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DERIVATIVES OF 1-(3-METHOXY-4-ACETOXYPHENYL)-
2,6-DICARBETHOXY-CYCLOHEXANEDIONE-3,5

BY

SISTER M. ADRIENNE ADRIAN, S.S.N.D.

A THESIS

Submitted to the Faculty of the Graduate School of The Creighton University in Partial Fulfillment of the Requirements for the Degree of Master of Sciences in the Department of Chemistry.

Omaha, Nebraska - August, 1949
INTRODUCTION

Papadakis\(^1\) has synthesized the following substances:

1-(p-Acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedione-3,5 (I),
4-Hydroxphenyl-cyclohexanedione-3,5 (II), 1-(p-Acetoxyphenyl)-
2,6-dicarbethoxy-4-carbethoxymethyl-cyclohexanedione-3,5 (III),
which are good starting materials for the further synthesis of
substitutes for cardiac glycosides (IV) and hormones\(^2\) because
they have the necessary functional groups in proper locations.
Papadakis and Scigliano have also synthesized 1-(3-Methoxy-4-acetoxyphenyl)-2,6-dicarbethoxy-cyclohexane-dione-3,5 (VII). They reacted vanillin with diethyl malonate to form Ethyl-(3-Methoxy-4-hydroxy)-benzalmononate (V). (V) was acetylated to form Ethyl-(3-Methoxy-4-acetoxy)-benzal-malonate (VI). (VI) was reacted with acetoacetic ester and sodium ethoxide to give (VII). The object of this investigation is to prepare derivatives of (VII) which may be of physiological importance. In this research the preparation of a dye and a sulfone gives a beginning to further research in the two fields of dyes and sulfones. It is known that some dyes are of pharmaceutical as well as industrial importance, such as prontosil. Lately sulfones have attracted more attention since 4,4'-diaminodiphenylsulfone has been shown to have effect against tuberculosis and leprosy.

Wislicenus5 had prepared the phenyldiazonium compound of 1,3-Indanedione, and Vorlander and Erig4 have prepared the diazonium compound of 1-phenyl-cyclohexanedione-3,5. The diazonium compound of 5,5-dimethyl-1,3-cyclohexanedione has also been formed by Balkrishna H. Iyer.5 Balkrishna H. Iyer coupled methone with tetrazoniumbenzidine. Since structure (VII) is a 1,3-dione as the compounds mentioned above, it seems reasonable that diazonium compounds could be coupled with substance (VII). In this work the tetrazonium derivative of benzidine was coupled with two molecules of compound (VII) as shown in Flow Sheet II. Bis-[1-(3-Methoxy-4-acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedione-3,5]-p,p'-tetraazobenzidine (VIII) was formed which is described in the experimental part. (The name of the compound is tentative.)
Flow Sheet I

Vanillin + Diethyl Malonate → Pyridine → (V)

(V)

Acetic Anhydride → (VI)

(VI)

(VII)

Acetic Anhydride + NaOR + C_{2}H_{5}COOC_{2}H_{5} → (VII)
Flow Sheet II

4-Sulfonamido-2',4'-diaminoazobenzene

2-Phenylhydrazone-indanedione-1,3

4-Phenylhydrazone-1-phenyl-cyclohexanedione-3,5

Bis-(5,5-Dimethyl-cyclohexanedione-1,3)-tetrazoniumbenzidine
Flow Sheet II
(cont.)

Benzidine + Benzidenediazonium chloride

\[
\text{NH}_2 \begin{array}{c}
\text{Cl-N-N-} \\
\end{array} \begin{array}{c}
\text{N=N-Cl} \\
\end{array}
\text{NH}_2
\]

\[
\text{NaNO}_2 + \text{HCl}
\]

(VII) +

(VIII)

\[
\begin{array}{c}
\text{CH}_3\text{C}-\text{O} \\
\end{array}
\begin{array}{c}
\text{OCH}_3 \\
\end{array}
\begin{array}{c}
\text{O} \\
\end{array}
\begin{array}{c}
\text{C}_2\text{H}_5\text{O}-\text{C} \\
\end{array}
\begin{array}{c}
\text{H} \\
\end{array}
\begin{array}{c}
\text{H} \\
\end{array}
\begin{array}{c}
\text{H} \\
\end{array}
\begin{array}{c}
\text{H} \\
\end{array}
\begin{array}{c}
\text{=O} \\
\end{array}
\begin{array}{c}
\text{C}_2\text{H}_5 \\
\end{array}
\begin{array}{c}
\text{O} \\
\end{array}
\begin{array}{c}
\text{C}_2\text{H}_5\text{O}-\text{C} \\
\end{array}
\begin{array}{c}
\text{C} \text{-O-C}_2\text{H}_5 \\
\end{array}
\begin{array}{c}
\text{H} \\
\end{array}
\begin{array}{c}
\text{H} \\
\end{array}
\begin{array}{c}
\text{H} \\
\end{array}
\begin{array}{c}
\text{=O} \\
\end{array}
\begin{array}{c}
\text{C}_2\text{H}_5 \\
\end{array}
\begin{array}{c}
\text{O} \\
\end{array}
\begin{array}{c}
\text{OCH}_3 \\
\end{array}
\begin{array}{c}
\text{O} \\
\end{array}
\begin{array}{c}
\text{C}_2\text{H}_5\text{O}-\text{C} \\
\end{array}
\begin{array}{c}
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\text{H} \\
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\begin{array}{c}
\text{H} \\
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\begin{array}{c}
\text{H} \\
\end{array}
\begin{array}{c}
\text{=O} \\
\end{array}
\begin{array}{c}
\text{C}_2\text{H}_5 \\
\end{array}
\begin{array}{c}
\text{O} \\
\end{array}
\begin{array}{c}
\text{OCH}_3 \\
\end{array}
\begin{array}{c}
\text{O} \\
\end{array}
\begin{array}{c}
\text{C}_2\text{H}_5\text{O}-\text{C} \\
\end{array}
\begin{array}{c}
\text{H} \\
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\text{H} \\
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\begin{array}{c}
\text{H} \\
\end{array}
\begin{array}{c}
\text{=O} \\
\end{array}
\begin{array}{c}
\text{C}_2\text{H}_5 \\
\end{array}
\begin{array}{c}
\text{O} \\
\end{array}
\begin{array}{c}
\text{OCH}_3 \\
\end{array}
\begin{array}{c}
\text{O} \\
\end{array}
\begin{array}{c}
\text{C}_2\text{H}_5\text{O}-\text{C} \\
\end{array}
\begin{array}{c}
\text{H} \\
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\end{array}
\begin{array}{c}
\text{H} \\
\end{array}
\begin{array}{c}
\text{=O} \\
\end{array}
\begin{array}{c}
\text{C}_2\text{H}_5 \\
\end{array}
\begin{array}{c}
\text{O} \\
\end{array}
\begin{array}{c}
\text{OCH}_3 \\
\end{array}
\begin{array}{c}
\text{O} \\
\end{array}
\begin{array}{c}
\text{C}_2\text{H}_5\text{O}-\text{C} \\
\end{array}\]
An attempt has been made to synthesize structure (IX) by reacting sulfuryl chloride with Product (VII) in the presence of pyridine, as shown in the following Flow Sheet.
EXPERIMENTAL

Structures (V), (VI), and (VII) were prepared according to the method of Papadakis and Scigliano as follows:

Ethyl-(3-methoxy-4-hydroxy)-benzalmalonate (V)

Vanillin was reacted with diethyl malonate and piperidene for four hours under a reflux condenser on a water bath. It was permitted to stand over night in the ice box. Red crystals settled out. The crystals were purified with absolute alcohol, m.p. 108-110.

Ethyl-(3-methoxy-4-acetoxy)-benzalmalonate (VI)

Product (V) was acetylated with acetic anhydride and refluxed in an oil bath for seven hours. It was allowed to stand over night in the ice box, and needle-like crystals settled out. They were recrystallized from absolute alcohol, m.p. 67-68.

1-(5-methoxy-4-acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedi-one-3,5 (VII) Acetoacetic ester and sodiumethoxide were allowed to react in anhydrous ether until the reaction was complete. Then (VI) was added to the flask containing the previous reaction, and was allowed to reflux on a water bath from four to five hours. After this the ether was distilled off, and the reaction mixture was dried by heating. Water was then added to dissolve the mixture. The unreacted parts were filtered off. To the filtrate was added cold hydrochloric acid drop by drop until the crystals were brought down. The crystals were recrystallized from ethyl alcohol, m. p. 157-157 1/2.
Diazonium compound of (VII), (VIII) Benzidine was reacted with sodium nitrite and hydrochloric acid at 0° to form benzidine diazonium chloride, and this was added to an alkaline solution of (VII). The temperature was maintained at 0° during the entire reaction. After the reaction was complete, the crystals failed to precipitate, so hydrochloric acid was added to bring down crystals. The crystals were a reddish brown in color. The melting point was too high to be determined under existing conditions.

Anal. Calcd. for C_{46}H_{49}N_{4}O_{16}  
C, 60.45; H, 5.40

Found  
C, 60.71; H, 5.55

Sulfone Derivative of (VII), (IX) Two moles of (VII) were dissolved in pyridine and reacted with one mole of sulfuryl chloride drop by drop under anhydrous conditions. The temperature was kept at 0° for approximately four hours. After that the reaction was allowed to stand at room temperature for about the same time. Then the mixture was refluxed in an oil bath for about seven hours, keeping the temperature at 130-135°. The resulting solution was poured into ice water. A heavy red liquid settled out. It was slightly soluble in ether but soluble in alcohol. It was, therefore, dissolved in alcohol, but no crystals were obtained. So the heavy red liquid was put into water and a few drops of dilute sodium hydroxide were added. The material dissolved immediately. When a few drops of dilute hydrochloric acid were added, cream to white crystals settled out. The melting point was between 70-80°. It was expected to be much higher. Further research will be necessary on this problem.
SUMMARY

1. Papadakis's work on intermediate compounds for substitutes of cardiac glycosides was reviewed.

2. Papadakis and Scigliano's preparation of 1-(3-methoxy-4-acetoxyphenyl)-2,6-dicarbetheyxycyclohexanedione-3,5 was used for the further preparation of

   a. Reaction of benzidinehydrazonium hydrochloride with (VII).

   b. An attempt to react sulfuryl chloride with (VII) to form the sulfone derivative.
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