

PART I

INVESTIGATION OF A NEW METHOD FOR THE
PREPARATION OF SUCCINODIALDEHYDE

PART II

STUDIES ON THE PREPARATION OF α,α' -DIFORMYL-
SUCCINONITRILE

PART III

STUDIES ON THE PREPARATION OF CERTAIN ETHOXYPROPIONYL
COMPOUNDS

By

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Thesis submitted to the Faculty of the Graduate School
of the University of Maryland in partial
fulfillment of the requirements for the
degree of Doctor of Philosophy

1943

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ACKNOWLEDGMENT

The author wishes to express appreciation to Dr. Nathan L. Drake of the Organic Chemistry Department at the University of Maryland for his suggestion of the problems and his counsel throughout the course of the research.

TABLE OF CONTENTS

	<u>Page</u>
PART I. INVESTIGATION OF A NEW METHOD FOR THE PREPARATION OF SUCCINDIALDEHYDE	
INTRODUCTION.	1
DISCUSSION.	4
EXPERIMENTAL PART	9
SUMMARY	19
PART II. STUDIES ON THE PREPARATION OF α, α'-DIFORMYL-SUCCINONITRILE	
INTRODUCTION.	20
DISCUSSION.	20
EXPERIMENTAL PART	26
SUMMARY	34
PART III. STUDIES ON THE PREPARATION OF CERTAIN ETHOXYPROPIONYL COMPOUNDS	
INTRODUCTION.	35
DISCUSSION.	35
EXPERIMENTAL PART	36
SUMMARY	38
BIBLIOGRAPHY	39

PART I

INVESTIGATION OF A NEW METHOD FOR THE PREPARATION OF SUCCINDIALDEHYDE

INTRODUCTION

Interest in the preparation of succindialdehyde¹ has been greatly abetted in recent years by its application in the preparation of therapeutically useful compounds containing the tropane nucleus following the work of Robinson, Willstätter, Ladenburg and others.

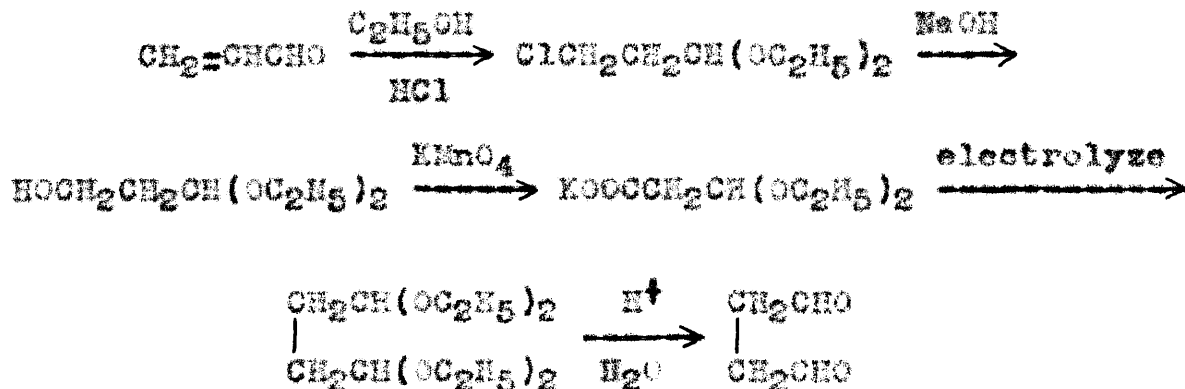
Perhaps the first mention of succindialdehyde in the chemical literature is that of Saytzeff (1) in 1873 who claimed to have prepared it by the reduction of succinyl chloride with sodium amalgam. It was shown later, however, by Wislicenus (2) that Saytzeff did not have the dialdehyde but γ -butyrolactone.

In 1884 Ciamician and Dennstedt (3) prepared succindialdoxime from pyrrole by treatment with hydroxylamine hydrochloride and sodium carbonate, and in 1901 Harries and coworkers (4) (5) converted the dioxime to the dialdehyde by treatment with nitrogen trioxide.

Since that time the preparation has been reported by various methods. Wohl and Schweitzer (6) in 1906 electrolyzed the potassium salt of malonic semialdehyde diethyl acetal to

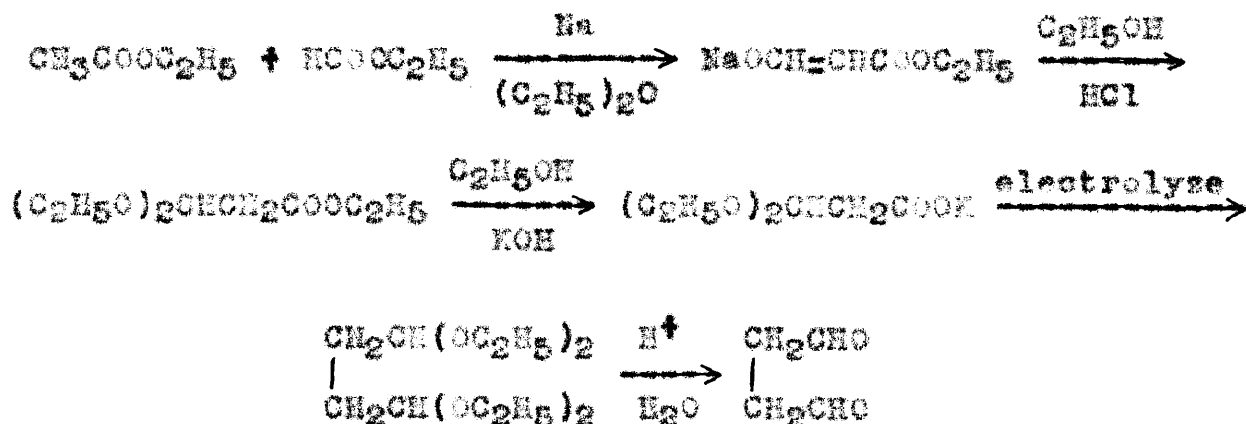
¹ The name "succindialdehyde" has become by usage the preferred nonsystematic name for butandial-1,3 rather than the more proper "succinaldehyde."

obtain succindialdehyde tetraethyl acetal which was hydrolyzed to the free aldehyde:

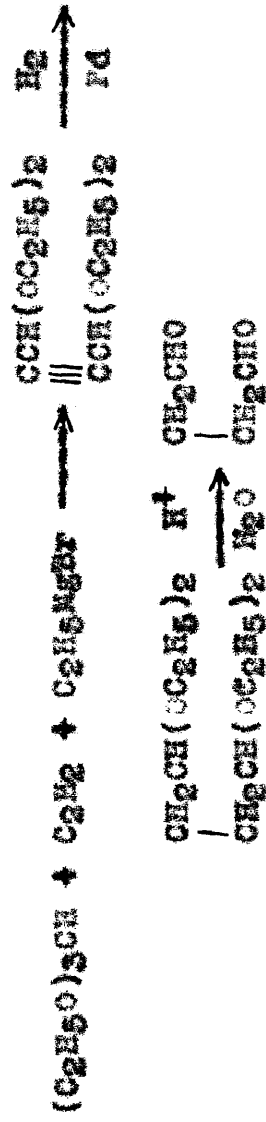


Marcilly and Blaise (7) in 1904 isolated a small amount of succindialdehyde among the oxidation products of certain unsaturated acids. Harries (8) in 1908 prepared it by the hydrolysis of cyclooctadiene 1,5 dioxonide.

Sugasawa (9) in 1927 obtained the dialdehyde by the method of Kohl and Schweitzer above but prepared the intermediate potassium salt of malonic semiacetal in different fashion:



Keimatsu and Yokota (10) in 1927 used acetylene, orthoformic ester and ethyl magnesium bromide followed by reduction of the substituted acetylene obtained to get the tetraethyl acetal of succindialdehyde:



H. Türk (11) in 1905 prepared the dialdehyde by hydrolysis of diallyl diacetate.

Harries (12) in 1912 obtained it by hydrolysis of the acetonides of certain butadiene polymers.

Succinaldehyde has also been obtained by hydrolysis of furane (13).

The dioxime has been obtained from *N*-ethyl pyrrole and hydroxylamine (14) and from reduction of 1,4-dinitrobutane (15).

In the methods of preparation for succinaldehyde mentioned here, the yields (where reported at all) are relatively low and in most cases the raw materials, the intermediates, and the processes involved are expensive.

The most practical method reported in the literature to date would seem to be that of Harries utilizing pyrrole and hydroxylamine and treating the dioxime obtained with HgO_2 . Schöpf and Lehman (16) in 1935 using this method claimed an overall yield of 30% succinaldehyde (in aqueous solution) based on pyrrole used.

DISCUSSION

The method for the preparation of succindialdehyde investigated in this research is the condensation of two moles of ethyl formate with one mole of ethyl succinate and subsequent hydrolysis and decarboxylation of any diformyl succinic ester formed to yield the desired dialdehyde.

Formylation of compounds containing active hydrogen on a carbon alpha to an activating group such as carbonyl or cyanide by means of formic ester in the presence of a suitable basic condensing agent is a well-known application of the classical Claisen reaction. An excellent review of this type of reaction including the latest mechanism is given by C. E. Hauser and E. E. Hulsen in Chapter 9 of Organic Reactions, Vol. I (1948).

Wislicenus and coworkers (17) in 1906 condensed ethyl formate and ethyl succinate by means of sodium to obtain ethyl monoformylsuccinate in 60-70% yield. Properties and reactions of this product were studied including its hydrolysis to β -formylpropionic acid which had previously been prepared by Perkin and Sprankling in 1899 (18) from the sodium enolate of malonic ester and bromoacetal with subsequent hydrolysis of the ester-acetal obtained.

Carrière in 1912 (19) and later in 1921 (20) carried out the same condensation using sodium ethoxide instead of sodium metal. The formylsuccinic ester was hydrolyzed to β -formylpropionic acid by means of aqueous oxalic acid.

This same condensation has been reported by several other workers in the course of their researches. Thus Folyakova and coworkers (21) in 1939 prepared ethyl monoformylsuccinate using sodium methoxide in the course of their work on the synthesis of pilocarpine.

No reference has been found to any extension of this condensation in an attempt to prepare the diformylsuccinic ester.

However, Wislicenus and coworkers (22) in 1939 condensed ethyl oxalate with ethyl succinate using sodium ethoxide and obtained either ethyl oxalylsuccinate or ethyl α, α' -dioxalylsuccinate (sodium salt) with good yields (ca 70%) in each case.

In the research here undertaken, the following aspects were considered in outlining the work:

1. Selection of the condensing agent.
2. Conditions for the reaction including reactant quantities, medium, temperature, and time of reaction.
3. Isolation and/or determination of the intermediate α, α' -diformylsuccinic ester.
4. Hydrolysis of this intermediate.
5. Isolation and recovery of the desired dialdehyde hydrolysate.

Alcohol-free sodium ethoxide was first choice for the condensing agent as it has proven most useful in similar condensations reported in the literature.

The action of sodium ethoxide on ethyl formate is a factor to be considered in Claisen condensations with this

ester. A study has been made by P. Adickes, G. Schäfer (23) (24), and others on this reaction without a complete elucidation. However, the equilibrium



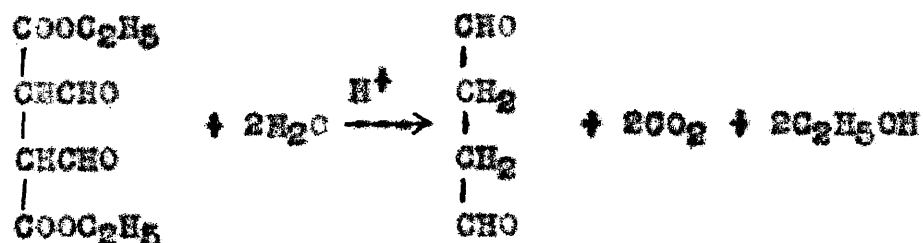
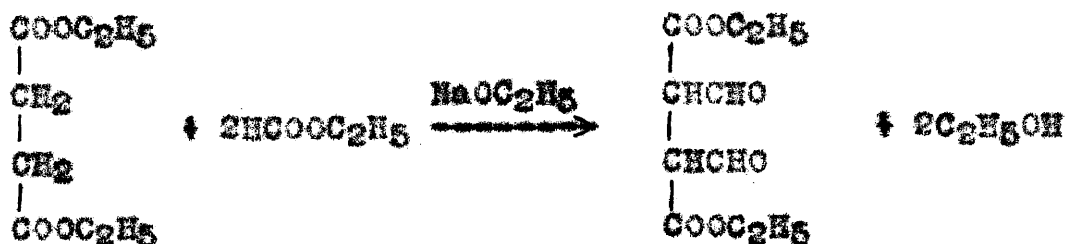
seems to be established and the decomposition is quite extensive at ordinary temperatures. Hence a lower temperature (0°) would seem to be indicated for most successful use of ethyl formate in the Claisen condensation, provided of course that the equilibria of the desired condensation are attained in a reasonable time at such temperature.

With the above in mind, the reactions were generally run at ice-bath temperatures for a rather long time with an excess of ethyl formate present. Ether was the reaction medium used.

Isolation of the intermediate ethyl α, α' -diformylsuccinate from the crude reaction mixture was not accomplished, but an attempt was made to gain some indication as to the amount of this desired intermediate present relative to the monoformyl ester by (a) determination of carbon dioxide liberated from decarboxylation after hydrolysis of the reaction mixtures and (b) titration of the carbonyl groups using hydroxylamine hydrochloride and bromphenol blue indicator.

Hydrolysis of the crude reaction mixtures was effected with 0.5N hydrochloric acid. The succinaldehyde was recovered by ether extraction and isolated in nearly pure form by distillation in vacuo.

The reactions under investigation are summarized as follows:



In addition to monomeric succindialdehyde, at least four polymeric forms have been described in the literature (25)(5). The monomer is a light, mobile liquid of sweetish but stinging odor; b.p.-760 169-170° (sl.d.); b.p.-71 65-7°; D_4^{18} 1.069; n_D^{18} 1.42397, n_D^{21} 1.42517, n_D^{30} 1.42667 (25)(28). It is easily soluble in all the common solvents (4). Its vapors are corrosive to the skin and mucous membrane (4). It is unstable in dilute acid solution and exceedingly unstable in dilute alkaline solution (4). It polymerizes readily on standing, especially under the influence of moisture, to a glassy form but will remain liquid for a long time in the dry, cold state in a well-stoppered container (26). It gives an intense blue color with Schiff's reagent (4), reduces Fehling's solution even in the cold (4), and yields derivatives with all the usual aldehyde reagents (25). Oxidation by potassium permanganate destroys the compound (5), nitrous acid yields succinic acid (27), and nitric acid yields oxalic acid (5). Sodium amalgam

in ether reduces the dialdehyde to tetramethylene glycol (5). With water (sealed tube at 180°), furane is formed; with phosphorous trisulfide, thiophene is produced; and with ammonia and acetic acid, pyrrole is the product (4).

The so-called "glassy" form (probably pentameric) is a tough sticky substance with biting odor. It liquifies at ca 65° and boils at 169-70° at atmospheric pressure to yield the monomer. It dissolves readily in alcohol but difficultly in water, ether, benzene, or acetic acid, yielding a solution of the monomer. Its $D^{19} = 1.23$ and $n_D^{20} = 1.47849$ (4)(5)(26).

Three other polymeric forms (5) are solids. One, m.p. 64°, is prepared by dropping the "melted" glassy form into water at 50°. Evaporation of a benzene solution of the monomer yields another form melting at 130-40°. An amorphous form, termed parascucindialdehyde, is produced when an acetone solution of the aldehyde is allowed to stand with anhydrous oxalic acid. This is a white powder decomposing at 90-100°.

EXPERIMENTAL PART

Preparation and Purification of Reagents

Ethyl succinate. The ester was prepared by reaction of succinic anhydride with excess absolute ethyl alcohol in the presence of p-toluene sulfonic acid, the water of reaction being removed by azeotropic distillation with benzene and ethyl alcohol.

Ester boiling at 119-120° at 20-30 mm. was taken for use. Ethyl formate. Commercial ethyl formate was fractionally distilled, placed over potassium carbonate for 24 hours, and finally distilled from phosphorous pentoxide immediately before use. Ester boiling at 54° to 54.5° was used.

Alcohol-free sodium ethoxide. The preparation was essentially according to the directions given in Houben-Weyl, Vol. II, 1926, p.748 [see also Hauser and Hudson (23)], except that anhydrous toluene was employed in place of xylene for the medium in which to powder the sodium metal and the ethoxide reaction was run under dry nitrogen.

Apparatus. The apparatus was the usual type for Claisen condensations - a three-necked flask fitted with reflux condenser, mercury-sealed stirrer, and addition funnel. A nichrome stirrer of the Herabberg type was used and all external outlets were protected with calcium chloride drying tubes. A gas inlet for dry nitrogen was also utilized.

The apparatus was oven dried before assembly and carefully flamed out after assembly while sweeping with dry nitrogen gas.

Ground glass connections were used where possible throughout the apparatus.

The Condensation Reaction

Run #1. To 4 moles of alcohol-free sodium ethoxide in 1500 cc. of ether cooled in an ice bath was added 1 mole of ethyl formate, then a mixture of 6 moles ethyl formate and 2 moles ethyl succinate during the course of $1\frac{1}{2}$ hours. The mixture was stirred during addition and thereafter for $5\frac{1}{2}$ hours at ice-bath temperature. It was allowed to stand overnight (12 hrs.) at room temperature and was then stirred an additional 4 hours. The mixture was a yellow-brown, cloudy liquid. This was poured over 1100 g. of ice and made acid to Congo Red with 30% sulfuric acid.

The light yellow ester layer was separated and the aqueous layer extracted three times with 500 cc. portions of ether.

The combined ester layer and extract were washed several times with 150 cc. portions of water to remove acid and placed over anhydrous sodium sulfate with a little calcium carbonate and let stand overnight in the icebox.

After removal of all material volatile on the steam bath under water pump vacuum, there remained about 390 g. of a yellowish, slightly thick liquid with a fruity ester odor.

This liquid was distilled in vacuo under nitrogen and yielded 240 ^(52%) g. of distillate boiling at $153-5^{\circ}$ at 30 mm. and a dark residue of ca 100 g. which did not distil at a bath temperature of 215° and a pressure of 10 mm.

The boiling point of this liquid indicated that it was probably monoformylsuccinic ester, and the following tests and derivatives verified this conclusion.

A strong positive test was obtained with Schiff's reagent and a deep red color with ferric chloride solution. The liquid was soluble almost completely in potassium carbonate, insoluble in water, easily soluble in alcohol and in ether.

A copper derivative was formed by treatment of a 50% alcoholic solution of the ester with copper acetate solution — pale green, amorphous, m.p. 132-4°. Wislicenus' value for the copper salt of the monoformyl ester is 132-3° (17).

A p-nitrobenzoyl derivative, green needles from alcohol, melted at 105-6° compared to 104° reported by Wislicenus (17).

A benzoyl derivative, pale green needles from petroleum ether, melted at 55-6° (Wislicenus' value, 57-8°) (17).

The nickel derivative, pale green amorphous material, melted at 218-9° (Wislicenus' value, 219-20°) (17).

A portion of this ester was redistilled to use in an attempt to effect the second stage of the condensation to the diformyl ester as a separate step (see Run #3). 150 g. boiling 126-140° at 8-10 mm. were collected. The wide boiling range here is probably explained by the keto-enol tautomerism of the ester since about two weeks elapsed between the initial recovery and the redistillation. Carrière (20) commented on this phenomenon and determined that there is about 50% enol form present in the equilibrium mixture after "several days" standing.

The redistilled product was completely soluble in 25% potassium carbonate.

An attempt to make a recovery from the dark residue after the initial distillation of the crude reaction mixture of Run #1 was unsuccessful. Any diformyl ester present was probably lost in this residue.

Run #2. To 2 moles of alcohol-free sodium ethoxide in 500 cc. of ether cooled in an ice bath was added a mixture of 1 mole of ethyl succinate and 2.5 moles of ethyl formate (0.5 mole excess) over a period of 20 minutes, with stirring. Stirring was continued with cooling for $4\frac{1}{2}$ hours and 2 additional moles of ethyl formate were added. The mixture was allowed to stand $12\frac{1}{2}$ hours, during which time it came to room temperature. It was then stirred for 6 hours and allowed to stand 39 hours. The total reaction time was thus 62 hours.

Recovery of the crude reaction product was as for Run #1 and yielded 160 g. of pale yellow liquid after removal of all material volatile at steam bath temperature under water pump vacuum.

A determination of carbon dioxide from the decarboxylation of the hydrolysate of a sample of this reaction mixture was run. Nitrogen gas was passed through a bubble counter and introduced into the hydrolysis flask beneath the surface of the liquid. To the flask was connected a reflux condenser from the top of which a tube led to a trap cooled in an ice bath and connected to a Drierite tube in train with an Ascarite absorption tube, a bubble counter, and finally a

protective Ascarite tube. In the hydrolysis flask was placed a weighed sample of the reaction product with 5 cc. concentrated hydrochloric acid and 45 cc. of water. The nitrogen gas served the double purpose of agitating the hydrolysis mixture and sweeping out the carbon dioxide evolved. The mixture was heated on the steam bath for 3 hours. Almost all the carbon dioxide was evolved during the first $\frac{1}{2}$ hour of heating. A 5-10 g. sample was used. Two check runs gave 23.9% carbon dioxide on the sample weight taken. The theoretical percentage for the monoformyl ester (1 mole carbon dioxide per mole ester) is 21.8% and for the diformyl ester (2 moles carbon dioxide per mole ester) is 38.3%. If it is assumed that the reaction product used here was composed entirely of these two esters, its composition was 37.5% mono- and 12.5% diformyl ester.

A determination of free carbonyl groups in the crude reaction product was undertaken by the hydroxylamine titration method. To a 1-3 g. sample was added 5 g. hydroxylamine hydrochloride, 25 cc. distilled water, and 20 cc. 95% alcohol. The mixture was warmed on the steam bath 15 minutes with frequent shaking, cooled and titrated with standard alkali in the presence of 5 drops of bromphenol blue indicator (0.04% solution). Blanks were run and also check determinations on samples of the redistilled ethyl monoformylsuccinate from Run #1.

The results are shown in the table below:

	Theoretical moles HCl/g. of sample	Actual moles HCl titrated /g. of sample	Percent
Monoformylsuccinic ester (Run #1)	0.00495	0.00497	100.4
Crude reaction product (Run #2)			
(a) calculated as 100% monoformyl ester	0.00495	0.00475	96
(b) calculated as 100% diformyl ester	0.00970	0.00475	54.5

These results do not agree with the carbon dioxide determination results given above. After further work with this titration method as run here, it is considered very doubtful that it gives a satisfactory indication in the case of the diformyl compound.

A 50 g. sample of the reaction mixture was taken for hydrolysis in an effort to isolate free succinaldehyde. 150 cc. of 0.5M hydrochloric acid was added to this in a 250 cc. round-bottomed flask with a gas inlet tube dipping to the bottom. A reflux condenser was attached, the mixture was heated on the steam bath, and a slow stream of nitrogen gas was bubbled through. The ester layer disappeared after about 45 minutes but heating was continued for a total of 2 hours. The solution showed only very slight darkening at

the end of this time. It was cooled, neutralized with sodium bicarbonate, and extracted six times with 40 cc. portions of ether. The combined extract was dried over anhydrous sodium sulfate with a small amount of calcium carbonate in the ice-box overnight. The volatile solvent was removed at room temperature with water pump aspiration under dry nitrogen gas, leaving a residue of about 4 g. of pale yellowish liquid with an exceedingly sharp, penetrating odor reminiscent of formaldehyde. This liquid was distilled in vacuo under dry nitrogen gas and the fraction boiling 61-65° at 10-12 mm. was collected as succindialdehyde. Harries (4)(26) reports the b.p. 65-6° at 11 mm. 2.6 g. were obtained, a yield of 9.5% based on the ethyl succinate used.

The physical and chemical properties of the liquid indicated that it was nearly pure succindialdehyde. It was a water-white, mobile liquid of exceedingly sweetish but sharp odor. The refractive index $n_D^{25} = 1.4292$ was determined for the freshly distilled substance. After three weeks this had increased to $n_D^{25} = 1.4406$. Harries (26)(28) reports $n_D^{21} = 1.42617$ and $n_D^{30} = 1.42667$ for the monomer, and $n_D^{20} = 1.47349$ for the polymeric glassy form. A brilliant blue color was obtained with Schiff's reagent, and Fehling's solution was reduced in the cold (4).

Known derivatives were prepared as follows:

<u>Derivative</u>	<u>M.P. Found</u>	<u>M.P. Reported in the Literature</u>
Dimethylhydroresorcinol derivative	219-20	218-20 (30)
Bis <i>p</i> -nitrophenylhydrazone	179-80 d.	178 d. (16)
Bis 2,4-dinitrophenylhydrazone	269-70 d.	278-80 d. (31)

The yields of the crude dimedon and p-nitrophenylhydrazine derivatives were 70-80% of the theoretical. Analysis of the dimedon derivative gave the following results:

20.71 mg. of sample gave 53.73 mg. of carbon dioxide and 15.21 mg. of water.

$$C = 70.80\% \quad H = 8.22\%$$

22.19 mg. of sample gave 57.53 mg. of carbon dioxide and 16.37 mg. of water.

$$C = 70.75\% \quad H = 8.25\%$$

19.55 mg. of sample gave 50.77 mg. of carbon dioxide and 14.66 mg. of water.

$$C = 70.87\% \quad H = 8.39\%$$

Calculated for $C_{36}H_{50}O_8$

$$C = 70.79\% \quad H = 8.25\%$$

Run #3. This run was made using the monoformylsuccinic ester from Run #1 as the starting product in an attempt to condense another mole of ethyl formate in a second step.

To 0.3 mole of sodium ethoxide cooled in an ice bath was added a mixture of 0.3 mole α -formylsuccinic ester and 0.45 mole ethyl formate (0.15 mole excess). The mixture was stirred $6\frac{1}{2}$ hours at 0° and allowed to stand $17\frac{1}{2}$ hours during which time it came to room temperature. Appearance of the reaction mixture was much like that of previous runs. Recovery was the same as for Run #2, yielding 62 g. of material non-volatile on the steam bath under water pump vacuum.

Carbonyl titration gave a value of 103% calculated as monoformyl ester and 58% calculated as diformyl ester. This

compares with 100.4% found on the pure monoformylsuccinate used as starting product and is a qualitative indication of some further formylation.

Hydrolysis of a 31 g. portion of the crude reaction mixture and recovery as for Run #2 yielded 1.3 g. of liquid boiling 60-65° at 9-11 mm. with $n_D^{26} = 1.4242$. An equal amount of distillate boiling 40-60° at this pressure was also collected which undoubtedly contained some succindialdehyde. The yield of dialdehyde based on the 1.3 g. of the purer fraction is ca 10% of theoretical from the 0.3 mole α -formylsuccinic ester used.

Run #4. This run was made using 50% excess sodium ethoxide with sufficient excess alcohol to obtain a solution of the condensing agent. This enables much more rapid preparation of the condensing agent, and the excess alcohol should have a retarding effect on the decomposition equilibrium of ethyl formate with sodium ethoxide.

1.5 moles of sodium ethoxide were prepared using 4.5 moles (3.0 moles excess) ethyl alcohol. To this was added 3 moles of ethyl formate (1.5 moles excess based on the ethoxide, and 2 moles excess based on the ethyl succinate) at ice-bath temperature over a 10-minute period. No vigorous reaction ensued but a pale yellow color developed. 0.5 mole of ethyl succinate was then introduced during 10 minutes with good stirring. A deeper yellow-brown color developed rapidly. Stirring in the ice bath was continued for 2½ hours, and the reaction mixture was then allowed to stand in the icebox for 50 hours. The mixture was a slightly cloudy, yellow-brown

solution such like those of previous runs.

Recovery was the same as for Run #2 and yielded 111 g. of crude product.

20 g. of this product was hydrolyzed as for previous runs. Ether extraction and vacuum distillation yielded 0.9 g. of succindialdehyde concentrate boiling 55-65° at 8-10 mm. pressure, $n_{25}^{25} = 1.425$. This is an 11.5% yield based on the ethyl succinate used.

Thus the excess condensing agent in excess alcohol would seem to be advantageous.

Purity of the Succindialdehyde Concentrate

The succindialdehyde concentrates were kept in well-stoppered containers in the icebox at all times. Thickening with some contraction in volume was observed after three or four weeks, and the viscous, glassy modification remained after one to two months.

The boiling point, refractive index, qualitative tests and yields of derivatives indicate a purity of certainly no less than 75% succindialdehyde. On this basis, the yields of pure dialdehyde for the various runs would be:

	<u>Yield</u>
Run #2	7.1%
Run #3	7.5%
Run #4	8.6%

SUMMARY

1. Succinaldehyde has been obtained in 7-10% yield by the condensation of ethyl succinate with ethyl formate followed by hydrolysis and decarboxylation of the intermediate diformyl ester.

2. The intermediate α, α' -diformylsuccinic ester could not be isolated from the condensation reaction mixture.

3. The use of an excess of sodium ethoxide condensing agent relative to the ethyl succinate and an excess of ethyl alcohol relative to the sodium ethoxide is advantageous in this reaction.

PART II

STUDIES ON THE PREPARATION OF α, α' -DIFORMYL SUCCINONITRILE

INTRODUCTION

The first preparation of α, α' -diformyl succinonitrile was by R. I. Longley (32) at this University in 1942. The method used was the condensation of ethyl formate with succinonitrile, sodium ethoxide being the condensing agent.

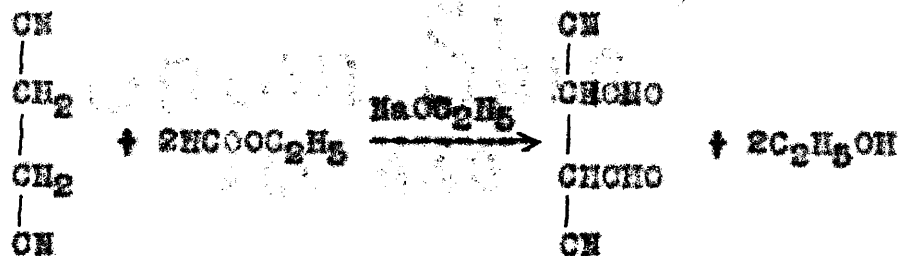
A survey of the chemical literature pertinent to this example of the classical Claisen reaction has been reported by Longley (32) and will not be given here.

In the preparation of this 1,4-dicarbonyl compound, Longley experienced considerable difficulty in the recovery of the product from the condensation reaction.

This research was undertaken to investigate methods of recovery and, if possible, to improve the yield obtained.

DISCUSSION

The reaction between ethyl formate and succinonitrile in the presence of sodium ethoxide to yield α, α' -diformyl succinonitrile may be represented as follows:



α, α' -Diformyl succinonitrile is a white to pale yellow solid crystallizing from water in small, shiny needles. It darkens slightly above 131° and decomposes sharply at $135-6^{\circ}$.

The principal factors considered in the investigation of this reaction were:

1. Preparation and purification of the reagent.
2. Choice of condensing agent.
3. The reaction medium.
4. Concentration of the reactants and the time and temperature of the reaction.
5. Methods for recovery of the free diformyl compound from the reaction mixture.
6. Purification of the diformyl compound.

The procedures for the preparation and purification of the reagents are given in the next section of this paper. The preparation of succinonitrile from ethylene bromide and sodium cyanide in alcoholic medium is essentially that of Fauconnier (33). Chloroform extraction was found to be the best method for recovery of the succinonitrile from the sodium bromide reaction sludge.

Sodium ethoxide was the condensing agent chosen since it has been successfully used in similar condensations as well as in previous work on this reaction (32).

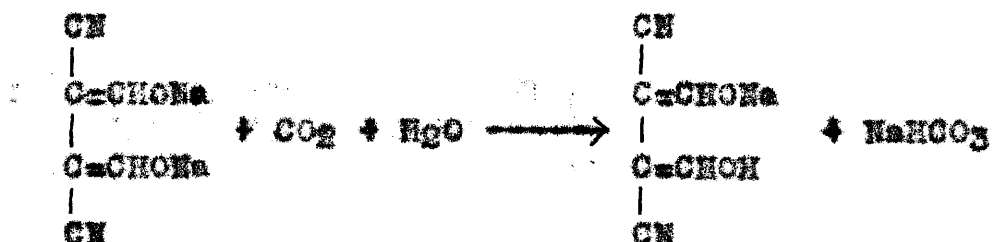
The most convenient reaction medium was found to be anhydrous toluene, although ether is almost as satisfactory, especially for smaller quantities. The reaction in toluene apparently does not proceed quite as vigorously on first mixing the reactants and temperature control is easier.

The same considerations hold as to time and temperature of reaction in condensations with ethyl formate and sodium ethoxide as discussed in Part I of this paper. (see page 6)

Simple acidification with mineral acids or with acetic acid (either aqueous or anhydrous) of the condensation reaction mixture does not cause any separation of the free diformyl nitrile. The aqueous acid solution darkens rapidly on standing. When the solid sodium enolate is filtered out of the reaction mixture, the same result is obtained on treatment with acid.

Since the diformyl compound is only limitedly soluble in common organic solvents, its extraction from the aqueous acid solution is not a practical means of recovery.

It was found that, on saturation of the concentrated aqueous alkaline enolate solution with carbon dioxide in an ice bath, a white crystalline precipitate was obtained which proved to be the monosodium enolate of the diformyl nitrile. If the reaction solution is considered to contain the disodium enolate, the reaction may be represented thus:



Carbonic is therefore a stronger acid than the "secondary" enol group in the diformyl nitrile but a weaker acid than the "primary" one, and the monosodium enolate precipitates out by virtue of its limited solubility in the cold sodium bicarbonate solution.

The free diformyl nitrile could not be isolated from the monosodium enolate by simple acidification in aqueous or methyl alcoholic solution, so an investigation was made of heavier metal enolates which might be used as intermediates in obtaining the free compound.

The lead compound proved useful. This precipitates on addition of lead acetate to aqueous solutions of the sodium enolate as a white to very pale yellow amorphous solid. It is very sensitive to hydrolysis and can not be precipitated even in very dilute acetic acid solution. Its lead content varies with conditions of precipitation. Thus, when it is precipitated from a solution containing an excess of alkali, it contains less lead than when formed in a solution of the monosodium enolate. On addition of dilute acetic acid to a water suspension of the lead compound, hydrolysis occurs immediately, and the free diformylsuccinonitrile is precipitated in fine, needle-like crystals.

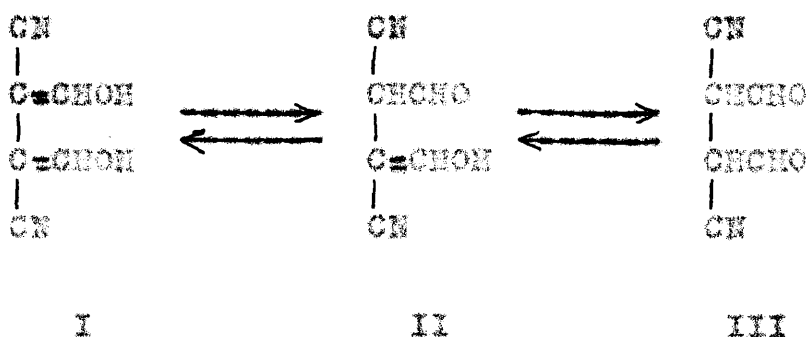
From the behavior of the lead compound and the analytical results, it is very likely that its composition is that of a basic monolead enolate hydrated in various degrees. A suggested formula is $(C_6H_4O_2N_2)(PbO)(H_2O)_x$, where $x = 2, 1,$ or 0 . The free diformyl compound can be readily sublimed out of this lead combination.

As a method of recovery of the diformyl nitrile from the condensation reaction mixture, the lead compound was precipitated together with lead hydroxide from the concentrated sodium enolate solution and then acidified with acetic acid.

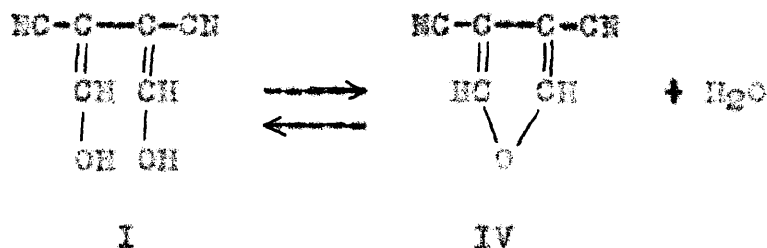
Purification of the diformyl nitrile was accomplished either by recrystallization from water or, in small quantity, by sublimation in vacuo.

A complete elucidation of the unusual behavior of the sodium enolate of this diformyl compound on acidification, with and without intermediate formation of the lead compound, has yet to be made. However, a careful examination of the evidence available leads to some interesting postulations.

The existence of the tautomeric equilibrium between the keto and the enol forms of the compound is important. The following equilibria are possible:



Another equilibrium which may exist is that between the 1,4 dihydroxymethylene compound (I) and its anhydride, the dicyanofurane (IV):



In strong alkaline solution, the salt of (I) would be expected to be present, and, on direct acidification, free (I) would first be formed. This would be expected to be quite

soluble in water, and the equilibrium with (IV) might be such that the formation of (III) is precluded under such conditions. The conversion of α, α' -diacetylsuccinic ester to the corresponding furane by means of concentrated acids is discussed by Knorr (34).

Formation of the lead compound from (I) may allow (II) to form and the equilibrium then, on acidification, favors (III) which is less soluble and precipitates out of water solution.

The acidified enolate solution (I) gives a very deep red color with ferric chloride, but a water solution of the free compound (III) gives a much lighter color which deepens only slowly.

Schiff's reagent gives no positive test in any case and Fehling's reduction is negative. However, the copper derivative, when freshly precipitated from the monosodium enolate solution and boiled, deposits cuprous oxide. Similarly the white silver salt forms momentarily but immediately blackens with metallic silver deposit.

In no case is decolorization of bromine water observed as might be expected from the enol compounds.

EXPERIMENTAL PART

Preparation and Purification of Reagents

Ethyl formate. Commercial ethyl formate was treated as described on page 9 and distilled from phosphorous pentoxide immediately before use.

Succinonitrile. The succinonitrile was prepared by reaction of ethylene bromide with sodium cyanide in aqueous alcoholic solution essentially as outlined by Pauconnier (33), a method similar to that described in Organic Syntheses for preparation of trimethylene cyanide (35). Chloroform was utilized to extract the nitrile from the crude reaction mixture and the dried extract was concentrated and distilled in vacuo. Nitrile boiling at $125-7^{\circ}$ at 6-7 mm., m.p. $52-3^{\circ}$, was taken for use.

Alcohol-free sodium ethoxide. This reagent was prepared as described on page 9, Part I of this paper. All preparations were carried out under dry nitrogen.

Apparatus. The apparatus used was identical with that described for the Claisen condensations in Part I of this paper.

The Condensation Reaction

Run #1. To 1.1 moles of alcohol-free sodium ethoxide in 500 cc. anhydrous toluene at ice-bath temperature was added 1 mole of ethyl formate during ten minutes with rapid stirring. A thick paste resulted, and 200 cc. of cold, anhydrous toluene were added for greater fluidity. 0.5 mole of succinonitrile

dissolved in 1 mole of ethyl formate was then introduced over a ten-minute period. The mixture assumed a pale yellow-brown color almost immediately which deepened only slightly during the remaining reaction period. Stirring at ice-bath temperature was continued for 20 hours, and the mixture was allowed to stand in the icebox for 30 hours.

During the last 5 hours, small portions of the reaction mixture were removed and various methods of recovery were tested. A small portion was added to a few grams of crushed ice, the toluene layer separated, and the cold alkaline enolate solution acidified in various ways. Mineral acids, potassium acid sulfate, and acetic acid were tried in both equivalent quantity (Methyl Red indicator) and in slight excess. Direct addition of acetic acid to the toluene suspension of the sodium enolate was also tried. No separation of free diformyl nitrile was observed in any of these tests. The acidified solutions darkened on standing overnight. Another recovery trial, made by neutralizing the concentrated aqueous enolate with carbon dioxide, yielded a white precipitate of the monosodium enolate, and this method of recovery was used for the main portion of the reaction mixture.

The toluene reaction mixture was poured over 300 g. of crushed ice. Then the toluene layer was separated and washed with 50 cc. of cold water, and the combined cold alkaline aqueous solutions saturated with carbon dioxide over a period of one hour. The white crystalline solid which separated was filtered off and washed once with a small amount of ice water.

A portion (about 5 g.) of this solid was taken separately and washed several times with water, a procedure which resulted in some loss due to water solubility.

Both portions of solid were dried as rapidly as possible over phosphorous pentoxide in vacuo at room temperature. The main portion (washed only once) was a slightly gray amorphous powder, the smaller portion (well washed) was a pure white granular product. A total of 25 g. was obtained. This is a yield of ca 31% monosodium enolate based on the succinonitrile when allowance is made for about 5% of the reaction mixture used in recovery tests.

The white, well-washed portion of the product was dried 2 hours over phosphorous pentoxide at 100° in vacuo and analysed for sodium and nitrogen. Sodium was determined by digestion of the sample in a platinum crucible with sulfuric acid and hydrogen peroxide, and evaporation to a sodium sulfate residue. Nitrogen was determined by the Kjeldahl method. The following results were obtained for these analyses:

26.35 mg. of sample yielded 11.64 mg. of sodium sulfate.

Na = 14.31%

24.54 mg. of sample yielded 11.07 mg. of sodium sulfate.

Na = 14.43%

Calculated for $C_6H_5O_2H_2Na$

Na = 14.55%

37.40 mg. of sample yielded ammonia equivalent to 9.60 ml. of 0.0484N potassium hydroxide.

K = 17.41%

36.31 mg. of sample yielded ammonia equivalent to 9.30 ml. of 0.0434N potassium hydroxide.

$$N = 17.37\%$$

Calculated for $C_6H_5O_2K_2Na$

$$N = 17.72\%$$

Thus the sample was nearly pure monosodium enolate.

The monosodium enolate is moderately soluble in cold water and very soluble in hot water. It is slightly soluble in hot 95% ethyl alcohol, moderately soluble in hot methyl alcohol, and insoluble in ether, benzene, and other less polar solvents. It could not be crystallized from any of these solvents. It is not appreciably hygroscopic and keeps well in a dry desiccator. A water solution of the compound darkens in a few hours. No test is obtained with Schiff's reagent (sample acidified before test) or with Fehling's solution. A deep red color is produced with ferric chloride solution. The compound does not melt but is gradually reduced to a charred mass from 200-260°.

No change is observed on acidifying a solution of the enolate. Calcium acetate gives no precipitate. Copper acetate yields a pale green precipitate of the copper enolate which deposits cuprous oxide on boiling but which is not readily soluble in acetic acid. Silver nitrate gives an immediate white precipitate which blackens very rapidly. Lead acetate with a solution of the monosodium enolate alone precipitates a gray-white to very pale yellow lead enolate but fails to do so if the sodium enolate is first acidified with acetic acid.

Study of the lead enolate compound of α, α' -diformyl-succinonitrile. 0.1 g. of the lead enolate compound, precipitated from a solution of the monosodium enolate of α, α' -diformyl-succinonitrile, was suspended in 2-3 cc. of water and acidified with acetic acid. An immediate formation of tiny, white, needle-like crystals of free α, α' -diformylsuccinonitrile occurred replacing the milky slurry of the amorphous lead compound. On warming the mixture, complete solution with slight darkening took place and, on cooling again, tiny iridescent needles crystallized out. These were filtered off, washed and dried. Pale yellow needles were obtained which decomposed at 130-1° and, on recrystallization from water, at 124-5°. This is the correct decomposition point for the α, α' -diformyl nitrile. The yield was about 80%, based on the monosodium enolate used.

The amount of acetic acid used for acidifying the lead enolate should at least be an amount equivalent to the lead present in the lead enolate when this compound is taken as a simple monolead enolate. A considerable excess does not seem to affect the yield from the conversion appreciably unless such a large amount is used that the increased solubility of the diformyl compound in acetic acid becomes a factor, i.e., 20-30%.

The lead compound was prepared by several different methods, and analyses for lead were run in an effort to determine whether or not the compound showed constancy of composition and whether some clue to its composition could be obtained. The following table shows the source of the compound and the

analyses for lead obtained by the dichromate precipitation method:

	<u>Precipitated with</u>	<u>From a Solution of</u>	<u>%Lead</u>
(a)	Lead acetate	Sodium enolate after removal of lead hydroxide	50.0%
(b)	Lead acetate	Monosodium enolate	51.2%
(c)	Lead nitrate	Monosodium enolate	52.7%
(d)	Lead acetate	Same as (a) but washed with hot absolute alcohol	63.8%

These analyses indicate strongly that there is only one lead atom per α, α' -diformylsuccinonitrile group in the molecule. The possibility of a double salt with lead acetate or nitrate is excluded by the failure to detect volatile acids on boiling portions of the lead compound with 20% sulfuric acid.

A carbon and hydrogen analysis was run on (d) with the following results:

22.01 mg. of sample yielded 15.49 mg. of carbon dioxide and 2.35 mg. of water.

$$C = 19.21\% \quad H = 1.20\%$$

22.01 mg. of sample yielded 15.25 mg. of carbon dioxide and 2.11 mg. of water.

$$C = 18.91\% \quad H = 1.07\%$$

If one lead atom per molecule is assumed, the percentages of lead given in the preceding table would indicate a molecular weight range of 325 to 415. On the basis of one

diferaylnitrile group per molecule, the carbon percentage would then range between 17.3% and 22.2%, which range includes the 19.1% of carbon found above.

In the melting point capillary, the lead compound showed a wide decomposition range beginning at about 180°.

It was found that the free α, α' -diferaylnitrile could be readily sublimed out of the lead compound at temperatures as low as 90-120° at ca 1 mm. pressure. The sublimate thus obtained was white but showed all the properties of the pale yellow form of the diferayl nitrile in regard to solubility, decomposition point, and reagent tests.

A suggested composition for the lead compound is given in the first section of this paper.

Run #2. This run was made to test the method for recovery of the diferayl nitrile utilizing the lead enolate compound.

To 0.42 mole alcohol-free sodium ethoxide in 450 cc. anhydrous ether at ice-bath temperature was added a mixture of 0.6 mole ethyl formate and 0.2 mole succinonitrile in 50 cc. anhydrous ether over a period of 1½ hours with good stirring. Stirring was continued for 3 hours, and the mixture was allowed to stand 12 hours in the ice bath.

The reaction mixture was poured over 150 g. ice and the ether layer separated and washed with 25 cc. of cold water. To the combined aqueous portions was added 65 g. of lead acetate (0.2 mole) in 150 cc. of water. To the slurry of precipitate produced was added 25 g. (0.4 mole) of glacial acetic acid and the mixture was warmed on the steam bath and

cooled in an ice bath. After one hour, the α, α' -diforoyl-succinonitrile which had precipitated was filtered off. Only about 4 g. were obtained. The filtrate was placed in the ice-box overnight and an additional 3.9 g. of diforoyl compound separated out. The yield after recrystallization from water was 7 g. or 26% of the theoretical.

Run #3. This run was made in the same manner as Run #2 except that a toluene medium was used and the reaction was stirred for 6 hours and allowed to stand for 34 hours at ice-bath temperature. In the recovery the lead enolate-lead hydroxide mixture was filtered off in a Büchner funnel and sucked as dry as possible. The concentrated sodium acetate medium was thus removed to avoid its buffering effect on addition of acetic acid.

The solid lead precipitate was mixed to a slurry in 150 cc. of water, and 25 g. of acetic acid was added. The mixture was warmed for 5 minutes on the steam bath, cooled in an ice bath for 1 hour, and the precipitated α, α' -diforoyl nitrile filtered off. 3.5 g. were obtained. The acidified filtrates yielded 1 g. more on standing overnight. The yield of recrystallized product (from water) was 3.8 g. or 32-3% of the theoretical.

Analysis of the α, α' -diforoylsuccinonitrile. A sample of the product from Run #3 was recrystallized three times from water and dried for 2 hours in vacuo over phosphorous pentoxide at 56° . The decomposition point remained constant at $134-5^\circ$ after the second recrystallization.

Analysis for carbon and hydrogen gave the following

results:

17.03 mg. of sample yielded 33.07 mg. of carbon dioxide and 4.90 mg. of water.

C = 52.99% H = 3.15%

22.28 mg. of sample yielded 43.18 mg. of carbon dioxide and 6.25 mg. of water.

C = 52.99% H = 3.14%

Calculated for $C_8H_4O_2N_2$

C = 52.34% H = 2.96%

SUMMARY

1. The monosodium enolate of α,α' -diformylsuccinonitrile has been prepared and studied.
2. A monolead enolate of α,α' -diformylsuccinonitrile of variable composition has been studied and its probable constitution suggested.
3. A convenient method for the isolation of α,α' -diformylsuccinonitrile in at least 32% yield from the ethyl formate-succinonitrile condensation reaction mixture has been worked out.
4. Further evidence has been accumulated toward the elucidation of the rather unusual behavior of α,α' -diformylsuccinonitrile.

PART III

STUDIES ON THE PREPARATION OF CERTAIN ETHOXYPROPIONYL COMPOUNDS

INTRODUCTION

Concurrently with the researches reported in Parts I and II of this paper and in connection with certain work being carried on in this laboratory, two unsuccessful reactions were encountered which are deemed of sufficient interest to report briefly here.

DISCUSSION

acetate by the reaction of ethyl benzoate and the sodiumacetylacetate by the reaction of ethyl benzoate and the sodium enolate of ethyl acetoacetate. An analogous transacylation reaction using ethyl β -ethoxypropionate in place of the ethyl benzoate in an attempt to obtain ethyl β -ethoxypropionyl acetate was without success.

In another reaction, methyl magnesium halide and β -ethoxy propionitrile was reacted in an attempt to prepare β -ethoxyethyl methyl ketone by the usual reaction of the Grignard reagent with nitriles. None of the expected ketone could be recovered from the intermediate adduct. This reaction has been run successfully in the case of α -alkoxy nitriles by Gauthier (38), by Soumelet (39), and more recently by Henze and coworkers (40)(41)(42).

EXPERIMENTAL PART

Attempted reaction of ethyl β -ethoxypropionate with the sodium enolate of ethyl acetoacetate to yield ethyl β -ethoxypropionyl acetate. In a 1-1. three-necked flask fitted with addition funnel, mercury-sealed stirrer and reflux condenser, 0.25 mole of the sodium enolate of ethyl acetoacetate was prepared by addition of 0.25 mole of ethylacetoacetate to a solution of 0.25 mole of sodium ethoxide in ethyl alcohol. A condenser set downward for distillation was attached and excess ethyl alcohol was distilled in vacuo under dry nitrogen at room temperature and the residual enolate entirely freed from alcohol by heating to 100° at 2 mm. pressure for two hours.

The alcohol-free enolate was cooled and 0.25 mole of ethyl β -ethoxypropionate was added. Vigorous stirring was begun and the mixture was heated gradually over a period of 1½ hours to 125°. A homogeneous solution was attained at 80-100°. After 30 minutes at 125°, a very vigorous reaction began so that the flask had to be cooled to prevent loss of the reaction mixture through the condenser. Rapid distillation of liquid boiling at 70-80° (ethyl acetate with some ethyl alcohol) began at this time. The reaction was now kept at 120° for 3 hours during which time distillate boiling at ca 77° (ethyl acetate) was collected at a diminishing rate. The temperature was finally raised to 135° over the course of ½ hour. A total distillate of 30 g. was collected (3 g. in excess of the theoretical amount for ethyl acetate alone.)

The reaction mixture solidified to a yellow-brown, glassy, resin-like solid on cooling. This was dissolved in ice water, acidified with sulfuric acid, and extracted with ether. The extract was washed with sodium bicarbonate solution to remove acid, dried over anhydrous sodium sulfate, freed of solvent ether on the steam bath, and an attempt was made to distil in vacuo the syrupy liquid remaining. Two to three grams of liquid boiling in the correct temperature range for ethyl acetacetate and ethyl β -ethoxypropionate were collected, but the thick syrupy residue did not distil up to a bath temperature of 225° at 1-2 mm. pressure.

Attempted preparation of β -ethoxyethyl methyl ketone by reaction of methyl magnesium chloride and β -ethoxypropionitrile.

To one mole of methyl magnesium chloride in one liter of ether was added one mole of β -ethoxypropionitrile over the course of 2 hours. The reaction mixture was well stirred and cooled in an ice bath during the addition. Reaction was indicated by separation of a yellowish-gray solid. The reaction mixture was allowed to stand for 12 hours, at which time the ether was removed by distillation on the steam bath and replaced by 750 cc. of anhydrous toluene and the toluene suspension heated at steam-bath temperature for 2 hours.

The reaction mixture was poured onto ice and addition of a 15% solution of hydrochloric acid was begun. A considerable amount of yellowish solid did not dissolve and the mixture became acid to Congo Red after addition of only one half the theoretical quantity (2 moles) of hydrochloric acid needed to

hydrolyze the normal magnesium halide adduct and the resultant ketimine. This yellow solid was filtered off. It was more soluble in hot water than in cold and easily soluble in ethyl alcohol or dioxane and seemed to be unaffected by further treatment with dilute mineral acid (10%) even in the warm.

The filtrate solution was made alkaline with ammonium hydroxide in the presence of enough ammonium chloride to prevent precipitation of magnesium hydroxide. An additional quantity of the yellow solid separated. This was filtered off and the alkaline filtrate extracted with ether, dried, and evaporated. The residue on distillation in vacuo yielded only a small amount of distillate boiling too high for the ketone and the major portion remained as a syrupy non-distillable residue.

The yellow solid was not further investigated.

SUMMARY

1. The transesterification reaction between ethyl acetoacetate and ethyl β -ethoxypropionate, which might be expected to yield ethyl β -ethoxypropionylacetate, yields only a syrupy, resinous product, at least under the conditions employed in this work.

2. The reaction between methyl magnesium halide and β -ethoxypropionitrile does not yield an adduct which, when hydrolyzed in the usual manner, produces the expected ketone.

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