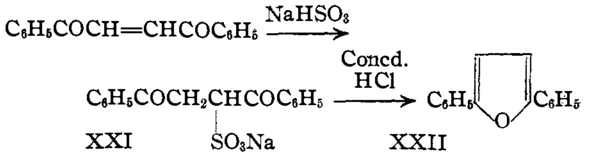
chief product; this is the only case aside from catalytic reduction where an open chain dimolecular product was formed in considerable amounts and isolated.

The sodium bisulfite addition compound XIX is a typical product of a 1,4-addition, and is formed nearly quantitatively when dibenzoylethylene is treated in 90% ethanol with sodium bisulfite. It is not easily hydrolyzed and is converted into diphenylfuran XXII by the action of boiling concd. hydrochloric acid.



The sulfonate was best prepared by allowing a mixture of 5 g. of *trans*-dibenzoylethylene, 4 g. of sodium bisulfite, and 110 cc. of 85% ethanol to stand for two hours. The solution was evaporated and the residue crystallized from ethanol: yield 84%; m. p. 255–262° (corr.). The analyses for S, C and H were unsatisfactory but approximated the values calculated for the formula XXI.

When refluxed for one hour with concd. hydrochloric acid, the sulfonate was converted into 2,5-diphenylfuran which was identified by mixed melting point with an authentic sample prepared by the action of acetic anhydride and a trace of concd. sulfuric acid on dibenzoylethane.[7]

Summary

The reduction of *trans*-dibenzoylethylene with zinc and acetic acid under varying conditions leads to the formation of dibenzoylethane and the cyclic dimolecular reduction product, *cyclo*-bis-dibenzoylethane-A, but *cis*-dibenzoylethylene gives largely, and other unsaturated 1,4-diketones exclusively, monomolecular products.

The formation of the cyclic dimolecular product is regarded as evidence for the conjugate mechanism.

The catalytic effect of zinc bromide in the reductions of dibenzoylphenylethylene and dibenzoylphenylbromoethylene is discussed, together with the probable mechanism.

The zinc–acetone reductions of the halogeno derivatives of dibenzoylethane are considered and a mechanism for the dimolecular reduction of the dibenzoyldibromoethanes is proposed.

Circumstances are described under which sodium hydrosulfite reduction of dibenzoylethylene gives large amounts of dimolecular products and sodium bisulfite addition compound.

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[7] *Cf.* Kapf and Paal, *Ber.*, **21**, 3057 (1888).

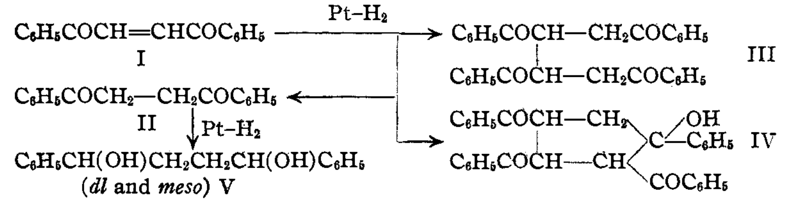
UNIVERSITY, VIRGINIA RECEIVED JUNE 6, 1935

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

The Catalytic Hydrogenation of Unsaturated 1,4-Diketones

BY ROBERT E. LUTZ AND FRED S. PALMER

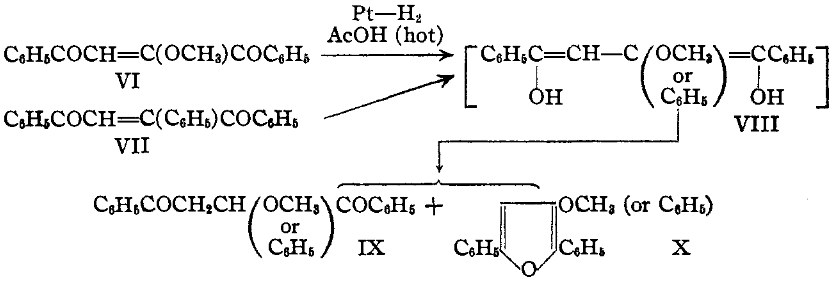
These studies were made in order to compare the catalytic hydrogenation of the unsaturated 1,4-diketones with reductions utilizing ordinary homogeneous and heterogeneous combinations. In the case of *trans*-dibenzoylethylene (Table I) chiefly the platinum catalyst was used with the following as solvents: methanol, 95% ethanol, dilute ethanol, acidified ethanol, glacial acetic acid, dioxane, ethyl acetate and decalin. With few exceptions there resulted mixtures of dibenzoylethane II and open chain and cyclic bis-dibenzoylethanes-A, III and IV, the relative yields varying considerably. Small yields of bis-dibenzoylethane-B also were obtained in many cases, but neither *cyclo*-bis-dibenzoylethane-B nor -C was isolated.



The yields of the difficultly soluble bis-dibenzoylethane-A, which crystallizes out during reaction, are probably fairly accurate as listed in the tables. However, the yields of the other products could be determined only approximately in many cases because of the difficulty of separating the mixtures and because there was undoubtedly some loss through further reduction. The primary stage of the reaction goes very rapidly, but the products are all reducible further slowly, as was shown in separate experiments, with the absorption of sufficient hydrogen to account for reduction of all of the carbonyl groups. The reductions listed in Table I were all stopped after the first and rapid phase of the reactions appeared to be complete, and involved usually the absorption of approximately 0.7–0.8 molecule of hydrogen. The dimolecular products upon further hydrogenation gave only non-crystalline products, but dibenzoylethane gave the two known stereoisomeric diphenylbutane-1,4-glycols V which were isolated in one experiment and identified. The material not accounted for in the tables was non-crystalline and was not identified.

When the rate of reduction is diminished through the use of smaller amounts of catalyst or lowered temperature, the *cyclic* dimolecular isomer-A (IV) predominates and very little of the open chain isomer III is formed. On the other hand, when the reaction proceeds very rapidly through the use of an excess of catalyst, the open chain isomer-A predominates and the yields of the monomolecular product and of the *cyclo*-bis-dibenzoylethane-A drop to a minimum. The total yield of dimolecular products, however, remains approximately constant.

In view of the effectiveness of small amounts of acid in promoting normal saturation of the alicyclic double bond in pseudocodeine,[1] two runs were made on dibenzoylethylene in alcohol with added hydrochloric or sulfuric acid. A striking increase in the yield of dibenzoylethane was observed (from 5–20 to 40%) and the yields of dimolecular products dropped almost to zero. Unfortunately the larger part of the product was non-crystalline and not identified, but the marked effect of the added acid on the course of the reduction was nevertheless unmistakable.



In glacial acetic acid the yield of the dimolecular product, *cyclo*-bis-dibenzoylethane-A, is consistently high (40–60%) regardless of the addition of ammonium chloride (to simulate conditions in the reduction of pseudocodeine hydrochloride) or of sodium acetate or hydrochloric acid. Only traces of the open chain bis-dibenzoylethane-A were found, together with bis-dibenzoylethane-B in yields varying from 5–20%. Considering all of the catalytic reductions undertaken, the yield of the normal reduction product, dibenzoylethane, reaches a minimum of 0–5% when glacial acetic acid–0.5% hydrochloric acid is the solvent. In all of the reductions in glacial acetic acid the main product is the same cyclic dimolecular isomer-A which is obtained in the zinc dust reductions under approximately similar solvent conditions.

It is noteworthy that reduction with platinum catalyst in dioxane as the solvent gives largely, and in ethyl acetate almost exclusively, monomolecular reduction. The use of Raney nickel catalyst in ethanol and in decalin also decidedly favors monomolecular reduction. In the inert solvents, then, the normal saturation of the ethylene double bond reaches a maximum.

It is a striking fact that *cis*-dibenzoylethylene, upon reduction under conditions wherein the *trans* isomer is converted chiefly into dimolecular products, gives largely the monomolecular product, dibenzoylethane, in 45–50% yields, together with about a 20% yield of a mixture of dimolecular products. This result finds a close parallel in the zinc–glacial acetic acid reduction where the *cis* isomer also shows a far greater reluctance to undergo dimolecular reduction than does the *trans* isomer.

In Table II is listed a series of experiments on various other unsaturated 1,4-diketones and related compounds. In every case the only crystalline products isolated were monomolecular, and no crystalline dimolecular products were found. Some dimolecular reduction may have occurred since in many cases considerable amounts of non-crystalline and unidentified by-products were formed. In any case the yields of monomolecular product were usually much greater than in the case of reduction of *trans*-dibenzoylethylene under comparable conditions. These results show dibenzoylethylene to be unique and the only compound of the series to undergo di-

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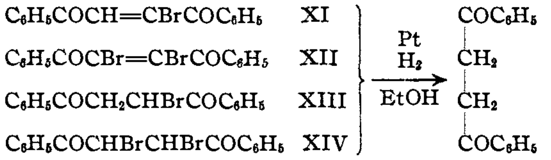
[1] Lutz and Small, THIS JOURNAL, **54**, 4715 (1932).

molecular reduction easily, a phenomenon already noted in the zinc–glacial acetic acid reductions.

The reduction of dibenzoylmethoxyethylene VI and of dibenzoylphenylethylene VII is of particular interest because furans are formed to a considerable extent, the conditions chosen being similar to those which lead to furan formation in zinc dust reductions.[2]

The mono and dibromo derivatives of both dibenzoylethylene and dibenzoylethane are reduced catalytically (using platinum) to dibenzoylethane without the formation in any case of appreciable amounts of the dimolecular products.



$$\left.\begin{array}{ll} C_6H_5COCH{=}CBrCOC_6H_5 & \text{XI} \\ C_6H_5COCBr{=}CBrCOC_6H_5 & \text{XII} \\ C_6H_5COCH_2CHBrCOC_6H_5 & \text{XIII} \\ C_6H_5COCHBrCHBrCOC_6H_5 & \text{XIV} \end{array}\right\} \xrightarrow[\text{EtOH}]{\text{Pt}\ H_2} \begin{array}{c} COC_6H_5 \\ | \\ CH_2 \\ | \\ CH_2 \\ | \\ COC_6H_5 \end{array}$$

Discussion of Results.—The formation of dimolecular products in catalytic hydrogenation was unexpected because, despite the many compounds that have been studied, this phenomenon has been observed in very few cases, namely, citral, dibenzalacetone, and certain α,β-unsaturated nitro compounds.[3]

A striking and significant parallelism exists between catalytic and zinc–acetic acid reductions of the unsaturated 1,4-diketones. The following facts are established in both types of reduction: (a) dimolecular reduction occurs to a very considerable extent with *trans*-dibenzoylethylene, (b) the same *cyclo*-bis-dibenzoylethane-A is obtained as the chief dimolecular product when glacial acetic acid is the solvent, (c) *cis*-dibenzoylethylene shows a far greater tendency to undergo normal saturation of the ethylene linkage than the *trans* isomer, (d) *trans*-dibenzoylethylene is the only unsaturated 1,4-diketone to give large yields of the dimolecular products under ordinary conditions, and (e) roughly the same degree of furan formation occurs during the reductions of VI and VII. It is quite likely therefore that the mechanism of the main course of catalytic and metal combination reductions of *these unsaturated 1,4-diketones* under conditions involved in the experiments covered by the above five points is similar.

The formation of the stable cyclic dimolecular compounds and furans during catalytic reduction in alcohol or in glacial acetic acid may be regarded as proof that in respect to the main course of these reactions a direct addition of hydrogen to the ethylene linkage does not occur but rather conjugate reactions involving one or both carbonyl groups, in the case of dibenzoylethylene giving enolic intermediates such as $C_6H_5\underset{\textstyle OH}{\underset{|}{C}}{=}CHCH{=}\underset{\textstyle OH}{\underset{|}{C}}C_6H_5$ and $C_6H_5COCHCH{=}C(OH)C_6H_5$, and in the cases of $\begin{array}{l} | \\ C_6H_5COCHCH{=}C(OH)C_6H_5 \end{array}$ VI and VII leading to the results summarized in the diagram (*cf.* discussion of mechanism in the preceding paper). The conjugate mechanism for catalytic hydrogenations of α,β-unsaturated ketones, which has been assumed without proof,[4] is open to some question.[5] Our results constitute positive evidence for the existence of such a mechanism in some cases, but it is obviously far from certain that the phenomenon is general.

In this connection it is noteworthy that sorbic and muconic acids[6] to some extent undergo conjugate hydrogenation but it is uncertain as to whether or not the carbonyl oxygens are involved.

Pertinent to this discussion is the work of Conant and co-workers[7] on irreversible reductions. Soluble reducing reagents are regarded as acting through electron transfer, and catalytic hydrogen by addition of a hydrogen molecule, the latter occurring in cases where the hydrogen electrode potential is considerably above the "apparent reduction potential" (*i. e.*, the highest potential of reducing agents which will cause appreciable reduction in a reasonable time).[8] Catalytic reduction of dibenzoylethylene which has an "apparent reduction potential" above that of the hydrogen electrode, involves, as might have been predicted, a mechanism in which hydrogen or more likely electrons add to oxygen; however, dibenzoylphenylethylene, which on catalytic hydrogenation also undergoes conjugate addition involving the oxygens, has an "apparent reduction potential" which is very considerably below that of the hydrogen electrode.[8]

Catalytic hydrogen, while it may add at the ends of conjugated systems which include ter-

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(2) (a) Lutz, THIS JOURNAL, **51**, 3008 (1929); (b) Lutz and Taylor, *ibid.*, **55**, 1593 (1933).

(3) Skita, *Ber.*, **42**, 1634 (1909); Vavon, *Ann. chim.*, [9] **1**, 144 (1914); Borsche, *Ber.*, **45**, 46 (1912); A. M. Kinney, Dissertation, Harvard University, 1921; Sonn and Schellenberg, *Ber.*, **50**, 1513 (1917); Kohler and Drake, THIS JOURNAL, **45**, 1281 (1923).

(4) Straus and Grindel, *Ann.*, **439**, 276 (1924).

(5) *Cf.* Kern, Shriner and Adams, THIS JOURNAL, **47**, 1147 (1925).

(6) Farmer and Galley, *J. Chem. Soc.*, 430 (1932); Farmer and Hughes, *ibid.*, 304 (1934).

(7) *Cf.* Conant and Cutter, *J. Phys. Chem.*, **28**, 1096 (1924).

(8) *Cf.* Conant and Lutz, THIS JOURNAL, **45**, 1047 (1923).

minal oxygen atoms and does so to a considerable extent in the case of *trans*-dibenzoylethylene, probably does not involve the conjugate mechanism exclusively. Under some conditions, notably in the solvents ethyl acetate, dioxan, decalin or acidified ethanol, *trans*-dibenzoylethylene gives largely dibenzoylethane. Possibly the ethylene linkage in these cases reacts to a large degree directly with hydrogen. Pertinent to this point is the problem of the stereochemistry of addition which can be followed when completely substituted ethylenes are used as in the case of salts of dimethylmaleic and fumaric acids and the dimethylstilbenes.[9] Addition of hydrogen to the oxygens in the case of unsaturated 1,4-dicarbonyl compounds would undoubtedly destroy the stereoisomerism and no oriented addition would be possible; this appears to be the case for example in the zinc–acetic acid reduction of *cis* and *trans* di-(2,4,6-trimethylbenzoyl)-dimethylethylenes where identical products are obtained regardless of the configuration of the starting material.[2b] When consistent *cis* addition does occur it seems reasonable to suppose that only the ethylene linkage is involved, as is undoubtedly the case in the catalytic hydrogenation of the dimethylstilbenes.[3] In the reduction of the salts of dimethyl maleic and fumaric acids both 1,6 and 1,2 reductions are possible; slow catalytic hydrogenation favors stereochemical orientation, and probably therefore involves exclusively 1,2 addition to the ethylene linkage; but in the case of metal combinations leading to unoriented addition, the conjugate type of reduction undoubtedly predominates.[10] We had hoped to obtain evidence along this line by catalytic hydrogenation of the diaroyldimethylethylenes, $ArCOC(CH_3){=}C(CH_3)COAr$; while zinc and acetic acid reductions have been successful,[2b] catalytic hydrogenations proceed very slowly and fail to give the expected and known crystalline primary reduction products.

Experimental Part

The various hydrogenations described in Tables I and II were carried out in the usual way. In the case of dibenzoylethylene in alcohol as solvent the material was partly in suspension at the beginning. Reduction with platinum catalyst proceeds very rapidly with absorption of from 10–50 cc. per minute in small runs of from 2–10 g. When the dibenzoylethylene is used up (evident from disappearance of the yellow color), the rate of absorption drops to 0.5–1.0 cc. per minute, at which point the absorption usually reached from 0.7–0.8 mole. The reaction ordinarily was stopped at this point to minimize the secondary stages of the reduction. Probably the oils and resins which comprise the residue of material not accounted for in the yields listed in the tables are partly the result of the secondary reductions involving one or more of the carbonyl groups of the various primary reduction products. In separate experiments it was shown that each of the dimolecular products slowly absorbs approximately 3–4 molecules of hydrogen under the usual conditions (platinum in alcohol), accounting for reduction of all of the carbonyl groups.

TABLE I

SOME TYPICAL CATALYTIC REDUCTIONS OF *Trans*-DIBENZOYLETHYLENE AT 25–27° AND ATMOSPHERE PRESSURE

The material not accounted for was non-crystalline.

Pt oxide catalyst per g. subs., g.	Solvent per g. subs., g.	Solvent	Dibenzoylethane %	% Dimolecular Cyclo A	Open chain A	B
0.002–0.004	..	95% ethanol	15–25	35–45	5–15	5–15
.01	..	95% ethanol	15–20	15–20	30–40	trace
.02	..	95% ethanol	5–10	5–10	25–30	trace
.1	..	95% ethanol	...	...	30	...
.1	70	70% ethanol	5–15	25–30	25–30	5–15
.1	60	95% EtOH-3% H_2SO_4	40	...	...	...
.1	60	95% EtOH-1% HCl	40	...	...	...
.01	40	Glacial AcOH	15	40–45	trace	10–15
.01	35	AcOH-5% NH_4Cl	5–10	50–60	0–5	5–10
.01	35	AcOH-0.5% HCl	0–5	55–60	trace	10–15
.01	30	AcOH-2.7% NaOAc	15–20	40–45	trace	5–10
.08	75	Dioxane	55–60	...	...	trace
.05	30	Ethylacetate	90–95[a]	...	...	5–10
Ni[c]	25	95% ethanol	60–65	S[b]	S	S
Ni[c]	30	Decalin	75[a]	...	...	...

A few qualitative experiments which were not worked up adequately deserve mention. With platinum catalyst (1–100 g. of substance) in 95% ethanol at 0°, results were obtained similar to those found with smaller amounts of catalyst at ordinary temperature, largely *cyclo*-bis-dibenzoylethane-A being obtained with smaller amounts of the open chain isomer-A. When ethanolic sodium acetate was used as solvent at room temperature chiefly the open chain bis-dibenzoylethane-A was obtained and little else but resinous material. Substitution of the palladium on barium sulfate catalyst in a few instances was without significant effect on the course of reduction.

[a] In some runs considerable amounts of the dimolecular product was formed and correspondingly less of dibenzoylethane. [b] S = small amounts, possibly as high as 10–15%. [c] Raney catalyst.

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[9] Ott, *Ber.*, **61**, 2124 (1928).

[10] The unoriented addition of hydrogen in the metal combination reduction of the dimethylstilbenes may possibly involve one or both of the phenyl groups through conjugate addition with consequent destruction of stereoisomerism in the intermediate step.

Hydrogenation of dibenzoylethane using platinum catalyst in ethanol proceeded with absorption of 2 moles of hydrogen, giving an oil which on fractional crystallization was separated into the *dl*- and *meso*-diphenylbutane-1,4-glycols which were identified by mixed melting points with authentic samples prepared by the catalytic reduction of the acetylenic glycols.[11]

TABLE II

CATALYTIC REDUCTION OF SOME TYPICAL UNSATURATED 1,4-DIKETONES AND RELATED COMPOUNDS

Except as otherwise indicated these reductions were carried out at 25–27° and atmospheric pressure, using the platinum oxide catalyst (0.01–0.02 g. per g. of substance) in 95% ethanol as solvent (35–70 cc. per gram of substance).

Compound	Yield of monomolecular product, %
Cis-dibenzoylethylene	45–50[a]
Trans-dibenzoylmethylethylene	75
Cis-dibenzoylphenylethylene	62 (25[b])
Trans-di(2,4,6-trimethylbenzoyl)ethylene	86
Trans-di(4-chlorobenzoyl)ethylene	44
Trans-di(4-methylbenzoyl)ethylene	19
Dibenzoylmethoxyethylene	[c]
Cis-dibenzoylbromoethylene[d]	40
Cis-dibenzoyldibromoethylene[d]	84
Dibenzoylbromoethane[d]	68
dl-Dibenzoyldibromoethane[d]	44

[a] The rest of the material was accounted for as oils and small amounts of dimolecular products totaling 10–20% in yield. [b] This yield was obtained from an experiment carried out in glacial acetic acid at 100°, and triphenylfuran was obtained also in yields of 45–50%. Dibenzoylphenylethane is unaffected by these conditions and catalyst, and was recovered nearly quantitatively unchanged in a typical experiment. [c] This experiment, carried out in glacial acetic acid at 75–80°, gave largely the oily dibenzoylmethoxyethane (not identified) and a yield of 35–40% of diphenylmethoxyfuran (identified by mixed melting point with an authentic sample). [d] Palladium on barium sulfate as catalyst (0.1–0.15 g. per g. of substance).

Summary

The catalytic hydrogenation of *trans*-dibenzoylethylene under different conditions results in both mono- and dimolecular products, while other unsaturated 1,4-diketones, including *cis*-dibenzoylethylene and the halogen derivatives, undergo largely monomolecular reduction.

The striking parallelism between catalytic and zinc combination reductions is shown and is regarded as indicative of a common reaction mechanism.

The formation of furans and of cyclic dimolecular products is adduced as evidence that in these cases catalytic hydrogenation involves conjugate addition.

[11] *Cf.* Zalkind and Isakowitch, *J. Russ. Phys.-Chem. Soc.*, **45**, 1902 (1913).

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[CONTRIBUTION FROM THE ABBOTT LABORATORIES, NORTH CHICAGO, ILLINOIS]

Sulfur-Containing Barbiturate Hypnotics

BY D. L. TABERN AND E. H. VOLWILER

Early in the history of barbituric acid synthesis, two or three simple 5,5-disubstituted 2-thio derivatives were made, with the aim of preparing from them by removal of the sulfur atom, the therapeutically promising oxygen analogs. Einhorn[1] and others studied the sulfur elimination through reduction, then oxidation and by the action of strong acids under pressure. They noted the comparative instability of the thiobarbiturate ring, reduction of the diethyl derivative by sodium amalgam, for instance, yielding chiefly the malonic diamide.

No serious attempt at pharmacologic evaluation seems to have been reported, and no study of higher homologs has been made as in the case of the simple barbituric analogs. Fischer and Mering[2] gave a 7-kilogram dog orally a dose of one gram of diethylthiobarbituric acid with the result that "one hour later he slept, did not react to any stimulation, and died after eight hours."

Dox and Hjort[3] have included mention of the same compound in a series of simple and N-alkyl barbiturates. They state that fine and coarse tremors mask the anesthesia which is characterized by preanesthetic excitement and cyanosis.

In spite of these unfavorable pharmacologic indications, the desire to secure hypnotics more readily broken down in the body for the production of short hypnosis and even surgical anesthesia, led to the decision several years ago to make a

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[1] Einhorn, *Ann.*, **359**, 145 (1908); see also German Patents 165,649, 166,266, 172,404, 182,764.

[2] Fischer and Mering, *Therapie der Gegenwart*, **44**, 100 (1903); Fränkel, "Arzneimittel Synthese," 6th ed., p. 510.

[3] Dox and Hjort, *J. Pharmacol.*, **31**, 455 (1927).