A THESIS

Entitled

STOBBE CONDENSATION

On

1-and 2- Acetylnaphthalene

Presented by

SOHAIR SHAWKY SALEH

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University College for Girls
Ain-Shams University
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NOTE

Besides the work carried out in this thesis the candidate has attended post-graduate course for two years in organic chemistry including the following topics :

1- Reaction mechanisms.

2- Electronic, Infrared, Raman and n.m.r. Spectroscopy of organic molecules.

3- Instrumentation and instrumental analysis.

4- Electronic theories of organic chemistry and Stereochemistry.

She has successfuly passed an examination in these topics.

Prof. Dr. W.I. Awad
Head of Chemistry Department,
University College for Girls,
Ain-Shams University.

بسم الله الرحمن الرحيم

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CONTANTS

SUMMARY

The Stobbe condensation of 1-acetylnaphthalene with dimethyl methylsuccinate yields a stereoisomeric mixture of *cis*- and *trans*-(Ar/COOCH$_3$)-3-methoxycarbonyl-2-methyl-4-(1'-naphthyl)-pent-3-enoic acids (CVII) and (CVIII).

The predominance of the *trans*-(Ar/COOCH$_3$)-half-ester (CVIII) was inferred from the cyclisation of the stereoisomeric mixture to methyl 1-acetoxy-2,4-dimethylphenanthrene-3-carboxylate (CIX). Alkaline hydrolysis of this acetoxy ester gives the phenolic acid (CX) which is methylated to the methoxy ester (CXI), then hydrolysed to the methoxy acid (CXII).

The stereoisomeric mixture of half-esters (CVII) and (CVIII) gives, upon saponification, predominantly the *trans*-(Ar/COOH)-3-carboxy-2-methyl-4-(1'-naphthyl)-pent-3-enoic acid (CXIX), which is converted with acetyl chloride to the corresponding anhydride (CXX).

The condensation of 2-acetylnaphthalene with dimethyl methylsuccinate gives *cis*- and *trans*-(Ar/COOCH$_3$)-3-methoxycarbonyl-2-methyl-4-(2'-naphthyl)-pent-3-enoic acids (CXIII) and (CXIV). Cyclisation of the pure

trans-($Ar/COOCH_3$)-half-ester (CXIV) gives methyl-4-acetoxy-1,3-dimethylphenanthrene-2-carboxylate (CXV). The acetoxy ester (CXV) gives upon saponification the phenolic acid (CXVI), which on methylation yields the methoxy ester (CXVII), which is then hydrolysed to the methoxy acid (CXVIII).

Saponification of the pure *trans*-($Ar/COOCH_3$)-half-ester (CXIV) leads to the formation of the *trans*-($Ar/COOH$)-3-carboxy-2-methyl-4-(2'-naphthyl)-pent-3-enoic acid (CXXI). Whereas, the alkaline hydrolysis of the stereoisomeric mixture of *cis*- and *trans*-($Ar/COOCH_3$)-half-esters (CXIII) and (CXIV) gives a mixture of *cis*- and *trans*-($Ar/COOH$)- dibasic acids, where the *trans*-($Ar/COOH$)-isomer (CXXI) is the predominant one.

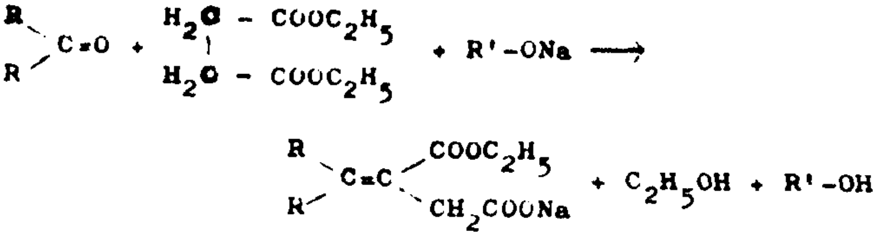
The *trans*-($Ar/COOH$)-dibasic acid (CXXI) gives with acetyl chloride the corresponding anhydride (CXXII).

INTRODUCTION

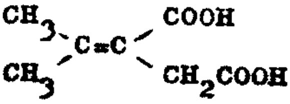
THE STOBBE CONDENSATION

I- GENERAL SURVEY OF THE STOBBE CONDENSATION

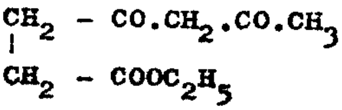
The condensation of aldehydes and ketones with an ester of succinic acid, under the influence of sodium alkoxides to give the corresponding alkylidene succinic acid (a substituted itaconic acid), or isomers formed by a tautomeric shift of hydrogen, is known as the stobbe condensation.[1] The primary product of the reaction is the salt of the half-ester as shown in the following :



H.Stobbe[1] noticed that acetone condenses with dialkyl succinate in the presence of sodium ethoxide to give teraconic acid (I) as the main reaction product. It was rather surprising that the reaction proceeded by an aldol-type of condensation between the carbonyl group of the ketone and the methylene group of the ester, and not by the expected claisen-type of condensation to give β-diketo compounds such as (II) or (III).

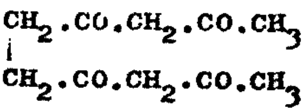


(I)



$$\begin{array}{l} CH_2 - CO.CH_2.CO.CH_3 \\ | \\ CH_2 - COOC_2H_5 \end{array}$$

(II)



$$\begin{array}{l} CH_2.CO.CH_2.CO.CH_3 \\ | \\ CH_2.CO.CH_2.CO.CH_3 \end{array}$$

(III)

Stobbe and his collaborators, after tedious trials, were able to generalise this type of condensation between carbonyl compounds and esters of the succinic acid.

Factors Affecting the Stobbe Condensation

The wide scope of the Stobbe Condensation is illustrated by the large variety of reaction components briefly outlined below :

1- Carbonyl compounds, these include :

(i) Aliphatic, aromatic and α,β-unsaturated aldehydes.

(ii) Aliphatic, alicyclic, and aromatic ketones.

(iii) Diketones.

(iv) Keto-esters.

(v) Cyanoketones.

2- Succinic esters : The nature of the carbalkoxy group may be varied, thus, diethyl, dimethyl, and di-tert-butyl succinate have been used.

α -Substituted aryl-, aralkyl-, alkyl-, as well as alkylidene succinic esters have also been employed in the Stobbe Condensation.

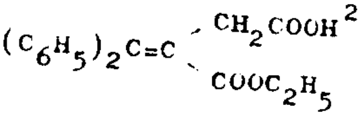
3- Condensing agents: Various basic reagents, such as sodium ethoxide, potassium tert.-butoxide, and sodium hydride have been employed. Other condensing agents such as sodium methoxide, metallic sodium, potassium ethoxide, and sodium triphenyl methyl have also been used though to a limited extent.

II- MECHANISM OF THE REACTION

Stobbe and his collaborators showed that the simplest interpretation that may be thought of concerning the mechanism of this reaction is to assume a preliminary condensation between the carbonyl compound and an active methylene group of the succinic ester with the elimination of water. The latter could then react with the added alkoxide to form the hydroxide ion which could effect partial hydrolysis of the first formed diester.

Such a mechanism was, however, rejected because of the following reasons :

1) It was observed that the Stobbe condensation is limited (with few exceptions) to succinic and substituted succinic esters. Thus, whereas benzophenone condensed readily with diethyl succinate to give an excellent yield of the arylidene succinic half-ester, it failed to react with ethyl or tert.butyl acetate[3], both of which contain active methylene groups. An even more striking observation, is the failure of benzophenone to condense with diethyl malonate[3], which has a very reactive methylene group.



$$(C_6H_5)_2C{=}C\begin{matrix} \diagup CH_2COOH \\ \diagdown COOC_2H_5 \end{matrix}$$

2

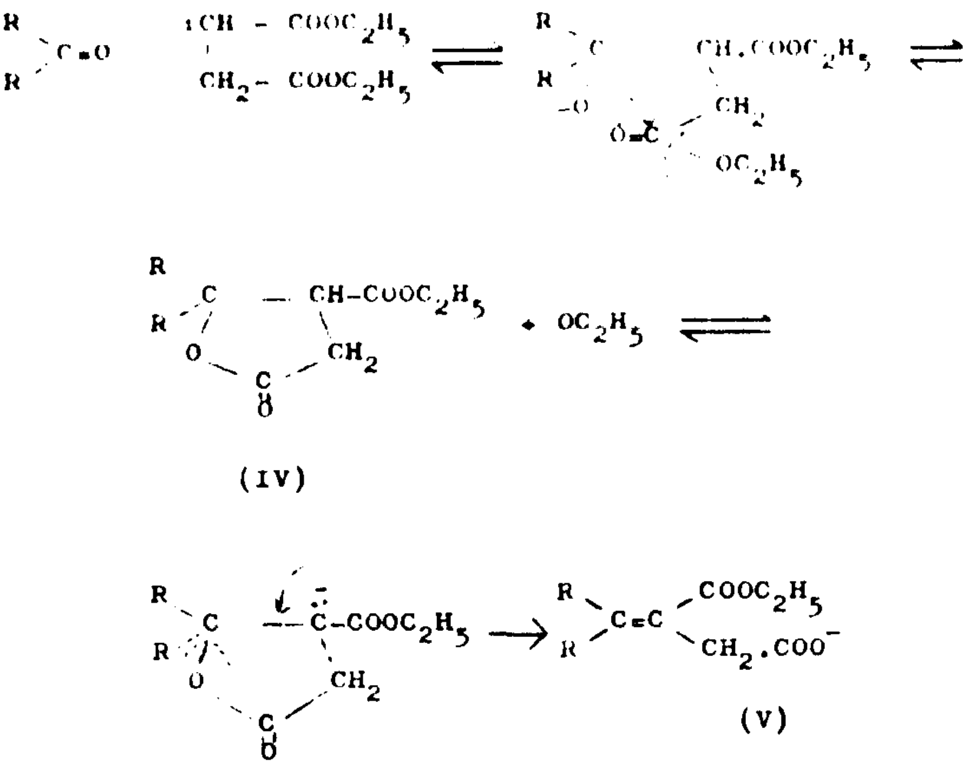
It was, therefore, concluded that the reactivity of the methylene groups of succinic esters is not the only factor responsible for the occurrance of the Stobbe condensation.

2) The intermediate unsaturated di-esters postulated in the above mechanism have never been isolated even when the experimental conditions were rendered most favourable for their separation. One way of attempting this isolation was the use of a large excess of diethylsuccinate[4] in order to provide a high concentration of competing ester groups which could consume most of the hydrolysing action of the limited amount of the hydroxide ion whose formation is assumed in the proposed mechanism.

3) Appropriate unsaturated di-esters failed to give good yield of half-esters on partial saponification.[5,6]

4) Isomers of the citraconic and mesoconic acid type, which are expected tautomers of certain alkylidenesuccinic di-esters,[7] have never been obtained from the Stobbe condensation.

Johnson *et al*,[3] put forward an acceptable mechanism which involves the initial addition of the carbanion derived from succinic ester to the carbonyl group of the second reaction component. This is followed by a cyclisation step leading to the formation of an intermediate paraconic ester (IV) which could be subsequently cleaved by alkoxide ion to the salt of the unsaturated half-ester as shown in the following reaction sequence. The irreversibility of the last step is the determining factor which drives the reaction to completion.



(IV)

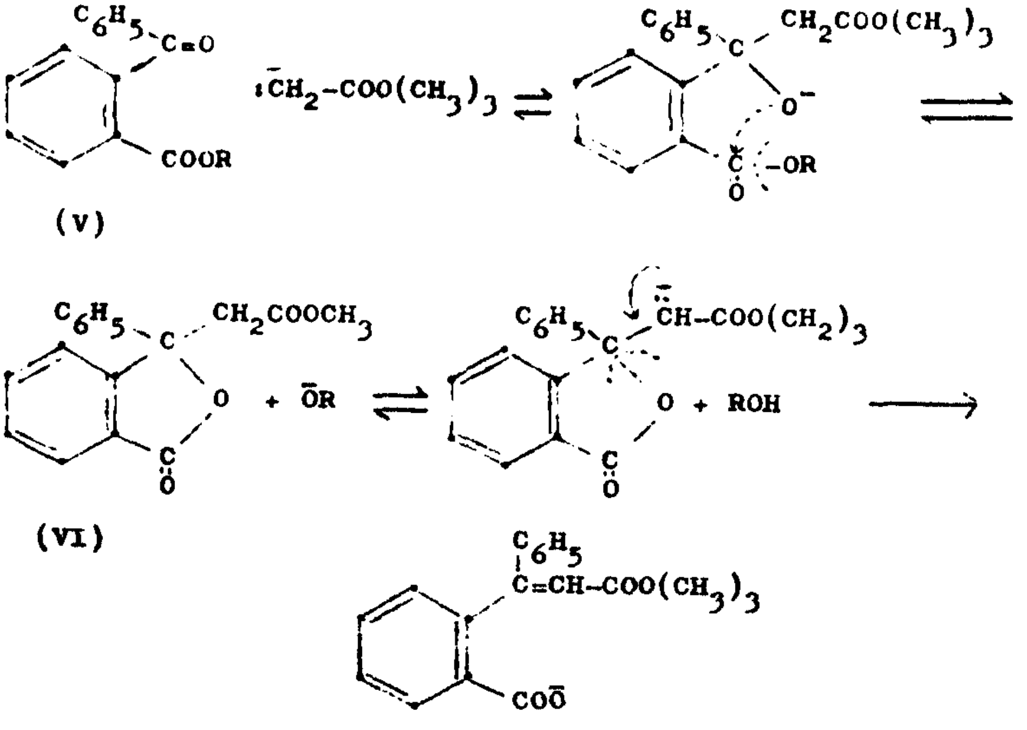
(V)

The validity of this mechanism can be readily appreciated from the following evidence :

1) The suggestion of an intermediate paraconic-ester is quite reasonable in view of the fact that they could be isolated[8], particularly when shorter reaction periods are employed;[9] and furthermore, they are cleaved by alkoxides in very good yields to give salts of the unsaturated half-esters.[10,11,12]

2) According to Johnson's mechanism, the most important factor which leads to the facile occurrence of the

Stobbe condensation with succinic ester, is the presence of a suitably situated carbalkoxyl group that enables cyclisation to an intermediate paraconic ester. Perhaps the most interesting piece of evidence which illustrates the importance of this factor is Johnson's observation that whereas benzophenone did not condense with ethyl or *tert.*-butyl acetate, yet an ester of *o*-benzoylbenzoic acid (V) condensed readily with *tert.*-butyl acetate in the presence of potassium *tert.*-butoxide to give the half-ester (VII).[3]

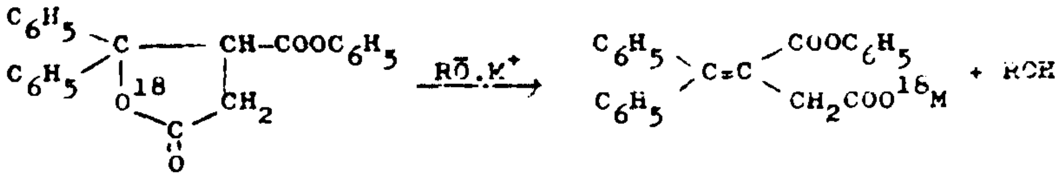


(V)

(VI)

(VII)

3) An elegant support for Johnson's mechanism was provided by the recent work of Jeffery and Fry[13] who carried out an oxygen-18 tracer study of the Stobbe condensation. They used benzophenone enriched with the oxygen isotope and found that the product contained all of the oxygen-18 enrichment of the starting ketone. Upon degradation all of the enrichment was found to be located in the free carboxyl group of the half-ester. These facts are consistent with the formation of the intermediate paraconic ester (VIII) and its subsequent cleavage by alkoxide ion as shown below.



(VIII)

According to the current mechanism, one should expect glutaric esters to undergo the Stobbe condensation readily, since they also have an ester group suitably situated for the formation of a lactonic ring. Experimentally, however these esters turned out to be relatively unreactive in the Stobbe condensation.[3] This surprising behaviour was explained by assuming that the δ-lactonic ring in the