[CONTRIBUTION FROM THE FULMER CHEMICAL LABORATORY, THE STATE COLLEGE OF WASHINGTON]

Stobbe-type Condensation of Ketones (Cyclohexanone and Acetone) with Diethyl Oxalacetate[1]

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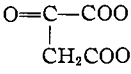
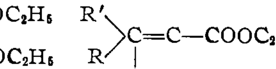
Although diethyl oxalacetate (I) condenses with cyclohexanone and acetone, respectively, in moderate to poor yields, it does not condense readily with ketones in general as does diethyl succinate (III) in the Stobbe condensation. Comments interpreting this behavior relative to III and the Stobbe condensation have been made. By comparison of the properties of the condensation products of the above ketones and I with those of known products derived from aldehydes and by examination of their infrared absorption spectra, it has been concluded that they possess an α-enol-γ-butyrolactone structure.

Although the condensation of aldehydes with diethyl oxalacetate (I) has been investigated extensively,[3] no examples of ketone condensation have been reported.[4] It is well known that ketones usually do not condense as readily as aldehydes with active methylene compounds; however, the Stobbe condensation,[5] in which ketones condense in excellent yield with alkylidene succinates (II) or with diethyl succinate (III), constitutes a striking exception.[6]

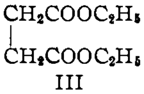


$$\begin{array}{l}\mathrm{O{=}C{-}COOC_2H_5}\\ \mid\\ \mathrm{CH_2COOC_2H_5}\end{array}$$

I



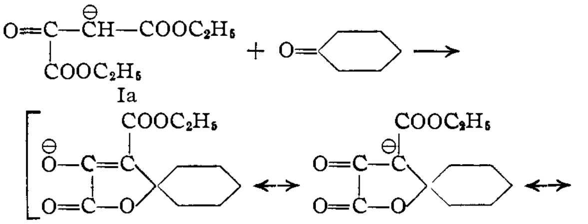
II



$$\begin{array}{l}\mathrm{CH_2COOC_2H_5}\\ \mid\\ \mathrm{CH_2COOC_2H_5}\end{array}$$

III

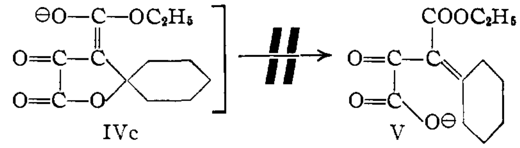
The close structural relationship of diethyl oxalacetate (I) to III and particularly to II suggested that it might readily undergo a Stobbe-type condensation with ketones.[3e] There is good evidence to suggest that the driving force of the Stobbe condensation is the tendency toward the formation of an intermediate γ-butyrolactone ring.[5] A similar possibility for γ-lactone formation exists in respect to diethyl oxalacetate (I) and, in fact, for the condensation of aldehydes with I, the final product is a γ-lactone similar to IV,[1] rather than a half-ester such as V.[5]



Ia

IVa

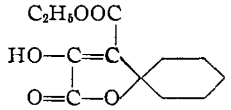
IVb



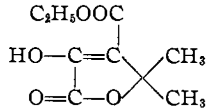
IVc

V

Since diethyl oxalacetate (I) forms a stable sodium salt, it is unnecessary to use a strong basic condensing agent to generate the anion Ia, as is the practice with the Stobbe condensation.[5] The usual procedure for aldehyde condensations[3] has been to suspend a quantity of the sodium salt Ia in absolute ethanol, add the desired aldehyde and warm the reaction mixture. When such conditions were employed in the present investigation, it soon became evident that condensations of I with ketones did not occur readily, an observation in sharp contrast to Stobbe condensations involving II or III. It was discovered that only more reactive ketones would condense with I, and at that in only relatively small yields as compared to aldehyde condensations. Less reactive ketones failed to condense. For example, although benzophenone condenses with III in an optimum yield of 97%,[7] condensation of this ketone failed to occur with I. Under similar conditions, however, acetone afforded a 1–2% yield of a condensation product, for which the structure VI tentatively was assigned, while cyclohexanone gave a relatively good yield of product IV (24–30%). When the ketone in question was employed in excess as solvent at 120°, somewhat higher yields were obtained. Attempts to bring about the condensation of other ketones, such as 2-heptanone and cyclopentanone, were negative, at least insofar as attempted isolation of products was concerned. It is to be noted that, also in the Stobbe condensation, cyclopentanone as compared to cyclohexanone appears to give a much poorer result, although in this case products have been isolated in low yield.[8]



IV



VI

Because considerable success has been achieved in the condensation of ketones with cyanoacetic ester (Cope–Knoevenagel condensation),[6] it was thought that investigation of such conditions in re-

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[2] Abstracted in part from theses submitted by James Wm. Cleary and Melvin J. Gortatowski in partial fulfillment of the requirements for the degrees of Doctor of Philosophy and Master of Science, respectively, the State College of Washington, February, 1956, June, 1952.

[3] (a) H. Gault and R. Durand, *Compt. rend.*, **216**, 848 (1943); (b) H. Gault, *et al.*, *Ann. chim.*, [12] **6**, 220 (1951); (c) C. H. Nield, THIS JOURNAL, **67**, 1145 (1945); (d) A. Rossi and H. Schinz, *Helv. Chim. Acta*, **31**, 473 (1948); (e) G. W. Stacy and G. D. Wagner, THIS JOURNAL, **74**, 909 (1952).

[4] The self-condensation of diethyl oxalacetate is an exception to this statement; W. Wislicenus and W. Beckh, *Ann.*, **295**, 339 (1897).

[5] W. S. Johnson and G. H. Daub, in R. Adams, Ed., "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951.

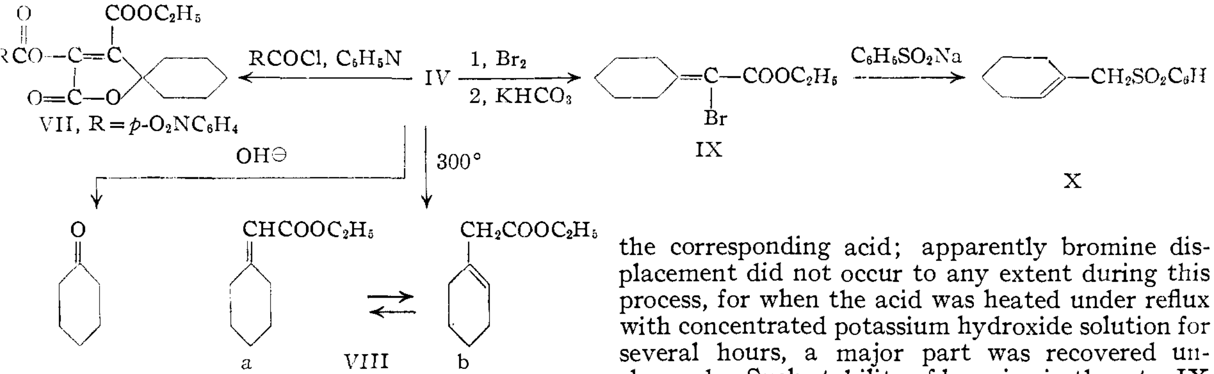
[6] Another notable exception is the Cope–Knoevenagel condensation: (a) A. C. Cope, C. M. Hofmann, C. Wyckoff and E. Hardenbergh, THIS JOURNAL, **63**, 3452 (1941); (b) E. J. Cragoe, C. M. Robb and J. M. Sprague, *J. Org. Chem.*, **15**, 381 (1950); (c) S. Dev, *J. Ind. Chem. Soc.*, **30**, 665 (1953).

[7] G. H. Daub and W. S. Johnson, THIS JOURNAL, **70**, 418 (1948); **72**, 501 (1950).

[8] H. Stobbe, *J. prakt. Chem.*, [2] **89**, 329 (1914); W. S. Johnson, C. E. Davis, R. H. Hunt and G. Stork, THIS JOURNAL, **70**, 3021 (1948).

spect to the present case would be desirable. However, application of such a procedure to the condensations of diethyl oxalacetate (I) and cyclohexanone was unsuccessful.

The structure of the condensation products IV and VI, like the well-known aldehyde-derived products, corresponds to that of an α-enol-γ-butyrolactone.[9] This was established by a comparison of properties of VI and of particularly IV[10] with those which have been reported for the aldehyde-derived products and by an examination of infrared absorption spectra. For example, the products in question gave a blood-red color with ferric chloride solution, reacted readily with sodium bicarbonate solution and failed to undergo reactions with carbonyl reagents, properties all common to the parallel aldehyde-derived products.[9] It was possible to prepare enol esters of IV and VI (*e.g.*, IV → VII), as it had been for aldehyde-derived products.[9]



Infrared absorption spectra strongly supported the enol ester structure assigned to VII and the parallel derivative obtained from VI. A strong absorption band at 1770 cm.$^{-1}$ was observed in the spectra of both these compounds; such a band is typical of an enol or vinyl ester group as compared with the spectrum of vinyl acetate.[11] Expected absorption bands corresponding to other elements of structure present also were observed (see Experimental).

Schinz and Rossi[12] had observed that α-enol-γ-lactones derived from aldehydes undergo pyrolysis resulting in simultaneous decarboxylation and decarbonylation to yield acrylate esters. Our cyclohexanone-derived product decomposed in a similar manner to yield a mixture of ethyl cyclohexylideneacetate (VIIIa) and ethyl cyclohexen-1-ylacetate (VIIIb).[13]

The treatment of such α-enol-γ-lactones with excess alkali has been shown to result in the cleavage of the lactone ring with the formation of the parent aldehyde, oxalic acid and acetic acid.[3b] In this study IV also exhibited similar behavior; cyclohexanone, isolated as its 2,4-dinitrophenylhydrazone, was obtained when IV was treated with 20% sodium hydroxide solution.

The bromination of α-enol-γ-lactones derived from aldehydes has been investigated.[3b,c,e] The α-keto-β-bromo-β-carbethoxy-γ-lactones initially produced have been found difficult to purify by distillation because of their instability; however, they have been treated with potassium bicarbonate solution to yield α-bromoacrylic esters. Again IV followed this expected pattern of behavior. It readily underwent bromination in aqueous methanol to produce what was presumably an α-keto-β-bromo-β-carbethoxy-γ-lactone.[3e] Without isolation this was treated with potassium bicarbonate solution to yield the α-bromoacrylic ester IX. This ester was saponified readily to give the corresponding acid; apparently bromine displacement did not occur to any extent during this process, for when the acid was heated under reflux with concentrated potassium hydroxide solution for several hours, a major part was recovered unchanged. Such stability of bromine in the ester IX and its corresponding acid in respect to possible displacement by hydroxyl under strong alkaline conditions might seem to be the expected behavior for a vinyl-type halide; however, displacements involving α-bromoacrylates have been observed and studied.[3b,14] We observed such a displacement when IX was heated with sodium benzenesulfinate. The reaction was complicated by the unanticipated loss of the carbethoxy group, and cyclohexen-1-ylmethyl phenyl sulfone (X) was obtained as the product. Assignment of the double bond to the endocyclic rather than the exocyclic position is tentative and based primarily on the infrared absorption spectrum. This assignment of the double bond position also was consistent with the finding[14] that such displacements occur after a shift of the double bond from the α,β- to the β,γ-position.

Prior to this, the infrared spectra of aldehyde-derived α-enol-γ-lactones of the series under consideration[15] had not been described. Therefore, the spectrum of such a product, ethyl α-hydroxy-β-(1-hydroxyisoamyl)-fumarate γ-lactone, was compared with the infrared spectra of IV and VI. The spectra of all these compounds strongly supported the enol assignment of structure. There was a strong absorption band at 3150–3250 cm.$^{-1}$, showing the presence of the enolic hydroxyl, and

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[9] Many of the properties of the condensation products derived from aldehydes suggest an enolic structure; H. Schinz and M. Hinder, *Helv. Chim. Acta*, **30**, 1349 (1947). Even though the nature of these substances has been recognized, they have been referred to consistently as α-*keto*-γ-butyrolactones. To emphasize their highly enolic character, in this paper we prefer to classify them as "α-*enol*-γ-butyrolactones."

[10] Minimal studies were carried out on VI because of the limited quantities available.

[11] R. B. Barnes, *et al.*, "Infrared Spectroscopy," Reinhold Publishing Corp., New York, N. Y., 1944, p. 72.

[12] H. Schinz and A. Rossi, *Helv. Chim. Acta*, **31**, 1953 (1948).

[13] Interconversion of these α,β- and β,γ-esters has been studied extensively by G. A. R. Kon and R. P. Linstead, *J. Chem. Soc.*, 1278 (1929).

[14] L. N. Owen and M. U. S. Sultanbawa, *ibid.*, 3089 (1949).

[15] While this investigation was under way, the infrared spectrum of a related α-enol-β-bromo-γ-lactone was reported. It has a spectrum similar to those reported here; E. D. Stecher and A. Clements, THIS JOURNAL, **76**, 503 (1954).

there was no indication of an absorption band in the ketone carbonyl region.[16] The enolic double bond was indicated by a medium to weak absorption band at 1640–1670 cm.$^{-1}$[17] and by strong absorption bands at 1700 cm.$^{-1}$, corresponding to that of a conjugated ester.[16] The γ-lactone carbonyl was suggested by strong absorption bands at 1735–1760 cm.$^{-1}$.[15,16]

Of interest is the fact that γ-lactones (corresponding to IVa, b, c) are obtained in condensations involving diethyl oxalacetate (I) and that half-esters (corresponding to V) are not obtained, as in the case of Stobbe condensations with diethyl succinate (III). These differences undoubtedly result from the relative stabilities of the anions involved. The γ-lactone anion IV would be expected to be more stable than the corresponding γ-lactone anion involved in the Stobbe condensation of III, such increased stability being due to resonance considerations involving the α-keto group IVa in addition to the ester carbonyl IVc. Also the γ-lactone anion apparently is more stable than the half-ester anion V.[18]

A consideration of anion stability also helps place aldehyde and ketone condensations of I in proper perspective with those of III. It is apparent that intermediate γ-lactone formation is a large factor in the condensation reactions involving III.[5] It appears from the present results that the success of such condensations depends on a favorable balance of three factors, which include not only the ability to form a γ-lactone ring but the relative reactivities of the anion and carbonyl.[19] Compound I would be expected to form a less reactive anion than III, as a result of resonance stabilization, so that it is not surprising that although Ia still is reactive enough to condense with the more reactive carbonyl of aldehydes, it is insufficiently reactive, even along with the driving force of γ-lactone formation, to condense with all but the most reactive ketones.

Experimental[20]

Condensation of Diethyl Oxalacetate with Acetone. Ethyl α-Hydroxy-β-(2-hydroxyisopropyl)-fumarate γ-Lactone[9] (VI).—To 450 ml. of absolute ethanol were added with stirring 114 g. (0.50 mole) of sodium diethyl oxalacetate (92% purity) and 38.0 g. (0.66 mole) of anhydrous acetone. The mixture was heated with stirring at 50° for 12 hr. When no evidence of product formation was observed,[3e] the mixture was heated under reflux for 37 hr. The mixture then was diluted with 1 l. of water, cooled to 10° and acidified with 6 *N* hydrochloric acid. The dark brown oil which separated was extracted with ether, and the combined ether extracts (A) were washed with several portions of 5% sodium bicarbonate solution (B).

The ether solution (A) was dried over anhydrous sodium sulfate. The ether was removed, and the residual, yellow oil was distilled under reduced pressure. The main fraction, b.p. 70–74° (0.1 mm.), readily formed derivatives of diethyl oxalacetate, thus identifying the bulk of the reaction mixture as unchanged starting material.

The sodium bicarbonate solution (B) from above was cooled to 10° and acidified with 6 *N* hydrochloric acid. The mixture was extracted with ether, and the combined ether extracts were dried over anhydrous sodium sulfate. After removal of the ether, the residual red-brown oil was distilled under reduced pressure. Some material of b.p. 106–110° (0.9 mm.) solidified in the receiver as long, colorless needles. This was recrystallized from petroleum ether (b.p. 30–50°) to afford VI as colorless needles, yield 1.80 g. (2%), m.p. 72–73°; repeated recrystallization for preparation of an analytical sample raised the melting point to 73–73.5°.

Anal. Calcd. for $C_9H_{12}O_5$: C, 53.99; H, 6.04. Found: C, 54.31; H, 6.09.

VI gave a blood-red coloration with ferric chloride solution and reacted readily with sodium bicarbonate solution. The infrared absorption spectrum showed bands that were assignable to OH (3250 cm.$^{-1}$, S), C=C (1670 cm.$^{-1}$, M), conjugated ester (1702 cm.$^{-1}$, S) and γ-lactone (1760 cm.$^{-1}$, S).

***p*-Nitrobenzoate of VI.**—To 10 ml. of pyridine were added 0.40 g. (2.0 mmoles) of VI and 0.87 g. (4.7 mmoles) of *p*-nitrobenzoyl chloride. The mixture was warmed to effect complete solution and allowed to stand overnight. The mixture again was heated to effect solution and poured into 50 ml. of cold water. After the mixture had been allowed to stand for 5 hr., the product was collected and washed with several portions of 5% sodium bicarbonate solution to yield 0.31 g. (44%) of a light tan solid, m.p. 104–107°. With charcoal decolorization, this was recrystallized from benzene to which a small amount of ligroin had been added, giving 0.26 g. (37% yield) of colorless crystals, m.p. 110.5°.

Anal. Calcd. for $C_{16}H_{15}NO_8$: C, 55.02; H, 4.33; N, 4.01. Found: C, 55.14; H, 4.51; N, 3.97.

The infrared absorption spectrum showed bands that were assignable to enol ester (1770 cm.$^{-1}$, S), C=C (1608 cm.$^{-1}$, W), conjugated ester (1720 cm.$^{-1}$, S) and γ-lactone (1750 cm.$^{-1}$, S).

Attempted Condensation of Diethyl Oxalacetate with Benzophenone.—A mixture of 22.7 g. (0.11 mole) of sodium diethyl oxalacetate and 18.2 g. (0.10 mole) of benzophenone in 100 ml. of absolute ethanol was heated at 40–75° for 30 hr. The mixture was worked up as in the above procedure. None of the desired product was obtained, although 88% of the benzophenone was recovered.

Condensation of Diethyl Oxalacetate with Cyclohexanone. Ethyl α-Hydroxy-β-(1-hydroxycyclohexyl)-fumarate γ-Lactone (IV). Procedure A.—The procedure is similar to that previously employed for aldehyde condensations.[3e] To 350 ml. of absolute ethanol were added with stirring 114 g. (0.50 mole) of sodium diethyl oxalacetate and 64.3 g. (0.66 mole) of cyclohexanone. The mixture was heated under reflux for 50 hr., cooled, diluted with 350 ml. of water and acidified with 6 *N* hydrochloric acid. One liter of water was added, and the resulting solution was extracted with five 200-ml. portions of ether. The combined ether extracts were washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. After the ether had been removed by distillation, the residual, red-brown oil was taken up in 200 ml. of ligroin (b.p. 60–90°). When the resulting solution was cooled in an ice–salt-bath, the γ-lactone crystallized to yield 26.0 g.; an additional 6.1 g. of product was obtained from the mother liquor as the sodium salt by washing the above filtrate with 100 ml. of a saturated solution of sodium bicarbonate followed by treatment of the salt as in **procedure B** which follows. The total amount of crude product isolated was 31.7 g. (26% yield), m.p. 106–113°. An analytical sample was prepared by recrystallization from ligroin (b.p. 60–90°) to give long, colorless needles melting at 119–119.5°.

Anal. Calcd. for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.92; H, 6.78.

This substance gave a blood-red coloration with ferric chloride solution and reacted readily with sodium bicarbonate solution. The infrared absorption spectrum revealed bands that were assignable to OH (3200 cm.$^{-1}$, S), C=C (1600 cm.$^{-1}$, M), conjugated ester (1704 cm.$^{-1}$, S) and γ-lactone (1735 cm.$^{-1}$, S). The infrared spectra of both the

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[16] F. A. Miller in H. Gilman, Ed., "Organic Chemistry," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1953, p. 143.

[17] W. H. T. Davison and G. R. Bates, *J. Chem. Soc.*, 2607 (1953).

[18] Stecher and Clements (ref. 15) in their β-bromo series were able to isolate both the acid corresponding to V and the α-enol–γ-lactone corresponding to IV. Interconversion of these two isomers took place readily.

[19] Ketones of very low reactivity, as a consequence of steric hindrance, have been found incapable of undergoing Stobbe condensations; M. S. Newman and J. Linsk, THIS JOURNAL, **71**, 936 (1949).

[20] All melting points are corrected, and boiling points are uncorrected. The microanalytical work was performed by Galbraith Laboratories, Knoxville, Tenn.

ketone-derived γ-lactones, IV and VI, were compared with that of a typical aldehyde-derived product, ethyl α-hydroxy-β-(1-hydroxyisoamyl)-fumarate γ-lactone,[21] which showed similar absorption bands for OH (3250 cm.$^{-1}$, S), C=C (1690 cm.$^{-1}$, M), conjugated ester (1702 cm.$^{-1}$, S) and γ-lactone (1740 cm.$^{-1}$, S).

Procedure B.—A mixture of 57.0 g. (0.25 mole) of sodium diethyl oxalacetate in 150 ml. (1.44 moles) of cyclohexanone was heated at 120° with stirring for 18 hr. The excess cyclohexanone was removed by distillation under reduced pressure, and the dark green residue was loosened by adding 200 ml. of water and warming on a steam-bath. After the material was poured into a beaker and cooled in an ice-bath, the precipitate (sodium salt of the γ-lactone IV) was collected by filtration, dried, pulverized and washed with ether repeatedly until the washings were nearly colorless. The resulting material had a light green coloration and amounted to 32.5 g. (50% yield).

The free γ-lactone was obtained by suspending the sodium salt in 300 ml. of water and by acidifying with 6 *N* hydrochloric acid; stirring of the mixture was continued for 1 hr. The crude product was collected by filtration, washed with cold water and dried to give 25.3 g. (42% yield), m.p. 113–116°.

In a number of other experiments,[2] variations in temperature and reaction time and various modifications in working up reaction mixtures were employed. In no case did any of these experiments lead to desirable simplifications or yields as good as those obtained in the procedures that are being reported. In attempts to apply Cope–Knoevenagel conditions using benzylamine–piperidine as catalyst,[6c] none of the desired IV could be isolated.

***p*-Nitrobenzoate of IV.**—From the reaction of 1.20 g. (5.0 mmoles) of IV and 1.87 g. (10 mmoles) of *p*-nitrobenzoyl chloride in 10 ml. of pyridine, which was worked up in a manner comparable to the *p*-nitrobenzoate of VI, there was obtained 1.63 g. (84% yield) of a *p*-nitrobenzoate, m.p. 96°. Recrystallization from dilute ethanol afforded short, colorless needles, yield 0.39 g. (20%), m.p. 98°.

Anal. Calcd. for $C_{19}H_{19}NO_8$: C, 58.61; H, 4.92; N, 3.60. Found: C, 58.61; H, 4.97; N, 3.46.

The infrared absorption spectrum showed bands that were assignable to enol ester (1770 cm.$^{-1}$, S), C=C (1608 cm.$^{-1}$, M), conjugated ester (1716 cm.$^{-1}$, S) and γ-lactone (1752 cm.$^{-1}$, S).

Pyrolysis of the α-Enol-γ-lactone IV.—A flask equipped with a still-head and a cooled receiver was heated under nitrogen by means of a metal-bath at 295°. To this was added in small portions 24.9 g. (0.10 mole) of IV. A clear, colorless liquid started to reflux almost immediately, and 5.49 g. (33% yield) of material was collected. This was redistilled under reduced pressure to yield 2.72 g. of a colorless oil boiling at 97–98° (13 mm.), n^{25}_{D} 1.4630, d^{25}_{4} 0.9730, M_{D} 47.62. When a sample of this material was treated with bromine–carbon tetrachloride, the color of the bromine was discharged rapidly.

From data reported in the literature for ethyl cyclohexylideneacetate (VIIIa, $n^{19.5}_{\text{D}}$ 1.4785, $d^{19.5}_{4}$ 0.9850),[22] the molecular refractivity was calculated, M_{D} 48.63; this substance is reported to absorb bromine very slowly. Literature data for ethyl cyclohexen-1-ylacetate (VIIIb, n_{D} 1.4617, d^{20}_{4} 0.9777[23]) gave a molecular refractivity closer to that of our product, M_{D} 47.30, and VIIIb is reported to absorb bromine rapidly. Very probably, the product obtained as a result of this pyrolysis was a mixture of VIIIa and VIIIb.[22]

Alkaline Decomposition of the α-Enol-γ-lactone IV.—To 1.00 g. (4.2 mmoles) of IV was added 25 ml. of 20% sodium hydroxide solution, and the mixture was heated under reflux for 1 hr., after which it was cooled and extracted with ether. After the ether had been removed, the residual oil was treated with 2,4-dinitrophenylhydrazine to give 0.59 g. (51% yield) of cyclohexanone 2,4-dinitrophenylhydrazone, m.p. 160–161°.[24]

Ethyl α-Bromocyclohexylideneacetate (IX) from IV.—A solution of 12.0 g. (0.05 mole) of IV in a mixture of 150 ml. of methanol and 20 ml. of water was cooled in an ice-bath, and 8.0 g. (0.50 mole) of bromine was added dropwise with stirring over a period of 25 minutes.[3e] This was stirred for 1.5 hr., and a solution of 20 g. of potassium bicarbonate in 15 ml. of water was added portionwise over a period of 20 minutes. Then 40 ml. of water was added in portions with stirring over a period of 1.3 hr., and the mixture was filtered to remove some insoluble material. A yellow oil separated, which was worked up in the usual manner[3e] and fractionally distilled to yield a main fraction boiling at 97–99° (0.4 mm.), yield 5.87 g. (48%), n^{25}_{D} 1.5100, d^{25}_{4} 1.3225.

Anal. Calcd. for $C_{10}H_{15}BrO_2$: C, 48.60; H, 6.12; Br, 32.34; M_{D}, 55.12. Found: C, 48.43; H, 6.12; Br, 32.22; M_{D}, 55.89.

The infrared spectrum indicated bands assignable to conjugated ester (1714 cm.$^{-1}$, S) and conjugated C=C (1602 cm.$^{-1}$, M).

α-Bromocyclohexylideneacetic Acid.—A mixture of 1.24 g. (5.0 mmoles) of IX, 10 ml. of ethanol and 10 ml. of 20% potassium hydroxide solution was heated at 50–55° for 40 minutes. After the solution had been cooled, 5 ml. of concentrated hydrochloric acid was added dropwise, and the mixture was allowed to stand 1.3 hr. There was obtained 0.83 g. (76% yield) of crude product melting at 119–121°. Recrystallization from dilute ethanol gave fine, colorless needles; yield 0.58 g. (53%), m.p. 120–120.5°.

Anal. Calcd. for $C_8H_{11}BrO_2$: C, 43.86; H, 5.06; Br, 36.48; neut. equiv., 219.1. Found: C, 44.02; H, 5.26; Br, 36.62; neut. equiv., 216.2.

The infrared spectrum indicated bands assignable to the carboxyl group (1680 cm.$^{-1}$, S) and conjugated C=C (1610 cm.$^{-1}$, M).

Treatment of α-Bromocyclohexylideneacetic Acid with Potassium Hydroxide Solution.—A sample of α-bromocyclohexylideneacetic acid, 1.24 g. (5.7 mmoles), was dissolved in 10 ml. of ethanol and 10 ml. of 20% potassium hydroxide solution, and the mixture was heated under reflux for 2.5 hr. Then 20 ml. of water was added, the solution was cooled in an ice-bath, and 4 ml. of concentrated hydrochloric acid was added slowly. The recovery of α-bromocyclohexylideneacetic acid was virtually quantitative (95%), m.p. 119–120°; this material was shown to be identical with the starting material by a mixed melting point determination. The absence of any cyclohexylpyruvic acid, which would have been formed by a displacement reaction, was shown by a negative test of the reaction mixture with 2,4-dinitrophenylhydrazine.[14]

Cyclohexen-1-ylmethyl Phenyl Sulfone (X).—Sodium benzenesulfinate, 0.86 g. (5.5 mmoles), was dissolved in a mixture of 4 ml. of ethylene glycol and 8 ml. of diethylene glycol monoethyl ether by warming[25]; 1.24 g. (5.0 mmoles) of IX was added, and the mixture was heated at 150° for 7 hr. The mixture was poured into 100 ml. of cold water and allowed to stand overnight; 0.63 g. of long, brown needles occluded in a brown oil was obtained. Recrystallization from ethanol with charcoal treatment gave 0.50 g. (42% yield) of tan crystals, m.p. 66–68°. This was recrystallized from dilute acetic acid to give 0.10 g. of fine, colorless needles, m.p. 76.5–77°.

Anal. Calcd. for $C_{13}H_{16}O_2S$: C, 66.07; H, 6.82; S, 13.57. Found: C, 65.90; H, 6.97; S, 13.28.

The infrared spectrum indicated bands assignable to the sulfone group (1300 cm.$^{-1}$, S), the benzene ring (1585 cm.$^{-1}$, 1480 cm.$^{-1}$, W) and C=C (1615 cm.$^{-1}$, W). No strong absorption band was noted in the conjugated C=C region, 1610–1580 cm.$^{-1}$.

Infrared Absorption Spectra.—These were obtained by means of a Perkin–Elmer double beam infrared spectrometer, model 21, with sodium chloride optics throughout. Samples of solid compounds were prepared by grinding with potassium bromide (concentrations of 1.5–3.5 mg. of compound per g. of potassium bromide) and pressing into thin disks.[26] The spectra of liquid compounds were determined using the pure liquid samples as such.

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(21) Obtained by the condensation of isovaleraldehyde with I (ref. 3e).

(22) S. F. Birch, G. A. R. Kon and W. S. G. P. Norris, *J. Chem. Soc.*, **123**, 1361 (1923).

(23) G. A. R. Kon and K. S. Nargund, *ibid.*, 623 (1934).

(24) C. F. H. Allen, THIS JOURNAL, **52**, 2955 (1930), reported m.p. 160°.

(25) C. W. Ferry, J. S. Buck and R. Baltzly in E. C. Horning, Ed., "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 239.

(26) U. Schiedt, *Z. Naturforsch.*, **76**, 270 (1952); M. M. Stimson and M. J. O'Donnell, THIS JOURNAL, **74**, 1805 (1952).

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[CONTRIBUTION FROM ABBOTT LABORATORIES]

An Improved Synthesis of Cyclopropyl Phenyl Ketone and Related Substances

BY W. J. CLOSE

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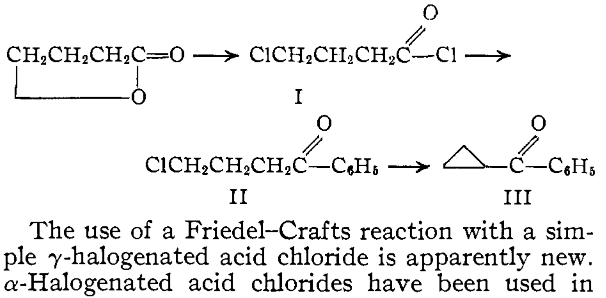
The synthesis of cyclopropyl phenyl ketone (III) in 75% yield from γ-butyrolactone is given. It is shown that the intermediate γ-chlorobutyryl chloride can be used to prepare other cyclopropyl aromatic ketones. Several new products derived from III are described.

In recent years there has been an increased interest in the study of compounds containing the cyclopropyl group. This is due in large part to the unique electronic nature of this arrangement of atoms; it is well known that the cyclopropane ring often possesses a large measure of unsaturated character.

Work with cyclopropane derivatives has been hampered by the relative unavailability of key intermediates. We have found a convenient method of preparing cyclopropyl phenyl ketone (III) which appears to be applicable to many other aromatic ketones and hence provides an entering wedge for the synthesis of numerous derivatives.

III has been prepared by a variety of methods. The most generally used procedures have utilized a γ-halogenated butyronitrile as the common intermediate.[1–3] The cost of this substance and the relatively low over-all yields have made it difficult to obtain large quantities of the ketone.

The availability of butyrolactone suggested to us a simpler and far cheaper process for obtaining III. The lactone, by successive treatment with hydrochloric acid and thionyl chloride, is converted to γ-chlorobutyryl chloride (I) in 88% yield. I is then condensed with benzene to give the chloroketone II, which is cyclized to III in the usual way with methanolic potassium hydroxide. The over-all yield from the lactone is 75–77%.



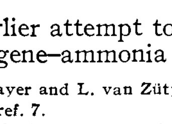
The use of a Friedel–Crafts reaction with a simple γ-halogenated acid chloride is apparently new. α-Halogenated acid chlorides have been used in this type of reaction, and it has been found that only the acyl halide enters into the reaction.[4] It has been reported[5] that either one or both of the halogen atoms in β-chloropropionyl chloride can be made to react with aromatic hydrocarbons in the presence of aluminum chloride. Hale and Britton[6] were able to obtain a reaction exclusively at the acid halide function with this substance.

Mayer and Fischbach[7] studied the Friedel–Crafts reaction of 2-(bromomethyl)-benzoyl bromide, which may be considered a special case of a γ-halogenated acid halide. They found that both the acyl and alkyl halide entered the reaction with the production of either a disubstituted derivative or an anthrone.

In our own case it was difficult to eliminate completely replacement of the γ-chloro group; however, when the reaction was carried out rapidly at moderately low temperatures (< 20°), the amount of by-product formed was minimal.

Presumably, the reaction sequence outlined can be followed with any aromatic compound which normally undergoes a Friedel–Crafts substitution. Toluene, chlorobenzene, phenetole and naphthalene were treated with I, and the expected products were obtained in all cases. No attempt was made to determine optimum operating conditions in these preparations.

Having on hand substantial quantities of III, we prepared several related compounds, many of which have not been described previously. Reduction of III with lithium aluminum hydride gave α-cyclopropylbenzyl alcohol (IV). The carbinol was converted to the carbamate in good yield by the method of McLamore[8]; it yielded an allophanate in poor yield when treated with cyanic acid.



IV, X = OH
V, X = Cl
VI, X = NH_2
VII, X = H

An earlier attempt to prepare the carbamate by the phosgene–ammonia method resulted in the for-

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[1] J. B. Conant, J. B. Segur and W. R. Kirner, This Journal, **46**, 1882 (1924).

[2] R. P. Mariella and R. R. Raube, *ibid.*, **74**, 521 (1952).

[3] H. R. Henze and C. W. Gayler, *ibid.*, **74**, 3615 (1952).

[4] A. Collet, *Bull. soc. chim.*, [3] **17**, 66 (1897).

[5] F. Mayer and L. van Zütphen, Dissertation, Frankfurt (1923); reported in ref. 7.

[6] W. J. Hale and E. C. Britton, This Journal, **41**, 841 (1919).

[7] F. Mayer and W. Fischbach, *Ber.*, **58**, 1251 (1925).

[8] W. M. McLamore, S. Y. P'an and A. Bavley, *J. Org. Chem.*, **20**, 1379 (1955).