Evidence In Favor of the Ketone Structure
of 1-(p-Acetoxyphenyl)-2,6-Dicarbethoxy-
Cyclohexanedicarboxylic Acid

By

Mary Petrikin Landrie B.S.

A Thesis

Submitted to the Faculty of The Creighton
University in Partial Fulfillment
of the Requirements for the
Degree of Master of Science in the Department of Chemistry

Omaha, Nebraska - 1948
Evidence in Favor of the Ketone Structure of 1-(p-Acetoxyphenyl)-2,6-Dicarbethoxy-Cyclohexanedione-3,5

Mary Petrikin Landrie B.S.
1948
Thesis Approved

By

P. E. Papadakis

C. L. Kenny

Major Advisor

Dean

Henry H. Creager, S. J.
To

Mother and Dad
I wish to express my sincere appreciation to Dr. Phillippos E. Papadakis for the advice and kindness he gave me during the work on my thesis.
Introduction

Much work in the purification, extraction and therapeutic standardization of cardiac glycosides has been brought together by Fieser and Strain. This has lead to the proof of the structure and essential functional groups of these substances.

Simpler substances having the same functional important groups of the naturally occurring cardiac glycosides have been the object of much investigation in recent years. Papadakis has prepared 1-(p-acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanecarbonyl-3,5 as an intermediate product for the preparation of a substitute for digitalis glycosides. From the method he used, it was evident that the compound should have Structure I as given below.

However, he has not made, up to the present time derivatives which would prove the presence of the ketonic group in this structure.

Because of the importance of this substance as an intermediate and the important role the carbonyl groups play in activating the hydrogen's of the fourth carbon in ring "B", which are necessary for further synthesis, the present work
was undertaken. Emile Fisher first introduced the use of phenylhydrazine in 1884. He used it to make derivatives of aldehydes and ketones, called hydrazones which serve to characterize such substances. It is also a well known fact that he applied this reagent to aldoses and ketoses thereby preparing osazones.

The present author prepared 1-(p-acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanедione-3,5 by Papadakis method, which involves the equations and reactions shown on the flow sheet. All the intermediate products, as well as the final check in physical properties as compared with the results of Papadakis. This product is insoluble in water and has a melting point of 207 degrees.

In the preparation of the new product with which the author is concerned, one mole of 1-(p-acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanедione-3,5 and three moles of phenylhydrazine were mixed and refluxed in 95% ethyl alcohol. The product has a melting point of 105 degrees and is insoluble in water.

In the experimental part of this paper there will be a complete account of all the steps involved in this present thesis. In such a way can a clear picture be had of all the steps leading up to the preparation of the product formed by the addition of the phenylhydrazine to 1-(p-acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanедione-3,5.
Experimental

The method followed for the preparation of 1-(p-acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedione-3,5 is given below.

1. p-ACETOXYBENZALDEHYDE

p-Hydroxybenzaldehyde in dry pyridine was acetylated in acetic anhydride at zero degrees. The reaction mixture was allowed to stand at room temperature for two days; then it was shaken with ice water in a separatory funnel. The separated oily material was washed three times with fresh portions of cold water; finally it was distilled after being dried with Calcium Chloride. Boiling Point. 266-268 degrees.

2. ETHYL 4-ACETOXYBENZALMALONATE

p-Acetoxybenzaldehyde, diethyl malonate and acetic anhydride were mixed and saturated with hydrogen chloride gas at zero degrees. The reaction mixture was allowed to stand for eight days. After this, dry air was passed through the solution for six hours. Then it was distilled under ordinary pressures up to 210 degrees; the remainder was fractionated off under reduced pressure into a receiver cooled with dry ice and acetone mixture. The distillate at 176 degrees and 0.6 mm. (bath temperature) consisted of a viscous liquid and shiny platelike crystals. The latter were filtered off with suction, washed with
ether and recrystallized from alcohol. Melting point 67-68 degrees.

3. 1-(p-ACETOXYPHENYL)-2,6-DICARBETHOXY-CYCLOHEXANEDIONE-3,5

Equimolar parts of ethyl 4-acetoxybenzalmalonate, ethyl acetoacetate and sodium ethoxide in absolute alcohol were refluxed for an hour and then allowed to stand at room temperature for several days. A crystalline precipitate formed which was soluble in water, giving a solution alkaline to litmus. The crystalline material treated with a water solution of acetic acid gave a yellowish precipitate. The latter was dissolved in boiling ethyl acetate, bone blacked, filtered and cooled in the refrigerator. The crystals formed were filtered off and recrystallized from absolute alcohol. Melting point 209-210 degrees.

4. PHENYL DERIVATIVE OF 1-(p-ACETOXYPHENYL)-2,6-DICARBETHOXY-CYCLOHEXANEDIONE-3,5

A portion of 1-(p-acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedione-3,5 was dissolved in 95% ethyl alcohol with phenylhydrazine hydrochloride and sodium acetate. There was a ratio of three moles of phenylhydrazine for one mole of 1-(p-acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedione-3,5. This was refluxed for an hour after which time a small amount of water was added and red crystals formed. Melting point 105 degrees. It was insoluble in water.

Anal. Calculated for; Carbon 67.34
Found   "  67.77
Calculated for; Hydrogen 6.00
Found   "  5.67
5. IODINE DERIVATIVE OF 1-(p-ACETOXYPHENYL)-2,6-DICARBETHOXY-
Cyclohexanedione-3,5

One mole of 1-(p-acetoxyphenyl)-2,6-dicarbethoxy-cyclohexan-
dione-3,5 and one mole of sodium ethoxide were refluxed in absolute alcohol, for an hour. After this, all the al-
cohol was driven off and Iodine was added in an ether solution. One-half mole of Iodine was used. This was re-
fluxed for a period of four hours. Yellowish crystals were formed but a melting point was not determined. This work has had to be abandoned for the present time.
Summary

All products that have been prepared have been explained in the experimental part of this report. The preparation of Acetoxybenzaldehyde; Ethyl 4-acetoxybenzalmalonate and 1-(p-acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedione-3,5 have been checked and the results coincide with those obtained by Papadakis.

The reaction of the phenylhydrazine with 1-(p-acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedione-3,5 proves the presence of the ketonic group which has not been shown up to this time.

An attempt was made to unite two moles of 1-(p-acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedione-3,5 with two moles of sodium ethoxide and one mole of Iodine. Unfortunately this work has not been completed at this time.
Flow Sheet

p-Hydroxybenzaldehyde + Acetic Anhydride → p-Acetoxybenzaldehyde

p-Hydroxybenzaldehyde + Acetic Anhydride + Diethyl Malonate → Ethyl 4-acetoxybenzalmalonate

p-Hydroxybenzaldehyde + Sodium Ethoxide + Acetoacetic Ester → 1-(p-Acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedione-3,5
Phenyl Derivative of 1-(p-acetoxyphenyl)-2,6-dicarbethoxy-cyclohexanedione-3,5
References

3. Elderfield and Co-Workers
   (7) 362, 374, 383, 444, (1942)
   (8) 29 (1943)
4. Fieser and Fieser Organic Chemistry Pages 219, 351