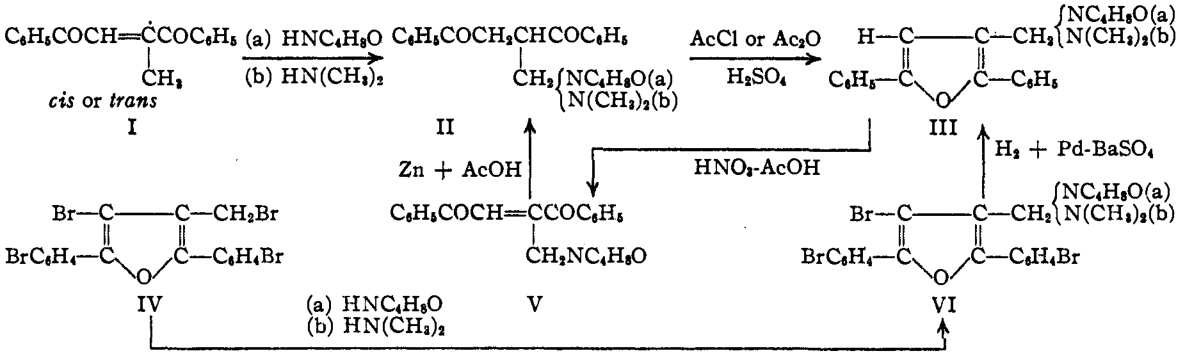
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

The Novel Reaction between Amines and Dibenzoylmethylethylene. Evidence for A Chelate Structure for *cis*-Dibenzoylmethylethylene[1]

BY ROBERT E. LUTZ AND PHILIP S. BAILEY[2]

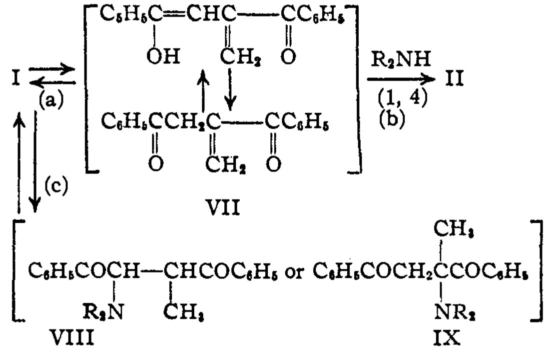
Amines have been added to dibenzoylethylene, $C_6H_5COCH{=}CHCOC_6H_5$, with straightforward results.[3] Some surprising and quite different results were encountered, however, when morpholine and dimethylamine reacted with *cis*- or *trans*-dibenzoylmethylethylene (I). The products proved to be dibenzoyl-(morpholinomethyl)- and (dimethylaminomethyl)-ethanes (II).

The structures of these two products were established as follows. Furanization under the usual conditions yielded compounds with properties which clearly indicated them to be the respective 3-(morpholinomethyl)- and 3-(dimethylaminomethyl)-2,5-diphenylfurans (III). The structures of these furans in turn were established by synthesis from the known 4-bromo-3-(bromomethyl)-2,5-di-(*p*-bromophenyl)-furan (IV) in two steps: (a) reaction with morpholine and dimethylamine, respectively, with displacement of the aliphatic and reactive bromine of the bromomethyl group to give VI, followed by (b) catalytic reduction which readily eliminated the remaining *β*- and *p*-bromine atoms.



Further evidence for the structure of 2,5-diphenyl-3-(morpholinomethyl)-furan (IIIa), and indirectly for that of the parent compound (IIa), was the facile and characteristic oxidative fission of the furan, by means of nitric acid in acetic acid solution, to a product corresponding to expectations in this general type reaction[4] and formulated as *cis*-dibenzoyl-(morpholinomethyl)-ethylene (V). Of particular importance in this connection was the reduction of this new compound (V), by means of zinc and acetic acid or catalytically in acetic acid solution, with regeneration of dibenzoyl-(morpholinomethyl)-ethane (IIa) and completion of the cycle of reactions typical for this class of compounds.

A suggested mechanism for the reaction between amines and dibenzoylmethylethylene (I) involves as the first step a reversible 1,5-enolization of the latter compound to give intermediate VII[5] (a) to which the amine adds 1,4 with subsequent irreversible ketonization to yield the (*t*-aminomethyl)-dibenzoylethane (II)(b). It is assumed that along with this reaction one or both of the originally expected direct 1,4-addition products (VIII or IX) are also formed, but that they are unstable and exist only for a time during the reaction in the equilibrium amounts of a reversible system (c). This assumption is reasonable in the light of the fact that those amines which add to dibenzoylethylene are easily split out from the resulting aminodibenzoylethanes to regenerate dibenzoylethylene.[3] The (*t*-aminomethyl)-dibenzoylethanes (II) on the other hand should be and are stable compounds, and the reactions leading to their formation (b) presumably involve a final irreversible step; thus the reaction goes to completion in this direction with II the only product isolated.



---

[1] A portion of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Virginia.

[2] Holder of Philip Francis du Pont Fellowships, 1942–1944.

[3] Results to be published shortly.

[4] Lutz and Wilder, THIS JOURNAL, **56**, 978 (1934).

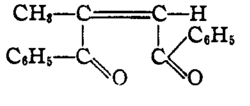
[5] Such an enolization of this type of compound is not a new proposal: see Fuson, Fleming and Johnson, *ibid.*, **60**, 1944 (1938).

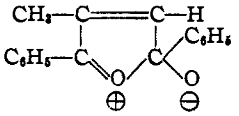
In order to test the validity of the above suggested enolization mechanism for the reaction of amines with dibenzoylmethylethylene (I), the *cis* and *trans* forms were each treated with triethylamine under precisely the same conditions as were used in the reaction with morpholine. It was expected that although no addition could occur, enolization would nevertheless be promoted, and that the *cis* and presumably *labile* isomer of I would be converted into the *trans* and presumably *stable* isomer. The results were consistent with the mechanism proposed, but the surprising discovery was made that the *cis* isomer was the *stable* and not the *labile* form as had been previously supposed.[6] The *trans* isomer was converted into the *cis* and not the *cis* into the *trans*.

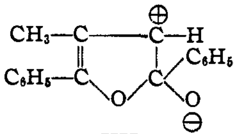
At first sight this finding seemed inconsistent with the fact that sunlight alone converts the *trans* isomer into the *cis*.[6] There can be no doubt about the configurations assigned to these compounds in view of the synthesis of the one from mesaconyl chloride by the Friedel–Crafts reaction and of the other from the furan by nitric acid oxidation.[7,4] However, the presumption that this *trans*-to-*cis* change involved absorption of light energy to produce a higher energy containing form is clearly unjustified because no corresponding change in the opposite direction has been accomplished by any of the catalytic means so far tried.

In contrast with this conversion from *trans* to *cis*, dibenzoylethylene itself when treated with triethylamine under the same conditions was converted from *cis* to *trans*; this would be expected from the fact that the *cis* isomer gives the *trans* under other catalytic conditions whereas the *trans* goes to *cis* under the influence of sunlight alone.[8]

The fact that *cis*-dibenzoylmethylethylene (I) is more stable thermodynamically than the *trans* isomer is contrary to expectations from classical theory and calls for explanation. This can be found in the hypothesis already put forward,[7] namely, that a *cis* unsaturated-1,4-diketone under some circumstances may cyclize or chelate through the carbonyl groups. This concept, involving resonance, would be a counterpart of ring-chain tautomerism where cyclization to stable ring compounds is the explanation for similar unexpected relative stabilities of *cis* forms as compared with *trans*; for example, dimethylmaleyl chloride is the *stable* stereoisomer in contrast with maleyl chloride itself which is the *labile* isomer.[9] On this theory a number of resonance forms are possible based on the open chain form (X), the cyclic form (XI) and forms with the positive charge on the α- or β-carbons of the ring (*cf.* XII).[10]


X


XI


XII

In favor of the resonance or chelation effect, then, are the two specific properties of the *cis* form relative to the *trans*: (a) its considerably greater cationoid reactivity and the greater facility with which it goes over to the furan structure, and (b) its greater thermodynamic stability.

Several points suggest themselves for further study. Obviously, the ability of a *cis* compound to undergo chelation of this type will depend on structure and steric hindrance. It would seem that substitution on the chain could to some extent favor chelation by forcing the carbonyls closer together in space, as it seems to do in ring-chain tautomerism of the unsaturated 1,4-dicarboxylic acids and ketonic acids, but that steric hindrance at one of the carbonyl carbons might have to be at a certain minimum. Presumably in dibenzoylmethylethylene (I), in contrast with dibenzoylethylene itself, there exists just the right combination of these factors.

In this connection it is noteworthy that neither *cis*- nor *trans*-dibenzoyldimethylethylene is affected by triethylamine or morpholine under conditions comparable with those which favor reaction in the dibenzoylmethylethylene series. This doubtless means that enolization from one of the two methyls does not occur as readily here. It is impossible to say whether or not chelation occurs in the *cis* form, however, because the relative stabilities of the two isomers are not yet established with certainty.

Further work along these lines in the types mentioned above is planned. If the oxygen to carbon chelation which is suggested here is real, then doubtless other analogous types will be found involving other elements besides oxygen. It is hoped that a suitable analog of (X–XI) may be made which because of its asymmetric center could be resolved, thereby demonstrating conclusively the ring structure proposed above.

Experimental[11,12]

Dibenzoyl-(morpholinomethyl)-ethane (IIa).—Twenty ml. of morpholine was added to a 50-ml. ether solution containing 5 g. of *trans*-dibenzoylmethylethylene (I).[5,6] After standing for fifteen hours at room temperature, the reaction mixture was washed several times with salt solution, dried over anhydrous sodium sulfate and evaporated. Crystallization of the residue from ethanol yielded 5.5 g. of material which melted at 85–86°; yield 82%. The

---

[6] Lutz and Taylor, This Journal, **55**, 1168 (1933).

[7] Lutz and McGinn, *ibid.*, **64**, 2585 (1942).

[8] Paal and Schulze, *Ber.*, **35**, 168 (1902).

[9] Lutz and Taylor, This Journal, **55**, 1585 (1933).

[10] A chelation of the enolic hydroxyl of VII with the carbonyl oxygen although conceivable is unlikely since this involves a seven membered ring and since the compound does not behave like an enol.

[11] All melting points reported in this paper are corrected.

[12] About one-half of the microanalyses reported here were performed by Miss Clara H. Vondra.

melting point was not changed by several recrystallizations from alcohol.

Anal. Calcd. for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.82; H, 7.02; N, 4.32.

cis-Dibenzoylmethylethylene,[8] when treated with morpholine in an identical manner, also gave an 82% yield of the morpholinomethyl compound (IIa).

Dibenzoyl-(dimethylaminomethyl)-ethane (IIb) hydrochloride was prepared by dissolving 1 g. of *trans*-dibenzoylmethylethylene (I) in a solution of approximately 4 g. of dimethylamine in 15 ml. of di-isopropyl ether. After standing overnight, the solution was diluted with ether, washed thoroughly with salt water, dried over anhydrous sodium sulfate and evaporated. The residue would not crystallize. It was dissolved in acetone and the resulting solution was acidified toward congo red with ethereal hydrogen chloride, diluted with dry ether, and the resulting colorless crystals were filtered off. The yield was 1.3 g. (98%) and the melting point after recrystallization from isopropanol was 152–153°.

Anal. Calcd. for $C_{19}H_{21}NO_2{\cdot}HCl$: C, 68.77; H, 6.68; N, 4.22. Found: C, 68.62; H, 6.52; N, 4.55.

2,5-Diphenyl-3-(morpholinomethyl)-furan (IIIa) Hydrochloride (SN-2629).[13]—A solution of 4 g. of the (morpholinomethyl)-ethane (IIa) in 20 ml. of acetyl chloride was treated dropwise with 4 ml. of concentrated sulfuric acid. The mixture was allowed to stand for twenty minutes, after which time it was poured into water, neutralized with sodium carbonate and extracted with ether. The ether extract was washed, dried over sodium sulfate, and evaporated under reduced pressure. The residual oil was converted into a crystalline hydrochloride by acidifying its acetone solution with an ethereal hydrogen chloride solution; yield, 3.4 g. or 79%; melting point 224–227°. Several recrystallizations from methanol–dry ether mixture raised the melting point to 226–229°.

Anal. Calcd. for $C_{21}H_{21}NO_2{\cdot}HCl$: C, 70.88; H, 6.23. Found: C, 70.62; H, 6.18.

4-Bromo-2,5-di-(*p*-bromophenyl)-3-(morpholinomethyl)-furan (VIa) was prepared by allowing a mixture of 2.8 g. of 4-bromo-3-(bromomethyl)-2,5-di-(*p*-bromophenyl)-furan (IV), 10 ml. of morpholine and 25 ml. of di-isopropyl ether to stand for two days. The precipitate which was formed was filtered off and washed first with water, to remove the morpholine hydrobromide, and then with ether. It weighed 2.3 g. and melted at 168–171°. When the filtrate was separated and the ether layer was washed, dried and evaporated, 0.4 g. of additional material was obtained; yield 97%. Three recrystallizations from isopropanol raised the melting point to 171–172°.

Anal. Calcd. for $C_{21}H_{18}Br_3NO_2$: C, 45.35; H, 3.26. Found: C, 45.24; H, 3.34.

Reduction of 4-Bromo-2,5-di-(*p*-bromophenyl)-3-(morpholinomethyl)-furan (VIa) to 2,5-Diphenyl-(3-morpholinomethyl)-furan (IIIa).—A suspension of 1 g. of the tribromo compound (VIa) in 55 ml. of ethanol was catalytically reduced with the aid of 0.5 g. of palladium–barium sulfate catalyst. The reduction was interrupted after 3.2 equivalents of hydrogen had been absorbed, because the rate of absorption had decreased considerably. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was suspended in sodium carbonate solution and extracted with ether. The ether extract was washed, dried and evaporated. The residual oil was converted into a crystalline hydrochloride by dissolving it in acetone and acidifying with ethereal hydrogen chloride solution. Thus was obtained 0.3 g. of crystals which melted at 215–221° and which showed no mixture melting point depression with the (morpholinomethyl)-furan (IIIa) hydrochloride obtained earlier.

3-Dimethylaminomethyl)-2,5-diphenylfuran (IIIb) Hydrochloride (SN-2593).[13]—To a suspension of 0.5 g. of dibenzoyl-(dimethylaminomethyl)-ethane (IIa) hydrochloride in 5 ml. of acetic anhydride was added ten drops of concentrated sulfuric acid. The mixture was allowed to stand for ten minutes, after which time it was poured into water, neutralized with sodium carbonate and extracted with ether. The ether extract was washed, dried and evaporated under reduced pressure, after which the residue was converted into a hydrochloride by dissolving it in acetone and acidifying with ethereal hydrogen chloride. A yield of 0.15 g. of material was obtained which melted at 218–220°. Recrystallization from acetone solution by the addition of dry ether did not change the melting point.

Anal. Calcd. for $C_{19}H_{19}NO{\cdot}HCl$: C, 72.71; H, 6.42. Found: C, 72.62; H, 6.68.

4-Bromo-2,5-di-(*p*-bromophenyl)-3-(dimethylaminomethyl)-furan (VIb) was prepared by adding 2.8 g. of 4-bromo-3-(bromomethyl)-2,5-di-(*p*-bromophenyl)-furan (IV) to a solution of approximately 10 g. of dimethylamine in 40 ml. of di-isopropyl ether. After two days the mixture was filtered and the precipitate was washed thoroughly with water to remove the dimethylamine hydrobromide; yield 1 g. which melted at 147–150°. Upon separation of the filtrate, evaporation of the ether layer and crystallization of the residue from isopropanol, 1.2 g. of additional material was obtained; total yield 85%. Recrystallization from isopropanol raised the melting point to 148–150°.

Anal. Calcd. for $C_{19}H_{16}Br_3NO$: C, 44.39; H, 3.14. Found: C, 44.25; H, 3.15.

Reduction of 4-Bromo-2,5-di-(*p*-bromophenyl)-3-(dimethylaminomethyl)-furan (VIb) to 3-(Dimethylaminomethyl)-2,5-diphenylfuran (IIIb).—Catalytic dehalogenation of 1 g. of the above tribromo compound (VIb) in 50 ml. of ethanol, using palladium–barium sulfate catalyst, proceeded smoothly with the absorption of 3 equivalents of hydrogen. Filtration and evaporation yielded an oil which was treated with sodium carbonate and extracted with ether. The ether extract was washed, dried and evaporated under reduced pressure and the residue was converted into a hydrochloride by acidifying it in acetone solution with ethereal hydrogen chloride. Upon filtration 0.4 g. of material was obtained which melted at 215–221° and which was shown by a mixture melting point to be identical with the (dimethylaminomethyl)-furan (IIIb) hydrochloride obtained earlier.

***cis*-Dibenzoyl-(morpholinomethyl)-ethylene (V) (SN-3256)**[13] was prepared by adding slowly, with stirring, a solution of 5 ml. of nitric acid in 15 ml. of glacial acetic acid to a solution of 5 g. of 2,5-diphenyl-3-(morpholinomethyl)-furan (IIIa) hydrochloride in 25 ml. of glacial acetic acid. The resulting solution was allowed to stand for one hour after which time it was poured into water, neutralized with sodium carbonate and extracted with ether. The ether extract was washed with water and extracted with dilute hydrochloric acid. The acid extract was filtered to remove some insoluble impurities, neutralized with sodium carbonate, and extracted with ether, after which the latter ether extract was washed, dried and evaporated under reduced pressure. Crystallization of the residue from ethanol yielded 2.2 g. of material which melted at 121–124°. The melting point was raised to 129–130° by several recrystallizations from ethanol.

Anal. Calcd. for $C_{21}H_{21}NO_3$: N, 4.18. Found: N, 4.08.

Hydrochloride.—In another preparation the final residue was converted directly into a hydrochloride rather than crystallized as the free base. A 67% yield of material was obtained which melted at 162–163° after several recrystallizations from methanol solution by the addition of dry ether. The salt was also prepared from some of the crystalline free amine.

Anal. Calcd. for $C_{21}H_{21}NO_3{\cdot}HCl$: C, 67.83; H, 5.96. Found: C, 67.66; H, 6.33.

The hydrochloride was easily reconverted to the free

---

[13] The Survey Number, designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

amine by shaking it with sodium carbonate solution, filtering, washing and recrystallizing the precipitate from ethanol.

Reduction of *cis*-Dibenzoyl-(morpholinomethyl)-ethylene (V), (a) Zinc-Acetic Acid Reduction.—One gram of the (morpholinomethyl)-ethylene (V) was dissolved in 20 ml. of acetic acid. To this solution was added a porcelain spatulaful of zinc dust. The resulting mixture was stirred for one minute (heat was generated), after which time it was filtered. The filtrate was diluted with water, made alkaline with sodium carbonate and extracted with ether. Evaporation of the ether extract, after it had been washed and dried, yielded 0.5 g. of material which melted at 79–80°. Several recrystallizations from ethanol changed the melting point to 85–86°. No depression occurred in a mixture melting point with known dibenzoyl-(morpholinomethyl)-ethane (IIa).

(b) Catalytic Reduction in Acetic Acid Solution.—Eight-tenths of a gram of the (morpholinomethyl)-ethylene (V) was reduced catalytically with the aid of 0.02 g. of platinum oxide in 35 ml. of glacial acetic acid. The rate of absorption began to decrease sharply after one equivalent of hydrogen had been absorbed and the reduction was stopped after about 1.5 equivalents had been absorbed. The mixture was filtered to remove the catalyst, diluted with water, neutralized with sodium carbonate and extracted with ether. The ether extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. Crystallization of the residue from ethanol yielded 0.3 g. of crystals which melted at 79–81° and was shown to be the (morpholinomethyl)-ethane (IIa) by a mixture melting point.

Treatment of *cis*- and *trans*-Dibenzoylmethylethylenes (I) with Triethylamine.—One gram of freshly prepared *trans*-dibenzoylmethylethylene was dissolved in a solution of 4 ml. of triethylamine and 10 ml. of ether, and the resulting solution was allowed to stand in the dark for twenty-four hours after which time it was evaporated under a stream of air. The crystalline residue upon recrystallization from ethanol weighed 0.5 g., melted at 62–64° and gave no mixture melting point depression with the *cis* isomer.

When the *cis* isomer was treated with triethylamine under the same conditions for three weeks, it was recovered unchanged.

The *cis* isomer does not react with ferric chloride solution or ethanolic bromine at room temperature and is not soluble in sodium hydroxide solution, showing that it exists in the keto form.

Treatment of *cis*- and *trans*-Dibenzoylethylenes with Triethylamine.—When 0.5 g. of *cis*-dibenzoylethylene was treated with triethylamine under the same conditions as were the dibenzoylmethylethylenes, 0.3 g. of the *trans* compound which melted at 108–110° was obtained as the product. It was identified by a mixture melting point with an authentic sample.

The *trans* compound when treated under these conditions was recovered unchanged.

Treatment of *cis*- and *trans*-dibenzoyldimethylethylenes with triethylamine and morpholine under the conditions which favored reaction with dibenzoylmethylethylene gave only unchanged material.

Treatment of *trans*-dibenzoylethylmethylene with the nitric–acetic acid reagent (1 g. in a solution of 1 ml. of nitric acid and 8 ml. of acetic acid) for five minutes at 10° followed by pouring into 25 ml. of cold water, gave 0.8 g. of nearly pure starting material.

This experiment shows that the *trans* compound is stable under conditions identical with those involved in the formation of the *cis* compound by the oxidation of 2,5-diphenyl-3-methylfuran.[7] Thus, there can be no doubt that the configurations assigned to the *cis* and *trans*-dibenzoylmethylethylenes on the basis of mode of synthesis, are correct.

Summary

Secondary amines react with dibenzoylmethylethylene to give (*t*-aminomethyl)-dibenzoylethanes. These are furanized to the 3-(*t*-aminomethyl)-2,5-diphenylfurans, the structures of which are proved by synthesis from known furans. Nitric acid oxidation of the (morpholinomethyl)-furan to *cis*-dibenzoyl-(morpholinomethyl)-ethylene and reduction of this to dibenzoyl-(morpholinomethyl)-ethane complete the cycle of reactions typical of this class of compounds.

trans-Dibenzoylmethylethylene is shown to be the *labile* isomer by conversion into the *cis* isomer by means of triethylamine. The bearing of this on the chelate ring structure proposed for the *cis* compound is discussed.

CHARLOTTESVILLE, VIRGINIA

RECEIVED SEPTEMBER 28, 1945

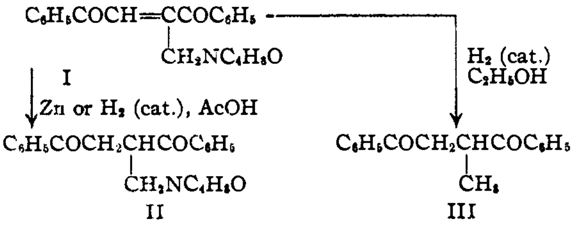
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY OF THE UNIVERSITY OF VIRGINIA]

Some Reactions of *cis*-Dibenzoyl-(morpholinomethyl)-ethylene. Reduction and Cyclization

BY PHILIP S. BAILEY[1] AND ROBERT E. LUTZ

In the preceding paper[2] is discussed the conversion of 2,5-diphenyl-3-(morpholinomethyl)-furan by the characteristic nitric acid oxidation into *cis*-dibenzoyl-(morpholinomethyl)-ethylene (I). This compound has proved to be especially interesting in its reactions and is the subject of the present paper.

Reduction of the unsaturated diketone (I) in *acetic acid* solution, catalytically or with zinc dust, gave the corresponding saturated diketone (II).[3] In contrast with this straightforward result, catalytic hydrogenation *in ethanol* solution, of the free amine (I) or its hydrochloride, using either platinum or palladium–barium sulfate catalyst,



---

(1) Holder of Philip Francis du Pont Fellowships 1942–1944.

(2) Lutz and Bailey, THIS JOURNAL, 67, 2229 (1945).

(3) This reaction was carried out in the course of a structural proof (*cf.* ref. 2).