the sulfonate ester, m.p. 37.5–39.5°. After 1 hr. at this temperature, the mixture was processed as described above under part A. The sulfonate ester was essentially completely consumed. Product analysis for the alcohols was performed on the TCEP column at about 150°, and the components were identified by their characteristic retention times. The absolute yield, determined as described above, of total alcohols was 36%, and consisted of the following proportions of individual components: 22% of V, 4% of VI, 12% of IX, 37% of II, 2% of III, 8% of X and/or XI, and 16% of three unidentified components. The olefin fraction was analyzed on Carbowax at about 90° and consisted of a single product (40% yield), namely the diene VII which was identified by its retention time.

D. **Formolysis of *cis*-2-(Δ^3-Butenyl)cyclohexyl *p*-Nitrobenzenesulfonate.**—To a stirred solution of 0.025 ml. of pyridine in 7.5 ml. of anhydrous formic acid at 50 ± 2° was added 51 mg. of the sulfonate ester, m.p. 54–56°. After 1 hr. the product was processed as described above in section A. The reaction was essentially complete. The alcohols were analyzed as described above, section C, and the absolute yield of total alcohols was 31%, consisting of the following proportions of individual components: 86% of V, 4% of IX, 7% of II, and 2% of X and/or XI. Analysis for olefins on a Carbowax column at *ca.* 80° showed a single peak corresponding to a 64% yield of the diene VII. The identity of these products was based on retention time data.

E. **Formolysis of Δ^3-Butenylcyclopentylcarbinyl *p*-Nitrobenzenesulfonate.**—A solution of 49 mg. of the sulfonate ester, m.p. 35–37°, and 0.025 ml. of pyridine in 7.5 ml. of anhydrous formic acid was heated for 1 hr. at 50 ± 2°. The mixture was processed as described above, section A. Analysis of the alcohol fraction as described above, section C, showed the following relative proportions of products: 6% of V, 22% of VI, 3% of IX, 18% of II, a trace of X and/or XI, and 50% of an unidentified alcohol which was not one of the 2-decalols. The identities of these components were established by peak-enhancement experiments. The hydrocarbon fraction was not examined.

Treatment of 1-(Δ^3-Butenyl)cyclohexene (VII) with Formic Acid.—A solution of 286 mg. of the diene[3] and 0.025 ml. of pyridine in 16 ml. of anhydrous formic acid was heated to 75° for 11.5 hr. under a nitrogen atmosphere. The product was processed and analyzed as for a solvolysis reaction (see description above under section A of the formolysis studies). Analysis of the alcohols on the Craig column indicated a total yield of 42% consisting of the following components in the specified proportions: 5% of V, 15% of an unidentified alcohol, 20% of a second unidentified alcohol, and 50% of XI. The remaining 10% was accounted for as six minor peaks in the gas chromatogram. Detectable amounts of *trans*-2-decalols were not observed. Analysis for olefins on the Carbowax column indicated a total yield of 19%. About 50% of this fraction corresponded to starting material, and the remainder was accounted for as four peaks in the gas chromatogram. The alcohols were separated by preparative gas chromatography on the PEGS column and examined by infrared methods. The unidentified alcohols corresponded with those obtained previously in the sulfuric–acetic acid cyclization.[7] Compound XI was obtained as a crystalline solid, m.p. 96–101° (lit.[17] m.p. 104°).

When a shorter reaction time (3.5 hr.) was used, the area under the peak corresponding to the tertiary carbinol V increased while that of the other alcohol peaks decreased. The absolute yield of decalol XI was 7%.

Treatment of 1-(Δ^3-Butenyl)cyclohexanol (V) with Formic Acid.—A solution of 341 mg. of the carbinol[3] and 0.025 ml. of pyridine in 15 ml. of anhydrous formic acid was heated for 21 hr. at 75°. The mixture was processed and the product was analyzed as in the preceding experiment. The gas chromatographic pattern for the alcohols was very similar to that obtained in the preceding experiment. About 50% of the alcohol mixture corresponded to the decalol XI, and the absolute yield of this material was 25%. The major alcohols were identified by preparative gas chromatographic separation and infrared spectral examination.

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[17] See R. P. Linstead, A. B. L. Wang, J. H. Williams, and K. D. Errington, *J. Chem. Soc.*, 1136 (1937).

The Reformatsky Reaction. I. Zinc and Ethyl α-Bromoisobutyrate*

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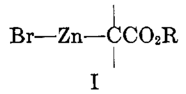
The behavior of the Reformatsky reagent prepared discretely from zinc and ethyl α-bromoisobutyrate in ether-benzene has been examined. Titration with a standard solution of fluorenone and vapor phase chromatography demonstrate that under normal conditions approximately 70% of active reagent is produced along with some 30% of a dimeric substance which affords ethyl isobutyrylisobutyrate on work-up. This dimeric product may be produced by zinc reduction of ethyl γ-bromoisobutyrylisobutyrate, whose presence in small amounts may be demonstrated on work-up, but it is shown that it can also be produced from the active reagent alone, with the elimination of the elements of ethoxyzinc bromide. The adduct formed from this reagent and 9-fluorenone in an instantaneous reaction is unusually prone to decompose into the ketone and ethyl isobutyrate on treatment with even weak bases. This suggests that the initial adduct has little ionic character in the β-oxido portion, and the infrared spectrum of a solution of the adduct implies a zinc chelate structure.

Two extreme views of the precise nature of Reformatsky reagent are possible: the older and more common view being that of an analog (I) of the classical Grignard reagent,[3] and a more recent view being that of the bromozinc enolate of an ester[4] (II). The latter view is implicit in arguments concerning the parallelism between the Reformatsky reaction and the Ivanov reaction[4] with which the paper cited deals explicitly.



$$\mathrm{Br{-}Zn{-}\overset{|}{\underset{|}{C}}CO_2R}$$

I

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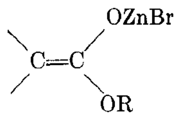
* To Professor Louis F. Fieser.

[1] (a) Abstracted in the main from the Ph.D. Dissertation of Stanley C. Bernstein, The University of Michigan, 1963. (b) Union Carbide Corp. Summer Research Fellow, 1960; Sun Oil Co. Fellow, 1961–1962; National Science Foundation Summer Fellow, 1962.

[2] Summer participant, National Science Foundation Grant 22898, 1963.

[3] R. L. Shriner in *Org. Reactions*, **1**, 1 (1942).

[4] H. E. Zimmerman and M. D. Traxler, *J. Am. Chem. Soc.*, **79**, 1920 (1957).



II

Arguments against a Grignard-like structure, though not necessarily in support of II, may be raised in spite of the similar adducts produced and the occasional destruction of the reagent by enolization of the carbonyl substrate.[3] Thus there are no recorded instances of *reduction* of the carbonyl substrate by the Reformatsky reagent, and conjugate addition to α,β-unsaturated carbonyl compounds is seldom encountered. Furthermore, it is significant that the Reformatsky reagent is far more reactive than other organozinc compounds[5] toward carbonyl substrates; and, whereas alkylzinc bromides or dialkylzincs can be used for the preparation of ketones from acid chlorides, reactions of Reformatsky reagents with ketones are virtually instantaneous, as will be shown in the sequel.

Normally the Reformatsky reaction is carried out by adding carbonyl substrate and bromo ester simultaneously to zinc in an appropriate solvent, although relatively recently it has been shown that it can be handled analogously to the Grignard reaction.[6,7] Possibly the reluctance to use the Grignard-like procedure has been due to reports of so-called "condensed ester" formation,[3] *e.g.*, reaction of unconverted ester as carbonyl substrate, especially notable when less reactive carbonyl components are used. This led Newman to propose that the condensed ester arises from a reaction of this type to produce a γ-bromo-β-keto ester which is then reduced by zinc to the condensed ester.[8] However, later workers[9] argue from analyses of precipitated "reagent" that condensed ester is produced by "dimerization" of an initially formed "monomeric" reagent (*i.e.*, I or II), a fact which discourages any isolation of the reagent for analytical examination.

Discussion

This paper and work currently in progress in this laboratory are designed to provide information relative to the character of the Reformatsky reagent in solution and the nature of the Reformatsky reaction. The present report deals primarily with a specific Reformatsky reagent and its behavior toward a specific carbonyl substrate. The reagent, derived from ethyl α-bromoisobutyrate, was chosen because it lacks α-hydrogens, which might lead to decomposition of the reagent by proton transfer,[10] especially from unreacted ester; and happily it is not a lachrymator. The ketone, 9-fluorenone, also lacks α-hydrogens, which might effect decomposition by proton transfer,[3,10] and in addition is brightly colored; hence disappearance of color affords a readily observable means of detection of reaction of the substrate with the Reformatsky reagent. Thus it was anticipated that we could examine the Reformatsky reagent itself, in solution, its "dimerization," and its behavior with a readily detectable carbonyl substrate.

Two noteworthy observations as to the adduct of reagent and carbonyl substrate derive from this study: (1) the reaction of reagent and substrate is virtually instantaneous, as is to be seen in the possibility of *titrating* a solution of the reagent with a solution of 9-fluorenone; and (2) the adduct contains a zinc–oxygen bond which is not appreciably ionic in character, since even weak bases instantly regenerate 9-fluorenone (color and actual isolation). This type of "reverse aldol addition" is not common but has been remarked upon before.[3] Consequently, if any intermediate on the way to the product possessed appreciable anionic character (in the oxido oxygen), no β-hydroxy ester would be isolable. The inference is that zinc forms a relatively nonionic bond with the oxido oxygen: ester carbonyl at 1647 cm.$^{-1}$.

If this inference is correct, and if II is a more accurate representation of the Reformatsky reagent than is I, the infrared spectrum of a solution of the reagent should *not* possess a band attributable to ester carbonyl (except insofar as unreacted bromo ester is present) but should more nearly resemble the spectrum of zinc acetylacetonate, which has two bands near 1525 cm.$^{-1}$ attributable to the hybrid bonds of the chelate system.[11] This is realized; except for a relatively weak band at 1730 cm.$^{-1}$ which carries over into the spectrum of the adduct with 9-fluorenone and which is attributable to unreacted bromo ester, there is no true carbonyl absorption in the spectrum of the Reformatsky reagent derived from zinc and ethyl α-bromoisobutyrate. The strongest absorption occurs at 1525 cm.$^{-1}$, suggesting a zinc–oxygen bond similar to that in the aforementioned chelate, *i.e.*, one with little true carbonyl character and hence considerable covalent character. Failure to precipitate with dioxane anything but solids, which on work-up proved identical with solute remaining in solution, supports this conclusion.

Titration of the reagent with standard 9-fluorenone solution permits experimental measurement of the amount of true reagent in a solution prepared from zinc and ethyl α-bromoisobutyrate (ether–benzene solution) and comparison with the amount of ethyl isobutyrate formed on treatment of the reagent solution with acid (*i.e.*, on work-up). The correspondence falls well within the limits of experimental error. Consequently, a study of the reagent solution in which conversion of the active reagent to "dimeric products" is feasible; *i.e.*, worked-up aliquots can be examined by v.p.c. for ethyl isobutyrate and "dimer" as a function of time and/or temperature.

By careful control of conditions we were able to effect reproducibly 90–100% conversion of the bromo ester into what we shall term "reagent A." This was accomplished by the procedure cited above[7] using excess zinc and carefully recovering and weighing the unreacted excess. Subsequent vapor phase chromatography of a worked-up aliquot showed only traces or complete absence of ethyl α-bromoisobutyrate.

Not all of reagent A is reactive as Reformatsky reagent (II), and the amount of II was initially determined by titration. A check on the accuracy of such titration was made by work-up and isolation of ethyl

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[5] D. A. Shirley, *Org. Reactions*, **8**, 33 (1954); *cf.* ref. 3.

[6] A. Siegel and H. Keckeis, *Monatsh.*, **84**, 910 (1953).

[7] C. A. Grob and P. Brenneisen, *Helv. Chim. Acta*, **41**, 1184 (1958). The senior author is indebted to Professor Grob for helpful discussion of this problem and of the Grignard-like preparation of the Reformatsky reagent.

[8] A. Hussey and M. S. Newman, *J. Am. Chem. Soc.*, **70**, 3024 (1948).

[9] J. F. J. Dippy and J. C. Parkins, *J. Chem. Soc.*, 1570 (1951).

[10] M. S. Newman, *J. Am. Chem. Soc.*, **64**, 2131 (1942).

[11] J. Lecomte, *Discussions Faraday Soc.*, **5**, 125 (1950).

2,2-dimethyl-2-(9-hydroxyfluoren-9-yl)acetate and by v.p.c. of a worked-up aliquot, and within the limits of experimental error 70% of reagent A was found to consist of active Reformatsky reagent. Since all of the added ketone can be accounted for, it appears that one and only one type of reaction is taking place between reagent A and ketone, *i.e.*, the normal Reformatsky reaction.

The possibility that the remaining 30% of reagent A might be a dimeric form of II capable of reversible dissociation was eliminated by titrating a sample of reagent A to the "end point" (color persists) and waiting for prolonged periods of time for the color to disappear, which it failed to do. In another experiment a calculated excess of fluorenone was added, and, after waiting for several hours, a material balance upon work-up permitted recovery of exactly the calculated amount of excess ketone. Thus whatever the nature of the inactive portion of reagent A, it is not formed reversibly from the Reformatsky reagent and hence must be formed either in competition with the latter from the initial reactants (zinc and bromo ester) or by irreversible reaction of the reagent with itself or with unreacted bromo ester at a relatively slow rate as formation of the reagent solution progresses.

It was anticipated that the unreactive portion of reagent A would be "dimeric" in the sense that 2 equiv. of bromo ester would be required for its production, and that in all probability it would be a precursor of "condensed ester" (ethyl isobutyrylisobutyrate).[8,9] V.p.c. analysis of a worked-up aliquot of reagent A showed essentially two components: ethyl isobutyrate and ethyl isobutyrylisobutyrate[12] in a molar ratio of 85:15. Thus the "dimer" is produced in about 30% yield from the reactants in the procedure used rather than essentially completely as when magnesium is used,[12] or under Newman's[8] rather similar conditions.[13]

The α-bromo-β-keto ester postulated by Newman[8] for "condensed ester" formation may be shown to be present in very small amounts in reagent A by very careful work-up and "programmed" v.p.c., identification being made by comparison of the v.p.c. with an authentic sample. Hence the Newman postulated reduction is at least possible.

The second hypothesis, dimerization of the initial Reformatsky reagent,[9] remained to be tested experimentally.[2] To this end reagent A was prepared as usual but with periodic examination of worked-up aliquots by v.p.c., and the reaction was allowed to proceed until v.p.c. analysis showed no ethyl α-bromoisobutyrate remaining. The resulting solution was then removed from contact with zinc, to prevent formation of additional "condensed ester" by reduction of bromo "condensed ester" already present in the solution. The zinc-free reagent A was then refluxed, with periodic v.p.c. analyses of worked-up aliquots.

The results of this series of analyses show clearly that ethyl isobutyrate disappears slowly and that ethyl isobutyrylisobutyrate increases slowly. Furthermore, by comparing the integrated areas of the bands arising from these two compounds with that due to an added inert reference compound, it is demonstrable that 1 molar equiv. of "condensed ester" is produced for each 2 molar equiv. of ethyl isobutyrate which disappear. Thus the Reformatsky reagent is in fact "dimerizing" in some manner.

Further information as to the nature of this "dimerization" emerges from the fact that it appears to be accompanied by the precipitation of a solid hygroscopic substance, qualitative analysis of which (*cf.* Experimental) shows it to consist only of the elements of ethoxyzinc bromide. Unfortunately, the nature of this precipitate renders both quantitative analysis and careful material balance difficult, if not impossible. However, since appreciable zinc and bromide ion are obtained on the work-up of the solution which remains after virtual disappearance of monomeric Reformatsky reagent, it is reasonable to assume that only 1 equiv. of ethoxyzinc bromide is formed for each mole of "dimer" produced.

If this ethoxyzinc bromide is eliminated from the Reformatsky reagent, the other product is monomeric dimethylketene. Now it has recently been shown that dimethylketene, *in the presence of a Lewis acid* (reported for aluminum chloride), is capable of adding to its own carbonyl group with the production of the so-called unsymmetrical dimer.[3,14] Consequently it is not impossible to conceive of the Reformatsky reagent adding to the carbonyl group of dimethylketene. Alternatively, ethoxyzinc bromide may be produced as the "dimerization" proceeds.

It is anticipated that the solvent system may be of great importance in realizing a good yield of active reagent,[12,15] and not only is it important to maintain as low a temperature as may be compatible with reaction of the bromo ester with zinc, but also the solution (*i.e.*, reagent A) should be assayed (*e.g.*, titration with standard fluorenone solution) to ensure that it contains reactive reagent, for individual bromo esters may well vary in their propensity to "dimerize" *via* either of the two paths. The extent of the third significant way in which the reagent may be destroyed *in situ*, by enolization of unreacted bromo ester,[8,10] which assuredly is a function of the basicity of the active reagent as well as of the acidity of the bromo ester, can be detected from any significant difference in the molar concentration of "reduced ester" as found from v.p.c. analysis of a worked-up aliquot and fluorenone titration data.

At the present writing a final decision as to whether Zimmerman's view[4] is correct or whether a β-lactonic adduct intermediate is initially formed is impossible. Arguments in favor of initial formation of such an intermediate are suggested chiefly by the Gilman β-lactam synthesis[16,17] and analogies to zinc-induced elimina-

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(12) Y. Salkind, *J. Russ. Phys. Chem. Soc.*, **38**, 97 (1906); J. Zeltmer, *Ber.*, **41**, 589 (1908). Preparation from ethyl α-bromoisobutyrate and magnesium.

(13) We were not able to reproduce Professor Newman's results, and we are at a loss to account for this failure but suggest that it may be due to subtle differences in solvents, physical state, and chemical purity.

(14) R. H. Hasek, R. D. Clark, E. U. Elam, and J. C. Martin, *J. Org. Chem.*, **27**, 60 (1962).

(15) In an extension of this investigation currently in progress in this laboratory, Mr. H. P. Knoess has observed that using pure tetrahydrofuran as solvent results in very rapid production of "condensed ester" at room temperature, apparently *via* addition of II to unreacted bromo ester in the presence of excess zinc.

(16) H. Gilman and M. Speeter, *J. Am. Chem. Soc.*, **65**, 225 (1943).

(17) H. B. Kagan, J. J. Basselier, and J. L. Luche, *Tetrahedron Letters*, **No. 16**, 941 (1964).

tions, ketene syntheses from α-bromo acid bromide,[18,19] and unsymmetrical ketene dimerization.[14] Consequently, work in this laboratory is currently being directed toward solution of this problem with the expectation that the results will provide increased scope for applications of the Reformatsky reaction in its new modification.

Finally, it is of interest to record that in the course of attempting to use the conventional Reformatsky procedure in a reaction involving 9-fluorenone and α-bromoisobutyryl bromide with the hope of obtaining the β-lactone, we observed that the expected reaction failed entirely. Instead, the fluorenone experienced pinacol reduction followed by rearrangement, the latter being induced either by the zinc bromide or by acid used in the work-up. This specific pinacol reduction is one which has been carried out with a magnesium–magnesium halide couple,[20] but it was also reported to fail when a zinc–zinc bromide couple was employed.[20] The product we obtained was identical with that reported, 6-keto-2,3,4,5,7,8,9,10-tetrabenzospiro[5.4]-decane.

Experimental[21]

Starting Materials.—The zinc used in these experiments was 20-mesh Baker and Adamson reagent grade. It was prepared by heating at 100° in a solution of a few drops of concentrated nitric acid in concentrated sulfuric acid for 15 min. After cooling to room temperature the zinc was separated from the acid by filtration through a coarse glass frit. The metal was then washed free of the acid with three portions of distilled water, free of the water with three portions of acetone and free of the acetone with three portions of anhydrous ether. After drying in a 110° oven overnight the zinc was ready for use.

Ethyl α-bromoisobutyrate was obtained from HI Laboratories, Whitmore Lake, Mich., and distilled twice through a 20-plate column packed with a stainless steel gauze spiral. Both times a middle fraction was taken, b.p. 59.5° at 17 mm.

The fluorenone used in these reactions was prepared by the method of Huntress, *et al.*[22]

Reagent benzene was dried by distilling away one-fourth of its total volume and collecting the rest at constant boiling point. Mallinckrodt anhydrous reagent ether was used directly with no preliminary drying.

Davison 100–200-mesh activated silica gel was used for column chromatography.

Reagent dioxane was dried by refluxing over calcium hydride for 2 hr. and distilling from this solid.

α-Bromoisobutyryl bromide was obtained from HI Laboratories, Whitmore Lake, Mich., and distilled twice through a Vigreux column, taking a middle fraction both times, b.p. 68° at 15 mm.

Reagent sodium methoxide was obtained from Matheson Coleman and Bell.

Estimated Experimental Error.—The average of several charts of each v.p.c. analysis was taken. In addition, the numbers reported are averages of many determinations for the fluorenone titrations and v.p.c. analyses. The standard deviations for these quantities lie between 1 and 6% of the quantity. This, then, is the estimated experimental error.

Reagent A by the Procedure of Grob and Brenneisen.[7]—The following procedure is typical of many such preparations. A 50-ml. three-necked flask was fitted with an efficient reflux condenser and a pressure-equalized dropping funnel. The apparatus was flame dried while a stream of dry nitrogen was admitted through the top of the condenser. All materials were added to the apparatus under a slight positive nitrogen pressure, and the reaction was run under dry nitrogen. In the flask were placed a Teflon-covered magnetic stirring bar, 0.59 g. (0.0090 g.-atom) of zinc, 4.7 ml. of an anhydrous 1:1 (by volume) ether–benzene solution (henceforth referred to as the usual solvent), and two small crystals of iodine. In the dropping funnel was placed a solution of 1.95 g. (0.0100 mole) of ethyl α-bromoisobutyrate in 2.0 ml. of the usual solvent. Several drops of the ester solution was admitted to the flask while the material in the flask was heating to boiling. Every 10 min. a few more drops of the ester solution was let into the flask until the reaction was initiated, as indicated by disappearance of the iodine color and clouding of the reaction mixture. This usually occurred between 5 and 30 min. after refluxing started. Occasionally initiation was extremely sluggish, and after 40 min. a few drops of methylmagnesium iodide solution was added to the material in the flask to initiate the reaction.

Upon initiation stirring was begun and the rate of addition of the ester solution was adjusted so that it required 2 hr. for the complete addition. After 1 hr. and 20 min. from initiation another 0.40 g. (0.0061 g.-atom) of zinc was added to the reaction mixture; and upon completion of the ester addition a final portion of 0.32 g. (0.0049-g.atom) of zinc was added. This brought the total amount of zinc to 1.31 g. (0.0200 g.-atom). The reagent was ready for use after 2 hr. more of refluxing. Unless otherwise noted, reagent A made by this procedure was used in all experiments below. The infrared spectrum in solution was taken in an "IR-tran" cell compensated with the sclvent mixture. In addition to a band at *ca.* 1730 (bromo ester) a very strong band appears at 1525 and a broad band at *ca.* 1450 cm.$^{-1}$.

Ethyl α-(9-Hydroxy-9-fluorenyl)isobutyrate.—A solution of 7.20 g. (0.0400 mole) of fluorenone in 30 ml. of the usual solvent was added, over 30 min., to a stirred and refluxing solution of reagent A made from 0.10 mole of bromo ester. After the addition the reaction was allowed to reflux for another 0.5 hr. The reaction mixture was then chilled and poured into 100 ml. of chilled 10% sulfuric acid. The layers were separated and the aqueous portion was extracted three times with a total of 150 ml. of ether. The combined organic portions were washed three times with a total of 75 ml. of water and then dried over magnesium sulfate. Upon filtration and solvent distillation, an oil remained which crystallized, and the resulting solid was recrystallized from alcohol: 11.05 g. (93.4% based on the amount of fluorenone used), m.p. 77.5–82.5°. Repeated recrystallizations of a portion of the product gave an analytical sample, m.p. 82.5–84.0° cor.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.99; H, 6.82.

All attempts at hydrolysis, even with very dilute alcoholic bases, led to recovery of 9-fluorenone. Likewise ester cleavage with lithium bromide–pyridine[23] afforded fluorenone.

Fluorenone Titration of Reagent A.—The following procedure is typical. Reagent A was made from 0.050 mole of bromo ester and 0.100 g.-atom of zinc. A solution of 6.30 g. (0.0500 mole) of fluorenone in 30 ml. of the usual solvent was placed in a graduated, pressure-equalized dropping funnel attached to the reaction flask. While the reagent was being stirred the ketone solution was slowly admitted into the flask until the yellow color permeated the reagent (30.5 ml. of the ketone solution, 0.0328 mole). Upon stirring and refluxing for 2 hr., the reaction mixture did not lose its yellow color.

The solution was decanted from the zinc and the residual metal was washed (water, acetone, and a small amount of dilute hydrochloric acid) into a coarse, fritted funnel. The zinc was then washed successively with dilute hydrochloric acid, water, and acetone, and finally dried at 100° overnight, residue 3.41 g.; therefore, 3.13 g. (0.047 g.-atom) of the zinc had reacted. Since 0.0479 mole of reagent A was prepared, and 0.0328 mole of fluorenone was taken up, 68.5% of reagent A was "active." Four runs provided a mean value of 68.2 ± 4.1%.

Chromatographic Material Balance.—A solution of 27.2 g. (0.150 mole) of fluorenone in 75 ml. of the usual solvent was

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[18] C. E. Boord, *et al.*, *J. Am. Chem. Soc.*, **52**, 651, 3396 (1930); **53**, 1505, 1533, 2427 (1931); **55**, 3293, 4930 (1933).

[19] W. E. Hanford and J. C. Sauer, *Org. Reactions*, **3**, 108 (1946).

[20] M. Gomberg and W. E. Bachmann, *J. Am. Chem. Soc.*, **49**, 236 (1927).

[21] Microanalysis were by Spang Microanalytical Laboratory, Ann Arbor, Mich. All melting points are uncorrected unless otherwise noted. Infrared spectra were recorded on a Perkin-Elmer Model 21 infrared spectrophotometer. Vapor phase chromatograms were recorded using a 6-ft. 10% silicone oil (Dow-Corning 550) on Chromosorb column unless otherwise noted.

[22] E. Huntress, E. B. Hershberg, and I. Cliff, *J. Am. Chem. Soc.*, **53**, 2720 (1931).

[23] F. Elsinger, J. Schreiberg, and A. Eschenmoser, *Helv. Chim. Acta*, **43**, 113 (1960).

added to a solution of reagent A made from 0.150 mole of the bromo ester.

Before the addition of the fluorenone, however, a 1-ml. aliquot of the reagent was taken (less than 1% of the total reagent) and hydrolyzed in 1 ml. of 10% sulfuric acid. After extracting the aqueous layer with ether and washing the combined organic portions with water, the dry solution (magnesium sulfate) was decanted from the desiccant and concentrated by distillation (~80°). The solvent vapors were not allowed to exceed 50°. The distillation was carried out in a side-arm test tube with a thermometer bulb about half-way between the bottom of the test tube and the side arm. In this way no significant amounts of ethyl isobutyrate (b.p. 112°) were lost. The concentrated solution was analyzed by v.p.c. The identification of the two product peaks was made by comparison of retention times with authentic samples under similar conditions. The mole fraction (measured areas in the chromatogram tracing) of ethyl isobutyrate was 0.84, and of ethyl isobutyrylisobutyrate was 0.16. In that there were no other significant peaks, it was assumed that these two accounted for all the reacted zinc which was found to be 0.139 g.-atom. Thus the number of moles of monomer was 0.10, and of "dimer," 0.02.[24]

After the addition of the fluorenone the crude product (including unreacted ketone) was isolated as before, 47.99 g. A 9.98-g. portion of this material was chromatographed on 500 g. of silica gel in a 4.5-cm.-diameter column. One-hundred-milliliter fractions were taken. The first 50 fractions were eluted with benzene, the next 10 with 10% (by volume) ether–benzene, and the final 10 with ethanol. Fractions 22–38 contained a total of 2.30 g. of fluorenone while fractions 53–57 yielded 6.28 g. of adduct. Adjusting these yields to the 47.99 g. of crude product, 11.05 g. (0.061 mole) of fluorenone was recovered and 30.23 g. (0.102 mole) of adduct was produced. This accounts for 0.163 mole of fluorenone. The discrepancy between this figure and the 0.150 mole of fluorenone originally added is small but may be accounted for by the fact that the eluted fractions contained varying small quantities of oily material besides the products.

V.p.c. of Hydrolyzed Reagent A.—This procedure is typical. During the course of one of the other experiments on reagent A a 1-ml. aliquot (a negligible amount compared with the total volume of the solution) of the reagent was removed and hydrolyzed in 1 ml. of 10% sulfuric acid. The layers were separated and the aqueous portion was extracted three times with ether. The combined organic layers were washed twice with small portions of distilled water and dried over magnesium sulfate. The dry solution was decanted from the solid and the solvent was carefully removed as with the aliquot in the preceding section.

The remaining organic solution was analyzed by v.p.c. Four charts were obtained for this sample and each contained the same four peaks. The first two peaks were due to ether and benzene, respectively, and the last two were due to ethyl isobutyrate and ethyl isobutyrylisobutyrate, respectively, as shown by comparisons of retention times with authentic samples. The area of the very sharp ethyl isobutyrate peak was obtained by triangulation, and the area of the broad condensed ester peak was obtained by using a planimeter. The average values of the mole fractions obtained from each chart was 0.85:0.15 ethyl isobutyrate to ethyl isobutyrylisobutyrate.

Dioxane and Reagent A.[25]—The following is a generalized procedure. To a solution of reagent A 2–5 molar equiv. of dioxane was added. Within a short time a white precipitate formed. The heterogeneous mixture was allowed to stir at room temperature for 18–24 hr.

The entire reaction mixture was hydrolyzed, or it was filtered through a medium glass frit and the solution and precipitate were hydrolyzed separately. Samples for v.p.c. analysis were prepared as in the preceding section. Besides a peak from dioxane, the charts obtained from these samples contained only the same peaks as did the charts from samples prepared directly from reagent A above.

The Infrared Spectrum of Fluorenone Adduct.—One-tenth of a mole of reagent A was titrated with 18.02 g. (0.10 mole) of fluorenone in 80 ml. of the usual solvent. The reagent took up 51.5 ml. of this solution to give a solution which was not entirely homogeneous. Nevertheless a 1.6-ml. aliquot was taken and diluted to 5 ml. with the usual solvent. An infrared spectrum of this solution was obtained in the same way as for the spectrum of reagent A. In addition to a band for the bromo ester (*ca.* 1730 cm.$^{-1}$), a strong band appears at 1647, but none at 1525 cm.$^{-1}$.

6-Keto-2,3,4,5,7,8,9,10-tetrabenzospiro[5.4]decane.—A solution of 23 g. (0.10 mole) of α-bromoisobutyryl bromide in 20 ml. of anhydrous tetrahydrofuran (THF) was allowed to drop, over the course of 2.5 hr., into a flask containing 5.95 g. (0.0910 g.-atom) of zinc and 47 ml. of anhydrous THF, while the material in the flask was stirred vigorously. After two-thirds of the acid bromide solution had been added another 3.97 g. (0.0607-g.-atom) of zinc was added to the flask, and at the conclusion of the acid bromide addition a final portion of 3.16 g. (0.0483 g.-atom) of zinc and a solution of 7.20 g. (0.0400 mole) of fluorenone in 30 ml. of anhydrous THF were added to the flask. After refluxing this reaction mixture for 2 days without apparent reaction of the fluorenone, 0.5 ml. of boron trifluoride etherate was added to the flask and refluxing was continued for 2 more days. The reaction was cooled to room temperature and hydrolyzed in 100 ml. of 10% sulfuric acid. The aqueous layer was extracted with three portions of ether and the combined organic layers were washed in succession with 10% sodium hydroxide, 10% hydrochloric acid, and distilled water, and finally dried over magnesium sulfate. An orange tar, which did not solidify in the refrigerator, remained after the organic solvent had been removed by distillation. It was boiled in ethanol and cooled to room temperature at which point a white solid separated. After one recrystallization from ethanol–chloroform the solid melted at 257–258° (lit.[20] m.p. 257–258°) and its infrared spectrum was entirely consistent with the expected product.

The Origin of "Dimer."[2]—Upon completion of the previously described studies of composition of reagent A, the following systematic investigation of the behavior of reagent A on prolonged heating was carried out. The original vapor chromatographic column was replaced by a 6-ft. silicone gum rubber column, and programmed chromatograms were obtained using an F and M Model 500 instrument. The six major components were identified by comparisons with authentic samples under identical conditions. Thus acidification of aliquots and v.p.c. analysis afforded ether, benzene (solvents), ethyl isobutyrate, ethyl α-bromoisobutyrate, ethyl isobutyrylisobutyrate, and ethyl γ-bromoisobutyrylisobutyrate.

(1) Reagent A was prepared in the usual manner, and half of it was worked up for analysis after work-up of an aliquot showed that all of the original bromo ester was gone. The usual components were present, with ethyl isobutyrate predominating. The remaining solution of reagent A was decanted from residual zinc and refluxed for 3 hr. and then worked up for analysis as before. The major change in appearance of the chromatogram was the lower per cent of ethyl isobutyrate and a relatively greater amount of ethyl isobutyrylisobutyrate.

(2) The preceding experiment was repeated with the addition of a small amount of naphthalene to the solution of reagent A just prior to dividing it in two parts. Once again the second part was decanted from zinc and refluxed for 3 hr., at the end of which time it was noted that the concentration of ethyl isobutyrylisobutyrate was relatively greater than in the initially examined sample as shown by integration and comparison with the naphthalene concentration.

(3) A number of runs were made, including naphthalene for reference, with different reflux times after careful separation of the reagent A solution from residual zinc. Invariably integration of the chromatograms obtained from worked-up aliquots showed that, for each mole of ethyl isobutyrylisobutyrate formed on heating, approximately 2 moles of ethyl isobutyrate disappeared. Gradually, but not significantly, a minor peak with longer retention time than any of the major peaks began to build up, and this is tentatively attributed to polymer formation.

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(24) Since the dimer is truly dimeric (*i.e.*, contains twice the number of carbon atoms as does the monomer) then

$$M + 2D = 1.00$$

where M is the number of moles of monomer per mole of reagent A, and D is the number of moles of dimer per mole of reagent A, but

$$\frac{M}{M + D} = 0.85$$

whence

$$M = 0.74 \text{ and } D = 0.13$$

(25) In another experiment a few drops of dioxane was added to 1 ml. of a solution of zinc bromide in ether. This led to the rapid formation of a precipitate.

Identification of the Precipitate Obtained on Heating Reagent A.[2]—As heating of reagent A progressed more and more of a very hygroscopic white to yellow solid separated on the walls of the reaction vessel. Solution in water followed by usual inorganic qualitative analysis showed the precipitate to be rich in zinc and bromide, as expected, but the presence of ethoxide could only be shown by the high alkalinity of the aqueous solution prior to acidification with dilute nitric acid. Consequently a carefully washed (toluene) sample of the precipitate was dissolved in *n*-butyl alcohol. The butanol solution was then subjected to v.p.c. analysis, and ethanol was identified by its retention time, which was found to differ from that of any other known components of the system. The only other "peaks" were very small (scarcely more than "blips") and they corresponded in retention times to the usual esters and a trace of toluene. The ethanol peak was substantial, and with the butanol peak constituted the only real absorptions in the chromatograms.

Ethyl γ-Bromoisobutyrylisobutyrate.—The following procedure is modified from directions for ketone bromination by Corey and Sneen.[26,27] A solution of 28.8 g. of reagent grade bromine (3% excess) in 100 ml. of glacial acetic acid was added dropwise to a solution of ethyl isobutyrylisobutyrate[12] (99.5% purity by v.p.c.) in 300 ml. of anhydrous ether and 60 ml. of glacial acetic acid. After refluxing for *ca.* 22 hr., water was added to the mixture until two layers formed, and then lithium bromide was added and the layers were separated. The solvents were distilled off on the steam bath under aspirator pressure, and the residual liquid was fractionated at 0.50–0.55 mm. A fraction boiling at 150° amounted to *ca.* 80% of the expected product. This was redistilled and the fraction boiling at 64° (0.25 mm.) was collected, 20.4 g. (45%).

Anal. Calcd. for $C_{10}H_{17}BrO_3$: C, 45.29; H, 6.46; Br, 30.14. Found: C, 45.43; H, 6.07; Br, 30.36.

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[26] E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **78**, 6269 (1956).

[27] This procedure carried out by Mr. H. P. Knoess.

Studies on the Acid-Catalyzed Esterification of Substituted o-Benzoylbenzoic Acids in Methanol*[,1]

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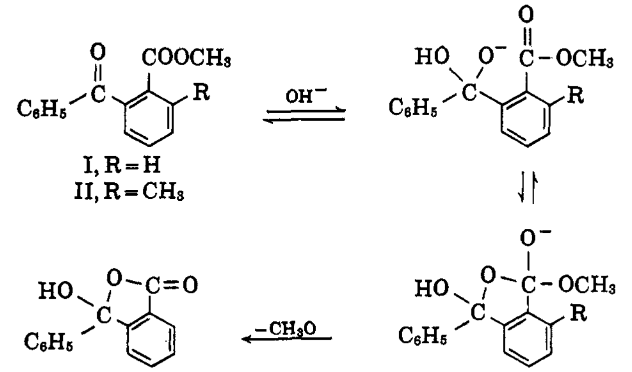
Studies on the acid-catalyzed esterification of a number of methylated *o*-benzoylbenzoic acids in methanol show that the composition of the esters formed under kinetic control is different from that formed under thermodynamic control in almost all cases. For the parent *o*-benzoylbenzoic acid *pseudo ester is formed more rapidly than normal ester* and the normal ester is formed almost exclusively under thermodynamic control. Four different routes of esterification are outlined and discussed.

The surprising fact that methyl 2-benzoyl-6-methylbenzoate (II) is hydrolyzed by alkali more rapidly than methyl *o*-benzoylbenzoate (I) was explained by a mechanism which involved primary attack of the hydroxide ion at the ketonic carbonyl group followed by intramolecular elimination of a methoxide ion.[2] The rate of this (intramolecular) reaction is greater than that of a similar reaction in the unsubstituted case because the methyl group in the 6-position causes the carbonyl group of the carbomethoxy group of II to be more favorably oriented for intramolecular attack than that in I. The conventional mechanism for ester hydrolysis, that involving attack of hydroxide ion at the carbonyl group of the carbomethoxy group, could also be involved.



However, in the case of II the presence of two *ortho* substituents would be expected to decrease greatly the probability of such an attack. In the case of I both mechanisms are likely. How much hydrolysis takes place by each path is not known.

In view of the above analysis a re-examination of the acid-catalyzed esterification of *o*-benzoylbenzoic acids with methanol seemed in order. In previous work, the proportions of normal and pseudo methyl esters obtained from a number of methylated *o*-benzoylbenzoic acids were determined.[3] However, these esters were those present after lengthy periods of esterification at reflux in methanol and, hence, the proportions were more likely those controlled by the various equilibria involved (see Scheme I[4]) and not the kinetically controlled ones.

Examination of this scheme reveals that normal ester I_n might be formed by route A directly from the keto acid I or by route B-C involving prior formation of pseudo ester I_p, or partly by each route. Similarly, pseudo ester I_p might be formed directly from I by route B, or *via* route A–C involving prior formation of I_n, or partly by each route.

We now find that when I is heated with methanolic hydrogen chloride at 55.5° the ester isolated in 13.5% yield after 15 min. contains about 51% of I_n and 49%

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* That this article should appear in an issue honoring Professor Louis F. Fieser is particularly fitting because of the fact that my (M. S. N.) interest in *o*-benzoylbenzoic acid chemistry first arose in connection with synthetic work done while serving as a postdoctoral fellow at Harvard in 1935–1936.

[1] This research was supported by Grant GP-718 from the National Science Foundation.

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

[3] M. S. Newman and C. W. Muth, *ibid.* **73**, 4627 (1951), Table I.

[4] The notations I_n and I_p, etc., mean normal and pseudo ester and will be used throughout this paper for all of the esters involved. No attempt has been made to show the catalytic protons. Throughout the discussion of mechanisms of esterification we have avoided routes which involve acylium ions of the type described by M. S. Newman [*ibid.* **64**, 2324 (1942)]. Such ions are present in about 100% sulfuric acid, but we do not believe they play an appreciable role in the methanolic solutions of the present study.