results were obtained. The product obtained in alkaline medium, mix-melted unchanged with that obtained in acid medium.

The importance of considering the medium in proposing a structure is shown again in the work done on *m*-nitrodibenzoylmethane. Bodforss[12] assigned a structure to the enol as the result of alkaline oxidation cleavage opposite to the one proposed by Barnes and Dodson[5] who worked in acidic medium.

However, in spite of the uncertainty of the mechanism of the hydroxylamine reaction with α,β-unsaturated ketones, their derivatives, and β-diketones, conclusive proof has been shown that according to its behavior toward hydroxylamine in acidic or basic media, *p*-bromodibenzoylmethane exists as both enolic modifications.

Experimental

Isoxazole of *p*-Bromodibenzoylmethane.—A solution of 5.0 g. of the enol in 75 cc. of boiling methanol was treated with 2 g. of hydroxylamine hydrochloride in 5 cc. of water. The solution was refluxed for three hours, during which time the isoxazole separated as colorless crystals. The solution was cooled and filtered. The yield was 4.3 g. The melting point after recrystallization from methanol was 174–175°.

A solution of 2.5 g. of the enol in 40 cc. of boiling methanol was treated with 1 g. of hydroxylamine hydrochloride in 5 cc. of water, followed by 2 g. of potassium hydroxide in 5 cc. of water. The solution was alkaline to litmus paper. A yield of 0.6 g. was obtained after three hours of refluxing. The product melted and mix-melted with the above described material at 174–175°. This substance melted and mix-melted identically with a 50–50 mixture of (IX) and (X).

3-*p*-Bromophenyl-5-phenylisoxazoline (VIII).—The isoxazoline was prepared from *p*-bromobenzalacetophenone according to Blatt's method.[8] The yield was 6.2 g. and after recrystallizing from methanol the melting point was 130.5–131°.

Anal. Calcd. for $C_{15}H_{12}BrNO$: C, 59.6; H, 3.9. Found: C, 59.2; H, 3.5.

3-Phenyl-5-*p*-bromophenylisoxazole (IX).—A solution of 3.4 g. of the monobromide (V) in 75 cc. of boiling methanol was treated with 1.37 g. of hydroxylamine hydrochloride in 2.5 cc. of water, followed by 3.33 g. of potassium hydroxide in 5 cc. of water. The reaction proceeds like that of the dibromide. On recrystallization from ethanol, the product melted and mix-melted at 178–179° with the other two isoxazoles obtained from (III) and (VII).

3-*p*-Bromophenyl-5-phenylisoxazole (X). A. From the Isoxazoline of *p*-Bromobenzalacetophenone.—The isoxazoline was oxidized according to the procedure described by Blatt.[8] The melting point of the isoxazole was 179–180°.

B. From the Monobromide of *p*-Bromobenzalacetophenone.—The monobromide in 75 cc. of methanol was treated as usual with 1.75 g. of hydroxylamine hydrochloride in 2.5 cc. of water and 4.25 g. of potassium hydroxide in 5 cc. of water. The isoxazole obtained melted and mix-melted with that described above at 179–181°.

Anal. Calcd. for $C_{15}H_{10}BrNO$: C, 60.0; H, 3.3. Found: C, 59.7; H, 3.5.

Summary

Herein, we have shown that according to its behavior toward hydroxylamine in acidic or basic media, *p*-bromodibenzoylmethane exists as both enolic modifications.

WASHINGTON, D. C. RECEIVED JUNE 28, 1944

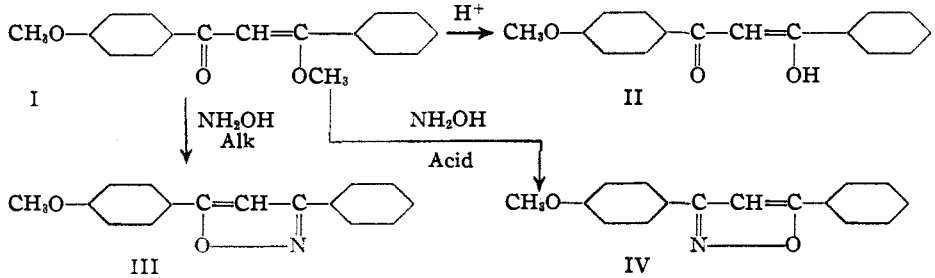
(12) Bodforss, *Ber.*, **49**, 2795 (1916).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HOWARD UNIVERSITY]

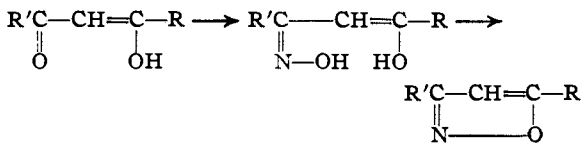
A Study of the Direction of Enolization of Mesitoyl-*m*-nitrobenzoylmethane

BY R. PERCY BARNES AND ALFRED S. SPRIGGS[1]

It has been shown[2,3,4] that isoxazole formation from enolic modifications of β-diketones is an important method for determining enolic structure. In this connection, it is interesting to note another fact regarding isoxazole formation. The conclusions of these last investigations, based on isoxazole formation, are valid only if we consider oxime formation by 1,2-addition to the carbonyl



as an intermediate process, according to the general scheme



(1) In partial fulfillment of the requirements for the Master's Degree.

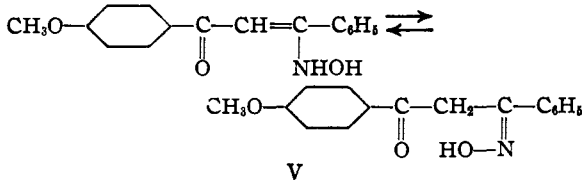
(2) Barnes and Brandon, THIS JOURNAL, **65**, 1070 (1943).

(3) Barnes and Dodson, *ibid.*, **65**, 1585 (1943).

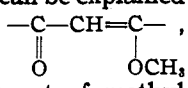
(4) Barnes and Dodson, *ibid.*, **67**, 132 (1945).

In the case of *p*-methoxydibenzoylmethane (II), whose direction of enolization has been proved,[2] the formation of an isoxazole from the methyl ether (I) gives rise to (IV) in acidic medium and to (III) in alkaline medium.[5]

In this particular case, the intermediate in the formation of (III), has been isolated,[5] and assigned the structure of an oxime (V)

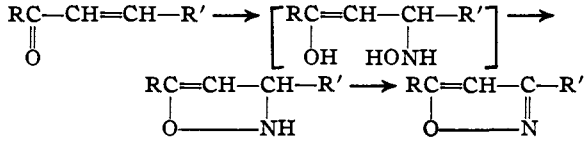


V

This oxime (V) could result in the formation of (III), by enolization and ring closure. The formation of this particular oxime can be explained only by 1,4-addition to the system,  with the intramolecular splitting out of methyl alcohol.

Thus any investigation concerning the structure of the enol as shown by isoxazole formation must take into consideration the particular reacting system and the nature of the medium in which the reaction takes place. In all of these studies, however, the fixing of the position of nitrogen in the isoxazole ring is of utmost importance.

One method of fixing the position of nitrogen in the isoxazole ring is that of isoxazoline formation,[6] and the oxidation of the isoxazoline to the isoxazole. This reaction involves the 1,4-addition of hydroxylamine to an α,β-unsaturated ketone in an alkaline medium.



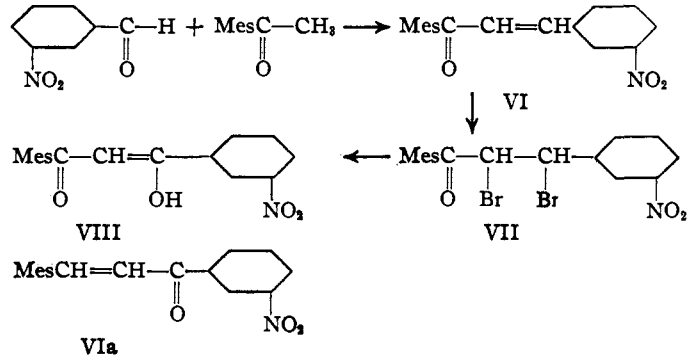
From this reaction, the structure of the isoxazole can be pointed out with some certainty. The above series of reactions of the α,β-unsaturated ketone from which the enol is derived, together with the reaction of the methyl ether of the enol, and the reaction of the enol itself can furnish rather definite evidence on the enolic form of the β-diketone.

With these facts in mind concerning the behavior and characterization of β-diketonic systems, this investigation had as its purpose the preparation and study of the previously unknown β-diketone, mesitoyl-*m*-nitrobenzoylmethane. The directive influence of the *m*-nitrophenyl group has been pointed out[8]; also, the directive and stabilizing influence of the mesityl nucleus has been shown.[7,8,9] In view of these known effects, the direction of enolization of a β-diketone containing both of these nuclei was to be ascertained.

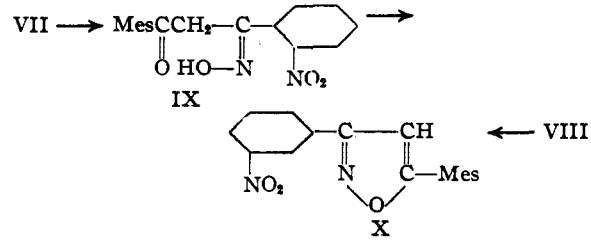
The synthesis of the α,β-unsaturated ketone, *m*-nitrobenzalacetomesitylene (VI), was effected by the condensation of *m*-nitrobenzaldehyde with acetomesitylene in the presence of sodium hydroxide. The chalcone (VI) was brominated to the dibromide (VII). The enol (VIII) was obtained from the dibromide, under the influence of potassium hydroxide.[10]

The next step in the investigation was to prepare 2,4,6-trimethylbenzal-*m*-nitroacetophenone. (VIa). Using 2,4,6-trimethylbenzaldehyde, attempts were made to condense it with *m*-nitroacetophenone. These attempts failed, always resulting in a small amount of brown colored solid which could not be purified and identified.

Not being able to synthesize (VIa), we could make no progress on the problem from this point of view. We therefore turned again to the study of (VII) and (VIII) in isoxazole formation. It will be noted that in the enol (VIII), and in the dibromide (VII), there is a mesityl nucleus adjacent to the carbonyl; therefore, it is not likely that isoxazole formation by 1,2-addition to the carbonyl will occur. By the treatment of the enol with hydroxylamine, an isoxazole (X) was obtained. By similar treatment of the dibromide with hydroxylamine, a crystalline solid (IX) melting at 88° was obtained. In view of the steric effect of the mesityl nucleus, it was thought that this compound was not an isoxazole but an intermediate in isoxazole formation. Our assumption proved true as was shown by the treatment of (IX) with hydrochloric acid to form (X).



VIa



X

(5) Weygand and Bauer, *Ann.*, **459**, 127 (1927).

(6) Blatt, THIS JOURNAL, **53**, 1133 (1931).

(7) Kohler and Blanchard, *ibid.*, **57**, 367 (1935).

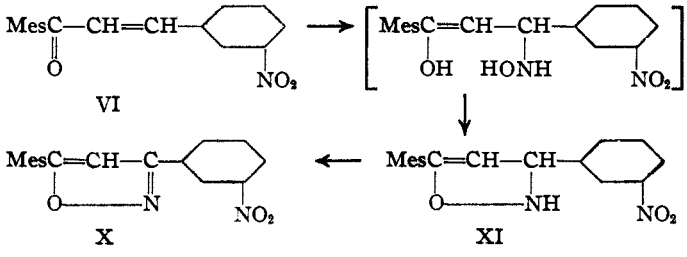
(8) Barnes, Pierce and Cochrane, *ibid.*, **62**, 1084 (1940).

(9) Barnes and Cochrane, *ibid.*, **64**, 2262 (1942).

(10) Bodforss, *Ber.*, **49**, 2795 (1916).

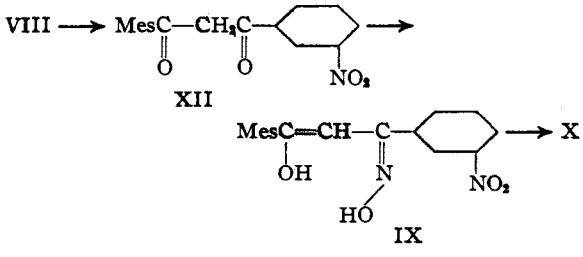
The intermediate (IX) in the formation of (X) is the oxime and the reaction to form the isoxazole is analogous to that found by Weygand and Bauer[5] in their investigation of *p*-methoxydibenzoylmethane. The oxime under the influence of acid enolizes and undergoes ring closure to form an isoxazole.

Having obtained the same isoxazole from both the enol and the dibromide, and having isolated an intermediate oxime in isoxazole formation from the dibromide, it was necessary to establish the structure of the isoxazole (X). This was done by the formation of the isoxazoline (XI) with hydroxylamine in alkaline medium. The isoxazoline (XI) was oxidized with chromic oxide in acetic acid solution and the isoxazole (X) was obtained. The reaction can be represented as follows

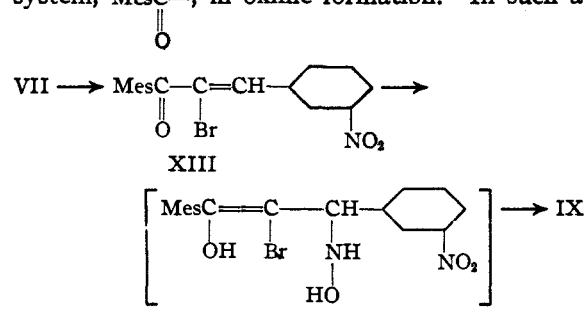


Isoxazoline formation proceeds by 1,4-addition to the conjugated system in (V) as indicated, and undergoes ring closure to form (XI). This isoxazoline was obtained as a brown oil which, after standing, began to crystallize. Either the crystals or the oil could be oxidized to (X) by chromic oxide. It was also found that on warming either the oil or the crystals with hydrochloric acid, the isoxazole (X) is formed. This phenomenon is peculiar for it involves the loss of two hydrogen atoms without employing an oxidizing agent. We must assume therefore that the oxidation is atmospheric oxidation catalyzed by the presence of the acid.

The isoxazole is therefore assigned the structure with the nitrogen attached to the carbon atom adjacent to the *m*-nitrophenyl group. Such a structure of the isoxazole, since it was also obtained from the enol (VIII), could result if (VIII) rearranged to the diketonic form (XII). This diketonic form could react with hydroxylamine and with subsequent enolization form (X).



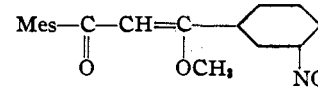
The isolation of (IX) is of interest, for it seems that the presence of both the *m*-nitrophenyl group and the mesityl group has stabilized the intermediate. The oxime, however, is not the oxime with the oximino group adjacent to the mesityl nucleus, but has the oximino group adjacent to the *m*-nitrophenyl group. This behavior is expected in view of known effects regarding the system, MesC—, in oxime formation. In such a



system oxime formation at the carbonyl does not occur. To trace the oxime formation stepwise, the monobromide (XIII) was formed from the dibromide (VII), using fused potassium acetate and acetic acid. On treatment of XIII with hydroxylamine, IX was obtained.

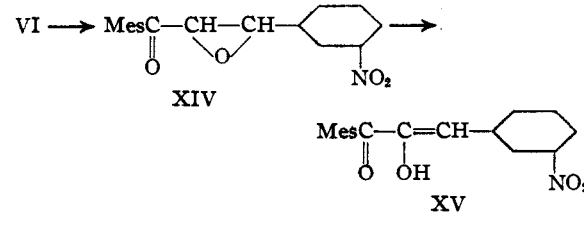
To determine the influence of the medium upon isoxazole formation, the enol was treated with hydroxylamine in alkaline medium, yielding the intermediate oxime (IX). The oxime was converted to the isoxazole on treatment with hydrochloric acid. The influence of the alkaline medium therefore was to stabilize the intermediate but not affect the nature of the isoxazole formed.

All attempts to isolate the methyl ether



as an intermediate in the preparation of the enol (VIII) from the dibromide (VII) failed because of its apparent extreme ease of hydrolysis. Thus the very nature of this substance has set limitations to this investigation.

In the course of the investigation, while attempting to establish the identity of certain substances, we had occasion to synthesize the α-diketone (XV). This was accomplished by oxidizing the α,β-unsaturated ketone (VI) to the oxide (XIV) with subsequent isomerization to (XV).



Experimental

m-Nitrobenzalacetomesitylene (VI).—To a solution containing 15 g. of *m*-nitrobenzaldehyde dissolved in 200 cc. of ethyl alcohol, was added 16.1 g. of acetylmesitylene.

The mixture was stirred and 2 g. of sodium hydroxide in 20 cc. of water was slowly poured in. The mixture was stirred with chilling. A light buff-colored solid separated at the end of an hour, and the mixture became brown. Stirring was continued for one hour more and the entire mixture chilled for an hour in the ice box. The solid was filtered, washed and dried, yielding 30 g. of crude product. On recrystallization of the solid from alcohol, bright yellow crystals melting at 98° were obtained.

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.2; H, 5.8. Found: C, 72.8; H, 5.7.

The Dibromide of *m*-Nitrobenzalacetomesitylene (VII).—Into a three-neck flask, fitted with a condenser, mercury sealed stirrer and separatory funnel, was poured 200 cc. of ether. To the ether was added 18 g. of *m*-nitrobenzalacetomesitylene. The apparatus was set up on the steam-bath and the mixture refluxed gently. Through the separatory funnel, 9.5 g. of bromine was dropped slowly into the mixture, with stirring and gentle refluxing. The bromine color was discharged as it dropped into the solution; however, when all the bromine was added, the mixture became a deep red. Stirring and refluxing were continued for half an hour. At the end of this time, a bit of solid had separated. The mixture was cooled, and a stream of air was then blown over it to evaporate the ether. After evaporation, a light yellow solid remained. This solid was washed with 30 cc. of methanol and became pure white. The solid was filtered, washed and dried, yielding 24 g. of material melting at 162–163°.

Anal. Calcd. for $C_{18}H_{17}Br_2NO_3$: C, 47.5; H, 3.8. Found: C, 47.7; H, 4.0.

Preparation of the Enol VIII.—To a refluxing solution containing 19.6 g. of the dibromide in 60 cc. of methanol was added slowly a solution of 5.4 g. of potassium hydroxide in 17 cc. of methanol. The mixture was colorless until over half the potassium hydroxide had been added, when it became orange-red in color. Refluxing was continued for one hour. The solution was then chilled and, with chilling and stirring, was acidified with dilute hydrochloric acid. A light tan solid separated. The mixture was chilled further for an hour, and was filtered, yielding 17 g. of a light tan solid. On recrystallization from ethanol, an almost colorless solid, melting at 122.5–123°, was obtained which gave a deep red coloration with alcoholic ferric chloride.

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.4; H, 5.5. Found: C, 69.0; H, 5.7.

Preparation of the Isoxazole (X): A. From the Enol (VIII).—To a hot solution of 4.2 g. of enol in 100 cc. of methanol was added 2.5 g. of hydroxylamine hydrochloride in 5 cc. of water. The mixture was refluxed for two hours. On cooling, a colorless solid separated. This solid was filtered, washed, and recrystallized from methanol to yield 3 g. of colorless crystals, melting at 118°.

B. From the Oxime (IX).—To a solution containing 0.5 g. of the oxime in 5 cc. of ethanol, 5 cc. of concentrated hydrochloric acid was added. The solution became milky, and 15 cc. more of ethanol was added. The mixture became orange-red and was refluxed for one hour on the steam-bath. On cooling, a colorless solid separated. This solid was filtered, washed and dried. On recrystallization from methanol, 0.4 g. of colorless solid melting at 118° was obtained. It mix-melted with the isoxazole prepared from the enol, without any depression.

C. By Oxidation of the Isoxazoline (XI).—To a solution containing 0.4 g. of isoxazoline in 25 cc. of acetic acid, was added 0.2 g. of chromic oxide. The mixture became green in color. This solution was heated on the steam-bath to 80° and kept at this temperature for one-half hour, with occasional stirring. The mixture was cooled and poured into 500 cc. of cold water. This aqueous mixture was extracted with ether, washed with bicarbonate and dried over sodium sulfate. On evaporation, a yellow oil resulted which crystallized from methanol as a colorless solid melting at 118°. It mix-melted with the isoxazole from the enol and the oxime at 118° with no depression.

D. By Acid Treatment of the Isoxazoline (XI).—A solution containing 0.5 g. of the isoxazoline in 20 cc. of methanol was acidified with 5 cc. of dilute hydrochloric acid. This solution was refluxed for one hour. On cooling, a very viscous brown oil resulted, which was separated by decantation, and washed several times with water. This oil crystallized from methanol as a light colored solid melting at 117–118°. It mix-melted with the isoxazole without depression.

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.1; H, 5.2. Found: C, 70.4; H, 5.3.

The Isoxazoline (XI).—To a solution of 5.9 g. of the α,β-unsaturated ketone (VI) in 50 cc. of methanol was added 2.3 g. of hydroxylamine hydrochloride in 5 cc. of water. To this solution was added slowly 4 g. of potassium hydroxide in 20 cc. of water, causing the yellow mixture to become deep brown. The solution was refluxed for two hours. On cooling, potassium chloride separated and was filtered off. The filtrate was then poured into 500 cc. of cold water, forming a red oil. The whole mixture was then extracted with ether, washed with water and dried over sodium sulfate. On evaporation, a brown oil was obtained which crystallized on standing to form a light tan solid. This solid was recrystallized from methanol, yielding 1.5 g. of light colored solid melting at 138–139°.

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.7; H, 5.9. Found: C, 69.3; H, 5.9.

Preparation of the Monobromide (XIII).—A solution containing 6 g. of dibromide, 6 g. of freshly fused potassium acetate and 50 cc. of glacial acetic acid was refluxed for three hours on a hot-plate. The mixture was cooled and poured into 500 cc. of cold water, forming a white crystalline solid. This solid was filtered, washed, and dried. Recrystallization from methanol yielded 3.5 g. of colorless crystals melting at 126.0–126.5°.

Anal. Calcd. for $C_{18}H_{17}BrNO_3$: C, 57.6; H, 4.6. Found: C, 57.3; H, 4.4.

Preparation of the Oxime (IX): A. From the Dibromide (VII).—To a suspension of 5 g. of dibromide in 100 cc. of hot ethanol, was added 2.5 g. of hydroxylamine hydrochloride in 5 cc. of water. The mixture was boiled five minutes on the steam-bath, then while still hot, 5 g. of potassium hydroxide in 5 cc. of water was slowly added. On addition of alkali, the solution became dark brown. The solution was allowed to stand for five minutes and potassium bromide separated and was filtered off. The filtrate was then chilled and slowly diluted dropwise with water and with constant swirling until the solution became cloudy. This solution was allowed to stand overnight in the ice box. A light yellow solid separated. It was filtered, washed, dried and recrystallized from ethanol yielding 0.8 g. of light yellow crystals melting at 88°.

B. From the Enol (VIII).—To a solution of 1 g. of enol in 35 cc. of hot ethanol was added 0.6 g. of hydroxylamine hydrochloride in 3 cc. of water and 0.5 g. of potassium hydroxide in 3 cc. of water. The mixture became brown and was refluxed for an hour on the steam-bath. On cooling, potassium chloride separated, but was not filtered. The solution was diluted to cloudiness with drops of water and set in the ice box overnight. A light yellow solid separated and was filtered, washed, dried and recrystallized from ethanol. The substance weighed 0.2 g. and melted at 87–88°. The mix-melt with the product from the dibromide above showed no depression.

C. From the Monobromide (XIII).—To a hot solution of 2.4 g. of monobromide in hot ethanol was added 2.4 g. of hydroxylamine hydrochloride in 3 cc. of water. To this was slowly added 3 g. of potassium hydroxide in 3 cc. of water. The solution became brown, and was refluxed for forty-five minutes. The mixture was chilled and diluted dropwise with water until it became cloudy and then placed in the ice box overnight. A light yellow solid formed which was filtered, washed, and recrystallized from methanol to give 0.8 g. of light yellow solid melting at 87–88°. It mix-melted with the above substances with no depression.

Anal. Calcd. for $C_{18}H_{16}N_2O_5$: C, 70.1; H, 5.2. Found: C, 69.9; H, 5.5.

α-*m*-Nitrophenyl-β-mesitoylethylene Oxide (XIV).—To a hot solution of 2 g. of the unsaturated ketone in 35 cc. of alcohol was added with cooling and rapid stirring 1 g. of superoxol. The solution was made alkaline by the slow addition of saturated aqueous sodium hydroxide (3 g. in 5 cc. of water) and stirring continued for thirty minutes. The solution became yellow and crystals began to form. The solution was diluted with 20 cc. of water and stirred for fifteen more minutes and then chilled. Colorless crystals which separated were filtered, washed and dried. The melting point was 115°.

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.4; H, 5.5. Found: C, 69.2; H, 5.7.

The Enol of Mesityl-*m*-nitrobenzyl Diketone (XV).—To a solution of 15 g. of the oxide in 25 cc. of methanol was added cautiously and with warming a solution of 0.9 g. of sodium hydroxide in 2 cc. of water. The solution was boiled for ten minutes. The resulting deep brown solution was chilled and acidified with dilute hydrochloric acid, yielding 1.3 g. of a colorless solid. The melting point was 144.5–145°. This compound gives a deep brown color with alcoholic ferric chloride solution.

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.4: H, 5.5. Found: C, 69.3; H. 5.7.

Summary

1. The β-diketone, mesitoyl-*m*-nitrobenzoylmethane, has been prepared, and certain chemical evidence, based on oxime, isoxazoline and isoxazole formation, given in support of its direction of enolization.

2. In connection with this work, the isomeric enolic modification of the α-diketone, mesityl-*m*-nitrobenzyldiketone, was made but not studied.

WASHINGTON, D. C. RECEIVED JUNE 28, 1944

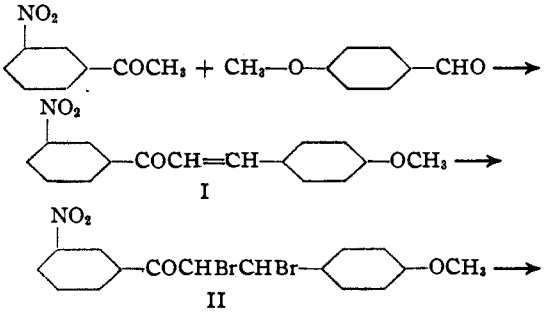
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HOWARD UNIVERSITY]

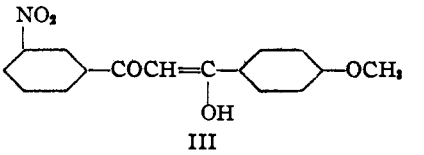
A Study of the Direction of Enolization of 3-Nitro-4′-methoxydibenzoylmethane[1]

BY R. PERCY BARNES AND JONATHAN L. SNEAD[1]

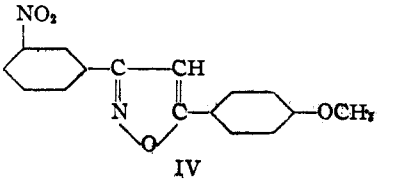
Because of the effect of the *p*-methoxy,[2] the *m*-nitro,[3] the *p*-bromo,[4] the mesityl and *m*-nitro groups[5] on the direction of enolization of β-diketones, and further in view of certain substituent effects on certain desoxybenzoins,[6] we made 3-nitro-4′-methoxydibenzoylmethane to study the combined substituent effect of these groups upon the direction and extent of enolization of this β-diketone.

To this end, we condensed *m*-nitroacetophenone with anisaldehyde, producing the α,β-unsaturated ketone (I). This compound was brominated, yielding the dibromide (II), which was refluxed with sodium methylate. The product of this reaction was acidified with hydrochloric acid, forming the enol (III).



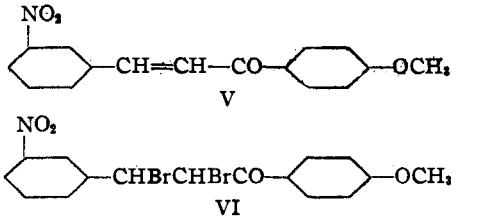


This diketone is essentially 100% enolic in methanol,[7] and upon treatment with hydroxylamine hydrochloride, yields the isoxazole (IV).



The dibromide (II) upon refluxing with hydroxylamine hydrochloride in aqueous alcoholic solution with subsequent treatment with potassium hydroxide gave rise to the isoxazole (IV).

The α,β-unsaturated ketone (V) was brominated to the dibromide (VI) which was refluxed with sodium methylate, giving a product which when acidified with hydrochloric acid also yielded the enolic modification (III).



(1) In partial fulfillment of the requirements for the degree of Master of Science; presented before the Fall Meeting of the Organic Division of the Washington, D. C., section of the American Chemical Society, October 12, 1944.

(2) Barnes and Brandon, THIS JOURNAL, **65**, 1070 (1943).

(3) Barnes and Dodson, *ibid.*, **65**, 1585 (1943).

(4) Barnes and Dodson, *ibid.*, **67**, 132 (1945).

(5) Barnes and Spriggs, *ibid.*, **67**, 134 (1945).

(6) Barnes, Cooper, Tulane and Delaney, *J. Org. Chem.*, **8**, No. 2 1943).

(7) Cooper and Barnes, *Ind. Eng. Chem.*, **10**, 379 (1938).