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STERIC EFFECTS IN ORGANIC CHEMISTRY:
PART I SOME CHEMISTRY OF DI-T-BUTYLKETENE;
PART II ALKALINE HYDROLYSIS OF SUBSTITUTED
METHYL BENZOATES.

The Ohio State University, Ph.D., 1967
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STERIC EFFECTS IN ORGANIC CHEMISTRY

PART I SOME CHEMISTRY OF DI-T-BUTYLKETENE

PART II ALKALINE HYDROLYSIS OF SUBSTITUTED METHYL BENZOATES

DISSERTATION

Presented in Partial Fulfillment of the Requirements
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The Ohio State University
1967

Approved by

Melvin S. Newman
Adviser
Department of Chemistry

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VITA

October 2, 1940	Born, Heerhugowaard, The Netherlands
1962	B.A. Calvin College Grand Rapids, Michigan
1962-1963	Teaching Assistant, Department of Chemistry, The Ohio State University, Columbus, Ohio
1963-1967	Research Assistant, Department of Chemistry, The Ohio State University, Columbus, Ohio

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PART I

SOME CHEMISTRY OF DI-T-BUTYLKETENE

INTRODUCTION AND HISTORICAL

The interesting and highly reactive cumulative system of olefin and carbonyl double bond ($>C=C=O$) present in ketenes drew little attention after Staudinger's classic work.[1] Only recently, the work of Hasek and Martin with dimethylketene[2] and n-butylethylketene[3] has aroused a new interest in ketene chemistry.[4] In general diphenylketene

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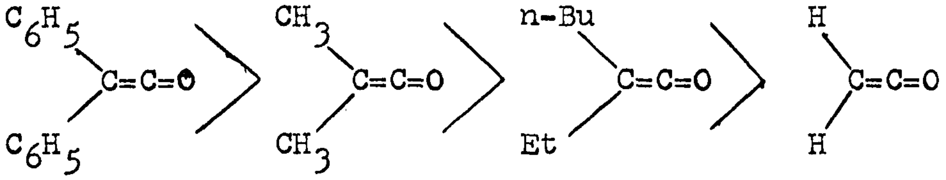
[1] H. Staudinger, "Die Ketene", F. Enke, Stuttgart, 1912.

[2] R. H. Hasek, R. D. Clark, and J. H. Chaudet, J. Org. Chem., 26, 3130 (1961); R. H. Hasek, E. U. Elam and J. C. Martin, ibid, 26, 4340 (1961); R. H. Hasek, E. U. Elam, J. C. Martin and R. D. Clark, ibid, 27, 60 (1962). J. C. Martin, V. W. Goodlett and R. D. Burpitt, ibid, 30, 4309 (1965).

[3] R. H. Hasek and J. C. Martin, J. Org. Chem., 28, 1468 (1963); R. H. Hasek, P. G. Gott and J. C. Martin, ibid, 29, 1239 (1964); J. C. Martin, P. G. Gott, V. W. Goodlett and R. H. Hasek, ibid, 30, 4175 (1965); R. H. Hasek, P. S. Gott and J. C. Martin, ibid, 31, 1931 (1966).

[4] For an excellent review, see R. H. Lacey, "The Chemistry of Alkenes", S. Patai, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, Chapter 14; see also, "Organic Reactions", Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 108.

and diphenyleneketene are more susceptible to reactions with nucleophilic reagents and in four-center cyclic reactions with other reagents containing multiple bonds than are the dialkylketenes. For some representative ketenes the following order of reactivity in 1,2 cycloadditions with olefins has been established.[5]



In 1960, di-t-butylketene[6] (I), the first aliphatic ketene stable as a monomer was synthesized. The absence of dimerization was attributed to the size of the two t-butyl groups. Two stable α-carbethoxyketenes, (α,α-dimethylbenzyl)carbethoxyketene (II) and

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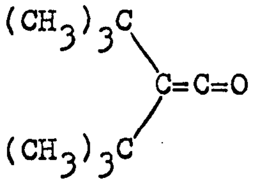
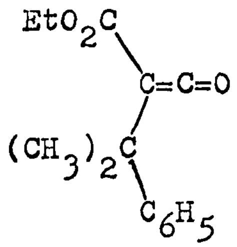
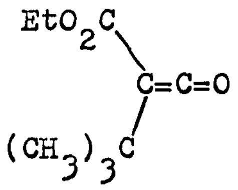
[5] J. C. Martin, P. G. Gott, V. W. Goodlett and R. H. Hasek, J. Org. Chem., 30, 4175 (1965).

[6] M. S. Newman, A. Arkell and T. Fukunaga, J. Am. Chem. Soc., 82, 2498 (1960).

t-butylcarbethoxyketene (III), were synthesized in 1962.[7]


I


II


III

Early exploratory experiments revealed that I was rather unreactive when compared to other ketenes.[6] For example, the addition of water to I occurred slowly unless catalyzed by acid or base, and furthermore, I could be generated in good yield by treating di-t-butylacetyl chloride with sodium amide in liquid ammonia.

The hindrance to nucleophilic attack was also observed by Hata.[8] When I was reacted with potassium methoxide in refluxing benzene for 194 hr. I was recovered in 41% yield with only a 59% yield of methyl di-t-butylacetate. Another example of the extreme

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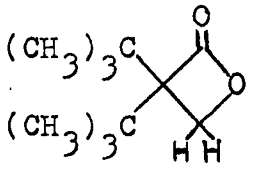
[7] M. S. Newman and E. A. Zuech, J. Org. Chem. 27, 1436 (1962).

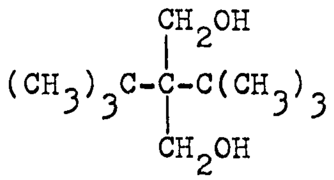
[8] Y. Hata, unpublished results.

conditions required for reaction was presented by Cope and Mehta.[9] A 68% yield of N,N-dimethyl-2,2-di-t-butylacetamide-2-d_1 was obtained by heating I, dimethylamine-N-d_1, and deuterium chloride in a pressure vessel at 200° and 1500 p.s.i. of nitrogen for 168 hr.

However, Hata,[8] performed an encouraging experiment in which a Lewis acid catalyzed addition of formaldehyde to I occurred to give α,α-di-t-butyl-β-propiolactone (IV). III was considered a potential precursor of 2,2-di-t-butyl-1,3-propanediol (V), a compound desired



IV



$(CH_3)_3C\text{-}C(CH_2OH)_2\text{-}C(CH_3)_3$

V

for kinetic and equilibrium studies of cyclic ketal formation by 2,2-dialkyl-1,3-propanediols.[10]

In view of these results, the primary aim of this research was to study further acid catalyzed additions to I as an avenue to a series of highly hindered molecules.

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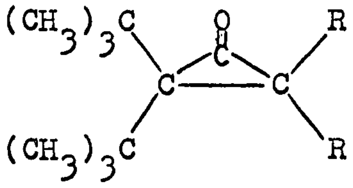
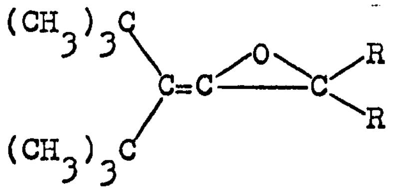
[9] A. C. Cope and A. S. Mehta, J. Am. Chem. Soc., 85, 1951 (1963).

[10] M. S. Newman and R. J. Harper, Jr., J. Am. Chem. Soc. 80, 6350 (1958); S. W. Smith, Ph.D. dissertation, The Ohio State University, Columbus, Ohio, 1967.

A secondary goal was a study of carbene and carbenoid additions to I with possible synthesis of stable cyclopropanones (VI) and/or allene oxides (VII).

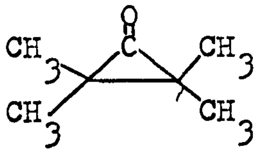


VI

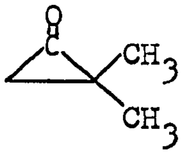


VII

Recent investigations have resulted in the synthesis of tetramethylcyclopropanone (VIII) by the photolysis of 2,2,4,4,-tetramethylcyclobutane-1,3-dione,[11] and of 2,2-dimethylcyclopropanone (IX) and cyclopropanone (X) by the addition of diazomethane to dimethylketene[12] and



VIII



IX

X

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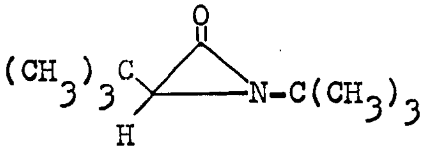
[11] N. J. Turro, W. B. Hammond and P. A. Leermakers, J. Am. Chem. Soc., 87, 2774 (1965).

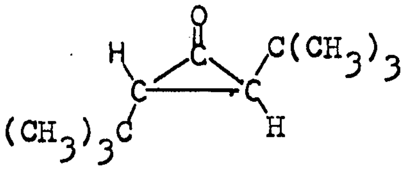
[12] N. J. Turro and W. B. Hammond, J. Am. Chem. Soc., 88, 2880 (1966).

ketene[13] respectively. All of these cyclopropanones were relatively stable in solution, but were not isolated. It was felt the gem-dialkyl effect of the two tertiary butyl groups would stabilize the three-membered ring sufficiently, so that isolation of the cyclopropanone might be possible.

Bulky tertiary substituents are known to stabilize α-lactams, e.g. 1,3-di-t-butylaziridinone (XI).[14] This concept led to the recent synthesis of a stable isolable cyclopropanone, trans-2,3-di-t-butylcyclopropanone (XII)



XI



XII

by reaction of α-bromodineopentyl ketone with the potassium

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[13] N. J. Turro and W. B. Hammond, ibid. 88, 3672 (1966).

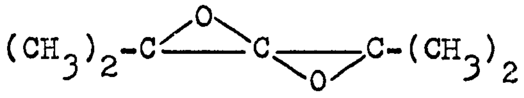
[14] J. C. Sheehan and J. A. Beeson, J. Am. Chem. Soc., 89, 362 (1967).

salt of p-chlorophenyldimethyl carbinol.[15]

Up to now, allene oxides have not been synthesized although they have been postulated as possible intermediates in the Favorskii type reactions of di(α-bromobenzyl)ketone[16] and the peracetic acid oxidation of tetramethylallene[17] to give 2-acetoxy-2,4-dimethyl-3-pentanone (XIII) and higher oxidation products derived presumable, from the 1,4-dioxaspiropentane (XIV).

$(CH_3)_2\text{-CH-CO-C}(CH_3)_2\ \text{OAc}$

XIII



XIV

The possibility of interconversion of cyclopropanones with their valence tautomers, allene-oxides, has as yet not been demonstrated.

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[15] J. F. Pazos and F. D. Greene, J. Am. Chem. Soc., 89, 1030 (1967).

[16] R. C. Cookson and M. J. Nye, J. Chem. Soc., 2009 (1965).

[17] J. K. Crandall and W. H. Machleder, Tet. Letters, No. 48, 6037 (1966).

RESULTS AND DISCUSSION

The results of the research reported in this section are discussed in the following sub-sections.

I. The preparation of di-t-butylketene.

II. The reactions of di-t-butylketene with formaldehyde, acetaldehyde and acetone.

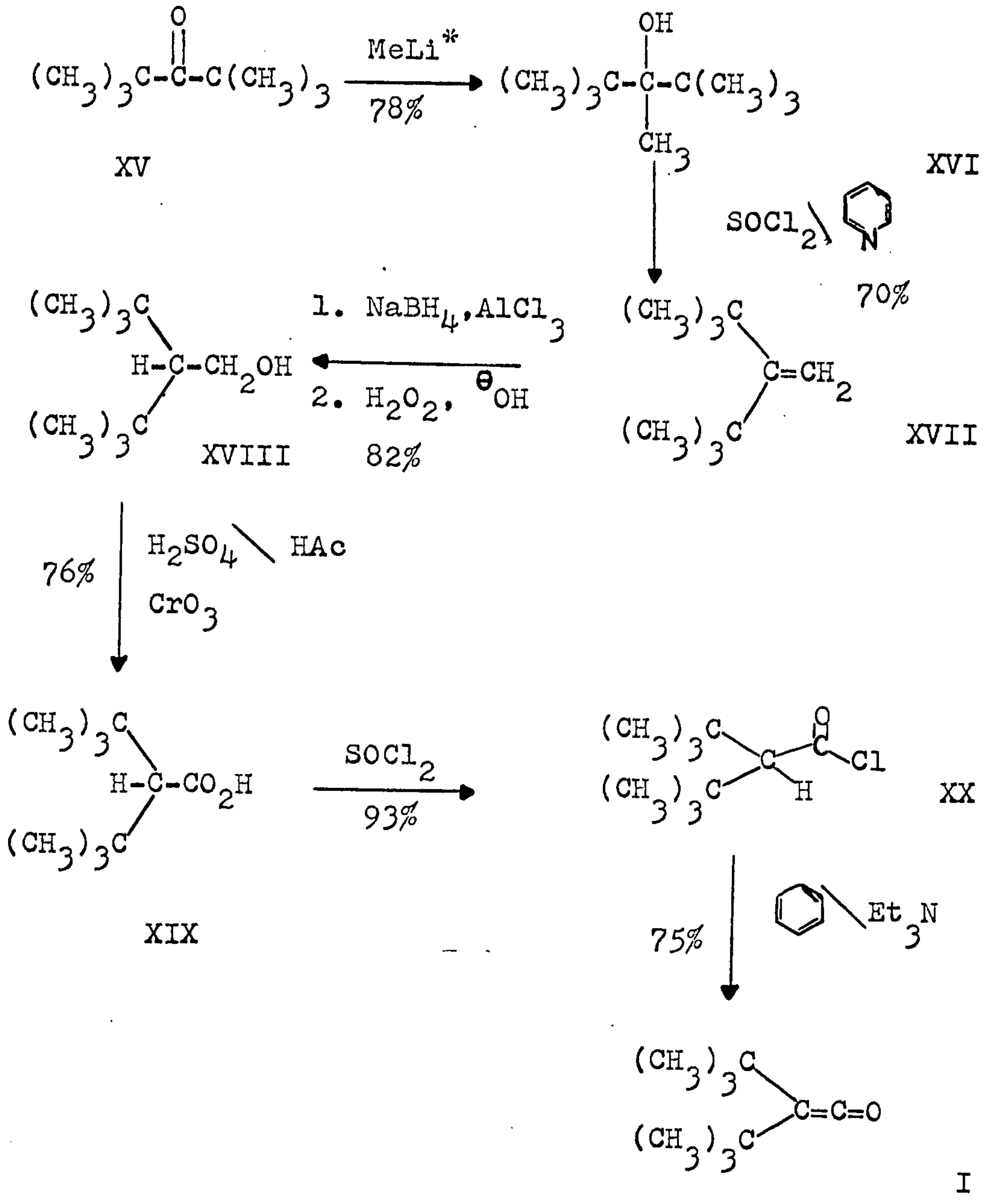
III. Attempted addition of reactive reagents to di-t-butylketene.

IV. Preliminary photochemical investigations of di-t-butylketene.

V. Conclusion and summary.

I. The preparation of di-t-butylketene.

Di-t-butylketene (I) was prepared in an overall yield of 24% from di-t-butylketone (XV) essentially as described.[6]



* Yields obtained are listed for each step in the synthesis of I.

Some of the di-t-butylketone (XV) required in this synthesis was prepared by the method of Cook and Percival[18] in yields of 30-40%, while the remainder was procured

$$(CH_3)_3CMgCl + (CH_3)_3COCl \xrightarrow{Cu_2Cl_2} (CH_3)_3CCOC(CH_3)_3 + MgCl_2$$

from Chemical Samples Co.[19]

The steps in the synthesis of I have been discussed previously in detail.[6] In general, similar yields were obtained for each step. The only exception is the formation of 2,2-di-t-butylethanol (XVIII) in 82% yield rather than in 65% yield from 1,1-di-t-butylethylene (XVII) even though the same procedure was employed. The one step essentially different is the use of triethylamine in refluxing benzene in forming I from di-t-butylacetyl chloride (XX) in 75% yield. Previously sodium amide in liquid ammonia was used to afford I in 57% yield. Thus

---

[18] N. C. Cook and W. C. Percival, J. Am. Chem. Soc., 71, 4141 (1949).

[19] Since this work, J. E. Bubois, B. Leheup, S. Molnarfi, F. Hennequin and P. Bauer, Bull. Soc. Chem. France, 8, 2024 (1964), reported new syntheses,

$$(CH_3)_3CLi + (CH_3)_3C\text{-}CO_2Et \xrightarrow{83\%} (CH_3)_3C\text{-}CO\text{-}C(CH_3)_3 + EtOLi$$

$$2(CH_3)_3CLi + CO_3Et_2 \xrightarrow{73\%} 2(CH_3)_3C\text{-}CO\text{-}C(CH_3)_3 + EtOLi$$

but these have not been checked.

a higher yield of I has been realized and the complication of amide formation has been avoided.

II. The reactions of di-t-butylketene with formaldehyde, acetaldehyde and acetone.

Addition of gaseous formaldehyde to an ether solution of I containing ca. 0.2 ml. of boron trifluoride-etherate as a catalyst resulted in the facile formation of α,α-di-t-butyl-β-propiolactone (IV) in 68% yield. The infrared spectrum of IV showed strong absorption at 1815 cm^{-1}, 5.51 μ, which is characteristic of α,α-disubstituted β-lactones.[20]

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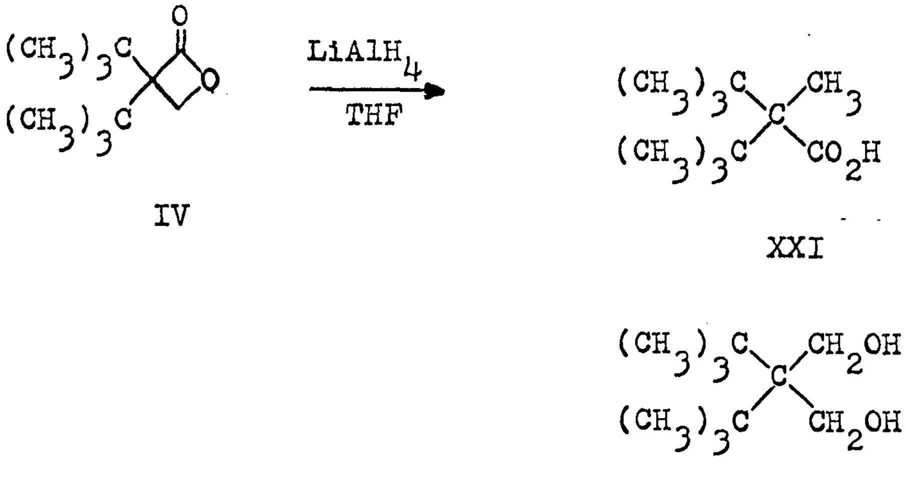
[20] For an excellent review of β-lactones, see Y. Etienne and N. Fischer, "Heterocyclic Compounds with Three-and Four-Membered Rings", Part II, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, Chapter 6; see also, H. Kroper, "Methoden Der Organischen Chemie", Bank VI/2, Georg Thieme Verlag, Stuttgart, 1963, p. 515.

Reduction of IV with lithium aluminum hydride in refluxing tetrahydrofuran gave a 70% yield of methyl-di-t-butylacetic acid (XXI), but no trace of the expected product 2,2-di-t-butyl-1,3-propanediol (V). Normally β-lactones are reduced with lithium aluminum hydride to yield 1,3-propanediols as, for example, with



IV

XXI

V

tetramethyl-β-propiolactone[21] and α,α-diphenyl-β-propiolactone.[22] Thus, the two t-butyl groups in the α position cause a carbon-oxygen single bond to be reduced in preference to a carbon-oxygen double bond. Other attempts to reduce IV with sodium in isopropyl alcohol and iso-propylmagnesium iodide were unsuccessful and resulted in recovery of starting material.

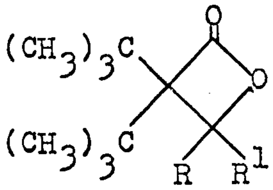
---

[21] G. Natta, G. Mazzanti, G. Pregaglia and M. Binaghi, J. Am. Chem. Soc., 82, 5511 (1960).

[22] H. E. Zaugg and B. W. Horrom, Anal. Chem. 20, 1026 (1948).

α,α-Di-t-butyl-β-propiolactone (IV) was also very stable to acid or base attack. Such reagents as hydrobromic acid, sodium peroxide, zinc in formic acid and sodium hydroxide in ethylene glycol (150°) had no effect on IV.

Although the synthesis of V was unsuccessful, a method of forming some highly hindered carboxylic acids seemed feasible if addition of acetone and acetaldehyde to I could be accomplished. However, the addition of acetone and acetaldehyde with boron trifluoride-etherate catalysis to I resulted in the formation of di-t-butylacetic acid (XIX) and in the case of acetaldehyde also small amounts of di-t-butylacetic anhydride. It appears that acetone and acetaldehyde are undergoing acid catalyzed aldol condensations and thus liberating the water required for formation of XIX. Attempts to prepare similar β-lactones (XXII) via alkylation of the preformed carbanion of IV with methyl iodide were also unsuccessful.



XXII

a. $R = CH_3$, $R^1 = H$

b. $R = CH_3$, $R^1 = CH_3$

III. Attempted addition of reactive reagents to di-t-butylketene.

As discussed previously (p. 6) diazomethane has been added to various ketenes to produce cyclopropanones. When a solution of diazomethane in methylene chloride at -78° was added to I no evolution of nitrogen occurred. Upon warming the solution the diazomethane decomposed, but no formation of a cyclopropanone or allene oxide was observed spectroscopically. Cuprous chloride catalysis[23] had no effect.

Treatment of I with methylene iodide and zinc-copper couple (Simmons-Smith reagent) led to the formation of a complex having absorption at 5.75 μ, 1740 cm^{-1}. However, when the solution was concentrated at room temperature the complex decomposed with evolution of heat and regeneration of I. Attempts to trap any cyclopropanone formed by a furan adduct were also unsuccessful.[24] These two facts seem to indicate that a cyclopropanone was not formed.

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[23] W. v. E. Doering and W. Roth, Tetrahedron, 19, 715 (1963).

[24] A. W. Fort, J. Am. Chem. Soc., 84, 4979 (1962).

Recent work by Seyferth and co-workers[25,26] with phenyl(trichloromethyl)mercury has provided a way of generating dichlorocarbene in neutral media. Treatment of I with phenyl(trichloromethyl)mercury in refluxing benzene and in 1,2-dimethoxyethane containing sodium iodide gave no evidence of cyclopropanone or allene-oxide formation. Similar results were obtained by generating dichlorocarbene from ethyl trichloroacetate with sodium methoxide.[27] A bulkier, but more electrophilic carbene, dicyanocarbene, was generated by treatment of bromomalononitrile with triethylamine[28], but did not add to I.

Since carbene additions to I proved unsuccessful, other additions such as sulfene, benzyne and ylids were

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[25] D. Seyferth, J. Mui, M. E. Gordon and J. M. Burlitch, J. Am. Chem. Soc., 87, 681 (1965).

[26] D. Seyferth, J. M. Burlitch and J. K. Heeren, J. Org. Chem., 27, 1492 (1962).

[27] W. E. Parham, E. E. Schweizer and S. A. Mierzwa, Org. Syn., 41, 76-8 (1961).

[28] J. S. Swenson and D. J. Renaud, J. Am. Chem. Soc., 87, 1394 (1965).

attempted. Alkanesulfonyl chlorides in the presence of triethylamine react with compounds containing electron-rich double bonds,[29] such as enamines, ketene acetals, ketene O, N-acetals and ketene N,N-acetals.[30]

Since the acetals of I are unknown, I was treated directly with methanesulfonyl chloride and triethylamine, but no addition of sulfene occurred. The only product was a resin formed from the sulfene.

Although, addition of benzyne to ketenes is unknown the ability of benzyne to undergo cycloadditions attracted attention. Formation of benzyne from *o*-bromoflurobenzene with magnesium in the presence of I did not result in adduct formation, but merely gave some triphenylene-a product of self-condensation of benzyne.

The successful addition of dimethyl-sulfoxonium methylid to diphenylketene to produce adduct XXIII in

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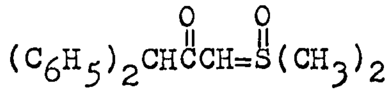
[29] For a recent review of sulfenes, see G. Opitz, Angew. Chem. Intern. Ed. Engl., *6*, 107 (1967).

[30] R. H. Hasek, P. G. Gott, R. H. Meen and J. C. Martin, J. Org. Chem., *28*, 2496 (1963); R. H. Hasek, R. H. Meen and J. C. Martin, *ibid*, *30*, 1495 (1965).

37% yield[31] suggested an analogous reaction with I.



$$(C_6H_5)_2CH\overset{O}{\overset{\|}{C}}CH{=}\overset{O}{\overset{\|}{S}}(CH_3)_2$$

XXIII

When I was added to pre-formed dimethylsulfoxonium ylid and stirred for 12 hr. at room temperature no adduct was formed and I was recovered intact.

IV. Preliminary photochemical investigations of di-t-butylketene.

The photolysis of ketenes has been studied both in vapor and condensed phases. The vapor phase photolysis of dimethylketene[32] and methylketene[33] has been investigated at various wavelengths. The principal photolytic products were carbon monoxide and low molecular weight olefins (C_nH_{2n} n=2,4; n=3,6). Condensed phase photolysis of dimesitylketene in

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[31] H. Konig and H. Metzger, Tet. Letters, #40, 3003 (1964).

[32] R. A. Holroyd and F. E. Blacet, J. Am. Chem. Soc., 79, 4830 (1957).

[33] G. B. Kistiakowsky and B. H. Mahan, J. Am. Chem. Soc., 79, 2412 (1957).

cyclohexane with a low-pressure mercury arc gave tetramesitylethylene (19%) and dimesitylketone.[34] Recently diphenylketene was photolyzed in various solvents with a 200-w high pressure mercury lamp.[35] For example, photolysis of diphenylketene in cyclohexene gave three isolable products: 3-benzhydrylcyclohexene (16%), 1,1,2,2-tetraphenylethane (22%), and bis-2-cyclohexen-1-yl (58%).

The photochemical behavior of I is characterized by extreme inertness. Photolysis of I in the condensed phase (cyclohexane, methanol) at 3130 A° and 2537 A° over extended periods of time did not lead to any decomposition of I as observed by vapor-phase chromatographic analysis. Vapor phase photolysis of I occurred only if mercury atom sensitization at 2537 A° was employed. The fact that 112 Kcal/mole of triplet energy is required indicates that I

$$\mathrm{Hg}\ ({}^1S_0) \xrightarrow{2537\ A^{\circ}} \mathrm{Hg}\ ({}^3P_1)$$

$$\mathrm{Hg}\ ({}^3P_1) \longrightarrow \mathrm{Hg}\ ({}^1S_0) + 112\ \text{K-cal}$$

---

[34] H. E. Zimmerman and D. H. Paskovich, J. Am. Chem. Soc., 86, 2149 (1964).

[35] H. Nozaki, M. Nakano and K. Kondo, Tet., 22, 477 (1966).

is, indeed, fantastically stable. This represents the first example of such unusual behavior in the area of ketene photochemistry.

V. Conclusion and summary.

This work has demonstrated that di-t-butylketene (I) provides, perhaps, the best example of steric retardation to chemical reaction in the whole of ketene chemistry. Only in the formation of α,α-di-t-butyl-β-propiolactone (IV) from I and formaldehyde and under the extreme conditions of mercury photosensitized photolysis did I undergo reaction. All other reactions with other reagents, reactive as they were, proved unsuccessful.

EXPERIMENTAL

Generalizations

Melting Points. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus using a standardized thermometer. No stem corrections were made.

Boiling Points. Boiling points were determined as the compound distilled. The thermometer was not standardized.

Elemental Analysis. Elemental analyses labelled g were by Galbraith Laboratories, Inc., Knoxville, Tenn., and those labelled m by Micro-Analysis, Inc., Wilmington, Delaware.

Infrared Spectra. Infrared spectra were determined with a Perkin-Elmer Infracord. Spectra of solid samples were obtained by potassium bromide wafers and those of liquids by liquid films on sodium chloride plates.

Ultraviolet Spectra. Ultraviolet spectra were obtained with a Perkin-Elmer Model 202 Spectrophotometer.

Nuclear Magnetic Resonance Spectra. Nmr spectra were determined in carbon tetrachloride with a Varian Associates A-60 instrument with tetramethylsilane as an internal standard.

Solvents. Ether for Grignard reactions were purified by distillation from Grignard reagent, while ether for lithium aluminum hydride reductions was distilled from lithium aluminum hydride. Tetrahydrofuran was treated with potassium hydroxide and distilled from lithium aluminum hydride. Bis-(2-methoxyethyl)ether (diglyme) was initially dried over calcium hydride and then distilled (75°, 35 mm.) from lithium aluminum hydride. Pentane was distilled and kept over molecular sieves. Benzene was purified by discarding the first 10% of the distillate.

The phrase "worked up in the usual way" means that the reaction mixture was taken up in ether-benzene (1:1), this solution was extracted with 10% sodium bicarbonate or 10% hydrochloric acid as needed, washed with saturated sodium chloride solution, filtered by gravity through anhydrous magnesium sulfate, and the solvents removed either in the rotatory evaporator or by distillation.

All reactions requiring anhydrous conditions were done in the traditional way i.e. protection from moisture by a drying tube and under dry nitrogen when necessary.

Intermediates

Preparation of 1,1-Di-t-butylethanol.

A few drops of methyl iodide (Columbia Chem. Co.) were added to initiate the reaction in a 3 l. round-bottomed flask containing 300 ml. of dry ether and 15.2 g.

(2.2 g-atom) of lithium wire which had been cut into small pieces. The remainder of the methyl iodide, 142.0 g. (1.0 mole), in 300 ml. of dry ether was added slowly during 3 hr. After stirring for 12 hr. at room temperature most of the lithium had disappeared. A solution of 71.1 g. (0.5 mole) of hexamethylacetone in 400 ml. of ether was added during 1 hr. under moderate reflux and vigorous stirring. The reaction mixture was stirred at reflux temperature for an additional 3 hr. and then added to 2 l. of crushed ice. The reaction mixture was made acid to litmus paper with 10% hydrochloric acid and worked up as usual, to afford 62.0 g. (78%) of colorless liquid,[1] b.p. 78-83° at 17-18 mm.

Preparation of 1,1-Di-t-butylethylene.

While the reaction temperature was maintained at 5 to 10°, 215 g. of thionyl chloride (purified by distillation from linseed oil) was added dropwise over a 2 hr. period to a 2 l. three-necked round-bottomed flask equipped with stirrer and condenser, and containing 650 ml. of dry pyridine (distilled from barium oxide) and 214.0 g.

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[1] A. Arkell, Ph.D. Thesis, O. S. U., 1958, p. 48, reports a yield of 75%.

(1.35 moles) of 1,1-di-t-butylethanol. After stirring for 4 hr. the reaction mixture was filtered. The filtrate was added to 500 g. of crushed ice and the product was taken up in 500 ml. of ether and worked up in the usual way. The crude product (red coloration) was distilled from potassium hydroxide pellets (to remove a foul sulfur compound) to give 132 g. (70%) of 1,1-di-t-butylethylene, b.p. 147-151°.[2] The product by gas chromatography was 96% pure, the remainder being probably another olefin[3], but not hexamethylacetone as reported.[4]

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[2] It is imperative that one uses thionyl chloride distilled from linseed oil, otherwise, one obtains excessive polymerization upon distillation of the product.

[3] M. S. Newman, A. Arkell, and T. Fukunaga, J. Am. Chem. Soc., 82, 2500 (1960), reported obtaining 1,1-di-t-butylethylene in 77-78% yield in a purity of 90-92%. An impurity of 6% was suggested as being the olefin, 2,3,3,4,4-pentamethyl-1-pentene.

[4] A. C. Cope and A. S. Mehta, J. Am. Chem. Soc., 85, 1951 (1963).

Preparation of 2,2-Di-t-butylethanol, Di-t-butylacetic Acid and Di-t-butylacetylchloride.

These compounds were prepared as described previously and with comparable yields.[3]

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[3] M. S. Newman, A. Arkell and T. Fukunaga, op.cit., p. 2500.

Preparation of Di-t-butylketene.

To a well stirred solution of 13.7 g. (0.072 mole) di-t-butylacetyl chloride and 20 ml. dry benzene was added 80 g. (0.79 mole) of triethylamine (Eastman). The solution was stirred for 4 hr. and refluxed slowly for 16 hr. After removal of triethylamine hydrochloride by filtration and excess triethylamine by distillation at atmospheric pressure, 8.3 g. (75%) of yellow liquid, b.p. 72-4° at 45 mm. was obtained.. The infrared spectrum showed strong absorption at 4.80 μ and the absence of absorption in the 5-6 μ region. The nmr spectrum showed a singlet at 8.78 tau.

Preparation of Phenylmecuric Bromide.

Under vigorous stirring 72 g. (0.20 mole) of mercuric bromide was added during 30 min. to a 500 ml.

three-necked round-bottomed flask which was equipped with an efficient stirrer and condenser and contained 0.204 mole phenylmagnesium bromide in 150 ml. of ether. The solution was refluxed for $3\frac{1}{2}$ hr. Upon cooling the ether was decanted and the residue boiled with 1% hydrochloric acid to remove excess mecuric bromide. The residue was washed with hot water, ethanol, and ether and dried at 100°. Recrystallization from a pyridine-benzene mixture gave 42.3 g. (59%) of colorless phenylmercuric bromide[5], m.p. 283-5°.

Preparation of Phenyl(trichloromethyl)mercury.

In a 500 ml. three-necked round-bottomed flask equipped with a high-speed mechanical stirrer and reflux condenser were placed 13.2 g. (0.037 mole) of phenylmercuric bromide, 24.0 g. (0.18 mole) of ethyl trichloroacetate and 200 ml. of anhydrous benzene. After the mixture was stirred and cooled in an ice bath for 15 min., 8.4 g. (0.154 mole) of sodium methoxide was added from an Erlenmeyer flask attached to the round-bottomed flask by means of Gooch tubing. The mixture was stirred with cooling

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[5] S. Hilpert and G. Gruttner, Chem. Ber. <u>46</u>, 1686 (1913), report a m.p. of 285°.

for an additional 1.5 hr. and then quenched with 250 ml. of water. After mixing the benzene layer was decanted and filtered. The aqueous layer was extracted with benzene (2x100 ml.). The organic layers were combined and dried by gravity filtration through anhydrous magnesium sulfate. Benzene was removed on a rotatory evaporator at 40-45°,[6] to give a white solid, m.p. 110-3°, which upon washing with 20 ml. of cold ethanol afforded 8.5 g. (58%) of phenyl(trichloromethyl)mercury,[7] m.p. 114-6°.

Preparation of Bromomalononitrile.

Bromine (10.2 ml.) was slowly added from a burette to a 100 ml. Ferlenmeyer flask containing 6.6 g. (0.10 mole) of malononitrile and 30 ml. of water. The mixture was shaken for 10 min. and allowed to stand overnight. The white solid which formed was collected and recrystallized from

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[6] It is necessary to keep the temperature below 50° otherwise the product will begin to decompose to phenylmercuric chloride and dichlorocarbene.

[7] E. E. Schweizer and G. J. O'Neill, J. Org. Chem., 28, 851 (1963), report a m.p. of 114-5°.

chloroform to afford 9.9 g. (74%) of bromomalononitrile[8], m.p. 64-5°.

Preparation of Trimethylsulfoxonium Iodide.

A solution of 32 g. of dimethylsulfoxide and 60 ml. of methyl iodide was heated at reflux for three days under nitrogen. The salt which separated was collected by filtration and washed with chloroform (2x100 ml.). Recrystallization from water gave 56.0 g. (62%) of trimethylsulfoxonium iodide,[9] m.p. 195° with decomposition, after the crystals were crushed and dried over phosphorus pentoxide under vacuum to a constant weight.

Reactions

Addition of Formaldehyde to Di-t-butylketene: α,α-Di-t-butyl-β-propiolactone.

A few drops (0.2 ml.) of boron trifluoride-etherate were added to a solution of 4.8 g. (0.031 mole)

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[8] L. Ramberg and S. Widequist, Arkiv Kemi, Mineral. Geol., 12A, No. 22, 6 (1937), report a m.p. of 64.5-5.1°.

[9] R. Kuhn and H. Trischmann, Ann. 611, 117 (1958), report a m.p. of 200° with decomposition.

of di-t-butylketene and 2.0 ml. of dry ether in a 100 ml. two-necked round-bottomed flask. While the mixture was stirred by a bar magnet, dry formaldehyde gas (generated by heating 4.5 g. paraformaldehyde previously dried over phosphorus pentoxide) was passed into the flask during 1 hr. The reaction mixture was stirred for an additional 1½ hr. at room temperature and then filtered to remove paraformaldehyde. After the filtrate was added to 50 ml. of water, the organic layer was collected and the aqueous layer extracted with ether (3x40 ml.). The organic layers were combined and dried by filtration through magnesium sulfate. Evaporation of the ether and recrystallization of the solid residue from n-hexane at -70° gave 3.9 g. (68%) of colorless α,α-di-t-butyl-β-lactone, m.p. 116-8°. A sublimed analytical sample melted at 118-9°. The infrared spectrum showed characteristic absorption at 1815 cm^{-1}, 5.51 μ[10]. The nmr spectrum showed a singlet of 9 protons (-CH$_3$) at 8.82 tau and a singlet of 1 proton (-CH$_2$O-) at 5.98 tau. Anal. Calcd. for C$_{11}$H$_{20}$O$_2$: C, 71.7; H, 10.9 Found[g]: C,71.8; H,11.1.

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[10] Y. Etienne and N. Fischer, "Heterocyclic Compounds with Three-and Four-Membered Rings," Part II, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, p. 779.

Attempted Addition of Acetone to Di-t-butylketene.

A solution of 4.1 g. (0.0266 mole) di-t-butylketene, 15 ml. of anhydrous ether and 0.2 ml. of boron trifluoride-etherate in a 100 ml. two-necked flask was stirred by a bar magnet while 20 ml. of anhydrous acetone was slowly added from an addition funnel during 1 hr. The color of the reaction mixture turned from yellow to black after 1 hr. After stirring 4 hr. at room temperature the ether and excess acetone were evaporated to give a tarry material, which when leached with Skellysolve B (b.p. 60-68°) gave a dark solution which was decolorized by treatment with activated charcoal (Darco G-60). Evaporation of the solvent and workup of the solid residue gave 4.2 g. of di-t-butylacetic acid, m.p. 72-4°. No trace of a neutral fraction was observed.

Attempted Addition of Acetaldehyde to Di-t-butylketene.

A mixture of 1.0 g. (0.0065 mole) di-t-butylketene, 5.0 ml. of acetaldehyde, 5 ml. dry ether and 0.2 ml. of boron trifluoride-etherate was stirred for 4 hr. at room temperature. Similar workup as in the above experiment gave 0.8 g. of di-t-butylacetic acid and a trace (0.09 g.) of neutral oil. This oil (identified as di-t-butylacetic anhydride) gave white crystals, m.p. 74-5°, upon low temperature recrystallization from pentane. The infrared spectrum (KBr) showed absorption at 1790 cm^{-1}, 5.58 μ, and 1720 cm^{-1}, 5.81 μ. The nmr spectrum showed a singlet of 18 protons ($-CH_3$) at 8.85 tau and a singlet of 1 proton (-CH) at 7.90 tau. Anal. Calcd. for $C_{20}H_{38}O_3$: C, 73.6; H, 11.7 Found[g]: C,73.3; H, 11.7.

Attempted Addition of Diazomethane to Di-t-butylketene.

Diazomethane (0.030 mole) in 25 ml. of cold (-78°) methylene chloride[11] was slowly added to 3.08 g. (0.020 mole) of di-t-butylketene in 10 ml. methylene chloride.[12] No solution of nitrogen was observed at this low temperature. The solution was slowly warmed to room temperature during 1 hr. V.p.c. analysis showed peaks associated with solvent and di-t-butylketene. By vacuum distillation 2.8 g. of di-t-butylketene was recovered.

Attempted Addition of Simmons-Smith Reagent to Di-t-butylketene.

A solution of 3.08 g. (0.02 mole) of di-t-butylketene

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[11] G. L. Closs and J. J. Coyle, J. Am. Chem. Soc., 87, 4270 (1965).

[12] This procedure is essentially that of W. B. Hammond and N. J. Turro, J. Am. Chem. Soc., 88, 3672 (1966).

and 5.36 g. (0.02 mole) of methylene iodide (freshly distilled; b.p. 61-2°, 10 mm.) in 20 ml. anhydrous ether and 1.96 g. (0.03 g-atom based on zinc) of a zinc-copper couple[13] were placed in a 50 ml. round-bottomed flask equipped with a condenser. While being stirred by a bar magnet, the contents of the flask were refluxed for 36 hr. An infrared spectrum of the crude reaction mixture showed absorption at 5.75 μ, but no absorption at 4.8 μ. After the zinc-copper couple was removed by filtration, the filtrate was slowly concentrated at room temperature. At approximately one quarter of the original volume the solution turned dark and heat was evolved. Vacuum distillation gave 2.5 g. of a yellow liquid, b.p. 58-9° at 24 mm., identified as di-t-butylketene.

Attempted Addition of Dichlorocarbene to Di-t-butylketene.

A. A suspension of 4.00 g. (0.011 mole) of phenyl-(trichloromethyl)mercury in 25 ml. of dry benzene[14] and

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[13] R. S. Shank and H. Shechter, J. Org. Chem. 24, 1825 (1959).

[14] D. Seyferth, J. M. Burlitch and J. K. Herren, J. Org. Chem., 27, 1492 (1962).

1.50 g. (0.01 mole) of di-t-butylketene was heated with stirring under reflux for 18 hr. The phenyl(trichloromethyl)mercury dissolved after 30 min. and phenylmercuric chloride precipitated (isolated in > 95% yield). An infrared spectrum of the crude mixture indicated ketene absorption at 4.8 µ, but no absorption in the 5-6 µ region. The ketene was recovered by vacuum distillation (1.2 g.). A sodium iodide modification[15] using 1,2-dimethoxyethane as a solvent was also attempted, but yielded identical results.

B. A solution of 3.08 g. (0.02 mole) of di-t-butylketene in 30 ml. of distilled pentane and 1.13 g. (0.021 mole) of sodium methoxide were placed in a 250 ml. three-necked round-bottomed flask. While the contents of the flask was stirred at 0°, 4.0 g. (0.021 mole) of ethyl trichloroacetate was added from an addition funnel during 30 min.[16] The reaction was stirred at -5° for 6 hr. An infrared spectrum showed no evidence for ketene loss or

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[15] D. Seyferth, J. Mui, M. E. Gordon and J. M. Burlitch, J. Am. Chem. Soc., 87, 681 (1965).

[16] W. E. Parham, E. E. Schweizer and S. A. Mierzwa, Org. Syn., 41, 76-8 (1961).

new carbonyl formation. After 50 ml. of water was added to the reaction mixture, workup gave 2.2 g. of recovered di-t-butylketene.

Attempted Addition of Dicyanocarbene to Di-t-butylketene.

Under nitrogen, 0.94 g. (0.0065 mole) of bromomalononitrile in 10 ml. of anhydrous ether was added during 1 hr. to a cold (-30°) solution of 1.0 g. (0.0065 mole) of di-t-butylketene, 0.657 g. (0.0065 mole) of triethylamine and 20 ml. of anhydrous ether in a 50 ml. flask.[17] After the reaction mixture was kept at -30° for an additional hour, a white precipitate, triethylamine hydrobromide, was collected by filtration. An infrared spectrum of the filtrate showed intense absorption at 4.8 µ. Workup allowed recovery of 0.80 g. of the ketene.

Attempted Addition of Sulfene to Di-t-butylketene.

A solution of 3.44 g. (0.03 mole) methanesulfonyl chloride in 75 ml. of anhydrous ether was added dropwise over a 2 hr. period to a stirred solution of 4.62 g. (0.03 mole) di-t-butylketene and 3.03 g. (0.03 mole) of

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[17] J. S. Swenson and D. J. Renaud, J. Am. Chem. Soc., 87, 1394 (1965).

triethylamine[18] in 150 ml. of anhydrous ether at room temperature. A white precipitate formed immediately, but soon coagulated to a brown tarry resin. The reaction mixture was allowed to stir overnight after the addition was complete. The resin was filtered from the solution and suspended in acetone. The acetone dissolved the resin and gave 2.6 g. (63%) of triethylamine hydrochloride. Combination of the acetone solution with the ether filtrate gave an oil (having strong absorption at 4.8 µ.) upon evaporation. Distillation of the oil led to the recovery of 3.1 g. of di-t-butylketene. No other volatile products were obtained and all attempts to crystallize the distillation residue failed.

Attempted Addition of Benzyne to Di-t-butylketene.

A few milliliters of a solution of 3.50 g. (0.02 mole) of 1-fluoro-2-bromobenzene in 25 ml. of dry tetrahydrofuran were added to a 100 ml. flask containing 0.54 g. (0.022 g-atom) magnesium turnings and 10 ml. of dry tetrahydrofuran while the temperature was maintained at 35°. After the reaction was initiated, 3.0 g. (0.0195 mole) of di-t-butylketene was added to the flask and then

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[18] W. E. Truce and J. R. Norell, J. Am. Chem. Soc., 85, 3231 (1963).

the remainder of the 1-fluoro-2-bromobenzene was added during 15 min. at 35-40°. The mixture was stirred 2 hr. and allowed to stand overnight. After a solution of 5 g. of ammonium chloride in 35 ml. of water containing ammonium hydroxide was added to the reaction mixture the layers were separated and the aqueous layer washed with ether. The washings were added to the tetrahydrofuran solution which was washed again with 0.1 N ammonium hydroxide. The organic layer was separated and dried over potassium carbonate. The ether and tetrahydrofuran were removed by distillation followed by 2.6 g. of di-t-butylketene. A trace (ca. 3%) of triphenylene[19], m.p. 200-5°, was obtained from the distillation residue.

Attempted Addition of Dimethylsulfoxonium Methylid to Di-t-butylketene.

Slow addition of 30 ml. dimethylsulfoxide (distilled from calcium hydride at 4 mm. and stored over molecular sieves) to a 100 ml. three-necked flask containing 0.468 g. (0.0195 mole) of sodium hydride and trimethylsulfoxonium iodide resulted in rapid hydrogen evolution.[20] As soon as

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[19] H. Heany and P. Lees, Tet. Letters, 41, 3049 (1964).

[20] E. J. Corey, and M. Chaykovsky, J. Am. Chem. Soc., 87, 1353 (1965).

hydrogen evolution had ceased 3.0 g. (0.0195 mole) of di-t-butylketene was slowly added to the flask by means of a syringe. The reaction was allowed to stir for 12 hr. at room temperature. After 50 ml. of water was added, the solution was extracted with ether-benzene and worked up in the usual manner. Distillation gave 2.5 g. of the ketene. No evidence for adduct formation as in the case of diphenylketene was observed.[21]

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[21] H. Konig and H. Metzger, Tet. Letters, 40, 3003 (1964).

Lithium Aluminum Hydride Reduction of α,α-Di-t-butyl-β-propiolactone: Methyl-di-t-butylacetic Acid.

A solution of 1.84 g. (0.01 mole) of α,α-di-t-butyl-β-propiolactone in 30 ml. of anhydrous tetrahydrofuran and 0.6 g. (0.015 mole) of lithium aluminum hydride was refluxed for 16 hr. The reaction mixture was poured into 50 ml. of water and then extracted with ether-benzene. Workup gave 1.48 g. of methyl-di-t-butylacetic acid. Recrystallization from methanol-water gave 1.3 g. (70%) of pure colorless acid, m.p. 179-80°.

Anal. Calcd. for $C_{11}H_{22}O_2$: C,70.9; H,11.9

Found[g]: C,71.1; H,12.0

No neutral fraction was obtained.

"Mixed" Hydride Reduction of α,α-Di-t-butyl-β-propiolactone: Methyl-di-t-butylacetic Acid.

A solution of 0.103 g. (0.0027 mole) lithium aluminum hydride in 25 ml. anhydrous tetrahydrofuran was prepared in a 100 ml. three-necked flask. At ice bath temperature a solution of 1.44 g. (0.0108 mole) aluminum chloride in 15 ml. anhydrous tetrahydrofuran was added to the reaction flask. After the reaction mixture was stirred 20 min.,[22] 0.5 g. (0.0027 mole) of α,α-di-t-butyl-β-propiolactone in 10 ml. of dry tetrahydrofuran was slowly added. The reaction mixture was refluxed for 2 days and then worked up to afford 0.33 g. (67%) of methyl-di-t-butylacetic acid, m.p. 178-180°. A small amount, 0.05 g., of the β-lactone was recovered from the neutral fraction.

Attempted Reduction of α, α-Di-t-butyl-β-propiolactone with Iso-propylmagnesium Iodide.

In a small scale reaction 0.006 mole of iso-propylmagnesium iodide was prepared in 20 ml. of anhydrous ether. α,α-Di-t-butyl-β-propiolactone, 0.5 g. (0.0027 mole), in 10 ml. of anhydrous benzene was added to the Grignard

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[22] E. L. Eliel, V. G. Badding and M. N. Rerick, J. Am. Chem. Soc., 84, 2371 (1962), proposed the following reaction:

$$LiAlH_4 + 3AlCl_3 \longrightarrow LiCl + 4AlHCl_2$$

solution and then the solution was refluxed for 2 days. Addition of water (30 ml.) to destroy the Grignard reagent, followed by the usual workup led to the recovery of 0.4 g. of the lactone.

Attempted Base Hydrolysis of α,α-Di-t-butyl-β-propiolactone.

A mixture of 0.65 g. (0.0035 mole) of the lactone, 15 ml. of methanol and 15 ml. of 30% sodium hydroxide was refluxed for 4 days.[23] By filtration and recrystallization from pentane at low temperatures, 0.60 g. of the lactone was recovered. A similar experiment using ethylene glycol as a solvent did not lead to any hydrolysis at 150° after 3 hr. The lactone was recovered by sublimation and no acid fraction was detected during workup.

Attempted Alkylation of α,α-Di-t-butyl-β-propiolactone by Methyl Iodide.

No heat was evolved, but small amounts of gas were given off when 0.71 g. (0.033 mole) of methyllithium in an ether solution was added through a syringe to a 50 ml. three-necked round-bottomed flask containing 0.3 g.

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[23] E. Testa, L. Fontanella, G. F. Christiani and L. Mariani, Ann. 639, 178 (1961), report α,α-di-n-butyl-β-propiolactone is hydrolyzed in 30 min. with 10% sodium hydroxide.

(0.0016 mole) of α,α-di-t-butyl-β-propiolactone in 10 ml. of anhydrous ether. The reaction was allowed to stir for 2 hr. and then 2.5 ml. (0.08 mole) of methyl iodide was slowly added through a syringe. After the reaction has stirred overnight at reflux temperature workup gave 0.23 g. of recovered lactone.

PART II

ALKALINE HYDROLYSIS OF SUBSTITUTED METHYL BENZOATES

INTRODUCTION AND HISTORICAL

Intramolecular catalysis by neighboring imidazole, amino, hydroxyl, carboxylate ion, carboxylic acid, and carboxamide groups in carboxylic ester hydrolysis has come under intensive study and review.[1,2,3] This interest has mainly centered around the use of these esters as possible models for the biochemical mechanisms of enzymatic reactions.

Neighboring carbonyl groups may also function as intramolecular catalysts in ester hydrolysis. This phenomenon was first postulated to account for the enhanced rate of hydroxide ion hydrolysis of methyl 2-benzoyl-6-methylbenzoate (II) when compared to the less sterically hindered methyl o-benzoylbenzoate (I).[4] The proposed

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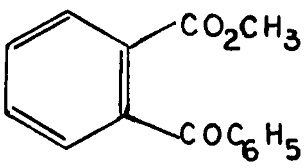
[1] M. L. Bender, Chem. Rev., 60, 53 (1960).

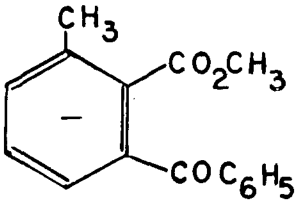
[2] B. Capon, Quart. Rev., 18, 45 (1964).

[3] T. C. Bruice and S. J. Benkovic, "Bio-organic Mechanisms", Vol. 1, W. A. Benjamin, Inc., New York, N. Y. 1966, p. 125.

[4] M. S. Newman and S. Hishida, J. Am. Chem. Soc., 84, 3582 (1962).

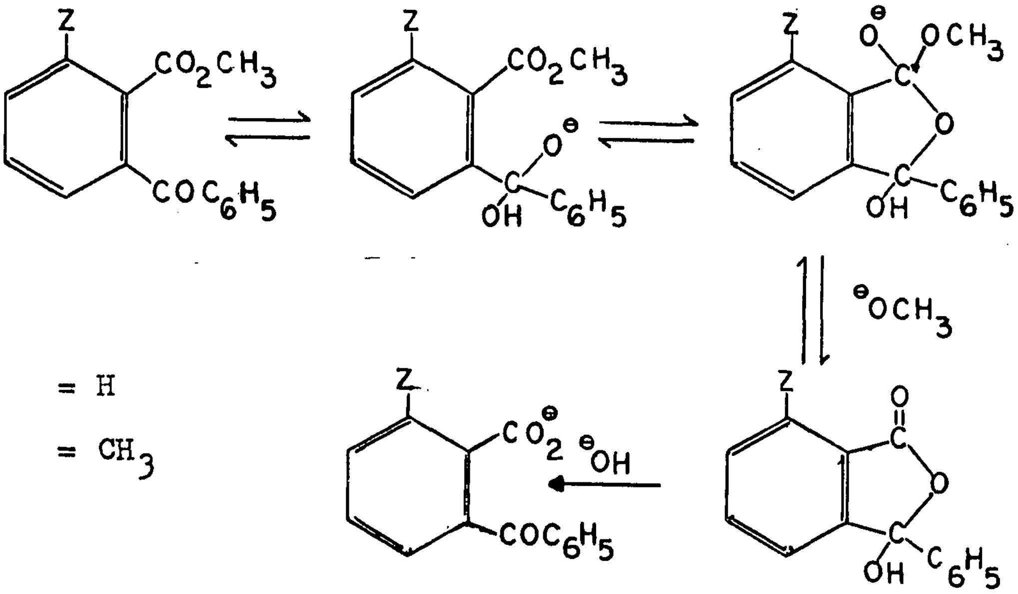


I



II

mechanism assumed attack of the hydroxyl ion on the ketonic carbonyl group followed by intramolecular displacement of methoxide by attack of the carbonyl hydrate



I. = H

II. = CH_3

anion on the carbomethoxy function. The normal mechanism of hydrolysis i.e. direct attack of the hydroxide ion on the carbomethoxy group, may also be involved, especially, in the case of I for which attack on the carbomethoxy group is not as hindered as in II.

Attack of the carbomethoxy group by the carbonyl hydrate anion should be faster for II than for I because the 6-methyl group, by forcing the carbomethoxy group to be in a plane perpendicular to the plane of the benzene ring, destroys resonance interaction of the carbomethoxy group with the ring and also allows the carbonyl hydrate anion to attack the carbomethoxy group from a direction perpendicular to it. By attacking from a perpendicular direction, maximum overlap of the carbonyl hydrate anion with the π-electron cloud of the ester is achieved in the transition state.[5,6]

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[5] M. L. Bender, Chem. Rev., 60, 60 (1960).

[6] W. P. Jencks, "Progress in Physical Organic Chemistry", Vol. 2, Interscience Publishers, New York, N. Y., 1964, p. 65.

Later work has shown that the carbonyl group may also be involved in the Fischer esterification of these particular acids, especially in the esterification of o-benzoylbenzoic acid.[7]

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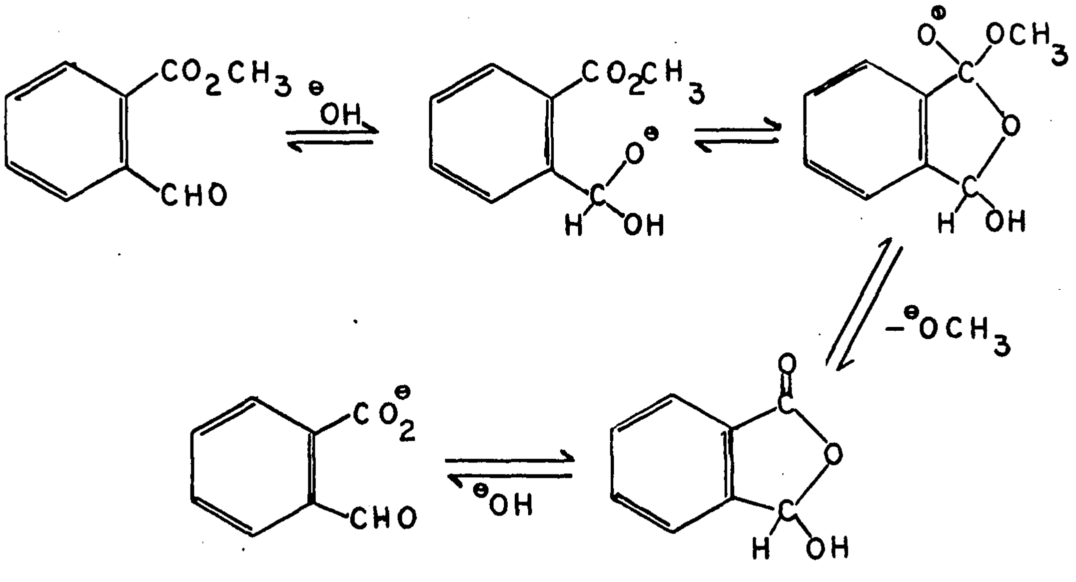
[7] M. S. Newman and C. Courduvelis, J. Org. Chem., 30, 1795 (1965).

Perhaps the most dramatic example of carbonyl participation in carboxylic ester hydrolysis is presented by the hydroxide ion and morpholine-catalyzed hydrolysis of methyl o-formylbenzoate.[8] The second-order rate constant (k_2 = 2000 $M^{-1}sec^{-1}$) for hydroxide ion hydrolysis is 10^5 faster than expected based on calculations involving the ratio of rate constants of the o-nitro- and p-nitrobenzoate esters and the rate constant of the p-formylbenzoate ester (corrected to aqueous solution). This value demands direct participation by the formyl group and thus the following mechanism was proposed.



The most convincing argument for this mechanism is the apparent analogous process in the morpholine-catalyzed hydrolysis in which 3-morpholinophthalide (A) was shown

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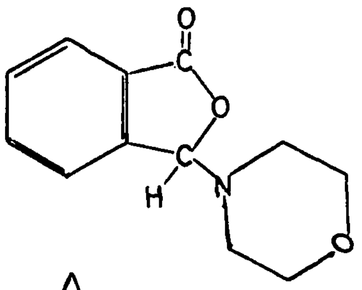
[8] M. L. Bender, J. A. Reinstein, M. S. Silver and R. Mikulak, J. Am. Chem. Soc., **87**, 4545 (1965); M. L. Bender and M. S. Silver, *ibid*, **84**, 4589 (1962).

to be an intermediate both by isolation from the reaction mixture and by spectrophotometric observation.



A

Rate enhancements have also been realized in the alkaline hydrolysis of other *o*-formyl compounds such as cinnamoylsalicylaldehyde (III), (k_2 = 1.2x10^4 M^{-1}sec^{-1} compared to a k_2 = 3.3x10^2 M^{-1}sec^{-1} for monocinnamoylcatechol)[9] and *o*-acetoxybenzaldehyde (IV), (k_2 = 11x10^4 M^{-1}sec^{-1} versus a k_2 = 25 M^{-1}sec^{-1} for the para compound).[10,11] Addition of a 0.002 M potassium

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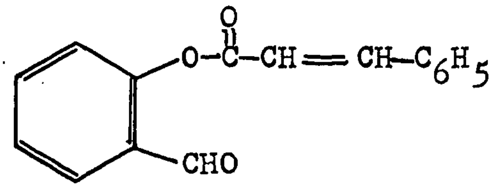
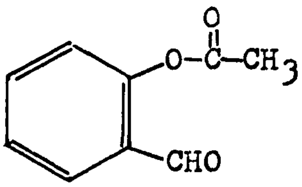
[9] Y. Shalitin and S. A. Bernhard, J. Am. Chem. Soc., *86*, 2292 (1964).

[10] L. Holleck, G. A. Melkonian, and S. B. Rao, Naturwiss., *45*, 438 (1958).

[11] G. Vavon and J. Scandel, Compt. rend., *223*, 1144 (1946).



III



IV

cyanide solution to the reaction mixture resulted in a rate enhancement of tenfold for III. This again suggests that carbonyl addition is of great importance in the hydrolysis of the ester. Shalitin and Berhard also performed the alkaline hydrolysis of the cinnamoyl ester of *o*-hydroxyacetophenone and established a $k_2 = 2.6\text{x}10^3\ M^{-1}\text{min}^{-1}$, which is 40 times faster than that of phenyl cinnamate.[12]

Neighboring groups can also participate in the hydrolysis of phosphates.[13,14] For example, the hydroxide

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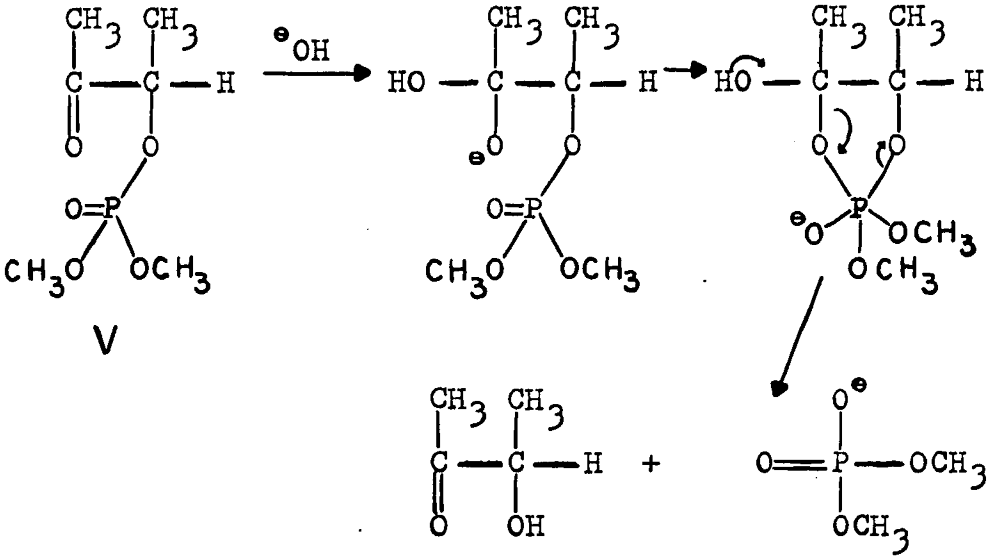
[12] Y. Shalitin and S. A. Bernhard, J. Am. Chem. Soc., 86, 2292 (1964).

[13] J. R. Cox, Jr., and O. B. Ramsay, Chem. Rev., 64, 317 (1964).

[14] T. C. Bruice and S. J. Benkovic, "Bio-organic Mechanisms", Vol. 2, W. A. Benjamin, Inc., New York, N. Y. 1966, pp. 35-59; see also, p. 103.

ion hydrolysis (pH 7.7-8.3) of dimethylphosphoacetoin (V) gives acetoin and dimethyl hydrogen phosphate.[15] The rate constant for hydrolysis is 2×10^6 times faster than that of trimethyl phosphate. A mechanism which was suggested involved carbonyl participation in the hyrolysis.


V

Carbonyl participation has also been invoked in solvolytic displacement of p-nitrophenol from p-nitrophenyl

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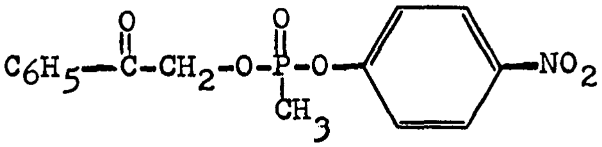
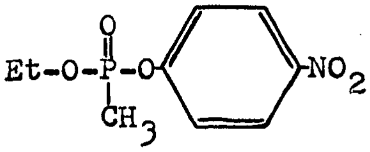
[15] F. Ramirez, B. Hansen, and N. B. Desai, J. Am. Chem. Soc., 84, 4588 (1962).

phenacyl methylphosphonate (VI) in aqueous dioxane.[16] Hydrolysis of VI at pH 7.81 is approximately 9000 times faster than the hydrolysis of ethyl p-nitrophenyl methylphosphonate (VII).



VI



VII

Based on the observations and results described above, a study of some of the substituent effects (steric and electrical) on carbonyl participation in alkaline ester hydrolysis was deemed of interest. Hence, we set forth to synthesize the following three classes of esters and study their rates of hydrolysis.

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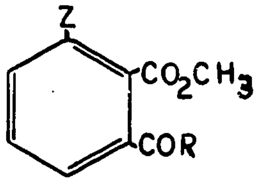
[16] C. N. Luske, E. G. Miller, Jr., J. J. Zeger and G. M. Steinberg, J. Am. Chem. Soc., 88, 188 (1966).



	Z	R
I	H	C_6H_5
II	CH_3	C_6H_5
III	Cl	C_6H_5
VIII	H	CH_3
IX	CH_3	CH_3
X	Cl	CH_3
XI	H	H
XII	CH_3	H
XIII	Cl	H

PREPARATION OF ACIDS AND ESTERS

Methyl *o*-benzoylbenzoate (I) and methyl 2-benzoyl-6-methylbenzoate (II) were obtained from previous workers.

Methyl 2-benzoyl-6-chlorobenzoate (III) was prepared from the parent acid by treatment with diazomethane. The acid was prepared as described from 3-chlorophthalic anhydride and phenylmagnesium bromide.[1] Methyl *p*-benzoylbenzoate was prepared in 78% yield by Fischer esterification of *p*-benzoylbenzoic acid.

The substituted (Z=Cl, CH_3) *o*-acetylbenzoic acids were prepared by employing a procedure used by Yale to make *o*-acetylbenzoic acid in 48.5% from phthalic anhydride, malonic acid and pyridine.[2] Fortunately only the

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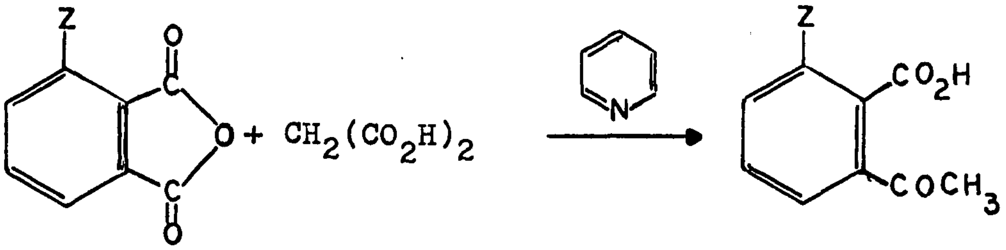
[1] M. S. Newman and P. G. Scheurer, J. Am. Chem. Soc., 78, 5004 (1956).

[2] H. L. Yale, J. Am. Chem. Soc., 69, 1547 (1947).



6-substituted acids were formed. 2-Acetyl-6-chlorobenzoic acid (structure proof in experimental p. 64) was prepared in 38% yield, while 2-acetyl-6-methylbenzoic acid was prepared in 33% yield.

2-Acetyl-6-methylbenzoic acid was also prepared in 31% yield by selectively hydrolyzing a mixture of methyl 2-acetyl-6-methylbenzoate, methyl 2-acetyl-3-methylbenzoate, and dimethyl 3-methylphthalate with a limited amount of sodium hydroxide. Methyl 2-acetyl-6-methylbenzoate undergoes alkaline hydrolysis much faster than the other esters and could, therefore, be effectively separated as 2-acetyl-6-methylbenzoic acid from the ester mixture. The ester mixture was produced from the acids obtained by treating 3-methylphthalic anhydride with methylmagnesium bromide.[3]

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[3] P. R. Jones and P. J. Desio, J. Org. Chem., 30, 4293 (1965), reported a 19% yield of 2-acetyl-6-methylbenzoic acid by direct isolation from the Grignard reaction.

Esterification of the substituted o-acetylbenzoic acids with dry diazomethane led to exclusive formation of the normal esters. It is imperative that pure diazomethane be used in these reactions.[4]

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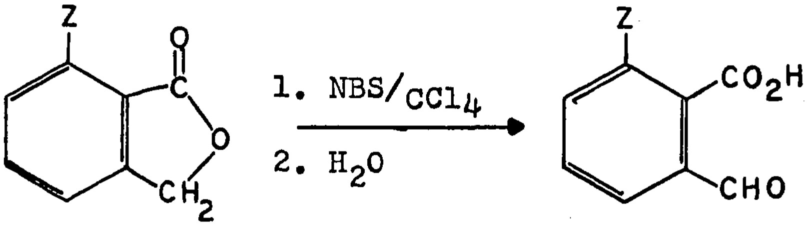
[4] See Experimental p. 59.

The pseudo esters of 2-acetyl-6-methylbenzoic acid and 2-acetyl-6-chlorobenzoic acid were prepared by Fischer esterification in 62% and 69% yields respectively.

The substituted (Z=Cl,CH_3) o-formylbenzoic acids were prepared as described below. The 7-substituted phthalides were treated with one equivalent of N-bromosuccinimide[5] in carbon tetrachloride. The crude 3-bromophthalides were refluxed with water[6] to form the substituted



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[5] I. A. Koten and R. J. Sauer, Org. Syn., Vol. 42, 26 (1962).

[6] R. L. Shriner and F. J. Wolf, Org. Syn., Coll. Vol., 3, 737 (1955).

phthalaldehydic acids. 6-Chloro-2-formylbenzoic acid and 6-methyl-2-formylbenzoic acid were prepared in yields of 47% and 36% respectively from their corresponding phthalides.

7-Chlorophthalide was prepared in 44% yield by reduction of 3-chlorophthalic anhydride with 0.75 equivalent of lithium aluminum hydride in ether.[7] Under similar conditions 7-methylphthalide was prepared in 69% yield. To insure that indeed the 7-methylphthalide and not the 4-methylphthalide was formed in the lithium aluminum hydride reduction, methyl 2,6-dimethylbenzoate was treated with 1 equivalent of N-bromosuccinimide in carbon tetrachloride and the resultant benzyl bromide treated with excess sodium hydroxide in methanol to afford 7-methylphthalide in 83% yield.[8]

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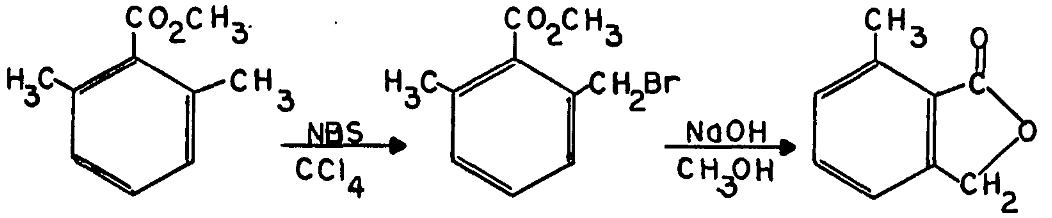
[7] J. Tirouflet, Compt. rend., 238, 2247 (1954) reports using 1 equivalent of lithium aluminum hydride, but does not report the yield of 7-chlorophthalide, m.p. 149.

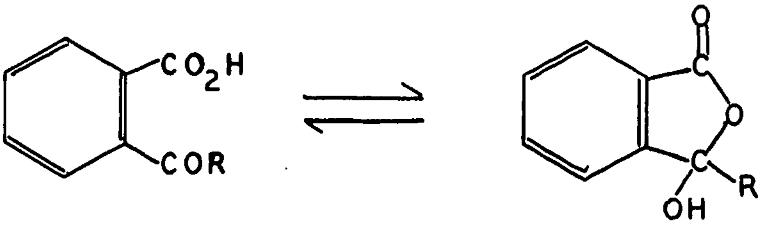
[8] J. H. Brewster and A. M. Fusco, J. Org. Chem., 28, 501 (1963), used this procedure to synthesize 4,5-benzophthalide.



Although we were able to synthesize the substituted phthaldehydic acids the normal esters could not be obtained in a pure form. Esterification with dry diazomethane always gave mixtures of normal and pseudo esters as determined by infrared spectroscopy. Furthermore, the esters were very sensitive to moisture. Thus the rates of alkaline hydrolysis of these esters were not obtained. The experimental method would also have come under extreme strain since the half-life of methyl *o*-formylbenzoate at a pH of 7.2 is only 29 min. in aqueous solutions and these esters would undoubtedly hydrolyze faster.

STRUCTURE OF ACIDS AND ESTERS

The normal and pseudo structures of the new acids and esters prepared in this work were determined by infrared spectroscopy. In the solid state, in non-polar solvents, and even in aqueous solution o-acylbenzoic acids exist to a large extent in the cyclic form.[1] The substituted o-acetylbenzoic acids and o-formylbenzoic acids displayed



keto acid lactol

infrared absorption at ca. 1740 cm^{-1}, 5.74 μ, (lactol carbonyl) and ca. 3340 cm^{-1}, 2.99 μ, (-OH) when potassium bromide wafers were used (See Table I). Their infrared spectra showed they existed exclusively in the lactol (cyclic) form in the solid state.

The solid state spectra of the substituted o-benzoylbenzoic acid are not as clearly defined. They demonstrate

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[1] P. R. Jones, Chem. Revs., 63, 461 (1963).

the characteristic broad spectrum of a carboxyl function and fail to show a sharp single carbonyl absorption. Thus, they exist as a tautomeric mixture in the solid state.

The transformation from the keto-acid to the lactol form is exceedingly fast for certain o-acylbenzoic acids. A lower limit of 100 sec^{-1} on the over-all rate constant for isomerization of o-acetylbenzoic acid and o-isobutyrylbenzoic acid has been determined using a stopped-flow spectrophotometer.[2]

The normal ester structure of the esters synthesized was established by the fact that two carbonyl peaks, one at 5.75 - 5.80 μ associated with the ester carbonyl and one at 5.80 μ to 6.05 μ associated with the ketone or aldehydic function, were present. The pseudo esters normally display carbonyl absorption at ca. 5.65 μ.[3]

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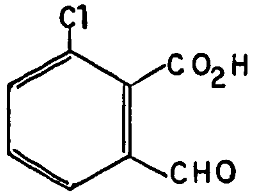
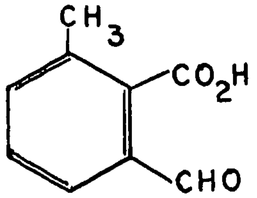
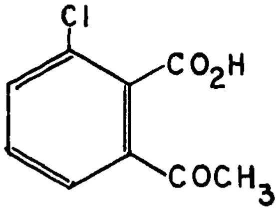
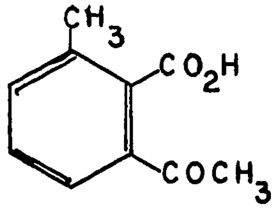
[2] M. L. Bender and E. T. Harper, J. Am. Chem. Soc., 87, 5627 (1965).

[3] C. I. Courduvelis, PhD. Dissertation, The Ohio State University, 1965, p. 11.

TABLE 1

Infrared Spectra of Some o-Acylbenzoic Acids - Potassium Bromide Wafers

Compound	I. R. Absorption (Strong)		
	3360 cm^{-1}	(2.98 μ)	-O-H
	1740 cm^{-1}	(5.75 μ)	$>$C=O
	3340 cm^{-1}	(2.99 μ)	
	1745 cm^{-1}	(5.73 μ)	
	3450 cm^{-1}	(2.90 μ)	
	1750 cm^{-1}	(5.71 μ)	
	3340 cm^{-1}	(2.99 μ)	
	1750 cm^{-1}	(5.71 μ)	

EXPERIMENTAL

Generalizations

The generalizations which applied to the experimental of Part I (see pp. 21-2) also apply in this part.

Preparation of Diazomethane.

Diazomethane was prepared from N-nitroso-N-methylurea according to the procedure of Arndt.[1] The resultant diazomethane-ether solution was either decanted and dried over potassium hydroxide pellets for 4 hr. at 0° or distilled directly (with caution) into a cooled receiving flask.

Intermediates

Preparation of 3-Methyl-3,6-endoxo-1,2,3,6-tetrahydrophthalic Anhydride.

A 2 l. Erlenmeyer flask was charged with 161.5 g. (1.66 mole) of maleic anhydride and enough dry ether (ca. 600 ml.) so that all the maleic anhydride was soluble near the boiling point of ether. While the solution was

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[1] F. Arndt, Org. Syn., Coll. Vol., 2, 165 (1943).

stirred with a magnetic stirrer 136.1 g. (1.66 mole) of 2-methylfuran (freshly distilled; 62.5 - 63.5° at 745 mm.) was rapidly added. A mild exothermic reaction resulted. After stirring for 4½ hr. the solution was allowed to stand overnight. The white crystals which had formed were collected, washed with cold ether, and dried under vacuum to remove adhering solvents. The reaction was repeated with 145.0 g. (1.51 mole) of maleic anhydride and 124.0 g. (1.17 mole) of 2-methylfuran. A total yield of 467.0 g. (82.5%) of 3-methyl-3,6-endoxo-1,2,3,6-tetrahydrophthalic anhydride,[2] m.p. 75-77°, was obtained.

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[2] D. M. Burness, J. Org. Chem., 21, 104 (1956), reports a m.p. of 78-9°.

Preparation of 3-Methylphthalic Anhydride.

A 3 l. three-necked round-bottomed flask equipped with a stirrer (Teflon blade), a low temperature thermometer and a powder funnel was charged with 1.1 l. of concentrated sulfuric acid. With rapid stirring the concentrated sulfuric acid was cooled to -15° to -20° by a dry ice-iso-propyl alcohol bath and 210 g. (1.17 mole) of 3-methyl-3,6-endoxo-1,2,3,6-tetrahydrophthalic anhydride (finely granulated) was added through the powder funnel during 30 min. The temperature of the solution was kept between -15° to -20° throughout and for 1 hr. afterward.

The dark red solution was allowed to warm to 5° and then poured into 4 l. of ice-water. The light-tan product was collected, washed throughly with cold water and pressed as dry as possible. The product was then stirred in a cold 10% sodium bicarbonate solution until no more carbon dioxide was evolved. The residue was collected, washed with cold water and air dried. Recrystallization from benzene (after decolorization with charcoal, Darco G-60) gave 89 g. (47%) of 3-methylphthalic anhydride,[3] m.p. 115-7°.

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[3] M. S. Newman and C. D. McCleary, J. Am. Chem. Soc., 63, 1542 (1941), report a m.p. of 114.5-117°.

Preparation of 3-Chlorophthalic Anhydride.

Chlorine was bubbled through twin pyrex tubes into a molten solution of 200 g. (1.04 mole) of 3-nitrophthalic anhydride (m.p. 169-70°) at 220 to 240° during 8 hr. Nitrogen dioxide was given off in large amounts the first 4 hr. The reaction mixture was distilled at 130-5° at 0.5 mm. into a solid receiver until the distillate came over yellow.[4] The solid was removed from the receiver and

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[4] The first sign of a yellow distillate indicates that 3-nitrophthalic anhydride is coming over.

recrystallized from benzene to afford 107.2 g. (57%) of colorless 3-chlorophthalic anhydride,[5] m.p. 126-7°.

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[5] M. S. Newman and P. G. Scheurer, J. Am. Chem. Soc., 78, 5004 (1956), report a 79% yield of 3-chlorophthalic anhydride, m.p. 124-6°, after 3.5 hr. of chlorination. This could not be duplicated. Even after 8 hr. of chlorination some 3-nitrophthalic anhydride was present as evidenced by infrared absorption at 1560 cm^{-1}, 6.41 μ.

Preparation of o-Benzoylbenzoic Acids and Esters.

o-Benzoylbenzoic acid and its normal and pseudo methyl esters came from preparations of previous workers.[6]

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[6] M. S. Newman and C. I. Courduvelis, J. Org. Chem. 30, 1795 (1965).

2-Benzoyl-6-methylbenzoic acid and its normal methyl ester, b.p. 158-9° at 0.75 mm., were prepared as reported with similar results.[7] 2-Benzoyl-6-chlorobenzoic acid was

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[7] M. S. Newman and C. D. McCleary, J. Am. Chem. Soc., 63, 1537 (1941).

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prepared as reported.[8] Once again a broad melting point

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[8] M. S. Newman and P. G. Scheurer, ibid., 78, 5004 (1956).

range (m.p. 90-105°) was observed for the acid. Esterification of this acid with a dry solution of diazomethane in ether gave a 94% yield of the normal methyl ester as a clear viscous oil, b.p. 190-2° at 1.2 mm.

The infrared spectrum showed absorption at 1740 cm^{-1}., 5.75 μ, and 1670 cm^{-1}, 6.00 μ.

Anal. Calcd. for $C_{15}H_{11}ClO_3$: C,65.6; H,4.0

Found[m]: C,65.4; H,4.0

Preparation of Methyl p-Benzoylbenzoate.

A solution of 5.0 g. (0.022 mole) of p-benzoylbenzoic acid in 30 ml. of methanol (saturated with dry hydrogen chloride) was refluxed for 4 hr. After the usual workup a solid was obtained which was recrystallized from methanol to give 4.1 g. (78%) of methyl p-benzoylbenzoate,[9] m.p. 108.5 - 109.5°.

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[9] B. B. Corson, J. Dorsky, J. E. Nickels, W. M. Kutz, and H. I. Thayer, J. Org. Chem. 19, 24 (1954) report a m.p. of 109.5-110.5°.

Preparation of 2-Acetyl-6-chlorobenzoic Acid.

A finely ground mixture of 10 g. (0.055 mole) of 3-chlorophthalic anhydride and 6.7 g. (0.064 mole) of malonic acid (dried in an oven at 105° for 3 hr.) was heated on a steam bath for 2 hr. with 7 ml. of dry pyridine. Carbon dioxide was evolved throughout the heating period. No solid separated when 50 ml. of water was added to the yellow solution. However, after 4 ml. of concentrated hydrochloric acid was added and the solution was allowed to stand for 2 days, 5.0 g. of white crystals, m.p. 124-6°, was filtered off. Recrystallization from benzene gave 4.1 g. (38%) of 2-acetyl-6-chlorobenzoic acid, m.p. 128-9°. The infrared spectrum showed strong absorption at 3450 cm^{-1}, 2.90 μ, and 1750 cm^{-1}, 5.70 μ.

Anal. Calcd. for $C_9H_7ClO_3$: C,54.5; H,3.6; Cl,17.8
Found[g]: C,54.3; H,3.6; Cl,17.8

Workup of the filtrate afforded 4.7 g. of 3-chlorophthalic acid, m.p. 184-6°.

The structure of 2-acetyl-6-chlorobenzoic acid was proved by degradation of m-chlorobenzoic acid. 2-Acetyl-6-chlorobenzoic acid was decarboxylated with copper powder and quinoline at reflux temperature (30 min.). The resultant oil was treated with sodium hypoiodite and after workup and recrystallization from water gave an acid of m.p. 156-8°. A mixed m.p. with an authentic sample of m-chlorobenzoic acid showed no depression.

Esterification of 2-acetyl-6-chlorobenzoic acid with a dry solution of diazomethane in ether gave a 92% yield of methyl 2-acetyl-6-chlorobenzoate, b.p. 107-9° at 0.5 mm. The infrared spectrum showed strong absorption at 1730 cm^{-1}, 5.78 µ, and 1695 cm^{-1}, 5.90 µ. No absorption at 1770 cm^{-1}, 5.65 µ, was observed.

Anal. Calcd. for $C_{10}H_9ClO_3$: C,56.5; H,4.3; Cl,16.7
Found[g]: C,56.4; H,4.2; Cl,16.4

Fischer esterification of 2-acetyl-6-chlorobenzoic acid for 3 hr. gave the pseudo ester, m.p. 79.5-81°, in 69% yield. The infrared spectrum showed strong absorption at 1770 cm^{-1}, 5.65 µ.

Anal. Calcd. for $C_{10}H_9ClO_3$: C,56.5; H,4.3; Cl,16.7
Found[g]: C,56.5; H,4.3; Cl,16.5

Preparation of 2-Acetyl-6-methylbenzoic Acid.

A. Methylmagnesium iodide was prepared from 2.4 g. (0.10 g-atom) of magnesium, 8.52 g. (0.06 mole) of methyl iodide and 100 ml. of dry ether. The Grignard reagent was then added to a 500 ml. three-necked round-bottomed flask containing 8.10 g. (0.05 mole) of 3-methylphthalic anhydride in 80 ml. of dry benzene and 50 ml. of dry ether during 30 min. The reaction mixture was refluxed with stirring for 8½ hr. The usual workup afforded 8.15 g. of an acid fraction and 0.8 g. of a neutral material, m.p. 64.5-66.0°. The acid fraction was esterified with a 0.1 mole of diazomethane in 150 ml. of dry ether to give 7.1 g. of esters, b.p. 121-5° at 2 mm. Vapor phase chromatographic analysis on various columns did not allow good separation of the esters. A solution of 7.0 g. (0.036 mole) of esters in 70 ml. of dioxane was treated with 175 ml. of 0.1 N sodium hydroxide (0.0175 mole) for 30 min. Workup and recrystallization from benzene afforded 2.7 g. (31% based on the anhydride) of 2-acetyl-6-methylbenzoic acid,[10] m.p. 127-8°. The infrared spectrum showed absorption at 3340 cm^{-1}, 3.00 µ, and 1750 cm^{-1}, 5.70 µ, and thus indicated a cyclic structure. The neutral fraction gave 4.1 g. of unreacted esters. These esters were again treated with limited amounts of base, but no pure crystalline acids could be obtained.

B. A finely ground mixture of 28.0 g. (0.173 mole) of 3-methylphthalic anhydride and 20.8 g. (0.2 mole) of malonic acid (dried in an oven at 100° for 4 hr.) was heated on a steam-bath for 5 hr. with 17 ml. of dry pyridine. The reaction was worked up as described before in the case of 2-acetyl-6-chlorobenzoic acid (see p. 63) to afford 10.2 g. (33%) of 2-acetyl-6-methylbenzoic acid, m.p. 126-7°. A total of 9.5 g. (31.2%) of 3-methylphthalic acid, m.p. 148-50°, was also obtained.

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[10] P. R. Jones and P. J. Desio, J. Org. Chem., 30, 4293 (1965), reported a 19% yield of 2-acetyl-6-methylbenzoic acid, m.p. 122-4°, when the employed the above Grignard reaction and direct workup.

Esterification of 2-acetyl-6-methylbenzoic acid with a dry solution of diazomethane in ether gave methyl 2-acetyl-6-methylbenzoate, b.p. 107-8° at 0.7 mm. The infrared spectrum showed absorption at 1695 cm^{-1}, 5.9 μ, and 1740 cm^{-1}, 5.75 μ.

Anal. Calcd. for $C_{11}H_{12}O_3$: C,68.7; H,6.3
Found[m]: C,68.8; H,6.4

Fischer esterification of 2-acetyl-6-methylbenzoic acid for 2 hr. afforded a 62% yield of the pseudo ester, m.p. 72.5° - 73.5°.[11] The infrared spectrum showed absorption at 1770 cm^{-1}, 5.65 μ. The nmr spectrum showed a multiplet of 3 protons (aromatic) centered at 2.75 tau, a singlet of 3 protons ($-OCH_3$) at 7.01 tau, a singlet of 3 protons ($Ar-CH_3$) at 7.31 tau, and a singlet of 3 protons ($-CH_3$) at 8.24 tau.

Anal. Calcd. for $C_{11}H_{12}O_3$: C,68.7; H,6.3
Found[m]: C,68.7; H,6.4

Preparation of Methyl o-Acetylbenzoate.

o-Acetylbenzoic acid (m.p. 115-6° after several

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[11] P. R. Jones and P. J. Desio, J. Org. Chem. 30, 4297 (1965) report an unusual m.p. of 170-180°.

recrystallizations from benzene of an Aldrich Chem. Co. sample) was treated with diazomethane in ether to give methyl o-acetylbenzoate,[12] b.p. 134-5° at 10 mm. (a second preparation gave a b.p. 94-5° at 0.6 mm.). The infrared spectrum showed absorption at 1695 cm^{-1}, 5.9 μ, and 1730 cm^{-1}, 5.78 μ.

Preparation of 2,6-Dimethylbromobenzene.

A suspension of 100 g. (0.83 mole) of 2,6-dimethylaniline (Aldrich Chem. Co.) in 250 ml. of 48% hydrobromic acid was stirred at 0-5° while a solution of 58 g. (0.84 mole) of sodium nitrite in 100 ml. of water was slowly added. The resulting solution was added during 30 min. to a boiling solution of 66 g. of cuprous bromide and 67 ml. of 48% hydrobromic acid. The product was steam distilled and worked up in the usual way to afford 70.1 g. (46%) of colorless 2,6-dimethylbromobenzene,[13] b.p. 53-5° at 2.3 mm.

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[12] R. Riemschneider, H. G. Kaahn and L. Herner, Monatsh. Chem., 91, 1040 (1960), report a b.p. of 137-9° at 14 mm.

[13] G. Vander Stouw, Ph.D. Dissertation, The Ohio State University, Columbus, Ohio, 1964, p. 45, reports a 34% yield of 2,6-dimethylbromobenzene, b.p. 64-7° at 5 mm.

Preparation of 2,6-Dimethylbenzoic Acid and Methyl 2,6-Dimethylbenzoate.

A solution of 70.1 g. (0.38 mole) of 2,6-dimethylbromobenzene, 83.0 g. (0.76 mole) of bromoethane, and 400 ml. of anhydrous ether was added during 2 hr. to a 1 l. three-necked round-bottomed flask containing 32.5 g. (1.35 g-atom) of magnesium turnings and 50 ml. of anhydrous ether. After the resulting solution was stirred under reflux for 2 hr., it was added to 400 g. of crushed dry ice. The dark solid which formed was treated with 20% hydrochloric acid and worked up in the usual way to afford 45 g. (79%) of 2,6-dimethylbenzoic acid,[14] m.p. 118-20°. Esterification of 2,6-dimethylbenzoic acid with diazomethane in ether afforded a 94% yield of methyl 2,6-dimethylbenzoate[15] b.p. 68-70° at 2 mm.

Preparation of 7-Methylphthalide.

A. A solution of 13.4 g. (0.082 mole) of methyl

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[14] B. van Zanten and W. Th. Nauta, Rec. trav. chem. 79, 1216 (1960), report a m.p. of 116°.

[15] B. van Zanten and W. Th. Nauta, ibid, 79, 1216 (1960), report a b.p. of 98-100° at 12 mm.

2,6-dimethylbenzoate in 250 ml. of dry carbon tetrachloride was added to a 500 ml. round-bottomed flask containing 14.6 g. (0.082 mole) of N-bromosuccinimide. The mixture was refluxed with a 300-w unfrosted lamp for 2 hr. After the succinimide was removed by filtration, the solution was concentrated to give an oil. This oil was treated with 20 ml. of methanol and 100 ml. of 20% sodium hydroxide under reflux for 20 hr. The solution was acidified and worked up in the usual way. Recrystallization of the product from petroleum ether (30-60°) and chloroform afforded 10.1 g. (83%) of 7-methylphthalide, m.p. 83-85°. A sublimed analytical sample melted at 84.0-85.5°. The infrared spectrum showed absorption at 1750 cm^{-1}, 5.71 µ. The nmr spectrum showed a multiplet of 3 protons (aromatic) centered at 2.80 tau, a singlet of 2 protons ($-CH_2O-$) at 4.88 tau, and a singlet of 3 protons ($-CH_3$) at 7.38 tau.

Anal. Calcd. for $C_9H_8O_2$: C,72.9; H,5.4
Found^m: C,72.6; H,5.4

B. A 500 ml. three-necked round-bottomed flask was charged with 2.8 g. (0.07 mole) of lithium aluminum hydride and 300 ml. of anhydrous ether. With rapid stirring and vigorous reflux, 15.0 g. (0.093 mole) of 3-methylphthalic anhydride was added through a solid addition funnel during 30 min. After the reaction mixture was refluxed for 3 hr., 50 ml. of water and 100 ml. of 20% sulfuric acid were carefully added. The usual workup afforded a white solid which was recrystallized from petroleum ether (30-60°) to give 9.5 g. (69%) of 7-methylphthalide, m.p. 83-5°. Continuous extraction of the aqueous layer with ether-benzene for 40 hr. did not afford any 3-methylphthalyl alcohol.

Preparation of 7-Chlorophthalide.

A 500 ml. three-necked round-bottomed flask was charged with 3.1 g. (0.082 mole) of lithium aluminum hydride and 300 ml. of anhydrous ether. With rapid stirring and vigorous reflux, 20.0 g. (0.109 mole) of 3-chlorophthalic anhydride was added through a solid addition funnel during 40 min. After the reaction mixture was refluxed for 5 hr. it was worked up as described in the above experiment. Recrystallization of the solid product from petroleum ether (60-90°) and chloroform afforded 8.1 g. (44%) of 7-Chlorophthalide,[16,17] m.p. 146-7°. The infrared spectrum showed absorption at 1755 cm^{-1}, 5.70 µ. No 3-chlorophthalyl alcohol could be extracted from the aqueous layer.

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[16] S. Biniecki, M. Moll, and L. Rylski, Ann. pharm. franc., 16, 421 (1958), report a m.p. of 146-7°.

[17] J. Tirouflet, Compt. rend. 238, 2246 (1954), reports a m.p. of 149°.

Preparation of 2-Formyl-6-methylbenzoic Acid.

A solution of 5.5 g. (0.0371 mole) of 7-methylphthalide in 150 ml. of dry carbon tetrachloride was added to a 250 ml. round-bottomed flask containing 6.6 g. (0.037 mole) of N-bromosuccinimide. The mixture was irradiated and refluxed with a 300-w unfrosted lamp for 2 hr. After the succinimide was removed by filtration, the carbon tetrachloride was removed on the rotatory evaporator to give a light-brown oil which could not be crystallized. The oil was refluxed in 75 ml. of water for 10 hr. Workup and recrystallization from benzene afforded 2.2 g. (36%) of 2-formyl-6-methylbenzoic acid, m.p. 112.5-114.0°. The infrared spectrum showed absorption at 3340 cm^{-1}, 3.0 µ, and 1745 cm^{-1}, 5.73 µ, and thus indicated a cyclic structure.

Anal. Calcd. for $C_9H_8O_3$: C,65.9; H,4.9

Found[g]: C,65.6; H,4.8

Preparation of 2-Formyl-6-chlorobenzoic Acid.

A solution of 2.9 g. (0.0172 mole) of 7-chlorophthalide in 50 ml. of dry carbon tetrachloride was added to a 100 ml. round-bottomed flask containing 3.06 g. (0.0172 mole) of N-bromosuccinimide. The mixture was irradiated and refluxed with a 300-w unfrosted lamp for 2 hr. After removal of the succinimide by filtration and the carbon tetrachloride by evaporation, the resultant oil was refluxed with 50 ml. of water for 2 hr. Workup and recrystallization from benzene afforded 1.5 g. (47%) of 2-formyl-6-chlorobenzoic acid, m.p. 187-9°. The infrared spectrum showed absorption at 3360 cm^{-1}, 2.98 μ, and 1740 cm^{-1}, 5.75 μ, indicating a cyclic structure.

Anal. Calcd. for $C_8H_5ClO_3$: C,52.1; H,2.7; Cl,19.2
Found[m]: C,52.3; H,2.9; Cl,18.9.

HYDROLYSES OF ESTERS

A. Experimental Procedure

The hydroxide ion catalyzed hydrolysis of the methyl esters in 70/30 (v/v) water-p-dioxane at 30° was carried out with a thermostated Beckman DU spectrophotometer. The reaction occurred in a thermostated buffer solution in a 3 ml. glass-stoppered quartz cell. The rate constants were determined by following the increase in carboxylate anion absorption with time at 310 mμ.[1]

The pH of the p-dioxane[2] - water solutions used in this work was determined using a Beckman Model 76 expanded scale pH meter with a calomel-fiber junction electrode (39170) and a glass electrode (41260, pH 0-14, Type E-2). The pH meter was standardized with aqueous

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[1] For an ester of each class studied, the rate was shown to be independent of the wavelength employed.

[2] The p-dioxane was purified as described in L. F. Fieser, "Experiments in Organic Chemistry", D. C. Heath, New York, N. Y., 1941, p. 369.

solutions, as recommended.[3] The glass electrode gives the correct pH at the concentration used in the p-dioxane-water mixtures.[4]

A stock solution of each buffer was prepared from aqueous buffers ($\mu = 0.15$ to 0.19) and the appropriate amount of p-dioxane. The pH of this stock solution was determined and of the reaction solution after a kinetic run. The pH remained constant within experimental error. After the cell compartment had come to thermal equilibrium, the reaction was initiated by adding 0.2 - 5 μl of ester (neat) or of a solution of ester in p-dioxane to the buffer solution. The optical density of the reaction mixture was measured against a blank of the appropriate buffer solution at convenient intervals until the optical density remained unchanged.

B. Calculation of Rate Constants.

The second order rate expression for ester

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[3] R. G. Bates, J. Research Natl. Bureau Standards, 66A, 179 (1962).

[4] H. P. Marshall and E. Grunwald, J. Chem. Phys., 21, 2143 (1953).

hydrolysis by hydroxide ion is shown below (eq. 1).

$$\text{rate} = k_2 \; [\text{OH}^-] \; [\text{ester}] \qquad (1)$$

Since the hydroxide ion concentration remains constant throughout the kinetic run this expression can be reduced to the following pseudo first-order expression (eq. 2).

$$\text{rate} = k_o \; [\text{ester}] \qquad (2)$$

Eq. 2 can be rewritten in terms of optical density measurements in the following form (eq. 3).

$$-k_o t/2.303 = \log(\text{O.D.}_\infty - \text{O.D.}_t) - \log(\text{O.D.}_\infty) \qquad (3)$$

k_o = rate constant (min^{-1})

t = time in minutes

O.D._t = optical density at time t

O.D._∞ = optical density at infinite time

This equation indicates that a plot of the quantity log ($\text{O.D.}_\infty - \text{O.D.}_t$) versus time should give a straight line of slope $-k_o/2.303$. For convenience, in plotting, the quantity $3 + \log(\text{O.D.}_\infty - \text{O.D.}_t)$ was plotted against time. The slope of the line was drawn by the method of least squares.

Once having determined k_o we can obtain k_2 by the following expression (eq. 4.).

$$k_2 = k_o/[\text{OH}^-] \qquad (4)$$

The problem is that we cannot determine the hydroxide ion concentration directly, since the autoprotolysis constant of water in water-dioxane mixtures is not 1×10^{-14}. We can, however, determine the pH[4], and so one can set up the following expressions (eqs. 5,6).[5]

$$k_2\ K_w = {}^{k_o}/_{[OH^-]}\ K_w \qquad (5)$$

$$k_2\ K_w = k_o\ [H^+] \qquad (6)$$

One can estimate the value of $K_{w_{(H_2O)}}$ in 30% dioxane-70% water, but since we are interested in relative rates it is not necessary to establish K_w. An example of an hydrolysis plot is shown in figure 1.

C. Kinetic Data.

This section contains the tables of rate data for each kinetic experiment.

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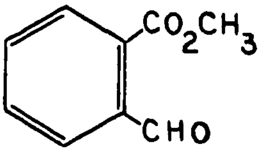
[5] M. L. Bender, F. J. Kezdy, and B. Zerner, J. Am. Chem. Soc., <u>85</u>, 3020 (1963).

TABLE 2

Kinetic Run No. 3



O.D.$_\infty$ = 0.795

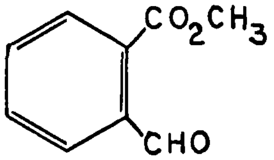
Solv. = 70/30 water-p-dioxane
pH = 7.93 (phosphate buffer)
Temp. = 30± 0.1°
Slit width = 0.08
O.D. measured at 310 mμ

Time (Min)	O.D.$_t$	O.D.$_\infty$ - O.D.$_t$	3+log(O.D.$_\infty$ - O.D.$_t$)
5	0.598	0.197	2.295
10	0.603	0.192	2.283
20	0.631	0.164	2.215
25	0.640	0.155	2.190
30	0.651	0.144	2.158
35	0.661	0.134	2.127
40	0.670	0.125	2.097
45	0.681	0.114	2.057
50	0.691	0.104	2.017
55	0.700	0.095	1.978
60	0.709	0.086	1.935
65	0.716	0.079	1.898
70	0.720	0.075	1.875
75	0.725	0.070	1.845
80	0.731	0.064	1.806
85	0.735	0.060	1.778
90	0.740	0.055	1.740
100	0.750	0.045	1.653
160	0.778	0.017	1.230

Slope = -0.0069 Min^{-1} k_o = 1.59x10^{-2} Min^{-1}

TABLE 3

Kinetic Run No. 4



$O.D._\infty$ = 0.508

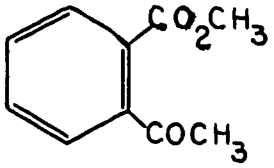
Solv. = 70/30 water-p-dioxane
pH = 7.93 (phosphate buffer)
Temp. = 30± 0.1°
Slit width = 0.08
O.D. measured at 310 mμ

Time (Min)	$O.D._t$	$O.D._\infty - O.D._t$	$3+\log(O.D._\infty - O.D._t)$
5	0.376	0.132	2.121
10	0.383	0.125	2.097
15	0.394	0.114	2.057
20	0.403	0.105	2.021
25	0.409	0.099	1.996
30	0.415	0.093	1.969
35	0.426	0.082	1.914
40	0.432	0.076	1.881
45	0.438	0.070	1.845
50	0.442	0.066	1.819
55	0.450	0.058	1.763
60	0.454	0.054	1.732
65	0.458	0.050	1.699
70	0.461	0.047	1.672
75	0.464	0.044	1.644
80	0.468	0.040	1.602
90	0.472	0.036	1.556
100	0.477	0.031	1.491
110	0.482	0.026	1.415
140	0.492	0.016	1.204

Slope = -0.0068 Min^{-1} $k_o = 1.57 \times 10^{-2}$ Min^{-1}

TABLE 4

Kinetic Run No. 1



O.D.$_\infty$ = 0.936

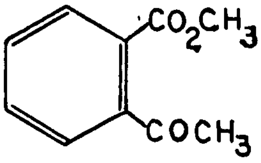
Solv. = 70/30 water-p-dioxane
pH = 9.95 (borate buffer)
Temp. = 30± 0.1°
Slit width = 0.08
O.D. measure at 310 mμ

Time (Min)	O.D.$_t$	O.D.$_\infty$ - O.D.$_t$	3+log(O.D.$_\infty$ - O.D.$_t$)
5	0.506	0.430	2.634
10	0.563	0.373	2.572
15	0.608	0.328	2.516
20	0.645	0.291	2.464
25	0.678	0.258	2.412
30	0.706	0.230	2.362
36	0.741	0.195	2.290
41	0.759	0.177	2.248
44	0.769	0.167	2.223
50	0.790	0.146	2.164
56	0.810	0.126	2.100
60	0.819	0.117	2.068
65	0.828	0.108	2.033
70	0.840	0.096	1.982
75	0.845	0.091	1.959
80	0.860	0.076	1.881
90	0.870	0.066	1.820
100	0.882	0.054	1.732
120	0.906	0.030	1.477

Slope = -0.00965 Min^{-1} k$_o$ = 2.23x10^{-2} Min^{-1}

TABLE 5

Kinetic Run No. 2



O.D.$_{\infty}$ = 0.467

Solv. = 70/30 water-p-dioxane
pH = 9.95 (borate buffer)
Temp. = 30 ± 0.1°
Slit width = 0.08
O.D. measured at 310 mμ

Time (Min)	O.D.$_t$	O.D.$_{\infty}$- O.D.$_t$	3+log(O.D.$_{\infty}$ - O.D.$_t$)
5	0.242	0.225	2.352
10	0.268	0.199	2.299
15	0.293	0.174	2.241
20	0.314	0.153	2.185
25	0.333	0.134	2.127
30	0.349	0.118	2.072
34	0.362	0.105	2.021
40	0.377	0.090	1.954
46	0.389	0.078	1.892
50	0.396	0.071	1.851
56	0.409	0.058	1.763
60	0.415	0.052	1.716
65	0.419	0.048	1.681
70	0.425	0.042	1.623
75	0.431	0.036	1.556
80	0.435	0.032	1.505
90	0.443	0.024	1.380

Slope = -0.0114 Min^{-1} k_o = 2.63x10^{-2} Min^{-1}

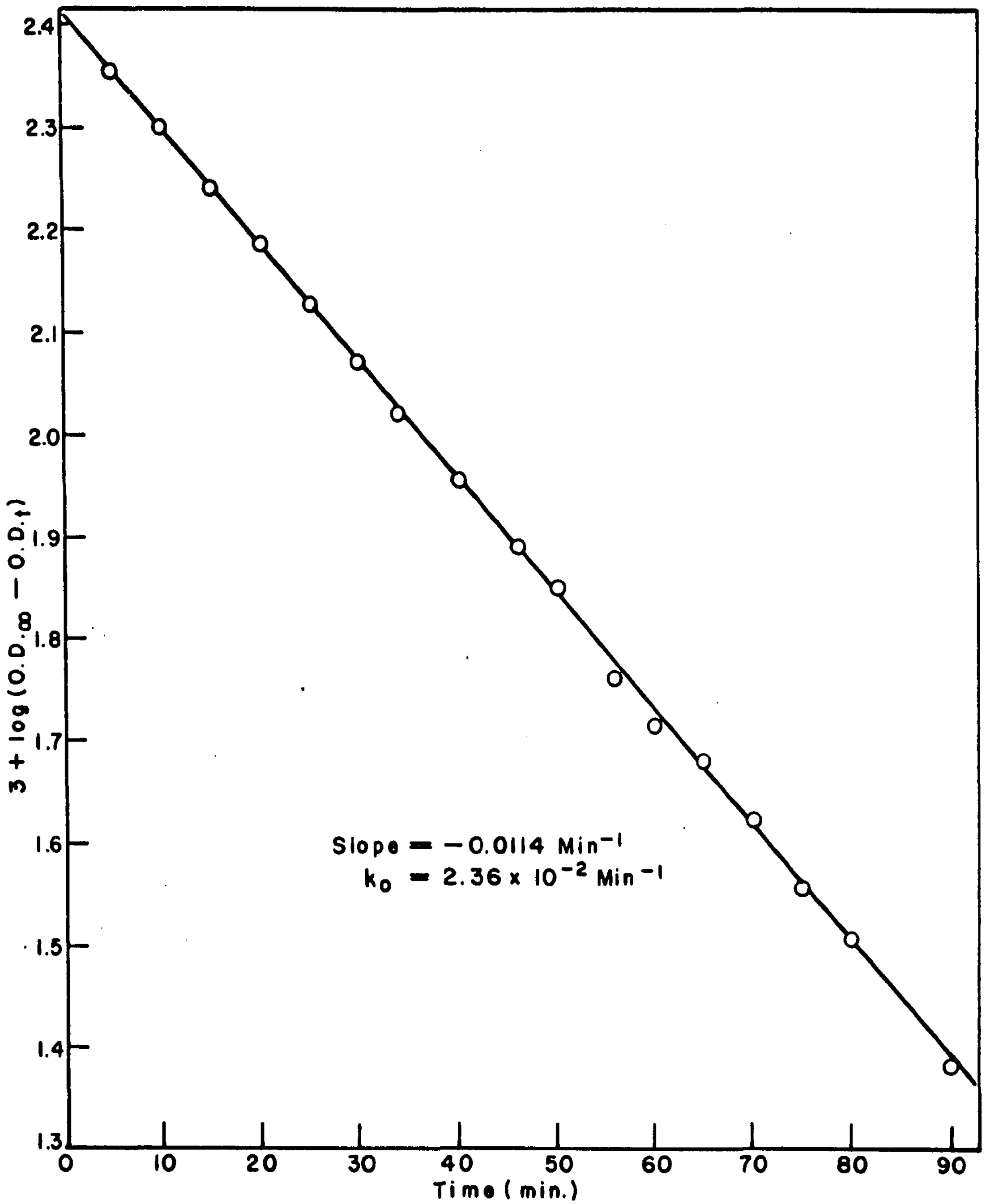


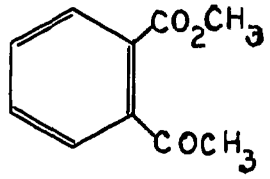
Figure 1

Alkaline Hydrolysis Plot of Methyl o-Acetylbenzoate

Kinetic Run No. 2

TABLE 6

Kinetic Run No. 11



O.D.$_\infty$ = 0.567

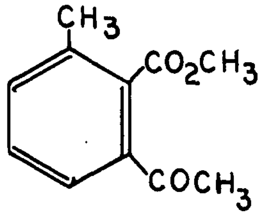
Solv. = 70/30 water-p-dioxane
pH = 9.95 (borate buffer)
Temp. = 30 ± 0.1°
Slit width = 0.36
O.D. measured at 310 mμ

Time (Min)	O.D.$_t$	O.D.$_\infty$-O.D.$_t$	3+log(O.D.$_\infty$-O.D.$_t$)
5	0.294	0.273	2.436
10	0.330	0.237	2.375
15	0.364	0.203	2.308
20	0.387	0.180	2.255
25	0.419	0.157	2.196
30	0.435	0.132	2.121
35	0.450	0.117	2.068
40	0.463	0.104	2.017
45	0.478	0.089	1.949
50	0.486	0.081	1.909
55	0.502	0.065	1.813

Slope = -0.0120 Min^{-1} k_o = 2.76x10^{-2} Min^{-1}

TABLE 7

Kinetic Run No. 7



O.D.$_\infty$ = 1.260

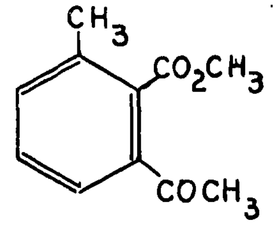
Solv. = 70/30 water-p-dioxane
pH = 9.95 (borate buffer)
Temp. = 30 ± 0.1°
Slit width = 0.34
O.D. measured at 310 mμ

Time (Min)	O.D.$_t$	O.D.$_\infty$ - O.D.$_t$	3+log(O.D.$_\infty$-O.D.$_t$)
5	0.612	0.648	2.812
10	0.725	0.535	2.728
13	0.795	0.465	2.668
15	0.832	0.428	2.631
17	0.855	0.405	2.608
20	0.910	0.350	2.544
23	0.932	0.328	2.516
25	0.960	0.300	2.477
30	1.010	0.250	2.398
35	1.035	0.225	2.352
40	1.090	0.170	2.230
45	1.120	0.140	2.146

Slope = -0.0163 Min^{-1} k_o = 3.76x10^{-2} Min^{-1}

TABLE 8

Kinetic Run No. 8



O.D.$_{\infty}$ = 0.612

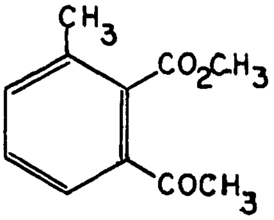
Solv. = 70/30 water-p-dioxane
pH = 9.95 (borate buffer)
Temp. = 30 ± 0.1°
Slit width = 0.34
O.D. measured at 310 mμ

Time (Min)	O.D.$_t$	O.D.$_{\infty}$ - O.D.$_t$	3+log(O.D.$_{\infty}$ - O.D.$_t$)
3	0.273	0.339	2.530
5	0.297	0.315	2.498
8	0.328	0.284	2.453
10	0.351	0.261	2.417
12	0.369	0.243	2.386
14	0.385	0.227	2.356
16	0.400	0.212	2.326
18	0.416	0.196	2.292
20	0.432	0.180	2.255
23	0.450	0.162	2.210
25	0.462	0.150	2.176
27	0.469	0.143	2.155
30	0.485	0.127	2.104
35	0.505	0.107	2.029
40	0.524	0.088	1.945
45	0.545	0.067	1.826

Slope = -0.0158 Min^{-1} k_o = 3.64x10^{-2} Min^{-1}

TABLE 9

Kinetic Run No. 9



O.D.$_\infty$ = 0.418

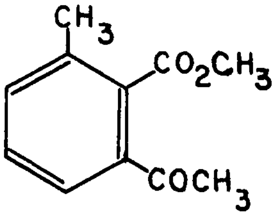
Solv. = 70/30 water-p-dioxane
pH = 9.95 (borate buffer)
Temp. = 30 ± 0.1°
Slit width = 0.24
O.D. measured at 310 mμ

Time (Min)	O.D.$_t$	O.D.$_\infty$ - O.D.$_t$	3+log(O.D.$_\infty$ - O.D.$_t$)
3	0.186	0.232	2.366
5	0.204	0.214	2.330
8	0.226	0.192	2.283
10	0.242	0.176	2.246
12	0.256	0.162	2.210
14	0.267	0.151	2.179
16	0.280	0.138	2.140
18	0.291	0.127	2.104
20	0.300	0.118	2.072
23	0.314	0.104	2.017
25	0.323	0.095	1.978
27	0.329	0.089	1.949
30	0.338	0.080	1.903
35	0.352	0.066	1.820
40	0.364	0.054	1.732
45	0.374	0.044	1.644
50	0.382	0.036	1.556
55	0.387	0.031	1.491
60	0.393	0.025	1.398
65	0.398	0.020	1.301

Slope = -0.0169 Min^{-1} k_o = 3.89x10^{-2} Min^{-1}

TABLE 10

Kinetic Run No. 10



$O.D._{\infty} = 0.259$

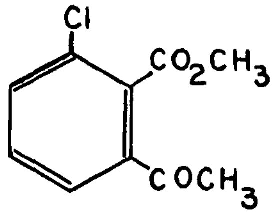
Solv. = 70/30 water-p-dioxane
pH = 9.95 (borate buffer)
Temp. = 30 ± 0.1°
Slit width = 0.08
O.D. measured at 310 mμ

Time (Min)	$O.D._t$	$O.D._{\infty} - O.D._t$	$3+\log(O.D._{\infty} - O.D._t)$
5	0.124	0.135	2.130
7	0.135	0.124	2.093
10	0.148	0.111	2.045
13	0.160	0.099	1.996
15	0.167	0.092	1.964
17	0.174	0.085	1.929
20	0.185	0.074	1.869
23	0.193	0.066	1.820
25	0.198	0.061	1.785
30	0.208	0.051	1.708
35	0.217	0.042	1.623
40	0.225	0.034	1.532
45	0.230	0.029	1.462

Slope = $-0.0169\ \text{Min}^{-1}$ $k_o = 3.89 \times 10^{-2}\ \text{Min}^{-1}$

TABLE 11

Kinetic Run No. 5



O.D.$_\infty$ = 0.580

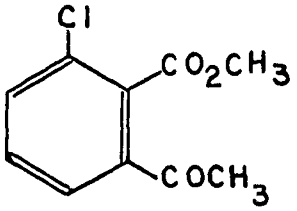
Solv. = $^{70}/_{30}$ water-p-dioxane
pH = 8.70 (phosphate buffer)
Temp. = 30 ± 0.1°
Slit width = 0.08
O.D. measured at 310 mμ

Time (Min)	O.D.$_t$	O.D.$_\infty$ - O.D.$_t$	3+log(O.D.$_\infty$ - O.D.$_t$)
5	0.280	0.300	2.477
10	0.297	0.283	2.452
16	0.316	0.264	2.422
20	0.329	0.251	2.400
24	0.340	0.240	2.380
30	0.354	0.226	2.354
35	0.368	0.212	2.326
40	0.380	0.200	2.301
45	0.389	0.191	2.281
50	0.402	0.178	2.250
55	0.412	0.168	2.225
60	0.421	0.159	2.201
65	0.431	0.149	2.173
70	0.441	0.139	2.143
75	0.448	0.132	2.121
80	0.457	0.123	2.090
90	0.468	0.112	2.049
102	0.480	0.100	2.000
110	0.490	0.090	1.954
120	0.499	0.081	1.909

Slope = -0.00495 Min^{-1} k_o = 1.14x10^{-2} Min^{-1}

TABLE 12

Kinetic Run No. 6



O.D.$_\infty$ = 0.648

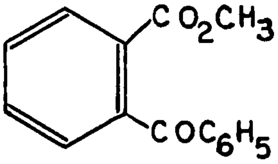
Solv. = 70/30 water-p-dioxane
pH = 8.70 (phosphate buffer)
Temp. = 30 ± 0.1°
Slit width = 0.08
O.D. measured at 310 mμ

Time (Min)	O.D.$_t$	O.D.$_\infty$ - O.D.$_t$	3+log(O.D.$_\infty$- O.D.$_t$)
5	0.316	0.332	2.521
10	0.334	0.314	2.497
15	0.352	0.296	2.471
20	0.367	0.281	2.449
25	0.383	0.265	2.423
30	0.395	0.253	2.403
35	0.411	0.237	2.375
40	0.420	0.228	2.358
45	0.431	0.217	2.337
50	0.442	0.206	2.314
55	0.457	0.191	2.281
60	0.465	0.183	2.263
65	0.477	0.171	2.233
70	0.485	0.163	2.212
75	0.493	0.155	2.190
80	0.500	0.148	2.170
90	0.516	0.132	2.121
100	0.531	0.117	2.068
110	0.542	0.106	2.025
120	0.552	0.096	1.982
130	0.565	0.083	1.919
140	0.573	0.075	1.875

Slope = -0.00480 Min^{-1} k_o = 1.11x10^{-2} Min^{-1}

TABLE 13

Kinetic Run No. 12



Solv. = 70/30 water-p-dioxane
pH = 11.58 (borate carbonate buffer)
Temp. = 30 ± 0.1°
Slit width = 0.34
O.D. measured at 310 mμ

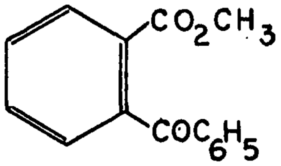
$O.D._\infty = 0.251$

Time (Min)	$O.D._t$	$O.D._\infty - O.D._t$	$3+\log(O.D._\infty - O.D._t)$
5	0.205	0.046	1.663
10	0.210	0.041	1.613
15	0.214	0.037	1.568
20	0.217	0.034	1.532
25	0.219	0.032	1.505
30	0.222	0.029	1.462
35	0.224	0.027	1.431
40	0.226	0.025	1.398
45	0.228	0.023	1.362
50	0.231	0.020	1.301
60	0.233	0.018	1.255
70	0.235	0.016	1.204
80	0.238	0.013	1.114
90	0.240	0.011	1.041

Slope = -0.00694 Min^{-1} $k_o = 1.59\text{x}10^{-2}$ Min^{-1}

TABLE 14

Kinetic Run No. 13



O.D.$_\infty$ = 0.370

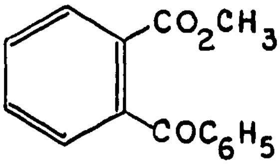
Solv. = 70/30 water-p-dioxane
pH = 11.58 (borate-carbonate buffer)
Temp. = 30 ± 0.1°
Slit width = 1.5
O.D. measured at 310 mμ

Time (Min)	O.D.$_t$	O.D.$_\infty$ - O.D.$_t$	3+log(O.D.$_\infty$ - O.D.$_t$)
5	0.304	0.066	1.820
10	0.312	0.058	1.763
15	0.317	0.053	1.724
21	0.323	0.047	1.672
25	0.327	0.043	1.634
30	0.331	0.039	1.591
35	0.334	0.036	1.556
40	0.337	0.033	1.519
50	0.344	0.026	1.415
60	0.348	0.022	1.342
70	0.352	0.018	1.255
80	0.355	0.015	1.176
90	0.358	0.012	1.079
100	0.360	0.010	1.000
120	0.363	0.007	0.845

Slope = -0.00850 Min^{-1} k_o = 1.96x10^{-2} Min^{-1}

TABLE 15

Kinetic Run No. 14



O.D.$_\infty$ = 0.330

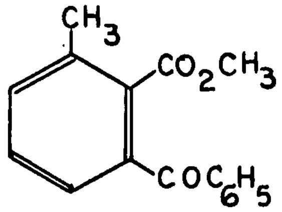
Solv. = 70/30 water-p-dioxane
pH = 11.58 (borate-carbonate buffer)
Temp. = 30 ± 0.1°
Slit width = 1.5
O.D. measured at 310 mμ

Time (Min)	O.D.$_t$	O.D.$_\infty$ - O.D.$_t$	3+log(O.D.$_\infty$- O.D.$_t$)
5	0.272	0.058	1.763
10	0.278	0.052	1.716
15	0.283	0.047	1.672
20	0.288	0.042	1.623
25	0.292	0.038	1.580
30	0.295	0.035	1.544
35	0.297	0.033	1.519
40	0.299	0.031	1.491
50	0.304	0.026	1.415
60	0.309	0.021	1.322
70	0.312	0.018	1.255
80	0.315	0.015	1.176
100	0.319	0.011	1.041
120	0.323	0.007	0.845

Slope = -0.00775 Min^{-1} k_o = 1.78x10^{-2} Min^{-1}

TABLE 16

Kinetic Run No. 15



O.D.$_{\infty}$ = 0.520

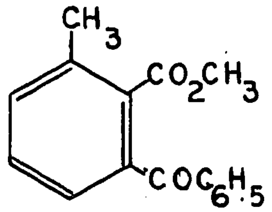
Solv. = 70/30 water-p-dioxane
pH = 11.58 (borate-carbonate buffer)
Temp.,= 30 ± 0.1°
Slit width = 1.5
O.D. measured at 310 mμ

Time (Min)	O.D.$_t$	O.D.$_{\infty}$ - O.D.$_t$	3+log(O.D.$_{\infty}$- O.D.$_t$)
3	0.402	0.118	2.072
5	0.420	0.100	2.000
7	0.433	0.087	1.940
10	0.450	0.070	1.845
12	0.461	0.059	1.771
14	0.470	0.050	1.699
18	0.484	0.036	1.556
20	0.489	0.031	1.491
23	0.495	0.025	1.398
25	0.499	0.021	1.322
27	0.503	0.017	1.230
30	0.506	0.014	1.146
35	0.510	0.010	1.000

Slope = -0.0330 Min^{-1} k_o = 7.60x10^{-1} Min^{-1}

TABLE 17

Kinetic Run No. 16



O.D.$_\infty$ = 0.720

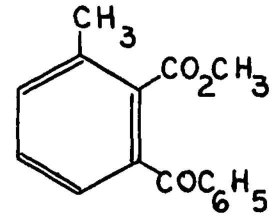
Solv. = 70/30 water-p-dioxane
pH = 11.58 (borate-carbonate buffer)
Temp. = 30 ± 0.1°
Slit width = 1.5
O.D. measured at 310 mμ

Time (Min)	O.D.$_t$	O.D.$_\infty$ - O.D.$_t$	3+log(O.D.$_\infty$-O.D.$_t$)
3	0.553	0.167	2.223
5	0.575	0.145	2.161
7	0.590	0.130	2.114
9	0.613	0.107	2.029
10	0.620	0.100	2.000
12	0.634	0.086	1.935
14	0.647	0.073	1.863
16	0.654	0.066	1.820
18	0.665	0.055	1.740
20	0.673	0.047	1.672
23	0.684	0.036	1.556
25	0.689	0.031	1.491
27	0.694	0.026	1.415
30	0.699	0.021	1.322
35	0.705	0.015	1.176

Slope = -0.0333 Min^{-1} k_o = 7.67x10^{-2} Min^{-1}

TABLE 18

Kinetic Run No. 17



O.D.$_\infty$ = 0.530

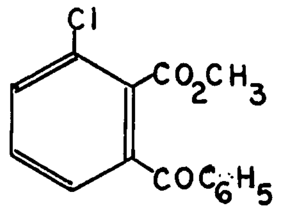
Solv. = 70/30 water-p-dioxane
pH = 11.58 (borate-carbonate buffer)
Temp. = 30 ± 0.1°
Slit width = 1.0
O.D. measured at 310 mμ

Time (Min)	O.D.$_t$	O.D.$_\infty$ - O.D.$_t$	3+log(O.D.$_\infty$ - O.D.$_t$)
3	0.412	0.118	2.072
5	0.428	0.102	2.009
7	0.443	0.087	1.940
10	0.460	0.070	1.845
12	9.471	0.059	1.771
14	0.478	0.052	1.716
16	0.487	0.043	1.634
18	0.493	0.037	1.568
20	0.498	0.032	1.505
23	0.505	0.025	1.398
25	0.509	0.021	1.322
27	0.513	0.017	1.230
30	0.516	0.014	1.146
35	0.520	0.010	1.000

Slope = -0.0335 Min^{-1} k_o = 7.72x10^{-2} Min^{-1}

TABLE 19

Kinetic Runs No. 18,19



O.D.$^a_\infty$ = 0.327

O.D.$^b_\infty$ = 0.386

Solv. = 70/30 water-p-dioxane
pH = 10.84 (borate-carbonate buffer)
Temp. = 30 ± 0.1°
Slit width = 1.5
O.D. measured at 310 mμ

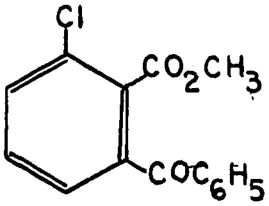
Time (Min)	O.D.$_t$	O.D.$_\infty$ - O.D.$_t$	3+log(O.D$_\infty$- O.D.$_t$)
2	0.298	0.029	1.462
3	0.300	0.027	1.431
5	0.306	0.021	1.322
7	0.310	0.017	1.230
9	0.314	0.013	1.114
11	0.316	0.011	1.041
13	0.317	0.010	1.000
20	0.321	0.006	0.778
25	0.324	0.003	0.477
2	0.353	0.033	1.519
3	0.357	0.029	1.462
5	0.362	0.024	1.380
7	0.366	0.020	1.301
9	0.369	0.017	1.230
11	0.373	0.013	1.114
15	0.375	0.011	1.041
20	0.381	0.005	0.699
25	0.383	0.003	0.477

Slope^a = -0.0453 Min^{-1} k_o^a = 1.04x10^{-1} Min^{-1}

Slope^b = -0.0450 Min^{-1} k_o^b = 1.04x10^{-1} Min^{-1}

TABLE 20

Kinetic Run No. 20



$O.D._\infty = 0.471$

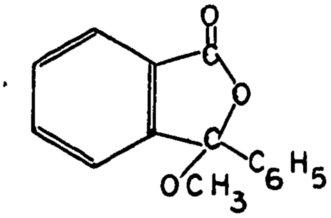
Solv. = 70/30 water-p-dioxane
pH = 10.84 (borate-carbonate buffer)
Temp. = 30 ± 0.1°
Slit width = 1.55
O.D. measured at 300 mμ

Time (Min)	$O.D._t$	$O.D._\infty - O.D._t$	$3+\log(O.D._\infty - O.D._t)$
2	0.427	0.044	1.644
3	0.430	0.041	1.613
5	0.438	0.033	1.519
7	0.444	0.027	1.431
9	0.448	0.023	1.362
11	0.453	0.018	1.255
15	0.459	0.012	1.079
20	0.464	0.007	0.845

Slope = -0.0450 Min^{-1} $k_o = 1.04\times10^{-1}$ Min^{-1}

TABLE 21

Kinetic Run No. 21



O.D.$_\infty$ = 0.107

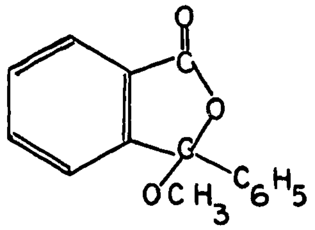
Solv. = 70/30 water-p-dioxane
pH = 11.58 (borate-carbonate buffer)
Temp. = 30 ± 0.1°
Slit width = 0.06
O.D. measured at 310 mμ

Time (Min)	O.D.$_t$	O.D.$_\infty$ - O.D.$_t$	3+log(O.D.$_\infty$- O.D.$_t$)
3	0.018	0.089	1.949
5	0.024	0.083	1.919
7	0.032	0.075	1.875
8	0.036	0.071	1.851
9	0.039	0.068	1.833
10	0.042	0.065	1.813
12	0.048	0.059	1.771
14	0.053	0.054	1.732
16	0.057	0.050	1.699
18	0.061	0.046	1.663
20	0.065	0.042	1.623
23	0.072	0.035	1.544
25	0.074	0.033	1.519
27	0.077	0.030	1.477
30	0.080	0.027	1.431
35	0.086	0.021	1.322
40	0.090	0.017	1.230
45	0.094	0.013	1.114
60	0.100	0.007	0.8451

Slope = -0.0197 Min^{-1} k_o = 4.54x10^{-2} Min^{-1}

TABLE 22

Kinetic Run No. 22



$O.D._\infty$ = 0.287

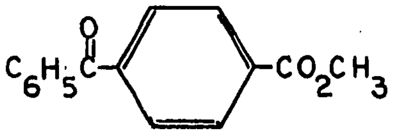
Solv. = 70/30 water-p-dioxane
pH = 11.58 (borate-carbonate buffer)
Temp. = 30 ± 0.1°
Slit width = 0.06
O.D. measured at 310 mμ

Time (Min)	$O.D._t$	$O.D._\infty - O.D._t$	$3+\log(O.D._\infty - O.D._t)$
3	0.038	0.249	2.396
5	0.058	0.229	2.360
7	0.077	0.210	2.322
9	0.095	0.192	2.283
10	0.103	0.184	2.265
12	0.118	0.169	2.228
14	0.128	0.159	2.201
16	0.144	0.143	2.155
18	0.158	0.129	2.111
20	0.168	0.119	2.076
22	0.176	0.111	2.045
24	0.186	0.101	2.004
26	0.194	0.093	1.969
28	0.201	0.086	1.935
30	0.208	0.079	1.898
33	0.217	0.070	1.845
35	0.223	0.064	1.806
37	0.228	0.059	1.771
40	0.234	0.053	1.724
45	0.244	0.043	1.634
50	0.252	0.035	1.544
55	0.259	0.028	1.447

Slope = -0.0182 Min^{-1} $k_o = 4.19 \times 10^{-2}\ \text{Min}^{-1}$

TABLE 23

Kinetic Run No. 23



O.D.$_\infty$ = 0.622

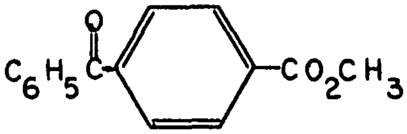
Solv. = 70/30 water-p-dioxane
pH = 11.58 (borate-carbonate buffer)
Temp. = 30 ± 0.2°
Slit width = 0.06
O.D. measured at 290 mμ

Time (Min)	O.D.$_t$	O.D.$_\infty$ - O.D.$_t$	3+log(O.D.$_\infty$ - O.D.$_t$)
5	0.488	0.134	2.127
10	0.509	0.113	2.053
16	0.526	0.096	1.982
21	0.534	0.088	1.945
25	0.540	0.082	1.914
30	0.550	0.072	1.857
35	0.561	0.061	1.785
40	0.570	0.052	1.716
45	0.578	0.044	1.644
50	0.583	0.039	1.591
60	0.594	0.028	1.447
70	0.600	0.022	1.342
80	0.605	0.017	1.230
90	0.609	0.013	1.114
100	0.612	0.010	1.000

Slope = -0.0120 Min^{-1} k_o = 2.76x10^{-2} Min^{-1}

TABLE 24

Kinetic Run No. 24



O.D.$_\infty$ = 0.335

Solv. = 70/30 water-p-dioxane
pH = 11.58 (borate-carbonate buffer)
Temp. = 30 ± 0.2°
Slit width = 0.06
O.D. measured at 300 mμ

Time (Min)	O.D.$_t$	O.D.$_\infty$ - O.D.$_t$	3+log(O.D.$_\infty$ - O.D.$_t$)
5	0.296	0.039	1.591
10	0.299	0.036	1.556
15	0.302	0.033	1.519
20	0.306	0.029	1.462
25	0.310	0.025	1.398
30	0.314	0.021	1.322
35	0.316	0.019	1.279
40	0.318	0.017	1.230
45	0.319	0.016	1.204
50	0.321	0.014	1.146
60	0.324	0.011	1.041
70	0.327	0.008	0.903
80	0.329	0.006	0.778
90	0.330	0.005	0.699
100	0.331	0.004	0.602

Slope = -0.0106 Min^{-1} k_o = 2.44x10^{-2} Min^{-1}

D. Discussion of the Kinetic Data

The kinetic data summarized in tables 25 and 26 clearly illustrates three outstanding features of the hydroxide ion ester hydrolysis.

1. The esters containing formyl groups hydrolyze at a faster rate than those containing acetyl groups, and these in turn hydrolyze faster than the esters containing benzoyl groups.

2. In a given series in which the additional carbonyl substituent (benzoyl and acetyl) is constant the 6-chloro esters hydrolyze at a faster rate than the 6-methyl esters, and these in turn hydrolyze faster than the unsubstituted esters.

3. The accelerating effect of the 6-chloro and 6-methyl group is greater in the benzoyl ester series than in the acetyl ester series (See Table 27).

In this discussion of the kinetic data we will assume that the hydroxide ion attacks the carbonyl group[1] in the case of the 6-substituted esters since the carbomethoxy group is extremely crowded due to the 2-and 6-substituents. By making this assumption we limit our comparison of rates to

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[1] From now on in this discussion the phrase, "attack at the carbonyl group" will imply initial attack at the ketone or aldehyde carbonyl and not at the ester carbonyl.

TABLE 25

SUMMARY OF KINETIC DATA

Solv. = 70/30 water-p-dioxane   Temp. = 30 ± 0.1°

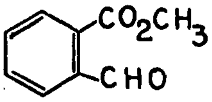
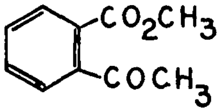
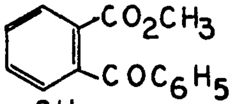
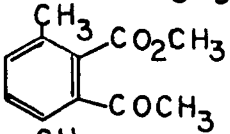
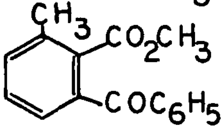
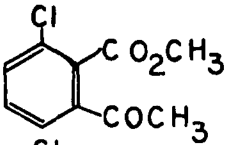
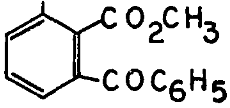
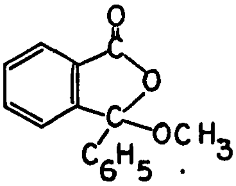
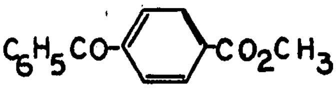
Ester	Kinetic Run Nos.	Table Nos.	$k_o \times 10^2 (\mathrm{Min}^{-1})$
	3,4	2,3	1.58 ± 0.01
	1,2,11	4-6	2.70 ± 0.07
	12-14	13-15	1.78 ± 0.12
	7-10	7-10	3.80 ± 0.10
	15-17	16-18	7.66 ± 0.04
	5, 6	11,12	1.13 ± 0.02
	18-20	19,20	10.4 ± 0.0
	21,22	21,22	4.37 ± 0.18
	23,24	23,24	2.60 ± 0.16

TABLE 26

SUMMARY OF KINETIC DATA

Solv. = 70/30 water-p-dioxane Temp. = 30 ± 0.1°

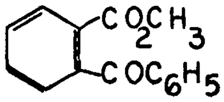
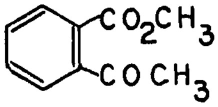
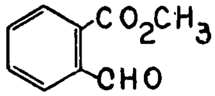
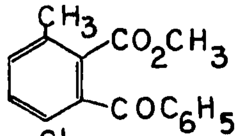
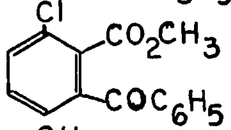
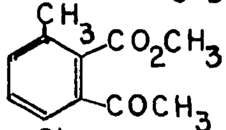
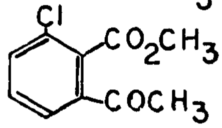
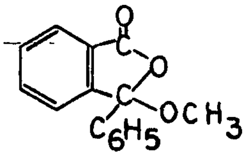
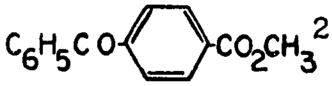
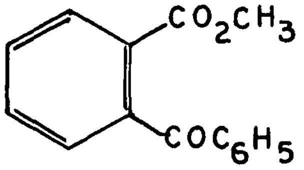
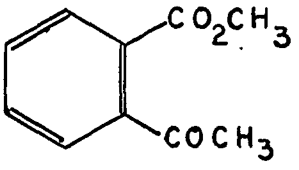
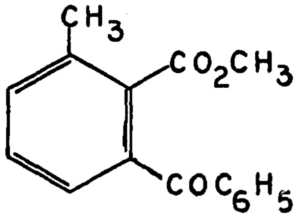
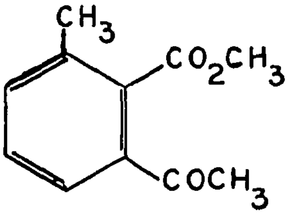
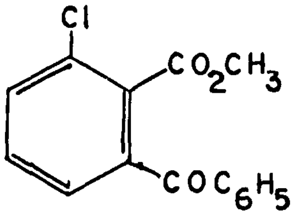
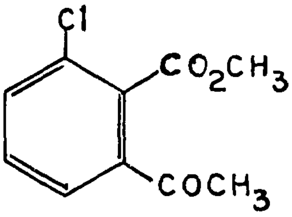
Ester	$k_o \times 10^2 (\text{Min}^{-1})$	pH	$k_2K_w \times 10^{14} M^{-1} sec^{-1}$	k_{rel}
	1.78 ± 0.12	11.58	0.078 =	1
	2.70 ± 0.07	9.95	5.05	64.8
	1.58 ± 0.01	7.93	310	3970
	7.66 ± 0.04	11.58	0.336	4.31
	10.4 ± 0.0	10.84	2.51	32.2
	3.80 ± 0.10	9.95	7.10	91.0
	1.13 ± 0.02	8.70	37.7	483
	4.37 ± 0.18	11.58	0.192	2.46
	2.60 ± 0.16	11.58	0.114	1.46

TABLE 27

Relative Rates of Hydrolysis of Benzoyl and Acetyl Esters[a]

 1.00[b]	 1.00[c]
 4.31	 1.41
 32.2	 7.47

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a. Solvent = 70/30 water-p-dioxane

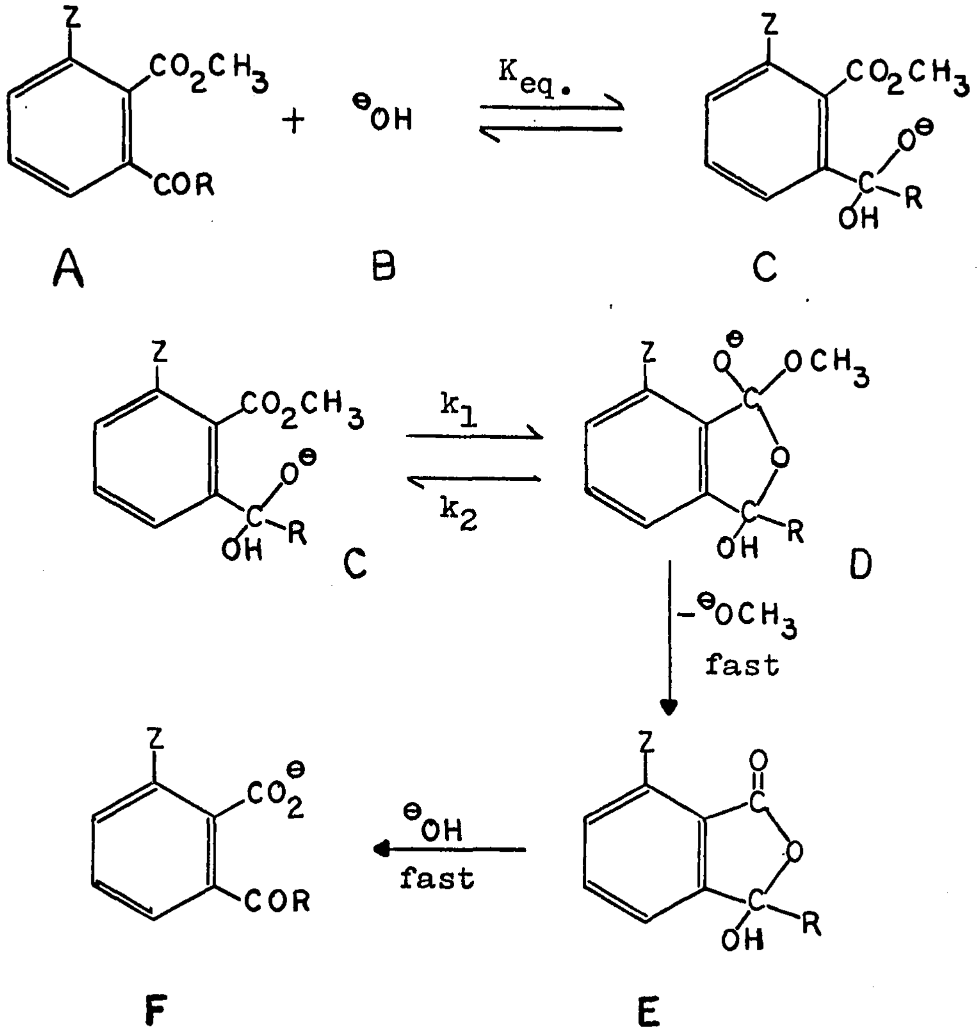
Temp. = 30 ± 0.1°.

b. This compound is taken as a standard with a relative rate of hydrolysis of 1.00 in the benzoyl series.

c. This compound is taken as a standard with a relative rate of hydrolysis of 1.00 in the acetyl series.

the 6-substituted esters as one class of compounds.

The following mechanism is proposed to account for the hydrolysis of the 6-substituted esters. A preequilibrium step involving attack of hydroxide ion on the carbonyl group followed by a rate determining step involving attack of the carbonyl hydrate anion on the carbomethoxy function:



The rate of hydrolysis of A can be expressed according to the following equation:

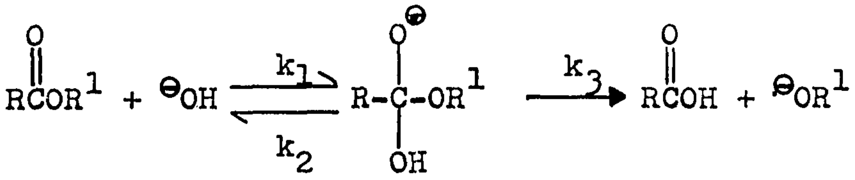
$$\text{rate} = k_1\,[C] = k_1\,K_{eq.}\,[A]\,[B]$$

$$\text{where}\quad K_{eq} = \frac{[C]}{[A]\,[B]}$$

Thus the observed rate constant is a product of an actual rate constant (k_1) for the rate determining step and an equilibrium constant (K_{eq}) for the antecedent equilibrium.

The chief argument for postulating a preequilibrium (K_{eq}) is that the 6-substituted esters all hydrolyze faster than the corresponding unsubstituted esters. This implies that the formation of the carbonyl hydrate anion (C) cannot be the rate determining step in the hydrolysis.

In normal alkaline hydrolysis of carboxylic acid derivatives the requirement for a genuine preequilibrium, i.e. $k_2 \gg k_3$, is not met and the observed rate constant



$$\overset{O}{\overset{\|}{RCOR^1}} + {}^{\ominus}OH \underset{k_2}{\overset{k_1}{\rightleftharpoons}} R\text{-}\overset{O^{\ominus}}{\overset{|}{\underset{OH}{\underset{|}{C}}}}\text{-}OR^1 \xrightarrow{k_3} \overset{O}{\overset{\|}{RCOH}} + {}^{\ominus}OR^1$$

is actually $k_1/\,(k_2/k_3+1)$. The ratio k_2/k_3 is usually represented by α (the partition coefficient). [2,3]

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[2] M. L. Bender, Chem. Revs., 60, 61 (1960).

[3] L. B. Jones and T. M. Sloane, Tet. Letters, No. 8, 831 (1966).

A genuine preequilibrium, for example, is found in the addition of hydroxylamine and semicarbazide to aldehydes and ketones under neutral conditions. A fast preequilibrium step is followed by slow dehydration to form the oxime or semicarbazone.[4] This is also found in the formation of the ketimine from acetone and methyl amine.[5]

The attack of the carbonyl hydrate anion (C) on the carbomethoxy function is considered rate determining with a rate constant k_1. As soon as "intermediate" D forms it can partition to form E or reform C. Intuitively one feels formation of C from D should be small compared to formation of E even though the transition states involved are very similar. To reform C from D (rate constant k_2) we would be going from one strained intermediate to another and not even gain any resonance stabilization since the carbomethoxy group in C is twisted out of the plane of the benzene ring. Formation of E will provide resonance

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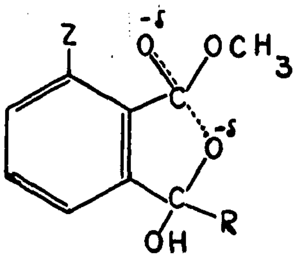
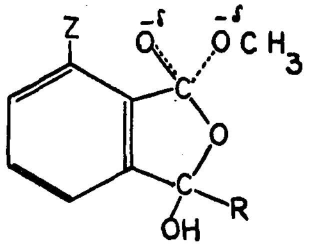
[4] W. P. Jencks, "Progress in Physical Organic Chemistry", Vol. 2, Interscience Publishers, New York, N. Y., 1964.

[5] A. Williams and M. L. Bender, J. Am. Chem. Soc., 88, 2508 (1966).



C↔D
T. S. I



D↔E
T. S. II

stabilization of the carbonyl function with the benzene ring. Partitioning of D to E would also be favored because of the driving force in going from tetragonal to trigonal geometry due to the steric interaction of Z. Thus k_2 is considered of minor importance relative to the fast formation of E.

The formation of F from E should not be rate determining since it merely involves abstraction of an acidic proton by hydroxide or methoxide ion.

In this discussion of the rates of hydrolysis of the 6-substituted esters we must relate the substituent to its effect on the equilibrium constant (K_{eq}) and on the rate constant (k_1) of the rate determining step. The following effects of the 6-substituent seem of major importance:

1. I_{eq}, the inductive effect of the 6-substituent (Z) on K_{eq}.

2. I_1, the inductive effect of the 6-substituent (Z) on k_1.
3. S_{eq}, the steric effect of the 6-substituent on K_{eq}.
4. S_1, the steric effect of the 6-substituent on k_1.

An increase in the election-withdrawing character of the 6-substituent (Z) should cause a more rapid attack of the hydroxide ion on the carbonyl group and also help stabilize the formed carbonyl hydrate anion (C). This inductive effect (I_{eq}) will result in an increase of K_{eq}. The inductive effect of an electron-withdrawing groups in the 6-position will facilitate attack of the carbonyl hydrate anion (C) on the carbomethoxy group and thus cause an increase in k_1. This inductive effect (I_1) will be in the opposite direction for electron-donating groups.

The steric effect (S_{eq}) of the 6-substituent (Z) on K_{eq} will consist mainly of a buttressing effect. By forcing the carbomethoxy function and the carbonyl function in close proximity, the 6-substituent (Z) will slow down attack of the hydroxide ion on the carbonyl function and reduce the stability of the carbonyl hydrate anion (C). This effect should cause a decrease in K_{eq}.

The steric effect (S_1) of the 6-substituent (Z) on

k_1 is twofold. First, k_1 should be enhanced because Z, by forcing the carbomethoxy group to be in a plane perpendicular to the plane of the benzene ring, destroys resonance interaction of the carbomethoxy group with the ring and also allows the carbonyl hydrate anion (C) to attack from a direction perpendicular to it. This perpendicular attack allows for maximum overlap of the carbonyl hydrate anion with the electron cloud of the ester.[6,7] Secondly, however, the steric effect (S_1) of the 6-substituent (Z) also has a retarding influence on k_1, since in the transition state leading to D the ester carbonyl becomes tetragonal and thus would interact sterically with Z. It is, of course, difficult to separate these two opposing steric effects (S_1), but the kinetic data indicates that the "enhancing power" outweighs the retarding influence.

For the 6-substituted esters studied the inductive effects, I_{eq} and I_1, of the 6-chloro group would cause an increase in K_{eq} and k_1 relative to the inductive effects, I_{eq} and I_1, of the 6-methyl group. The steric effects, S_{eq} and S_1, of the 6-chloro substituent would be similar

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[6] M. L. Bender, Chem. Revs., <u>60</u>, 60 (1960).

[7] W. P. Jencks, "Progress in Physical Organic Chemistry", Vol. 2, Interscience Publishers, New York, N. Y., 1964, p. 65.

to those of the 6-methyl substituent. A rigorous comparison of the steric effects of the chloro group versus the methyl group is not possible since they differ slightly in size and in dipole moment. The van der Waal's radius for the chloro group is 1.80 A^{o}, while it is 2.0 A^{o} for the methyl group.[8]

Based on the above observations and the kinetic expression one would expect the 6-chloro esters to hydrolyze faster than the 6-methyl esters.

To compare the rates of the 6-substituted acetyl esters to those of the 6-substituted benzoyl esters one must relate the R group (CH_3 or C_6H_5) to its effect on the equilibrium constant (K_{eq}) and the rate constant (k_1) of the rate determining step. Although no comparative study of carbonyl reactivity between benzophenone and acetophenone is known, one feels the acetyl function should be more easily attacked by hydroxide ion than the benzoyl function because of less steric interaction in the transition state leading to the tetragonal intermediate (C) and less resonance stabilization of the ground state in the acetyl esters. In other work, K_{eq}. should be greater for the acetyl esters than for the benzoyl esters.

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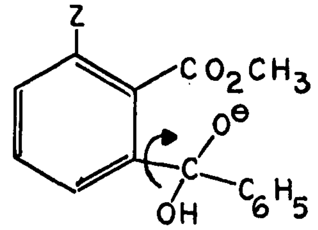
[8] L. Pauling, "The Nature of the Chemical Bond", Cornell Univ. Press, 1960, p. 260.

The effect of the R group on k_1 is difficult to ascertain. It would seem, however, that the carbonyl hydrate anion (C') of the benzoyl ester would have less freedom of rotation than the carbonyl hydrate anion of the



C'

acetyl ester. This loss of entropy should cause k_1 for the benzoyl ester to increase. Whether the relative inductive effects of the methyl and phenyl groups are of importance is difficult to judge. Based on the observation that the acetyl esters do hydrolyze faster than the benzoyl esters, it seems the effect of R on K_{eq}. is of overriding importance.

In the three unsubstituted esters, methyl o-formylbenzoate (XII), methyl o-acetylbenzoate (IX), and methyl o-benzoylbenzoate (I), the alkaline hydrolysis may conceivably proceed via two mechanisms: (1) attack of hydroxide ion at the carbonyl function as in the case of the 6-substituted esters, and (2) the normal attack of the hydroxide ion at the carbomethoxy function. Since Bender has shown that methyl o-formylbenzoate (XII) hydrolyzes 10^5 faster than methyl p-formylbenzoate the main path undoubtedly involves carbonyl attack.[9] With the unsubstituted benzoyl esters the situation is actually reversed. Methyl *p*-benzoylbenzoate hydrolyzes 1.46 times faster than methyl *o*-benzoylbenzoate (I). This indicates that direct attack of hydroxide ion on the carbomethoxy group may be the sole mechanism involved.

The rate of hydrolysis of methyl *o*-acetylbenzoate (IX) is intermediate between that of methyl *o*-formylbenzoate (XII) and methyl *o*-benzoylbenzoate (I) as is expected. Because of the great difference in rates the rate determining step in the hydrolysis of IX and XII may well be the formation of the carbonyl hydrate anion or the hydrate. Unfortunately, a comparative study involving benzophenone, acetophenone, and benzaldehyde has as yet not been made.

Tables 27 and 28 reveal that under the kinetic conditions used the relative rate constant for methyl 2-benzoyl-6-methylbenzoate (II) ($k_{rel} = 4.31$) is not as large as that reported ($k_{rel} = 9.1$).[10] However, the rate

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[9] M. L. Bender, J. A. Reinstein, M. S. Silver, and R. Mikulak, J. Am. Chem. Soc., 87, 4545 (1965).

[10] M. S. Newman and S. Hishida, J. Am. Chem. Soc., 84, 3582 (1962).

constant of II does compare favorably with the reported rate constant of γ-methyl *o*-benzoylbenzoate (See Table 28). The reported rate constant of hydrolysis of I seems, therefore, to be too low.[11]

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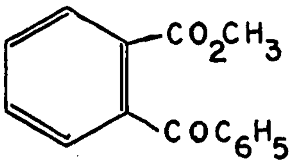
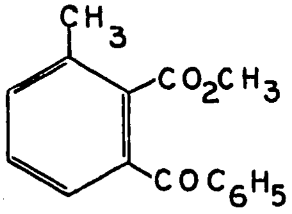
[11] Under similar solvent and temperature conditions K. Bowden, U. of Essex, Colchester, Essex, reports a rate constant of $8.98 \mathrm{x} 10^{-2}$ M^{-1} sec^{-1} compared to 3.47×10^{-2} M^{-1} sec^{-1} as determined by Newman and Hishida (ref. 10).

TABLE 28

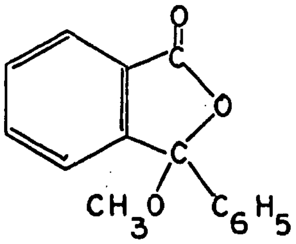
Relative Rates of Hydrolysis of Some n-and ψ-Methyl o-Benzoylbenzoates[a]



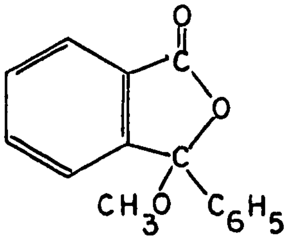
1.00[b]



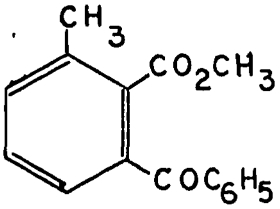
4.31[c]



2.46



1.00[d]



1.74[e]

a. Solvent = 70/30 water-p-dioxane

Temp. = 30 ± 0.1°

b. This compound is taken as a standard with a relative rate of hydrolysis of 1.00.

c. M. S. Newman and S. Hishida, J. Am. Chem. Soc., <u>84</u>, 3582 (1962), report a value of 9.1

d. This compound is taken as a standard with a relative rate of hydrolysis of 1.00.

e. M. S. Newman and S. Hishida, ibid., <u>84</u>, 3582 (1962), report a value of 1.54.