[Contribution from the George Herbert Jones Laboratory, the University of Chicago]

REACTIONS OF DIAZOACETATES AND DIAZOKETONES. I. REACTION OF ETHYL DIAZOACETATE WITH CYCLOHEXANONE AND WITH ACETONE[1]

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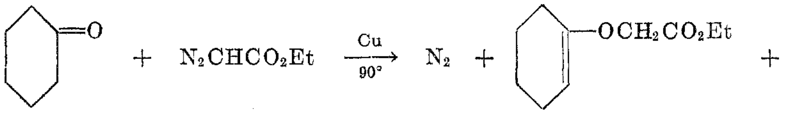
The products formed in the reactions of diazomethane with ketones (acyclic and cyclic) have been thoroughly investigated. *A priori*, it would appear that ethyl diazoacetate should give rise to similar products. This is not, however, the case.

The ketones (cyclohexanone and acetone) here investigated did not react with ethyl diazoacetate below 120°. The use of promotors, however, permitted the reaction to be conducted at lower temperatures. Among the promoters tested (Pt, Pd, Raney Ni, Ag_2O, $AgNO_3$, Cu), copper was most effective, facilitating smooth reaction with steady evolution of nitrogen gas at 90°.

Early in the investigation it became apparent that complex mixtures of products are formed in reactions of ethyl diazoacetate with ketones. For this reason trial experiments were performed with several ketones. Cyclohexanone was finally selected for intensive study. Progress was hampered for some time by ignorance of the effects of atmospheric oxygen on the reaction products. All efforts to purify even the simplest adduct, **A**, (see reaction scheme below) resulted in a product which, although apparently homogeneous, still gave low and inconsistent carbon and hydrogen analyses. The chemical reactions of this adduct, however, had clearly shown it to be the cyclohexen-1-ol ether of ethyl glycolate. The difficulty was finally traced to the peroxidation of the reaction products. Oxygen was, therefore, rigorously excluded from the initial reaction and from all subsequent operations. Once this precaution was taken, the analytical difficulties previously encountered disappeared, and the separation of individual reaction products became much less difficult.

The reaction of ethyl diazoacetate with cyclohexanone in the presence of copper powder. The course of the reaction of ethyl diazoacetate with cyclohexanone in the presence of copper powder is indicated below.



A (43% crude)

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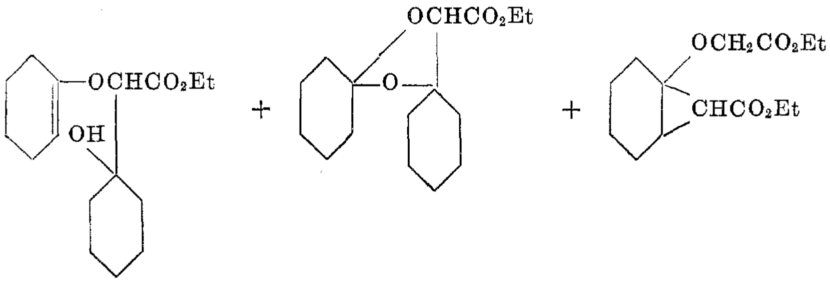
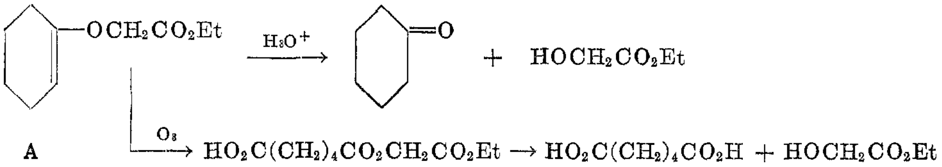
[1] For a bibliography of reaction of ethyl diazoacetate with a miscellany of inorganic compounds, the Doctoral Dissertation of Rudy (University of Chicago, 1953) should be consulted.

[2] Atomic Energy Commission Predoctoral Fellow.

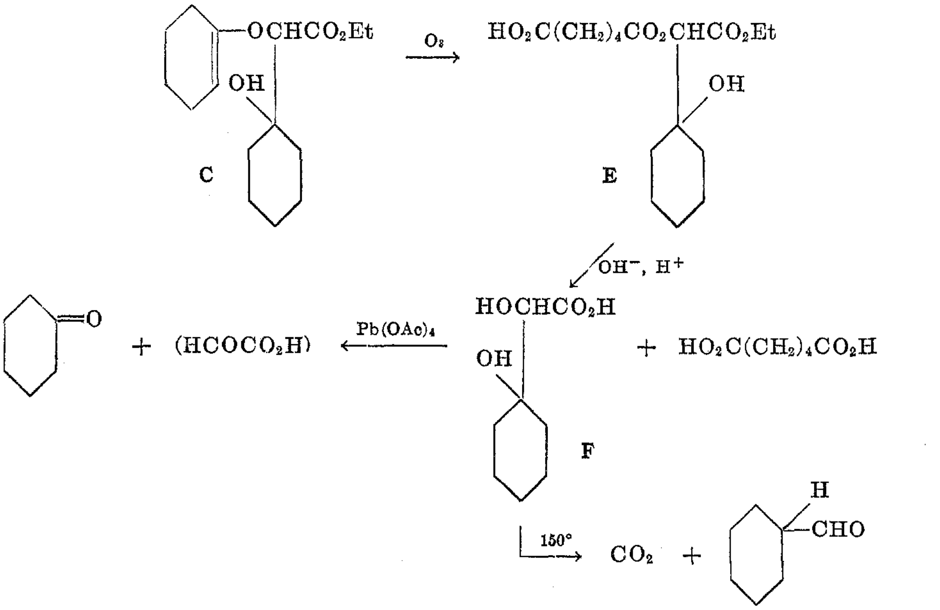


C (16%) **G** (4% est.) I(1% est.)

Separation and characterization of Compound **A**. Compound **A** was separated from the reaction mixture by distillation. Analyses, molecular weight, and saponification equivalent indicated that **A** is a 1:1 adduct.[3] The structure of this compound was established by the following sequence of reactions.



Separation and characterization of Compound **C**. Compound **C** was removed from the mixture of **C**, **G**, and **I**[4] as indicated in the experimental part. Analyses, molecular weight, and saponification equivalent indicated that **C** is a 1:2 adduct. The structure of this compound was established by the following sequence of reactions.



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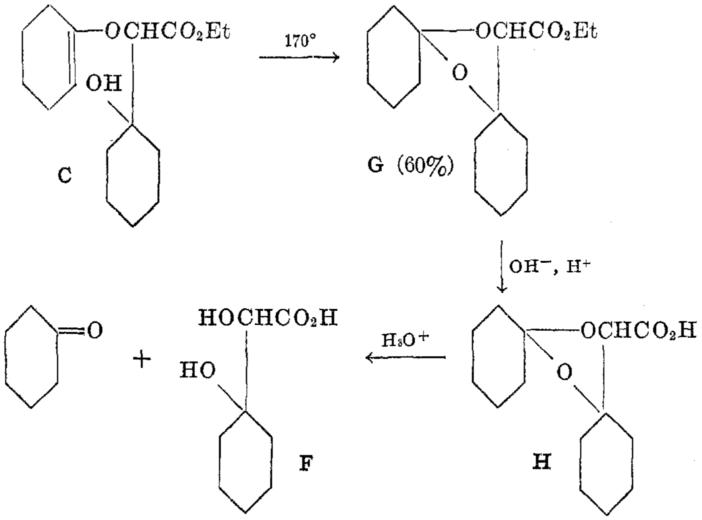
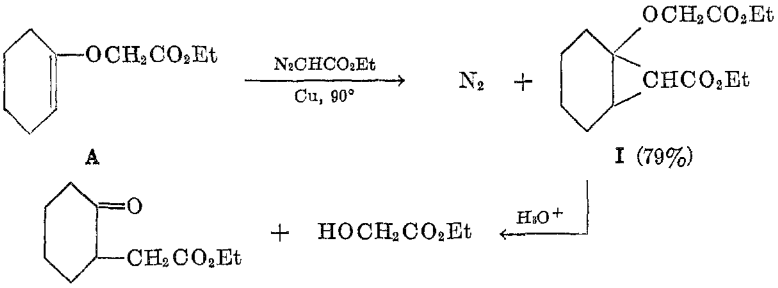
[3] When reference is made to a 1:1, 1:2, 2:1, or 3:1 adduct, the first number refers to the

Characterization of the mixture of Compounds **G** *and* **I**. After removal of **C** from mixture **B** there remained a difficulty separable mixture which exhibited the properties of **G** and **I**.[5] These compounds were prepared independently and characterized as indicated below.

Preparation and characterization of Compound **G**. Compound **G** was prepared by heating pure **C** in an evacuated sealed tube or a solution of **C** in cyclohexanone. Unchanged **C** was removed by ozonolysis, leaving pure **G**. Analyses, molecular weight, and saponification equivalent of **G** showed it to be an isomer of **C**. The structure of **G** was established by the following sequence of reactions.



Preparation and characterization of Compound **I**. Compound **I** was prepared by the reaction of ethyl diazoacetate with **A** in the presence of copper powder. Distillation, followed by ozonolysis to remove unsaturated impurities, gave pure **I**. Analyses, molecular weight, and saponification equivalent of **I** showed it to be a 2:1 adduct. The structure of **I** was determined by the following sequence of reactions.



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number of —$CHCO_2Et$ groups in the molecule, while the second number refers to the number of ketone molecules similarly incorporated.

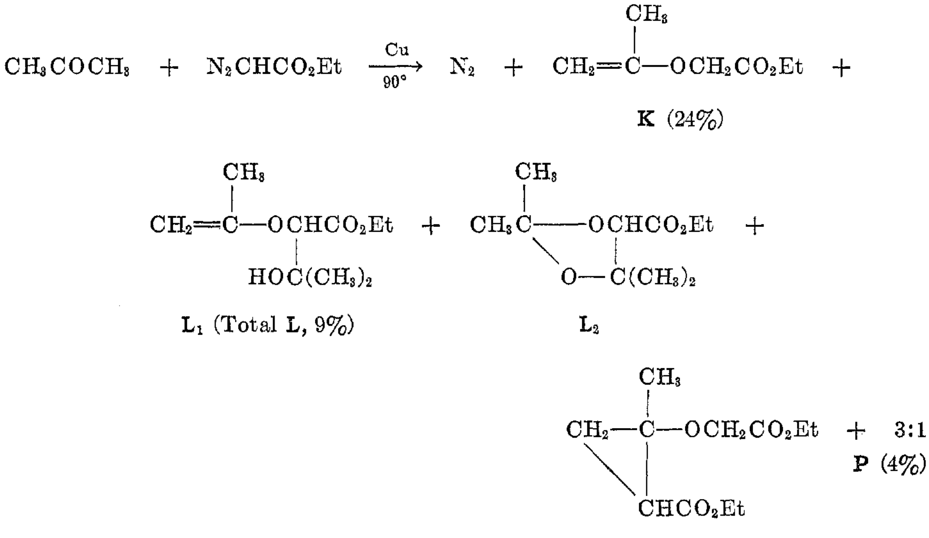
[4] This mixture is referred to as **B** in the Experimental Part.

[5] This mixture is referred to as **D** in the Experimental Part.

A similar reaction takes place when cyclohexen-1-ol acetate is used instead of **A** (see experimental part).

The reaction of ethyl diazoacetate with cyclohexanone in the absence of copper powder. The reaction of ethyl diazoacetate with cyclohexanone in the absence of copper powder was conducted at the reflux temperature of cyclohexanone. The evolution of nitrogen was sluggish; the products were mostly the previously described compounds **A** and **G**. In view of the observed thermal isomerization of **C** it appears probable that the primary products are the same in the presence or absence of copper powder.

The reaction of ethyl diazoacetate with acetone in the presence of copper powder. A large number of reaction products are formed when ethyl diazoacetate is heated with acyclic ketones in the presence of copper powder. In general, the separation of these compounds is difficult. The separation of the reaction products was found less difficult when acetone was used. The reaction was carried out in a pressure vessel at 90° and at a pressure of 30 lb./sq. in. (gauge). The following reaction products were isolated.



$$CH_3COCH_3 + N_2CHCO_2Et \xrightarrow[90^\circ]{Cu} N_2 + CH_2{=}C(CH_3){-}OCH_2CO_2Et +$$

K (24%)

$$CH_2{=}C(CH_3){-}OCH(CO_2Et)C(CH_3)_2OH + \ldots +$$

L$_1$ (Total **L**, 9%) **L**$_2$

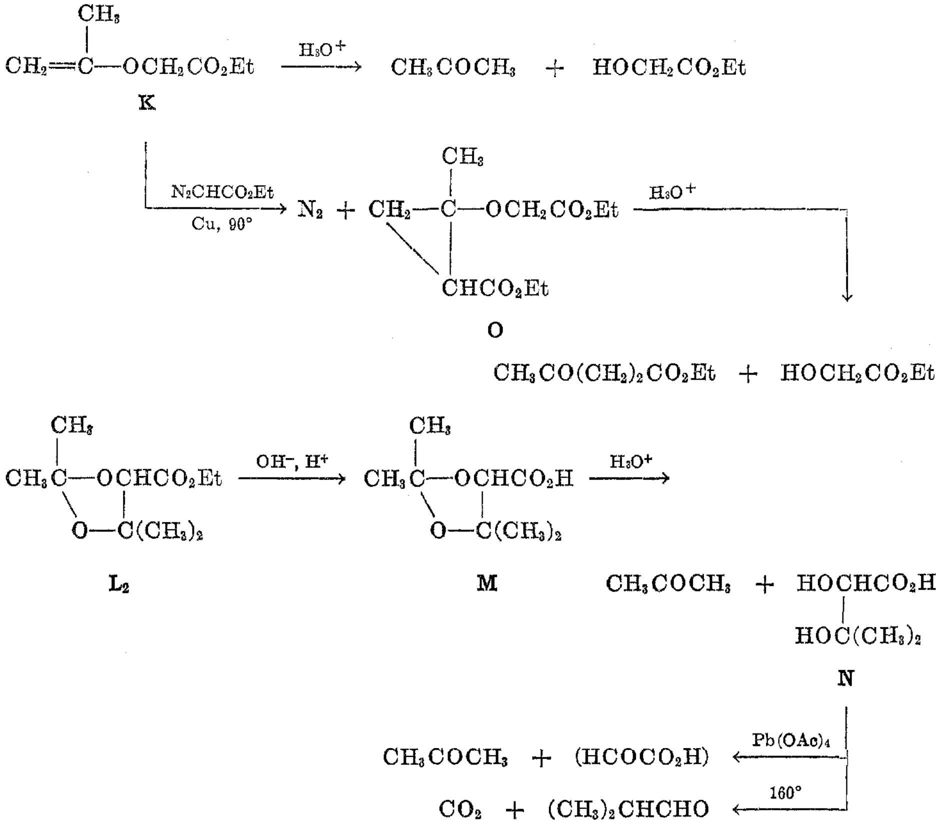
$$+ \ 3{:}1$$

P (4%)

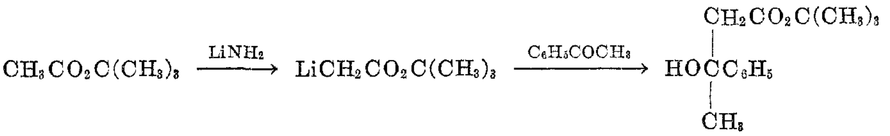
O (23%)

Examination shows the reaction products to be similar to those formed when ethyl diazoacetate reacts with cyclohexanone. The following significant differences were noted: (*a*) the 1:2 adduct **L**$_1$ appeared to be largely isomerized to **L**$_2$; (*b*) what appears to be a 3:1 adduct, compound **P**, was isolated. No such adduct was isolated in the reaction with cyclohexanone. The structure of the 3:1 adduct has not been determined, but it appears unlikely that any of the characterized products can be precursors. It is concluded that compound **P** is formed by a reaction which is independent of those established for the formation of the other reaction products.

Characterization of the products of the reaction of ethyl diazoacetate with acetone in the presence of copper powder. The structures of the products of this reaction (compounds **K**, **O**, and **L**$_2$) were determined by the same methods that were used for the products of the cyclohexanone reaction. The methods are indicated in the following reaction sequence.



The mechanism of the reaction of ethyl diazoacetate with ketones. As previously indicated, ethyl diazoacetate, when heated with either cyclohexanone or acetone in the presence of copper powder, gives rise to a variety of products (**A**, **C**, **G**, and **I** with cyclohexanone; **K**, **L**$_1$, **L**$_2$, **O**, and **P** with acetone). In the consideration of the mechanism of this reaction it is of utmost importance to ascertain whether all of these compounds are primary products, or whether some of them result from the interaction of ethyl diazoacetate or the ketone with a primary reaction product. It has been demonstrated that the unsaturated 1:2 adduct **C** rearranges at elevated temperatures to give compound **G**. Likewise, the unsaturated 1:2 adduct **L**$_1$ undergoes thermal rearrangement to give **L**$_2$. Furthermore, it has been demonstrated that the 2:1 adducts, **I** and **O**, are formed by the reaction of ethyl diazoacetate with the 1:1 adducts, **A** and **K**, respectively. The 1:1 adducts, **A** and **K**, are obviously primary reaction products. Therefore, it remains only to consider the unsaturated 1:2 adducts, **C** and **L**$_1$.[6] The unsaturated 1:2 adduct **C** could not be prepared by treatment (under a variety of conditions) of the 1:1 adduct **A** with cyclohexanone, although a similar reaction between *tert*-butyl acetate and acetophenone has been successfully carried out with the aid of lithium amide (1).



$$CH_3CO_2C(CH_3)_3 \xrightarrow{LiNH_2} LiCH_2CO_2C(CH_3)_3 \xrightarrow{C_6H_5COCH_3} HO\overset{CH_2CO_2C(CH_3)_3}{\underset{CH_3}{C}}C_6H_5$$

It appears, therefore, that a satisfactory reaction mechanism must account for the formation of the 1:1 adducts, **A** and **K**, and the 1:2 adducts, **C** and **L**$_1$, as primary reaction products.

At first glance, the compounds **A** and **K** formed in the reaction of ethyl diazoacetate with cyclohexanone and with acetone, respectively, suggest that the enolic forms of the ketones react in much the same manner as carboxylic acids react with ethyl diazoacetate or enols react with diazomethane. However, the strength of this argument is somewhat weakened since only a very small amount of reaction product similar to **A** is formed when ethyl methylacetoacetate (2) (which is two hundred times more highly enolized than cyclohexanone) is heated with ethyl diazoacetate in the presence of copper powder. In this instance a large quantity of ethyl fumarate is obtained, whereas only traces of it are formed when ethyl diazoacetate is heated with cyclohexanone or with acetone.

It is submitted that neither the experimental work with diazomethane, nor the theoretical speculations which have been suggested to account for reactions of the latter reagent with acidic hydrogen atoms, carbonyl compounds, etc. (3), permits an unequivocal choice of a mechanism or mechanisms to account for the primary reaction products formed when ethyl diazoacetate reacts with ketones. The formation of these products may be rationalized on the basis of the following sequence of reactions.[7]

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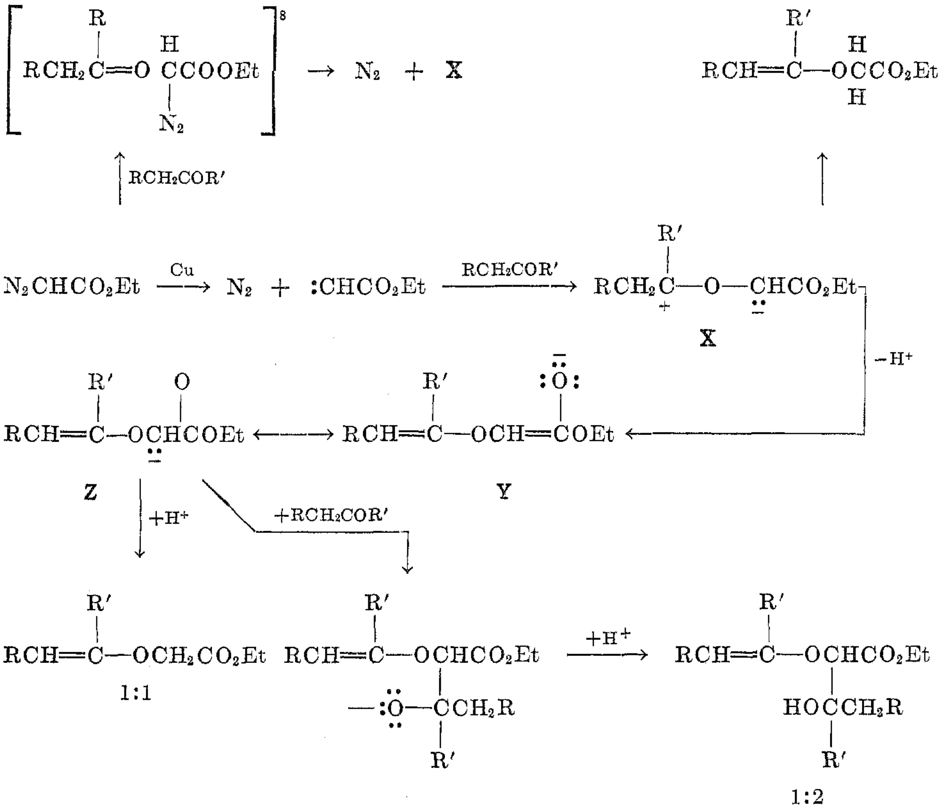
[6] The 3:1 adduct, **P**, is formed in small amount (4%). It is regarded as a primary reaction product. The structure of this substance has not been determined.

[7] It should be borne in mind that ethyl diazoacetate reacts with unsaturated compounds and ketones to give primary products, the nature of which is independent of the presence or absence of copper powder in the reaction mixture. The only apparent effect of the copper powder is to lower the temperature at which reaction takes place.



The interpretation here advanced satisfactorily accounts for the formation of the primary reaction products (**A**, **C**, **K**, and **L**$_1$). Formation of the secondary reaction products (**G**, **I**, **L**$_2$, and **O**) is in accord with the chemistry of the former substances.

EXPERIMENTAL PART

REAGENTS

Ethyl diazoacetate. Ethyl diazoacetate was prepared according to the directions given by Hickinbottom (4) with the following important modifications. Four times the indicated quantities of reagents may be safely used. Sodium sulfate was used in place of cal-

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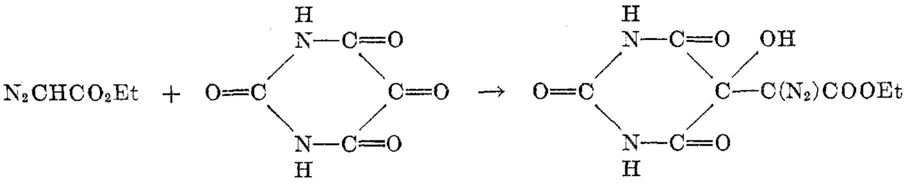
[8] It is claimed that alloxan forms a stable adduct of the type



[Biltz and Kramer, *Ann.*, **436**, 160 (1924)].

cium chloride to dry the ethereal solution of the crude product. Most of the ether was removed by distillation at atmospheric pressure until the temperature of the residue reached 45°. The remaining ether was removed at 6 mm. pressure. Distillation at reduced pressure gave a pure product (82%; b.p. 32–33°/6 mm.). Temperature control of the reaction was not critical as long as the temperature was kept below 20°. Furthermore, larger quantities of dilute sulfuric acid may be used without sacrifice in yield, thereby decreasing the time required for the preparation.

Cyclohexanone. Eastman's white label cyclohexanone was distilled through a 15 × 700 mm. Fenske column (b.p. 97°/130 mm.).

Acetone. Reagent grade acetone (Merck) was used without further purification.

Other ketones. All other ketones (the reaction products of which were not rigorously investigated) were purified by simple distillation at atmospheric or reduced pressure.

Copper powder. Venus natural copper (United States Bronze Powder Works) was used.

APPARATUS AND PROCEDURE

The reaction of ethyl diazoacetate with ketones, except acetone, was conducted in a three-necked, round-bottomed flask of suitable capacity, which was equipped with an internally-vented dropping-funnel, a silicone-lubricated Trubore bearing stirrer, and a reflux condenser with gas outlet. A thermometer suspended in the reflux condenser was arranged to measure the temperature of the contents of the reaction vessel. The reaction vessel was heated by an electric mantle which could be removed easily when cooling was necessary. The gas evolved in the reaction (nitrogen) was measured by a Precision Wet-test meter.

The ketone and copper were placed in the reaction vessel, and a mixture of ketone and ethyl diazoacetate was placed in the dropping-funnel. All ground glass joints were lubricated with silicone grease. The entire system, with the exception of the gas meter, was evacuated and refilled with pure, dry nitrogen gas three times in order to remove oxygen gas. A slight positive pressure of nitrogen was maintained while the gas meter was connected to the gas outlet of the reflux condenser. Not until the contents of the reaction vessel were heated to the desired temperature, was the flow of nitrogen stopped. When pressure equilibrium was established, the initial reading of the gas meter was taken, stirring was begun, and addition of the ethyl diazoacetate-ketone mixture was started. The addition was performed cautiously and gradually until evolution of nitrogen became apparent. Since the reaction is exothermic, and temperature dependent, it was occasionally necessary to remove the heating mantle in order to maintain temperature control. Adjustment of the rate of addition, in conjunction with adjustment of the heating mantle, served to control the temperature of the reaction. When addition was complete, the temperature of the reaction mixture was maintained until nitrogen evolution ceased. The final reading of the gas meter was then taken, stirring was stopped, and a slight positive pressure of pure, dry nitrogen was again applied. The reaction mixture was cooled under the nitrogen atmosphere and subsequently worked up as indicated in a following section.

The reaction of ethyl diazoacetate with acetone was conducted in a one-piece glass apparatus which was capable of withstanding internal pressures up to 150 lb./sq. in. The apparatus consisted of a long-necked reaction vessel with an internally-vented dropping-funnel. Acetone and copper powder were placed in the vessel, while a mixture of acetone and ethyl diazoacetate was placed in the dropping funnel. The apparatus was connected by pressure tubing to a pressure gauge and a three-way needle valve. The valve arrangement permitted the apparatus to be evacuated and filled with pure, dry nitrogen gas. It further permitted controlled release of evolved nitrogen through a gas meter. The system was evacuated and refilled with nitrogen gas three times, the pressure being raised to 30 lb./sq. in. with the last filling. The apparatus was suspended so that the reaction vessel only was immersed in a steam-heated water-bath, and a shaking device was attached. A thin layer of mineral oil on the surface of the water bath prevented steaming at bath temperatures up to 95°. As the temperature of the water bath was raised, the increased pressure of gas was relieved through the needle valve. The vented gas passed through the gas meter at atmospheric pressure. The temperature of the contents of the reaction vessel (under reflux) was regulated by maintaining the pressure at a suitable value. When the reaction mixture reached the desired temperature, and equilibrium was established with shaking, the initial reading of the gas meter was taken, and addition of the acetone-ethyl diazoacetate mixture was begun. The rate of addition was adjusted so that the reaction mixture refluxed gently in the long neck of the apparatus. Nitrogen pressure was maintained at the initial value by careful and frequent adjustment of the needle valve. When the evolution of nitrogen decreased to an inappreciable rate, the final reading of the gas meter was taken, the needle valve was closed, and the reaction mixture was cooled under the nitrogen atmosphere. The nitrogen gas was then allowed to escape, and the reaction mixture was worked up as indicated in a following section.

The reaction of ethyl diazoacetate with cyclohexanone in the presence of copper powder. A mixture of ethyl diazoacetate (22.0 g., 0.19 mole) and cyclohexanone (44.0 g., 0.45 mole) was slowly added (1.5 hours) to a suspension of copper powder (0.1 g.) in cyclohexanone (88.0 g., 0.90 mole). The reaction mixture was maintained at 90–95°. Nitrogen evolution began when about 10 ml. of the ethyl diazoacetate-cyclohexanone mixture had been added. Steady nitrogen evolution continued throughout the addition of the ethyl diazoacetate-cyclohexanone mixture. Five minutes after the addition was complete, the evolution of nitrogen ceased rather abruptly. The total volume of evolved nitrogen was 4.25 l. N.T.P. (Calc'd 4.25 l.). Excess cyclohexanone was removed from the reaction mixture by distillation[9] (b.p. 30–36°/9 mm.). Distillation of the residue gave the following fractions: Crude **A** (15.0 g., b.p. 55–110°/0.06 mm.); Crude **B** (13.6 g., b.p. 110–145°/0.07 mm.); Dark viscous residue (3.2 g.).

Purification and characterization of fraction **A**. Two fractional distillations of the crude **A** (15.0 g.) through a small Vigreux column gave pure **A** (10.2 g., b.p. 103.5–104.5°/6 mm., n_D^{20} 1.4665).

Anal. Calc'd for $C_{10}H_{16}O_3$: C, 65.2; H, 8.7; Mol. Wt. 184.

Found: C, 65.1; H, 8.9; Mol. Wt.,[10] 188; Sapon. Equiv., 186.

On exposure to air and light the refractive index of **A** increased, its carbon and hydrogen contents decreased, and it liberated I_2 when shaken with aqueous iodide solution.[11] Treatment of **A** with a 2,4-dinitrophenylhydrazine reagent (5) gave a heavy precipitate of the 2,4-dinitrophenylhydrazone of cyclohexanone. The material melted at 160–161° and did not depress the melting point of an authentic sample. Treatment of **A** with a methanolic solution of semicarbazide acetate failed to give a derivative when the mixture was allowed to stand for 12 hours. Hydrolysis of **A** (7.0 g.) was effected by 1.5-hour reflux in 25 ml. of a 2% solution of HCl in 90% ethanol. After removal of the ethanol at reduced pressure, distillation of the residue gave 4.5 g. of a mixture of cyclohexanone (the semicarbazone of this material melted at 165–165.5°, and the melting point was not depressed by admixture with an authentic sample) and ethyl glycolate. Treatment of the mixture with *p*-nitrobenzoyl chloride in dry pyridine gave the *p*-nitrobenzoate of ethyl glycolate. Upon crystallization from aqueous methanol the material separated as pale yellow needles, which melted at 38.8–39.2°. The melting point of this material was not depressed upon admixture with an authentic sample of the *p*-nitrobenzoate of ethyl glycolate.

Anal. Calc'd for $C_{11}H_{11}NO_6$: C, 52.2; H, 4.3; N, 5.5.

Found: C, 52.4; H, 4.6; N, 5.3.

At −60° in ethyl acetate 2.06 g. of **A** absorbed approximately 13 mmoles. of ozone (Calc'd for one double bond, 11.2 mmoles.). The ethyl acetate was removed at reduced

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[9] This, and all subsequent distillations, were performed under a nitrogen atmosphere.

[10] All molecular weights were determined cryoscopically in benzene.

[11] The facile peroxide formation by compounds of this type is currently under investigation in this laboratory.

pressure, and the ozonide was hydrolyzed by heating with water for 16 hours on a steam-bath. Upon cooling, 0.4 g. of a white crystalline solid separated from the aqueous solution. The solid, when crystallized from aqueous ethanol, melted at 86–87°.

Anal. Calc'd for $C_{10}H_{16}O_6$: C, 51.7; H, 6.9.
Found: C, 51.7; H, 7.2.

This compound is acidic and is presumably the half ester of adipic acid. Repeated concentration and cooling of the aqueous solution of the hydrolyzed ozonide gave 0.8 g. of adipic acid which melted at 150–151°. The melting point of the acid thus obtained did not depress the melting point of an authentic sample of adipic acid. The mother liquor from these crystallizations gave a positive color test for glycolic acid (6).

Separation of fraction **B** *into components.* Repeated fractional distillation of **B** failed to yield a homogeneous product. The combined fractions (12.5 g.) were dissolved in 75 ml. of 30–35° ligroïn. The solution was cooled to approximately −60° in a Dry Ice-acetone bath. A stream of warm, moist air was adjusted to agitate the surface of the liquid. After five minutes the temperature of the solution had risen to −20°, and a white crystalline substance had separated and was collected on a filter. The filtrate was returned to the Dry Ice-acetone bath and was again cooled to −60°, and the above treatment repeated. The procedure was repeated three times. The combined precipitates were washed several times with 30–35° ligroïn which had been cooled to −80°. The crystalline material thus obtained melted at 40–45°, and could be recrystallized only by repetition of the above technique. A sample of the material placed in a vacuum-desiccator readily lost water and was converted to **C**, while a suspension of the material in water remained unchanged. The crystalline solid (m.p. 42°) (10.1 g.) was dissolved in the minimum of warm ethanol and transferred to a Claisen distillation flask. After removal of the ethanol at reduced pressure, distillation gave pure **C** (8.4 g., b.p. 113°/0.05 mm., n_D^{20} 1.4905).

Evaporation of the ligroïn from the mother liquor and washings gave 3.2 g. of **D**.

Characterization of Compound **C**. Analyses of Compound **C** were made on samples obtained as described above.

Anal. Calc'd for $C_{16}H_{26}O_4$: C, 68.1; H, 9.2; Mol. Wt., 282.
Found: C, 67.8; H, 9.4; Mol. Wt., 285; Sapon. Equiv. 278.

Determination of active hydrogen by the Zerewitinoff method gave an equivalent weight of 276. The behavior of **C** with respect to neutral and acidic carbonyl reagents was identical with that of **A**. At −60° in ethyl acetate 1.75 g. of **C** absorbed approximately 6 mmoles. of ozone (Calc'd for one double bond, 6.2 mmoles.). The ethyl acetate was removed at reduced pressure, and the ozonide was decomposed by catalytic hydrogenation, using 2% Pd on $CaCO_3$ in ethanol. The catalyst was collected, and the solvent was removed at reduced pressure. Distillation of the residue yielded a fraction which gave a positive test with fuchsin-aldehyde reagent (0.85 g., b.p. 153–154°/0.05 mm., n_D^{20} 1.4742), an acidic fraction (0.7 g., b.p. 170–205°/0.05 mm.), and 0.15 g. of residue. The acidic fraction crystallized on standing. Recrystallization from aqueous ethanol gave Compound **E** (0.55 g., m.p. 91.5–93°). On exposure to air or when shaken with neutral 5% H_2O_2, the aldehydic fraction was converted into Compound **E**.

Anal. Calc'd for $C_{16}H_{26}O_7$: C, 58.2; H, 7.9; Mol. Wt., 330.
Found: C, 58.5; H, 7.9; Neutr. Equiv. (cold), 335.

Compound **E** had a saponification equivalent of 114 (Calc'd for 3 carboxyl groups, 110). A 2.0-g. sample of it was saponified by refluxing for four hours in a solution of 2.5 g. KOH in 30 ml. of 80% ethanol. The saponification mixture was acidified to Congo Red with concentrated HCl and evaporated to dryness at reduced pressure. The solid residue was extracted several times with boiling ethanol, and the combined extracts were evaporated to dryness. The solid residue was crystallized from water. Adipic acid (0.25 g.) was thus obtained. The melting point of the acid thus obtained did not depress the melting point of an authentic sample of adipic acid. The combined mother liquors and washings were evaporated to dryness, and the solid residue was crystallized from chloroform. The crystalline material (0.7 g.) was Compound **F**. It melted at 117–118°.

Anal. Calc'd for $C_8H_{14}O_4$: C, 55.1; H, 8.0; Mol. Wt., 174.
Found: C, 54.9; H, 8.1; Neut. Equiv., 172.

A solution of Compound F in an excess of a saturated solution of lead tetraacetate in glacial acetic acid was allowed to stand for 14 hours. Water was then added, and the solution was distilled. Cyclohexanone was identified in the distillate. When Compound F was subjected to pyrolysis at temperatures slightly above 150°, CO_2 was evolved. The liquid residue from pyrolysis gave a positive test with fuchsin-aldehyde reagent and a yellow 2,4-dinitrophenylhydrazone which melted at 168–169°. The recorded melting point of the 2,4-dinitrophenylhydrazone of cyclohexanecarboxaldehyde is 168–169° (7).

Investigation of Fraction D. Repeated distillations of Fraction D failed to give a homogeneous fraction. At a pressure of 0.07 mm. the boiling point rose gradually from 90–110°. Ozonolysis, followed by reduction of the ozonide (using the techniques previously described), indicated approximately 10% unsaturation if the average molecular weight of the compounds present is assumed to be approximately 280. The products of distillation of D, after ozonolysis and reduction, are as indicated below. The results of several experiments are summarized.

D₁ (approximately 75%, b.p. 95–97°/0.07 mm., n_D^{20} 1.4733–1.4756, *Anal.* C, 65.2–65.5; H, 9.2–9.0); **D₂** (approximately 10%, b.p. 97–105°/0.07 mm.); **D₃** (approximately 10%, residue).

Various samples of D_1 had saponification equivalents ranging from 190–200 and molecular weights of the order of 280. The reaction of D_1 with 2,4-dinitrophenylhydrazine reagent was slow. A mixture of the 2,4-dinitrophenylhydrazones of cyclohexanone and cyclohexanone-2-acetic acid ethyl ester were formed. These compounds were separated by chromatography (on silicic acid-Celite), using benzene-ligroïn as an eluent. The latter derivative is discussed in more detail in a later section. Fraction D_2 reacted rapidly with 2,4-dinitrophenylhydrazine reagent to give the hydrazone of cyclohexanone-2-acetic acid ethyl ester. Crystallization of D_3, first from benzene-ligroïn, then from ethanol-water, showed it to be approximately 50% E. In the light of evidence presented in following sections, it appears that D_1 consists of a mixture of G and I, while D_2 consists mostly of I. The presence of E in D_3 indicates that most, if not all, of the unsaturation of D is due to the presence of C.

Thermal isomerization of compound C. Compound C (5.7 g.) was maintained at 170° for two hours in an evacuated, sealed tube.[12] The reaction mixture, when dissolved in ethyl acetate and cooled to −60°, absorbed 4.8 mmoles. of ozone (Calc'd for unchanged C, 20 mmoles.). The ozonide formed was reduced catalytically, and the resulting products were separated by distillation. Thus there was obtained G (3.4 g., b.p. 84–86°/0.05 mm., n_D^{20} 1.4790).

Anal. Calc'd for $C_{16}H_{26}O_4$: C, 68.1; H, 9.2; Mol. Wt., 282.
Found: C, 68.0; H, 9.4; Mol. Wt., 284; Sapon. Equiv. 287.

The residue from the distillation (1.5 g.) gave Compound E (0.6 g.) by crystallization from a mixture of benzene-ligroïn. The remainder of the residue was presumably the aldehydic analog of Compound E, since it gave a positive test with fuchsin-aldehyde reagent. Compound G reacted slowly (overnight) with 2,4-dinitrophenylhydrazine reagent to give the hydrazone of cyclohexanone. Saponification of 1.33 g. of Compound G in 5% aqueous NaOH, followed by acidification to Congo Red with concentrated HCl, produced a water-insoluble liquid acid (Compound H). The aqueous suspension of H was extracted with 30–35° ligroïn; the ligroïn solution was dried over sodium sulfate; the sodium sulfate was collected, and the filtrate evaporated, and the resulting residue was distilled. Thus there was obtained 1.0 g. of pure Compound H (b.p. 125–127°/0.05 mm.).

Anal. Calc'd for $C_{14}H_{22}O_4$: C, 66.1; H, 8.6; Mol. Wt., 254.
Found: C, 66.0; H, 8.9; Neut. Equiv., 244.

Hydrolysis of compound H (0.5 g.) was effected by heating for two hours a solution

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[12] Approximately the same results were obtained by refluxing Compound C in cyclohexanone under a nitrogen atmosphere for one hour.

of the compound in a 2% solution of HCl in 50% aqueous ethanol. The reaction mixture was distilled, and the first 20 ml. of distillate was collected. The distillate (4.0 ml.), on treatment with an excess of 2,4-dinitrophenylhydrazine reagent, rapidly gave a precipitate of the hydrazone of cyclohexanone (0.16 g.). The undistilled portion of the solution was evaporated to dryness at reduced pressure, and the residue upon crystallization from chloroform gave compound F (0.3 g.).

Reaction of ethyl diazoacetate with Compound **A** *in the presence of copper powder.* A mixture of ethyl diazoacetate (14.0 g., 0.12 mole) and Compound **A** (27.0 g., 0.15 mole) was heated to 90° in the presence of copper powder (p.1 g.). A total of 2.8 ml. N.T.P. of nitrogen was evolved (Calc'd 2.8 l. N.T.P.). Distillation of the reaction mixture gave: Recovered **A** (8.0 g.); crude fraction of Compound **I** (21.5 g., b.p. 90–126°/0.07 mm.); residue (7.3 g. dark and viscous).

Distillation of the crude fraction of Compound **I** did not give any separation (19.2 g., b.p. 107–110°/0.1 mm.). This impure fraction of Compound **I** (7.2 g.) was ozonized in the previously described manner. Approximately 4 mmoles. of ozone was absorbed. The ozonide was reduced catalytically; acidic components were removed by extraction of an ethereal solution of the products with saturated bicarbonate solution; and the neutral products were separated by distillation. In this manner there was obtained a pure fraction of Compound **I** (4.8 g., b.p. 108–110°/0.08 mm., n_D^{20} 1.4712).

Anal. Calc'd for $C_{14}H_{22}O_5$ C, 62.2; H, 8.1; Mol. Wt., 270.

Found: C, 61.9; H, 8.3; Mol. Wt. 272.

Compound **I** had a saponification equivalent of 137 (Calc'd for two carboxyl groups, 135). Treatment of Compound **I** with 2,4-dinitrophenylhydrazine reagent rapidly gave the hydrazone of cyclohexanone-2-acetic acid ethyl ester. The melting point (126–127°) of this hydrazone was not depressed by admixture with an authentic sample.

Anal. Calc'd for $C_{16}H_{20}N_4O_6$: C, 52.7; H, 5.5.

Found: C, 52.6; H, 5.8.

Treatment of Compound **I** with a methanolic solution of semicarbazide acetate failed to give a derivative when the mixture was allowed to stand for 24 hours. However, when Compound **I** was warmed for 10 minutes with ethanol containing traces of sulfuric acid, treatment of the resulting alcoholic solution with semicarbazide acetate rapidly gave the semicarbazone of cyclohexanone-2-acetic acid ethyl ester. The melting point (191.5–192.5°) of this semicarbazone was not depressed by admixture with an authentic sample.

Anal. Calc'd for $C_{11}H_{19}N_3O_3$: C, 54.8; H, 7.9.

Found: C, 54.8; H, 7.9.

The products of acid hydrolysis of Compound **I** gave a positive color test for glycolic acid.

Reaction of ethyl diazoacetate with cyclohexen-1-ol acetate in the presence of copper powder. A mixture of ethyl diazoacetate (30.0 g. 0.26 mole) and cyclohexenol acetate[13] (74.0 g., 0.53 mole) was heated to 90° in the presence of copper powder (0.1 g.). Nitrogen gas was evolved (5.6 l. at N.T.P.; Calc'd 5.9 l. at N.T.P.). After treatment of the reaction mixture as described for the purification of Compound **I**, a liquid (27.0 g., b.p. 80–81°/0.3 mm., n_D^{20} 1.4666) was obtained (Compound **J**).

Anal. Calc'd for $C_{12}H_{18}O_4$: C, 63.7; H, 7.9; Mol. Wt., 226.

Found: C, 63.5; H, 8.0; Mol. Wt., 224.

The saponification equivalent of Compound **J** was 115 (Calc'd for two carboxyl groups, 113). The behavior of Compound **J** with ketonic reagents was in all respects similar to the behavior of Compound **I**.

Thermal reaction of ethyl diazoacetate with cyclohexanone. A mixture of ethyl diazoacetate (20.0 g., 0.175 mole) and cyclohexanone (120 g., 1.22 moles) was heated to 155° (reflux temperature of cyclohexanone). The evolution of nitrogen was sluggish (4.0 l. N.T.P.; Calc'd 4.0 l. N.T.P.). The products were isolated by the methods previously described: Compound **A** (12.2 g.); Compound **G** (5.2 g.); Compound **C** (trace); Compound **I** (trace).

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[13] Prepared by the method of Bedoukian [*J. Am. Chem. Soc.*, **67**, 1430 (1945)].

At 90° in the absence of copper powder there was apparently no reaction between ethyl diazoacetate and cyclohexanone. In any event, no product boiling higher than the reagents was formed. The following molecular weights were determined: cyclohexanone, 98.6 (Calc'd 98.1); ethyl diazoacetate, 114.8 (Calc'd 114.1); an equimolar mixture of cyclohexanone and ethyl diazoacetate which had been heated to 90° for 15 minutes, 108 (Calc'd 106).

Reaction of ethyl diazoacetate with acetone in the presence of copper powder. Ethyl diazoacetate (20.0 g., 0.175 mole) dissolved in acetone (23.7 g., 0.41 mole) was added to acetone (47.4 g., 0.82 mole) containing suspended copper powder (0.1 g.) over a period of 2¾ hours. The temperature of the reaction mixture was approximately 93° (30 lb./sq. in.) at all times. The evolution of nitrogen was sluggish (3.25 l. N.T.P.; Calc'd 4.0 l. N.T.P.). At the end of three hours, the rate of nitrogen gas evolution was very slow. Distillation of the reaction mixture gave, in addition to recovered acetone and some ethyl diazoacetate, the following fractions: Crude Fraction **K** (7.50 g., b.p. 52–66°/9 mm.); Crude Fraction **L** (3.60 g., b.p. 40–47°/0.1 mm.); Crude Fraction **O** (4.65 g., b.p. 76–87°/0.1 mm.); Crude Fraction **P** (5.50 g., b.p. 105–112°/0.1 mm.); Residue (1.85 g.).

Purification and characteristics of fraction **K**. Contamination of fraction **K** by unreacted ethyl diazoacetate was apparent from the yellow color of the crude material. To destroy this latter material, this fraction was heated, in the presence of a small amount of copper, until no more nitrogen gas was evolved and the yellow color had disappeared. Two distillations of this fraction gave pure Compound **K** (6.0 g., b.p. 50–52°/9 mm., n_D^{20} 1.4290).

Anal. Calc'd for $C_7H_{12}O_3$: C, 58.3; H, 8.3; Mol. Wt., 144.

Found: C, 58.1; H, 8.4; Mol. Wt., 141.

The behavior of Compound **K** with carbonyl reagents was identical with that of **A**, except that derivatives of acetone were obtained. These derivatives (2,4-dinitrophenylhydrazone, m.p. 125–126°, and the semicarbazone, m.p. 185–186°) were identified by the usual method. Compound **K** (3.0 g.) was refluxed two hours in 90% ethanol containing 2% HCl. The solvent and volatile products were removed by evaporation below 20° at 9 mm., and were trapped at Dry Ice temperature. Treatment of one-quarter of the trapped material with an excess 2,4-dinitrophenylhydrazine reagent gave the 2,4-dinitrophenylhydrazone of acetone (0.3 g.). The residue from the evaporation was distilled. Ethyl glycolate (1.1 g., b.p. 35–45°/9 mm.) was thus obtained. The ethyl glycolate was identified as previously described. The residue from this distillation (0.3 g.) was assumed to be unchanged Compound **K**. Compound **K** reacted with ethyl diazoacetate to give Compound **O**. The reaction conditions and yield were comparable to the reaction of **A** with ethyl diazoacetate.

Purification and characterization of fraction **L**. Repeated distillations of the crude fraction **L** gave Compound **L** (presumably a mixture of two isomers; 3.1 g., b.p. 85–90°/10 mm., n_D^{20}.1.4248).

Anal. Calc'd for $C_{10}H_{18}O_4$: C, 59.4; H, 8.9; Mol. Wt., 202.

Found: C, 59.2; H, 8.9; Sapon. Eq., 195.

Compound **L** (2.95 g.) was ozonized at −60° in ethyl acetate. Less than 2 mmoles. of ozone was absorbed (Calc'd for one double bond, 14.6 mmoles.). The ozonide was reduced catalytically, and the products were separated by distillation. Thus there was obtained Compound $\mathbf{L_2}$ (2.0 g., b.p. 87°/12 mm., n_D^{20} 1.4212).

Anal. Calc'd for $C_{10}H_{18}O_4$: C, 59.4; H, 8.9; Mol. Wt., 202.

Found: C, 59.2; H, 9.0; Sapon. Eq., 198.

Compound $\mathbf{L_2}$ (2.0 g.) was saponified by two hours reflux in excess 10% aqueous NaOH. The aqueous basic solution was extracted with ether. This ethereal extract gave no derivative with 2,4-dinitrophenylhydrazine reagent. The aqueous basic solution was acidified to Congo Red with concentrated HCl, saturated with ammonium sulfate, and extracted with ether. This ethereal extract was dried over sodium sulfate; the ether was evaporated; and the residue was distilled. Thus there was obtained Compound **M** (1.1 g., b.p. 95–97°/12 mm., n_D^{20} 1.4359).

Anal. Calc'd for $C_8H_{14}O_4$: C, 55.1; H, 8.0; Mol. Wt., 174.
Found: C, 54.8; H, 7.9; Neut. Equiv., 172.

Compound **M** (0.3 g.) was refluxed two hours in 7 ml. of 3% aqueous HCl. The water and volatile products were removed at reduced pressure and trapped at Dry Ice Temperature. Addition of 2,4-dinitrophenylhydrazine reagent to this trapped material gave an immediate precipitate of the 2,4-dinitrophenylhydrazone of acetone (0.13 g.). The residue from the aforementioned evaporation was dried for four hours in a vacuum (0.05 mm., 50°). This residue, **N**, had a neutralization equivalent of 138 (Calc'd for $C_5H_{10}O_4$ with one carboxyl group, 134). **N** was oxidized by periodic acid and by lead tetraacetate to give acetone (identified as the 2,4-dinitrophenylhydrazone). Pyrolysis of **N** at approximately 160° gave carbon dioxide and isobutyraldehyde (identified as the 2,4-dinitrophenylhydrazone, m.p. 181–182°).

Purification and characterization of fraction **O**. Distillation of crude fraction **O** (4.65 g.) gave pure Compound **O** (4.3 g., b.p. 69°/0.05 mm., n_D^{20} 1.4448).

Anal. Calc'd for $C_{11}H_{18}O_5$: C, 57.4; H, 7.8.
Found: C, 57.1; H, 7.9.

Treatment of Compound **O** with 2,4-dinitrophenylhydrazine reagent gave an immediate and heavy precipitate of the hydrazone of ethyl levulinate (m.p. 101–102°; no depression of melting point was noted upon admixture with an authentic sample of the hydrazone of ethyl levulinate). When Compound **O** was heated with dilute H_2SO_4, the resulting aqueous solution gave a positive color test for glycolic acid.

Investigation of fraction **P**. Crude fraction **P** (2.0 g.) was refluxed three hours in 10 ml. of a solution of 5% HBr in 85% ethanol. The reaction mixture was cooled, 25 ml. of ether was added, and, after shaking with solid sodium bicarbonate, the solution was dried over a mixture of sodium bicarbonate and sodium sulfate. The ether and ethanol were evaporated at reduced pressure, and the residue was distilled. Thus there was obtained ethyl glycolate (0.35 g., identified by boiling point and the melting point of its *p*-nitrobenzoate), ethyl levulinate (0.45 g., identified by boiling point and the melting point of its 2,4-dinitrophenylhydrazone), and **P** (0.8 g., b.p. 97–98°/0.05 mm., n_D^{20} 1.4474).

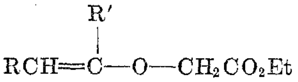
Anal. Calc'd for $C_{15}H_{24}O_7$: C, 56.9; H, 7.6; Mol. Wt., 316.
Found: C, 56.8; H, 7.8; N, 0.0; Mol. Wt., 309.

Compound **P** had a saponification equivalent of 115 and an equivalent weight per alkoxyl group by the Zeisel method of 104 (calc'd for three carbalkoxyl groups, 105). Alkaline hydrolysis, followed by acidification, or acidic hydrolysis of Compound **P** gave a viscous, water-soluble acid which could be esterified by the Fischer method to give **P**. This viscous acid could not be properly purified for analysis, and attempts to prepare crystalline derivatives, or to oxidize it, were without success. Compound **P** did not react with ozone or carbonyl reagents.

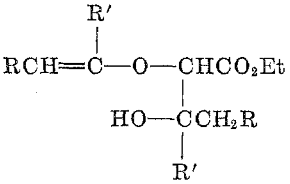
The formation of ethyl glycolate and ethyl levulinate by HBr treatment (see above) is attributed to the presence of **O** in the crude **P**. It was found that an increased yield of **P** could be obtained by rapid addition of the ethyl diazoacetate-acetone mixture in the original reaction. The reaction of ethyl diazoacetate with **K**, **L**, **O**, ethyl levulinate, ethyl fumarate, or ethyl methylacetoacetate failed to produce Compound **P**. Decomposition of ethyl diazoacetate in 90–100° ligroïn or *n*-decane (b.p. 174°) in the presence of copper powder at 90° gave no product boiling in the proper range of Compound **P**.

SUMMARY

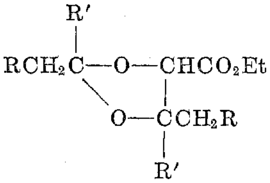
1. The reactions of ethyl diazoacetate with acyclic and cyclic ketones in the absence of oxygen have been investigated. It has been established that the reaction with either type of ketone (here represented as RCH_2COR') proceeds to give the following products:

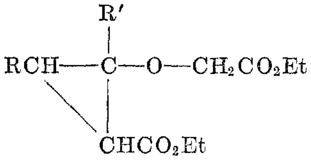
(a)  (1:1 adduct)

$$\mathrm{RCH{=}C(R'){-}O{-}CH_2CO_2Et}$$

(b)  (1:2 adduct)

$$\mathrm{RCH{=}C(R'){-}O{-}CH(CO_2Et){-}C(OH)(R')CH_2R}$$

(c)  (1:2 adduct)

(d)  (2:1 adduct)

The structures of these compounds have been established by conventional chemical methods.

2. It has been established that compound *c* is formed by isomerization of *b*.

3. A mechanism which accounts for the formation of products *a*, *b*, *c*, and *d* is suggested.

CHICAGO 37, ILLINOIS

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