Summary

The synthesis and antispasmotic properties of twenty-one esters are described. Variation of the acid portion of these esters to include unsaturated and partially saturated derivatives of naphthalene, indene, 9-alkylfluorene, anthracene, xanthene, thioxanthene, acridine and phenanthrene in some instances causes pronounced changes in pharmacological properties.

Of this series, β-diethylaminoethyl xanthene-9-carboxylate appears to possess the greatest activity against spasm induced by acetylcholine, while the corresponding ester of 9,10-dihydroanthracene-9-carboxylic acid is the most effective against histamine.

CHICAGO, ILLINOIS RECEIVED MARCH 18, 1943

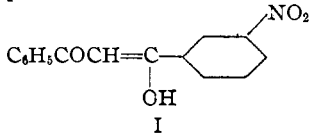
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, HOWARD UNIVERSITY]

The Properties of *m*-Nitrodibenzoylmethane

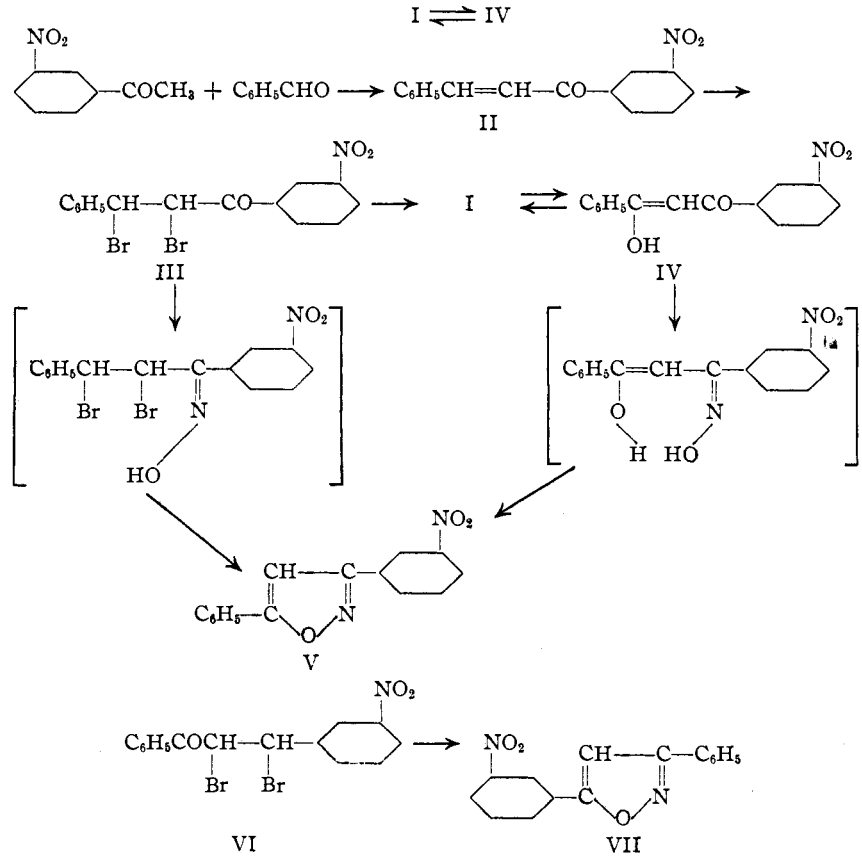
BY R. PERCY BARNES AND LOUIS B. DODSON[1]

In a recent communication[2] we established the fact that *p*-methoxydibenzoylmethane reacts as 1-phenyl-3-*p*-methoxyphenylpropene-one-3-ol-1 in isoxazole formation. Because of the effect of the nitro group on the acetylation of desoxybenzoins,[3] we decided to test the behavior of *m*-nitrodibenzoylmethane in isoxazole and pyrazole formation.

By starting with the dibromide of *m*-nitrobenzalacetophenone (VI), Bodforss[4] prepared *m*-nitrodibenzoylmethane and showed that on permanganate oxidation in alkaline medium it gives *m*-nitrobenzoic and phenylglyoxylic acids, thus establishing that under these conditions *m*-nitrodibenzoylmethane behaves as *m*-nitro-α-oxy-benzalacetophenone (I).



I



II III IV V VI VII

We have condensed *m*-nitroacetophenone with benzaldehyde producing benzal-*m*-nitroacetophenone (II). This substance was brominated to the corresponding dibromo compound (III), which was refluxed with sodium methylate and hydrochloric acid in turn, giving rise to a pale yellow enolic substance, melting and mix-melting identically with the enol as prepared by Bodforss.

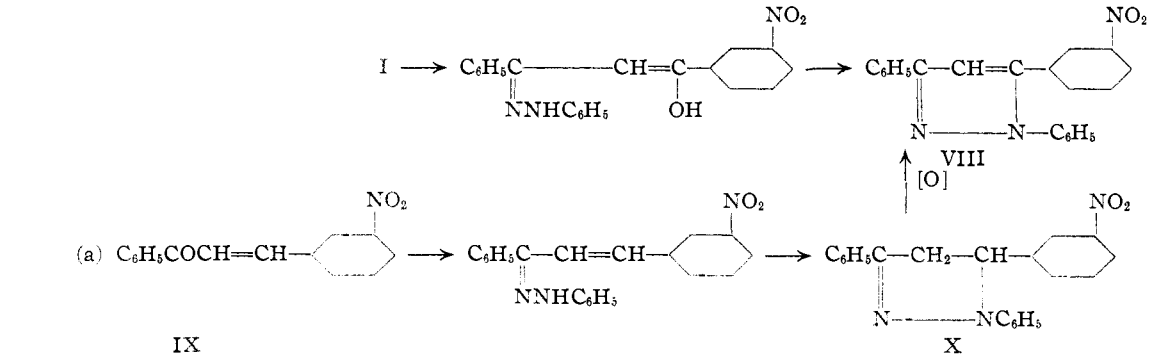
m-Nitrodibenzoylmethane gives rise to an

(1) Candidate for the Master's Degree.

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

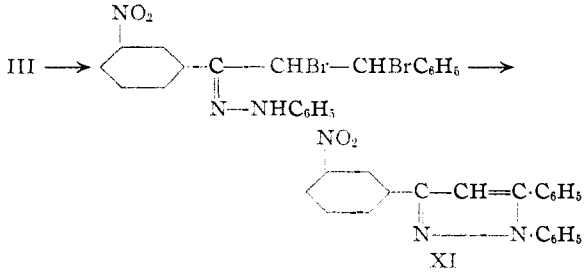
(3) R. P. Barnes, S. R. Cooper, Victor J. Tulane and Harold Delaney, *J. Org. Chem.*, **8**, 153 (1943).

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



isoxazole (V), which is identical in every respect with that obtained from (III). On the other hand, however, the dibromide (VI) produces an isomeric isoxazole (VII). Thus it seems that Bodforss' oxidation products and the isoxazole (V) arise, respectively, from the extreme forms of the resonating hybrid.

The behavior of hydroxylamine toward the dibromo compounds and the enolic modification



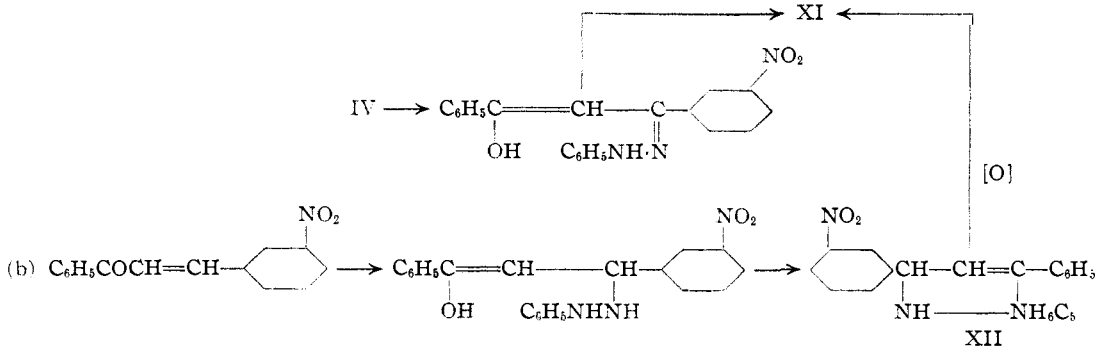
of *m*-nitrodibenzoylmethane must thus inevitably involve 1,2-addition to the carbonyl, with subsequent loss of water to give the oxime which undergoes ring closure.

Furthermore Bodforss[4] interprets pyrazole formation as taking place by way of 1,2-addition of phenylhydrazine to the enol (I) and to *m*-nitrobenzalacetophenone (IX) with subsequent loss of water producing the respective phenylhydrazones which undergo ring closure, producing the pyrazole (VIII) and the pyrazoline (X) which pyrazoline is oxidized to (VIII).

The authors of this paper believe that a different mode of interpretation represents the facts better, giving rise to different but isomeric formulas for both the pyrazole and pyrazoline.

Thus from phenylhydrazine and dibromobenzal-*m*-nitroacetophenone (III) we have made the pyrazole (XI) which is identical with that reported by Bodforss. It thus appears that the structures (I) and (VIII) assigned by Bodforss to the enol and pyrazole, respectively, are incorrect and should be substituted by (IV) and (XI), respectively.

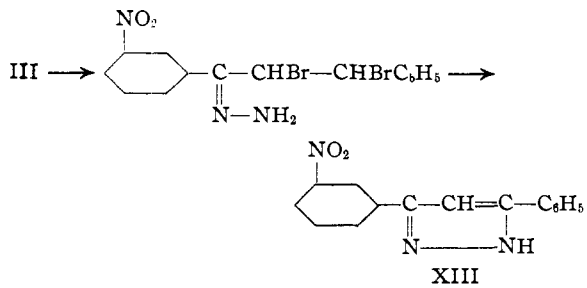
It is also apparent that the pyrazoline (X) interpreted as resulting according to scheme (a) by way of a 1,2-addition, since it is oxidizable to the pyrazole, must result by way of a 1,4-addi-



tion reaction (b), giving the pyrazoline the structure (XIII).

Finally dibromobenzal - *m* - nitroacetophenone (III) was treated with hydrazine hydrate in methyl alcoholic solution, with subsequent addition of aqueous potassium hydroxide, whereupon a pyrazole identical with that described as 3-phenyl-5-*m*-nitrophenyl pyrazole, obtained from the enolic modification of the diketone, resulted. Thus here also according to the manner of forma-

tion, this pyrazole must be 3-*m*-nitrophenyl-5-phenylpyrazole (XIII)



XIII

Experimental

Benzal-*m*-nitroacetophenone (II).—A mixture of 10 g. of *m*-nitroacetophenone and 7 g. of benzaldehyde was dissolved in 400 cc. of methanol, and to this solution, with stirring, was added slowly an aqueous solution of 2.6 g. of sodium hydroxide in 20 cc. of water. The solution developed a red color and a light colored solid began to separate. After stirring for two hours, it was chilled, filtered, washed with cold methanol, water and finally cold methanol. The product was 9 g. of a cream-colored solid, melting at 125–127° on crystallization from methanol.

Anal. Calcd. for $C_{15}H_{11}O_3N$: C, 71.1; H, 4.3. Found: C, 71.3; H, 4.7.

Benzal-*m*-nitroacetophenone Dibromide (III).—To a solution of 6 g. of benzal-*m*-nitroacetophenone in 75 cc. of chloroform was added dropwise, with stirring, a solution of 4 g. of bromine in 10 cc. of chloroform. On evaporation, 7.2 g. (72% of the theoretical) of buff-colored solid was obtained. Recrystallization from methanol yields an almost colorless solid melting at 162–162.3°.

Anal. Calcd. for $C_{15}H_{11}O_3Br_2N$: C, 43.6; H, 2.7. Found: C, 43.8; H, 3.0.

1-Phenyl-3-*m*-nitrophenylpropene-one-3-ol-1 (IV).—To a solution of 2 g. of sodium in 40 cc. of methanol was added 9.5 g. of the dibromide in solution in 100 cc. of methanol. After refluxing for one hour, the solution was chilled and the potassium bromide filtered off. The filtrate was acidified with hydrochloric acid and refluxed for one hour. On cooling, it was poured into water, extracted with ether, washed with sodium bicarbonate solution, washed with water and finally dried over anhydrous sodium sulfate. On evaporation and solution in methanol, it crystallized as a yellow solid, melting at 131–134°.

This enol was also prepared by Bodforss' method[4] by treating the dibromide (III) with alcoholic potassium hydroxide, with subsequent acidification and refluxing with hydrochloric acid.

The product obtained by both of these methods was the same as that obtained by Bodforss as indicated by melting point and mix-melting point with a sample prepared according to his directions.

3-Phenyl-5-*m*-nitrophenylisoxazole (V).—Five grams of the dibromide (III) was dissolved in boiling ethanol and treated with 1.75 g. of hydroxylamine hydrochloride in solution in 2.5 cc. of water. While hot, this solution was treated with 4.25 g. of potassium hydroxide in 5 cc. of water. The solution became red, potassium bromide separated. It was allowed to stand for five minutes and filtered. On cooling, the filtrate yielded cream-colored crystals, which upon recrystallization from ethanol melted at 169.5–170°.

Five grams of the enol (IV) in solution in 100 cc. of methanol was heated for thirty minutes with 2 g. of hydroxylamine hydrochloride in 5 cc. of water. On cooling, a cream-colored solid separated which, upon recrystallization from ethanol, melted and mix-melted at 169.5–170° with the above-described material.

Anal. Calcd. for $C_{15}H_{10}O_3N_2$: C, 67.6; H, 3.8. Found: C, 67.6; H, 3.9.

3-*m*-Nitrophenyl-5-phenylisoxazole (VII).—Five grams of the dibromide (VI) was treated identically as (III) above. It behaved similarly. Upon crystallization, there was obtained an almost colorless solid, melting at 180°. This substance mix-melted with the isoxazole (V) at 172–175°.

Anal. Calcd. for $C_{15}H_{10}O_3N_2$: C, 67.6; H, 3.8. Found: C, 67.4; H, 4.0.

1,5-Diphenyl-3-*m*-nitrophenylpyrazole (XI).—Three grams of the dibromide (III) was suspended in 100 cc. of methanol. To this suspension was added 3 g. of phenylhydrazine, and the mixture was warmed. In one hour the dibromide had dissolved and the solution was deep yellow. The solution was rendered alkaline with 2 g. of potassium hydroxide in 10 cc. of water and warmed. The solution became red and, on cooling, potassium bromide separated. The reaction mixture was poured into water and extracted with ether. The ethereal solution was washed with water, with dilute hydrochloric acid and with water, and dried over anhydrous calcium chloride. It was filtered and evaporated, yielding a yellow oil. The oil was taken up in methanol from which it crystallized in yellow needles. The crude yield was 1 g. On repeated recrystallizations from methanol, it resulted as cream-colored needles, melting at 131°, and mix-melting the same with a sample prepared according to Bodforss' method from the enolic modification of the diketone.

3-*m*-Nitrophenyl-5-phenylpyrazole (XIII).—Five grams of the dibromide (III) was suspended in 100 cc. of hot methanol and treated with 3 g. of 85% hydrazine hydrate. Gradually the solution became yellow, and the dibromide dissolved. The solution was made alkaline with 4 g. of potassium hydroxide dissolved in 10 cc. of water. On cooling potassium bromide separated. The solution was concentrated by evaporation, poured into water, extracted with ether, washed with water, washed with dilute hydrochloric acid and dried over anhydrous calcium chloride. The resulting yellow solution was concentrated, and an almost colorless solid began to separate. On chilling a yield of 2 g. of crude pale yellow crystals was obtained. Recrystallization from methanol yielded an almost colorless product which melted and mix-melted at 206° with a sample prepared according to Bodforss from the enolic modification of the diketone.

The effect, therefore, of both the *p*-methoxy group[2] and the *m*-nitro group in dibenzoylmethane is to promote enolization in the direction which is away from the substituted nucleus.

Summary

We have shown:

1. That *m*-nitrodibenzoylmethane is obtained by way of a different series of reactions.

2. That *m*-nitrodibenzoylmethane reacts toward hydroxylamine, phenylhydrazine and hydrazine as 1-phenyl-3-*m*-nitrophenylpropene-one-3-ol-1, giving rise to 3-phenyl-5-*m*-nitrophenylisoxazole (V), 1,5-diphenyl-3-*m*-nitrophenylpyrazole (XI) and 3-*m*-nitrophenyl-5-phenylpyrazole (XIII), respectively.

3. That phenylhydrazine reacts by way of 1,4-addition to *m*-nitrobenzalacetophenone to yield 1,5 - diphenyl - 3 - *m* - nitrophenylpyrazoline (XII).

WASHINGTON, D. C. RECEIVED MAY 10, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

Azoyl Derivatives of Sugars and Separation by Chromatographic Adsorption.[1] II

BY GEORGE H. COLEMAN AND CHESTER M. MCCLOSKEY[2]

In a previous paper[3] it was shown that the azoyl derivatives of monosaccharides could be separated from azoyl derivatives of disaccharides and trisaccharides by means of chromatographic adsorption. A ketohexose azoate, β-D-fructose tetraazoate, was separated from each of several aldohexose azoates. This type of separation had been reported previously by Reich.[4] It was also shown that in certain cases disaccharides could be partially separated.

The chromatograhic adsorption technique has been further developed and the separation of two closely related compounds, α-D-galactose pentaazoate and β-D-galactose pentaazoate, carried out. β-D-Glucose pentaazoate has been separated from both α-D-xylose tetraazoate and β-L-arabinose tetraazoate. No separation was obtained with the azoates of the enantiomorphs, β-D-arabinose and β-L-arabinose.

The method also has been applied to azoyl derivatives of methyl glycosides and to azoyl derivatives of partially acetylated sugars. The separation of methyl heptaazoyl-β-D-cellobioside and methyl tetraazoyl-α-D-glucoside was accomplished, and an unusually sharp separation made with 1-azoyltetraacetyl-β-D-glucose and 1-azoyl-heptaacetyl-β-D-cellobiose. The separation of azoates of the methyl glycosides was not as clean cut under the conditions used as was that of the 1-azoylacetyl sugars. The preparation and use of the latter type of derivative was undertaken with the thought of working with a derivative in which the original sugar represented a higher percentage of the molecular weight.

The chromatographic technique has been applied to the separation of a mixture of more than two sugar derivatives. A mixture of β-L-arabinose, β-D-glucose, α,α-trehalose and β-cellobiose azoates has been separated. The purity of each band is difficult to estimate on the basis of optical rotation in such a case. Several generalizations have been noted which lead us to believe that a purity of at least 90% for each compound has been obtained. In working with a mixture of two derivatives only, it was observed that the lowest band usually leaves a small amount of material behind which contaminates the higher band. Thus the principal contamination of a given band comes from the bands below. The amount of contamination decreases as the distance between the bands is increased. The higher bands are in such a case apt to be more highly contaminated than the lower.

The separation of the four azoates was made on one column. It is probable, however, that in instances where several derivatives are present the most efficient method of separation is to develop the chromatogram until it is separated into groups such as monosaccharides, disaccharides, etc., which separate quickly and then isolate each group and develop it separately. This permits maximum development for slower moving bands, diminishes contamination from previous bands and diminishes the effect of faults in the column.

In the previous work a mixture of equal volumes of commercial chloroform, benzene and ligroin was used to develop the chromatogram. It was found that if alcohol-free chloroform was used

(1) Presented at the 105th Meeting of the American Chemical Society, Division of Sugar Chemistry and Technology, April, 1943.

(2) Research Fellow of the Corn Products Refining Company.

(3) I, THIS JOURNAL, **64**, 1501 (1942).

(4) Reich, *Biochem. J.*, **33**, 1000 (1939).