Isomyristic Acid.—The hydroxy-isomyristic ester from the preceding preparation was converted to the unsubstituted acid according to the method used by Noller and Adams for n-tridecanoic acid. The crude isomyristic acid was esterified by warming with ethyl alcohol ($+H_2SO_4$) and the resulting ester was carefully fractionated. The yield of purified ethyl isomyristate was 45–50% (based on the hydroxy ester); b. p. 140–142° at 5 mm., n_D^{20} 1.4342. Hydrolysis of the ester gave isomyristic acid, which after recrystallization melted at 50–50.5°. This acid showed no depression of the m. p. when mixed with that obtained from 10-keto-isomyristic acid.

Reduction of ethyl isomyristate with sodium and alcohol gave isomyristyl alcohol (75–80% yield); b. p. 145–150° at 6 mm., m. p. 10–11°, d_{20}^{20} 0.8429, n_D^{20} 1.4437. This alcohol on warming with a large excess of 48% hydrobromic acid ($+H_2SO_4$) gave iso-myristyl bromide (80% yield); b. p. 120–122° at 3 mm., d_4^{20} 1.0241, n_D^{20} 1.4598.

Summary

The selective action of alkylmagnesium halides upon sebacyl chloride and 9-carbethoxynonoyl chloride has been used for the synthesis of straight and branched chain ketonic acids of high molecular weight (C_{14}–C_{18}). This reaction constitutes a simple method for the addition of ten atoms to a carbon chain.

Isomyristic, isopalmitic and isostearic acids were prepared by reduction of the corresponding ketonic acids.

The Structure of α-Benzoyl α-Bromo Esters

BY B. W. HOWK AND S. M. McELVAIN

The unusual properties of those organic bromo compounds in which a bromine atom has replaced a hydrogen of an active methylene group have been recognized for some time.   The fact that certain of these substances are hydrolyzed by sodium hydroxide solution into sodium hypobromite led the earlier investigators[1] to the view that such substances contained an oxygen to bromine linkage.   This view was regarded as untenable by MacBeth[2] who, in the course of a study of certain members of this class, found that, while these substances oxidized hydrazine quantitatively to nitrogen, they gave absorption spectra characteristic of compounds having an ordinary carbon to halogen bond.   In a more recent paper, which admirably reviews the literature of this class of compounds, Schmidt, Ascherl and von Knilling[3] emphasize the similarity between the chemical behavior of this type of halide, which they term a persubstituted halogen compound, and the N-halogenated acylamines.   They showed that persubstituted bro-
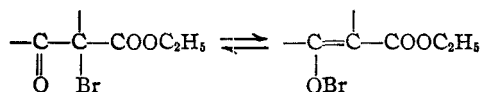
(1) Willstätter and Hottenroth, *Ber.*, **37**, 1776 (1904); Flatow, *ibid.*, **37**, 1787 (1904).

(2) MacBeth and Graham, *J. Chem. Soc.*, **121**, 1115 (1922).

(3) Schmidt, Ascherl and von Knilling, *Ber.*, **59**, 1876 (1926).

mides in methyl alcohol solution cause the elements of methyl hypobromite to add to the carbon to carbon double bond of cyclohexene to form 1-bromo-2-methoxycyclohexane.   Since carbon tetrabromide does not show this reaction but does give sodium hypobromite when hydrolyzed with sodium hydroxide, and since both bromonitromalonic ester and dibromomalonic ester undergo the cyclohexene reaction while the former gives sodium hypobromite and the latter sodium bromide on hydrolysis with sodium hydroxide, Schmidt and co-workers expressed the opinion that the postulation of an oxygen to bromine linkage on the basis of sodium hypobromite formation is unjustified.

In a previous paper[4] the reaction of piperidine with ethyl benzoylbromoacetate, ethyl α-benzoyl-α-bromopropionate and ethyl phenylbenzoylbromoacetate was described.   The nature of the products obtained from these reactions indicated that each of the former two bromo esters reacted simultaneously as an alkyl halide and as a brominating agent.   It was suggested then that this behavior might be due to the presence of a hypobromite structure which exists in equilibrium with the ordinary C–Br form

$$-\overset{\displaystyle |}{\underset{\displaystyle \|}{C}}-\overset{\displaystyle |}{\underset{\displaystyle |}{C}}-COOC_2H_5 \ \rightleftharpoons\ -\overset{\displaystyle |}{C}=\overset{\displaystyle |}{\underset{\displaystyle |}{C}}-COOC_2H_5$$
$$\ \ \ O\ \ Br \qquad\qquad\qquad OBr$$

It therefore seemed desirable to test the validity of this hypothesis by a further study of the behavior of these particular bromo esters with other reagents.

One phase of the work which is now reported has been concerned with a study of the rate of reaction of these bromo esters with potassium iodide and hydrazine.   With the former reagent the bromo esters were converted into iodo esters and the rate of reaction was followed by determination of the amount of unreacted potassium iodide from time to time.   The rate of the hydrazine reaction was followed by the amount of nitrogen evolved from the reaction, which proceeds, according to MacBeth, in the following manner

$$2RBr + 3H_2NNH_2 \longrightarrow 2RH + N_2 + 2H_2NNH_2 \cdot HBr$$

The results which were obtained are shown graphically in Fig. 1.

Certain features of these curves should be noted.   With potassium iodide both of the bromo esters give a rather large amount of immediate reaction, about 20% in the case of the propionate and 65% in the case of the acetate. Thereafter the rate drops off markedly and it is only after twenty-four hours that the reactions come to completion.   Since both of these reactions were carried out in alcohol solution and at a temperature (1°) at which very little if any free iodine was produced, it may be assumed that the reaction involved simply the replacement of bromine by iodine.   Conant and co-

(4) Howk and McElvain, THIS JOURNAL, 54, 282 (1932).

workers[5] have shown that a similar reaction between potassium iodide and a variety of chloro compounds (including chloro esters) in acetone solution is bimolecular. It is obvious from the curve showing the reaction between potassium iodide and ethyl benzoylbromoacetate that the rate is too rapid for the determination of the type of reaction to have any meaning, but a
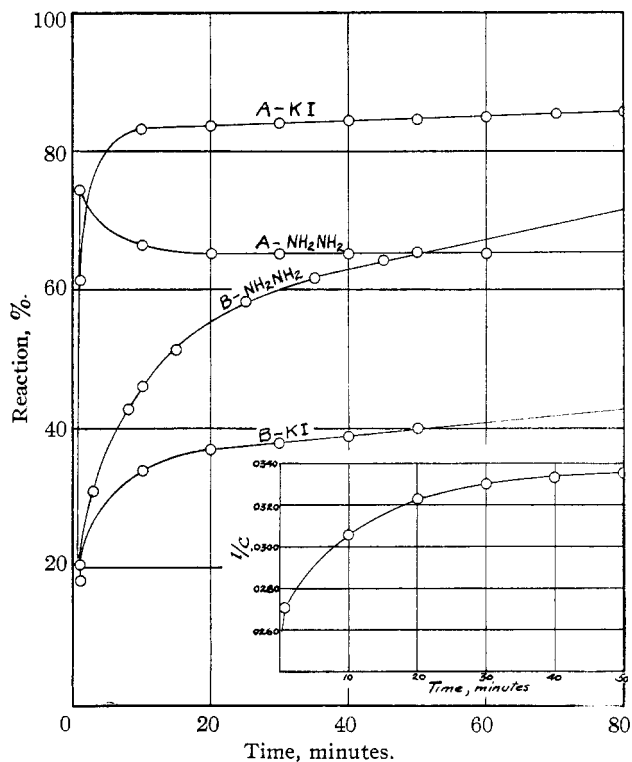

Fig. 1.—Rate of reaction of ethyl benzoylbromoacetate (A curves) and ethyl α-benzoyl-α-bromopropionate (B curves) with potassium iodide and hydrazine. Inset. Plot of $1/C$ ($C =$ concentration in millimoles per liter of the remaining potassium iodide taken from curve B-KI) against time.

plot of the reciprocal of the concentration of the remaining potassium iodide in the ethyl benzoylbromopropionate reaction against time (see inset, Fig. 1) shows that the reaction is not simply bimolecular. The complexity of this reaction would seem to indicate that different types of bromine linkages were involved.

In the reaction with hydrazine both of these bromo esters show approximately the same amount of immediate reaction that they did with po-

(5) Conant and co-workers, THIS JOURNAL, **46**, 232 (1924); **47**, 476, 488, 587 (1925); *cf.* also van Duin, *ibid.*, **47**, 585 (1925).
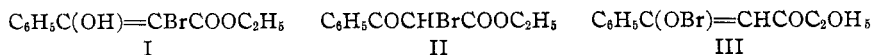
tassium iodide. The peak in the curve representing the reaction of ethyl benzoylbromoacetate was due to the expansion of the volume of nitrogen by the heat of reaction. As the temperature of the evolved gas returned to that of its surroundings the volume of nitrogen decreased to a constant value that indicated 65% reaction. The failure of the hydrazine to react further was due, no doubt, to reaction of the reagent with other functional groups in the bromo ester molecule. Ethyl benzoylbromopropionate reacts much more slowly with hydrazine, consequently the curve shows no effects from the heat of reaction. In this case, also, some of the hydrazine is used up in reactions with other groups in the bromo ester molecule for the curve becomes horizontal after about 85% reaction. For this reason hydrazine does not appear to be a very suitable reagent[6] for the study of this particular type of active bromine compound, and the chief significance which may be attached to its behavior is the similarity in the amounts of immediate reaction obtained with it and potassium iodide.

The second phase of the work was a study of the course of the reaction between each of these bromo esters and phenylmagnesium bromide.[7] In the case of ethyl benzoylbromopropionate the reaction with the Grignard reagent was relatively simple, the only reaction products being bromo-benzene and the magnesium enolate of ethyl α-benzoylpropionate. The bromobenzene and ethyl benzoylpropionate were isolated in 81 and 85% yields, respectively. This reaction may be represented thus

$$C_6H_5COCBr(CH_3)COOC_2H_5 + C_6H_5MgBr \longrightarrow$$
$$C_6H_5C(OMgBr)=C(CH_3)COOC_2H_5 + C_6H_5Br$$
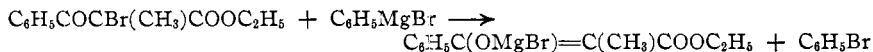
With ethyl benzoylbromoacetate the reaction with the Grignard reagent was more complex. The amounts and yields of the various reaction products which were isolated are summarized in Table I. The products derived from phenylmagnesium bromide were benzene, bromobenzene and di-phenyl and were found at the end of the reaction in the ether solution in which the reaction was carried out. The other reaction products, derived from ethyl benzoylbromoacetate, were, at the completion of the reaction, in the form of —OMgBr compounds which were partially insoluble in ether and completely insoluble in petroleum ether.

The assumption that ethyl benzoylbromoacetate exists in the following three forms

$$C_6H_5C(OH)=CBrCOOC_2H_5 \qquad C_6H_5COCHBrCOOC_2H_5 \qquad C_6H_5C(OBr)=CHCOC_2OH_5$$
$$\text{I} \qquad\qquad\qquad \text{II} \qquad\qquad\qquad \text{III}$$

allows for a ready explanation of the course of the reaction of this ester with phenylmagnesium bromide. The formation of benzene is due to the reaction of the Grignard reagent with enolic structures and, since some of

(6) MacBeth and Hirst [*J. Chem. Soc.*, **121**, 905 (1922)] report that hydrazine is oxidized quantitatively to nitrogen by the active bromine in such compounds as dibromomalonic ester, dibromobarbituric acid, etc.

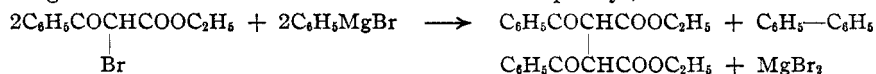(7) *Cf.* Kohler and Tishler, THIS JOURNAL, **54**, 1594 (1932).

TABLE I

YIELDS OF PRODUCTS ISOLATED FROM THE REACTION OF 0.37 MOLE (100 G.) OF ETHYL BENZOYLBROMOACETATE AND 0.37 MOLE OF PHENYLMAGNESIUM BROMIDE
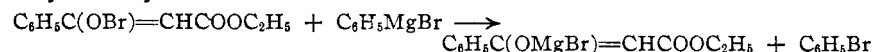
Product	Weight, g.	Yield, %
Benzene	6.2	22.0[a]
Bromobenzene	32.0	56.0[a]
Diphenyl	3.2	11.3[a]
		89.3[b]
Ethyl benzoylbromoacetate	14.5	14.5[c]
Ethyl benzoylacetate	39.9	56.5[c]
Diethyl α,α'-dibenzoylsuccinate	7.6	10.8[c]
		81.8[d]

[a] Based on phenylmagnesium bromide used. [b] Percentage of phenylmagnesium bromide accounted for. [c] Based on ethyl benzoylbromoacetate. [d] Percentage of ethyl benzoylbromoacetate accounted for. The failure of the values b and d to approach 100% more closely is due to the losses associated with the isolation of the various reaction products.

the bromo ester was precipitated from the reaction as a magnesium enolate, this portion of the bromo ester must have existed as form I.   The remainder of the benzene resulted from the reaction of phenylmagnesium bromide with the enolic form of dibenzoylsuccinic ester (IV).   This latter compound undoubtedly resulted from a coupling of form II by the Grignard reagent[8] with the simultaneous formation of diphenyl, thus

$$2C_6H_5COCHCOOC_2H_5 + 2C_6H_5MgBr \longrightarrow C_6H_5COCHCOOC_2H_5 + C_6H_5—C_6H_5$$
$$\qquad\qquad | \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad | $$
$$\qquad\quad Br \qquad\qquad\qquad\qquad\qquad\qquad C_6H_5COCHCOOC_2H_5 + MgBr_2$$

since the succinic ester and diphenyl were obtained in approximately equivalent amounts.   The reaction of forms I and II as outlined above leaves form III to account for the formation of the debrominated ester, ethyl benzoylacetate and bromobenzene.

$$C_6H_5C(OBr)=CHCOOC_2H_5 + C_6H_5MgBr \longrightarrow$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad C_6H_5C(OMgBr)=CHCOOC_2H_5 + C_6H_5Br$$

These two compounds were isolated in almost exactly equivalent quantities.

The amount of this latter reaction corresponds quite closely to the amount of immediate reaction which ethyl benzoylbromoacetate shows with both potassium iodide and hydrazine.   It would hardly seem likely that this similarity in behavior with three widely different reagents was fortuitous.

The results which have been presented thus far seem to offer additional chemical evidence in support of the previously suggested hypothesis[4] that these bromo esters exist, to some extent at least, in the hypobromite form. Further evidence in favor of this hypothesis is given by the molecular refractions of these bromo esters.   Table II gives the calculated molecular refractions of the various possible structures together with those obtained from the densities and refractive indices of the esters.

(8)   *Cf.* Fuson and others, THIS JOURNAL, **48**, 830, 2681, 2937 (1926); **55**, 720 (1933).

TABLE II

MOLECULAR REFRACTION OF α-BENZOYL α-BROMO ESTERS

No.	Structure	d_4^{20}	n_D^{20}	Calcd. M_D	Found
1	$C_6H_5COCHBrCOOC_2H_5$	1.4067	1.5470	58.82	61.24
2	$C_6H_5C(OH){=}CBrCOOC_2H_5$			59.87	
3	$C_6H_5C(OBr){=}CHCOOC_2H_5$			59.99	
4	$C_6H_5COCBr(CH_3)COOC_2H_5$	1.3476	1.5340	63.45	65.55
5	$C_6H_5C(OBr){=}C(CH_3)COOC_2H_5$			64.62	
6	$C_6H_5COC(CH_3)_2COOC_2H_5$	1.0719	1.5046	60.30	60.80

It is seen that the found molecular refractions of both of these bromo esters are decidedly higher than the corresponding values calculated for the various structures from the atomic refractions. Such an exaltation is characteristic of a structure having a carbon to carbon double bond adjacent to a phenyl group.[9] While this exaltation might be attributed to the enolic structure (2) in the case of ethyl benzoylbromoacetate, no such recourse is possible with ethyl benzoylbromopropionate. The close agreement between found and calculated values in the case of ethyl benzoyldimethylacetate (6) shows that such an exaltation is not a characteristic of the keto structures and leaves the hypobromite structure (5) as the only explanation of the exaltation of ethyl benzoylbromopropionate.

Experimental

Ethyl benzoylbromoacetate and ethyl α-benzoyl-α-bromopropionate were prepared by a previously described method.[4] These esters were distilled previous to their use in the following experiments; they boiled at 139–140° (1 mm.) and 144–145° (1 mm.), respectively.

Ethyl Benzoyldimethylacetate.—This ester was prepared by the methylation of ethyl α-benzoylpropionate with methyl iodide by the procedure of Hope and Perkin.[10] It boiled at 109–110° (3 mm.). Other physical properties of this ester are listed in Table II.

Reaction of the Bromo Esters with Potassium Iodide.—A sample of 4–5 g. of ester was weighed out into a 100-cc. volumetric flask, made up to volume with 95% alcohol and cooled to 1°. An exactly equivalent quantity of pure potassium iodide was likewise dissolved in sufficient cold 95% alcohol to make a total volume of 100 cc. The potassium iodide solution was placed in a 1-liter flask and cooled in an ice-bath. The flask was fitted with an efficient stirrer and the bromo ester solution added. A 10-cc. sample was removed immediately by means of a pipet and allowed to run into 100 cc. of carbon tetrachloride in a separatory funnel. This procedure stopped the reaction at once by precipitating the unreacted potassium iodide. Thereafter samples of 10 cc. were taken at ten-minute intervals. Then 100 cc. of water was added to the carbon tetrachloride and the aqueous solution extracted five times with 100-cc. portions of carbon tetrachloride to remove any unused bromo ester and a trace of iodine which, in some cases, was liberated. Care was taken to avoid loss of the water solution. The time consumed in completing the first extraction was about thirty seconds. The amount of unchanged potassium iodide in each sample was determined by the distillation method.[11]

(9) Henrich–Johnson and Hahn, "Theories of Organic Chemistry," John Wiley and Sons, New York, 1922, p. 298.

(10) Hope and Perkin, *J. Chem. Soc.*, **95,** 2046 (1909).

(11) Treadwell and Hall, "Analytical Chemistry," Vol. II, 6th ed., 1924, p. 559.

At room temperature there was a considerable liberation of iodine in this reaction. However, at 1° very little iodine formed in the case of benzoylbromoacetic ester and the amount in the case of benzoylbromopropionic ester was hardly noticeable. The formation of iodine is a secondary reaction involving the decomposition of the iodo organic compound and had no noticeable effect on the determination of potassium iodide. An attempt to isolate the iodo organic compound which was formed in the reaction was unsuccessful. Evaporation of the solvent from the combined residues of several completed runs gave a thick sirup which was deeply colored with iodine. This was taken up in ether, washed with potassium carbonate solution, and the ether layer dried. A clear, pale yellow solution resulted, but after standing a short while the iodine color reappeared and became deeper as time passed. Attempted vacuum distillation of the residual oil, left after evaporation of the solvent, resulted in complete decomposition of the iodo compound with the formation of iodine crystals in the receiving flask.

The rates of reaction of each of the bromo esters are shown graphically in Fig. 1.

Reaction of the Bromo Esters with Hydrazine Hydrate.—The procedure followed in this case was adapted from that recommended by MacBeth and Pratt.[12] An approximately 1-g. sample of the bromo ester was weighed accurately into the reaction bulb of a modified Van Slyke nitrometer. A 10% solution of hydrazine hydrate in absolute alcohol containing a 100% excess of hydrazine (calculated from the equation below) was placed in a dropping funnel sealed to the side of the flask. The eudiometer was filled with absolute alcohol to avoid differences in vapor pressure in different parts of the apparatus. The entire system was swept out with dry nitrogen gas and closed. The shaker was started and allowed to run until the vapor pressures in the apparatus were equalized. The levels were adjusted in the eudiometer and the hydrazine solution run into the reaction bulb containing the bromo ester. A volume reading was taken immediately and the subsequent readings were made at intervals of five or ten minutes. The evolution of nitrogen was complete in twenty minutes in the case of the acetate and in five hours in the case of the propionate. The shaking was continued throughout the course of the reaction. The weight of nitrogen which would theoretically be evolved from the weight of bromo ester used in each case, was computed from the equation given by Hirst and MacBeth[6] for reactions of this type

$$2RBr + 3H_2NNH_2 \longrightarrow 2RH + N_2 + 2H_2NNH_2 \cdot HBr$$

The volume which this weight of nitrogen gas would occupy when measured over absolute alcohol at the temperature and pressure of the experiment was calculated and from this theoretical volume of nitrogen and the volumes evolved at the various time intervals the percentages of reaction were determined.

The data for a representative run of each of the bromo esters with hydrazine are shown graphically in Fig. 1. The peak in the bromobenzoylacetic ester curve at the beginning of the reaction is due to a volume expansion caused by the heat of reaction. This effect was not observed in the case of benzoylbromopropionic ester as this reaction proceeded much more slowly.

Reaction of Ethyl Benzoylbromoacetate and Phenylmagnesium Bromide.—To a vigorously stirred solution of 100 g. (0.37 mole) of the bromo ester in 400 cc. of absolute ether contained in a 1-liter three-necked flask was added slowly an ether solution of 0.37 mole of phenylmagnesium bromide[13] over a period of two hours. The heat of reaction was sufficient to cause the ether to reflux slowly. As the reaction proceeded, a thick brownish sirup separated. The reaction mixture was stirred for twenty-four hours,

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(12) MacBeth and Pratt, *J. Chem. Soc.*, **119**, 1357 (1921).

(13) Prepared from bromobenzene (1 mole) and an excess of magnesium (2 atoms), *cf.* Kohler and Tishler (Ref. 7). The yield of phenylmagnesium bromide, as determined by titration of an aliquot, was 99% of the theoretical.

after which time it was cooled in an ice–salt bath and the ether layer decanted. The sirupy precipitate was washed by decantation with another 300 cc. of cold, dry ether.

The ether of the decanted solutions was removed by distillation through a water cooled Vigreux column and the residue transferred to a modified Claisen distilling flask which was carefully heated in an oil-bath until all the benzene present had distilled; 6.2 g. of this product, b. p. 78–80°, was obtained. The residue from this distillation was dissolved in a small amount of dry ether and transferred to a 1-liter Erlenmeyer flask. Addition of about 700 cc. of petroleum ether to the solution caused the organo-magnesium complexes which had remained in the ether solution to separate as a light brown flocculent precipitate. The solution was filtered and the solid material on the filter washed with petroleum ether. The petroleum ether was evaporated from the solution and the residual oil distilled; 30.0 g. of bromobenzene, b. p. 154–156°, was obtained. From the residue which crystallized in the distilling flask, 3.2 g. of diphenyl, m. p. 68–70°, was isolated.

The solid organo-magnesium compounds, which precipitated from the petroleum ether solution, were decomposed with iced dilute hydrochloric acid and the mixture extracted with ether. After drying and evaporation of the solvent, fractional distillation of the remaining oil gave 19.7 g. of ethyl benzoylacetate, b. p. 118–120° (1 mm.), and 7.0 of ethyl benzoylbromoacetate, b. p. 138–140° (1 mm.). Two grams of tarry residue remained after the distillation.

The layer of sirupy magnesium compounds which precipitated originally from the ether solution was worked up in the following manner. The precipitate was covered with 300 cc. of ether and treated with 200 cc. of iced, dilute hydrochloric acid. The ether layer was separated, washed thoroughly with water, dried over calcium chloride, and the ether removed by distillation. The reddish oil which remained was shaken in a flask with 100 cc. of light petroleum ether. Two liquid layers formed and after cooling in an ice-bath the petroleum ether was decanted. This washing process was repeated five times. The petroleum ether was evaporated from these washings and the residue distilled; 2.0 g. of bromobenzene, b. p. 48–50° (13 mm.), and 20.2 g. of ethyl benzoyl-acetate, b. p. 118–120° (1 mm.), were obtained. The viscous red oil which was insoluble in the petroleum ether consisted of some unchanged bromo ester and a crystalline compound which was separated by cooling a mixed ether–petroleum ether solution of the oil to −20° in an ice–hydrochloric acid mixture. Five grams of the crystalline compound, m. p. 128–130°, was obtained in this way and was identified as diethyl-α,α′-dibenzoylsuccinate.[14] Hydrolysis of this product with 5% alcoholic potassium hydroxide gave 1,2-dibenzoylethane, m. p. 144–145°; dioxime, m. p. 203–204°.[15]

Oxidation of the 1,2-dibenzoylethane with alkaline permanganate gave only benzoic acid, but mild oxidation with dilute nitric acid gave dibenzoyl glyoxal (α,δ-diphenyl-tetraketone) hydrate, m. p. 87–88°.[16]

Hydrolysis of the mother liquors, from which the above diethyl dibenzoylsuccinate was obtained, gave dibenzoylethane equivalent to an additional 2.6 g. of diethyl dibenzoylsuccinate, bringing the total yield of this product to 7.6 g. The hydrolysis mixture was found to contain sufficient bromide ion to account for an additional 7.5 g. of unchanged bromo ester. In one experiment this residual oil was distilled without attempting to separate the dibenzoylsuccinic ester and 8 g. of unchanged bromo ester, b. p. 138–140° (1 mm.), was recovered. Likewise, from another run, in which the bromo ester was disregarded, 7.35 g. of dibenzoylsuccinic ester was isolated by crystallization. These values verify those determined indirectly above, as the experiments were carried out under the same conditions and with the same quantities of reagents.

(14) Perkin, *J. Chem. Soc.*, **47**, 264 (1885).

(15) *Cf.* Kapf and Paal, *Ber.*, **21**, 3056 (1888).

(16) Abenius and Söderbaum, *ibid.*, **24**, 3034 (1891).

A summary of the weights and yields of the products of this reaction is given in Table I.

Reaction of Phenylmagnesium Bromide with Ethyl α-Benzoyl-α-bromopropionate.—This reaction was carried out in the same manner as described above for the acetate, except that 50 g. of bromo ester and an equivalent quantity of Grignard reagent were used. At the completion of the reaction most of the ether was removed by distillation and the magnesium enolate precipitated by the addition of dry petroleum ether. This salt was filtered off, decomposed with cold dilute hydrochloric acid, and the keto ester extracted with ether. After drying and removal of the ether, distillation of the residue gave 30.4 g. (85%) of ethyl α-benzoylpropionate, b. p. 127-128° (1 mm.). The petroleum ether was distilled from the filtrate through a 30-cm. Vigreux column and the residue fractionated at atmospheric pressure. A yield of 22.0 g. (81%) of bromobenzene, b. p. 154-155°, was obtained. The above products were the only substances which could be isolated from the reaction mixture.

Summary

The rates of reaction of ethyl benzoylbromoacetate and ethyl α-benzoyl-α-bromopropionate with potassium iodide and hydrazine and the course of the reaction of each of these bromo esters with phenylmagnesium bromide have been determined. The results which were obtained, together with the values found for the molecular refractions of these bromo esters, indicate that they exist to a certain extent in a hypobromite structure.

Crystalline Antineuritic Vitamin (B₁) Obtained with the Aid of Picrolonic Acid

BY ATHERTON SEIDELL AND MAURICE I. SMITH

It was shown several years ago[1] that by means of benzoylation at one stage of the process an acetone precipitated concentrate of high antineuritic activity could be prepared. Since then such concentrates have been subjected to a great variety of fractionation procedures. Until recently no notable advance in their purification has been attained.

Although the preparation of a picrolonate of the antineuritic vitamin has been reported by several workers,[2] in each case some other compound, usually the hydrochloride, was first isolated and, for purposes of confirmatory evidence, this was converted to the picrolonate or other well characterized salt. The procedures by which crystalline compounds of the

(1) Seidell, *J. Biol. Chem.*, **82**, 633–640 (1929); Seidell and Smith, *U. S. Pub. Health Reports*, **45**, 3194–3200 (1930); Seidell and Birckner, THIS JOURNAL, **53**, 2288–2295 (1931).

(2) Jansen and Donath, *Med. Dienst. Volkogezondheid Ned-Indie*, Part I (1927); Windaus, Tschesche, *et al.*, *Nachr. Ges. Wiss. Goettingen*, 207 (1931); same paper, *Z. physiol. Chem.*, **204**, 123–128 (1932); Ohdake, *Proc. Imp. Acad. (Japan)*, **7**, 102–105 (1913); **8**, 179–182 (1932); *Bull. Agr. Chem. Soc. (Japan)*, **8**, 11–46, 111–119 (1932); Kinnersley, O'Brien and Peters, *J. Physiol.*, **76**, 17 P (1932).