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

# THE REACTIONS OF THE DIBROMIDES AND BROMO DERIVATIVES OF DIBENZOYLETHYLENE WITH AMINES[1]

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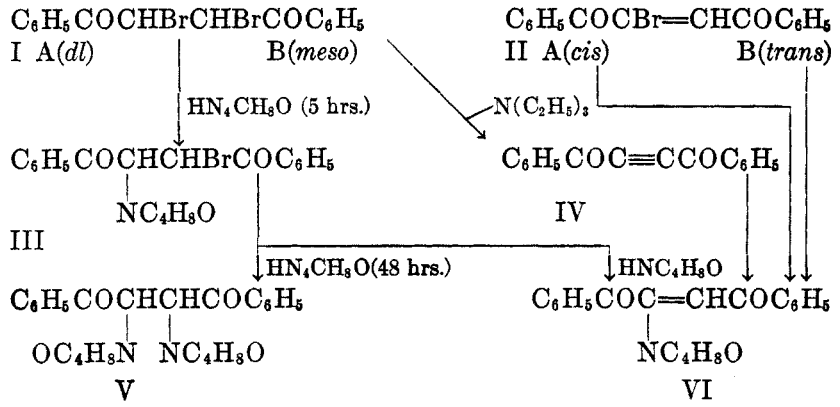
The reactions of amines with dibenzoylethylene dibromide (IB) and dibenzoylacetylene (IV) have been considered in earlier papers (1–4). Attempts to prepare dimorpholinyldibenzoylethane (3) (V) gave a mixture which appeared, after the isolation from it of the major component, morpholinyldibenzoylethylene (VI), and from analyses, to consist of about 70% of this compound (VI) and 30% of the diamino diketone (V). The latter compound (V)[3] was particularly desired for chemical and pharmacological comparison with the $\alpha,\beta$-dimorpholinylbenzylacetophenones which have already been studied extensively (5, 6) and which have proved to be unique in possessing antimalarial activity (5). It has now been isolated in good yield by the action of morpholine on *dl*- or *meso*-dibenzoylethylene dibromide (I) in acetone and has been separated from small amounts of the more soluble morpholinyldibenzoylethylene (VI); but in no case has a stereoisomer been detected. In experiments at higher temperatures, *e.g.*, using the *meso*-dibromide (IB) at the temperature of refluxing acetone, the yield of the dimorpholinyl diketone (V) was much lower (39%) and that of morpholinyldibenzoylethylene (VI) higher (50%).




Dimorpholinyldibenzoylethane (V) proved to be inactive against avian malaria.[4]

Bromomorpholinyldibenzoylethane[3] (III) has been obtained in excellent yields in one configuration only from *dl*- and *meso*-dibenzoylethylene dibromides (I)

[1] Taken from a Doctorate Dissertation, University of Virginia, 1949.

[2] Present location, Birmingham-Southern College, Birmingham, Ala.

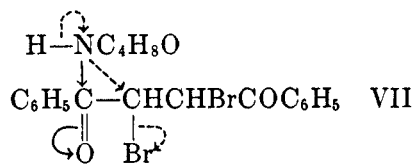
[3] For ultraviolet absorptions of these compounds see ref. 4.

[4] Tested against *Plasmodium gallinaceum* in the chick, at the National Institutes of Health.

by the action of morpholine under conditions similar to those employed in the preparation of the dimorpholinyl diketone (V) but involving a much shorter reaction time. Stereochemical differences are lost in this step. The facility of the formation of the same product in the two cases strongly indicates that it is the primary reaction product and that it is formed by a direct displacement of a halogen by morpholine. That this is indeed the mechanism has been shown by exclusion of the other possibilities which require as the first step elimination of hydrogen bromide to give one or both of the *cis*- and *trans*-bromodibenzoylethylenes; *i.e.*, it has been demonstrated that these two possible intermediates (II) which are known, actually give quite different results under comparable reaction conditions, as will be described below.

The second step in the formation of dimorpholinyldibenzoylethane (V) is the displacement of the remaining halogen from the primary product, bromomorpholinyldibenzoylethane (III). A mechanism involving loss of hydrogen bromide (from III) to give the morpholinyldibenzoylethylene (VI) followed by addition of the second molecule of morpholine, is excluded here because additions of this latter type are not known to, and theoretically should not, occur (*cf.* 4).

It should be noted incidentally that the successive displacements of halogen may involve cyclic transitions one of which is represented by the abbreviated formulation VII (*cf.* 7, 8, 9) (*cf.* also 6).

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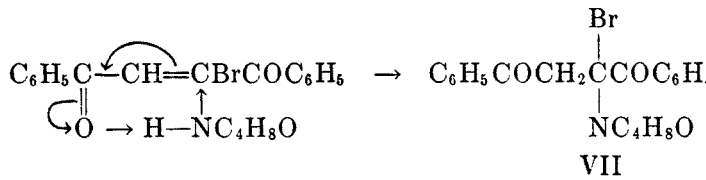
The action of morpholine on *cis*- and *trans*-bromodibenzoylethylenes (II) under comparable conditions was undertaken because it was suspected from the readiness of the conversion of the dibromides (I) into bromomorpholinyldibenzoylethane (III) that direct substitution rather than elimination-and-addition was involved, although it was recognized that elimination of hydrogen bromide can occur under some conditions, *e.g.*, in ethanol solution under prolonged refluxing (1). It was hoped that the bromo unsaturated diketones would behave in a distinctively different fashion, and fortunately for the speculations in regard to mechanism, they did so. Under conditions comparable with those which brought about displacement of bromine of the dibromides by morpholine, *cis*-bromodibenzoylethylene gave a 96% yield of morpholinyldibenzoylethylene (VI) and the *trans*-isomer gave 70% of this compound (VI) along with a significant but distinctively small amount (10%) of the dimorpholinyldibenzoylethane (V). Although there seems to be an appreciable difference between the behaviors of the *cis*- and *trans*-isomers, this may not be significant because the conditions of the two experiments, though close, were not identical; in any case it is clear that the main course of neither reaction involves addition of morpholine to give bromomorpholinyldibenzoylethane (III).

As to the steps by which *cis*- and *trans*-bromodibenzoylethylenes (II) go to morpholinyldibenzoylethylene (VI) under these conditions, the possibility that addition of morpholine involves a diastereoisomer of bromomorpholinyldibenzoylethane (III) appears to be unlikely because no such isomer has been detected and because it would require an utterly different behavior of two diastereoisomers in the next step in the reaction, a difference which is conceivable but unlikely to such an extreme. One possible path involves a different mode of addition of morpholine to give 1-bromo-1-morpholinyldibenzoylethane (VIII) which could lead only to morpholinyldibenzoylethylene (VI) by elimination of hydrogen bromide. This type of intermediate although obviously impossible in the case of $\alpha$-bromobenzalacetophenone is a logical intermediate in this series, and there is analogy for it in the reactions leading to the formation of



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derivatives of 2-hydroxy-2,5-diphenyl-3-furanone (10) from various substituted dibenzoylethylenes, and in the conversion of bromomethyl- and dibromodibenzoylethylenes (4, 11) to the amino unsaturated 1,4-diketones. However, since primary amines react with I to give dibenzoylethylene imines and with II to give aminodibenzoylethylenes, and do not give compounds of the 2-hydroxyfuranone type (4), and since tertiary amines react readily to give dibenzoylacetylene (IV), the alternative path through the acetylene (I) seems probable. Such a mechanism is not involved in the analogous reactions in the benzalacetophenone series because in that series the $\alpha$-bromobenzalacetophenone (*cf.* 12, 13) in contrast to the $\beta$-bromo analog is not convertible into benzoylphenylacetylene under such mild conditions involving a tertiary amine, but requires a stronger base, presumably because of the weaker activity of the $\beta$-hydrogen which is involved in the elimination; furthermore unsaturated compounds when formed in this series are never of the $\beta$-type which would be required of reactions proceeding through $\beta$-bromobenzalacetophenone and benzoylphenylacetylene. In the case of the bromodibenzoylethylenes (II) there is an active $\alpha$-hydrogen, and dibenzoylacetylene (IV) is in fact easily produced by the action of tertiary amines on dibenzoylethylene dibromide (Ib), as would be expected. Dibenzoylacetylene itself, of course, can do only one thing in reaction with morpholine, *e.g.*, add once, as it does, to give morpholinyldibenzoylethylene (VI).

It should be noted that *trans*-bromodibenzoylethylene (IIB), while it gave mainly morpholinyldibenzoylethylene (VI in 70% yield), gave also a 10% yield of dimorpholinyldibenzoylethane (V) which could not have been formed through a mechanism involving the acetylene (IV); therefore to this small extent (10%) it must have reacted by way of competing addition to give III, with subsequent substitution.

In the reaction between morpholine and *meso*-dibenzoylethylene dibromide and bromomorpholinyldibenzoylethane under the more drastic conditions (at boiling acetone temperature) where the yields of the dimorpholinyl ketone (V) were only 39 and 26% respectively and that of morpholinyldibenzoylethylene (VI) 50%, it is evident that competing mechanisms are involved.

The reaction between dimesitoylethylene dibromide and morpholine, unfortunately, did not give a tractable product, but diethyl- and dibutyl-amines gave the corresponding dialkylaminodimesitoylethylenes.

## EXPERIMENTAL

*1-Bromo-2-morpholinyl-1,2-dibenzoylethane* (III). A suspension of 50 g. (0.126 mole) of *meso*-dibenzoylethylene dibromide (IB) in 300 ml. of acetone was cooled in an ice-bath with stirring; 50 g. of morpholine (0.58 mole) was added slowly. The temperature rose slightly but at no point exceeded 28°. The solution remained nearly colorless. After 15 minutes, during which time the addition of morpholine was completed, the mixture was allowed to come to room temperature, was stirred for 5 hours, filtered, and the residue (68.6 g.) was digested with water to remove morpholine hydrobromide and again filtered, giving 42.8 g. (84.5%) of pure product; colorless; m.p. 154–155°; it was recrystallized from absolute ethanol.

*Anal.* Calc'd for $C_{20}H_{20}BrNO_3$: C, 59.71; H, 5.01; N, 3.48.
Found: C, 59.30; H, 4.86; N, 3.47.

From the acetone filtrate was obtained a small amount of the yellow morpholinyldibenzoylethylene (VI).

*1,2-Dimorpholinyl-1,2-dibenzoylethane* (V) is best obtained by continued action of morpholine on III (*cf.* B and C below). After recrystallizations from acetone or absolute ethanol it melted at 177–179° decomp.; colorless. Admixture with VI gave a melting point depression of ten degrees.

*Anal.* Calc'd for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86.
Found: C, 70.84; H, 6.82; N, 6.70.

This compound (V) was recovered largely unchanged after solution for 48 hours in refluxing acetone, with or without added morpholine hydrochloride.

## REACTIONS OF MORPHOLINE WITH VARIOUS COMPOUNDS

(A) *Meso-dibenzoylethylene dibromide* (IB) (50 g., 0.126 mole) was suspended in 300 ml. of acetone and 50 g. (0.58 mole) of morpholine was added slowly with stirring, over 15 minutes; the temperature rose quickly to refluxing as the solution assumed a yellow coloration. After a total of 30 minutes and reversion to room temperature, stirring was continued for 48 hours. The crystalline precipitate (60.5 g.) was digested with hot water which removed 40.5 g. (95%) of morpholine hydrobromide. The 20 g. of slightly yellow residue (m.p. 166–168°) (39%), was identified as almost pure V. From the original acetone filtrate there was isolated upon concentration and crystallization a 50% yield of morpholinyldibenzoylethylene (VI).

(B) *dl-Dibenzoylethylene dibromide* (IA) (5 g., 0.0126 mole) was suspended in 100 ml. of acetone at 10° (maintained in an ice-bath) and treated dropwise with 5 g. (0.058 mole) of morpholine with continuous stirring. After one hour the mixture was allowed to come to room temperature and to stand for 10 hours at 28–31°. The precipitate was filtered (4 g.) and washed with water to remove morpholine hydrobromide. A small residue (10%) of m.p. 169–174° was purified further and identified as dimorpholinyldibenzoylethane (V). Evaporation of the acetone filtrate to a small volume gave 4.5 g. of colorless crystals of m.p. 153–155° (90%) which was purified further and identified as bromomorpholinyldibenzoylethane (III) by mixture melting point with the sample obtained above from IB.

(C) *Bromomorpholinyldibenzoylethane* (III) (4 g., 0.01 mole) was suspended in 100 ml.

of acetone and with stirring and cooling in an ice-bath was treated with 3 g. (0.034 mole) of morpholine; this mixture was maintained at room temperature for 48 hours. The precipitate (4.5 g.) was washed with water to remove morpholine hydrobromide, and the residue (3.4 g.) of m.p. 175–177° (85%) was purified further and identified as dimorpholinyldibenzoylethane (V). Evaporation of the filtrate gave 0.2 g. (6%) of m.p. 174–176° which was identified as morpholinyldibenzoylethylene (VI).

(D) *An experiment similar to* (C) on 10 g. (0.025 mole) of III in 200 ml. of acetone at 54° for one hour, using 5 g. (0.058 mole) of morpholine, gave some unchanged material which was subjected to a second treatment for an additional 4 hours. The precipitate (5.6 g.) was washed with water and the residue of m.p. 177–179° (2.6 g., 26%) was purified further and identified as dimorpholinyldibenzoylethane (V). The acetone filtrate on evaporation to *ca.* 50 ml. gave 4 g. of m.p. 155–156° (50%) which was purified further and identified as morpholinyldibenzoylethylene (VI).

(E) *cis-Bromodibenzoylethylene* (IIA) (10 g., 0.032 mole), dissolved in 150 ml. of acetone and cooled to 5° in an ice-bath, was treated with stirring with 9 g. (0.13 mole) of morpholine, added slowly over 30 minutes. After another 30 minutes the mixture was allowed to come to room temperature (25°) and stirred for 48 hours. The colorless solid (4.8 g.) was identified as morpholine hydrobromide (91%). Apparently none of the dimorpholinyldibenzoylethane (V) had been formed (it would have crystallized at this point if present in significant amounts). Evaporation of the acetone solution to 25 ml. gave 9.8 g. of crude morpholinyldibenzoylethylene (96%), which was purified further and identified. In a repeat experiment at 10° and a reaction time of 30 minutes, a yield of 88% of nearly pure VI and none of V was obtained.

(F) *trans-Bromodibenzoylethylene* (IIB) (10) (3 g., 0.0095 mole), dissolved in 200 ml. of acetone cooled to 10° in an ice-bath, was treated dropwise with 4 g. (0.046 mole) of morpholine. After one hour the reaction mixture was allowed to come to room temperature and to stand with stirring for 36 hours. The colorless precipitate (2.0 g.) was washed with water to remove morpholine hydrobromide. The residue (0.8 g.), m.p. 171–174°, was identified as dimorpholinyldibenzoylethane (V) (10%). Evaporation of the filtrate to 25 ml. and cooling gave 2.6 g. of yellow crystals of m.p. 169–173° (70%) which was purified further and identified by mixture melting point as morpholinyldibenzoylethylene (VI).

(G) *Dibenzoylacetylene* (IV) (2 g.), dissolved in 100 ml. of acetone, was treated with 2 g. of morpholine and the mixture was then cooled in ice for ten minutes. Evaporaton under an air stream to a volume of 15 ml. gave 2.5 g. of yellow product (VI) of m.p. 176–177° (92%) which was identified by mixture melting point with samples previously prepared (3).

*Diethylamino-1,2-dimesitoylethylene.* Diethylamine (7 g.) was added slowly to a suspension of 10 g. of *meso*-dimesitoylethylene dibromide in 150 ml. of absolute ether and the mixture was stirred at room temperature for one hour and refluxed for 20 minutes. After filtering the diethylamine hydrobromide (yield 91%) and evaporating to a small volume, 5.8 g. of light yellow product of m.p. 109–111° was obtained (71%). After repeated recrystallizations from 60% ethanol it melted at 116–117°; light yellow.

*Anal.* Calc'd for $C_{26}H_{33}NO_2$: C, 79.75; H, 8.50.

Found: C, 79.55; H, 8.32.

*Di-n-amylamino-1,2-dimesitoylethylene.* Diamylamine (15 g.) was added to a suspension of 10 g. of *meso*-dimesitoylethylene dibromide in 150 ml. of absolute ether. After stirring for one hour at room temperature the diamylamine hydrobromide was filtered, the solution concentrated, and again filtered from a second crop of amine hydrobromide (total yield 98%). Addition of ether and ethereal hydrogen chloride precipitated the rest of the unused diamylamine. Filtering and evaporating to a volume of 15 ml. gave a yellow solid; 3 g. (30%) of m.p. 94–96°. It was recrystallized from 50% ethanol; m.p. 97–98°.

*Anal.* Calc'd for $C_{32}H_{45}NO_2$: C, 80.79; H, 9.47.

Found: C, 80.50: H, 9.36.

A number of attempts under a variety of conditions to make the piperidyl and morpholinyl dimesitoylethylenes failed.

*Dibenzoylacetylene* (*cf.* D) (IV) was prepared in an improved procedure from 25 g. of *meso*-dibenzoylethylene dibromide (IB) by treatment with 15 g. of purified triethylamine in 200 ml. of benzene or acetone and heating the mixture under reflux for four hours (one hour in the case of acetone). The precipitate of triethylamine hydrobromide (23 g.) was filtered. It is important to work up the product promptly, since it is sensitive and tends to polymerize readily. The filtrate was evaporated under reduced pressure and the orange-red residue was crystallized from absolute ethanol; yield 12–15 g. (82–95%); m.p. 110–111°.

*1,2-Di-(p-bromobenzoyl)acetylene* was made in 92% yield from dibromobenzoylethylene dibromide, like dibenzoylacetylene, using benzene and triethylamine but with stirring at room temperature for one hour and refluxing for one hour longer. It is much less soluble in benzene than dibenzoylacetylene, and it partly crystallizes out with the triethylamine hydrobromide. It was crystallized repeatedly from absolute ethanol, m.p. 182–183°.

*Anal.* Calc'd for $C_{16}H_8Br_2O_2$: C, 49.00; H, 2.05.

Found: C, 48.72; H, 2.34.

*1,2-Dimesitoylacetylene* was made in similar fashion from *meso*-dimesitoylethylene dibromide using acetone and triethylamine and stirring the mixture for 24 hours, filtering the amine hydrobromide and evaporating. It crystallized from absolute ethanol (49%) and on recrystallization melted at 115–117°.

*Anal.* Calc'd for $C_{22}H_{22}O_2$: C, 82.96; H, 6.97.

Found: C, 82.80; H, 6.74.

SUMMARY

Both *meso*- and *dl*-dibenzoylethylene dibromides react under controlled conditions with an excess of morpholine to give first bromomorpholinyldibenzoylethane and then dimorpholinyldibenzoylethane. That these are substitution reactions and that they do not involve elimination of hydrogen bromide as the first step, is shown by the fact that both *cis*- and *trans*-bromodibenzoylethylenes react quite differently with morpholine to give morpholinyldibenzoylethylene as the chief product. In the latter reactions the mechanism may involve as the first step formation of dibenzoylacetylene by elimination of hydrogen bromide.

The practical preparation of diaroylacetylenes by the action of triethylamine on the diaroylethylene dibromide is described. Two new dialkylaminodimesitoylethylenes have been made.

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REFERENCES

(1) CONANT AND LUTZ, *J. Am. Chem. Soc.*, **47**, 881 (1925).
(2) LUTZ, *J. Am. Chem. Soc.*, **48**, 2905 (1926).
(3) LUTZ, BAILEY, AND SHEARER, *J. Am. Chem. Soc.* **68**, 2224 (1946).
(4) LUTZ, AMACKER, KING, AND SHEARER, *J. Org. Chem.*, **15**, 181 (1950).
(5) LUTZ, MARTIN, *et al.*, *J. Org. Chem.*, **14**, 982 (1949).
(6) CROMWELL, *Chem. Revs.*, **38**, 83 (1946).
(7) MICHAEL AND PALMER, *Amer. Chem. J.*, **6**, 253 (1884).
(8) STEVENS, MALIK, AND PRATT, "A reactive intermediate in the reaction of an α-haloketone with base," Philadelphia Meeting, Amer. Chem. Soc., April, 1950 (abstracted).
(9) DEWAR, *The Electronic Theory of Organic Chemistry*, Oxford University Press, pp. 73, 80 (1949).
(10) LUTZ AND MCGINN, *J. Am. Chem. Soc.*, **64**, 2585 (1942).
(11) LUTZ AND STUART, *J. Am. Chem. Soc.*, **59**, 2316 (1937).
(12) BICKEL, *J. Am. Chem. Soc.*, **69**, 2134 (1947).
(13) LUTZ, JORDAN, AND HINKLEY, results to be published shortly.