

Reactions of Methylene Hydrogen

by E. L. Griffin

1912

Submitted to the School of Engineering of the
University of Kansas in partial fulfillment of the
requirements for the Degree of Bachelor of Science

REACTIONS OF METHYLENE HYDROGEN

With Special Reference to the
Formamidine Reactions.

by

E. L. Griffin.

A Thesis

Presented to the Faculty

of the

SCHOOL OF ENGINEERING

of the

University of Kansas,

In Partial Fulfillment of the Requirements

For the Degree of

BACHELOR OF SCIENCE.

May 15, 1912.

RD0107 48066

REACTIONS OF METHYLENE HYDROGEN.

With Special Reference to the Formamidine Reactions.

--

Methylene hydrogen is the term applied to the hydrogen in certain groups of the formula CH_2 : when the two unsaturated bonds shown, are filled by some group, or groups, which are negative enough to make the hydrogens act as acid hydrogens and be replacable by metals. When the bonds are filled by positive groups, such as hydrogen or the alkyl radicals, these hydrogens are not especially reactive. This property is shown very well in the aliphatic hydrocarbons or alcohols where the grouping is $\text{CH}_3\text{CH}_2\text{CH}_2-$. On the other hand, when attached to two negative groups, this hydrogen becomes very reactive. The ketone group, $-\text{CO}-$, seems to have a very strong effect, and, in those compounds where both bonds of the methylene group are replaced by ketone groups, the acid properties of the hydrogen are especially marked. This action is explained by the fact that the grouping $\cdot\text{CO} \cdot \text{CH}_2 \cdot \text{CO} \cdot$ is tautomeric with a second grouping $-\text{COH} = \text{CH} \cdot \text{CO} \cdot$ which is the structure of an ordinary carboxylic acid in which the oxygen is

substituted by a $\text{:CH}\cdot\text{CO}\cdot$.

Other groups which have a tendency to make hydrogen more active are cyanogen, which is present in cyanacetic ester, nitro groups, as in nitro ethane, which in many ways seems to contain methylene hydrogen, and the double bonded carbon which appears in some of the ring structures.

A few of the best known of these compounds are aceto acetic ester, benzoyl acetic ester, malonic ester, cyanacetic ester, and, of course, their acid derivatives. Some of the ring structures, such as methyl and phenyl isoxazolone, and the pyrazolones also have methylene properties.

As noted above, these compounds have been found to react with a very large number of other substances, and have been of great value in the building up of organic compounds. Some of the more important of the substances with which this methylene hydrogen reacts are given in the list following.

1. Metallic sodium replaces either one, or both of the hydrogens, the latter being given off as a free gas.
2. Sodium hydroxide replaces the hydrogen by the metal, with a splitting off of water.
3. Sodium ethylate reacts, giving the metal

substituted compound, and free C_2H_5OH .

4. The alkyl halides and sodium ethylate together, replace the hydrogens by alkyl groups. Both hydrogens may be replaced by the same alkyl group or, by changing the alkyl halide, different groups may be introduced.

5. Aldehydes condense with the methylene group, splitting off water. One molecule of aldehyde may react with either one or two molecules of the methylene compound.

6. Halogens will replace the hydrogens directly.

7. Diazo compounds react with compounds containing methylene hydrogen, splitting off an acid and giving the same compound which would result if a hydrazine were to react with a similarly placed carboxyl group.

8. Mercuric oxide will replace one of the hydrogens by the metal, mercury.

9. Alkyl substituted diformamidines of the structure $HC \begin{smallmatrix} \nearrow NHR \\ \searrow NR \end{smallmatrix}$ react, setting free a primary amine, and producing a substance of the structure $:C:CHNHR$.

10. Cyanogen, with these compounds, forms addition products with either one or two moles of the reacting substance.

11. Nitrous acid oxidizes away the two hydrogens and leaves a nitroso compound. Where one or both of the hydrogens have been replaced by alkyl groups this reaction does not take place.

12. With unsaturated compounds such as ethylene, the compound containing methylene hydrogen will break the double bonding and replace one by a hydrogen; the other by the remainder of the compound. It is also possible to break down triple bondings by this same method.

13. With some of these compounds, carbon bisulfide will re-act, evolving H_2S , and replacing the two hydrogens by $:\text{CS}$. With other compounds, it is necessary to first replace the hydrogens by sodium and let the resulting substance be acted upon by CSCl_2 .

14. Where the methylene group is attached to a ketone, or carboxyl, there is a tautomeric form, $-\text{CO}\cdot\text{CH}_2\cdot$ going over to $\cdot\text{COH}:\text{CH}-$. Then the OH, together with the hydrogen from any amine present, will split off water and leave the amide $\cdot\text{CNH}_2:\text{CH}$, where ammonia is used, or $\cdot\text{CNHR}:\text{CH}$ where a primary amine is used and R is the alkyl radical.

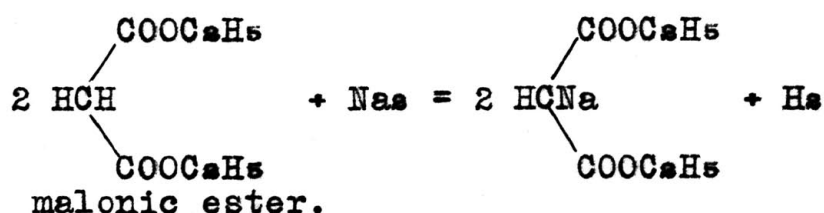
15. Sulphuryl chlorid will re-act in two ways substituting either one or both of the hydrogens by chlorine.

This comprises a rather incomplete list of the reactions and includes some reactions which take place with only certain compounds or groups of compounds. It will, therefore, probably be better to give a survey of some of the reactions of two or three of the better known compounds of this type.

MALONIC ESTER.

One of the best known of these methylene-hydrogen compounds is malonic ester, $\text{COOC}_2\text{H}_5 \cdot \text{CH}_2 \cdot \text{COOC}_2\text{H}_5$. This has been especially studied because of the great variety of syntheses into which it and its analogues enter. Malonic acid is a white, crystalline compound, melting point 132°C . Heated to about 140°C , it loses CO_2 and forms acetic acid. Its ethyl ester is a fragrant smelling liquid which is fairly stable.

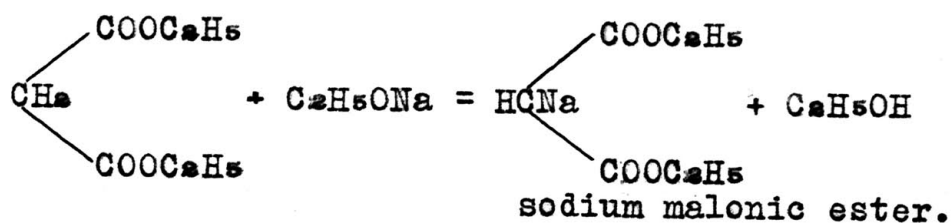
Malonic ester re-acts with sodium, replacing one of the methylene hydrogens by sodium and evolving free hydrogen according to the reaction



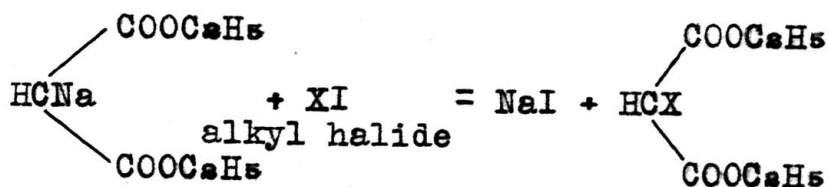
This reaction takes place very slowly at room temper-

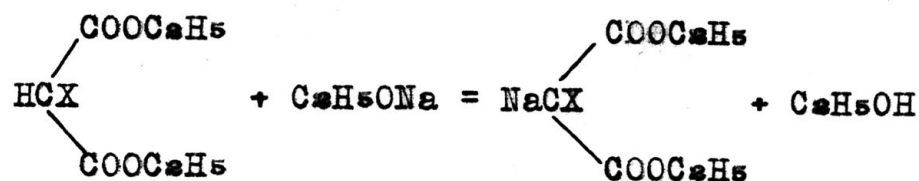
'). Ann. 204, 129. Conrad.

ature, moderately fast at the temperature of the boiling water bath, and briskly at the temperature of the boiling ester. The low rate of reaction at room temperature is due to the fact that the sodium derivative, produced, forms a coating over the metal and, so, slows down the reaction. The resulting compound is so much of a hindrance to the reaction that even at the higher temperature, it will not go to completion. In obtaining the sodium derivative, it is therefore better to let a ten per cent solution of $\text{C}_2\text{H}_5\text{ONa}$ in alcohol re-act with the ester. The sodium salt will then crystallize out as a white solid. Sodium malonic ester has not been formed, as far as I was able to find, by the direct action of NaOH . The reaction with sodium ethylate is as follows.

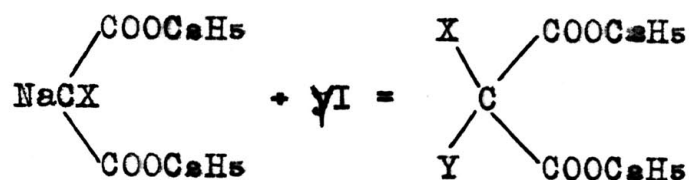


An alkyl halide will re-act with sodium malonic ester, replacing the metal by an alkyl group. Then a second mole of sodium ethylate will re-act with the substituted malonic ester as follows.



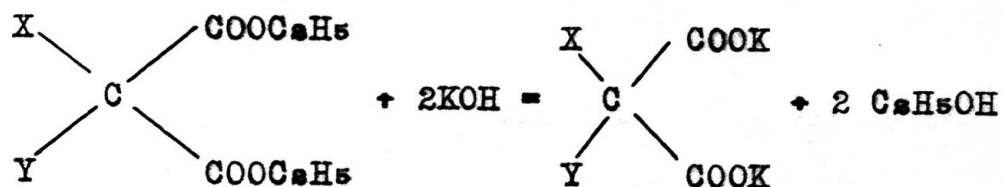


This second sodium can, in turn, be substituted by a second alkyl group which may or may not be the same as the one first substituted, according to what alkyl halide is used.



In practice these products are made by heating either one or two moles of sodium ethylate with the proper quantities of malonic ester and alkyl halide. The reactions have been carried out using methyl, ethyl, propyl, isopropyl, octyl, amyl, benzyl, and allyl iodides.

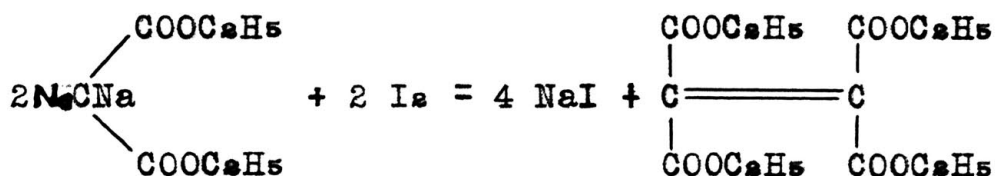
The ester can be broken down to form the potassium salt by the action of potassium hydroxide, and these salts when heated give off CO_2 , going over to the mono-basic acid.



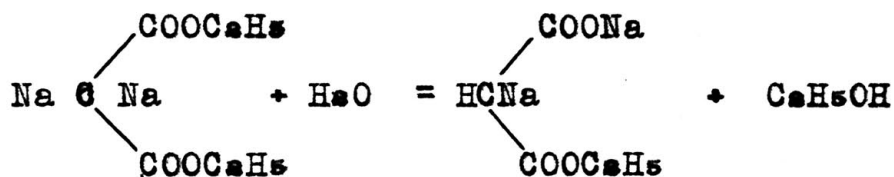


This gives an easy method for the synthesis of a di-substituted acetic acid, or a forked chain aliphatic acid.

When two molecules of sodium malonic ester react with iodine ¹⁾, sodium iodide is freed, and ^{dicarbon} ~~acetylene~~ tetracarboxylic ester is formed.



In making the disodium malonic ester for this reaction, the salt must be separated from the solution in which it is made at once, or it will break down give the following reaction:

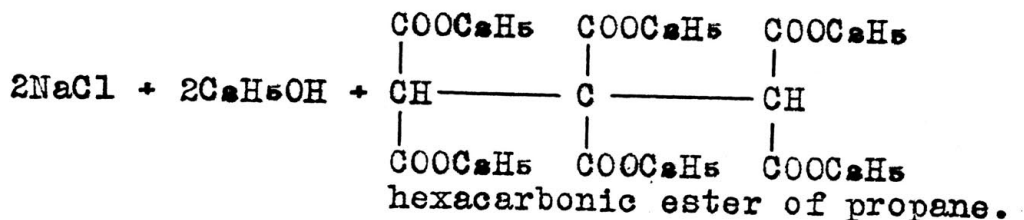
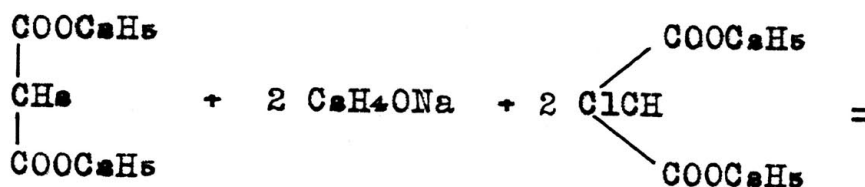
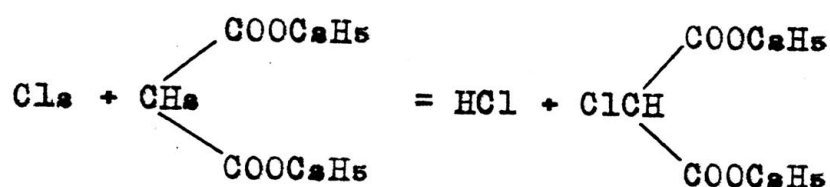


Substitution products of acetylene tetra carbonic ester

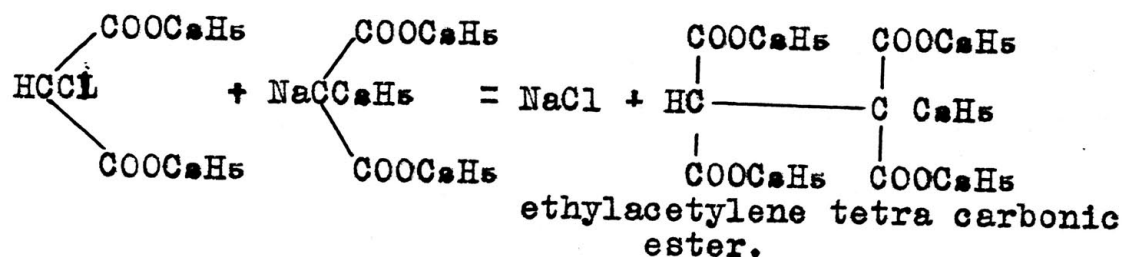
1). Ber. 17. 2782. Bischoff and Rach.

may be made in the following ways:

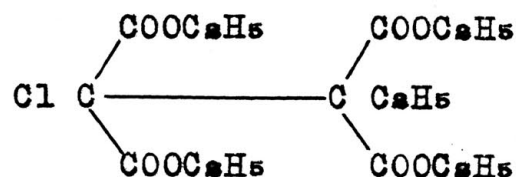
a). By the direct action of halogen compounds on the sodium salt at higher temperatures. An example of this would be the formation of the hexacarboxic ester of propane by the following reactions:



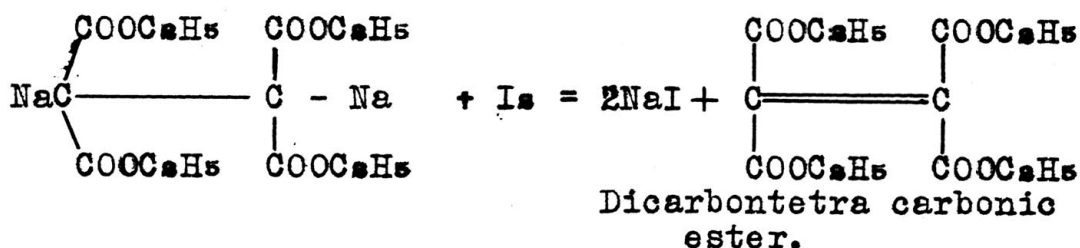
b). By the reaction of a sodium mono alkyl substituted malonic ester on a chlor substituted malonic ester.



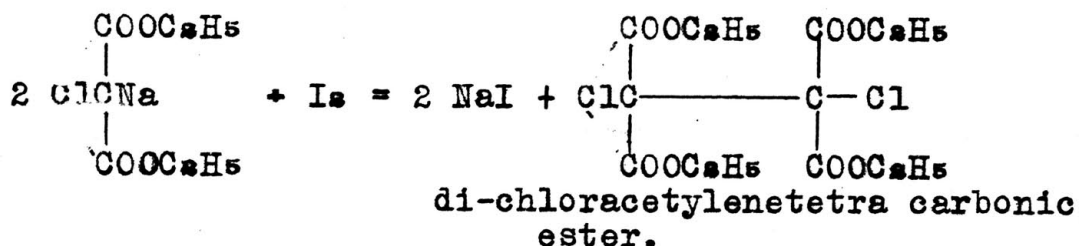
This, in turn, when treated with chlorine gas, forms ethyl chlor acetylene tetra carbonic ester.



c). By the action of iodine on the sodium acetylene tetracarmonic ester or its derivatives.



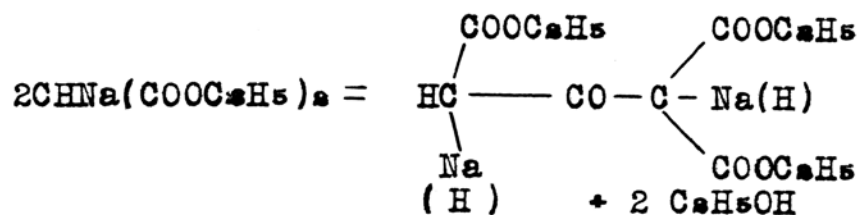
or, by the reaction of iodine on disodium di-chlor tetra carbonic ester, di-chlor acetylene tetracarmonic ester is obtained.



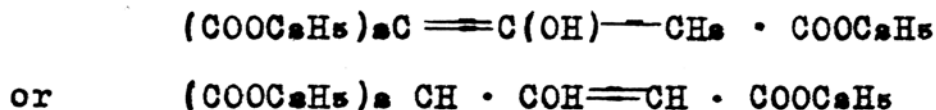
When sodium is allowed to re-act with malonic¹⁾ ester at 60 - 100°, alcohol splits off and two molecules join together as follows to form disodium acetone tri-

1). Ber. 32. 1273 Willstätter.

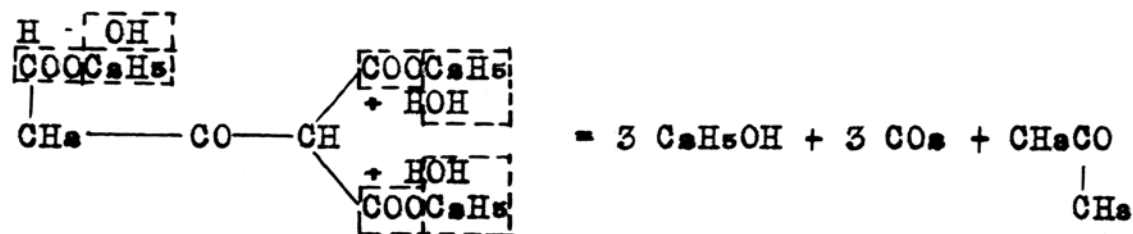
carbonic ester.



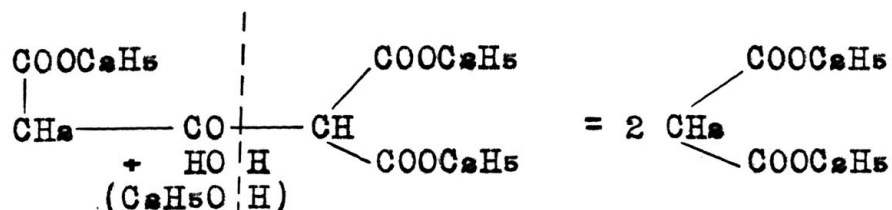
This forms an acid which is strong enough to dissolve carbonates and bicarbonates and to turn litmus red. With ferric chlorid, it has the characteristic red color, which is shown by the enol form of aceto acetic ester. It can be shown as having either of the following two formulae to account for this.



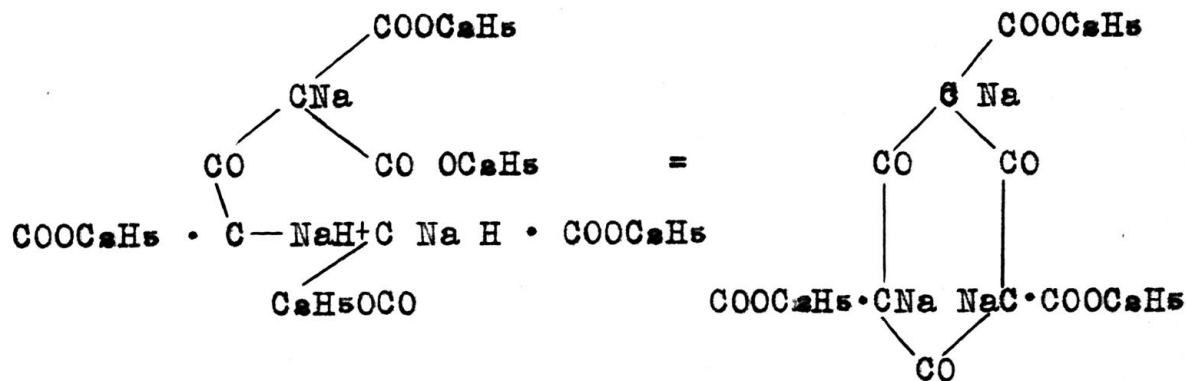
This compound should and does react very much like aceto acetic ester. It undergoes both the ketonic and acid splittings. The ketonic splitting yields acetone according to the following reaction.



The acid splitting yields simply two molecules of malonic acid ester.



This acetone tricarboxylic ester gives rise to a method of making phloroglucinol. The sodium salt will condense with sodium malonic ester, eliminating water between them.

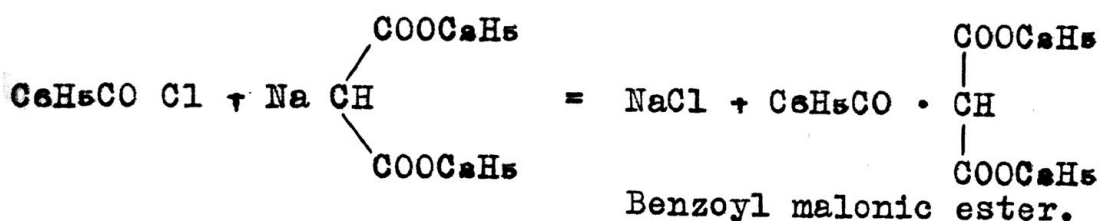


Phloroglucinol

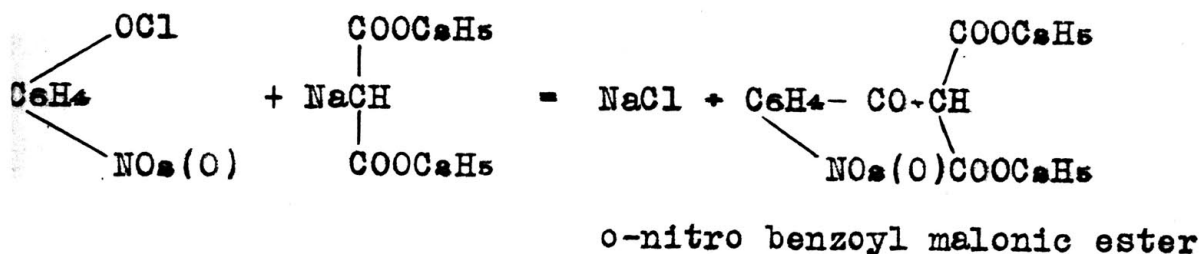
+ 2 C₂H₅OH

The acid chlorides 1.) re-act with sodium malonic ester to give the acyl derivatives of the malonic ester; and, since the second hydrogen will still re-act as before, this leads to another important set of syntheses. With benzoyl chloride and sodium malonic ester, benzoyl malonic ester is obtained.

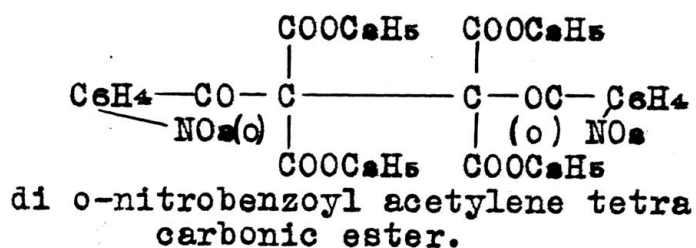
1.) Ber. 16. 1044 Bischoff.



With ortho nitro benzoyl chlorid, ortho nitro benzoyl malonic ester can be obtained; and then, from this, by a reaction with sodium and iodine similar to that for the preparation of acetylene tetra carbonic ester, di-o-nitro benzoyl acetylene tetra carbonic ester can be obtained.

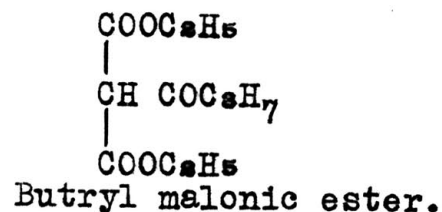
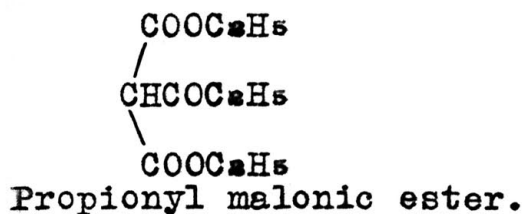


Na + I₂

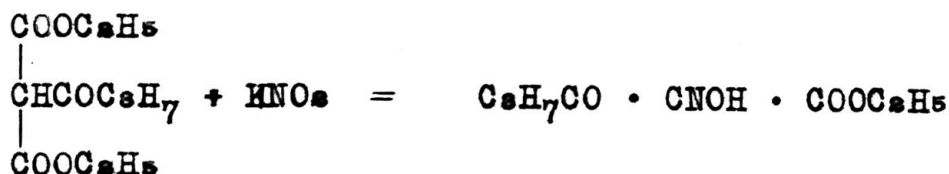


Propionyl chlorid¹⁾ re-acts with sodium malonic ester to give propionyl malonic ester. The butryl malonic ester has also been made by the same sort of a reaction.

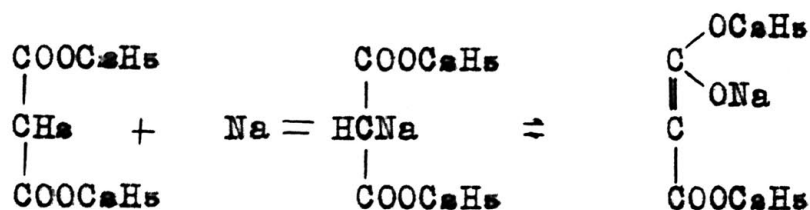
1.) Ber. 20. 1325. Lange.



By the action of KNO_3 these acid radical substituted malonic esters may be made into iso-nitroso, substituted aceto acetic esters.



Nef¹⁾ gives the formula of sodium malonic ester similar to that of the sodium aceto acetic ester, enol form, that is, the sodium shifting to the carboxyl carbon and forming a double bond.

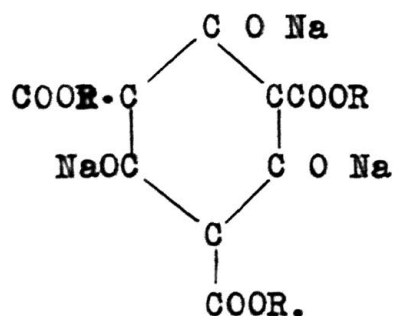


and for the disodium compound.

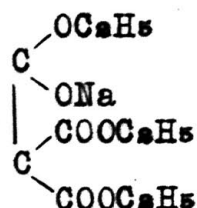


1.) Ann. 266. 67 Nef.

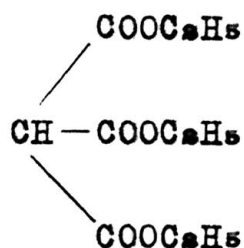
He says that the reactions can not be explained by the saturated formula, because the sodium should not be very replacable when attached to carbon. In the unsaturated form there is, on the other hand, a chance for other substances to add directly and then split off the sodium salt. As a second reason, he brings forward the fact that at a higher temperature^{2.)} the sodium malonic ester loses alcohol and forms the acetylene derivative $\text{CONa}\equiv\text{C COOR}$ which polymerizes to form sodium phloroglucin tricarboxylic ester.



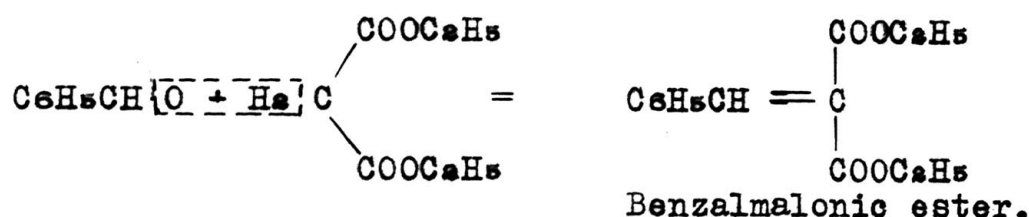
Sodium malonic ester re-acts with chlorcarbonic ester to give an acid, $\text{C}_{10}\text{H}_{16}\text{O}_6$, which is stronger than carbonic acid, and Nef thinks that this is explained better by his structure,



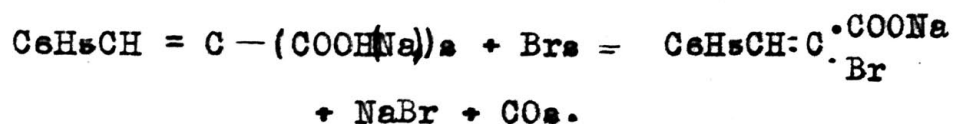
than by the ordinary structure,



Benzaldehyde^{1.)} re-acts with malonic ester in the presence of either fuming hydrochloric acid or of acetic anhydride^{2.)} to give Benzal malonic ester and water.



Benzal malonic ester re-acts with bromine with difficulty. The brom addition product may be made by letting the two stand dissolved in chloroform. If the ester is warmed with baryta solution and then neutralized with hydrochloric acid, the free benzal malonic acid is obtained. This acid is fairly strong, forms metallic salts, and can be reduced to benzyl malonic acid $\text{C}_6\text{H}_5\text{CH}_2 \cdot \text{CH} \cdot (\text{COOH})_2$. With bromine it breaks down as follows:



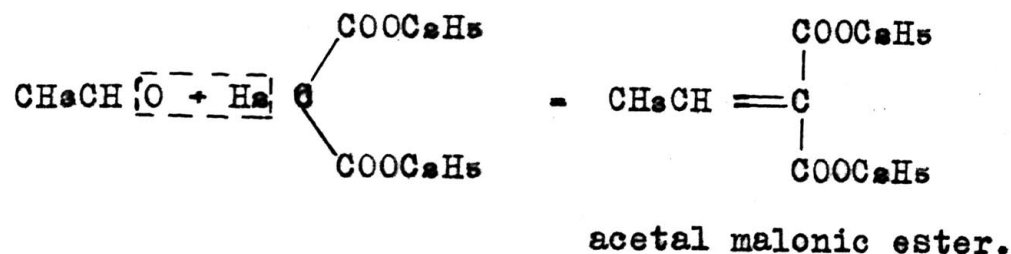
Acetaldehyde in the presence of acetic anhydride forms two condensation products with malonic ester,

1.) Ber. 14 348

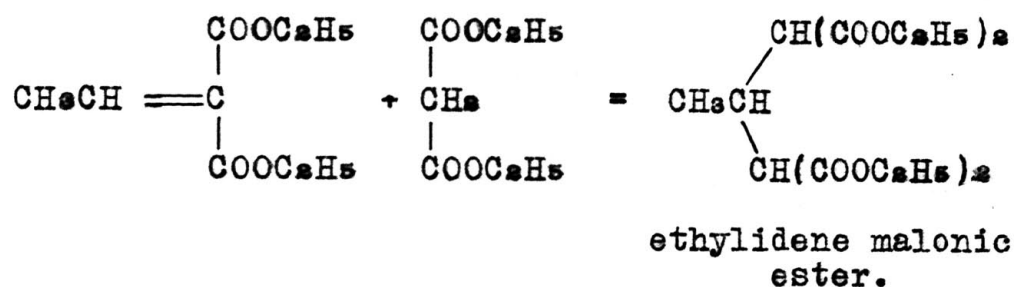
2.) Ann. 218. 132 Claisen.

reaching with either one or two moles of the ester.

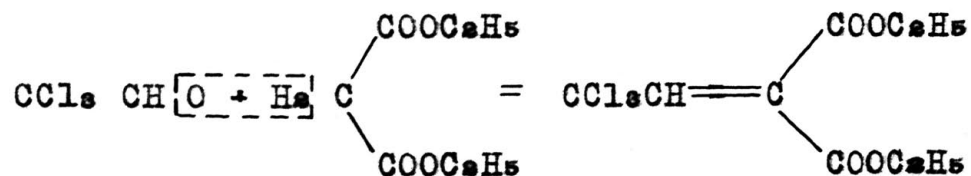
The reaction may be considered to go on as follows:



Then a second molecule of malonic ester re-acts with the acetal malonic ester to give ethylidene malonic ester.

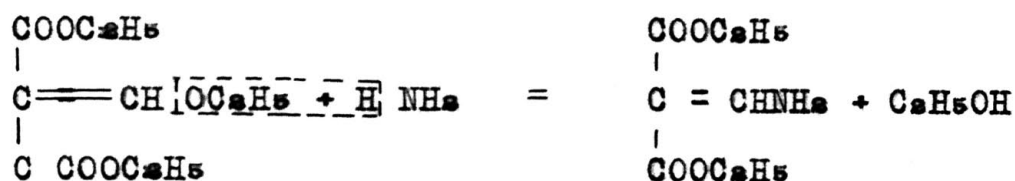


Paraldehyde^{1.)} in the presence of acetic anhydride condenses with malonic acid, breaking off CO_2 , and forming crotonic or β methyl glutaric acid, according as one or two molecules of the malonic acid re-act with the paraldehyde.



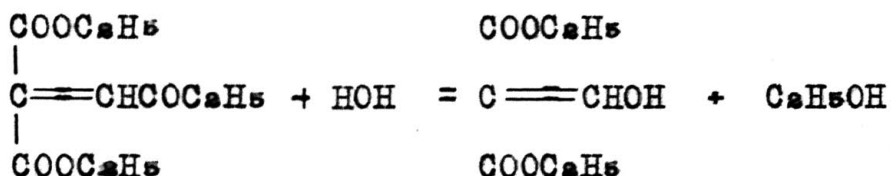
1.) Ann. 218. 145. Kommenos.

The reactions of ortho formic ester 2.) with malonic ester in the presence of acetic anhydride and of ZnCl_2 give another method for synthesis. Alcohol is split off, and ethoxy methylene malonic ester formed. This compound is very reactive. With ammonia, it goes over to amido methylene malonic ester.



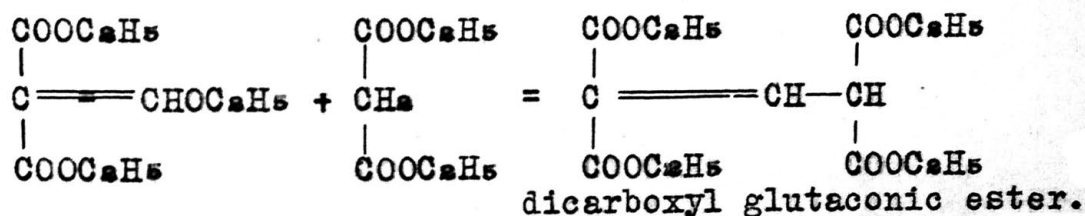
Ethoxy methylene malonic ester.

With aniline it forms a similar anilido compound. In the presence of caustic potash, the $\text{C}_2\text{H}_5\text{OH}$ is split off and hydroxy methylene malonic ester formed.



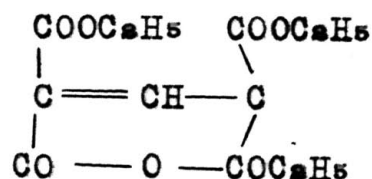
This is an acid which forms metallic salts.

Ethoxy methylene malonic ester can also react with malonic ester to form carboxyl glutaconic ester eliminating alcohol.

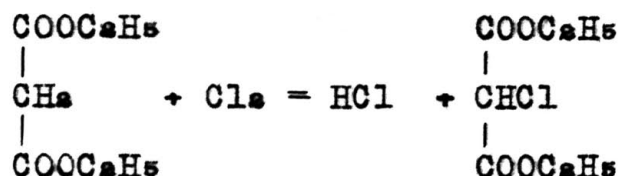


2.) Ann. 297. 1, 75 Claisen.

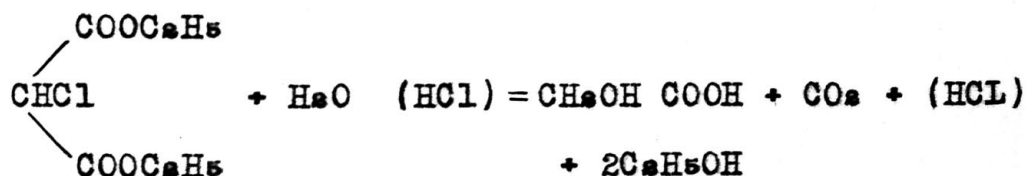
With loss of alcohol this goes over to ethoxy cumalin dicarbonic ester.



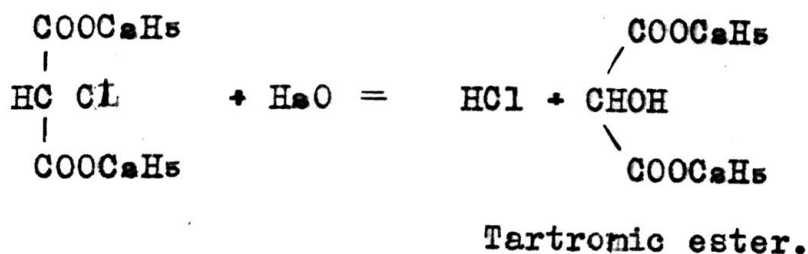
Halogens^{1.)} will replace the methylene hydrogen directly, forming either mono or di substituted products. When chlorine gas is led into malonic ester, the hydrogen is replaced.



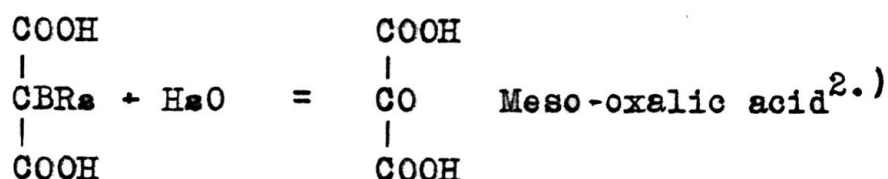
By boiling with hydrochloric acid, the chlor malonic ester hydrolyzes to hydroxy acetic acid. By hydrolysis with caustic potash and then neutralizing with HCl tartaric acid is obtained.



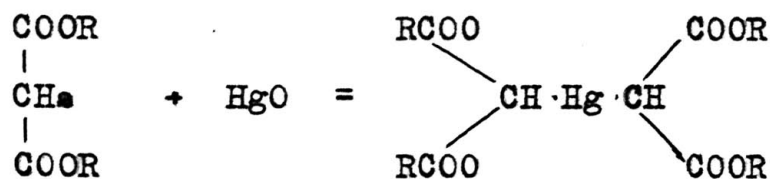
1.) Ann. 209. 218 Conrad and Bischoff.



Dibrom^{1.)} malonic acid can be made by the action of bromine on malonic acid in formic acid solution in the sunlight. It breaks down when hydrolyzed with baryta to form meso-oxalic acid.



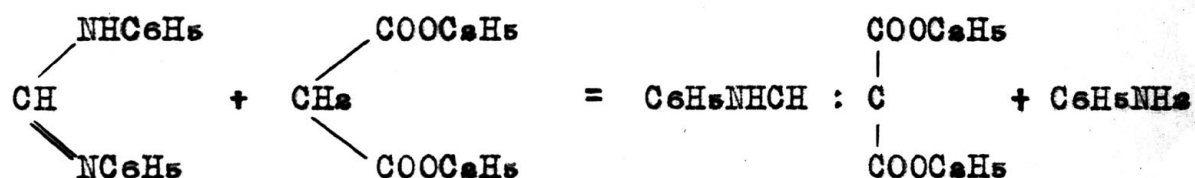
By the action of freshly precipitated mercuric oxide^{3.)} on malonic ester the methylene hydrogen is replaced by mercury.



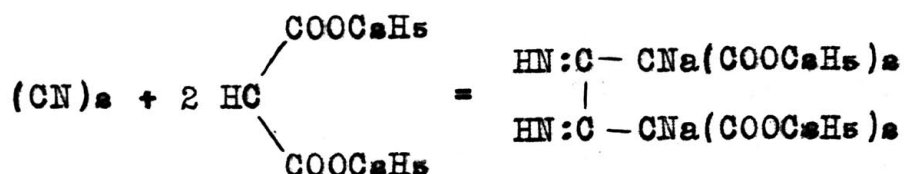
The calcium^{4.)} Salt of malonic ester $\text{Ca}(\text{C}_7\text{H}_{11}\text{O}_4)_2$ is formed by the action of calcium on malonic ester. Aluminum amalgam replaces a hydrogen, giving $\text{Al}(\text{C}_7\text{H}_{11}\text{O}_4)_3$

- 1.) Ber. 35. 1374. Willstätter.
- 2.) Ber. 35. 1819. Conrad and Rembach.
- 3.) Ber. 41. 2087. Schranth and Schoeller.
- 4.) Meyer and Jacobson I, II, 2; 335.

The alkyl, disubstituted, formamidines react with the methylene hydrogens of malonic ester,^{1.)} splitting off the primary amines and substituting, for the H₂ of the :CH₂, the group :CHNHR. This reaction takes place when the formamidine has been heated with the malonic ester. With diphenyl formamidine the reaction is as follows:



Cyanogen^{2.)} re-acts with malonic ester to give two compounds. When cyanogen gas is led into a solution of sodium, malonic ester a dark red crystalline precipitate is formed. This is a dimido derivative of oxaly^{3.)} dimalonic ester.

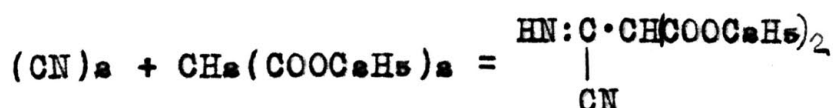


By the action of more cyanogen on a solution containing sodium ethylate a second compound is formed, a dicyanmalonic^{3.)} ester.

1.) Ber. 35. 2496. J. Am. Chem. Soc. 31. 1148 Dains.

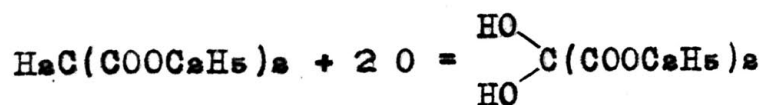
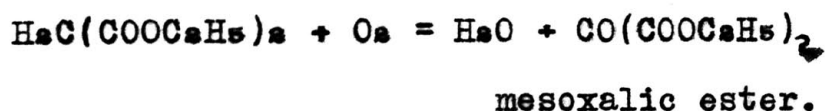
2.) Ber. 31. 191 Traube.

3.) Ber. 31. 2946, Traube.



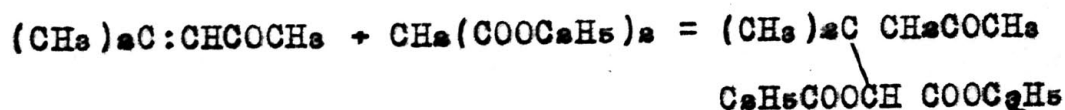
dicyan malonic ester.

Nitrous^{1.)} acid re-acts with malonic ester oxidizing it to mesoxalic ester and to dioxy malonic ester.

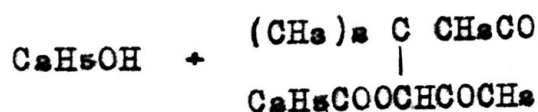


dioxy malonic ester.

Malonic ester also shows its acid properties by breaking into the $\text{H}\cdot$ and $\cdot\text{HC}(\text{COOC}_2\text{H}_5)_2$ groups and adding to either two or three bond, unsaturated compound. With mesityl oxide it re-acts to form di-methyl di-hydro resorcylic ester.^{2.)}



which with loss of alcohol goes over to



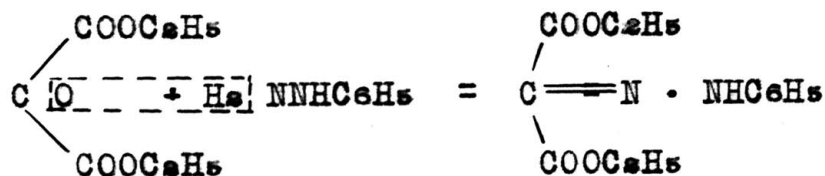
di-methyl dihydro resorcylic ester.

- 1.) Meyer and Jacobson I, II 2. 335.
- 2.) Meyer and Jacobson I, II 2. 335.

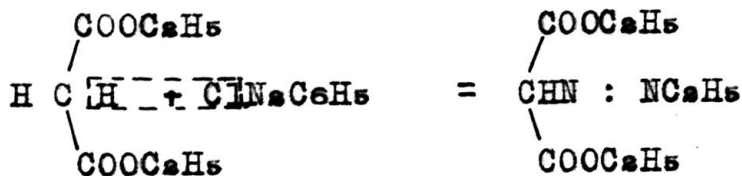
Sodium malonic ester re-acts with CsCl_2 replacing the H groups by a : CS group.



With diazo benzene chlorid^{1.)} malonic ester re-acts, splitting off one molecule of HCl , and giving a substitution product which is the same as that gotten by treating mesoxalic ester with phenyl hydrazine. This requires a re-arrangement of the hydrogen in either one group or the other.



Mesoxalic ester



As the compound formed is not soluble in caustic potash, the probability lies with the hydrazine formula, the second hydrogen going over to the nitrogen to which the phenyl group is attached.

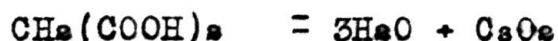
Later^{2.)}, however, R. Meyer found that this benzene azo malonic ester would form silver salts. This

1.) Ber. 21, 11 Victor Meyer.

2.) Ber. 24, 1241. R. Meyer.

would point to the second form. It may be that the two are tautomeric.

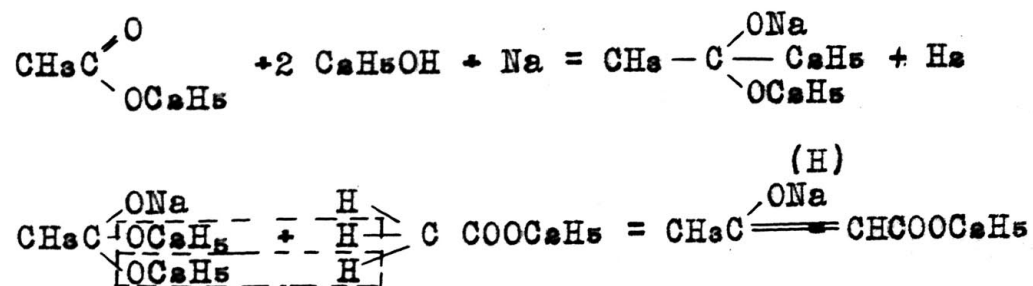
By distilling with phosphorous pentoxide^{1.)} a rather unusual reaction takes place. The malonic ester is dehydrated to form carbon sub-oxide or C_3O_2 .



This may be collected by using a receiver which is cooled to $-50^{\circ}C$ by liquid air. It oxidizes readily to carbon dioxide and can be analyzed by that method.

ACETOACETIC ESTER.

Acetoacetic ester is another compound containing methylene hydrogen and it is found to have a large number of reactions similar to those of malonic ester. It is formed by the action of sodium on ethyl acetate in the presence of alcohol.



This structure is analogous to one of those given for

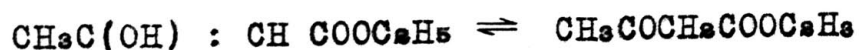
1.) Ber. 39, 689. Diels, Wolf.

malonic ester, and is tautomeric with the formula $\text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5$, which is the formula usually used for aceto acetic ester. It has been proven that both structures exist tautomeric when the aceto acetic ester goes into solution.

With sodium^{1.)}, the aceto acetic ester in solution, in alcohol- and water,-free benzene or ether reacts, giving off hydrogen and forming sodium aceto acetic ester. This reaction takes place as follows probably:



It is probable that the sodium salt has the enol form, because it is possible to obtain only the mono sodium aceto acetic ester, which would be explained by assuming that the sodium would replace only the hydrogen of the hydroxyl group. Other reactions, however, lead to the assumption that both forms are present in a solution of of sodium aceto acetic ester.

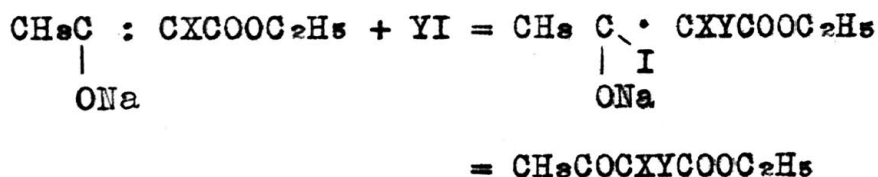
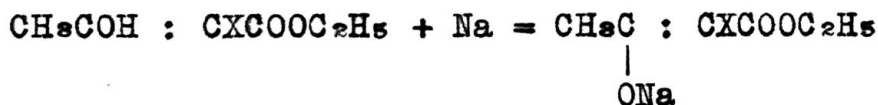
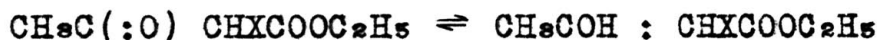
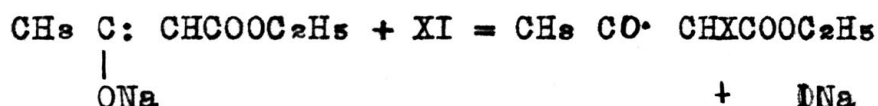


Sodium aceto acetic ester can also be formed by the action of sodium ethylate in solution on aceto acetic ester. The resulting compound is the same as that above and in this case, too, it is impossible to

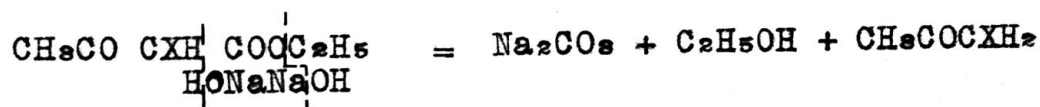
1.) Ann. 186 184. Williams.

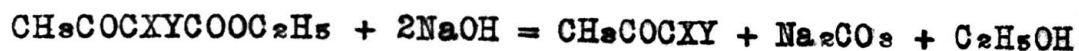
obtain more than the mono substitution product.

By the use of the alkyl iodides, the sodium may be replaced by an alkyl group, and after the one alkyl group has been introduced, the second hydrogen becomes replacable by sodium and then, by a second alkyl group which may be the same, or different from the first. The mechanism of the reaction may be as follows:



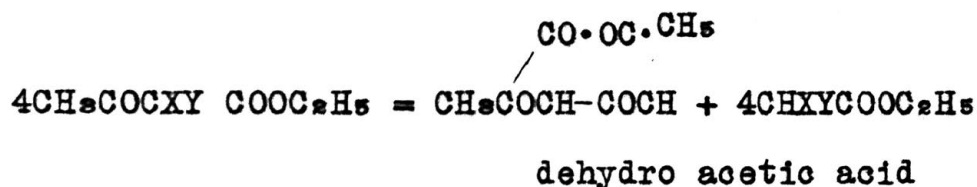
The sodium salt exists in the enol form. The alkyl iodide adds directly at the double bond and then splits off a sodium iodide. The above structure is given to the substituted aceto acetic ester because when it is hydrolyzed with NaOH, a ketone is formed which seems to have that structure. The hydrolysis is as follows:



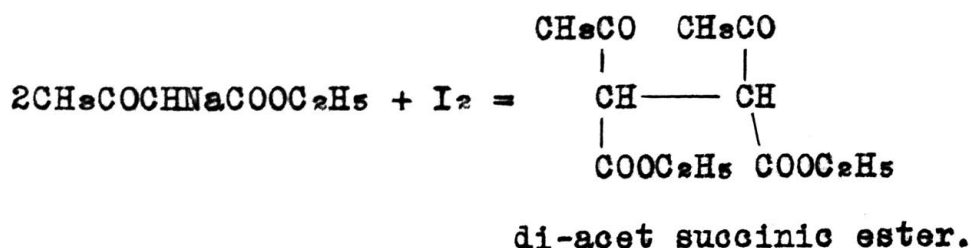


This is a synthetic method for the preparation of the higher ketones. When the X or Y are acid groups, the ketonic acids may be formed. It is therefore possible to synthesize a large number of preparations by this method.

This also gives a synthesis for the higher fatty acids, for by heating the disubstituted aceto acetic ester with sodium ethylate dehydro acetic acid and the disubstituted acetic ester are obtained.



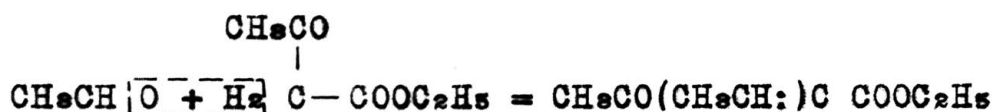
As with sodium malonic ester the halogens react with sodium aceto acetic ester to make two or more molecules add together.



By replacing the second hydrogen by a sodium and then treating with iodine, it should be possible to get the ethylene derivative and other products.

With halogens ¹⁾ aceto acetic ester re-acts to give either mono or di-halides with the structure $\text{CH}_3\text{COCHCl} \cdot \text{COOC}_2\text{H}_5$ and $\text{CH}_3\text{COCCL}_2 \cdot \text{COOC}_2\text{H}_5$.

With aldehydes, ²⁾ aceto acetic ester condenses, yielding an alkyl methylene substitution product. By the action of dry hydrogen chloride on an ice cold mixture of acetaldehyde and aceto acetic ester, a condensation product methyl methylene aceto acetic ester is obtained.



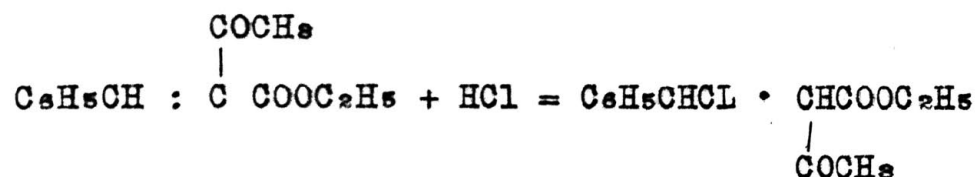
This with Bromine gives a disubstitution product, the bromine probably entering at the double bond.



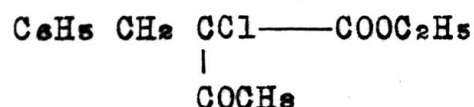
When dry hydrogen chloride is led into a cold solution of benzaldehyde with sodium aceto acetic ester, the phenyl methylene aceto acetic ester is formed. This like the acetaldehyde derivative forms a di-brom addition product. With benzaldehyde saturated with dry

- 1) Ann. 186, 232 Conrad.
- 2) Ber. 14; 345. Claisen.

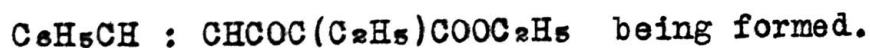
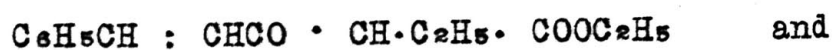
hydrogen chloride it forms an addition product.



Which can be changed over to its isomer

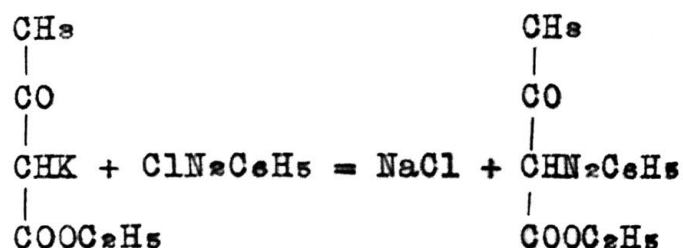


Chloral undergoes condensation with aceto acetic ester to form the tri-chloral addition product and isobutyl aldehyde also forms an analogous product. Aldehydes react with mono-or di-alkyl substituted aceto acetic esters only with great difficulty and then the condensation is with the hydrogen in the acetyl group rather than with the methylene hydrogen.

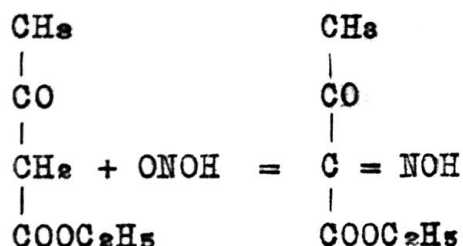


When aceto acetic ester is dissolved in dilute caustic potash solution and to it is added a dilute solution of benzene diazonium chloride¹⁾ and the solution then filtered and acidified, one gets a phenyl diazo salt. This may go over the hydrazine form as the malonic ester derivative of diazo benzene chlorid does.

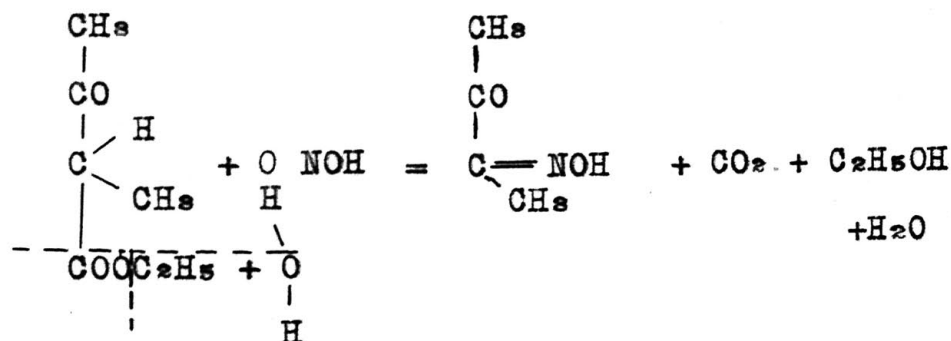
1) Ber. 10. 2075. Victor Meyer.



Nitrous acid¹⁾ oxidizes away the methylene hydrogen of the aceto acetic ester and forms with it nitroso aceto acetic ester.



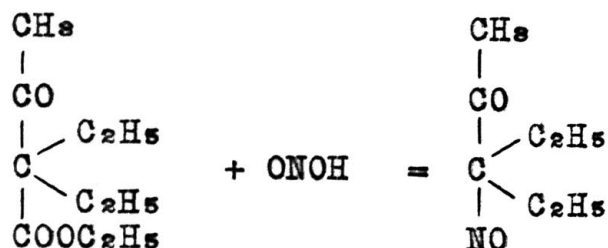
This reaction with nitrous acid does not take place quite as easily when the hydrogens are substituted by one or two alkyl groups. When these are present, carbon dioxide is evolved and ethyl alcohol freed, the reaction being as follows.



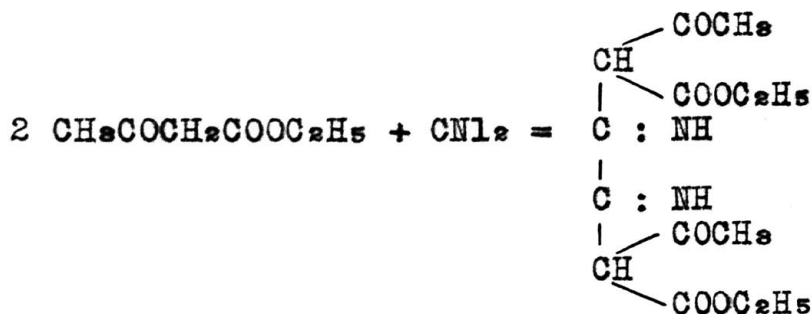
1) Ber. 10. 2075. Victor Meyer.

Ber. 15. 3067. V. Meyer and Ceresole.

With the disubstituted ester the di-ethyl derivative is given.

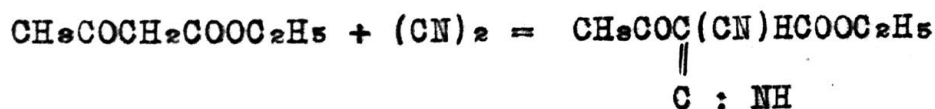


When cyanogen gas is led into a solution containing aceto acetic ester and some sodium ethylate, a white, crystalline, product of di-cyan-di-aceto acetic ester crystallizes out. This, on further addition of cyanogen, goes over to di-cyanaceto acetic ester.



or

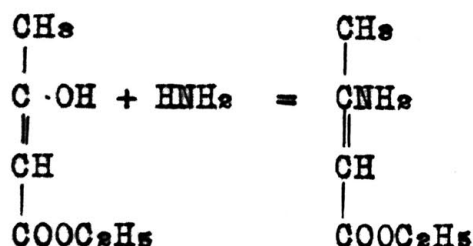
dicyan diacetoacetic ester



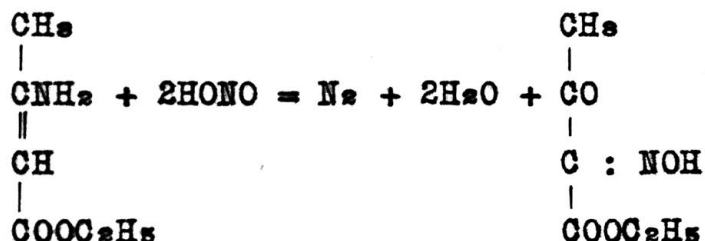
dicyan aceto acetic ester.

Ammonia¹⁾ re-acts with aceto acetic ester to form paramido aceto acetic ester

1) Ann 226. 298. Collie.

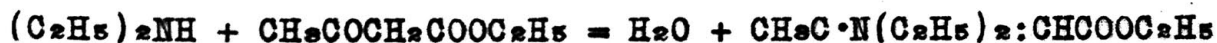
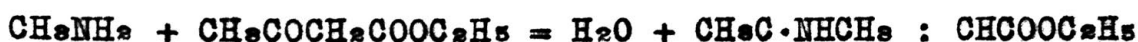


With sodium nitrite in acetic acid solution this goes over to nitroso aceto acetic ester with evolution of nitrogen.



With acetic anhydride, paramido aceto acetic ester condenses to form a pyridine ring, splitting off ammonia and alcohol and yielding hydroxylutidin carbonic ester $\text{C}_5\text{NH} \cdot \text{OH} \cdot \text{CH}_3 \cdot \text{COOC}_2\text{H}_5 \cdot \text{CH}_3$ 1, 3, 5, 6.

Methyl amine¹⁾ and aceto acetic ester re-act to give a di-ethyl paramido aceto acetic ester.

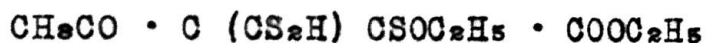


Aniline re-acts with aceto acetic ester at room temperature in from ten to twelve hours to give paranilido

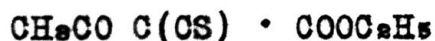
1) Ann 236. 70 Knorr.

acetoacetic ester and this, at higher temperatures, splits off an alcohol replacing it by an anilido group.

Acetoacetic ester re-acts with carbon bisulfid¹⁾ in the presence of alcohol to give thio-rufic acid.



With a metallic oxide, on the other hand a product is obtained which contains one less alcohol and carbon disulfid than th^o rufic acid.



Sulfuryl chlorid²⁾ gives two reactions with aceto acetic ester. It may replace either one or both of the methylene hydrogens by chlorine forming either



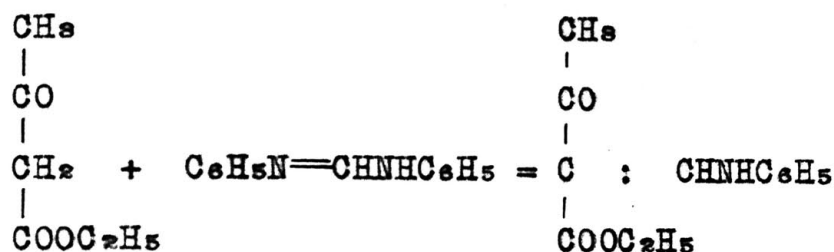
Phosphorous pentachlorid dehydrates aceto acetic ester and replaces one H by a Cl giving $\text{CH}_3\text{CCl} : \text{CH} \cdot \text{COOC}_2\text{H}_5$.

With the disubstituted formamidines³⁾ aceto acetic ester re-acts like malonic ester did, splitting off a primary amine, and forming a methylene anilido (or amino) derivative.

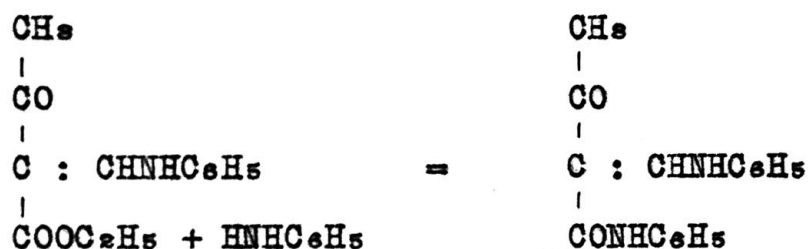
1) Ber. 10. 701. Norton and Oppenheim.

2) Ber. 11. 567.

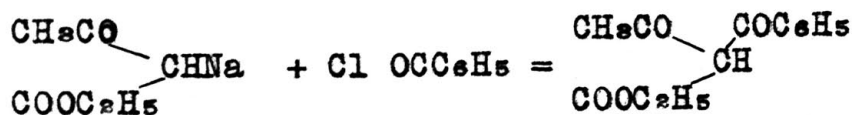
3) Ber. 35. 2496. Dains.



This however at a higher temperature is acted upon by the molecule of the amine, formed, splitting off alcohol and forming the anilido derivative according to the following reaction.



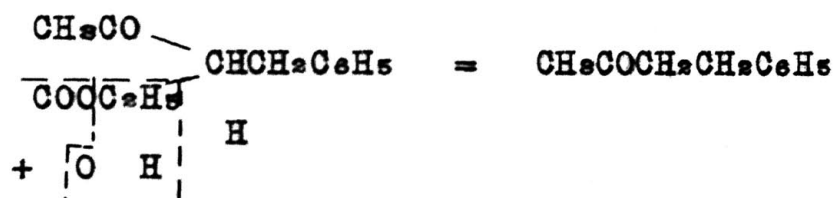
When aceto acetic ester is treated with either an acid chlorid or any straight chain substituted chlorid, in the presence of sodium ethylate, it seems to be very easy to split off an NaCl and form an addition product. Thus, with acetyl chlorid, diacetyl acetic ester¹⁾ is formed. With benzoyl²⁾ chlorid, benzoyl aceto acetic ester is formed.



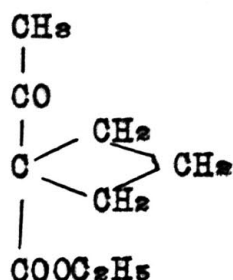
1) Ber. 16. 1368. and 2762. Elion.

2) Ann. 187. 1. Bonne'

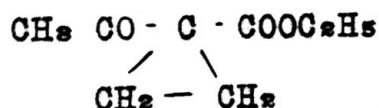
Benzyl¹⁾ chlorid also gives an addition product, which, on undergoing ketonic hydrolysis, yields methyl phenyl-ethyl ketone according to the following reactions.



In the same way it is possible to form some ring compounds by the use of di-substituted halides with sodium aceto acetic ester. Trimethylene²⁾ bromide re-acts with aceto acetic ester to form a four carbon ring.



Ethylene bromide re-acts to give a triatomic ring



Thus aceto acetic ester can be used in a number of

1) Ann. 187. 11. Ehrlick.

2) Ber. 16. 1787 and 2136. W. H. Perkins Jr.

syntheses for ring compounds and their derivatives.

CYANACETIC ESTER.

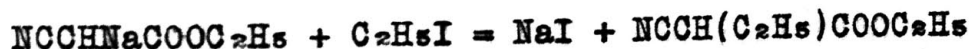
Cyanoacetic ester is another compound in whose structure is found a CH_2 group connected with two very negative groups, a cyanogen and a carboxyl;



and which may be considered to have the two tautomeric structures for its salts:

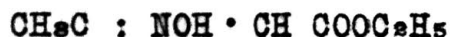


Its reactions are very similar to those already given for malonic ester and for aceto acetic ester. Only a few of the more important ones, then, will be noted. Its hydrogen is, as has been noted for the others, very acid, and is, therefore, replaceable by metals. The sodium salt may be made by the treatment of the ester with either metallic sodium or sodium ethylate. This sodium salt re-acts with alkyl halides to give the alkyl derivatives by a reaction analogous to that with malonic ester or with aceto acetic ester.

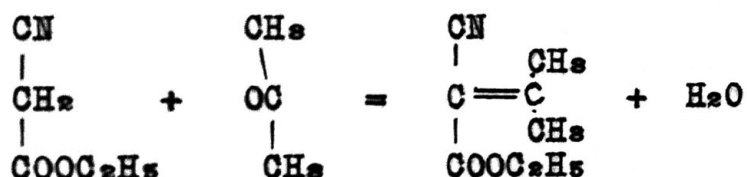


Acyl chlorides replace the sodium of sodium cyanoacetic ester by the acyl group. Acetyl chlorid gives aceto cyan acetic ester $\text{CH}_3\text{CO} \cdot \text{CH}(\text{CN}) \cdot \text{COOC}_2\text{H}_5$.

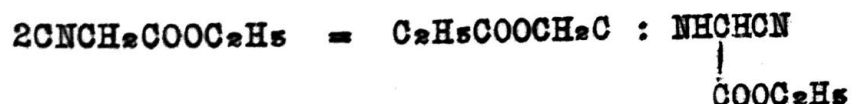
With nitrous acid, cyanoacetic ester gives oximino cyanoacetic ester which has practically the same structure as the aceto acetic ester derivative



Acetone condenses with cyanoacetic ester in the presence of diethyl aniline to form isopropyliden cyanoacetic ester.

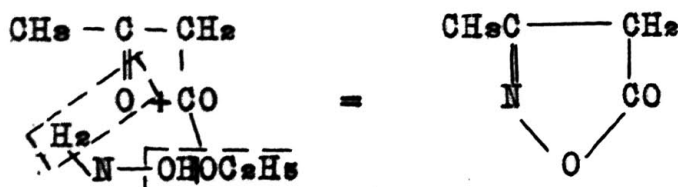


With ammonia and acetone another condensation takes place yielding a dioxypyridine derivative. Aldehydes, with ammonia, also form condensation products when added to cyanoacetic ester. Indeed, the cyanoacetic ester is so reactive that it even forms addition products with itself.



METHYL ISOXAZOLON.

Hantzsch¹⁾ prepared methyl isoxazolon by the action of hydroxyl amine on aceto acetic ester in alkaline solution. He dissolved one and one-third moles of hydroxyl amine hydrochlorid in water, neutralized this with caustic soda solution and then added a volume of the caustic soda equal to that necessary for the neutralization. He then heated the solution to 40° - 50° C. and added, without cooling, one mole of aceto acetic ester. After standing several hours, the solution should give, with an excess of concentrated hydrochloric acid, a yellow, crystalline mass which may be crystallized from hot water or purified by making the barium salt.



Whlenhuth²⁾ found this method very uncertain, and so advised a second method. He prepares the oxime of aceto acetic ester by adding a concentrated water solution of hydroxylamine (one mol.) to an equimolecular mixture of aceto acetic ester and aniline. The oxime is extracted with ether and the ether left to

1) Ber. 24. 497.

2) Ann. 296, 46.

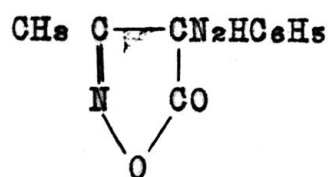
evaporate off by standing. The oxime is then put into a test tube and two-and-a-half times its volume of concentrated ammonia water added. The mixture is boiled until it is brought down to the volume of the oxime used and is then poured out onto a watch glass. When treated with a little concentrated hydrochloric acid, the ammonia salt is broken down and free methyl isoxazolon obtained. This method can be used only for very small quantities. Uhlenhuth says that not more than two cubic centimeters can be worked up at one time. If a larger quantity is used, the methyl isoxazolon breaks down.

The CH_2 group in the methyl isoxazolon is between two negative groups, and so the hydrogens should, and do, have acid properties. In fact, there is enough ionization so that the water solution re-acts acid with indicators. It forms metallic salts with potassium, barium, silver, and in fact, with almost any metal. With amines, either primary or secondary, addition products are formed. Ammonia and methyl isoxazolon gives $\text{C}_8\text{H}_{11}\text{O}_3\text{N}_3$ which is a white salt. Di-ethyl amine and methyl isoxazolon re-act to form a white salt $\text{C}_{12}\text{H}_{19}\text{O}_3\text{N}_3$. Anilin, naphthylamine, and phenyl hydrazine addition products have also been made.

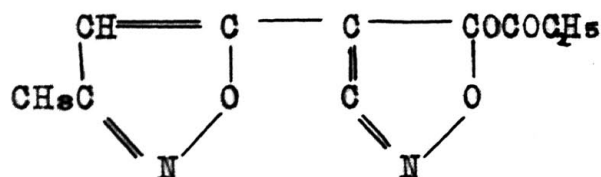
The esters of methyl isoxazolon can be prepared by the action of the alkyl halide on the silver

salt. Both the methyl and ethyl esters have been prepared. They are white, crystalline, salts melting at 74°C . and 91°C . respectively.

Diazo benzene chlorid¹⁾ re-acts, as with other compounds containing methylene hydrogen, splitting off an HCl and forming



With acetic anhydride, two methyl isoxazolon rings condense to form



Since the hydrogen of methyl isoxazolon was acid and since the compound has been found to give several of the reactions which methylene hydrogen gives, work was started to see whether a reaction would take place with disubstituted formamides according to the method discovered by Dr. Dains²⁾. To do this, however, it was necessary to get some methyl isoxazolon to work with.

1) Ber. 27. 1174. Knorr and Reuter.

2) Ber. 35. 2496.

EXPERIMENTAL.

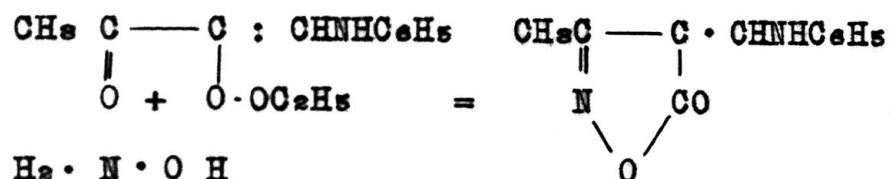
---0---

For this preparation the method of Hantzsch¹⁾ was first tried. Twenty-seven grams of $\text{H}_2\text{NOH} \cdot \text{HCl}$ was dissolved in a little water and neutralized with thirty-two grams of caustic soda. To this was added thirty-nine grams of aceto acetic ester, the container being shaken meantime, and the temperature kept below 55°C . The solution was carefully neutralized with concentrated hydrochloric acid; and, as nothing crystallized out on standing, some of the solvent was distilled off under reduced pressure at $40^\circ - 50^\circ\text{C}$. Now, when it stood, a white solid crystallized out. This was not methyl isoxazolon because it burns with explosive violence. It has no definite melting point, but when heated to about 250°C ., it turns black and breaks down.

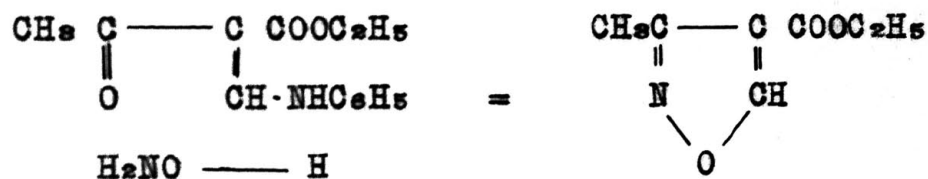
The same method was tried using a little pyridine as a catalizer, but it was again unsuccessful. A third trial was made by keeping the reacting substances cold with ice when they were mixed, and then heating them an hour at $40^\circ - 50^\circ\text{C}$., but with the same results.

1) Ber. 24. 497.

It was thought that if the anilido methylene derivative of aceto acetic ester was obtained, this might react with hydroxylamine to form the isoxazolon just as aceto acetic ester did.



This should give the same derivative as would be obtained by the reaction of methyl isoxazolon with diphenyl formamidine. A second reaction, however, is also possible, and this is the one that more probably took place.



This compound was not described in the literature, but the dimethyl isoxazole carbonic ester was described as an oil with an odor like pyridine. This corresponds with the properties of the substance obtained from this reaction. In carrying out these reactions, the o-anisyl and o-phenetetyl derivatives were used because aniline tends to form di-anilido derivatives with aceto

acetic ester and these would not re-act as well as the mono derivatives.

EXPERIMENTAL

---o---

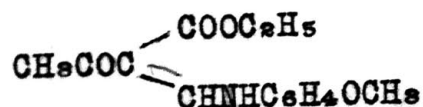
Di-o-anisyl formamidine was made by heating forty grams of o-anisidine and twenty-five grams of orthoformic ester on an oil bath at 140°C . for two hours. On cooling, the whole mass solidified, and was re-crystallized from benzene diluted with ligroin. I obtained a yield of thirty-one grams, melting point $105^{\circ} - 106^{\circ}\text{C}$.

About twenty grams of this di-o-anisyl formamidine was then added to twenty grams of aceto acetic ester and heated on the oil bath at 125°C . for an hour. A product was obtained which was very soluble in benzene, alcohol and gasoline. This product was re-crystallized by dissolving it in alcohol, acidifying, and then precipitating with water. After a second re-crystallization from gasoline, it was found to have a melting point at 107°C . An analysis for nitrogen showed:

Found N = 5.86%

N = 5.50%

Theory for



N = 5.32%

A smaller amount of a second product was obtained from the reaction above, which was only slightly soluble in gasoline and which had a higher melting point than the first, 225° - 226°C . This was probably the secondary product.

In a second trial of this reaction, it was found that by heating the oil bath to only about 80°C . for one hour, very little of the secondary product was formed, the primary reaction taking place almost completely.

A solution of five grams of hydroxyl amine and four grams of sodium carbonate in water was then made and added to about one hundred and fifty cubic centimeters of alcohol in which was suspended ten grams of the o-ethoxy anilido methylene aceto acetic ester. The mixture was allowed to stand several days and then the alcohol was distilled off. An oil separated from the mixture, and this was freed from the water by the use of a separatory funnel. This oil had an odor like pyridine. It began to distill at 224°C , with decomposition. A white crystalline solid was left in the condenser tube, Melting point, 170°C .

Di o-phenetdyl formamidine was made in exactly the same manner as the di -o-anisyl formamidine

and then by heating this with aceto acetic ester on the oil bath at 120°C . for one hour, the o-ethoxy anilido methylene aceto acetic ester was obtained and recrystallized from gasoline. Melting point, 111° .

Analysis:

Calculated for $\text{C}_{15}\text{H}_{19}\text{NO}_4$; N = 5.05%

Found N = 4.75%

N = 4.84%

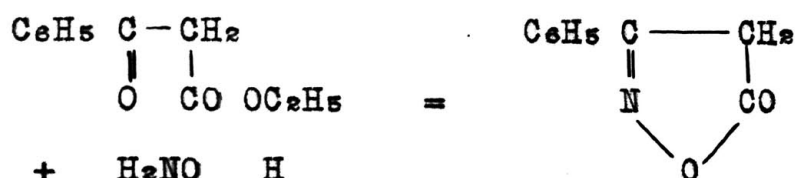
Two grams of this were then dissolved in alcohol, and to it was added a water solution of two grams hydroxylamine hydrochloride and two grams of sodium carbonate. On adding this solution to the alcohol, the original aceto acetic ester derivative separated out, but on standing this re-dissolved. After several days, the alcohol was distilled off and obtained as an oil which was insoluble in water and which had the same odor as the one obtained from the o-anisyl derivative. There was not enough of it, however, to do any further work with.

PHENYL ISOXAZOLON

Phenyl isoxazon¹⁾ was made by dissolving benzoyl acetic ester in alcohol or acetic acid and adding to it a solution of one mol of hydroxyl amine

1) Ber. 24. 140. Claisen and Zedel.

hydrochlorid in water. The mixture is then heated for thirty minutes and the phenyl isoxazon allowed to crystallize out.



Phenyl isoxazon

Phenyl isoxazon may also be obtained by the action of hydroxyl amine hydrochlorid on benzoyl acetamide¹⁾, the reaction being the same as above except that ammonia is split off instead of alcohol. It is a white, crystalline compound. Melting point 152°C. From alcohol it crystallizes in needles which seem to be very pure.

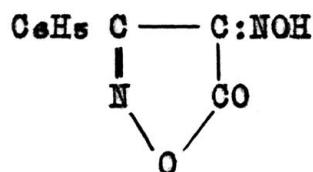
As is seen in the above structural formula, phenyl isoxazon has a methylene hydrogen and it has been found that its reactions correspond very closely with those of other compounds containing methylene hydrogen. In water solution it is a fairly strong acid, one hydrogen being replacable by a metal.²⁾ The salts of quite a number of metals have been obtained. The alkali and alkali earth metals form salts which are soluble in water. The other salts are only slightly

1) Ann. 266, 334. Obrégio.

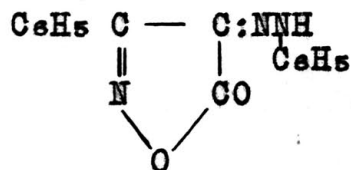
2) Ber. 24. 140. Claisen.

soluble. Addition products are formed with amines. Those with ammonia, methyl amine, ethyl amine, aniline and mono methyl aniline have been obtained. The phenyl hydrazine addition product reduces Fehlings solution.

Esters¹⁾ of Phenyl isoxazolon may be obtained by the action of alkyl iodides on the silver salt of the isoxazolon. The methyl and ethyl esters have been obtained. With nitrous acid, phenylisoxazolon yields iso nitroso phenyl isoxazolon²⁾



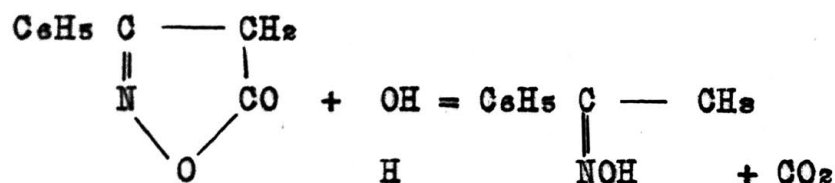
With benzene diazonium chlorid a reaction similar to that with aceto acetic ester is given. The product being



With bromine³⁾ a substitution product $\text{C}_9\text{H}_8\text{O}_2\text{NBr}$ is obtained. Acetic anhydride when boiled for an hour

- 1) Ann. 266. 33.
- 2) Ber. 24. 140.
- 3) Ber. 39. 352. Posner.

with phenyl isoxazolon yields an acetyl derivative of phenyl isoxazolon. Heated with concentrated hydrochloric acid, phenyl isoxazolon breaks down with a loss of carbon dioxide.



Since so many reactions of the methylene hydrogen were obtained, it was thought that there should also be a reaction with the formamidines. Experiments were therefore carried out to make these compounds and to study their properties.

EXPERIMENTAL

— 0 —

Phenyl isoxazolon was made by the reaction of hydroxylamine hydrochloride on benzoyl acetic ester. In the preparation, twenty grams of benzoyl acetic ester were added to about one hundred and fifty cubic centimeters of alcohol and to this was added a concentrated solution of ten grams of hydroxylamine hydrochloride in water. The mixture was heated on a water bath and then, on standing, the phenyl isoxazolon crystallized out as a white salt. Yield fifteen grams.

It was re-crystallized from alcohol and had a melting point at 152°C . Analysis showed:

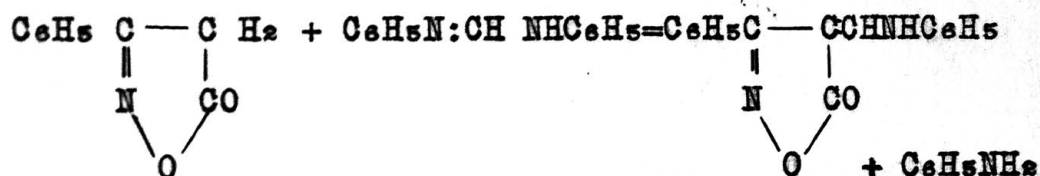
Calculated for $\text{C}_9\text{H}_7\text{O}_2\text{N}$ $\text{N} = 8.71\%$

Found - - - - - $\text{N} = 8.53\%$

$\text{N} = 8.56\%$

ANILIDO METHYLENE PHENYL ISOXAZOLON

When equal molar quantities of phenyl isoxazolon and diphenyl formamidine were heated in an oil bath, at 120°C ., for one hour, the mixture melted and, on cooling, solidified. This solid was dissolved in hot alcohol and, on cooling, a yellow crystalline compound separated out. This, on being crystallized from ethyl acetate, comes out as beautiful rhombic crystals, melting point 145°C . The alcohol residue from which this product was crystallized gave, after it had been evaporated down and treated with benzoyl chlorid, a large amount of benzanilid. Melting point 160°C . The reaction was probably as follows:



Analysis:

Calculated for $C_{16}H_{12}N_2O_2$ N = 10.62%

Found N = 10.28%

N = 10.29%

Heated gently with dilute sodium hydroxide, this compound breaks down and forms a white, flaky, crystalline sodium salt which, when re-crystallized from alcohol, turned brown at $269^{\circ}C$. and then melted with decomposition at $278^{\circ}C$. An analysis of this salt for sodium, using about one-tenth gram sample gave

Na = 10.5%.

Theory for $C_6H_5C \cdot CH:CH NHC_6H_5$

\parallel
NO Na

Na = 8.85%

When a solution of this salt was acidified, if it had not been crystallized and separated from the original solution, carbon dioxide was evolved, proving that it was split off in the reaction. The acid was also formed and a nitrogen analysis was made of it.

Calculated for $C_6H_5C : NOH \cdot CH : CHNHC_6H_5$

N = 11.72%

Found

N = 11.68%

An unsuccessful attempt was also made to get the same product from the anilido derivative of

benzoyl aldehyde and hydroxyl amine.

Benzoyl aldehyde¹⁾ was made by the action of sodium ethylate on aceto phenone and ethyl formate in ether solution. Then the anilido product was obtained on the action of aniline on the benzoyl aldehyde. Melting point 138°C.

This anilido derivative was then dissolved in alcohol and to this solution was added hydroxylamine and sodium carbonate in slightly more than molar quantities. After standing several days, the alcohol was distilled off and an oil remained. On standing, this gave an impure solid, melting point 98°C., whose properties were not like those of the compound sought. The solution gave no test for aniline.

p-ETHOXY ANILIDO METHYLENE PHENYL ISOXAZOLON

Four grams of di p-phenetdyl formamidine were heated at 120°C. for one hour with two grams of phenyl isoxazon and then a ~~salt~~ ^{product} crystallized from alcohol. Melting point 174°C.

Calculated for $C_{18}H_{16}O_3N$ N = 9.12%

Found

N = 8.85%

1) Ber. 34, 3891.

The residue when treated with caustic soda and benzoyl chlorid gave benz-p-phenetid^{id}

o-TOLUIDO METHYLENE PHENYL ISOXAZOLON

Equal molar quantities of di o-tolyl formamidine and phenyl isoxazolon were heated at 120°C. on an oil bath. The product was crystallized out as a yellow solid from alcohol and then from ethyl acetate. Melting point 170°C.

Analysis:

Calculated for $C_{17}H_{14}O_2N$ N = 10.10%

Found N = 10.02%

SUMMARY

-----o-----

It was found that the methods given in the literature for the preparation of methyl isoxazolon were very uncertain, but that it could be prepared from the oxime. If the distillation of the ammonia from the oxime, in the method of Uhlenhuth¹⁾, was done under reduced pressure a better yield was obtained.

The anilido methylene derivatives of methyl isoxolon could not be made by the action of hydroxyl

1) Ann. 296. 46.

amine on anilido methylene aceto acetic ester, but an oil was gotten which was probably an isoxazole derivative.

Anilido methylene phenyl isoxazolon derivatives were obtained by the action of the di-formamidines on phenyl isoxazolon at temperatures above 120°C . These are broken down by either acids or bases giving off carbon dioxide.

Work on these reactions is as yet very incomplete and will be continued along the same lines. A more detailed study is necessary of the breaking down product of anilido methylene phenyl isoxazolon. It will also be undertaken to make the anilido methylene methyl isoxazolon derivatives by other methods.