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

THE ACTION OF HYDROGEN BROMIDE IN ACETIC ACID ON UNSATURATED 1,4-DIKETONES

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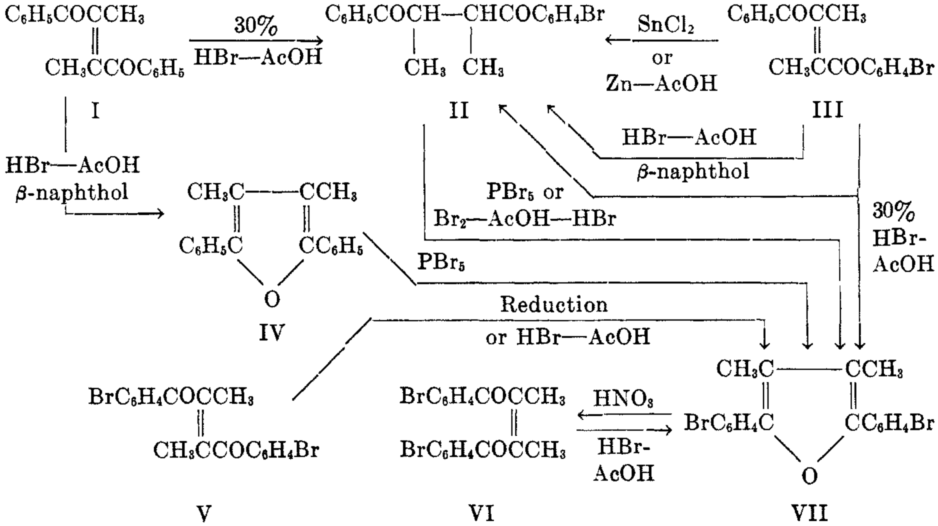
Some time ago a crystalline monobromo compound was obtained in good yield by the action of 30% hydrogen bromide in concentrated acetic acid on *trans* 1,2-dibenzoyldimethylethylene (I) (1). It was recognized that this was not a simple addition compound, because the halogen could not be removed by hydrolysis or reduction, and presumably therefore was in aromatic combination. Investigation of this compound revealed that the bromine had entered the para position of one of the phenyl groups and at the same time reduction had occurred. This report deals with experiments which were carried out in an attempt to gain an understanding of this interesting and unexpected reaction.



The first clue to the structure of the new product came through oxidation which gave a small amount of *p*-bromobenzoic acid. This demonstrated conclusively the location of the bromine. The saturated diketone structure (II) was then deduced from analysis and the stability towards hydrolyzing and reducing agents. The compound was not easily furanized, however, contrary to expectation based on the ease of formation of the furans (IV) and (VII). The structure was proved by synthesis from α-(*p*-bromobenzoyl)-α,β-dimethyl-

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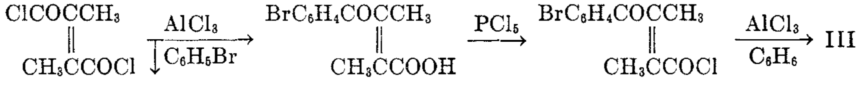
acrylic acid (IX) through conversion into the acid chloride (X), condensation with benzene by the Friedel-Crafts reaction, and reduction of the resulting unsaturated diketone (III).



$$\begin{matrix}\text{ClCOCCH}_3\\ \|\\ \text{CH}_3\text{CCOCl}\end{matrix}\ \underset{\downarrow \text{C}_6\text{H}_5\text{Br}}{\xrightarrow{\text{AlCl}_3}}\ \begin{matrix}\text{BrC}_6\text{H}_4\text{COCCH}_3\\ \|\\ \text{CH}_3\text{CCOOH}\end{matrix}\ \xrightarrow{\text{PCl}_5}\ \begin{matrix}\text{BrC}_6\text{H}_4\text{COCCH}_3\\ \|\\ \text{CH}_3\text{CCOCl}\end{matrix}\ \xrightarrow[\text{C}_6\text{H}_6]{\text{AlCl}_3}\ \text{III}$$

VIII V IX X

In connection with this synthesis, it is interesting to note that the starting material, bromobenzoyldimethylacrylic acid (IX), has been made in a new way directly from dimethylfumaryl chloride (VIII) by the Friedel-Crafts reaction. This reaction slowly goes on to completion with the formation of the expected di(bromophenyl) unsaturated diketone (V).

The monobromo unsaturated diketone (III), prepared in the above described synthesis, was also treated with the 30% hydrogen bromide-acetic acid reagent. It was converted into a mixture of the corresponding saturated diketone (II) and di(bromophenyl)dimethylfuran (VII). The ratio of yields of the two products was 4:1, with reduction and dehydration the dominant reaction. At the same time the solvent must have undergone bromination to an extent equivalent to the amount of reduction.

The structure of the di(bromophenyl)dimethylfuran (VII) was demonstrated by synthesis in two ways; through bromination of dimethyldiphenylfuran (IV), and by reduction of the corresponding *trans* di(bromophenyl) unsaturated diketone (V). Consistent with this structure is the fact that the furan underwent the characteristic oxidative fission with nitric acid to give the *cis* unsaturated diketone (VI), which in turn could be reduced back to the furan with great facility.

Both the *cis* and the *trans* di(*p*-bromophenyl) unsaturated diketones (V and VI) have been treated with the hydrogen bromide-acetic acid reagent and gave the furan (VII) in good yield. These results involved both reduction and dehydration.

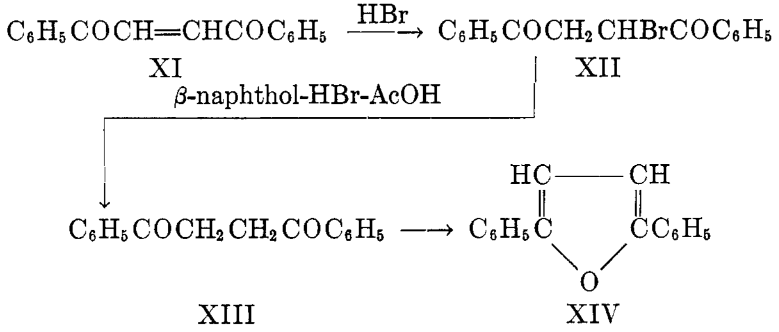
In connection with these experiments it should be noted that bromination of the saturated diketone (II) with an excess of free bromine in the hydrogen bromide-acetic acid reagent gave the di(bromophenyl)dimethylfuran (VII). No particular significance can be attached to this fact, however, because this reaction undoubtedly involved first bromination at an α-position to give the α-bromo diketone, followed by loss of hydrogen bromide. This reaction, therefore, is in the same category as that of the unsaturated diketone (III).

In none of the above described reactions between hydrogen bromide and the four unsaturated diketones (I, III, V, and VI) was there ever obtained any evidence of a compound containing more than two bromine atoms. Bromination occurred in two cases and involved only the para positions, and reduction occurred in all cases; no simple hydrogen bromide addition compound was isolated.

In these reactions it seemed probable that hydrogen bromide was adding reversibly to the molecule, the bromine then being transferred to the para position of the same or another molecule or to the solvent. The hypothetical hydrogen bromide addition compound would be an α-bromo ketone or an enol of it, and in the presence of hydrogen bromide would function as a brominating agent. It therefore seemed worth while to re-examine the action of the hydrogen bromide-acetic acid reagent on the unsaturated diketones (I and III) and also on dibenzoyl- and dimesitoyl-ethylenes (XI and XV), where hydrogen bromide addition compounds have actually been isolated, introducing into the various reaction mixtures a bromine acceptor such as β-naphthol to divert the brominating action and to confine the changes in the compounds in question to reduction.

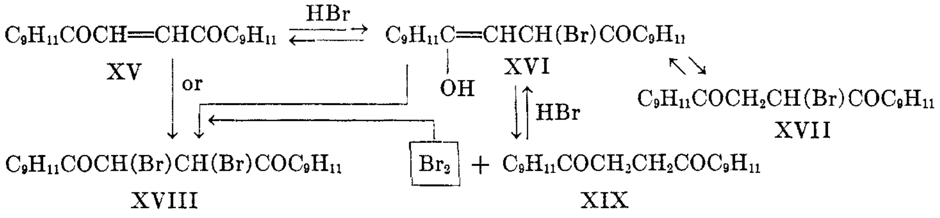
The reactions between hydrogen bromide-acetic acid and the unsaturated diketones (I and III) where both bromination and reduction had occurred, were repeated in the presence of β-naphthol. As was anticipated only the reduction products (IV and II, respectively) were obtained under these conditions, and α-bromo-β-naphthol could be isolated as a by-product.

Dibenzoylethylene (XI) is known to add hydrogen bromide in acetic acid; the addition compound, dibenzoylbromoethane (XII) crystallizes promptly from the reaction mixture in good yield. This reaction was repeated in the presence of β-naphthol, the mixture being allowed to stand until further reaction beyond the initial addition had occurred. 2,5-Diphenylfuran (XIV) and α-bromo-β-naphthol were isolated as the products. In an independent experiment it was shown that the saturated diketone (XIII) is readily dehydrated to the furan under the conditions of this experiment and undoubtedly was formed as an intermediate. The course of the reactions, disregarding equilibrations and intermediate steps, must be as follows:



The case of dimesitoylethylene (XV) is of interest in this connection. The hydrogen bromide addition compound (XVII) is unstable and not easily isolated, and it breaks up readily into the components. Here the reaction is slowly reversible, and in this respect occupies a position intermediate between those of dibenzoylethylene (XI) and dibenzoyldimethylethylene (I). It had previously been observed that in the reaction with dimesitoylethylene (XV) there was produced a small amount of dimesitoyldibromoethane (XVIII) (2). This product undoubtedly was formed by the action of free bromine which was generated through the interaction of hydrogen bromide and the addition compound

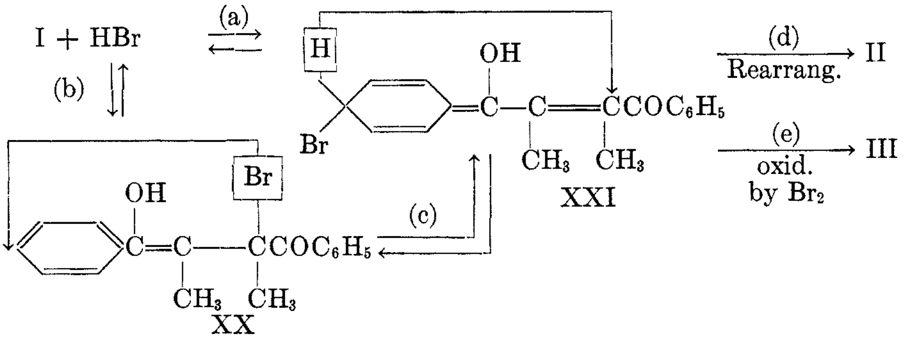
(XVI) or (XVII);[2] the bromine liberated would act upon the starting material (XV) or upon the intermediate enolic addition compound (XVI) which must be present also in equilibrium. This is pictured in the following diagram.



In the total reaction outlined above, the saturated diketone (XIX) should be formed in an amount proportional to that of the dibromide (XVIII) but its presence was not suspected at the time this experiment was performed (2). This experiment was therefore repeated with β-naphthol present to absorb the bromine and to prevent the formation of the dibromide. Under these conditions the saturated diketone (XIX) was obtained in good yield as the chief product.

It seems reasonable from the foregoing to assume that the diaryldimethyl unsaturated diketones (I, III, V, and VI) add hydrogen bromide reversibly, and that the hypothetical addition compounds or the enols resulting from 1,4-addition possess a very reactive bromine which to some extent may be transferred irreversibly to a para position. Probably free bromine is generated by the action of hydrogen bromide on the bromo diketone and is present in the equilibrium mixture. The entrance of the bromine into the para position rather than the meta, however, is a striking point. Obviously the saturated 1,4-diketones would not directly undergo para bromination; however, intermediate enols produced by 1,4-addition or enolization, or compounds resulting from addition at the carbonyl group, might well be able to do so.

An alternative and plausible mechanism for para bromination is reversible addition of hydrogen bromide to the conjugated unsaturated ketone system of the benzoyl group (path "a" in the diagram below), or a 1,7-shift of bromine of the enolic hydrogen bromide 1,4-addition compound (XX) from the chain



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[2] The basis for assuming the reversible liberation of bromine is the recent work of Altschul and Bartlett (3).

to the para position to give XXI (path "b-c"). This would be followed by irreversible migration of the para hydrogen (step "d") or oxidation by the bromine in the equilibrium mixture (step "e").

Naturally in reactions such as those described above, where equilibria are involved throughout down to the fixation of the bromine in the para position of a phenyl group, it would be difficult to determine the specific mechanism involved. Conjugate additions and migrations are subject to elaboration and expression in electronic and ionic terms. Possibly various of the paths suggested are in reality equivalent; for example, (c) may occur indirectly through reversal of (b) followed by (a).

The results of this investigation serve as added illustration of the complications which may arise in reactions which involve α-halogeno ketones. Knowing of these complications it has been possible in several bromine additions (4) to improve the reactions markedly by taking care to remove the hydrogen bromide that was formed as the result of secondary or side reactions.

EXPERIMENTAL PART

trans *1-Benzoyl-2-*(p*-bromobenzoyl)-1,2-dimethylethylene* (III). *trans* 2-(*p*-Bromobenzoyl)-1,2-dimethylacrylyl chloride, prepared from 0.4 g. of phosphorus pentachloride and 0.5 g. of the parent acid, without removal of the phosphorus oxychloride produced, was taken up in 5 ml. of benzene. This solution was added dropwise at room temperature during 15 min. to a mechanically stirred mixture of 0.75 g. of aluminum chloride and 15 ml. of benzene. Stirring was continued with refluxing for 30 min. and the mixture was hydrolyzed by prolonged stirring in dilute hydrochloric acid. Separation and evaporation of the solvent gave a nearly quantitative yield of crude product (0.6 g.). Recrystallization from ethanol gave colorless needles of melting point 125°.

Anal. Calc'd for $C_{18}H_{15}BrO_2$: C, 63.0; H, 4.4; Br, 23.3.
Found: C, 63.1; H, 4.3; Br, 23.3.

4-(p*-Bromophenyl)-2,3-dimethyl-1-phenylbutanedione-1,4* (II). A mixture of 0.05 g. of the *trans* unsaturated diketone (III) and 0.1 g. of stannous chloride in one ml. of a 7:3 mixture of conc'd acetic and hydrochloric acids was refluxed for 30 min. On cooling, 0.04 g. of product separated; melting point 105–115°. Crystallization from ethanol-ethyl acetate mixtures raised the melting point to 125°. The compound showed no mixture melting point depression with the products obtained by the action of hydrogen bromide-acetic acid on dibenzoyldimethylethylene and by reduction of the *trans* unsaturated diketone (III).

trans *1,2-Di-*(p*-bromobenzoyl)-1,2-dimethylethylene* (V). (a) Ten grams of dimethylfumaryl chloride was added dropwise during one hour to a mechanically stirred and refluxing mixture of 17 g. of anhydrous aluminum chloride in 80 ml. of carbon disulfide and 26 g. (3 equiv.) of bromobenzene. After refluxing for another hour the mixture was hydrolyzed in ice and 35 ml. of conc'd hydrochloric acid. Fifteen grams of product was filtered off and an additional crop was obtained by evaporation of the solvent. Leaching with dilute alkali was necessary to free the material from acidic by-products. The yield of fairly pure compound was 80%; colorless prisms; melting point 172.5–173°.

Anal. Calc'd for $C_{18}H_{14}Br_2O_2$: C, 51.2; H, 3.3.
Found: C, 51.2; H, 3.3.

(b) In a second experiment, dimethylfumaryl chloride was added over 30 min. at room temperature to the carbon disulfide-bromobenzene-aluminum chloride mixture, using two equivalents of bromobenzene but with the other amounts of materials and conditions similar to those described in (a). There was isolated a 30% yield of 2-(*p*-bromobenzoyl)dimethylacrylic acid (IX), a 14% yield of the unsaturated diketone (V) and a 4% yield of dimethylfumaric acid.

2,5-Di-(p-*bromophenyl)-3,4-dimethylfuran* (VII). A mixture of one gram of the *trans* unsaturated diketone (V) and 2 g. of stannous chloride in 10 ml. of 7:3 conc'd acetic and hydrochloric acids was refluxed for one hour. The resulting suspension was diluted with water, and gave a nearly quantitative yield of the furan, which crystallized from benzene as colorless hair-like needles of melting point 181°. Crystallization from ethanol-ethyl acetate mixtures in one experiment resulted in a monohydrate, which gave the expected analysis only after vacuum sublimation.

Anal. Calc'd for $C_{18}H_{14}Br_2O$: C, 53.2; H, 3.5.
Found: C, 53.3, 53.4; H, 4.0, 3.8.

The furan was obtained also in 30% yield upon refluxing a mixture of the *trans* unsaturated diketone (V), an equal weight of zinc dust and five times its weight of conc'd acetic acid. The remainder of the product in this experiment was accounted for as oils and a low-melting mixture presumably containing the expected saturated diketone. A more tractable mixture results from sodium hydrosulfite reduction, in which the saturated diketone could be seen under the microscope as characteristic compact hexagonal prisms.

The furan was also prepared in low yield by the action of phosphorus pentabromide both on 3,4-dimethyl-2,5-diphenylfuran (IV) and on 4-bromophenyl-2,3-dimethyl-1-phenylbutanedione-1,4 (II). Equal weights of starting material and phosphorus pentabromide were heated for 10 minutes on a steam-bath. The result was a mixture from which the furan was leached out by solvents and identified by mixture melting point.

cis *1,2-Di-*(p-*bromobenzoyl)-1,2-dimethylethylene* (VI). To 0.5 g. of di-(*p*-bromophenyl)-dimethylfuran (VII) and 10 ml. of propionic acid, in an ice-salt-bath, was added 2 ml. of a 3:1 mixture of propionic and conc'd nitric acids. After 15 minutes the reaction mixture was removed from the bath and diluted by the addition of ice. The crystals separating weighed 0.47 g. The compound was soluble in methanol and benzene. It was purified by recrystallizations from ligroin containing small quantities of ethyl acetate; melting point 138–139°.

Anal. Calc'd for $C_{18}H_{14}Br_2O_2$: C, 51.2; H, 3.34.
Found: C, 51.4; H, 3.76.

The action of $HBr\text{-}CH_3COOH$ *on* trans *dibenzoyldimethylethylene* (I). Hydrogen bromide in acetic acid (30–32%) was used in these reactions and will be referred to as the hydrogen bromide-acetic acid reagent, or $HBr\text{-}CH_3COOH$. The inactivity of this reagent towards β-naphthol was shown by recovery of starting material in good yield after treatment for two hours at room temperature. A nearly quantitative yield of crude α-bromo-β-naphthol was obtained under similar conditions when one equivalent of bromine was added.

The conditions described by Lutz and Taylor (1) were found to be critical, since both heating and varying the ratio of materials resulted in a green resin. Purification of the product, *1-bromophenyl-4-phenyl-2,3-dimethylbutanedione-1,4* (II), was best effected by recrystallization from a 4:1 ethanol-ethyl acetate mixture, although this did not furnish material melting as high as that obtained by reduction of the corresponding unsaturated diketone. The purest sample obtained from the hydrogen bromide reactions melted at 118–119°, and was probably contaminated with the ortho-brominated isomer; the analytical results were satisfactory. The product is also crystallizable from acetic acid, ligroin, and isopropyl ether. An attempt to purify it by vacuum sublimation was fruitless, although the sublimed diketone was shown by analysis to have undergone no significant change. The various samples showed no mixture melting point depressions with each other.

Anal. Calc'd for $C_{18}H_{17}BrO_2$: C, 62.7; H, 5.0; mol. wt., 345.
Found: C, 62.6, 62.6; H, 4.75, 4.7; mol. wt. (Rast), 365.

In the most drastic attempt at hydrolysis, the saturated monobromophenyl diketone (II) was recovered in 75% yield after refluxing for 17 hours with 25 equivalents of alcoholic potassium hydroxide. A colorless oil accounted for the remainder of the starting material.

No reduction resulted from the action of refluxing zinc-acetic acid mixtures, or from prolonged catalytic hydrogenation with either platinum or palladium-barium sulfate catalysts.

Oxidation by hot conc'd nitric acid gave 0.9 mole of *p*-bromobenzoic acid (identified by mixture melting point). The same product was isolated from a more drastic potassium permanganate oxidation, and identified.

Furanization attempts met with surprising resistance. No furan was obtained upon treatment with boiling acetic anhydride containing sulfuric acid, or with boiling acetic acid saturated continuously with dry hydrogen chloride.

Bromination of 20 mg. of II by the action of one equivalent of bromine in 0.4 ml. of the hydrogen bromide-aceitic acid reagent, upon standing for one hour at room temperature, gave di(bromophenyl)dimethylfuran (VII) in good yield. Identification was by mixture melting point.

The reaction between $HBr\text{-}CH_3COOH$ *and dibenzoyldimethylethylene in the presence of β-naphthol.* The action of 6 ml. of the hydrogen bromide-acetic acid reagent through contact at room temperature for one hour with 0.3 g. of *trans* dibenzoyldimethylethylene (I) and 0.33 g. of β-naphthol, gave upon filtration 0.2 g. of 3,4-dimethyl-2,5-diphenylfuran of melting point 116–117° (identified by mixture melting point with an authentic sample). Dilution of the filtrate with water brought the yield to 87%. The product gave a sharp mixture melting point depression with II which had been obtained by reaction in absence of β-naphthol.

The action of $HBr\text{-}CH_3COOH$ *on* trans *1-benzoyl-2-bromobenzoyldimethylethylene* (III). Five-tenths gram of the unsaturated diketone was allowed to stand at room temperature, with 10 ml. of the hydrogen bromide reagent for one hour and the resulting precipitate was filtered off. Upon fractional crystallization of this product from ethanol containing a little ethyl acetate, there was obtained a small quantity of 2,5-di(bromophenyl)-3,4-dimethylfuran (VII) of m.p. 176–179°, and a larger amount of the more soluble saturated diketone (II) melting at 117–119°. Identifications were by mixture melting point; the ratio of VII:II was approximately 1:4.

The reaction in the presence of β-naphthol. Trans 1-benzoyl-2-bromobenzoyldimethylethylene (0.05 g.) was added to 1.0 ml. of the hydrogen bromide-acetic acid reagent containing 0.04 g. of β-naphthol. After standing for one hour at room temperature 0.04 g. of solid was filtered off and identified as 1-benzoyl-2-bromobenzoyldimethylethane (II) by the melting point 121.5–123.5° and by mixture melting point. No di(bromophenyl)dimethylfuran was found.

The action of $HBr\text{-}CH_3COOH$ *on* trans *1,2-di(bromobenzoyl)dimethylethylene* (V). Nine milliliters of the hydrogen bromide-acetic acid reagent was added to 0.45 g. of the unsaturated diketone (V) and the mixture was stirred frequently for one hour at room temperature. Filtration gave 0.44 g. of product, which was crystallized from benzene and identified as 2,5-di(bromophenyl)-3,4-dimethylfuran (VII) by mixture melting point.

The reaction in the presence of β-naphthol. To 0.3 g. of *trans* di(bromobenzoyl)dimethylethylene was added 0.1 g. (approx. 1 equiv) of β-naphthol and 6 ml. of the hydrogen bromide-acetic acid reagent. After frequent stirring for one hour at room temperature the mixture was poured into water. The resulting mixture was made alkaline with sodium carbonate solution and was extracted with ether. Evaporation of the ether and leaching with 5% sodium hydroxide gave a residue weighing 0.34 g. From this product, melting at 145–162°, 2,5-di(bromophenyl)-3,4-dimethylfuran (VII) was isolated by crystallization from an ethanol-ethyl acetate mixture and was identified by mixture melting point. The aqueous layer from the ether extraction upon acidification gave 0.12 g. (78%) of α-bromo-β-naphthol which was identified by mixture melting point with a known sample.

The action of $HBr\text{-}CH_3COOH$ *on* cis *1,2-di(bromobenzoyl)dimethylethylene* (VI). A mixture of 1 ml. of the hydrogen bromide-acetic acid reagent and 0.05 g. of the unsaturated diketone was allowed to stand for one hour at room temperature. The solid phase did not disappear. Filtration gave 0.05 g. of product of melting point, 155–165°, which on crystallization from ligroin gave 0.02 g. of pure 2,5-di(bromophenyl)-3,4-dimethylfuran (VII) (identified by mixture melting point).

The reaction between HBr-CH₃COOH and trans *1,2-dibenzoylethylene (XI) in the presence of β-naphthol.* In each of three experiments the unsaturated diketone and β-naphthol were added in a weight ratio of 5:3 to 100 parts by volume of the hydrogen bromide-acetic acid reagent, and the mixtures were shaken at room tempeature. Solid dibenzoylbromoethane separated first and then gradually disappeared. Interruption of one experiment after 1.75 hours and filtering gave a mixture of starting material and the bromo saturated diketone (XII) in a combined yield of approximately 60%. Crystallization from ethyl acetate containing ethanol gave dibenzoylbromoethane in 18% yield; this was identified by a mixture melting point. From the filtrate, made alkaline and extracted with ether, was obtained a small quantity of diphenylfuran which was identified similarly. A second reaction mixture after six hours standing became a clear solution, from which an 80% yield of impure diphenylfuran was obtained by diluting the mixture with water, filtering, leaching the solid with 5% alkali, and crystallizing from methanol. The third mixture was allowed to stand for 17 hours, and upon diluting the clear reaction mixture, making alkaline, extracting thoroughly with ether, and acidifying the aqueous layer, a 71% yield of α-bromo-β-naphthol was obtained and identified by mixture melting point.

The action of HBr-CH₃COOH on 1,2-dibenzoylethane (XIII). A solution of 0.5 g. of dibenzoylethane in 10 ml. of the hydrogen bromide-acetic acid reagent was allowed to stand for 17 hours at room temperature. The solution was diluted with water and filtered to give 0.45 g. of impure diphenylfuran of melting point 83–90°. After one crystallization from methanol the melting point reached 90–92°, and the product was identified by a mixture melting point.

The action of HBr-CH₃COOH on trans *1,2-dimesitoylethylene (XV) in the presence of β-naphthol.* A mixture of 6 ml. of the hydrogen bromide-acetic acid reagent, 0.3 g. of dimesitoylethylene and 0.135 g. of β-naphthol was allowed to stand for 15 min. at room temperature. An immiscible oil formed. The mixture was diluted with water, made alkaline with sodium carbonate and extracted with ether. The ether extracts furnished a residue which was leached with cold 5% alkali and was again extracted with ether; 0.29 g. of alkali-insoluble pale yellow crystals was obtained. Recrystallization from ethanol yielded 1.65 g. of dimesitylbutanedione (XIX) of melting point 130–132°; it was identified by mixture melting point. Acidification of the aqueous solutions from the above procedure gave a 67% yield of α-bromo-β-naphthol, which was similarly identified.

Reactions with other unsaturated diketones. Conditions could not be found under which the hydrogen bromide-acetic acid reagent would give a crystalline product with *cis* 1,2-dibenzoyldimethylethylene. The reagent was without effect on *trans* 1,2-dibenzoyldibromoethylene after one hour under the usual condltions. The reagent, both with and without β-naphthol, quickly converted *trans* 1,2-dimesitoyl-1,2-dimethylethylene into an oil which has not been investigated further.

SUMMARY

Hydrogen bromide in acetic acid reacts with four 1,4-diaryl-2,3-dimethyl unsaturated 1,4-diketones. In two cases the result was essentially reduction, and in the other two the result was both reduction and bromination in the para position of a phenyl group.

The structures of the new compounds involved were demonstrated by interrelationship and by synthesis.

β-Naphthol when present in the reactions between hydrogen bromide and these four unsaturated 1,4-diketones and also in the reactions with dibenzoyl

and dimesitoylethylenes, served as a bromine acceptor; the reactions were confined to reduction (and furanization also in two cases).

A possible mechanism for the para bromination is suggested.

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