Anal. Calcd. for $C_{10}H_{14}O_3$: C, 66.00; H, 7.74. Found: C, 66.34; H, 7.56.

The substance when pure possessed a pleasant camphoraceous odor. It was very volatile with steam, and on heating with water was converted into **desoxycantharidinic acid,** m. p. 164–168°. The acid on distillation with steam was reconverted into desoxycantharidine, as shown by Rudolph and Gadamer for the natural acid.

Natural Desoxycantharidine.—In an initial attempt to prepare the natural substance, 1.8 g. of cantharic acid dissolved in 6 cc. of fifteen per cent. aqueous sodium hydroxide and 25 cc. of water was shaken with hydrogen over Adams catalyst for twelve hours. After filtration to remove catalyst, acidification brought down long (1 cm.) flat needles, m. p. 272–273°. On recrystallization from boiling water 1.6 g. of pure **dihydrocantharic acid** separated, m. p. 274–275°. No steam volatile material was found. It is evident that under these conditions, unlike those used by Gadamer,[7] no hydrogenolysis of the lactone ring with formation of desoxycantharidine takes place.

The desired substance was then made essentially by the method of Rudolph,[1c] with these modifications: (a) the "dibromide" was not isolated from the crude mixture of products formed on treatment of cantharidine with hydrogen bromide; the crude reaction mixture was reduced directly with zinc and acetic acid, and the desoxycantharidine isolated by steam distillation. (b) The final purification of the substance was achieved by vacuum sublimation in a Fischer pistol, as described above in the case of the synthetic compound.

Desoxycantharidine, obtained in this manner, had m. p. 126–128.5°, and mixed with the synthetic substance, m. p. 129–129.2°, had m. p. 126.8–127.5°.

Hydrogenation of the Molecular Compound.—A solution of 1.05 g. of the molecular compound, m. p. 64–65°, in 15 cc. of absolute ethyl acetate was shaken over prereduced Adams catalyst with hydrogen (t = 27°, p = 760 mm.). In four hours 167 cc. of hydrogen had been absorbed, and the absorption had stopped. Calcd. for $C_{16}H_{18}O_6$ (2|=), 169 cc.; for $C_{10}H_{12}O_3$ (1|=), 135 cc.

Although it was not possible to effect a satisfactory separation of the mixture of desoxycantharidine and dimethylsuccinic anhydride remaining after careful removal of the solvent, crystallization from petroleum ether resulted in the separation of a small quantity (150 mg.) of **dimethylsuccinic anhydride,** m. p. 80–88°, which after sublimation *in vacuo* had m. p. 87–88.5°.

Summary

The skeletal structure proposed for cantharidine by earlier workers on the basis of analytic evidence has been confirmed by the synthesis of desoxycantharidine.

A critical evaluation of the evidence now available reveals that cantharidine is best formulated as *exo*-3,6-endoxo-1,2-dimethylcyclohexane-1,2-dicarboxylic anhydride.

CAMBRIDGE, MASS. RECEIVED MAY 26, 1941

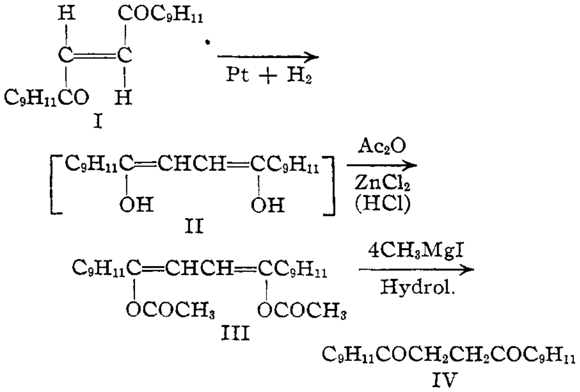
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

The Acylation of the Di-enolate of 1,4-Dimesitylbutanedione-1,4

BY ROBERT E. LUTZ, WILLIAM G. REVELEY[1] AND VERNON R. MATTOX

The formation of persistent di-enols of the type II in the reduction of dimesityl unsaturated 1,4-diketones, and the independent existence of several magnesium di-enolates, has been demonstrated[2]; but only one di-enol has actually been isolated in crystalline form.[2b] This investigation deals with a first attempt to fix and characterize some of these compounds as diacetates.[3]

The first di-enol studied (II) was produced by the catalytic hydrogenation of the *trans*-unsaturated diketone (I). Acylation experiments carried out after reduction was complete were without success. However, when the hydrogenation was carried out in acetic anhydride containing zinc chloride, a di-enol diacetate (III) was obtained in good yield. This diacetate must have been formed directly by acylation of the di-enol produced in the reduction and not through secondary enolization of the saturated diketone which is stable under the conditions of the experiment. The diacetate reacted with methylmag-



$$\begin{array}{cc} \mathrm{H} & \mathrm{COC_9H_{11}} \\ | & | \\ \mathrm{C} & {=}\,\mathrm{C} \\ | & | \\ \mathrm{C_9H_{11}CO} & \mathrm{H} \end{array} \xrightarrow[\mathrm{Pt\ +\ H_2}]{}$$

I

$$\left[\mathrm{C_9H_{11}}\underset{\mathrm{OH}}{\mathrm{C}}\mathrm{{=}CHCH{=}}\underset{\mathrm{OH}}{\mathrm{C}}\mathrm{C_9H_{11}}\right] \xrightarrow[\mathrm{ZnCl_2\ (HCl)}]{\mathrm{Ac_2O}}$$

II

$$\mathrm{C_9H_{11}}\underset{\mathrm{OCOCH_3}}{\mathrm{C}}\mathrm{{=}CHCH{=}}\underset{\mathrm{OCOCH_3}}{\mathrm{C}}\mathrm{C_9H_{11}} \xrightarrow[\text{Hydrol.}]{\mathrm{4CH_3MgI}}$$

III

$C_9H_{11}COCH_2CH_2COC_9H_{11}$

IV

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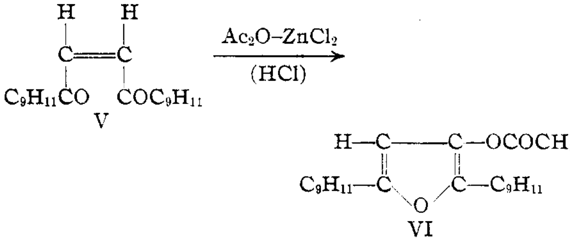
[1] Philip Francis du Pont Fellow, 1939–1940; present location, National Aniline and Chemical Company, Buffalo.

[2] (a) Lutz and Reveley, THIS JOURNAL, **61**, 1854 (1939). (b) Lutz and Kibler, *ibid.*, **62**, 360 (1940).

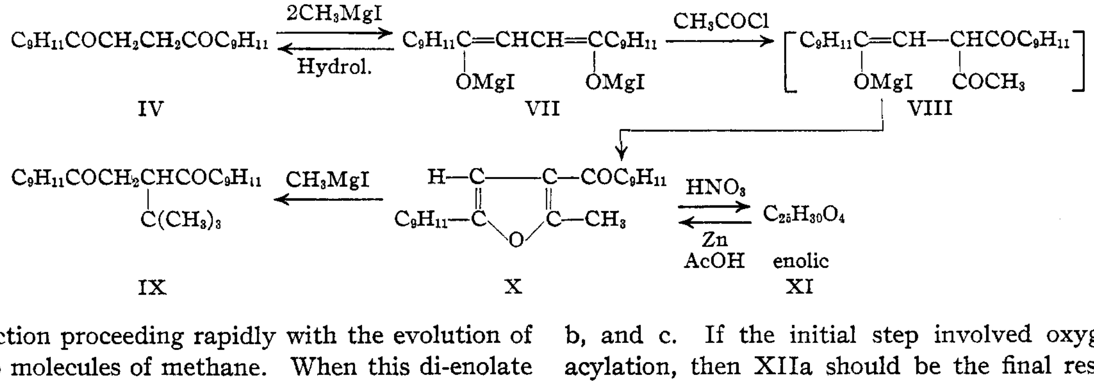
[3] *Cf.* Lutz and Reveley, *ibid.*, **63**, 3175 (1941).

nesium iodide, showing over three additions and no active hydrogen, and hydrolysis of the resulting mixture gave the saturated diketone (IV).

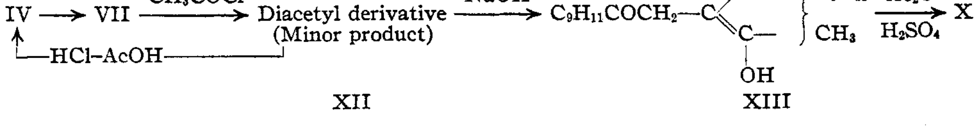
An attempt was made to reduce *cis*-1,4-dimesitylbutenedione-1,4 (V) by the above described method using acetic anhydride and zinc chloride, with the thought in mind that possibly a stereoisomeric diacetate might be produced. However, no hydrogen was absorbed and there was obtained instead the acetoxyfuran (VI) formed directly by the action of the solvent through addition and dehydration. This is interesting as an illustration of the generally greater reactivity of *cis*-forms as compared with that of the *trans*. However, it was somewhat surprising to us that this *cis*-compound which is known to be labile and rearranged with great ease, should be stable enough to persist and to react as such under these conditions, and it implies a very great facility in the addition reaction in the case of the *cis*-compound as compared with the *trans*.



A di-(halogenomagnesium) di-enolate (VII) was obtained by the action of methylmagnesium iodide on the saturated 1,4-diketone (IV), the reaction proceeding rapidly with the evolution of two molecules of methane. When this di-enolate was treated with acetyl chloride, two compounds were produced. The major product proved to be the furan (X) which must have resulted from carbon-acylation at one enolate group of VII, giving VIII, followed by furanization through the new acetyl carbonyl. The structure of this furan was demonstrated by (a) analysis, (b) stability toward hydrolysis, (c) nitric acid oxidation to a new enolic compound[4] (XI), which could subsequently be reduced back to the furan by means of zinc and acetic acid, and (d) conversion by means of methylmagnesium iodide into 1,4-dimesityl-2-*t*-butylbutane-1,4-dione (IX) where the *t*-butyl group has since been demonstrated by synthesis.[4]



The minor product of the reaction between the di-enolate (VII) and acetyl chloride was at first thought to be a stereoisomer of the diacetate (III) because of the analysis and the great ease of acid hydrolysis to the saturated diketone (IV). However, it reacted with four molecules of methylmagnesium iodide, showing three additions and one active hydrogen. This suggested the possibility that one of the acetyl groups was attached directly to carbon. Alkali hydrolysis caused elimination of one acetyl group and produced a new enolic compound which was shown to be XIII through conversion into the furan (X) by means of acetic anhydride and sulfuric acid. It is clear from this that the formation of the diacetyl compound (XII) actually did involve carbon-acylation at one of the enolate groups, but it is not certain whether this was the initial or the secondary reaction. The structure has not been determined completely, and the several possibilities are XIIa, b, and c. If the initial step involved oxygen-acylation, then XIIa should be the final result, but this formulation is open to question because



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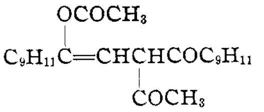
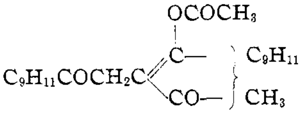
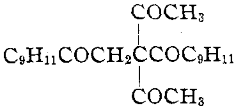
(4) Lutz and Reveley, THIS JOURNAL, 63, 3180 (1941).

the compound, unlike XIII, is not enolic. The other possibilities, XIIb and c, which would account for the facility of hydrolysis to XIII, involve as the first step carbon-acylation and then reaction at the newly formed β-diketone system of VIII. In view of the analogy to the dimesitylphenyl series[4] where a similar compound has been assigned an enol acetate structure, the formulation XIIb seems to be the more likely.


$C_9H_{11}\overset{OCOCH_3}{C}=CH\underset{COCH_3}{C}HCOC_9H_{11}$

XIIa


XIIb


$C_9H_{11}COCH_2\overset{COCH_3}{\underset{COCH_3}{C}}COC_9H_{11}$

XIIc

It is evident from the above experiments that carbon- rather than oxygen-acylation is the dominant initial reaction of the di-magnesium di-enolate of dimesitylbutanedione, and that oxygen-acylation plays only a minor or secondary role, if any.

It would be of interest to find the other of the three possible di-enolates of dimesitylbutanedione and to determine the effect of configuration on the relative ease of carbon and oxygen-acylation. Some studies along this line are in progress in another series.

Experimental Part

1,4-Dimesitylbutanedione-1,4 Di-enol Diacetate (III).—A mixture of 4 g. of *trans*-1,4-dimesitylbutenedione-1,4 (I), 0.06 g. of platinum oxide, 25 cc. of acetic anhydride, 4 g. of fused zinc chloride, and 1.5 cc. of 12 *N* aqueous hydrochloric acid was shaken with hydrogen. Within one hour the reaction stopped after absorption of one molecule of hydrogen. The product separated from the solution upon thorough cooling, and on recrystallization from ethanol 1.36 g. melting at 160–161° was obtained. A second crop from the original acetic anhydride solution brought the yield to 1.66 g. Upon purification, two types of crystals were encountered. It was found that these represented two crystalline modifications of the same compound. The product upon careful crystallization was obtained as rhombic plates which melted sharply at 162.5°, but the melt solidified in the second form which melted sharply at 172°. When a sample of the higher melting form was recrystallized from ethanol or from ethyl acetate or ligroin, with boiling out to exclude solvent of crystallization, it melted again at 162.5°.

Anal. Calcd. for $C_{26}H_{30}O_4$: C, 76.8; H, 7.4. Found: C, 76.7; H, 7.7.

Upon analysis in the Kohler–Richtmyer apparatus, a 0.1 g. sample showed 0.18 equivalent of active hydrogen and 3.3 equivalents of addition of methylmagnesium iodide. Acidification of the resulting solution, evaporation of the isoamyl ether in an air stream, and extraction with ethyl ether gave a product which on crystallization from ethanol yielded 0.06 g. of dimesitylbutanedione (IV).

The action of sunlight on samples of the diacetate in chloroform containing iodine and in pure 95% ethanol was without effect.

Conversion of *cis*-Dimesitylbutenedione (V) into 3-Acetoxy-2,5-dimesitylfuran (VI).—The experimental conditions were identical with those employed in the above described catalytic reduction of the *trans*-isomer. Two experiments were performed, one without the catalyst and hydrogen. The product was isolated by evaporation of the acetic anhydride with a current of air, treatment of the residue with water, extraction by means of ether, and crystallization from ethanol; yield, 70–75%; identified by mixture melting point with an authentic sample.

Attempts to acylate dimesitylbutanedione (IV) directly by means of acetic anhydride and pyridine, acetic anhydride and anhydrous sodium acetate, and acetyl chloride and pyridine were unsuccessful.

The Di-enolate of 1,4-Dimesitylbutanedione-1,4 (VII).—The saturated diketone, IV, reacted readily with methylmagnesium iodide in the Zerewitinoff apparatus at room temperature under nitrogen with the quantitative evolution of two molecules of methane. Hydrolysis produced the saturated diketone, and decomposition in alcoholic iodine gave the corresponding unsaturated diketone. Attempts to stop the enolization at the monoenolate were without success. In one experiment, after one molecule of methane was evolved, the reaction mixture was added to alcoholic iodine, cooled in a bath of ether and solid carbon dioxide; a mixture of the saturated and unsaturated diketones was obtained.

Acylation of the Di-enolate (VII).—Four equivalents of phenylmagnesium bromide in ethyl ether (37 cc.) was added to a suspension of 5.5 g. of dimesitylbutanedione in 50 cc. of dry ether, the operation protected by an atmosphere of dry nitrogen. The mixture was refluxed for two hours and cooled. Twenty-one grams (4 equivalents) of acetyl chloride was added slowly and a heavy white precipitate formed. A 25-cc. portion of ether was added. The mixture was refluxed for one hour, cooled, and treated cautiously with cold water. The precipitate which did not dissolve in ether was filtered off; yield, 1.15 g.; m. p. 202.5–203.5°. This was identified as 3-mesitoyl-5-mesityl-2-methylfuran (X), which is described below. The ethereal layer after separation and partial evaporation gave 0.29 g. of the same product, bringing the total yield to 1.44 g. The material obtained upon evaporation of the ether filtrate was crystallized from ethanol and gave 0.12 g. of nearly pure diacetyl derivative (XII) melting at 190–192.5° (described below).

Similar results and yields were obtained under a variety of conditions; *e. g.*, when the time of heating the mixture was diminished to ten minutes instead of one hour, when allowed to stand at room temperature, and also when a large excess of acetyl chloride was used.

3-Mesitoyl-5-mesityl-2-methylfuran (X) was obtained in the acylation of the di-enolate (VII), as described above, and also by the following two procedures.

(a) One drop of concd. sulfuric acid was added to a boiling solution of 0.1 g. of XIII in 3 cc. of acetic anhydride. Upon immediate cooling, a colorless crystalline precipitate formed of melting point 201–202° and in yield 0.08 g. This was identified as the furan (X) by purification and mixture melting point.

(b) A solution of 0.1 g. of the nitric acid oxidation product of the furan (XI) in 10 cc. of concd. acetic acid, was treated with 1 g. of zinc dust, boiled for two minutes, and poured into water. The organic material was dissolved out of the resulting mixture by means of ether and the residue upon evaporation of the ether was crystallized from ethanol (yield, 0.03 g.) and identified by mixture melting point.

The furan was crystallized repeatedly from ligroin–ethyl acetate mixtures and melted at 204°.

Anal. Calcd. for $C_{24}H_{26}O_2$: C, 83.17; H, 7.56. Found: C, 83.15; H, 7.65.

2-Acetyl-1,4-dimesitylbutanedione-1,4 enol acetate (XII), prepared as described above, was purified by repeated crystallization first from ethanol and then from ligroin–ethyl acetate mixtures. It melted at 193°.

Anal. Calcd. for $C_{26}H_{30}O_4$: C, 76.8; H, 7.4. Found: C, 76.7; H, 7.7.

In the Kohler–Richtmyer apparatus it showed 0.98 equivalent of active hydrogen and 3.1 equivalents of addition of methylmagnesium iodide.

2-Acetyl-1,4-dimesitylbutanedione-1,4 Enol (XIII).—A solution of 1 g. of XII in 73 cc. of 0.1 *N* ethanolic sodium hydroxide was refluxed for thirty minutes. Upon acidification, evaporation of the ethanol, addition of water, and extraction with ether, a residue was obtained which on crystallization from ethanol gave 0.47 g. of colorless needle crystals of melting point 105–107°. Upon repeated crystallizations from dilute ethanol and, best, from methanol, it was obtained as thin hexagonal scales of melting point 109–110°. It gave a brilliant red ferric chloride color test in alcohol.

Anal. Calcd. for $C_{24}H_{28}O_3$: C, 79.09; H, 7.74. Found: C, 78.94; H, 8.00.

Dibenzoyl Derivatives.—The di-enolate (VII) reacted with benzoyl chloride to give in two experiments under similar conditions, respectively, very small yields of two different dibenzoyl derivatives. One of these was readily hydrolyzed by alkali to the saturated diketone (IV); the other also underwent hydrolysis but did not give a known product. The former of these might be presumed from the ease of hydrolysis to be the di-enol dibenzoate, but the possibility of carbon-benzoylation was not excluded. Because of the very small yields of these two dibenzoyl derivatives, little if any significance was to be expected from the results and attention was therefore turned toward acylation.

The first dibenzoyl derivative was obtained as follows. A solution of the di-magnesium di-enolate (VII) prepared in 50 cc. of isoamyl ether at 110° was cooled and treated at 0° with 5 g. of benzoyl chloride in 30 cc. of benzene. After refluxing for two hours, cooling, and hydrolyzing with water and hydrochloric acid, the organic solvent layer was separated and evaporated under reduced pressure. From the residual oil 0.44 g. of colorless rhombic crystals was obtained and crystallized from ligroin; melting point, 186.5°.

Anal. Calcd. for $C_{36}H_{34}O_4$: C, 81.5; H, 6.5. Found: C, 81.5; H, 6.8.

Hydrolysis with 0.6 *N* sodium hydroxide in 60% ethanol (refluxing for three hours) gave a quantitative yield of dimesitylbutanedione (IV).

The second dibenzoyl derivative was obtained in repetitions of the above experiment in which no trace of the first compound was isolated. This compound was obtained as diamond shaped prisms from ethanol–ethyl acetate mixtures and melted at 181°. It did not give a color test with ferric chloride.

Anal. Calcd. for $C_{36}H_{34}O_4$: C, 81.5; H, 6.5. Found: C, 81.5; H, 6.6.

Attempts to hydrolyze this compound by alkali or Grignard reagent led to intractable resins.

Summary

The di-enol diacetate of 1,4-dimesitylbutanedione-1,4 has been made by acylation of the di-enol formed during catalytic reduction of *trans*-dimesitoylethylene. *cis*-Dimesitoylethylene under the same conditions underwent addition and furanization.

Acylation of the di-enolate obtained by direct enolization of the saturated diketone gave two compounds, both of which involved carbon-acylation. The major product was 3-mesitoyl-5-mesityl-2-methylfuran, and the minor, a diacetyl compound which on hydrolysis gave 2-acetyl-1,4-dimesitylbutanedione-1,4 enol.

CHARLOTTESVILLE, VA. RECEIVED SEPTEMBER 5, 1941