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The Preparation of α, α-Disubstituted Glycolic Acids

by

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Chemical Research Division
Directorate of Weapons Systems

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FOREWORD

The work described in this report was performed under Project 1C522301A060, Chemical Agents (U). The experimental data are contained in notebooks 6898, 7112, and 7200. The work was started in August 1963 and completed in March 1965.

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Disposition

When this report has served its purpose, DESTROY it.

DIGEST

Improved syntheses of benzilic acid and of 9-fluorenol-9-carboxylic acid by the respective carbonation of disodium benzophenone ketyl and of disodium fluorenone ketyl in dioxane are described. Potassium 4,4'-di(dimethylamino)benzilate was similarly prepared from dipotassium 4,4'-di(dimethylamino)benzophenone ketyl.

The rearrangements of 1,1-di(p-chlorophenyl)-1,2,2,2-tetrachloroethane to 4,4'-dichlorobenzil and of 1,1-diphenyl-1,2,2,2-tetrachloroethane to benzil, under the influence of hot sulfuric acid, are described. 4,4'-Dichlorobenzil was treated with aqueous potassium hydroxide to obtain 4,4'-dichlorobenzilic acid. 4,4'-Anisil could not be prepared in a similar fashion from 1,1,1-trichloro-2,2-bis(p-methoxyphenyl)ethane (methoxychlor).

Cyclopentylphenylglycolic acid was prepared by the ethynylation of cyclopentylphenyl ketone and subsequent oxidation of the substituted propynol.

In the study of the synthesis of acyloins, which can be rearranged in the presence of an oxidant to glycolic acids, 1-phenyl-1-hydroxy-2-pentanone was prepared by the action of potassium cyanide upon an equimolar mixture of butyroin and benzoin.

Of the various approaches to the α,α-disubstituted glycolic acids studied, only the carbonation of the dimetallic ketyls from aromatic ketones showed merit. By careful adjustment of the reaction conditions, the yields of certain benzilic acids could be raised considerably above those reported in the literature. No satisfactory synthesis of mixed aliphatic-aromatic or fully aliphatic glycolic acids was found. This study was not concerned per se with an improvement of established synthetic procedures, but had as its main objective the investigation of certain reactions that might be applicable to a general method.

CONTENTS

THE PREPARATION OF α,α-DISUBSTITUTED GLYCOLIC ACIDS

I. INTRODUCTION.

There is no general procedure for the synthesis of glycolic acids of the type $RR'C(OH)CO_2H$, where R and R' designate the same or different alkyl, cycloalkyl, aryl, and heterocyclic groups. Various laboratory methods are available, but these are limited in scope, and often the yield is poor. Procedures that have been employed by previous investigators are briefly discussed in the paragraphs that follow.

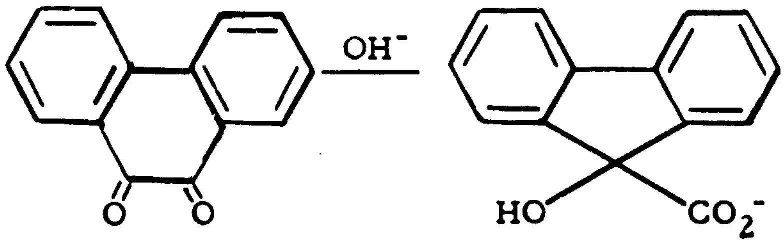
A. The Benzilic Acid Rearrangement.

This reaction, which was discovered by von Liebig[1] in 1838 and was reviewed by Selman and Eastham,[2] is a base-induced transformation of an α-diketone into the salt of an α-hydroxyacid. It can be effected in certain aromatic, semiaromatic (o-quinones), alicyclic, aliphatic, and heterocyclic vicinal diketones. The following equations illustrate the rearrangement:

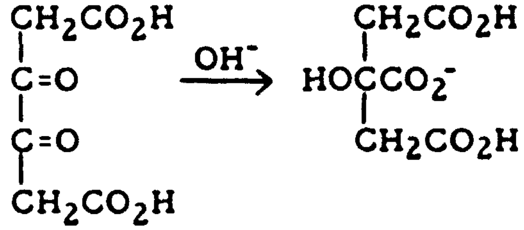
Aromatic diketone[1]:

$$C_6H_5COCOC_6H_5 \xrightarrow{OH^-} (C_6H_5)_2C(OH)CO_2^-$$

Semiaromatic diketone[3,4]:

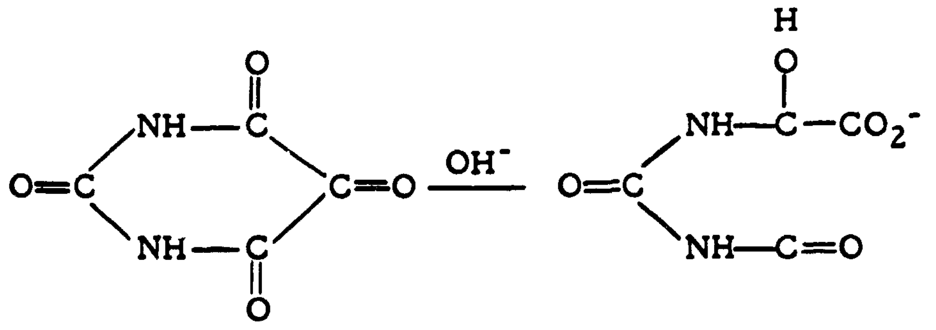


Aliphatic diketone[5]:



$$\begin{array}{l} CH_2CO_2H \\ | \\ C{=}O \\ | \\ C{=}O \\ | \\ CH_2CO_2H \end{array} \xrightarrow{OH^-} \begin{array}{l} \quad CH_2CO_2H \\ \quad | \\ HOCCO_2^- \\ \quad | \\ \quad CH_2CO_2H \end{array}$$

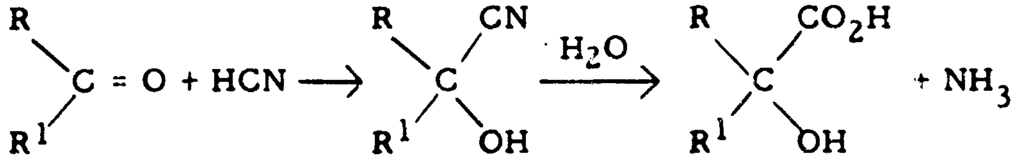
Heterocyclic diketone[6]:



The reaction is simple and, except for isolated instances,[7] irreversible. Its application, however, to the synthesis of α-hydroxycarboxylic acids from dialkyl and alkylaryl diketones has resulted, where successful, in poor yields only.[8]

B. Hydrolysis of Cyanohydrins.

Upon hydrolysis, cyanohydrins derived from ketones yield α,α-disubstituted glycolic acids:



Cyanohydrin can be prepared either by standard procedures (by the reaction of the ketone with hydrogen cyanide in the presence of a basic catalyst) or by the treatment of the ketone-bisulfite addition product with an equivalent of sodium cyanide. The scope of the reaction is very limited, however, since the presence of one aromatic substituent strongly reduces the yield of the corresponding cyanohydrin, and two aryl groups on the carbonyl completely prevent the formation of isolable cyanohydrins.[9]

C. Hydrolysis of α-Halocarboxylic Acids.

α-Halocarboxylic acids of the type $RR'CClCO_2H$ and their derivatives are hydrolyzable to the corresponding glycolic acids. By this procedure, Welch and Smith[10] prepared 4,4'-dichlorobenzilic acid from 4,4'-di(p-chlorophenyl)-acetic acid in 49.3% yield:

$$(p\text{-}ClC_6H_4)CHCO_2H \xrightarrow[PCl_3]{SOCl_2} (p\text{-}ClC_6H_4)_2CClCOCl \xrightarrow{H_2O} (p\text{-}ClC_6H_4)_2C(OH)CO_6H$$

D. Addition of a Grignard Reagent to an α-Ketoacid or Ester.

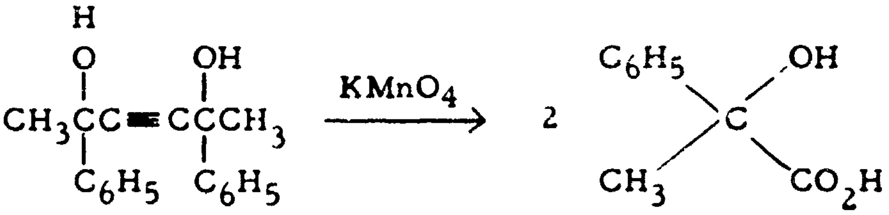
Glycolic acids and their esters are formed from the corresponding α-ketocompounds with Grignard-type reagents according to the following reaction scheme:

$$RCOCO_2H(CO_2R') + R''MgX \rightarrow RR''C(OMgX)CO_2MgX(CO_2R') \rightarrow RR''C(OH)CO_2H(CO_2R')$$

This is a convenient small-scale laboratory method,[11] but it is not suitable for large-scale production.

E. Oxidation of α-Hydroxyalkynes by Potassium Permanganate.

This method was used by Dupont[12] to prepare atrolactic acid from 2, 5-dihydroxy-2, 5-diphenyl-3-hexyne:



The yields were poor because of a competing reaction in which the glycolic acid was oxidized to acetophenone. Kadin and Cannon[13] have prepared cyclopropylphenylglycolic acid in 30% yield and cyclobutylphenylglycolic acid in 24% yield by the permanganate oxidation of the appropriate propynols.

F. Carbonation of a Dimetallic Ketyl.

Beckmann and Paul[14] first reported the observation that aromatic ketones react with sodium in anhydrous ether to form deeply colored derivatives containing one sodium molecule per ketone molecule. Later, Schlenk[15] found that the ketones are capable of forming disodium derivatives, which are also deeply colored. He converted benzophenone to benzilic acid by allowing the ketone to react with sodium in ether and carbonating the resulting organometallic compound:

$$(C_6H_5)_2CO \xrightarrow{Na} (C_6H_5)_2C(Na)ONa \xrightarrow{CO_2} (C_6H_5)_2C(ONa)CO_2Na$$

Following Schlenk's work, Hamrick and Hauser[16] obtained a 50% yield of benzilic acid from the carbonation of benzophenone dipotassioketyl in liquid ammonia. Selman[17] improved the yield to 62% by using dimethoxyethane as the solvent for the formation of benzophenone disodioketyl. He also obtained a yield of 41% of 4-methylbenzilic acid from 4-methylbenzophenone and a yield of 85% of 3,4'-dimethylbenzilic acid from 3,4'-dimethylbenzophenone. 4,4'-Dimethoxybenzilic acid, however, was not accessible from the corresponding ketone by the same procedure. Kadin,[4] using the procedure of Hamrick and Hauser, prepared 9-fluorenol-9-carboxylic acid from 9-fluorenone and benzilic acid in 67% yield from benzophenone. The α-hydroxycarboxylic acids, however, were not accessible by this method from xanthone, acetophenone, or cyclopropylphenyl ketone. Buehler[18] was partially successful in using Selman's method to prepare aminothiol esters of benzilic acids by the reaction of di(2,N,N-diethylaminoethylthiol) carbonate with the disodioketyls of aryl ketones in liquid ammonia. Buehler prepared 2-(2-diethylamino)-ethanethiol benzilate from benzophenone disodioketyl and the carbonate, but when the ketone was 2,3-dimethylbenzophenone, only the corresponding benzhydrol was isolated. With 4,4'-dimethylbenzophenone, a product the structure of which corresponded to $[(4\text{-}CH_3C_6H_4)_2C(OH)_2]_2CO$ was obtained.

G. Oxidative Rearrangement of Benzoin.

Ballard and Dehn[19] describe the conversion of benzoin to benzilic acid in 84% to 90% yield by the action of alkaline sodium bromate:

$$C_6H_5CHOHCOC_6H_5 \xrightarrow[NaOH]{NaBrO_3} (C_6H_5)_2C(OH)CO_2Na$$

II. OBJECTIVE.

This study was conducted with the aim of finding a general method, preferably adaptable to large-scale production, for the preparation of α,α-disubstituted glycolic acids from readily available materials.

III. PROCEDURES.

A. Materials and Equipment.

Ordinary laboratory glassware and equipment were used in all steps of these syntheses. Benzene, toluene, ether, etc., were dried over sodium. Dioxane was purified as suggested by Fieser,[20] with the following modification: After the dioxane had been refluxed for several hours with sodium, some benzophenone was added to the mixture. Complete removal of moisture was indicated by the appearance of the blue color of the sodium ketyl. If the mixture turned yellow or green, more sodium was added, followed by about 2 gm of benzophenone some 30 min later. When the blue color of the ketyl had appeared, the dioxane was distilled and stored over sodium. Unless otherwise noted, the other chemicals used were commercial samples.

B. Experimentation.

1. Preparation of Benzilic Acid From Benzophenone Using Liquid Ammonia and Toluene as Solvents.

Diced sodium metal (12.7 gm, 0.55 mole) was added to 500 ml of liquid ammonia in a 2-*l*, quadrinecked, round-bottomed flask equipped with a thermometer, a gas-inlet tube, a condenser, and an oil-sealed stirrer. The mixture was stirred until the sodium had completely dissolved, and the ammonia was allowed to evaporate while 500 ml of toluene was added to maintain the original volume; dry argon gas was used to purge the reaction vessel. A solution of 45.6 gm (0.25 mole) of benzophenone in 200 ml of dry, warm toluene was added to the sodium dispersion. The color of the mixture gradually changed from gray to green to deep blue. It was refluxed for an additional hour, by which time the blue color had changed to purple. Heating was discontinued, and carbon dioxide was bubbled very rapidly into the stirring mixture. The mixture was cooled to room temperature, and, while it was still under a carbon-dioxide atmosphere, a solution of 85 ml of concentrated hydrochloric acid in 250 ml of water was slowly added. Then the two layers were separated, and the organic phase was washed with a 20% sodium-hydroxide solution. The aqueous phase was made alkaline with sodium hydroxide, combined with the aqueous alkaline extract, and extracted once with toluene. The combined toluene solutions were stripped of solvent. The residue, a viscous, yellow-orange liquid, solidified as long needles and was found by gas-chromatographic analysis to contain 70% of benzhydrol and 30% of benzophenone. The aqueous solution was acidified with concentrated hydrochloric acid and cooled in an ice bath to deposit 39.6 gm (69.5%) of benzilic acid.

2. Preparation of Benzilic Acid From Benzophenone in Tetrahydrofuran With Sodium-Potassium Alloy.

A mixture of 6.9 gm (0.30 mole) of diced sodium and 9.7 gm (0.25 mole) of diced potassium was added to 500 ml of dry tetrahydrofuran (THF) in the apparatus described in experiment 1. The mixture was heated to reflux, under argon, with rapid stirring in order to produce a fine dispersion of the liquid alloy. A solution of 45.6 gm (0.25 mole) of benzophenone in 150 ml of THF was slowly added to the mixture. The blue color of the ketyl appeared immediately. After the entire solution had been added, the color changed to violet. The mixture was refluxed for 1 hr and then treated with a vigorous stream of dry carbon dioxide until the violet color had changed to orange-yellow. Although the mixture was still being heated during the addition of carbon dioxide, the temperature dropped from 66° to 57°C. Heating was discontinued after 45 min. The mixture was treated carefully with 200 ml of ethanol to destroy any unreacted metal, followed by 100 ml of water, and, finally, by 100 ml of concentrated hydrochloric acid. The precipitated sodium chloride was removed by filtration, and the solution was stripped of solvent. The solid residue was recrystallized from toluene to yield 34.2 gm (60%) of benzilic acid, mp 148° to 150°C.

3. Preparation of Benzilic Acid From Benzophenone Disodioketyl in Dioxane.

Diced sodium (12.7 gm, 0.55 mole) was added to 500 ml of dioxane in a 2-ℓ, quadrinecked, round-bottomed flask equipped with a thermometer, a gas-inlet tube, a condenser, and an oil-sealed stirrer. The mixture was stirred and heated to reflux in an atmosphere of dry argon. When the sodium was molten and dispersed in the solvent, a solution of 45.6 gm (0.25 mole) of benzophenone in 150 ml of dioxane was added during a time interval of about 10 min. The blue color of the sodium ketyl appeared almost at once, and, after a period of 10 min, the violet color of the disodium adduct began to develop. The mixture was stirred and refluxed for an additional hour, then allowed to cool to 40°C. The argon was replaced by dry carbon dioxide gas, which was bubbled as rapidly as possible through the mixture; this resulted in a temperature rise to 58°C and the successive changes of the violet color to blue, green, and yellow-brown. The mixture was stirred, allowed to cool to 40°C, and hydrolyzed carefully with a solution of 5 ml of water in 100 ml of concentrated hydrochloric acid. The reaction mixture consisted of a white solid and two liquid phases. The solid was collected by filtration; the liquid phases were separated. The lower (aqueous) phase was recombined with the solid, and the mixture was extracted with ether. The extract was combined with the upper (dioxane) phase, and the solution was stripped of solvent. The solid residue was dissolved in warm toluene and the solution treated with Norite and filtered. The filtrate was extracted with a 10% sodium hydroxide solution, and this solution was re-extracted once with toluene. The toluene extracts were combined and stripped of solvent. The cold aqueous extract was acidified with concentrated hydrochloric acid. The precipitated benzilic acid was collected by filtration and air-dried for several hours. It weighed 55 gm. The acid was placed in a vacuum desiccator over phosphorus pentoxide and dried to a constant weight of 47.0 gm (82.5% of theory), mp 150°C.

The solid residue from the toluene extract weighed 13 gm and was found by gas-chromatographic analysis to be a mixture of benzhydrol (17%) and benzophenone (83%).

4. Preparation of 4,4'-Di(dimethylamino)benzilic Acid.

In 800 ml of dioxane contained in the equipment described in experiment 1 was placed 21.4 gm (0.55 mole) of potassium metal. The mixture was stirred and refluxed in an argon atmosphere. A warm solution of 67.1 gm (0.25 mole) of 4,4'-di(dimethylamino)benzophenone (Michler's ketone) in 400 ml of warm, anhydrous benzene was rapidly added to the mixture, which was stirred and refluxed for 1 hr and then allowed to cool to 40°C. A stream of carbon dioxide was bubbled vigorously into the mixture. The temperature rose to 65°C. After the reaction had subsided and the temperature had dropped back to 40°C, 250 ml of water were carefully added. The solvent was stripped, and the residue was stirred in hot methanol to precipitate potassium carbonate, which was filtered off. The filtrate was stripped of solvent, and the residue was triturated with hot benzene. This dissolved the neutral portion (the uncharged ketone, carbinol, etc.); the insoluble portion (52 gm) was redissolved in ethanol, and this solution was diluted with diethyl ether. Potassium 4,4'-di(dimethylamino)benzilate precipitated. It was collected and dried in vacuo over calcium chloride and paraffin wax. The yield was 40.0 gm (45.5%). Examination of the product by infrared spectrophotometry confirmed the structure of the salt. The benzene containing the neutral fraction was stripped of solvent, leaving 40 gm of a dark, viscous residue, which was discarded. The product was submitted for carbon, hydrogen, and nitrogen analysis.

Analysis of $C_{18}H_{20}KN_2O_3$:

Calculated: C, 61.0; H, 6.0; N, 7.9
Found: C, 60.2; H, 6.2; N, 7.9

An attempt to prepare the methyl ester of the acid by the Fischer esterification procedure was unsuccessful. The potassium salt is soluble in alcohol and water, the pH of the latter being about 7.5. As hydrochloric acid is added to the aqueous solution, the solution goes through a series of color changes, from light blue to purple; as the acidity is increased, the color eventually disappears. These changes are rather sluggish. Addition of base will cause the color to return; as the pH is increased, the color will also disappear.

The results and reaction conditions of a series of additional runs for the preparation of benzilic acid and some of its analogs and homologs by the carbonation of the di(alkali) ketyls of aromatic ketones are summarized in the table.

5. Attempted Preparation of Methylphenyltrichloromethylcarbinol.

To 500 ml of dry formaldehyde dimethylacetal (methylal) cooled to -10°C in a 2-ℓ, quadrinecked, round-bottomed flask equipped with a thermometer, a condenser, and a stirrer, was added through the fourth neck 120 gm of freshly molten, powdered, 85.0% potassium hydroxide (102 gm KOH, 1.8 moles) with vigorous stirring. At the same temperature, a solution of 215 gm (1.8 moles) of chloroform and 240 gm (2 moles) of acetophenone was added in the course of 2 hr, and agitation was continued for an additional 2 hr. The orange reaction mixture was poured into a mixture of 1 kg of crushed ice and 118 gm (2 moles) of sulfuric acid. Sufficient water was added to dissolve the potassium salts. The aqueous layer was separated and extracted with ether. The organic extracts were combined, dried, and distilled at reduced pressure. At 75°C (6 mm) there was obtained 222 gm of acetophenone; the pot residue weighed 33 gm. The residue was steam-distilled, and the organic layer of the distillate was separated from the water, dried, and stripped of solvent. The residue weighed 20 gm; it reacted with 2,4-dinitrophenylhydrazine to give a hydrazone, mp 248°C. Examination of the product by infrared spectrophotometry showed the product to be unchanged acetophenone. The use of powdered technical potassium hydroxide in another experiment gave the same results.

6. Preparation of 1,1-Di(p-chlorophenyl)-1,2,2,2-tetrachloroethane.

This procedure was described by Grummitt and coworkers.[21] 1,1,1-Trichloro-2,2-bis(p-chlorophenyl)ethane (DDT) (20 gm, 0.056 mole) was dissolved in 130 ml of carbon tetrachloride containing 1.0 gm of phosphorus trichloride in a 500-ml, dual-necked, round-bottomed flask equipped with a gas-inlet tube and a condenser with a calcium chloride tube. Chlorine gas was passed vigorously into the solution for 3 hr while it was gently refluxed and irradiated with an ultraviolet lamp. The solution was purged with nitrogen to remove excess chlorine, and the solvent was stripped. The residue was dissolved in 100 ml of hot ethanol, treated with Norite, and the solution was allowed to stand for 2 hr at room temperature. The crystals were collected by filtration and air-dried. The product, 1,1-di(p-chlorophenyl)-1,2,2,2-tetrachloroethane, mp 91° to 92°C, weighed 14.5 gm (66% of theory). The reaction was repeated with 50.0 gm (0.140 mole) of DDT. The yield of product was 43.0 gm (78.5% of theory).

The following methods were used in the attempt to convert the "chloro-DDT" to 4,4'-dichlorobenzilic acid:

a. Refluxing with potassium hydroxide in aqueous diethylene glycol.

b. Refluxing in water with various bases; i.e., sodium carbonate, sodium hydroxide, and potassium hydroxide.

c. Refluxing with potassium carbonate in aqueous dioxane in the presence of iron filings.

d. Refluxing with aqueous calcium hydroxide in the presence of iron filings.

e. Refluxing with aqueous alcoholic potassium hydroxide. None of these attempts was successful. Either unchanged "chloro-DDT" was recovered, or a polymeric gum was formed that could not be characterized.

7. Preparation of 4,4'-Dichlorobenzil.

A mixture of 10.0 gm (0.0256 mole) of 1,1-di(p-chlorophenyl)-1,2,2,2-tetrachloroethane and 250 ml of concentrated sulfuric acid was stirred and warmed at 65° to 75°C for 8 hr in a 500-ml flask equipped with a condenser. During this time, hydrogen chloride gas evolved. The reaction mixture was cooled and poured, with vigorous stirring, onto chipped ice. The solid, which was collected and recrystallized from ethanol, was identified by mass-spectrographic analysis as 4,4'-dichlorobenzil. The product weighed 7.1 gm (98.5%). The experiment was repeated with 67% sulfuric acid at 100°C, but only 28% of the benzil was isolated.

TABLE

REACTION OF CARBON DIOXIDE WITH DIKETYLS OF ARYL KETONES

Ketone a/	Reaction medium	Metal used	Reflux time	Yield		
				$RR'C(OH)CO_2H$	RR'CHOH	RR'CO
			hr		%	
Benzophenone	Dioxane	Sodium	1	81.6	ca. 1.6	0.4
Benzophenone	Dioxane	Sodium dispersion b/	— c/	53	— d/	—
Benzophenone	Toluene	Sodium	1	46.6	—	ca. 50
Benzophenone	Di-n-butyl ether	Sodium	1	50	50	—
Benzophenone	Dioxane	Sodium	— e/	12.3	— f/	—
Benzophenone	Dioxane	Excess sodium, 0.75 mole	1	68.5	17.8	39.5
Benzophenone	Dioxane	Sodium	3	39.5	— g/	—
Benzophenone	Dioxane	1 Equivalent of sodium	1.5	17.8	— h/	—
Benzophenone i/	Dioxane	Sodium	1	68.4	—	—
4-Methylbenzophenone	Dioxane	Sodium	1	3.3	—	29.3 j/
4-Chlorobenzophenone	Dioxane	Sodium	1	None	— k/	—
4-Chlorobenzophenone	Dioxane	Sodium, 0.30 mole; potassium, 0.25 mole	6	None	— l/	—
4-Chlorobenzophenone	Diglyme	Sodium	6, at 135°C	None	— m/	—
9-Fluorenone	Dioxane	Sodium	1	93.4	—	—
Anthrone	Dioxane	Sodium	1	None n/	—	43.3
4,4-Dimethylbenzophenone	Dioxane	Sodium	1	None n/	94.3	—
Benzil	Dioxane	Sodium	1	— o/	—	—
4-Methoxybenzophenone	Dioxane	Sodium	1	— p/	—	—

a/ The quantity of ketone used was 0.25 mole; 0.55 mole of sodium was used except where noted otherwise.

b/ A commercial sodium dispersion, 50% in xylene, from Westville Chemical Corp., Monroe, Conn., was used here.

c/ The reaction mixture was heated to 75° to 80°C for 1 hr and then cooled to 40°C before carbon dioxide was bubbled into the mixture.

d/ The neutral fraction weighed 22 gm; it was not analyzed.

e/ Benzophenone was added to sodium sand in dioxane at 30°C and was stirred at this temperature for 2 days, prior to the addition of carbon dioxide.

f/ The neutral fraction weighed 38 gm.

g/ The neutral fraction weighed 15 gm.

h/ The neutral fraction weighed 40 gm.

i/ Sodium and benzophenone were mixed with dioxane in a reaction vessel and heated to reflux temperature; the neutral fraction weighed 16.5 gm.

j/ The ketone was isolated from 49 gm of neutral residue as the 2,4-dinitrophenylhydrazide.

k/ The neutral fraction weighed 62 gm.

l/ The neutral fraction weighed 55 gm, it was a tar.

m/ The neutral fraction weighed 60 gm.

n/ An "acid" fraction, 8.6 gm, mp 285°C, was isolated; the empirical formula corresponded to $C_{29}H_{20}O_2$.

o/ The products isolated were 2% benzilic acid and 95% benzoin.

p/ An acidic product (0.8 gm) was isolated that was gummy and could not be crystallized; the neutral fraction weighed 63 gm.

8. Preparation of 4, 4'-Dichlorobenzilic Acid.

To a solution of 20 ml of distilled water and 25 ml of ethanol containing 10 gm of potassium hydroxide in a 500-ml reaction flask equipped with a condenser was added 13.3 gm (0.096 mole) of 4, 4'-dichlorobenzil. The mixture was refluxed on a steam cone for 30 min and was allowed to cool to room temperature. Any unchanged benzil was removed by extraction with ether. The aqueous extract was acidified with 5% sulfuric acid to pH 3 and extracted with ether. The extract was stripped of solvent, and the residue was mixed with hot ligroin. Immediately, the 4, 4'-dichlorobenzilic acid precipitated; its structure was confirmed by infrared spectrophotometry. The product weighed 10.0 gm (39% of theory).

9. Preparation of 1, 1-Diphenyl-1, 2, 2, 2-tetrachloroethane.

This procedure was described by Grummitt and coworkers.[21] A solution of 18.5 gm (0.33 mole) of potassium hydroxide and 1, 1-diphenyl-2, 2, 2-trichloroethane in 2 *l* of ethanol was refluxed for 10 hr in a 3-*l* reaction flask equipped with a condenser with a Drierite tube. One-half of the solvent was stripped off, and the residue was poured onto 1 kg of ice. The precipitate, 1, 1-diphenyl-2, 2-dichloroethylene, was collected and air-dried; it melted at 77°C; the yield was 23.0 gm (92.5%).

1, 1-Diphenyl-1, 2, 2, 2-tetrachloroethane was synthesized according to the procedure of Bergmann and Kaluszyner.[22] A solution of 11 gm of chlorine in 200 ml of acetic acid was prepared in a 500-ml Erlenmeyer flask, and to this was added 22.0 gm (0.885 mole) of 1, 1-diphenyl-2, 2-dichloroethylene. The container was stoppered and allowed to stand for 3 days. A small amount of solid was removed (it was less than 0.1 gm), and the filtrate was warmed at 100°C while dry chlorine was bubbled into the solution for 2 hr. Nitrogen gas was then passed into the solution to remove the excess chlorine. The solvent was stripped off, and the viscous residue was crystallized from ethanol and recrystallized from methanol to yield 18.0 gm (63.5%) of 1, 1-diphenyl-1, 2, 2, 2-tetrachloroethane, mp 85°C.

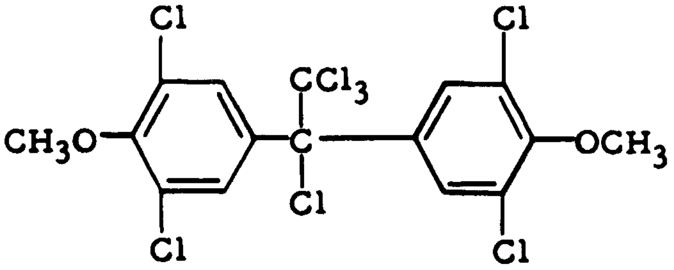
A 17-gm portion of the product was added to 250 ml of concentrated sulfuric acid, and the mixture was stirred for 4 hr at 60° to 70°C in a 500-ml Erlenmeyer flask. The resulting black mixture was cooled to room temperature and poured onto 2 kg of cracked ice. The yellow precipitate was dried over Drierite in vacuo (crude weight 10.0 gm) and recrystallized from ethanol to yield 9.0 gm (81% yield) of benzil, mp 192°C. The mixed melting point with an authentic sample of benzil showed no depression.

10. Attempted Conversion of Methoxychlor to Anisil.

A solution of 31.4 gm of potassium hydroxide and 58.0 gm (0.168 mole) of 1,1,1-trichloro-2,2-bis(p-methoxyphenyl)ethane (methoxychlor) in 1,500 ml of ethanol was refluxed for 12 hr in a 3-ℓ flask equipped with a condenser. The solution was concentrated at atmospheric pressure, and the concentrate was mixed with 2 kg of ice. The precipitate was collected and dried on a porous plate. The yield of 1,1-di(p-anisyl)-2,2-dichloroethylene was 51.0 gm (98.4%), mp 107°C.

A solution of 12 gm of chlorine gas in 200 ml of acetic acid was prepared in a 500-ml Erlenmeyer flask, and 30.9 gm (0.10 mole) of 1,1-di-(p-anisyl)-2,2-dichloroethylene was dissolved in it. The flask was stoppered and allowed to stand for 2 days. Then it was heated to 100°C, and for 2 hr dry chlorine gas was bubbled into the solution. The excess chlorine was removed by sweeping nitrogen through the system. During this process a precipitate formed that was collected and dried. The solid weighed 22.2 gm and melted at 148° to 149°C. Recrystallization from ethanol raised the melting point of the product to 156°C.

On the basis of its infrared and nuclear-magnetic-resonance spectra, the compound is apparently the octachloro derivative,



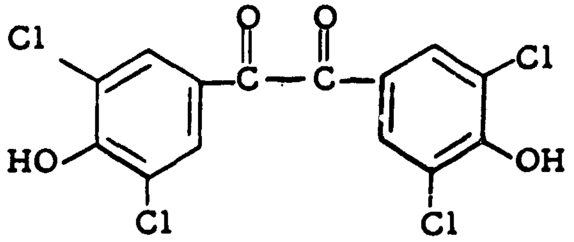
The empirical formula was confirmed by analysis, as shown below:

Analysis of $C_{16}H_{10}Cl_8O_2$:

Calculated: C, 37.1; H, 2.0; Cl, 54.8
Found: C, 37.1; H, 1.1; Cl, 50.3

Chlorination of the ethylene derivative was repeated by passing the chlorine into the solution at room temperature. The octachloro compound, however, was again the only product.

The octachloro derivative (15 gm, 0.026 mole) was heated in 150 ml of concentrated sulfuric acid at 65° to 70°C for 4 hr, and the cooled reaction mixture was poured into ice water. A light-yellow solid weighing 2.5 gm and melting above 300°C was isolated. Examination of the product by infrared spectrophotometry revealed that rearrangement of the octachloro compound to a benzil had occurred. The spectrum, however, indicated the presence of hydroxyl groups and not ether groups. A comparison of the spectrum to Sadtler Standard Spectrum No. 17,340 (4,4'-dihydroxybenzil) showed that the spectra were similar. Therefore, the product obtained was presumably



The chlorination of methoxychlor was tried by the procedure described by Balaban.[23] In the apparatus used in experiment 7, a solution of 10.4 gm (0.03 mole) of methoxychlor in 100 ml of carbon tetrachloride was treated with 0.5 ml of phosphorus trichloride. Chlorine gas was bubbled briskly into the solution for 4 hr as it was irradiated with ultraviolet light. The solvent was stripped on a rotating evaporator, and a yellow, tacky residue remained. This material could not be induced to crystallize from alcohol or petroleum ether. The experiment was repeated, but the carbon tetrachloride solution was heated during the chlorination. This product was also a gum. The same results were obtained when phosphorus trichloride was omitted from the reaction.

1,1-Di(p-anisyl)-2,2-dichloroethylene was prepared from methoxychlor by the procedure described by Grummitt and coworkers[21] for the preparation of 1,1-di(p-chlorophenyl)-2,2-dichloroethylene. The yield of product was 97%. A solution of 25.4 gm (0.0823 mole) was dissolved in 350 ml of carbon tetrachloride, and the solution was gently refluxed while chlorine gas was bubbled into it for 4 hr. The reaction mixture was worked up in the manner described above. The gummy residue could not be induced to crystallize from ethanol, benzene, carbon tetrachloride, petroleum ether, diethyl ether, or dioxane.

11. Attempted Preparation of Ethyl Atrolactate.

The tetrahydropyranyl ether of methylphenylcarbinol (16.0 gm, 0.130 mole), prepared by the procedure described by Woods and Kramer,[24] was dissolved in 100 ml of dry toluene and slowly added to a solution of 3.0 gm (0.130 mole) of sodium in 500 ml of liquid ammonia in a 1-*l*, quadrinecked, round-bottomed flask equipped with a gas-inlet tube, a thermometer, a stirrer, and a condenser. The blue color of the ammonia solution changed after 5 min to a brownish yellow. The ammonia was allowed to evaporate as 200 ml of toluene was slowly added. Evaporation was hastened by sweeping the system with dry argon gas. The flask was heated to 30°C and stirred until all traces of ammonia had disappeared. Then 17.0 gm (0.156 mole) of ethyl chloroformate in 50 ml of toluene was slowly added to the solution. The temperature rose to 65°C. After the addition was completed, the mixture was stirred until the temperature had dropped to 30°C. After the solvent had been removed under reduced pressure, the residue was mixed with a solution of 50 ml of hydrochloric acid and 50 ml of water and stirred for 1 hr. The two phases were separated, the aqueous phase was extracted with benzene, and the organic solutions were combined. The solvent was stripped at atmospheric pressure, and the residue was distilled at reduced pressure under nitrogen. Infrared spectrophotometric analysis showed the products to be starting material plus ethyl α-methylbenzyl carbonate.

After the addition of the ethyl chloroformate solution in a duplicate run, the reaction mixture was heated for 1 hr at 75° to 80°C. The results, however, were the same. The use of carbon dioxide gas instead of ethyl chloroformate was also tried, but no atrolactic acid was isolated; only methylphenylcarbinol and the tetrahydropyranyl ether of the carbinol were found in the reaction mixture.

12. Attempt to Form the Dilithium Derivative of Methylphenylcarbinol With Lithium.

A solution of 2.8 gm (0.40 mole) of lithium in 500 ml of ammonia was prepared in the apparatus described in experiment 11 and blanketed under argon. A solution of 24.4 gm (0.20 mole) of methylphenylcarbinol in 100 ml of toluene was added to the solution. There was no color change. The ammonia was allowed to evaporate and was replaced by 350 ml of toluene. The mixture was refluxed for 2 hr, but the dimetal derivative did not form. The excess metal remained floating in the liquid phase. The experiment was discontinued.

13. Attempted Preparation of Ethyl Benzilate.

Sodium dimethylsulfoxide was prepared in a 500-ml, triple-necked, round-bottomed flask equipped with a thermometer, a stirrer, and a condenser with a Drierite tube by adding 1.2 gm of 50% sodium hydride dispersion in mineral oil (0.05 mole NaH) to 50 ml of dry dimethyl sulfoxide, blanketed under argon, and heated at 80° to 90°C until the solid had dissolved and the evolution of hydrogen had ceased. The reaction was complete in 45 min. A solution of 13.4 gm (0.050 mole) of the tetrahydropyranyl ether of benzhydrol in 15 ml of dry dihydropyran was added to the gray sulfoxide solution, which had been cooled to 30°C. The reaction mixture turned deep red without a temperature rise and was stirred for 1 hr. Then, 5.4 gm of ethyl chloroformate in 10 ml of dihydropyran was slowly added. The temperature rose to 80°C, and the red color changed to brown. Stirring was continued for another hour, and the mixture was poured into a mixture of 500 gm of ice and 20 ml of hydrochloric acid. The aqueous mixture was stirred for 1 hr. A solid formed; this was collected and air-dried. It weighed 15.0 gm, melted at 35° to 40°C, and smelled of dimethyl sulfide. A sublimed sample was identified by infrared and mass spectrometry as the tetrahydropyranyl ether of benzhydrol.

In another experiment, the lithium salt of benzhydrol was treated with sodium dimethylsulfoxide, and the mixture was in turn treated with a solution of ethyl chloroformate in ether. The main product was ethyl benzhydryl carbonate.

14. Attempt to Prepare Cyclopentylphenylglycolic Acid From Benzaldehyde.

A solution of lithium amide was prepared in a 2-ℓ, quadrinecked, round-bottomed flask equipped with a gas port, a thermometer, a stirrer, and a condenser from 1.4 gm (0.20 mole) of lithium in 500 ml of liquid ammonia and 0.3 gm of ferric nitrate. An ethereal solution of mandelonitrile was prepared by treating 10.6 gm (0.10 mole) of benzaldehyde with 15.0 gm (0.15 mole) of sodium bisulfite in 120 ml of water. The mixture was warmed on a steam bath until it became homogeneous, then it was cooled to room temperature and extracted once with ether. The aqueous solution was chilled to 0°C, covered with 50 ml of ether, and stirred while 4.9 gm (0.10 mole) of sodium cyanide was added to it over a period of 30 min. The ether phase was separated from the aqueous phase, and the latter was extracted once with 50 ml of ether. The ether extracts were combined, dried over magnesium sulfate, and then added to the lithium amide solution. An additional 300 ml of dry ether was added, and the ammonia was allowed to evaporate under an argon atmosphere. The brown, ethereal mixture was stirred and refluxed for 5 hr. The flask was cooled to room temperature, and 14.9 gm (0.10 mole) of freshly distilled cyclopentyl bromide in 50 ml of ether was added to the mixture. There was no temperature rise or color change. The mixture was kept overnight and then was mixed with 50 ml of water. The solvent was stripped on a rotating evaporator, and the residue was diluted with a solution of 50 ml of hydrochloric acid in 100 ml of water. The mixture was heated on a steam bath for 1 hr and then extracted with ether. The extract was dried and distilled. Aside from the solvent, two fractions were obtained, one distilling at 135° to 137°C at atmospheric pressure and the other at 59° to 63°C at 10 mm. By infrared spectrophotometric analysis, these fractions were found to be cyclopentyl bromide and benzaldehyde, respectively. The pot residue contained some solid material, presumably benzoic acid.

15. Preparation of Cyclopentylphenylglycolic Acid.

Cyclopentylphenyl ketone was prepared by the method of Hey and Musgrave[25] in 63.2% yield. The ethynylation of the ketone and its subsequent oxidation to cyclopentylphenylglycolic acid are based upon procedures described by Kadin and Cannon.[13] Acetylene was bubbled for 45 min into the apparatus described in experiment 14 containing 500 ml of ammonia and sodium amide prepared from 5.8 gm (0.25 mole) of sodium. A solution of 34.0 gm (0.20 mole) of cyclopentylphenyl ketone in 150 ml of dry ether was added dropwise during 1 hr. The mixture was stirred for an additional 2 hr, and the ammonia was allowed to evaporate. Powdered ammonium chloride (15 gm) was added portionwise to the stirred residue, and the mixture was then poured into 500 ml of ice water. The organic layer was separated, and the aqueous layer was extracted once with ether. The ether extracts were combined, dried, and distilled at 138° to 141°C (7 mm) to give 30 gm (75% yield) of 1-cyclopentyl-1-phenyl-2-propyn-1-ol. The structure was verified by infrared spectrophotometric analysis.

A solution of 21.4 gm (0.14 mole) of potassium permanganate in 350 ml of water was added slowly over a 3-hr period to a vigorously stirred, cold mixture of 10 gm (0.05 mole) of 1-cyclopentyl-1-phenyl-2-propyn-1-ol in 50 ml of water in a 1-*l*, quadrinecked, round-bottomed flask fitted with a stirrer, a thermometer, and a condenser. The mixture was stirred for a period of 1 hr and filtered twice through Celite. The filtrate was extracted once with ether and acidified with 10% hydrochloric acid. The solution was extracted with ether, and the extract was dried and stripped of solvent. The residue was allowed to stand for 3 days, during which time it solidified. The solid was recrystallized from toluene; the crystals were collected, triturated with 40° to 60°C petroleum ether, and dried in vacuo at 80°C. The product, cyclopentylphenylglycolic acid, weighed 2 gm (20% of theory) and melted at 145°C. The crystals did not depress the melting point of an authentic sample of the acid. The oxidation was repeated and the yield this time was 3.0 gm (30% of theory).

16. Attempted Reaction of Butyraldehyde With Benzoin.

A solution of 106.2 gm (0.50 mole) of benzoin and 72.1 gm (1.00 mole) of butyraldehyde in 650 ml of hot ethanol was prepared in a 2-*l*, triple-necked, round-bottomed flask fitted with a stirrer, a condenser, and a dropping funnel. A solution of 20 gm of potassium cyanide in 100 ml of 50% ethanol was added to the vessel, and the solution was refluxed on a steam bath for 3 hr. The mixture was cooled to room temperature, and the fraction boiling below 25°C was stripped under reduced pressure (10 to 15 mm). The viscous residue was dissolved in diethyl ether and washed with water. The ether solution was dried, and the solvent was removed at atmospheric pressure. When the clear-red, viscous residue was subjected to low-pressure distillation (0.3 mm), only two fractions were obtained: the forerun, which contained butyraldehyde, and about 0.1 ml of a liquid boiling at 120° to 124°C. The remainder of the reaction mixture could not be distilled. The residue was a clear-red, highly viscous, tacky substance. It was examined by infrared spectrophotometry and was found to be a complex mixture of materials. This experiment was discontinued.

17. Reaction of Benzaldehyde and Butyroin.

Butyroin was prepared by the procedure described by Snell and McElvain.[26] In the apparatus described above, a solution of 36.8 gm (0.348 mole) of benzaldehyde and 25.0 gm (0.174 mole) of butyroin in 200 ml of ethanol was mixed with a solution of 5 gm of potassium cyanide in 10 ml of water. This solution was stirred and refluxed for 16 hr. The reaction mixture was poured into ice water, and the mixture was extracted with diethyl ether. The extract was dried, the solvent was taken off, and the residue was distilled at reduced pressure. The following fractions were obtained:

(1) Forerun, to 50°C (0.4 mm); 10.2 gm. n_D^{20} 1.4375
(2) 60° to 70°C (0.4 mm); 5.1 gm. n_D^{20} 1.4360
(3) 82° to 90°C (0.4 mm); 5.5 gm; n_D^{20} 1.4630
(4) Residue (hard polymer); 12.0 gm

According to infrared spectrophotometry, the three liquid fractions were primarily butyroin with some aromatic impurity, presumably benzaldehyde and benzoic acid.

18. Reaction of Benzoin With Butyroin.

A solution of 5 gm of potassium cyanide in 10 ml of water was added to a 1-*l*, triple-necked, round-bottomed flask equipped with a stirrer, a condenser, and a dropping funnel that contained a solution of 36.8 gm (0.174 mole) of benzoin and 25.0 gm (0.174 mole) of butyroin in 250 ml of ethanol. The solution was refluxed with stirring for 16 hr and then allowed to cool to room temperature. A crop of small plates (2.0 gm), melting point above 300°C, was identified by its infrared spectrum as potassium benzoate. The rest of the reaction mixture was mixed with ice water and extracted with chloroform. The extract was distilled, first at atmospheric pressure to remove the solvent and finally at reduced pressure. The following fractions were collected:

(1) 40°C (0.08 mm); 12 gm; 0.113 mole; n_D^{20} 1.5450
[2,4-dinitrophenylhydrazone, mp 235°C (benzaldehyde)]

(2) 48° to 55°C (0.08 mm); 11 gm; n_D^{20} 1.4575

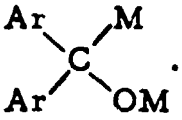
(3) 96° to 105°C (0.08 mm); 3.6 gm; n_D^{20} 1.4872

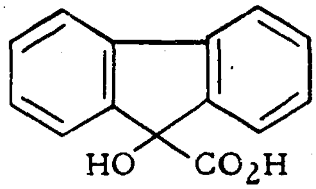
(4) Residue; 17 gm

The liquid fractions were examined by infrared spectrophotometry. Fraction (1) gave the spectrum of benzaldehyde. Fraction (2) was apparently the desired product, $C_6H_5CHOHCOCH_2CH_2CH_3$, along with some unidentified materials. The spectrum of fraction (3) showed the presence of a hydroxyl group, an α-diketo group, a phenyl ring, and a hydrocarbon chain. Fraction (2) represents an 18% yield of product.

IV. DISCUSSION AND RESULTS.

Several approaches to the synthesis of α,α-disubstituted glycolic acids without the use of Grignard reagents as intermediates appeared promising and were, therefore, studied in some detail. These were (1) the carbonation of disodium or dipotassium ketyls of aryl ketones to give benzilic acids, (2) the hydrolysis of trichloromethylcarbinols and of unsymmetrical diaryltetrachloroethanes to α,α-disubstituted glycolic acids, (3) the reaction of ethyl chlorocarbonate and of carbon dioxide with the disodium or dilithium derivatives of secondary aralkyl alcohols or with the monometallic derivatives of the corresponding tetrahydropyranyl ethers, (4) the ethynylation of ketones by acetylene and the oxidation of the resulting propynols to glycolic acids, and (5) the preparation of mixed acyloins and their rearrangement to glycolic acids by alkaline sodium bromate or sodium iodate.

Selman[17] discussed the exceptional nature of the dialkali ketyls—  . Since these possess a carbon-metal bond vicinal to an oxygen-metal bond, it might be expected that the compounds would exhibit the properties of both organometallics and alkoxides, with the metal on the carbon atom being the more reactive one of the two. These compounds should thus show all of the usual organometallic reactions in addition to the reactions of the alkali salt of an alcohol. As Selman points out, these expectations are not entirely fulfilled, as the metal-oxygen bond is rather unreactive and only in certain instances does the dimetallic ketyl act both as an organometallic and as an alkoxide. The investigations conducted in these Laboratories involved only the reactions of the carbon-metal bond of the ketyls. Dioxane (bp 101° to 102°C) was found to be an excellent reaction medium for the formation of the dimetallic ketyls from sodium (mp 97°C) and potassium (mp 64°C) because these metals can be melted in the refluxing solvent and dispersed into fine granules without resorting to a second solvent. By this modification, the yield of benzilic acid from benzophenone could be raised to 82.5%, as compared with a yield of 67% realized by Selman,[17] when conducting the carbonation of the disodiobenzophenone in dioxane. In the same reaction medium, the yield of 9-fluorenol-9-carboxylic acid

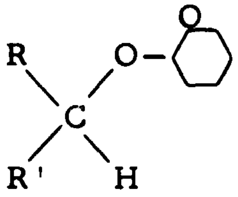


was increased from 55.5% to 93.4%. To obtain these greatly improved yields, it was necessary to carbonate the dimetallic ketyls in the dioxane medium by passing as rapid a stream of carbon dioxide into the reaction mixture as the equipment could withstand.

Unfortunately, this method has severe limitations and is only applicable to purely aromatic ketones, since a hydrogen atom on a carbon atom adjacent to the carbonyl groups, as in mixed aliphatic- or cycloaliphatic-aromatic ketones, leads to the enolization of the carbonyl groups and subsequent formation of an alkali enolate, preventing the formation of a metal-to-carbon bond. Michler's ketone was converted in the same manner to potassium 4,4'-di(dimethylamino)benzilate in 45.5% yield. The yield of 4-methylbenzilic acid, however, was only 3.3%, and with 4-methoxybenzophenone, 4-chlorobenzophenone, and 4,4'-dimethylbenzophenone, none of the corresponding benzilic acids was formed. When benzil was used as the carbonyl component of the ketyl reaction, 2% benzilic acid and 95% benzoin were isolated.

Although several benzilic acids could be prepared in very satisfactory yields by the dimetalation and subsequent carbonation of aromatic ketones, aliphatic or mixed aliphatic-aromatic ketones are not suitable as starting materials because of their enolization under conditions that are successful in the case of aromatic ketones. If, however, in the alkoxides of aliphatic or mixed aliphatic-aromatic secondary alcohols, RR'CHOM, the hydrogen atom of the carbinol group were sufficiently active to be replaced by the alkali metal, M, the resulting dimetalated products, RR'C(M)-COM, would correspond to the aromatic dimetal ketyl derivatives and should yield by carbonation the corresponding glycolic acids, $RR'C(OH)CO_2H$.

The direct replacement of both hydrogen atoms of the secondary carbinol group, -CHOH, of α-phenylethanol by metallic lithium in toluene was unsuccessful. Similarly, etherification of the hydroxyl group with dihydropyran, and treatment of the resulting tetrahydropyranyl ether with the sodio derivative of dimethylsulfoxide, $Na[CH_2SOCH_3]$, did not result in the desired replacement of the hydrogen atom directly attached to the carbinol carbon atom of the ether derivative,



A related approach was taken in the attempt to metalate mandelonitrile, $C_6H_5CH(OH)CN$, with lithium amide in ammonia, assuming that, after the replacement of the hydrogen atom of the alcoholic function, the residual hydrogen atom might be sufficiently activated by the concerted effect of both the phenyl and nitrile groups to submit to substitution by alkali metal for further reaction with an alkyl or cycloalkyl halide. This approach was also unsuccessful.

Weizmann and coworkers[27] reported the formation of methylphenyltrichloromethylcarbinol, $CH_3(C_6H_5)C(OH)CCl_3$, in 41% yield by the alkali-catalyzed addition of chloroform to acetophenone without giving specific conditions for this preparation. The application of the conditions reported by these authors for the preparation of dimethyltrichloromethylcarbinol, $(CH_3)_2C(OH)CCl_3$, to acetophenone gave the present authors only unreacted starting material in several attempts. These experiments were conducted because it seemed that the hydrolysis of the trichloromethyl groups in these carbinols might be readily hydrolyzable to carboxyl groups, thus leading, in two simple steps, from a ketone to the corresponding α,α-disubstituted glycolic acids.

α-Halocarboxylic acids of the type $RR'CXCO_2H$, wherein R and R' are alkyl, cycloalkyl, or aryl groups and X represents chlorine or bromine, can be readily hydrolyzed to the corresponding glycolic acids, $RR'C(OH)CO_2H$. Since compounds of the type Ar_2CHCCl_3 are readily accessible by the condensation of chloral with aromatic hydrocarbons or substituted hydrocarbons, the chlorination and subsequent hydrolysis of these condensation products to the corresponding benzilic acids, $Ar_2C(OH)CO_2H$, appeared to be a relatively simple and inexpensive route to their synthesis. The seemingly analogous alkaline hydrolysis of DDT in 69% to 73% yield to di(p-chlorophenyl)acetic acid by Grummitt and coworkers[28] offered some support to the above-outlined approach involving the tetrachloro analog. The 1-chloro derivative of DDT, however, resisted all attempts of alkaline hydrolysis, but when the chlorinated hydrocarbon was stirred with 98% sulfuric acid at 65° to 75°C, 4,4'-dichlorobenzyl was formed in 98.5% yield instead of the expected 4,4'-dichlorobenzilic acid. A similar rearrangement had been reported by Barry and Boyer,[29] in their attempts to prepare 1,1,1-trichloro-2-hydroxy-2,2-di(p-chlorophenyl)ethane from DDT and from 1,1-di(p-chlorophenyl)-1,2,2,2-tetrachloroethane. 1,1-Diphenyl-1,2,2,2-tetrachloroethane, prepared from 1,1-diphenyl-2,2,2-trichloroethane by chlorination in acetic acid according to the procedure of Bergmann and Kaluszyner,[22] was rearranged similarly to benzil in an overall yield of 49.4%. Methoxychlor could not be converted to the tetrachloro derivative by the procedures used for DDT or for 1,1-diphenyl-2,2,2-trichloroethane. When a solution of methoxychlor in carbon tetrachloride was heated while chlorine was passed into it, a tacky polymer was isolated. When methoxychlor was treated by Bergmann's method, the product was an octachloro derivative, as described in experiment 10. This compound rearranged when treated with sulfuric acid, but the yield was low and the methoxy groups were cleaved.

Sodium acetylide will react with a ketone to form a propynol, which in turn can be oxidized to a glycolic acid, as shown in the following equations:

$$R_2C{=}O + NaC{\equiv}CH \longrightarrow R_2C(ONa)C{\equiv}CH$$

$$R_2C(ONa)C{\equiv}CH + H_2O \longrightarrow R_2C(OH)C{\equiv}CH$$

$$R_2C(OH)C{\equiv}CH \xrightarrow{\text{oxidation}} R_2C(OH)CO_2H + CO$$

This method was first reported by Kadin[4, 13] and was used by other investigators[9, 12] to synthesize α-hydroxyacids in low yields. In this study, cyclopentylphenyl ketone could be converted by Kadin's procedure to cyclopentylphenylglycolic acid in only 30% yield. Besides the unsatisfactory yields, the method is hazardous, since acetylene is a necessary reactant in the reaction.

One additional attempt to develop a general method for the synthesis of mixed glycolic acids of the type $ArRC(OH)CO_2H$ was concerned with the preparation of mixed aryl-alkyl acyloins, RCH(OH)COR', and their subsequent oxidative rearrangement. Ballard and Dehn [19] and Evans and Dehn[30] had converted benzoin to benzilic acid in excellent yield by the action of alkaline sodium bromate or sodium iodate. This procedure, in combination with the procedure used by Buck and Ide[31] to prepare mixed benzoins, seemed to offer a possible method for the preparation of the desired glycolic acids.

Benzoin tends to revert to benzaldehyde in the reaction mixture in which it is synthesized. Other products, such as benzyl benzoate, mandelonitrile, benzoic acid, etc., are also present. Although benzoin can be formed from benzaldehyde in the presence of potassium cyanide and in the absence of water, the reverse process requires water. This fact has been used as a basis for synthesizing unsymmetrical benzoins. By addition to an aqueous alcoholic solution of potassium cyanide of 1 mole of a benzoin and 2 moles of an aldehyde or of 1 mole of each of the two symmetrical benzoins, it is possible to obtain a new benzoin by redistribution, as illustrated by the following equations (Ar, Ar', Ar'' = aryl groups):

$$ArCHOHCOAr + 2\ Ar'CHO \longrightarrow Ar'CHOHCOAr + ArCHOHCOAr' \qquad (1)$$

$$ArCHOHCOAr' + 2\ Ar''CHO \longrightarrow ArCHOHCOAr'' + Ar''CHOHCOAr' \qquad (2)$$

$$ArCHOHCOAr + Ar'CHOHAr' \longrightarrow 2\ ArCHOHCOAr' \qquad (3)$$

Although there was no evidence that the desired acyloins could be prepared by these methods, this approach appeared to be worth investigating. The experiments were based upon the reactions outlined by equations (1) and (3). Three reaction systems were investigated: butyraldehyde and benzoin, butyroin and benzaldehyde, and butyroin and benzoin, all in the presence of aqueous potassium cyanide. In the first system, the product was a tacky, clear-red polymer. In the second system, benzaldehyde and butyroin were recovered unchanged. The products from the attempted reaction of butyroin with benzoin were potassium benzoate, benzaldehyde, and an 18% yield of the mixed acyloin, 1-phenyl-1-hydroxy-2-pentanone ($C_6H_5CHOHCOCH_2CH_2CH_3$). The complexity of the reaction and the unsatisfactory yield of product did not warrant further expenditure of effort.

V. CONCLUSIONS.

Of the various approaches to the α,α-disubstituted glycolic acids studied, only the carbonation of the dimetallic ketyls from aromatic ketones showed merit. By careful adjustment of the reaction conditions, the yields of certain benzilic acids could be raised considerably above those reported in the literature. No satisfactory synthesis of mixed aliphatic-aromatic or fully aliphatic glycolic acids was found. This study was not concerned per se with an improvement of established synthetic procedures, but had as its main objective the investigation of certain reactions that might be applicable to a general method.

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13 ABSTRACT

Several methods for the synthesis of glycolic acids of the type RR'C(OH)COsub2H, in which R and R' are aryl, alkyl, or cycloalkyl groups (equal or different), were investigated to find a practicable route not requiring use of Grignard reagents. Benzilic acid, 9-fluorenol-9-carboxylic acid, and potassium 4,4'-di-(dimethylamino) benzilate were obtained in yields of 82.5%, 93.4%, and 45.5%, respectively, by the carbonation in dioxane of benzophenone disodioketyl, fluorenone disodioketyl, and dipotassioketyl of 4,4'di-(dimethylamino)benzophenone[Michler's ketone]. The conversion of 1,1-di-(parachlorophenyl)-1,2,2,2-tetrachloroethane to 4,4'dichlorobenzil in a 98.5% yield was effected by the action of sulfuric acid at from 65 degrees to 75 degrees C. A 39% yield of 4,4'-dichlorobenzilic acid was obtained by the benzilic acid rearrangement of 4,4'-dichlorobenzil. Cyclopentylphenylglycolic acid in 30% yield resulted from oxidation of 1-cyclopentyl-1-phenyl-2-propyn-1-ol. This method is unsatisfactory, however because of poor yield and hazards encountered in the preparation of the propynol from acetylene and ketone. With desired-product yield only 18%, the synthesis of a mixed acyloin (as a glycolic acid precursor) was unsatisfactory when aqueous potassium cyanide acted on an equimolar mixture of an acyloin and a benzoin.

14. KEYWORDS
Grignard reagent Acyloin Yield 9-Fluorenol-9-carboxylic acid
Glycolic acids Propynol Acetylene 4,4'-Dichlorobenzilic acid
Cycloalkyl groups Ketone Benzoin Cyclopentylphenylglycolic acid
Aryl groups Benzilic acid Alkyl groups Michler's ketone
Potassium 4,4'-di (dimethylamino) benzilate

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