

with 40 cc. of ether and filtered again. The reaction product, which weighed 2.9 g. after crystallization from a small amount of a mixture of equal volumes of alcohol and acetone, was identified as 3-nitrophthalimide.

3-Nitrophthalimide.—By use of the procedure described above, we obtained 2.1 g. of 3-nitrophthalimide by heating 5 g. of 3-nitrophthalimide with 5 g. of glacial acetic acid and 8 g. of acetic anhydride for six hours at 145°. A small amount of impure acetamide was secured by fractionation of the distillate.

Summary

Phenol-3-nitrophthalein and resorcinol-3-nitrophthalein are formed by the condensation of 3-nitrophthalic anhydride with phenol and resorcinol respectively. Phenol-3-nitrophthalein dissolves in sodium hydroxide solution with the development of a violet color. A dilute alkaline solution of resorcinol-3-nitrophthalein exhibits a green fluorescence, but not nearly to the same extent as a solution of fluorescein.

When 3-nitrophthalic acid monomethyl ester (1) and dimethyl 3-nitrophthalate are heated with acetic anhydride, each ester remains unchanged. Under similar conditions 3-nitrophthalic acid monomethyl ester (2) yields 3-nitrophthalic anhydride. The isomeric 3-nitrophthalamic acids and 3-nitrophthalamide are converted into 3-nitrophthalimide by treatment with acetic anhydride.

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A NEW MODIFICATION OF THE REFORMATSKY REACTION

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RECEIVED JANUARY 19, 1931

PUBLISHED MAY 6, 1931

Reformatsky published a new method for making β -hydroxy acids from ketones or aldehydes by condensing them with α -iodo esters in the presence of zinc.¹ Later, he and his associates and others² published records of reactions in which bromo acid esters had been substituted for iodo esters. Reformatsky also made the statement that chloro esters react with ketones in a manner analogous to bromo and iodo esters but do not react with aldehydes.³

Although β -hydroxy acids have been made from chloro esters by the use of sodamide,⁴ with an aldehyde or ketone, there is no record in the literature to show that it has been done with zinc as a condensing agent.

We have found that chloro esters do not condense with ketones or aldehydes in the presence of zinc alone, but that the reaction can be effected

¹ Reformatsky, *J. Russ. Phys.-Chem. Soc.*, **22**, 44 (1890).

² Reformatsky, *J. prakt. Chem.*, **54**, 469 (1896); Reformatsky and Plesconosoff, *Ber.*, **28**, 2838 (1895); Lindenbaum, *ibid.*, **50**, 1272 (1917).

³ Reformatsky, *ibid.*, **28**, 2842-2847 (1895); *J. Chem. Soc.*, **70**, 126 (1896).

⁴ Feyerabend, *Ber.*, **38**, 697 (1905).

by the addition of copper powder to the reaction mixture. The following is typical of the procedure used and is a modification of the method of Lindenbaum and others.^{2,5}

A mixture of 35 g. of acetophenone, 38 g. of chloroacetic ester and 35 g. of benzene with 18 g. of zinc and 3 g. of copper is refluxed and heated with a small flame until the most vigorous reaction subsides. When the reaction mixture is shaken frequently the unused zinc does not cake.

After cooling, the mixture is decomposed with 20% solution of ice-cold sulfuric acid, which is added slowly until all the solid matter in the reaction mixture has dissolved. The oily layer is separated and the water layer extracted several times with ether. The ether extract and oil are combined and allowed to remain overnight on anhydrous sodium sulfate. The liquid is decanted and after the ether and benzene have been removed on a water-bath it is fractionated under diminished pressure.

The ester is saponified with 25% alcoholic sodium hydroxide, and refluxed for two hours. The alcohol is then distilled off on a water-bath, the solid salt dissolved in a small quantity of water and the acid precipitated with concentrated hydrochloric acid. In most cases an oil as well as a white precipitate of acid forms in the water solution. When the oil does not disappear on standing or by reprecipitating the acid from sodium carbonate solution, it is removed by drying the crystals of the acid between filter papers or on a porous plate.

Among the condensations accomplished in this way are those of the esters of chloroacetic acid, phenylchloroacetic acid and chlorobutyric acid, respectively, with benzaldehyde, benzophenone, propiophenone, *p*-methoxyacetophenone, *p*-tolyl methyl ketone, acetophenone, ethyl acetoacetate and acetone. These reactions were carried out under varied conditions. The results are indicated in the following table.

Percentage yield is calculated from the original quantity of aldehyde or ketone used

	Product formed	In benzene	In xylene	Without solvent
1 ^a	Cinnamic acid	35% acid	10% acid	22% acid
2 ^a	2,2-Diphenylhydracrylic acid	30% acid	47% acid	52% acid
3	2-Ethylcinnamic acid		33% acid	
4 ^a	<i>p</i> -Methoxy-2-methylcinnamic acid	52% ester	48% ester	
5	<i>p</i> -Tolyl-2-methylacrylic acid	13% ester		No ester
6	2-Methylcinnamic acid	40% ester	10.5% ester	No ester
7	2-Hydroxy-2-methylglutaric acid	27% ester		
8	1-Ethyl-2-methyl-2-hydroxymethylbutyrate	33% ester		No ester
9	1-Phenylcinnamic acid	18% ester		No ester
10 ^a	1-Phenyl-2,2-hydroxy- <i>p</i> -methoxyphenylbutyric acid	27% ester		No ester

^a Some of the original ketone may be recovered.

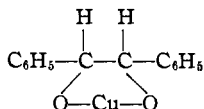
⁵ Rupe and Busolt, *Ber.*, 40, 4537 (1907).

The acids and esters synthesized were identified by their physical constants recorded in the literature, with the exception of 1-phenyl-2,2-hydroxy-*p*-methoxy-phenylbutyric acid. This compound is not described in the literature. From analysis and the Zeisel reaction its formula is $\text{CH}_3\text{-C}(\text{OH})\text{C}_6\text{H}_4\text{OCH}_3\text{CHC}_6\text{H}_4\text{COOH}$.

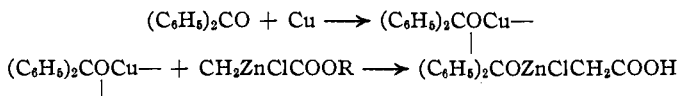
The methyl ester is a colorless liquid, boiling at 113–115° at 20 mm. A yield of about 64% is obtained when calculation is based on the amount of unused ketone recovered. Although the methyl ester has a constant boiling point, the saponification product from it is a mixture of white crystalline solid and oil. This oil is probably one or more of the possible isomers of the acid, since on standing it solidifies to a white crystalline solid. The crystals, white leaflets, dried on filter paper to remove traces of oil, melt at 75°. They dissolve readily in alcohol, ether, benzene and hot water and to some extent in cold water.

Anal. Calcd. for $\text{C}_{18}\text{H}_{20}\text{O}_4$: C, 71; H, 6.71; O, 21.23. Found: C, 72.8; H, 6.8; O, 20.4. Zeisel reaction for methyl group in methyl ester: Calcd.: OMe, 20.6; equivalent, 300.016. Found: 19.82.

The effect produced by copper powder in β -hydroxy acid synthesis is probably due to the formation of a copper-ketone compound such as has been described by Bernoulli and Schaaf.⁶ Two moles of benzaldehyde is combined with copper. The formula assigned by them to the compound is



Since such compounds as this, once formed, do not, as a rule, break up readily, it seems more reasonable to attribute the accelerating effect to some copper-containing radical in solution. In that case a reaction such as the following might be offered as a plausible explanation



According to Bernoulli and Schaaf,⁶ the copper-aldehyde compounds do not form with pure aldehyde or ketone, but only in the presence of a solvent. The rate of formation is dependent on the fluidity of the solvent and the temperature of the solution. These compounds form most readily in benzene as a solvent. Their presence is detected by the green, green-blue or green-yellow color of refluxed solutions of copper powder and an aldehyde or ketone dissolved in benzene or in a chloro ester. These solutions, freed from all unused copper powder, effect β -hydroxy syntheses. A synthesis is also accomplished when dry copper oxide is substituted for copper powder,

⁶ Bernoulli and Schaaf, *Helv. Chim. Acta*, **5**, 721–731 (1922); Fritz Schaaf, *Z. anorg. allgem. Chem.*, **126**, 237–253 (1923).

but no synthesis takes place with anhydrous copper sulfate as a catalyst. Zinc bronze also fails to promote synthesis.

All efforts to form and use the zinc-chloro ester compound, $\text{CH}_2\text{ZnCl-COOH}$, assumed by Reformatsky,² instead of zinc metal and a chloro ester, were unsuccessful.

Cadmium powder alone, as well as cadmium powder with copper powder as condensing agents, fails to promote a β -hydroxy acid synthesis.

In general, then, the reaction is most satisfactory in a medium of benzene (Table). This is not because the copper-aldehyde or copper-ketone compound forms most readily in benzene; the same reaction occurs in some cases (Table) with no solvent other than a chloro ester added to the ketone or aldehyde. The fact leads to the conclusion that the primary function of the additional solvent is the regulation of the temperature of the reaction mixture.

The importance of benzene as a temperature regulator can be seen in its use with phenylchloroacetic ester. If the temperature in these reactions be high, diphenylsuccinic ester is formed. High temperature also destroys some ketones, as methoxyacetophenone, so that a low boiling point solvent must be present to prevent decomposition. In small quantities of benzene (equivalent molar quantities of ketone and solvent), *p*-methoxyacetophenone condenses with chloroacetic ester to a β -hydroxy acid ester, but decomposes with an equivalent quantity of benzene with phenylchloroacetic ester. If, however, enough benzene is used to keep the boiling point of the mixture between 98 and 100°, synthesis takes place.

The length of time for the reaction has a notable effect on the yield of β -hydroxy acid ester. When the calculation is based on the amount of zinc dissolved, the theoretical yield of β -hydroxy acid ester is never obtained. If the percentage yield be calculated from the amount of aldehyde or ketone used, which is found by deducting the amount of unused aldehyde or ketone recovered, fairly high percentage yields are obtained. If the reaction runs long enough to use the theoretical amount of zinc, a viscous residue with high boiling point results, no ketone can be recovered, and the percentage yield of β -hydroxy acid ester is low.

The effects of temperature and reaction time on these reactions are illustrated by the results obtained from successive runs of acetophenone with chloroacetic ester, in various solvents and during periods of time extending from thirty minutes to eight hours. With benzene as a solvent, a one-hour run gave 42% ester and an eight hour gave 38% ester; with xylene as a solvent the yield for a one-hour run was 28% ester and for an eight-hour run, 10.5% ester; without a solvent, the corresponding yields were, respectively, 14% ester and no ester.

High temperature as well as prolonged heating tends to increase the quantity of viscous material formed. For example, when xylene is used

as a solvent, the reaction product forms a char-cake with zinc in the bottom of the flask. With benzene as a solvent, even on prolonged heating, the reaction products continue to dissolve in the solvent.

There is evidence then of reactions subsequent to the formation of β -hydroxy esters and runs of brief periods and minimum reaction temperatures are the most satisfactory. So that, in general, the most satisfactory yields are obtained when the reaction time is limited to the period of most vigorous reaction and when an optimum reaction temperature is secured. Benzene is the best solvent, since it brings the temperature into the necessary range; it also keeps free metal surface available since the reaction products are soluble in it; it obviates the formation of char-cake.

Summary

1. A β -hydroxy synthesis is obtained from α -chloro esters and aldehydes or ketones and zinc, through the action of copper metal or cupric oxide.

2. The catalytic action of copper is accounted for by the formation of an intermediate between copper and the aldehyde or ketone present, which then reacts with the zinc-chloro ester compound of the chloro esters and accelerates the synthesis.

3. Benzene is the best solvent, since it brings the temperature into the necessary range. It also keeps free metal surface available since the products are soluble in it.

Limited reaction time increases yields.

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CYCLIC AMMONO KETONES¹ AND ACID CHLORIDES OF THE QUINOXALINE SERIES

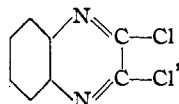
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RECEIVED JANUARY 30, 1931

PUBLISHED MAY 6, 1931

In a previous communication^{1a} quinoxaline was shown to be formally an ammono glyoxal, and experimental evidence was presented in confirmation of this view. In the present article it is desired to consider a number of derivatives of quinoxaline from the standpoint of the ammonia system, and to give the results of the experimental work supporting the analogies advanced.

2,3-Dichloroquinoxaline.—From its structural formula,



¹ The strict ammonia analogues of the aquo ketones are unknown. Because of the third valence of the nitrogen, all ammono ketones are acetals at the same time. Strain, *THIS JOURNAL*, 49, 1559 (1927).

^{1a} Ogg and Bergstrom, *ibid.*, 53, 245 (1931).