given 2.3 cc. per kilo; after chlorination, the product killed at 8.6 cc. per kilo. The unchlorinated ortho isomer was lethal for half of the animals at 4.0 cc. per kilo; after chlorination the product was slightly less toxic at 4.5 cc. per kilo. For rats, the order of toxicity was similar except that the unchlorinated para compound was most toxic. Detailed pharmacological reports will be published elsewhere.[20]

TABLE V

CHLORINE CONTENTS OF CHLOROTOLYL *n*-CAPROATES, 6-*n*-HEXOYLCHLOROCRESOLS AND 6-*n*-HEXYLCHLOROCRESOLS

Compounds	Formula	Chlorine, % Calcd.	Found	
4-Chloro-*o*-tolyl-*n*-caproate	$C_{13}H_{17}O_2Cl$	14.73	14.94	14.85
4-Chloro-*m*-tolyl-*n*-caproate	$C_{13}H_{17}O_2Cl$	14.73	14.89	14.91
2-Chloro-*p*-tolyl-*n*-caproate	$C_{13}H_{17}O_2Cl$	14.73	14.62	14.87
4-Chloro-6-*n*-hexoyl-*o*-cresol	$C_{13}H_{17}O_2Cl$	14.73	14.96	14.85
4-Chloro-6-*n*-hexoyl-*m*-cresol	$C_{13}H_{17}O_2Cl$	14.73	14.95	14.84
2-Chloro-6-*n*-hexoyl-*p*-cresol	$C_{13}H_{17}O_2Cl$	14.73	14.64	14.70
4-Chloro-6-*n*-hexyl-*o*-cresol	$C_{13}H_{19}OCl$	15.64	15.57	15.60
4-Chloro-6-*n*-hexyl-*m*-cresol	$C_{13}H_{19}OCl$	15.64	15.56	15.58
2-Chloro-6-*n*-hexyl-*p*-cresol	$C_{13}H_{19}OCl$	15.64	15.67	15.61

(20) Hu and Anderson, paper in press.

Summary

Detailed data regarding the methods used for the preparation of the isomeric *n*-hexyl- and *n*-hexoylcresols as well as their monochloro derivatives and their properties are described.

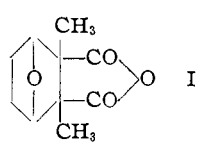
PEIPING, CHINA RECEIVED SEPTEMBER 13, 1941

[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Structure of Cantharidine and the Synthesis of Desoxycantharidine

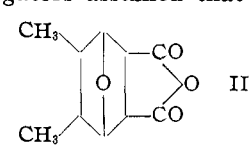
BY R. B. WOODWARD AND R. B. LOFTFIELD

Cantharidine, the active principle of *cantharis vesicatoria*, has been assigned the structure I on the basis of analytic evidence, much of which was amassed in a series of brilliant investigations by Gadamer and his collaborators,[1a,b,c,d] although the substance has attracted the attention of many chemists since its isolation in 1810 by Robiquet.[2]



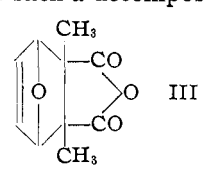
I

The decision in favor of I over the alternate formulation II, which may likewise be accommodated with the bulk of the earlier evidence, was made largely as a result of the work of von Bruchhausen and Bersch,[3] who obtained small amounts of dimethylmaleic anhydride on passing cantharidine over palladium-asbestos at > 280°. These investigators assumed that the anhydride



II

was formed by an inverse Diels–Alder reaction of the hypothetical dehydrocantharidine III. The assumption that such a decomposition would take



III

place is an eminently reasonable one, in view of the ready reversibility of the furan–maleic anhydride reaction,[4] and the failure of numerous attempts to add dimethylmaleic anhydride to furan to obtain III.[3,4] However, we feel that the experiments of von Bruchhausen and Bersch, while pointing toward structure I for cantharidine, do not afford unequivocal proof of this structure. Applying to formula II the breakdown mechanism adduced by these authors, the initial products would be 3,4-dimethylfuran and maleic anhydride. Under the conditions of the experiment it is not inconceivable that partial oxidation of 3,4-dimethylfuran could account for the small amounts of dimethylmaleic anhydride observed.[5]

Thus, while the analytic evidence indicates that cantharidine has the structure I, no synthetic

(1) (a) Danckwortt, *Arch. Pharm.*, **252**, 632 (1914); (b) Gadamer, *ibid.*, **252**, 636 (1914); (c) Rudolph, *ibid.*, **254**, 454 (1916); (d) Gadamer, *ibid.*, **252**, 623, 660 (1914), and many other papers.

(2) Robiquet, *Ann. chim.* [1] **76**, 307 (1810).

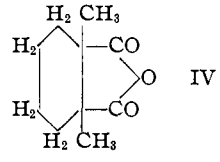
(3) Von Bruchhausen and Bersch, *Arch. Pharm.*, **266**, 697 (1929).

(4) Diels and Alder, *Ber.*, **62**, 554 (1929).

(5) *Cf.* Milas and Walsh, THIS JOURNAL, **57**, 1389 (1935), for the conversion of furan to maleic anhydride under somewhat comparable conditions.

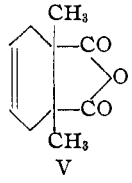
work has been forthcoming which would permit an unequivocal decision in favor of this formulation.[6] The ideal objective of such synthetic work is desoxycantharidine,[1c,7] which contains the same carbon skeleton as cantharidine, differing from the latter only in that the oxygen of the oxide ring has been removed.[8]

In this communication we describe the synthesis of *cis*-1,2-dimethylcyclohexane-1,2-dicarboxylic anhydride[9] (IV) and establish the full identity of

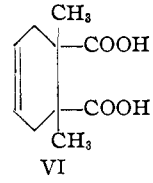


this substance with desoxycantharidine obtained from the natural product. *Our work thus constitutes final evidence that the proposed structure (I) for cantharidine is correct.*

Although butadiene and dimethylmaleic anhydride do not combine under the conditions ordinarily used to effect the Diels–Alder reaction, combination does take place on heating the reactants at temperatures in the neighborhood of 200° for long periods of time. The best yield of adduct was obtained on heating the components in benzene at 190–205° for seventy-two hours. The product (V) is best isolated as the acid (VI) by extraction of the crude reaction product with

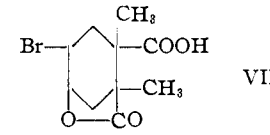


V



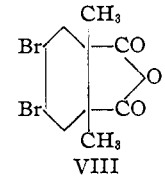
VI

strong alkali, since the concomitant production of large amounts of butadiene-rubber does not permit the facile isolation of the anhydride. The crude acid, which is contaminated with considerable amounts of dimethylmaleic anhydride, cannot be obtained pure by direct crystallization, since the two substances form a continuous series of mixed crystals. The separation was carried through smoothly by extraction of the anhydride with chloroform, in which the acid is only very slightly soluble. On subsequent recrystallization from alcohol, 1,2-dimethyl-Δ^4-cyclohexene-1,2-dicarboxylic acid was obtained in white microcrystalline needles, m. p. 202° (dec.). Bromination of the acid in acetic acid led to the formation of the bromolactone VII, m. p. 198.5–199°.

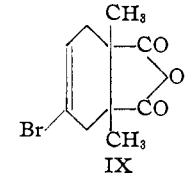


The *pure* acid, on heating overnight with acetyl chloride was converted into the anhydride (V), which crystallized in splendid stout flat needles, m. p. 99.2–99.6°. Attempts to prepare the anhydride from samples of the acid which had not been completely purified led to the formation of a beautifully crystalline substance, m. p. 64–65°, which was shown by analysis, quantitative hydrogenation, and bromination to be a molecular compound of dimethylmaleic anhydride with the anhydride V.

1,2-Dimethyl-Δ^4-cyclohexene-1,2-dicarboxylic anhydride on treatment in carbon tetrachloride solution with one mole of bromine was converted into a mixture of 4,5-dibromo-1,2-dimethylcyclohexane-1,2-dicarboxylic anhydride (VIII) and a monobromo compound $C_{10}H_{11}BrO_3$. The two substances were easily separated by taking advantage of the much greater solubility in chloroform of the monobromo derivative. The dibromide VIII, unlike the isomeric 3,6-dibromo-1,2-dimethylcyclohexane-1,2-dicarboxylic anhydride from cantharidine, lost only its bromine on boiling with alkali, the carboxyl groups being untouched. Since the monobromo derivative lost an insignificant proportion of its bromine on long boiling with alcoholic silver nitrate, there can be little doubt that the halogen atom is attached directly to a double-bonded carbon atom, and that the



VIII



IX

(6) The work of Coffey, *Rec. trav. chim.*, **42**, 1026 (1923), on the synthesis of the desoxy compound corresponding to II cannot be considered conclusive, since there are numerous stereoisomeric possibilities, and no pure product was isolated.

(7) Gadamer, *Arch. Pharm.*, **255**, 302 (1917), subsequently obtained the substance in a pure state by the catalytic hydrogenation of cantharic acid.

(8) Previous, unsuccessful attempts at synthesis: Coffey, *loc. cit.*; Steele, THIS JOURNAL, **53**, 283 (1931); Iyer and Guha, *J. Indian Inst. Sci.*, **14A**, 31 (1931); Pai and Guha, *J. Indian Chem. Soc.*, **11**, 231 (1934).

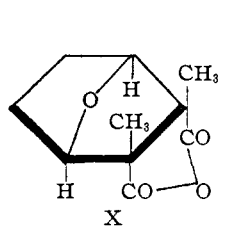
(9) We have supplied no direct proof that our synthetic anhydride has the *cis* configuration. However, the proof that such is the case, though indirect, is unequivocal. Our substance is identical with natural desoxycantharidine. The latter is obtained from cantharidine by a series of reactions which cannot involve inversion. In turn, cantharidine has been shown by Gadamer[1d] to be symmetrical, and consequently *cis*.

substance is 4-bromo-1,2-dimethyl-Δ^4-cyclohexene-1,2-dicarboxylic anhydride, IX.

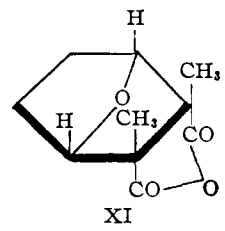
On hydrogenation in dry ethyl acetate, over Adams catalyst, the anhydride V rapidly absorbed one mole of hydrogen with the formation of 1,2-dimethylcyclohexane-1,2-dicarboxylic anhydride. This substance sublimes with extreme ease and in contradistinction to its unsaturated progenitor, is inordinately soluble in all organic solvents, and its isolation from small scale hydrogenations was in consequence attended with considerable difficulty. However, on repeated sublimation *in vacuo* of the crude reaction product left after careful removal of the solvent, the pure saturated anhydride was obtained as a camphoraceous crystalline mass, m. p. 129–129.2°. The pure synthetic 1,2-dimethylcyclohexane-1,2-dicarboxylic anhydride, mixed with an authentic sample of desoxycantharidine, m. p. 126–128.5°, had m. p. 126.8–127.5° and, like the latter substance, had a pleasant camphoraceous odor. On heating with water, it was converted into desoxycantharidinic acid which, like the natural acid, was volatile with steam with reconversion to desoxycantharidine.[10]

The formulation of cantharidine as 3,6-oxido-1,2-dimethylcyclohexane-1,2-dicarboxylic anhydride (I), being accepted, there still remains a stereochemical point of some importance to which attention has not hitherto been directed.

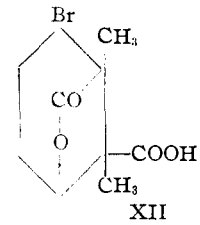
There are two structures to be considered, in one of which the anhydride ring is *endo* (X), while in the other the anhydride ring is *exo* (XI) with reference to the 3,6-oxido bridge. While an unequivocal resolution of the problem in favor of either alternative structure is perhaps not possible at this time, we feel that the available evidence points strongly to XI as the correct formulation. Thus, the loss of both hydrogen bromide and carbon dioxide from 3,6-dibromo-1,2-dimethylcyclohexane-1,2-dicarboxylic anhydride on treatment with bases[1b,c] is probably best interpreted as proceeding through an attack of the carboxylate ions on the *backs* of the carbons bearing the bromine atoms, with the intermediary formation of a di-β-lactone (or an equivalent activated molecule). This view places the bromine atoms on the opposite side of the ring from the carboxyls, and since the oxido bridge was almost certainly replaced *with inversion*, the conclusion is that the oxido bridge was originally on the same side as the anhydride ring. A like conclusion results from a consideration of the formation by the action of hydrogen bromide on cantharidine of the intermediate lactones, bromodihydrocantharic acid XII and cantharic acid XIII, for which the following sequence of changes may be visualized (p. 3170).



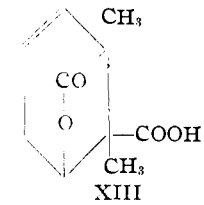
X



XI



XII



XIII

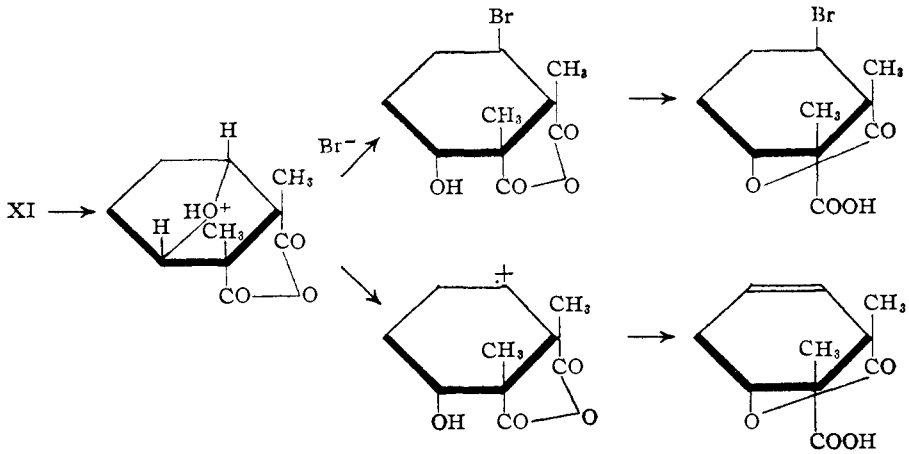
Experimental

cis-1,2-Dimethyl-Δ^4-cyclohexene-1,2-dicarboxylic Acid.—Dimethylmaleic anhydride (12 g.) and 10 g. of butadiene dissolved in 30 cc. of benzene were heated seventy-two hours at 190–205° in a strong sealed Pyrex tube. The reaction mixture at this stage was a clear brownish sirupy liquid. The contents of the tube was poured into 80 cc. of 10% aqueous sodium hydroxide. After heating for *ca.* one hour on the steam-bath, the benzene had been completely driven off, and the basic solution was filtered from the rubbery mass of butadiene polymer which had separated. Acidification with dilute hydrochloric acid precipitated a mixture of the desired acid and dimethylmaleic anhydride. (Small amounts of product may be obtained by further extraction of the polymer with sodium hydroxide solution.) This mixture was dried in air and extracted twice with 5-cc. portions of chloroform. After three crystallizations 4 g. of *cis*-1,2-dimethyl-Δ^4-cyclohexene-1,2-dicarboxylic acid was obtained as a white microcrystalline powder, m. p. 197.5° (dec.). The purest sample of the acid had m. p. 202.4° (dec.).

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.60; H, 7.12. Found: C, 60.72; H, 7.29.

(10) The desoxycantharidinic acid obtained in this way, as first shown by Gadamer, is not a pure substance, but is a mixture of the true desoxycantharidinic acid with about 10% of desoxycantharidine. The facility of the interconversion *desoxycantharidine* $\rightleftarrows$ *desoxycantharidinic acid* is shown by a chance observation by one of us. A water suspension of desoxycantharidinic acid was allowed to stand for some weeks in a small closed flask. During this time almost all of the material sublimed up into the neck of the flask as desoxycantharidine.

This ready anhydride formation is of interest in connection with the anhydride character of cantharidine itself. It is apparent that the presence of the 1,4-oxido bridge in the latter substance enhances the already pronounced tendency toward anhydride formation (as evidenced by the behavior of desoxycantharidinic acid) to the point where the corresponding acid defies isolation except in the form of its salts.



3.3 Grams of dimethylmaleic anhydride was recovered from the chloroform extracts.

Bromolactonic Acid VII.—To 2.5 g. of the above acid, suspended in 22 cc. of glacial acetic acid, 1.5 g. of bromine in 6 cc. of acetic acid was added. The bromine was quickly absorbed, and 1 g. more (0.5 g. excess) was then added. After ten minutes, 200 cc. of cold water was added. The resultant precipitate redissolved within a short time. On heating to boiling, the separation of the bromolactonic acid began. After standing overnight at 10°, the precipitate was removed and recrystallized from a small amount of ethanol, from which the bromolactonic acid separated in needles, m. p. 198.5–199°.

Anal. Calcd. for $C_{10}H_{13}BrO_4$: Br, 28.4. Found: Br, 27.6.

The substance was saturated to alkaline permanganate.

***cis*-1,2-Dimethyl-Δ^4-cyclohexene-1,2-dicarboxylic Anhydride.**—Two and three-tenths grams of the acid VI was heated under reflux with 15 cc. of acetyl chloride for twenty hours. The solvents were boiled off by heating on the steam-bath. On cooling the residue crystallized as stout rhombs. Recrystallized once from ligroin (60–90°), the pure anhydride (1.9 g.) separated in stout flat needles, m. p. 99.2–99.6°.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.72. Found: C, 66.84; H, 6.89.

Molecular Compound of the Above Anhydride with Dimethylmaleic Anhydride.—Six grams of acid, m. p. 196–198°, obtained by direct crystallization from alcohol of the hydrochloric acid precipitate from the diene addition (*vide supra*), on treatment with acetyl chloride as in the above experiment, gave a *substance* crystallizing from petroleum ether as colorless prisms, m. p. 64–65° (2.9 g.).

Anal. Calcd. for $C_{16}H_{15}O_6$: C, 62.40; H, 5.96. Found: C, 62.10; H, 5.96.

Addition of Bromine to *cis*-1,2-Dimethyl-Δ^4-cyclohexene-1,2-dicarboxylic Anhydride.—2.3 g. of bromine in 5 cc. of chloroform was added to a solution of 2.35 g. of the anhydride in 10 cc. of chloroform. A fine nodular precipitate formed immediately. After evaporation of the solvent and the slight excess of bromine, the residue was crystallized from ether–chloroform. **4,5-Dibromo-1,2-dimethylcyclohexane-1,2-dicarboxylic anhydride** (2.0 g.) separated in beautiful fine white needles, m. p. 179–180°.

Anal. Calcd. for $C_{10}H_{12}Br_2O_3$: Br, 47.00. Found: Br, 47.09.

After evaporation of the mother liquors, the residue was dissolved in chloroform and ten volumes of petroleum ether added. Within five minutes beautiful inch-long flat needles of **4-bromo-1,2-dimethyl-Δ^4-cyclohexene-1,2-dicarboxylic anhydride** (0.8 g.), m. p. 89–90°, had separated.

Anal. Calcd. for $C_{10}H_{11}BrO_3$: Br, 30.84. Found: Br, 31.17.

The monobromo derivative, on heating under reflux with alcoholic silver nitrate solution, gave a negligible amount of silver bromide. On boiling the dibromide with 10% aqueous sodium hydroxide, the material dissolved to give a clear solution, which responded to tests for bromide ion. Even on long boiling no hydrocarbon odor could be detected.

Reaction of the Molecular Complex with Bromine.—When 1 g. of the molecular compound in 4 cc. of chloroform was treated as above with 1 g. of bromine in 3 cc. of chloroform, 0.5 g. of the dibromide separated immediately. Crystallized from ether–chloroform, it separated in shining needles, m. p. 179.5–180°, mixed with the above dibromide, m. p. 179–180°.

The residue from the bromination reaction, after removal of solvent, was a difficultly separable mixture, from which dimethylmaleic anhydride, m. p. 95°, could be isolated by distillation *in vacuo*. Mixed with an authentic sample of dimethylmaleic anhydride, m. p. 95°.

Synthetic Desoxycantharidine.—A solution of 0.25 g. of analytically pure *cis*-1,2-dimethyl-Δ^4-cyclohexene-1,2-dicarboxylic anhydride in 7 cc. absolute ethyl acetate was shaken with hydrogen over pre-reduced Adams catalyst (t = 27°, p = 750 mm.). After two hours 39 cc. of hydrogen had been absorbed (calcd., 35 cc.) and absorption had stopped. After filtration to remove catalyst, the solvent was carefully removed. The residue crystallized shortly to a camphoraceous mass, which was transferred to a Fischer pistol (boiling methanol) and sublimed *in vacuo*. The sublimate had m. p. 126–129° (0.25 g.). Resublimation gave **desoxycantharidine** as a crystalline mass, m. p. 127.5–128°, which after standing in air for ten hours had m. p. 129–129.2°.

Anal. Calcd. for $C_{10}H_{14}O_8$: 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

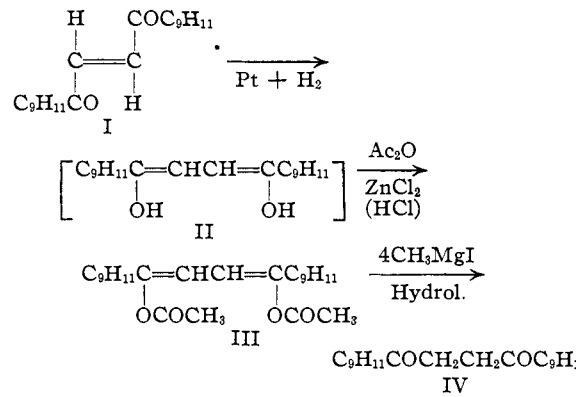
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

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-



(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).