Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.1; H, 5.2. Found: C, 70.4; H, 5.6.

Preparation of the Isoxazole (XI′) from Enol (VII′).—To a hot solution of 1 g. of enol in 35 cc. of methanol was added 0.6 g. of hydroxylamine hydrochloride in 5 cc. of water. The mixture was refluxed for three hours. On cooling, a colorless solid separated. This solid was filtered, washed and recrystallized from methanol. It gave 0.7 g. of a material melting at 141°. A negative ferric chloride test was observed.

Preparation of the Isoxazole (XI′) by Acid Treatment of the Isoxazoline (XII).—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, very light colored crystals began falling out. The solid was filtered and recrystallized from methanol, yielding 0.2 g. of material melting at 141°. On mix-melting with the isoxazole from the enol no depression was found.

Anal. Calcd. for $C_{18}H_{16}N_2O_3$: C, 70.1; H, 5.2. Found: C, 70.3; H, 5.3.

Preparation of the Isoxazoline (XII).—To a solution containing 6 g. of the α,β-unsaturated ketone (I′) in 140 cc. of methanol was added 5 g. of hydroxylamine hydrochloride in 5 cc. of water and 4 g. of potassium hydroxide in 20 cc. of water. The potassium hydroxide solution was added slowly. The mixture turned a reddish brown. It was refluxed for two hours. Upon cooling potassium chloride fell out, but was not filtered. The mixture was then poured into 500 cc. of cold water and allowed to stand over night. The next day light tan crystals were found to have settled out. They were filtered and recrystallized from methanol, yielding 2.2 g. of a material melting at 177–178°.

Anal. Calcd. for $C_{18}H_{18}N_2O_3$: C, 69.7; H, 5.9. Found: C, 69.8; H, 5.8.

Summary

The β-diketones mesitoyl-*o*-nitrobenzoylmethane (VII) and mesitoyl-*p*-nitrobenzoylmethane (VII′) have been prepared. Chemical evidence indicates that they react preponderantly as 1-*o*-nitrophenyl-3-mesitylpropeneone-3-ol-1 (VIIa) and 1-mesityl-3-*p*-nitrophenylpropenone-3-ol-1 (VII′c), respectively, in isoxazole formation.

WASHINGTON, D. C. RECEIVED MAY 1, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HOWARD UNIVERSITY]

A Study of the Direction of Enolization of *p*-Methoxybenzoylmesitoylmethane

BY R. PERCY BARNES AND GEORGE W. REED[1]

It has long been known that the di-ortho substituents in the mesityl nucleus offer spatial interference to reactions of 1,2-addition to an adjacent carbonyl. More recently, however, it has been shown that the presence of certain groups in the mesityl nucleus or the phenyl group of benzils serves to activate the hindered carbonyl to the extent that such substances undergo quinoxaline formation.[2] It has also been reported that the presence of a nitro group in the para position of the phenyl ring of benzoylmesitoylmethane serves to enhance the activity of the hindered carbonyl, so much so that enolization occurs toward the mesityl nucleus.[3]

The purpose of this investigation was to determine the effect of the *p*-methoxy group on the direction of enolization of *p*-methoxybenzoylmesitoylmethane.

Thus we prepared chalcone (II) and converted it and its isomer, *p*-methoxybenzalacetomesitylene[4] (I), into their dibromides (III) and (IVa) and (IVb). The dibromides (IVa) and (IVb) derived from the chalcone (II) melted at 105 and 152°, respectively, and behaved alike chemically.

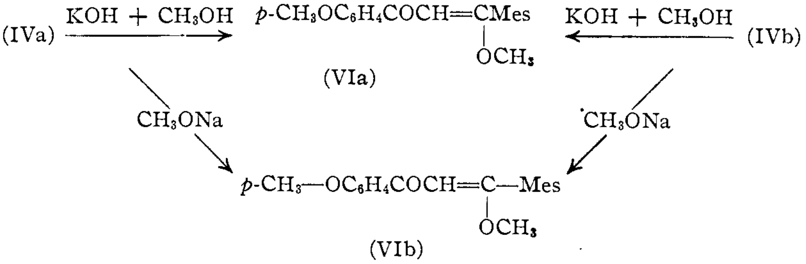
$$\underset{\text{I}}{p\text{-CH}_3\text{—OC}_6\text{H}_4\text{CH}{=}\text{CHCOMes}} \longrightarrow \underset{\text{III}}{p\text{-CH}_3\text{—OC}_6\text{H}_4\text{CHBrCHBrCOMes}}$$

$$p\text{-CH}_3\text{—OC}_6\text{H}_4\text{—COCH}_3 + \text{MesCHO} \longrightarrow \underset{\text{II}}{p\text{-CH}_3\text{—OC}_6\text{H}_4\text{COCH}{=}\text{CHMes}} \longrightarrow \underset{\text{IVa and IVb}}{p\text{-CH}_3\text{OC}_6\text{H}_4\text{COCHBrCHBr Mes}}$$

The dibromide (III) was easily converted into the α-bromo-unsaturated ketone (V).

$$(\text{III}) \longrightarrow \underset{\text{V}}{p\text{-CH}_3\text{—O—C}_6\text{H}_4\text{CH}{=}\text{CBrCOMes}}$$

Neither (III) nor (V) gave rise to a stable methyl ether. On the other hand, neither of the isomeric dibromides (IVa) and (IVb) yielded a monobromide. Dibromides (IVa) and (IVb) under one set of conditions yield (VIa); under a different set of conditions they yield (VIb).



$$(\text{IVa}) \xrightarrow{\text{KOH + CH}_3\text{OH}} \underset{\text{(VIa)}}{p\text{-CH}_3\text{OC}_6\text{H}_4\text{COCH}{=}\underset{\text{OCH}_3}{\text{C}}\text{Mes}} \xleftarrow{\text{KOH + CH}_3\text{OH}} (\text{IVb})$$

$$(\text{IVa}) \xrightarrow{\text{CH}_3\text{ONa}} \underset{\text{(VIb)}}{p\text{-CH}_3\text{—OC}_6\text{H}_4\text{COCH}{=}\underset{\text{OCH}_3}{\text{C}}\text{—Mes}} \xleftarrow{\text{CH}_3\text{ONa}} (\text{IVb})$$

Both the dibromide (III) and the monobromide (V) upon treatment with methyl alcoholic potassium hydroxide gave the enol (VII). The methyl ether (VIa) was hydrolyzed with difficulty to the

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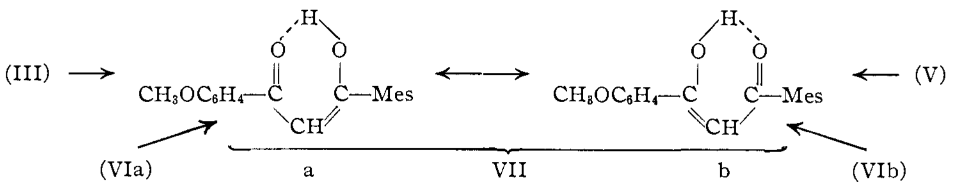
[1] In partial fulfillment of the requirements for the Master's Degree.

[2] Reynold C. Fuson and Quentin F. Soper, *J. Org. Chem.*, **9**, 193 (1944).

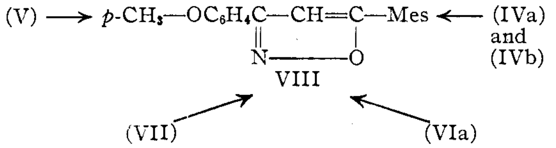
[3] R. Percy Barnes, Gladys Estelle Pinkney and William A. DaCosta, THIS JOURNAL, **69**, 3129 (1947).

[4] R. Percy Barnes and Harold Delaney, *ibid.*, **65**, 2155 (1943).



enol (VII), whereas (VIb) was hydrolyzed with ease.

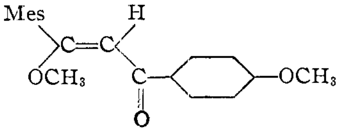
Dibromide (III) when subjected to such treatment as would be expected to yield an isoxazole was recovered unchanged. This may be attributed to the highly hindered carbonyl group. On the other hand, the monobromide (V) which also has a highly hindered carbonyl conjugated with an ethylenic group, and the dibromides (IVa) and (IVb) yield the same isoxazole (VIII) as does the enol (VII).



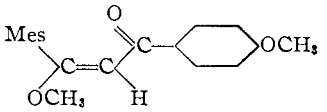
It seems obvious, therefore, that the isoxazole formation from the monobromide (V) goes by way of 1,4-addition to the conjugated system, while that involving the dibromide (IVa) and (IVb) goes by way of 1,2-addition to the unhindered carbonyls.

Very significantly, the methyl ether (VIb), which hydrolyzes easily to the enol, does not react with hydroxylamine to give an isoxazole; whereas the methyl ether (VIa), which hydrolyzes with difficulty, reacts readily, yielding the osaxazole (VIII). This reaction must therefore go by way of 1,2-addition to the carbonyl.

On the basis of the behavior of the methyl ethers (VIa) and (VIb), and on the basis of the Fisher–Hirschfelder models for configurational geometric isomers of these substances, it seems likely that these isomers may be represented as



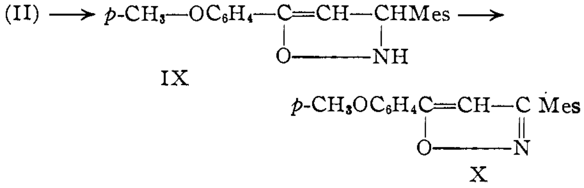
VIa



VIb

In 1926, Charles Dufraisse and Alfred Gillet[5] reported stable geometric ethyl ethers of dibenzoylmethane.

The chalcone (I) does not react with hydroxylamine to produce an isoxazoline. The chalcone (II) reacts smoothly, yielding the isoxazoline (IX), which is readily oxidized to the isoxazole (X). The fact that chalcone oximes are not converted to isoxazolines under the same conditions that chalcones produce isoxazolines excludes the possibility of 1,2-addition of hydroxylamine and favors 1,4-addition. Thus the position of the nitrogen in the isoxazoline (IX) ring and the isoxazole (X) ring seems well established.



Experimental

2,4,6-Trimethylbenzal-*p*-methoxyacetophenone (II).—To a solution of 19.7 g. of *p*-methoxyacetophenone in 100 cc. of methanol was added an equal amount (19.7 g.) of mesityl aldehyde followed by 5.2 g. of sodium hydroxide in 12 cc. of water. The solution was warmed and stirred on the steam cone for one and a half hours. An oil formed and at the time limit water was added slowly to the mixture until the volume was nearly doubled. The steam was cut off and the stirring continued while the mixture cooled. The material crystallized in lumps. A 93% crude yield was obtained which on recrystallization with methanol melted at 90°.

Anal. Calcd. for $C_{19}H_{20}O_2$; C, 81.4; H, 7.1. Found: C, 81.6; H, 7.4.

Dibromo-*p*-methoxybenzalacetomesitylene (III).—A solution of 5.72 g. of bromine in carbon disulfide was added to a solution of 10 g. of the unsaturated ketone (I) in 100 cc. of carbon disulfide. The solution was stirred during the addition. The solvent was removed with a stream of air and the solid remaining was taken up in hot methanol, filtered, washed with cold methanol and dried. The crude yield of 14.8 g. was recrystallized from methanol and gave a product melting at 153.5–154.5°.

Anal. Calcd. for $C_{19}C_{20}O_2Br_2$: C, 51.8; H, 4.5. Found: C, 51.7; H, 4.5.

Dibromo-2,4,6-trimethylbenzal-*p*-methoxyacetophenone (IVa and (IVb).—To 15 g. of 2,4,6-trimethylbenzalacetophenone (II) in 100 cc. of carbon disulfide was added with stirring 8.57 g. of bromine. The solvent was removed as described, and the residue dissolved in hot methanol and recovered as white crystals on chilling. The first crystals to fall out were filtered and dried. We shall refer to this material as (IVa). Another batch came out on further concentration (IVb). The less soluble substance (IVa), obtained in the smaller yield, 2.3 g., melted at 152°. The more soluble (IVb), 8.0 g., melted when pure at 105°.

Anal. Calcd. for $C_{19}G_{20}O_2Br_2$: C, 51.8; H, 4.5, Found: (A) C, 51.6; H, 4.5; (B) C, 51.6; H, 4.8.

α-Bromo-*p*-methoxybenzylacetomesitylene (V).—A. To 5 g. of the dibromide (III) in 25 cc. of glacial acetic acid was added 3.5 g. of potassium acetate, and the mixture was refluxed gently one-half an hour. When cool, it was poured into a large volume of water and a light yellow oil settled out. The water was poured off and the oil taken up in methyl alcohol from which it was crystal-

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[5] Charles Dufraisse and Alfred Gillet, *Compt. rend.*, **183**, 746 (1926).

lized. The yield was 4 g. and the pure material melted at 87.5°.

B. Five grams of the dibromide (III) dissolved in methanol was refluxed for one hour with 1.5 g. of potassium hydroxide in 5 cc. of methanol. On chilling, a colorless precipitate separated. The precipitate was filtered, washed with cold methanol, with water, and finally with cold methanol and dried. The yield was 3 g. Crystallization from methanol gave a pure substance melting at 87.5° and mix-melting unchanged with the above substance.

Anal. Calcd. for $C_{19}H_{19}O_2Br$: C, 63.5; H, 5.3. Found: C, 63.8; H, 5.6.

The Methyl Ether (VIa).—Five grams of each of the two dibromides (IVa) and (IVb) were dissolved separately in 40 cc. of methanol with refluxing. To each solution was added 1.5 g. of potassium hydroxide dissolved in 5 cc. of methanol, and the solutions were refluxed for fifteen minutes. On cooling, needle-like crystals separated. After recrystallization, 1 g. of colorless needles, melting at 91°, was obtained in each case.

Anal. Calcd. for $C_{20}H_{22}O_3$: C, 77.4; H, 7.1. Found: C, 77.4; H, 7.3.

The Methyl Ether (VIb).—Two grams of each of the dibromides (IVa) and (IVb) were dissolved in 25 cc. of methanol. To the solutions was added 0.6 g. of sodium dissolved in 20 cc. of methanol. The solutions were refluxed for one hour, and then poured into large volumes of water. Needle-like crystals separated. On filtering and recrystallizing from methanol, long silken needles, melting at 102° were obtained.

Anal. Calcd. for $C_{20}H_{22}O_3$; C, 77.4; H, 7.1. Found: C, 77.4; H, 7.3.

***p*-Methoxybenzoylmesitoylmethane (VII). A. From the Dibromide (III).**—A suspension of 22 g. of the dibromide (III) in 75 cc. of methanol was refluxed for half an hour with 5 g. of potassium hydroxide dissolved in 25 cc. of methanol. The dibromide dissolved and the solution turned red. The solution was acidified with dilute hydrochloric acid and refluxed for thirty minutes. The solution became pale yellow. On chilling, an oil separated which slowly crystallized yielding 12 g. of an almost colorless solid. On recrystallizing from methanol a colorless solid, melting at 105°, was obtained.

B. **From the Dibromide (IVa) and (IVb).**—Five grams of each of the dibromides (IVa) and (UVb) were separately suspended in 25 cc. of methanol and refluxed for thirty minutes with 1.5 g. of potassium hydroxide dissolved in 5 cc. of methanol. Dilute hydrochloric acid was added to the hot solutions until they were acidic. The solutions were refluxed for four hours and then chilled. Colorless solids separated. Upon filtering and recrystallizing the substances melted and mix-melted at 105° with that from (A).

C. **From the Monobromide (V).**—One gram of the monobromide (V) was dissolved in 20 cc. of methanol and refluxed for thirty minutes with 0.5 g. of potassium hydroxide dissolved in 5 cc. of methanol. The solution was acidified with dilute hydrochloric acid and refluxed for thirty minutes. Upon cooling, a colorless solid, melting and mix-melting at 105° was obtained.

D. **From the Methyl Ethers (VIa) and (VIb).**—Solutions of 0.5 g. of each of the ethers in 20 cc. of methanol were refluxed with 5 cc. of concentrated hydrochloric acid. Ether (VIb) was completely hydrolyzed in thirty minutes; ether (VIa) was hydrolyzed only after four hours of refluxing. Each solution deposited colorless crystals, melting and mix-melting at 105°. The enol is 100% enolic in methanol.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.0; H, 7.1. Found: C, 77.3; H, 7.1.

3-*p*-Methoxyphenyl-5-mesitylisoxazole (VIII). A. From the Dibromide (IVa) and (IVb).—Five grams of each of the dibromides (IVa) and (IVb) were treated in hot methanol with 1.75 g. of hydroxylamine hydrochloride in 2.5 cc. of water. While hot, the solutions were treated with 4.25 g. of potassium hydroxide in 5 cc. of water. The solutions became red and a white precipitate formed. The precipitate was filtered and washed with water and then with alcohol. There was obtained in each case 1.5 g. of material which, after several recrystallizations from methanol, melted at 149°.

The isomeric dibromide (III) was recovered unchanged after an identical treatment.

B. **From the Monobromide (V).**—One gram of the monobromide was refluxed for half an hour in 25 cc. of methanol with 0.7 g. of hydroxylamine hydrochloride and 0.6 g. of potassium hydroxide in a minimum of water. The solution was concentrated and chilled, whereupon white crystals fell out. These, on recrystallization, melted and mix-melted unchanged with the above material from (A).

C. **From the Diketone (VII).**—To two grams of the diketone in 40 cc. of methanol was added 2 g. of hydroxylamine hydrochloride in 5 cc. of water and a few cc. of concentrated hydrochloric acid. The solution was refluxed two hours, cooled, chilled, filtered and the precipitate recrystallized from methanol. Repeated recrystallizations gave a material identical with that from (A) and (B).

The reaction was also run in alkaline medium by treating the material with hydroxylamine hydrochloride in an excess of potassium hydroxide. The identical isoxazole was obtained.

D. **From the Methyl Ether (VIa).**—A solution of 0.7 g. of the ether (VIa) in 20 cc. of methanol was refluxed for one and one-half hours with 0.25 g. of hydroxylamine hydrochloride dissolved in 2 cc. of water and 1.0 g. of potassium hydroxide in 5 cc. of water. The colorless solution turned yellow. On cooling, a crystalline solid separated. Recrystallized from methanol, the colorless solid melted at 149° and mix-melted unchanged with the substances from (A), (B) and (C).

Anal. Calcd. for $C_{19}H_{19}O_2N$: C, 77.8; H, 6.5. Found: C, 77.6; H, 6.4.

The methyl ether (VIb) upon identical treatment was recovered unchanged.

3-Mesityl-5-*p*-methoxyphenylisoxazoline (IX).—A solution of 1.5 g. of the chalcone (II) in 20 cc. of methanol was refluxed for one hour with 0.5 g. of hydroxylamine hydrochloride dissolved in 2 cc. of water and 1 g. of potassium hydroxide in 2 cc. of water. The solution turned orange colored. Upon chilling a heavy precipitate separated. It was filtered, washed, dried and recrystallized from methanol. It melted at 131.5–132°. The yield was 0.9 g. of colorless material.

Anal. Calcd. for $C_{19}H_{21}O_2N$: C, 77.3; H, 7.1. Found: C, 77.0; H, 7.0.

The isomeric chalcone, *p*-methoxybenzalacetomesitylene, did not yield an isoxazoline.

3-Mesityl-5-*p*-methoxyphenylisoxazole (X).—To 0.5 g. of the isoxazoline (IX) dissolved in 25 cc. of acetic acid at 80° was added 0.3 g. of red chromic anhydride. The solution turned green. The temperature was maintained at 80° for forty-five minutes. It was then poured into 200 cc. of cold water. The aqueous solution was extracted with ether. The acetic acid was shaken out of the ethereal solution with sodium bicarbonate solution. The ether was evaporated, and the residual oil taken up in methanol. A colorless substance crystallized from the solution. The recrystallized material melted at 141.5–142.5°. It mix-melted at 145–146° with the isomeric isoxazole.

Anal. Calcd. for $C_{19}H_{19}O_2N$: C, 77.8; H, 6.5. Found: C, 77.3; H, 6.8.

Summary

1. By two different series of reactions, we have made the β-diketone, *p*-methoxybenzoylmesitoylmethane, which is 100% enolic in methanol solution.

2. We have shown that it reacts toward hydroxylamine as 1-mesityl-3-*p*-methoxyphenylpropenone-3-ol-1 (VIIa), since it gives rise to an isoxazole (VIII) which is isomeric with the isoxazole

(X) in which the position of the nitrogen is established by the fact that isoxazolines are not formed by way of the 1,2-addition reaction to the carbonyl of chalcones.

3. We have reported isomeric ethers (VIa) and (VIb) which react differently and probably are geometric isomers.

WASHINGTON, D. C. RECEIVED MAY 1, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, HOWARD UNIVERSITY, WASHINGTON 1, D. C.]

A Study of the Direction of Enolization of *p*-Methoxy-*p*'-bromodibenzoylmethane and *p*-Methoxy-*p*'-ethoxydibenzoylmethane

BY R. PERCY BARNES, THOMAS C. GOODWIN, JR.,[1] AND THOMAS W. COTTEN, JR.[1]

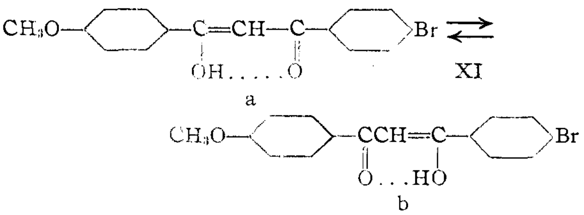
In a previous report to THIS JOURNAL[2] we have discussed enolization of β-diketone. In continuation of this investigation we have made chalcones (I), (II), (V) and (VI), and converted them to their respective dibromides (III), (IV), (VII) and (VIII). The dibromides (III) and (IV) were smoothly converted to the completely enolic diketone (XI); the dibromides (VII) and (VIII) were converted to the 100% enolic substance (XII).

The dibromides (VII) and (VIII) also gave rise to the α-bromochalcones (IX) and (X), respectively.

$$p\text{-}CH_3OC_6H_4CHO + CH_3COC_6H_4Br\text{-}p \longrightarrow p\text{-}CH_3\text{—}OC_6H_4CH{=}CHCOC_6H_4Br\text{-}p \quad \text{I}$$

$$p\text{-}BrC_6H_4CHO + CH_3COC_6H_4OCH_3\text{-}p \longrightarrow p\text{-}CH_3OC_6H_4COCH{=}CHC_6H_4Br\text{-}p \quad \text{II}$$

$$\text{(I)} \longrightarrow p\text{-}CH_3OC_6H_4CHBrCHBrCOC_6H_4Br\text{-}p \longrightarrow \quad \text{III}$$



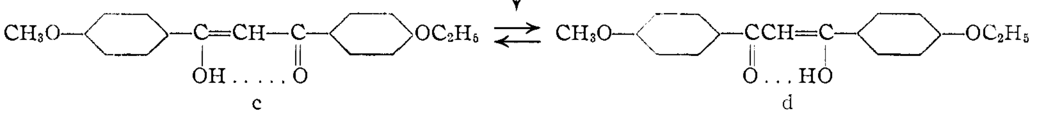
$$\text{(II)} \longrightarrow pCH_3OC_6H_4COCHBrCHBrC_6H_4Br\text{-}p \longrightarrow \text{XI} \quad \text{IV}$$

$$p\text{-}CH_3OC_6H_4CHO + CH_3COC_6H_4OC_2H_5\text{-}p \longrightarrow p\text{-}CH_3OC_6H_4CH{=}CHCOC_6H_4OC_2H_5\text{-}p \quad \text{V}$$

$$p\text{-}C_2H_5OC_6H_4CHO + CH_3COC_6H_4OCH_3\text{-}p \longrightarrow p\text{-}CH_3OC_6H_4COCH{=}CHC_6H_4OC_2H_5\text{-}p \quad \text{VI}$$

$$p\text{-}CH_3OC_6H_4CH{=}CBrCOC_6H_4OC_2H_5\text{-}p \quad \text{IX}$$

$$\text{(V)} \longrightarrow p\text{-}CH_3OC_6H_4CHBrCHBrCOC_6H_4OC_2H_5\text{-}p \quad \text{VII}$$



$$\text{(VI)} \longrightarrow p\text{-}CH_3OC_6H_4COCHBrCHBrC_6H_4OC_2H_5\text{-}p \longrightarrow \text{XII} \quad \text{VIII}$$

$$\text{VIII} \longrightarrow p\text{-}CH_3OC_6H_4COCBr{=}CHC_6H_4OC_2H_5\text{-}p \quad \text{X}$$

It is agreed that β-diketones which are enolic involve resonance, and that differences in the terminal groups influence both the equilibrium and the reaction rate of the resonating forms. In the case of the enol (XII), in which the terminal groups, anisyl and phenetyl, are only slightly different, one would predict that the equilibrium concentrations of the two isomers (c) and (d) and their reaction rates, would not be far different. The same prediction might be made in reference to enol (XI), but possibly with less accuracy, since the inductive effect of —Br is large.

Dipole Moments[3]	$\text{—}OCH_3$	1.16
	$\text{—}OC_2H_5$	1.00
	—Br	1.51

These predictions are borne out remarkably, for each enol (XI) and (XII) gives rise to a mixture of isoxazoles which undoubtedly arise from the resonating forms (XIa) ⇄ (XIb) and (XIIc) ⇄ (XIId). There isn't the slightest doubt as to the non-identity of the isomeric isoxazoles, because of the manner in which each has been prepared.[4]

The chalcones (I) and (II) yield the respective isoxazolines (XIII) and (XIV), which are oxi-

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

(2) R. Percy Barnes and George W. Reed, Jr., THIS JOURNAL, **69**, 3132 (1947).

(3) W. J. Svirbely and J. C. Warner, *ibid.*, **57**, 655 (1935).

(4) A. H. Blatt, *ibid.*, **53**, 1133 (1931).