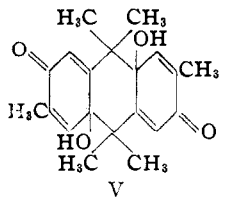


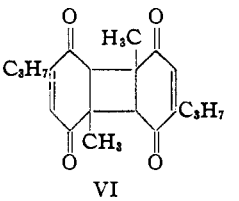
Fig. 1.—Absorption spectra: Curve I, O, dithymoquinone in 95% alcohol; Curve II, ●, thymoquinone in 95% alcohol.

or starting material could be isolated. Dithymoquinone was completely inert to the action of ferric chloride, quite in contrast to the behavior of diduroquinone, which reacted smoothly to give a *p*-quinone. It followed that dithymoquinone could not possibly be a *p*-hydroxychroman such as IV. The absorption spectra of the dimer and monomer were measured[6]; the curves (Fig. 1) fail to provide any unusual characteristics and they give no evidence for the presence of a phenolic hydroxyl group in the dimer.

When all the facts concerning the chemistry of dithymoquinone are assembled, they lead to consideration of two structures, V and VI, for the substance. Structure V, the result of a double aldol condensation, shows two carbonyl groups and two active hydrogen atoms, and would satisfy the results of the Grignard analysis. The hydroxyl groups are tertiary and are hindered; therefore, the formation of esters or ethers would be difficult or impossible.



V



VI

Formation of a diphenylhydrazone and a dioxime, and the reduction of the latter to *p*-aminothymol, would be expected. But formation of a tetraoxime, which on reduction would give *p*-diaminocymene, cannot be readily explained on the basis of structure V.

Structure VI represents dithymoquinone as a cyclobutane derivative formed by dimerization in the same way that the truxillic and truxinic acids are formed from cinnamic acid—a dimerization also brought about by action of light. Wessely and his associates[7] have shown that various coumarins, including coumarin itself as well as the natural products pimpinellin and herniarin, undergo dimerization to cyclobutane derivatives in the presence of light. Of the possible structures for dithymoquinone derived in this way, VI appears to be the most probable when steric factors are considered. By means of this structure, formation of a diphenylhydrazone, a dioxime, a tetraoxime, reduction of the dioxime to *p*-aminothymol, and reduction of the tetraoxime to *p*-diaminocymene, all can be explained readily, but the results of the Grignard analysis are difficult to reconcile with structure VI unless it is assumed that VI undergoes a tautomeric change in the presence of the Grignard reagent.

On the whole, however, VI appears to be the most satisfactory structure for dithymoquinone in the light of present knowledge concerning the chemistry of this substance.

Experimental Part

Dithymoquinone.—A solution of thymoquinone (3 g.) in a small amount of ether was distributed as evenly as possible over the inside surface of a 5-liter round-bottomed Pyrex flask. Evaporation of the ether left the quinone as a thin film. The flask was then exposed to bright daylight (but not direct sunlight) for five days during June, 1943. The yellow solid, which had become tan and opaque, was removed and washed with dry ether. It weighed 2.27 g. (76%) and melted at 158–196°. Two crystallizations from alcohol gave a product (2.08 g., 70%) which melted at 199.5–200°.

The dimer (50 mg.) was dissolved in acetic anhydride (3 cc.) containing sulfuric acid (1 drop). No visible change occurred; after the solution had stood for two days at room temperature, water (5 cc.) was added and the yellow precipitate was removed. The material was unchanged dimer, m. p., and mixed m. p., 196–200°.

The dimer (50 mg.) was dissolved in acetyl chloride (2 cc.). The solution was allowed to stand for five minutes and then was evaporated slowly to dryness on the steam-bath. The residue (45 mg.) was dithymoquinone, m. p., and mixed m. p., 196–199°.

The dimer (100 mg.) was dissolved in phosphorus trichloride (15 cc.) and the solution was allowed to stand overnight. The solution was poured into water, the solid (80 mg.) was removed and crystallized from ethanol. It was unchanged material, m. p., and mixed m. p., 197–200°.

A solution of the dimer (100 mg.) in cold sulfuric acid (5 cc.) was poured into methanol (15 cc.). The mixture was heated on the steam-bath for thirty minutes and then cooled. Dithymoquinone (80 mg.), m. p., and mixed m. p., 198–200°, separated.

(6) A Beckman Quartz Spectrophotometer was used.

(7) (a) Wessely and Dimjaski, *Monatsh.*, **64**, 131 (1934); (b) Wessely and Kallab, *ibid.*, **59**, 161 (1932); (c) Wessely and Plaichinger, *Ber.*, **75**, 971 (1942).

The dimer (100 mg.) was dissolved in acetic acid (8 cc.) containing hydrobromic acid (8 cc., 48%), and the solution was boiled for twenty minutes. The mixture rapidly became dark and no pure product could be isolated from it.

Dithymoquinone (100 mg.) in ether (30 cc.) was shaken with a solution of sodium hydrosulfite (2 g.) in water (20 cc.) until the color was discharged (forty minutes). From the ether layer there was isolated thymohydroquinone (100 mg.), m. p., and mixed m. p., 138–141°. Reduction of thymoquinone (100 mg.) by exactly the same procedure was complete in thirty seconds; the hydroquinone melted at 142°.

A solution of ferric chloride hexahydrate (0.62 g.) in ethanol (20 cc.) was added to a solution of dithymoquinone (150 mg.) in ethanol (20 cc.). The mixture was heated (steam-bath) for thirty minutes and then poured into water. The yellow precipitate (140 mg.) was unchanged dimer, m. p., and mixed m. p., 196–199°.

Thymoquinone (1 g., m. p., 45–47°) was dissolved in warm ethanol (15 cc.) and two drops of aqueous potassium hydroxide (15%) was added. The solution immediately became dark; it was allowed to stand for four hours at room temperature. No precipitate formed, even when the solution was cooled to 0°. Water was added, the mixture was cooled, and thymoquinone (0.22 g.) was recovered. No other product could be isolated; no dimer was formed.

Summary

1. Dithymoquinone, the dimer of thymoquinone, is not a *p*-hydroxychroman analogous to diduroquinone.

2. The absorption spectra of thymoquinone and dithymoquinone have been measured.

3. Two structures for dithymoquinone merit consideration. One, V, represents the substance as a hexahydroanthracene derivative containing two tertiary hydroxyl groups and two carbonyl groups. The other structure, VI, represents the substance as a cyclobutane derivative containing four carbonyl groups and no hydroxyl groups, formed in a manner analogous to the dimerization of cinnamic acid and certain coumarins.

4. These two structures are discussed in the light of present chemical knowledge concerning dithymoquinone. Although neither structure is in accord with all of the known facts, structure VI is the more satisfactory of the two.

MINNEAPOLIS 14, MINNESOTA RECEIVED MAY 12, 1944

[CONTRIBUTION FROM THE LABORATORIES OF W. J. BUSH & CO., LTD.]

A New Synthesis of α-Bromoaldehydes

BY PAUL Z. BEDOUKIAN

Methods of preparation of α-bromoaldehydes that have been reported involve protection of the carbonyl group followed by direct bromination. Some of these methods suffer from the disadvantage of low yields and limited applicability[1] and others from drastic and lengthy procedures.[2]

All are based upon a replacement reaction, and it was thought that if the bromination could be carried out as an addition reaction, a simpler method resulting in higher yields might be expected.

It is well known that enols add bromine very rapidly and although aldehydes do not exist in enolic form in appreciable quantities, it is possible to prepare stable enol acetates[3] by boiling aldehydes with acetic anhydride in the presence of a catalyst. It was expected that addition of bromine to the double bond of an enol acetate would take place rapidly and because of the presence of a halogen and an ester grouping on the same carbon atom, the resulting compound would undergo alcoholysis with great facility. Such compounds would yield bromoacetals on treatment with alcohol. Filachione[4] has reported the synthesis of bromoacetaldehyde acetal by brominating vinyl acetate in alcohol at low temperatures. It was realized that vinyl acetate is in effect the enol acetate of acetaldehyde. Since higher aldehydes containing an α-hydrogen are readily converted to enol acetates, it seemed desirable to determine whether they would react with bromine in a similar manner to give bromoaldehydes. The present paper is a report of the results of this work.

Isobutyraldehyde, heptaldehyde and phenylacetaldehyde were chosen for this work. The enol acetates were prepared in the usual manner by boiling with acetic anhydride and potassium acetate. The yields of enol acetates varied according to the nature of the aldehyde. The balance of the products consisted largely of the unreacted aldehyde and aldehyde diacetate which may be hydrolyzed to the original aldehyde by boiling with water or distilling at atmospheric pressure.[5]

It was found that addition of theoretical quantities of bromine to the enol acetate proceeded rapidly and smoothly in cold carbon tetrachloride solution. Upon adding excess methyl alcohol (99.5–100%) to the brominated mixture and allowing it to stand two or three days, dimethyl acetals of α-bromoaldehydes were obtained in 75–80% yields. When highly purified, these acetals were found to be stable, but slight impurities, especially traces of acids, caused decomposition and darkening. Hydrolysis of dimethyl acetals

(1) Franke, *Ann.*, **351**, 423 (1907); Dworzak and Pfifferling, *Monatsh.*, **48**, 251 (1927); Dworzak and Enenkel, *ibid.*, **50**, 449 (1928); Dworzak and Pierri, *ibid.*, **52**, 141 (1929); Dworzak and Prodinger, *ibid.*, **53** to **54**, 588 (1929).

(2) Kirrmann, *Compt. rend.*, **184**, 525 (1927); *Ann. chim.*, [10] **11**, 223 (1929); Madinaveitia and Puyal, *Anal. soc. españ. fis. quim.*, **16**, 329 (1918); *C. A.*, **13**, 2677 (1919).

(3) Semmler, *Ber.*, **42**, 1161 (1909).

(4) Filachione, THIS JOURNAL, **61**, 1705 (1939). See also McElvain and Kundiger, "Organic Syntheses," **23**, 8 (1943).

(5) Wegscheider and Späth, *Monatsh.*, **30**, 825 (1909).