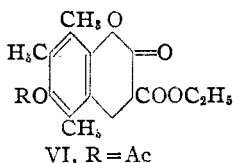
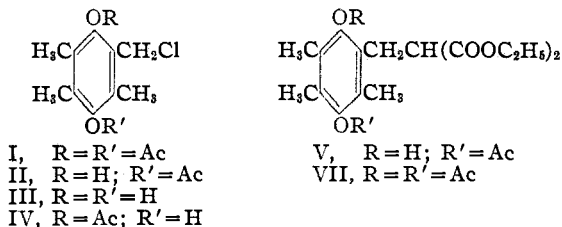


[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Structure of the Chloromethylation Product of Trimethylhydroquinone Diacetate¹BY LEE IRVIN SMITH AND ROBERT B. CARLIN²

A short time ago, it was reported³ that the diacetate of trimethylhydroquinone, when subjected to the action of formaldehyde and hydrochloric acid, gave the corresponding benzyl chloride (I) which melted at 150–151°.



It has now been found that this product does not possess structure I, but instead must be represented by structure II.

The substance gave a strong phenol test (Folin) and rapidly deposited silver halide when treated with alcoholic silver nitrate. Analysis, however, was of little use in establishing the structure, because the theoretical values for I, II, III and IV all lie close together, and the values found, while checking best for structure II (or IV), could be reconciled with any of the four structures. Structure III was eliminated by the synthesis of III from trimethylhydroquinone, formaldehyde and hydrochloric acid. The product, obtained in 60% yield, melted at 115–116° with vigorous decomposition. It rapidly deposited silver chloride from alcoholic silver nitrate, and when reduced with zinc and acetic acid, it gave durohydroquinone. When acetylated, II and III gave the same product, m. p. 165°, which was the diacetate of trimethylchloromethylhydroquinone (I) and which gave no phenol test and only a slow deposition of silver chloride from alcoholic silver nitrate.

It thus appeared that the substance melting at

150–151° was a mono acetate, either II or IV. A choice between the two structures was reached by a consideration of the work of v. Auwers⁴ and others upon the *o*- and *p*-hydroxybenzyl halides (pseudophenol halides). The halogen atom in these compounds possesses great reactivity, but when the phenolic hydroxyl group is masked as an ester or an ether, the halogen atom is relatively inert. Both II and III reacted rapidly with silver nitrate and with sodioacetoacetic ester, whereas I, in which the hydroxyl group ortho to the chloromethyl group is esterified, reacted only slowly with silver nitrate and did not alkylate sodio acetoacetic ester under any of the conditions tried. Substance II was not soluble in cold, dilute sodium hydroxide, a behavior which is characteristic of the pseudophenol halides and quite at variance with the behavior to be expected from a compound of structure IV, in which the phenolic hydroxyl group is meta to the chloromethyl group. This structure, II, was confirmed by the nature of the products obtained when the substance reacted with sodiomalonic ester.

When II was permitted to react for not longer than two hours at room temperature with an equivalent of sodiomalonic ester in dry ether, the product was the monoalkylated malonic ester (V) which was readily converted into the diacetate (VII). On the other hand, when a slight excess of the enolate was present, or when the reaction time was prolonged, the main product was the known 3-carbethoxy-6-acetoxy-5,7,8-trimethyldihydrocoumarin (VI).⁵ Both V and VI were accompanied by a substance which melted at 175° and which had the composition of a substance derived from the dialkylated malonic ester analogous to V by the elimination of a molecule of alcohol. The amount of this material varied greatly from one experiment to another; sometimes only traces of it were formed, whereas at other times it accounted for half of the starting material.

The monoalkylated malonic ester (V) was converted into the hydrocoumarin (VI) by action of sodiomalonic ester or sodium hydroxide in ether.

(1) Paper XV on Quinones and Metallic Enolates; XIV, THIS JOURNAL, **63**, 937 (1941).

(2) Abstracted from a thesis by Robert B. Carlin, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, June, 1941.

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

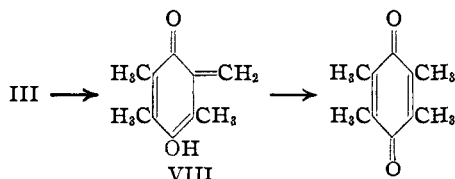
(4) v. Auwers, *Ann.*, **301**, 203 (1898).

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

Sodium acetate was without effect, and the conversion of V into VI appears to be analogous, in some respects, to the Claisen condensation in which the driving force of the reaction is the tendency for a stronger acid to liberate a weaker one from its salts. When either sodiomalonic ester or sodium hydroxide was added to an ether solution of V, there was an instantaneous conversion of V—the next stronger acid—into its salt, a change that was actually visible in the reaction mixture. In time, the alkali catalyzed the change of the sodium derivative of V into that of the next stronger acid, the hydrocoumarin VI. The hydrocoumarin VI was always obtained from the reaction mixture in the form of its ether-insoluble sodium enolate, and if insufficient time were allowed, a mixture of enolates resulted, acidification of which produced a mixture of V and VI. Moreover, V was always accompanied by some malonic ester which was present as such in the ether-soluble, non-enolic portion of the reaction mixture.

No methods other than the ones outlined were found by means of which V could be converted into VI. Addition of acidic or basic reagents in polar solvents such as ethanol or acetic acid produced only dark, high-melting products, apparently hydroquinones. Alkylation of malonic ester by II in benzene gave oils from which no solid material could be obtained.

The chloromethylhydroquinone (III) was a compound possessing unusual properties. It was relatively unstable and, on standing for three weeks at room temperature, it developed a strong odor of hydrogen chloride. On steam distillation, III was converted largely into red, sticky materials, but the distillate contained enough duroquinone for identification. This transformation of III into tetramethylquinone by loss of hydrochloric acid requires an intermediate methylenequinone (VIII). Substances of this type have often been postulated as intermediates in reac-



tions involving pseudophenol halides, and they have also been regarded as intermediates in reactions between metallic enolates and highly alkylated quinones.⁶ Several attempts were made

to convert III into duroquinone in quantity, but none were successful. This, however, might have been expected because it is known⁷ that excess basic reagents in polar solvents convert duroquinone into diduroquinone and red, tarry materials. However, when the diacetate (I) was treated under hydrogen with two equivalents of sodium ethoxide and one of sodioacetoacetic ester in alcohol no alkylation product was obtained, but duroquinone was isolated in an amount corresponding to 10% of the halide I. Assuming that the alkali first converted I into duroquinone, the quinone would then react with the enolate to produce a coumarin, an equivalent amount of durohydroquinone, and some diduroquinone.⁷ Direct isolation of any solid from this mixture was not possible. Accordingly, the mixture was shaken with aqueous copper acetate to convert the hydroquinone to quinone, and the latter was then isolated by steam distillation. Since the weight of quinone corresponded to 10% of the amount of I used, the actual conversion of I to duroquinone amounted to at least 20%.

The diacetate (I) was so inert that it could be recrystallized from alcohol, and it was recovered unchanged when attempts were made to alkylate sodiomalonic ester with it in boiling benzene or dioxane, even after several days of treatment. In alcohol, I and sodiomalonic ester reacted with deposition of sodium chloride, but no alkylation products could be isolated. In contrast to this behavior, III was extremely sensitive to all basic reagents. Ammonia in ether produced a white, insoluble and high-melting solid, and although the ether solution was bright yellow, evaporation left no appreciable residue. The action of pyridine, or of quinoline, on III produced dark red, tarry solids, but no material volatile with steam. Likewise the monoacetate II was extremely sensitive to basic reagents; alkylation of enolates by II could not be carried out in alcohol because the halide was attacked by this solvent.

Experimental⁸

Chloromethylations.—The product resulting from chloromethylation of trimethylhydroquinonediacetate was found to depend greatly upon the experimental conditions, and particularly upon the temperatures at which the reaction was carried out. When the temperature of the reaction mixture was maintained at 0°, the main product, formed in excellent yields, was a white solid which melted

(7) Smith and Dobrovolny, *ibid.*, **48**, 1693 (1926).

(8) Microanalyses by E. E. Renfrew, E. E. Hardy and C. H. Stratton.

(6) Smith and Johnson, *THIS JOURNAL*, **59**, 675 (1937).

at 228–229°. When a temperature of 15–20° was maintained throughout the reaction, the chief product was a substance which melted at 167–168°, but this was accompanied by small amounts of the high-melting material together with some of II. The nature of these other substances will form the subject of a later communication; they are mentioned here only to emphasize that, in the preparation of II, the experimental directions must be followed closely if good yields are to be obtained.

3-Acetoxy-6-hydroxy-2,4,5-trimethylbenzyl Chloride (II).—A solution of aqueous formaldehyde (60 cc., 40%) in hydrochloric acid (80 cc.) was saturated with gaseous hydrogen chloride at 10–20°. The temperature was raised to 30° and trimethylhydroquinonediacetate (20 g.) was then added. The suspension was stirred vigorously for one hour while a brisk stream of hydrogen chloride was passed through it. The diacetate dissolved almost completely during the first ten minutes, then solid material began to deposit and in a few moments there was a sudden deposition of large, semi-solid masses. These masses gradually disintegrated, and the originally colorless reaction mixture became first pink and then red to purple. The end of the reaction was usually indicated by the appearance of a copious froth at the top of the mixture. The temperature was usually maintained sharply at 30° by the heat of the reaction, except for a short time when the solid first began to deposit. At this point it was frequently necessary to apply some outside cooling, but care was exercised not to cool too much.

The reaction mixture was poured onto ice (100 g.) and the solid material adhering to the apparatus was washed into the beaker with a stream of cold water. The solid was removed and washed thoroughly with cold water (by decantation) until the washings were colorless. The dried solid (8–10 hours over potassium hydroxide in a vacuum desiccator) was refluxed with ether (300 cc.), the hot solution was filtered and the filtrate was shaken occasionally during an hour with Norit (3 g.). After removal of the Norit, the ether solution was concentrated to 75 cc. and then diluted with an equal volume of petroleum ether (b. p. 77–115°). On cooling, the product (17.8 g., 89%) crystallized in clumps of small needles which melted at 147–148°. This product was pure enough for most purposes, but recrystallization of it gave a product which was white and which melted at 150–151°. When mixed with the product previously described as I,⁸ there was no melting point depression.

Anal. Calcd. for $C_{14}H_{17}O_4Cl$ (I): C, 59.05; H, 5.98. For $C_{12}H_{14}O_8Cl$ (II and IV): C, 59.36; H, 6.22. For $C_{10}H_{13}O_2Cl$ (III): C, 59.82; H, 6.53. Found: C, 59.63; H, 6.45.

3,6-Dihydroxy-2,4,5-trimethylbenzyl Chloride (III).—Trimethylhydroquinone (2.5 g.) was chloromethylated by the same procedure as that described above. The other reagents were aqueous formaldehyde (7.5 cc., 40%) and hydrochloric acid (10 cc.). The reaction mixture was poured into water (100 cc.) containing cracked ice (50 g.) and the product was thoroughly washed and then dried for twelve hours over solid potassium hydroxide in a vacuum desiccator. The dried solid was refluxed with ether (150 cc.) for five minutes and the hot solution was filtered. The filtrate was concentrated to 50 cc. and an equal volume

of petroleum ether (b. p. 77–115°) was added. A white solid separated, but this turned brown by the time crystallization was complete. The brown material melted at 114–115° to a black liquid which effervesced vigorously. The substance could not be prepared sufficiently pure and dry for analysis. In the drying pistol it became extremely dark and was transformed into red amorphous material which contained small amounts of a white material melting at different temperatures in the range 200–300°. The substance III gave a strong phenol test (Folin) and rapidly deposited silver chloride from methanolic silver nitrate.

When III (500 mg.) was refluxed for thirty minutes in acetic acid (20 cc.) with zinc dust (1 g.), the original orange-yellow solution became red and then the color slowly faded to a pale yellow. The solution was filtered onto cracked ice (75 g.) and neutralized (litmus) with ammonia. The solution was then concentrated under reduced pressure until considerable solid had formed. The solid was removed, dried on a porous plate, and triturated with petroleum ether. It then melted at 202–209° to a black liquid. When mixed with durohydroquinone (m. p. 233°), the substance melted at 213–221°. The solid and the filtrate from it were steam distilled from ferric chloride (10 g.). Duroquinone, m. p. and mixed m. p. 109–110°, was isolated from the distillate.

A sample of III which had stood for three weeks, and which had a pronounced odor of hydrogen chloride, was steam distilled. Duroquinone (about 10 mg.) melting at 107° was isolated from the distillate.

3,6-Diacetoxy-2,4,5-trimethylbenzyl Chloride (I).—Either the monoacetate (II) or the hydroquinone (III) was converted into I by covering the solid with acetic anhydride, adding one drop of sulfuric acid, and warming the mixture just to the boiling point. The crude product (nearly quantitative yields) melted at 162–163°; after crystallization from benzene-petroleum ether (b. p. 60–68°), it formed long, white, glistening prisms which melted at 165°. The substance gave a negative phenol test (Folin) and very slowly deposited silver chloride from methanolic silver nitrate.

Anal. Calcd. for $C_{14}H_{17}O_4Cl$: C, 59.05; H, 5.98. Found: C, 58.94; H, 5.98.

Acetoacetic ester (1.3 g., 0.01 mole) was added to a solution of sodium ethoxide (sodium, 0.69 g., 0.03 mole, dry alcohol, 25 cc.), and this solution was slowly dropped into a solution of I (2.8 g., 0.01 mole) in boiling absolute ethanol (75 cc.), through which a stream of hydrogen was passing. The mixture was refluxed for thirty minutes and was then cooled and neutralized (litmus) with dilute sulfuric acid. The inorganic salts were removed and washed with hot alcohol, and the combined filtrates and washings were concentrated almost to dryness, taken up in water, and the solution was extracted with three portions (25 cc. each) of ether. The ether solution was then shaken with aqueous copper acetate. Reduction of the salt occurred, with the formation of red cuprous oxide. The mixture was filtered and the ether was evaporated. The residue was then steam distilled. From the distillate there was isolated duroquinone (300 mg.), which melted at 106–109°. When mixed with an authentic specimen (m. p. 111°), this quinone melted at 109–110°.