A THESIS ENTITLED

STUDIES ON STOBBE CONDENSATION

Presented by

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STOBBE CONDENSATION

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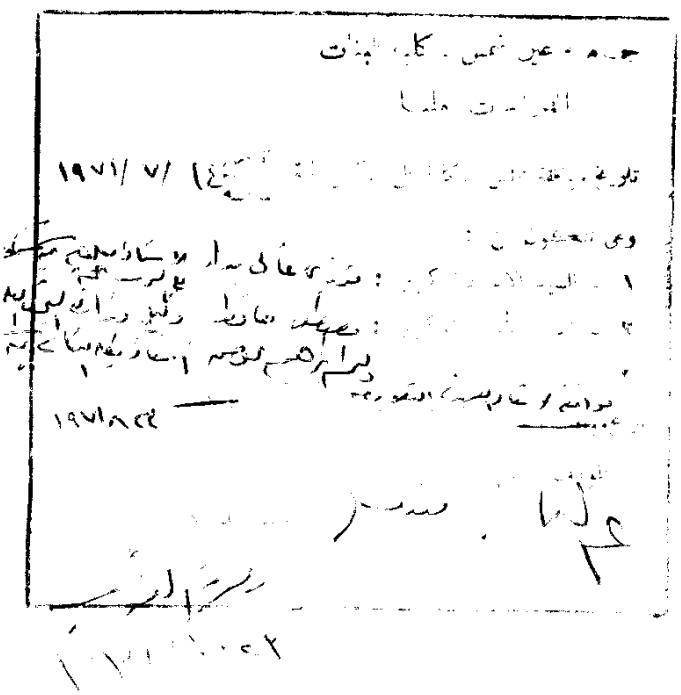

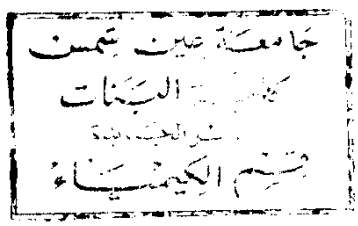

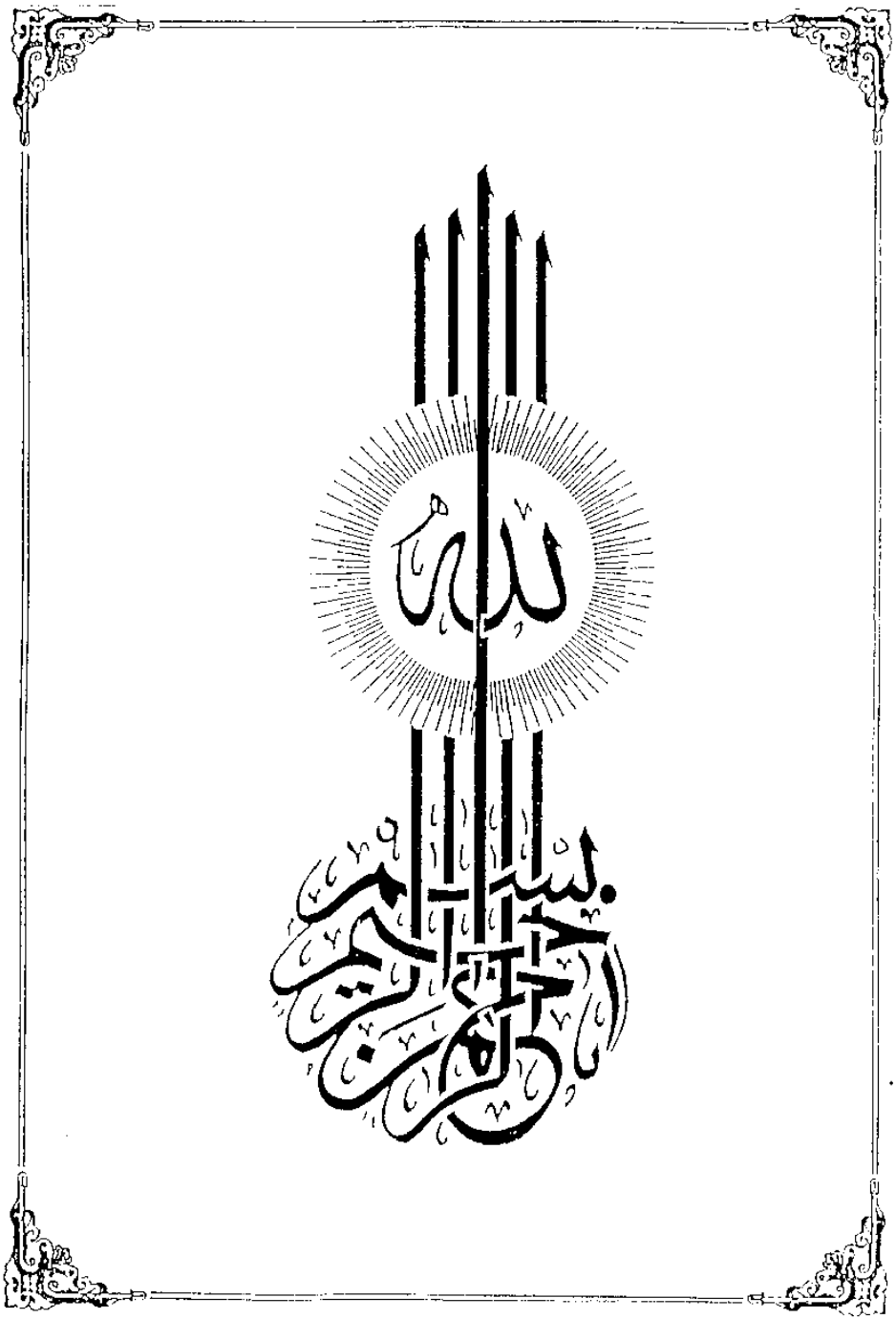

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SUMMARY

Stobbe condensation is carried out using two non-symmetrical and one symmetrical ketones.

I- Stobbe Condensation Involving 3,4-Dichloro-4'-methoxybenzophenone :

The Stobbe condensation of 3,4-dichloro-4'-methoxybenzophenone with dimethyl succinate gives a mixture of cis and trans-(3,4-dichlorophenyl/$COOCH_3$)-3-carbomethoxy-4-(3',4'-dichlorophenyl)-4-p-methoxyphenyl-but-3-enoic acid (CLXIa and b) in 89% yield. The crude mixture of half-esters is cyclised with sodium acetate in acetic anhydride to give an oily mixture of methyl 4-acetoxy-6-methoxy-1-(3',4'-dichlorophenyl)-2-naphthoate and methyl 4-acetoxy-6,7-dichloro-1-(p-methoxyphenyl)-2-naphthoate (CLXIIa and b). From this mixture a crystalline product is obtained which proved to be (CLXIIa).

The acetoxy-ester (CLXIIa) is hydrolysed to 4-hydroxy-6-methoxy-1-(3',4'-dichlorophenyl)-2-naphthoic acid (CLXIIIa), which is methylated to methyl 4,6-dimethoxy-1-(3',4'-dichlorophenyl)-2-naphthoate, (CLXIVa). This is hydrolysed to 4,6-dimethoxy-1(3',4'-dichlorophenyl)-2-naphthoic acid (CLXVa) which is decarboxylated to 4,6-dimethoxy-1-(3',4'-dichlorophenyl)-naphthalene (CLXVIa). The methoxy acid

(CLXVIIa) is cyclised to give 3,10-dichloro-5,7-dihydro-7h-tetrazo(c)fluoren-7-one (CLXVIIa).

The crude oily acetoxy ester (CLXIIa and b) is hydrolysed to give a mixture of phenolic acids (CLXIIIa and b), from which (CLXIIIa) is isolated in a poor yield. The remaining mixture of phenolic acid is methylated to give two products by fractional crystallisation, the predominant which is proved to be (CLXIVa) by m.p. and mixed m.p. and methyl 5,7-dichloro-4-methoxy-1-(p-methoxyphenyl)-2-naphthoate (CLXIVb). The characterisation of the two isomeric methoxy-esters is accomplished by dechlorination of each isomer, then hydrolysed to give 4,5-dimethoxy-1-phenyl-2-naphthoic acid (CLXVIIIa), m.p. 236°C, and 4-methoxy-1-p-methoxyphenyl-2-naphthoic acid (CLXVIIIb), which has the same m.p. given by Baddar et al.[27]

The crude oily half-esters is hydrolysed to a mixture of dibasic acids which is separated by fractional crystallisation to cis and trans-(3',4'-dichlorophenyl/COOH)-3-carboxy-4-(3',4'-dichlorophenyl)-4-p-methoxyphenyl-but-3-enoic acid (CLXIXa and b).

Treatment of the dibasic acid (CLXIXa) with acetyl chloride produces the corresponding anhydride cis-γ-(3',4'-dichlorophenyl)-γ-p-methoxyphenyl itaconic anhydride (CLXXa). The anhydride is treated with aluminium chloride in nitrobenzene to give a mixture of two isomeric indenyl-acetic

acid mixture is separated by fractional crystallisation to 3,4-dichloro-3-p-methoxyphenyl-1-oxo-inden-2-yl acetic acid (CLXXI) and 3-(3',4'-dichlorophenyl)-6-methoxy-1-oxo-inden-2-yl acetic acid (CLXXII). Cyclisation of the crude indenyl acetic acid (CLXXI and CLXXII) gives 5-acetoxy-9,10-dichloro-3-methoxy-7H-benzo(c)fluoren-7-one (CLXXIII) and 5-acetoxy-2,3-dichloro-9-methoxy-7H-benzo(c)fluoren-7-one (CLXXVI). Hydrolysis of the acetoxy fluorenones (CLXXIII) and (CLXXVI) then methylation gives 9,10-dichloro-3,5-dimethoxy-7H-benzo(c)fluoren-7-one (CLXVIIa) and 2,3-dichloro-5,9-dimethoxy-7H-benzo(c)fluoren-7-one (CLXXVIII).

II- Stobbe Condensation Involving 3,4-Dimethoxy-4'-chloro-benzophenone :

The Stobbe condensation of 3,4-dichloro-4'-methoxy-benzophenone with dimethyl succinate gives a mixture of cis and trans-(CLXXXa and b) (p-chlorophenyl/$COOCH_3$)3-carbomethoxy-4-p-chlorophenyl-4-(3',4'-dimethoxyphenyl)-but-3-enoic acid. From this mixture a crystalline solid is isolated which proved to be (CLXXXa). The half-ester (CLXXXa) is cyclised to give methyl 4-acetoxy-6,7-dimethoxy-1-p-chlorophenyl-2-naphthoate (CLXXXIa), which is hydrolysed to 4-hydroxy-6,7-dimethoxy-1-p-chlorophenyl-2-naphthoic acid (CLXXXIIa). Methylation of (CLXXXIIa) produces

...methyl 4,5,7-trimethoxy-1-p-chlorophenyl-2-naphthoate (CLXXXIIIa) which is hydrolysed to 4,5,7-trimethoxy-1-p-chlorophenyl-2-naphthoic acid (CLXXXIVa). Decarboxylation of the methoxy-acid (CLXXXIVa) gives 4,5,7-trimethoxy-1-p-chlorophenylnaphthalene, also cyclisation of the methoxy-acid gives 9-chloro-2,3,5-trimethoxy-7H-benzo(c)fluoren-7-one (CLXXXVIa).

The structure assigned to the methoxy acid (CLXXXIVa) is substantiated by dechlorination of its methoxy-ester (CLXXXIIIa) then hydrolysed to give 4,5,7-trimethoxy-1-phenyl-2-naphthoic acid (CLXXXVIIa), it structure is established by spectral evidence.

Cyclisation of the remaining oily half-esters gives the acetoxy-esters (CLXXXIa) and methyl 4-acetoxy-5-chloro-1-(3',4'-dimethoxyphenyl)-2-naphthoate (CLXXXIb) which are isolated by fractional crystallisation.

The pure half-ester (CLXXXa) is hydrolysed to give the cis(p-Cl-C_6H_4/COOH)-3-carboxy-4-p-chlorophenyl-4-(3',4'-dimethoxyphenyl)-but-3-enoic acid (CLXXXVIIIa), however hydrolysis of the oily Stobbe product gives two isomers (CLXXXVIIIa) and traces of its isomer (CLXXXVIIIb).

Treatment of the dibasic acid with acetyl chloride produces its corresponding anhydride cis-γ-p-chlorophenyl-γ-(3',4'-dimethoxyphenyl)-itaconic anhydride.

anhydride is treated with acetyl chloride in nitrobenzene or in 1,1,2,2-tetrachloroethane to give a mixture of two products, the phenolic acid (CLXXXIIa) and 3-p-chlorophenyl-5,6-dimethoxy-1-oxo-2-indenyl acetic acid (CLXL). The structure of the indenyl acetic-acid (CLXL) is established by cyclisation with sodium acetate in acetic anhydride to give 5-acetoxy-3-chloro-9,10-dimethoxy-7H-benzo(c)fluoren-7-one (CLXLI). The acetoxy fluorenone is hydrolysed then methylated to give 3-chloro-5,9,10-trimethoxy-7H-benzo(c)fluoren-7-one (CLXLIII), its structure is established by spectral evidence.

III) Stobbe Condensation Involving 3,3'-Dibromo-4,4'-dimethoxybenzophenone :

The condensation of 3,3'-dibromo-4,4'-dimethoxy-benzophenone[50] with dimethyl succinate gives an oily half-ester which failed to solidify. Cyclisation of the oily half-ester gives two isomers methyl 4-acetoxy-7-bromo-6-methoxy-1-(3'-bromo-4'-methoxyphenyl)2-naphthoate and methyl 4-acetoxy-5-bromo-6-methoxy-1-(3'-bromo-4'-methoxyphenyl)-2-naphthoate (CLXLVa and b). Hydrolysis of the acetoxy-ester (CLXLVa) gives 7-bromo-4-hydroxy-6-methoxy-1-(3'-bromo-4'-methoxyphenyl)-2-naphthoic acid (CLXLVI). Methylation of the phenolic acid gives

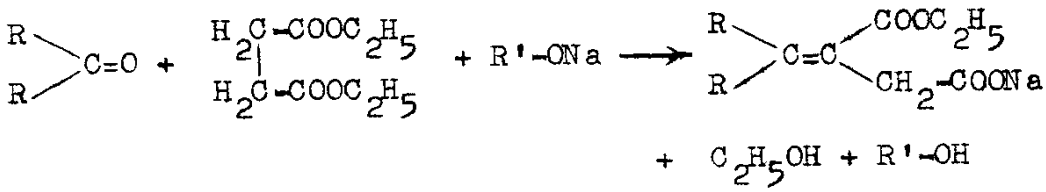
methyl 7-bromo-4,6-dimethoxy-1-(3'-bromo-4'-methoxyphenyl)-2-naphthoate (CLXLVII). This ester is hydrolysed to 7-bromo-4,6-dimethoxy-1-(3'-bromo-4'-methoxyphenyl)-2-naphthoic acid (CLXLVIII). The ester (CLXLVII) is debrominated then hydrolysed to give 4,6-dimethoxy-1-p-methoxyphenyl-2-naphthoic acid.

INTRODUCTION

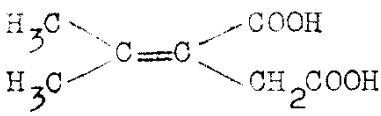
THE STOBBE CONDENSATION

1) General Survey of the Stobbe Condensation

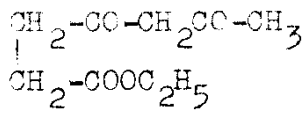
The condensation of carbonyl compounds with an ester of succinic acid, under the influence of sodium alkoxides to give the corresponding alkylidene succinic acid (a substituted itaconic acid), or isomers formed by a tautomeric shift of hydrogen, is known as the Stobbe condensation.[1] The primary product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



The reaction orginally was described and developed by Hans Stobbe[1] who found that acetone condenses with dialkyl succinate in the presence of sodium ethoxide to give tetraconic 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 a 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)



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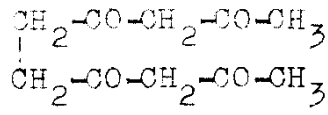
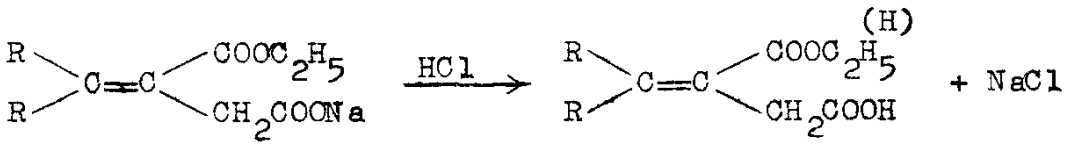


(III)

Further investigation by Stobbe as well as by other workers have shown that aldehydes and ketones condense with succinic ester or α-substituted succinic esters in the manner first observed by Stobbe, in this way, the general nature of this special type of condensation was established.

The liberation of the acidic material from the salt fraction gives the alkylidene succinic acid, or a tautmer, in the form of either the half-ester or the dibasic acid produced by hydrolysis.



Scope of the reaction

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) Condensation 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, have also been used though to a limited extent.

II- Theoretical Aspects of the Stobbe Condensation

(A) Mechanism of the reaction:

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 the 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