sented in Table II, were obtained by the reaction of the substituted aminoacetals with thiocyanic acid. The preparation of 1-[β-(o-chlorophenyl)ethyl]-2-mercaptoimidazole is illustrative of this procedure:

To a solution of 57 g. (0.135 mole) of N-[β-(o-chlorophenyl)ethyl]aminoacetaldehyde diethylacetal in 125 ml. of ethanol was added 18.2 g. (0.16 mole) of potassium thiocyanate and 75 ml. (0.15 mole) of 2N hydrochloric acid. The mixture was heated on the steam bath for 4 hr., during which time most of the ethanol was allowed to evaporate. The dark, oily organic layer solidified on cooling. This was filtered and washed with water. The damp filter cake was dissolved in a solution of 5.4 g. of sodium hydroxide in 300 ml. of water. This solution was heated to boiling, treated with decolorizing carbon, filtered, and acidified with concentrated hydrochloric acid. The pink colored precipitate was filtered and washed with water. The sample for analysis was recrystallized from ethanol.

1-Substituted imidazoles. These compounds, described in Table III, were, with one exception as noted in the table, prepared by the Raney nickel desulfurization of the mercaptoimidazoles. The preparation of 1-[β-(p-methoxyphenyl)ethyl]imidazole serves to illustrate this procedure.

The mercaptoimidazole, 11.7 g. (0.05 mole) was dissolved in 250 ml. of ethanol with gentle warming. To this solution was added an excess of ethanol-wet Raney nickel. Some frothing was noted. The resulting mixture was stirred under reflux for 5 hr. The mixture was filtered, and the filter cake washed with more ethanol. The combined filtrate and washings were concentrated *in vacuo*. The residue was dissolved in diethyl ether, and the ether solution washed with 100 ml. of 10% sodium hydroxide solution, and then with water. The alkaline wash, on acidification with concentrated hydrochloric acid, produced none of the original mercaptoimidazole. The ether solution, after drying over anhydrous magnesium sulfate, was evaporated and the residue distilled under reduced pressure. The product distilled at 158° (0.5 mm.) to give 5.5 g. of a clear, viscous liquid.

1-Substituted-2-methylmercaptoimidazole hydrochlorides. All of the compounds described in Table IV were prepared by the same general method.[4] The preparation of 1-(2-heptyl)-2-methylmercaptoimidazole hydrochloride illustrates this method.

There was added 21.3 g. (0.15 mole) of methyl iodide to a solution of 19.8 g. (0.1 mole) of 1-(2-heptyl)-2-mercaptoimidazole in 100 ml. of ethanol. The mixture became quite warm, and cooling in an ice bath was necessary. After the initial reaction had subsided, the flask was stoppered and kept overnight at room temperature. An excess of diethyl ether was added to complete the precipitation of the hydroiodide salt. This salt was removed by filtration and washed with more ether. The salt was added to a solution containing 4 g. of sodium hydroxide in 500 ml. of water. The organic phase was extracted into diethyl ether and washed twice with water. The ether solution was dried over anhydrous magnesium sulfate, and the drying agent then removed by filtering. The ethereal filtrate upon treatment with anhydrous hydrogen chloride precipitated the product as a white, crystalline solid. This was filtered and washed well with ether. The sample for analysis was recrystallized twice from a mixture of ethanol and ether.

1-[β-(3,4-Dimethoxyphenyl)ethyl]-2-substituted mercaptoimidazole hydrochlorides. These compounds, described in Table V, were prepared in a manner similar to the above, using the appropriate bromo compounds in place of methyl iodide.

Acknowledgment. The authors are grateful to W. L. Brown, G. Beckmann, H. L. Hunter, and G. M. Maciak for the microanalyses.

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(4) W. Marckwald, *Ber.,* 25, 2360 (1892).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF CALIFORNIA]

Reactivity of Organocadmium Reagents toward Halides Other than Acid Chlorides. Improvement of Conditions for the Reformatsky Reaction[*,1]

JAMES CASON AND RALPH J. FESSENDEN

The organocadmium reagent has been found to be considerably more inert than the Grignard reagent towards coupling with alkyl halides. In boiling ether solution, there was no significant rate of reaction of the cadmium reagent with either 2-iodooctane or allyl bromide. Reaction with a tertiary chloride is vigorous, but the principal products are the alkene resulting from dehydrohalogenation of the tertiary halide and the alkane corresponding to the alkylcadmium reagent. Reaction with α-bromo esters is also rapid, but in this instance the products are the alkyl bromide corresponding to the alkylcadmium reagent and the metal enolate (cadmium reagent) of the bromo ester. The reagent obtained from α-bromo esters in this way gives the same reactions as those observed in the Reformatsky reaction with zinc. An initial impression that the cadmium reagents give better yields in reaction with hindered ketones than are obtained in parallel Reformatsky reactions later proved to be a solvent effect. With hindered ketones, Reformatsky reactions in benzene-ether solvent give significantly better yields than in the conventional benzene or benzene-toluene solvent. Better yields were also realized in β-keto ester synthesis from a nitrile, zinc and α-bromo ester (Blaise reaction) when a benzene-ether solvent was used. Thermal cracking of three of the β-hydroxy-α,β-dialkyl esters prepared during this investigation yielded β,γ-unsaturated esters containing little, if any, of the α,β-unsaturated isomers.

In the initial investigation of the organocadmium reagents by Gilman and Nelson,[2] it was reported that these reagents exhibit a very low order of re- activity towards polar multiple bonds, but are re-

(2) H. Gilman and J. F. Nelson, *Rec. trav. chim.,* 55, 518 (1936).

active towards acid chlorides. These characteristics have rendered the organocadmium reagents of considerable utility for synthesis of ketones, especially polyfunctional ketones containing other groups with polar multiple bonds.[3-5] Reaction of organocadmium compounds with other types of halogen derivatives has been reported relatively infrequently. Coupling occurs with α-halogen ethers,[6] including carbohydrate derivatives of this type;[7] and alkylquinolinium iodides[8] have been described as reacting in the 2-position with alkylcadmium reagents. Benzenesulfonyl chloride reacts to give diphenyl sulfone and benzenesulfinic acid,[2] while tert-butyl chloride has been reported[2] to yield isobutylene, although no experimental details for the latter reaction were given.

In the present work, no significant quantities of coupling products could be isolated from reactions in which an alkylcadmium reagent had been heated under reflux in ether solution with 2-iodooctane or allyl bromide. Thus, the cadmium reagent is less reactive towards alkyl halides than is the Grignard reagent. It would follow that extraction of halogen by a cadmium reagent from an acid chloride results, not from a high order of reactivity towards the halogen, but rather because the cadmium reagent is so inert towards addition to the carbonyl group that there is sufficient time for the alternative reaction with halogen.

In accord with the report of Gilman and Nelson,[2] both tert-butyl chloride and 3-chloro-3-propylheptane were dehydrohalogenated by a cadmium reagent. In the former instance, in which the n-octylcadmium reagent was used, a 76% yield of n-octane was isolated as the other product of the reaction. Although the dehydrohalogenation may have proceeded by an E_1 mechanism, it seems more probable that there is involved a cyclic transition state (I), which is analogous to the intermediate involved in conversion of a ketone to the enolate by a Grignard reagent.

I

II
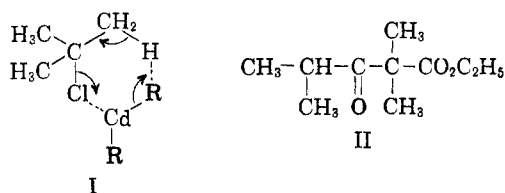
When the butylcadmium reagent was allowed to react with ethyl α-bromoisobutyrate there was obtained in rather good yield (72%) a product which

was eventually identified as ethyl 2,2,4-trimethyl-3-oxopentanoate (II). When the dodecylcadmium reagent was substituted for the butylcadmium reagent in reaction with ethyl α-bromoisobutyrate, the product was again keto ester II. In this instance, the other product of the reaction was shown to be dodecyl bromide, isolated in 62% yield. The only reasonable fomulation for production of keto ester II appears to be condensation of the enolate of ethyl isobutyrate with ethyl α-bromoisobutyrate, followed by removal of the halogen from the bromo keto ester by the cadmium reagent. Although ethyl isobutyrate is known to give relatively poor yields in the Claisen ester condensation,[9] in the present instance the condensation may be promoted by an increase in the reactivity of the condensing carbonyl on account of electron withdrawal by alpha bromine. It has been reported[10] that similarly good yields of keto ester II may be secured by reaction of ethyl α-bromoisobutyrate with magnesium. In that instance, the enolate is no doubt obtained through reaction of magnesium with halogen in the manner of formation of a Grignard reagent. When the cadmium reagent is used to secure the enolate, it seems probable that reaction proceeds by way of a transition state such as shown in formula III. This transition state is similar to that proposed by Hauser and Walker[11] in formation of the enolate of ethyl isobutyrate by diethylaminomagnesium bromide except that in this instance hydrogen is abstracted. In the case of an α-bromo ester, co-ordination of halogen with cadmium is no doubt discouraged by the relatively positive nature of the halogen. Tnus, positive halogen is removed by the alkylcadmium to give the alkyl halide. It seems probable that the metallic enolate, rather than the dissociated enolate ion, reacts with bromo ester to give bromo keto ester, for the sodium enolate reacts in an entirely different manner. When the sodium enolate of ethyl isobutyrate, prepared with sodium triphenylmethyl, is allowed to react[12] with ethyl α-bromoisobutyrate the product proves to be diethyl tetramethylsuccinate (IV).

III

IV
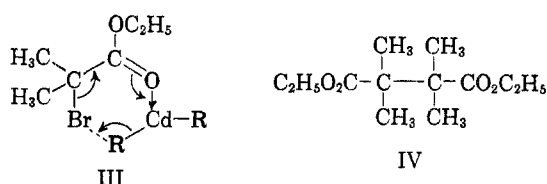
If the intermediate in formation of keto ester II is indeed the enolate of ethyl isobutyrate, then it

(3) J. Cason, Chem. Revs., 40, 15 (1947).

(4) D. A. Shirley, Org. Reactions, 8, 28 (1954).

(5) C. H. Wang, R. Isensee, A. M. Griffith, and B. E. Christensen, J. Am. Chem. Soc., 69, 1909 (1947).

(6) R. K. Summerbell and L. N. Bauer, J. Am. Chem. Soc., 58, 759 (1936).

(7) C. D. Hurd and R. P. Holysz, J. Am. Chem. Soc., 72, 2005 (1950).

(8) W. Bradley and S. Jeffrey, J. Chem. Soc., 2770 (1954).

(9) C. R. Hauser and W. B. Renfrow, Jr., J. Am. Chem. Soc., 59, 1823 (1937); F. C. Frostick, Jr., and C. R. Hauser, J. Am. Chem. Soc., 71, 1350 (1949).

(10) B. E. Hudson, Jr., and C. R. Hauser, J. Am. Chem. Soc., 61, 3568 (1939).

(11) C. R. Hauser and H. G. Walker, Jr., J. Am. Chem. Soc., 69, 295 (1947).

(12) B. E. Hudson, Jr., and C. R. Hauser, J. Am. Chem. Soc., 63, 3161 (1941).

TABLE I

COMPARISON OF THE REFORMATSKY REACTION WITH CONDENSATIONS PROMOTED BY CADMIUM REAGENTS

| Reagents Condensed | | Average Yields (%) | |
Ketone	α-Bromo ester	Cadmium reagent	Reformatsky reaction
CH_3—C—C_6H_{13} (with O double bond)	CH_3—CH—$CO_2C_2H_5$ (with Br)	75	79
CH_3—C—C_6H_{13} (with O double bond)	CH_3—C—$CO_2C_2H_5$ (with CH₃ and Br)	83	78
CH_3—CH—CH_2—C—CH_2—CH—CH_3 (with CH₃, O, CH₃)	CH_3—CH—$CO_2C_2H_5$ (with Br)	47	68

would seem probable that reaction could be secured with other carbonyl components. This has proved to be the case; in fact, reaction with 2-octanone gives a rather high yield (83%) of ethyl 2,2,3-trimethyl-3-hydroxynonanoate. It has also been found that ethyl α-bromopropionate yields the enolate of ethyl propionate, which may be similarly condensed with aldehydes or ketones.

When the enolate of ethyl propionate, prepared from the cadmium reagent, was allowed to condense with diisobutyl ketone, there were obtained yields of β-hydroxy ester in the range 40–50%, whereas the Reformatsky reaction carried out in an orthodox manner[18] proved to give yields of this hydroxy ester amounting to only about 25%. This difference was shown to be a solvent effect, rather than any difference in reactivity of the reagent obtained from zinc or the cadmium reagent; in fact, when the Reformatsky reaction was carried out in a 1:1 mixture of benzene and ether, rather than in benzene, the yield was somewhat higher than had been obtained by use of the cadmium reagent. In other examples investigated, as shown in Table I, yields in the Reformatsky reaction and in the reaction utilizing the cadmium reagent were quite similar. Furthermore, as shown in Table II, yields in the Reformatsky reaction are higher when the benzene-ether solvent is used, rather than benzene, in instances where there is significant steric hindrance in the carbonyl component. These findings are in contrast with an earlier report,[14] in which benzene or a benzene-toluene mixture was recommended as the solvent of choice for the Reformatsky reaction. The yield obtained in the present work (52%) with 2-heptadecanone and ethyl α-bromopropionate in the Reformatsky reaction in

benzene-ether solvent is of particular interest on account of the poor results obtained previously in this laboratory[15] and the difficulties encountered in securing a 2,3-disubstituted acid by other routes.[16]

TABLE II

SOLVENT EFFECTS IN REFORMATSKY REACTIONS

| Reagent Condensed with Ethyl α-Bromopropionate | Average Yields (%) | |
	Benzene solvent	Benzene-ether solvent
CH_3—$(CH_2)_5$—CHO	64	73
CH_3—C—C_6H_{13} (with O double bond)	79	76
C_3H_7—C—C_3H_7 (with O double bond)	66	80
CH_3—CH—CH_2—C—CH_2—CH—CH_3 (with CH₃, O, CH₃)	25	68
CH_3—$(CH_2)_6$—CN	44	55

Since the use of ether-benzene solvent seems to be especially favorable with less reactive carbonyl components, it seemed of interest to examine the effect of solvent on the reaction of an ester enolate with a nitrile (sometimes called the Blaise reaction[17]). In this instance also, considerably higher yields were obtained than have been previously reported[17] when benzene was used as solvent. With the ether-benzene solvent, better yields have been obtained with ethyl α-bromopropionate than had been obtained previously with sec-butyl α-bromopropionate.[17]

(13) J. Cason and K. L. Rinehart, Jr., J. Org. Chem., 20, 1591 (1955); K. L. Rinehart, Jr., and E. G. Perkins, Org. Syntheses, 37, 37 (1957).

(14) The use of a benzene-ether mixture as solvent in the Reformatsky reaction has not been uncommon (for example, cf. ref. 18, pp. 17 and 18); however, no specific advantage appears to have been recognized for this mixture. A general preference for a benzene or benzene-toluene solvent has been reported by S. Natelson and S. P. Gottfried, J. Am. Chem. Soc., 61, 970 (1939).

(15) J. Cason, H. J. Wolfhagen, W. Tarpey, and R. E Adams, J. Org. Chem., 14, 147 (1949).

(16) Reduction of 2,3-dimethyl-4-oxooctadecanoic acid proved to give very low yields [J. Cason, G. Sumrell, and R. S. Mitchell, J. Org. Chem., 15, 850 (1950)], and synthesis via alkylation of diethyl methylmalonate also proved unsatisfactory on account of the low yield of pure 2-bromoheptadecane obtained in the silver salt and bromine reaction (unpublished work in this laboratory by Bradford H. Walker).

(17) J. Cason, K. L. Rinehart, and S. D. Thornton, Jr., J. Org. Chem., 18, 1594 (1953); K. L. Rinehart, Jr., Org. Syntheses, 35, 15 (1955).

It has been observed that the tertiary β-hydroxy esters prepared in the present work are cracked only slowly at temperatures below 200°, and dehydration is facilitated little, if any, by addition of iodine. After ethyl 2,3-dimethyl-3-hydroxynonanoate had been heated at 150° in presence of iodine for 3 hours, about one third of the hydroxy ester was recovered. The unsaturated ester obtained in this way consisted almost entirely of the β,γ-isomer (cf. Fig. 1), which is a less substituted alkene than
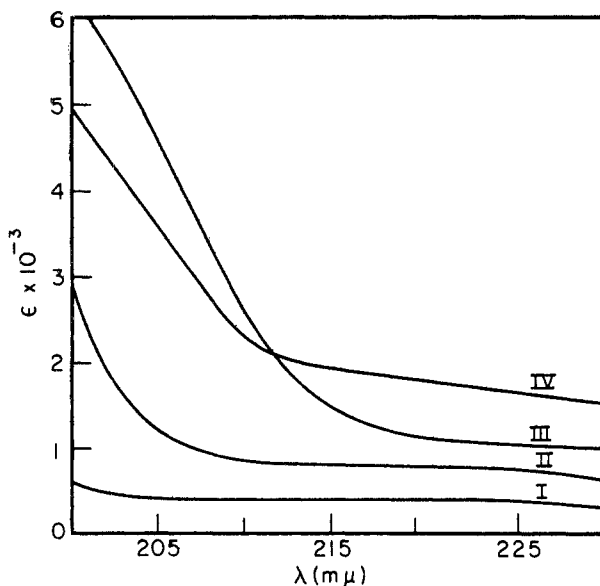

FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA OF UNSATURATED ESTERS. I, reaction product from 2-heptadecanone and ethyl α-bromopropionate, Frac. (c). II, reaction product from 2-heptadecanone and ethyl α-bromopropionate, Frac. (b). III, ethyl 2,5-dimethyl-3-isobutyl-3-hexenoate. IV, ethyl 2,3-dimethyl-3-hexenoate.

the α,β-isomer, in addition to being non-conjugated. Thermal dehydration of ethyl 2,5-dimethyl-3-isobutyl-3-hydroxyhexanoate and of ethyl 2,3-dimethyl-3-hydroxyoctadecanoate yielded the β,γ-unsaturated esters containing such small amounts of the α,β-isomers that none could be detected in the ultraviolet spectra (cf. Fig. 1). These results are in contrast with many previous reports[18] of dehydration of β-hydroxy esters by use of various reagents. There has normally been obtained a mixture of the α,β- and β,γ-unsaturated isomers, frequently a predominance of the α,β-unsaturated isomer. The presently observed results may be unique to thermal cracking; however, there are uncontrolled or unknown variables in the present work, and the investigation has not yet been pursued further.

It is of interest that the β-hydroxy esters prepared in the present investigation uniformly showed evidence of infrared absorption at two frequencies in the carbonyl region: a doublet, a

(18) For a review of products obtained by dehydration of β-hydroxy esters, refer to R. L. Shriner, Org. Reactions, 1, 12 (1942).

shoulder on the main band, or a broad band. It seems reasonable to ascribe this effect to chelation of the β-hydroxyl with the ester carbonyl. This effect was especially striking in the reaction product of ethyl α-bromopropionate with 2-heptadecanone, which consisted of a mixture of the β-hydroxy ester with the unsaturated ester (cf. Experimental). In different fractions, the strength of the doublet band in the carbonyl region was proportional to the intensity of absorption in the hydroxyl region.

EXPERIMENTAL[19]

Attempted reaction of 2-iodooctane with di-n-propylcadmium. 2-Iodooctane was prepared by heating 2-bromooctane overnight under reflux with excess of sodium iodide in acetone. Distillation of the product gave, after a considerable forerun of unsaturated material, a 64% yield of product with b.p. 90–92°/15 mm., n_D^{25} 1.4860 [literature,[20] b.p. 101°/22 mm., n_D^{20} 1.4896].

A Grignard reagent was prepared in the usual fashion from 29.5 g. (0.24 mole) of distilled n-propyl bromide (n_D^{25} 1.4326) and 6 g. (0.25 mole) of magnesium turnings in 125 ml. of ether. The Grignard reagent was converted to the cadmium reagent by heating under reflux with stirring for 45 min. with 29.3 g. (0.16 mole) of anhydrous cadmium chloride. To the solution of cadmium reagent, cooled to room temperature, there was added in one portion a solution of 50 g. (0.20 mole) of 2-iodooctane in 20 ml. of benzene. There was no evolution of heat or other evidence of reaction after this addition or during a subsequent period of heating for 1 hr. under reflux. Decomposition of the reaction mixture with ice and acid, followed by work-up in the usual fashion and distillation of the product at 17 mm. pressure, yielded 1.1 g. of fore-run, b.p. 80–94°, n_D^{25} 1.4800, and 37.6 g. (75%) of recovered 2-iodooctane, b.p. 94–96°, n_D^{25} 1.4852. No other products were isolated.

In similar experiments with 2-bromobutane, no coupling products were obtained.

Attempted reaction of allyl bromide with di-n-octylcadmium. There was prepared, by the procedure described for preparation of the propylcadmium reagent, a cadmium reagent from 56 g. (0.29 mole) of distilled n-octyl bromide. To the stirred solution of cadmium reagent, at room temperature, there was added in one portion a solution of 24.2 g. (0.20 mole) of distilled allyl bromide (n_D^{25} 1.4657) in 50 ml. of ether. There was no evidence of reaction during the addition or a subsequent 5-hour period of heating under reflux with stirring. A usual work-up of the reaction mixture, followed by distillation, yielded the following fractions: (a) fore-run, 0.8 g., b.p. 75–120°, n_D^{25} 1.4785–1.4058; (b) n-octane, 23.3 g. (71%), b.p. 120–124°, n_D^{25} 1.3975–1.3978, probably con-

(19) Melting points are corrected and boiling points are uncorrected. All distillations, unless otherwise specified, were through a 65-cm. column of the simple Podbielniak design with heated jacket and partial reflux head (cf. J. Cason and H. Rapoport, *Laboratory Text in Organic Chemistry*, Prentice-Hall, Inc., New York, 1950, p. 237). Infrared spectra were recorded on a Baird recording spectrophotometer, using thin films. Ultraviolet spectra were determined on a Beckman model DU spectrophotometer with fused quartz prism, in optically pure heptane at concentrations such that optical densities were in the range 0.15–1.5. Microanalyses are by the Microanalytical Division, Department of Chemistry, University of California, Berkeley.

(20) A. Audsley and F. R. Goss, *J. Chem. Soc.*, 358 (1942); R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, 99, 45 (1911).

taining a little n-octene (literature,[21] for n-octane, b.p. 125°, n_D^{20} 1.3988); (c) 2.8 g., b.p. 87–89°/32 mm., n_D^{25} 1.4338. The highest boiling fraction, which gives a positive qualitative test for halogen and has d^{25} 0.8927, is believed to be a mixture of n-octyl bromide and a hydrocarbon, possibly a very small amount of coupling product. n-Octyl bromide has n_D^{25} 1.4501 and is reported[22] to have d^{25} 1.1099, while 1-undecene is reported[23] to have b.p. 188–190°, n_D^{20} 1.4284, d^{20} 0.7630.

Reaction of tert-butyl chloride with di-n-octylcadmium. A cadmium reagent was prepared as described above from 46.4 g. (0.23 mole) of distilled n-octyl bromide (b.p. 66–67°/4.8 mm., n_D^{25} 1.4501). The reaction was carried out under nitrogen, as usual, and any gas passing out of the system through the mercury valve was led through two wash tubes maintained at 10–20°, each containing 30 g. of bromine, and finally through a gas trap cooled in Dry Ice and acetone.

The stirred solution of cadmium reagent was cooled in an ice bath as there was added, in two portions, 18.5 g. (0.2 mole) of distilled tert-butyl chloride (b.p. 49–52°, n_D^{25} 1.3825). After addition of the first portion, there was a brief induction period, after which a vigorous reaction occurred. When this reaction had subsided, the second portion was added, then the mixture was stirred in the ice bath for 30 min. and finally for 2 hr. under reflux. Since there was no condensate retained in the cold trap, products were obtained by working up the solution in the reaction flask and the bromine in the wash bottles.

The ether solution of the reaction mixture was treated with water and the aqueous phase was extracted with benzene. The ether solution and benzene extract were combined, solvent was removed by distillation through the column, and the residue was distilled to yield: (a) 17.3 g. (76%, based on tert-butyl chloride) of n-octane, b.p. 123–124°, n_D^{25} 1.3970 (literature[21] b.p. 125°, n_D^{20} 1.3988); (b) 2.0 g. of hexadecane, b.p. 127°/4.5 mm., n_D^{25} 1.4328 (literature[24] b.p. 156–158°/18 mm., n_D^{20} 1.4321).

Excess bromine in the wash bottles was decomposed by shaking with aqueous sodium sulfite, and the oily residual liquid was extracted with ether. Distillation of the dried extracts yielded 9.2 g. (21%) of 1,2-dibromo-2-methylpropane, b.p. 72–73°/60 mm., n_D^{25} 1.5050 (literature[25] b.p. 149°).

Reaction of di-n-butylcadmium with 4-chloro-4-n-propylheptane. 4-n-Propyl-4-heptanol was prepared by reaction of n-propylmagnesium bromide with 4-heptanone by a procedure similar to that described by Blatt and Stone.[26] The crude undistilled carbinol was then converted to the tertiary chloride by the procedure which has been described for preparation of tert-butyl chloride.[27] After a fore-run consisting largely of alkene, the tertiary chloride was obtained in 56% overall yield, b.p. 78–79°/11 mm., n_D^{25} 1.4372 (literature[28] b.p. 80°/12 mm., n_D^{15} 1.4421).

The reaction of 0.20 mole of 4-chloro-4-n-propylheptane with the butylcadmium reagent was carried out as described for the reaction with tert-butyl chloride except that the organometallic reaction mixture was worked up for alkene. Distillation of the product yielded the following fractions: (a) 22.1 g. (79%) of 4-n-propyl-3-heptene, b.p. 61–62°/18

mm., n_D^{25} 1.4265 (literature[29] b.p. 160–162°/734 mm., n_D^{20} 1.4386); (b) 1.6 g. of 4-chloro-4-n-propylheptane, b.p. 83–88°/18 mm., n_D^{25} 1.4360; (c) 1.1 g. of b.p. 108–110°/18 mm., n_D^{25} 1.4342. The final fraction probably consists of an impure sample of the coupling product 4,4-di-n-propyloctane (literature[30] b.p. 104–105°/18 mm., n_D^{15} 1.4358).

Although the observed index of refraction of 4-n-propyl-3-heptene is in disagreement with the literature value it agrees with the value observed by us for the alkene obtained as a by-product in preparation of 4-chloro-4-n-propyl heptane; also, it is consistent with the value, n_D^{20} 1.4303, which has been reported[31] for 3-ethyl-2-octene. In addition, this alkene gave an infrared spectrum containing only bands characteristic of alkenes; and on quantitative catalytic hydrogenation, absorption of hydrogen was equal to 105% of theory for one double bond.

Ethyl 2,2,4-trimethyl-3-oxopentanoate. A Grignard reagent was prepared in the usual manner under nitrogen from 3.9 g. (0.16 mole) of magnesium turnings and 20 g. (0.15 mole) of distilled n-butyl bromide (b.p. 99–100°, n_D^{25} 1.4376). This reagent was converted to the cadmium reagent by heating under reflux with stirring with 13.7 g. (0.075 mole) of anhydrous cadmium chloride. After a negative Gilman test for Grignard reagent had been obtained, ether was distilled from the mixture until distillation became slow, then 100 ml. of benzene was added.

After the slurry containing the cadmium reagent had been cooled to room temperature, there was added drop-wise with vigorous stirring a benzene solution of 17.9 g. (0.1 mole) of ethyl α-bromoisobutyrate (n_D^{25} 1.4438). A mildly exothermic reaction occurred during the addition. The mixture was finally heated under reflux with stirring for 1 hr. and then decomposed by addition of ice and 6N sulfuric acid. The product was extracted with benzene, the extracts were washed with water, solvent was removed by flash distillation, and the residue was distilled at reduced pressure. Except for a small fore-run, the only product was keto ester, 6.7 g. (72%), b.p. 89–90°/17 mm., n_D^{25} 1.4216. The infrared spectrum shows two bands in the carbonyl region, a strong band at 5.85 μ and a weaker band at 5.70 μ. Although this keto ester has previously been reported,[10] b.p. 93–94°/15 mm., it was characterized by analysis, conversion to a solid derivative, and cleavage to diisopropyl ketone.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.52; H, 9.68. Found: C, 65.01; H, 9.73.

The *pyrazolone*, 1-(2,4-dinitrophenyl)-3-isopropyl-4,4-dimethyl-5-pyrazolone, was prepared by the procedure of von Auwers,[32] except that 2,4-dinitrophenylhydrazine was used in place of phenylhydrazine. Crystallized from ethanol until the melting point became constant, the pyrazolone had m.p. 169.5–170°.

Anal. Calcd. for $C_{14}H_{16}N_4O_5$: C, 52.50; H, 5.00; N, 17.50. Found: C, 52.56; H, 4.87; N (Dumas), 17.41.

Basic cleavage of the keto ester was accomplished by heating 5.0 g. under reflux overnight with a solution of 4.5 g. of potassium hydroxide dissolved in 100 ml. of absolute ethanol. Work-up of the reaction mixture for neutral material yielded 2 g. of a volatile oil (infrared band at 5.85 μ) which was converted[33] to the 2,4-dinitrophenylhydrazone. After recrystallization from ethanol, this had m.p. 96.5–97° (literature[34]

(21) K. von Auwers and F. Eisenlohr, *Z. Physik. Chem.*, **83**, 429 (1913).

(22) A. I. Vogel, *J. Chem. Soc.*, **1943**, 636.

(23) J. Braun, H. Deutsch, and A. Schmatloch, *Ber.*, **45**, 1246 (1912).

(24) H. Waterman, P. van't Spijker, and H. A. van Westen, *Rec. trav. chim.*, **48**, 1103 (1929).

(25) T. E. Thorpe and L. M. Jones, *J. Chem. Soc.*, **63**, 273 (1893).

(26) A. H. Blatt and J. F. Stone, *J. Am. Chem. Soc.*, **54**, 1495 (1932).

(27) J. F. Norris and A. W. Olmsted, *Org. Syntheses*, Coll. Vol. 1, 144 (1941).

(28) M. O. Halse, *J. prakt. Chem.*, [2] **89**, 456 (1914).

(29) J. M. Church, F. C. Whitmore, and R. V. McGrew, *J. Am. Chem. Soc.*, **56**, 176 (1934).

(30) A. D. Petrov and E. A Chernyshev, *Doklady Akad. Nauk. S.S.S.R.*, **86**, 957 (1952); *Chem. Abstr.*, **47**, 10453 (1953).

(31) F. C. Whitmore and F. E. Williams, *J. Am. Chem. Soc.*, **55**, 406(1933).

(32) K. von Auwers and F. Dersch, *Ann.*, **462**, 115 (1928).

(33) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, 3rd ed., John Wiley and Sons, New York, 1948, p. 171.

(34) Ref. 33, p. 262.

for the 2,4-dinitrophenylhydrazone of diisopropyl ketone, m.p. 95°).

Anal. Calcd. for $C_{13}H_{18}N_4O_4$: C, 53.06; H, 6.12. Found: C, 53.28; H, 6.20.

For *identification of the bromide resulting from enolate formation*, a Grignard reagent was prepared from 12.3 g. (0.5 mole) of magnesium turnings and 75 g. (0.3 mole) of distilled *n*-dodecyl bromide (b.p. 126–128°/4.7 mm., n_D^{25} 1.4557). The solution of Grignard reagent was separated from excess magnesium by transferal under nitrogen pressure to another flask, then it was converted to the cadmium reagent and used for preparation of β-keto ester in the manner described above. Distillation of the product at 5.5 mm. pressure yielded: (*a*) 24.9 g. of a mixture of dodecane and β-keto ester, b.p. 66–75°; (*b*) 1.3 g. of intermediate fraction; (*c*) 30.9 g. of *n*-dodecyl bromide, b.p. 120–125°, n_D^{25} 1.4515–1.4555. The major portion (24.3 g.) of fraction (*c*), which was collected at 123–125°, n_D^{25} 1.4555, exhibited an infrared spectrum and index of refraction identical with those of an authentic sample of *n*-dodecyl bromide. The residue from the distillation, 7.7 g., yielded on crystallization from ethanol the coupling product, tetracosane, m.p. 47–48° (literature[35] m.p. 51°).

Preparation of β-hydroxy esters. Specific directions are given for the preparation of ethyl 2,3-dimethyl-3-hydroxynonanoate according to both the cadmium and Reformatsky condensations. For similar preparations of the other β-hydroxy esters, only pertinent results are reported. In summary, it may be noted that a large excess of cadmium reagent over ketone and α-bromo ester is of no advantage, while an excess of cadmium reagent and α-bromo ester over ketone results in a lower yield based on ketone. In the Reformatsky reaction, excess of α-bromo ester and zinc over ketone appears to be of little or no advantage, even with hindered ketones. This is in contrast to the previously published[13] procedure.

Ethyl 2,3-dimethyl-3-hydroxynonanoate. A. Cadmium condensation. The Grignard reagent was prepared in an atmosphere of nitrogen in the usual manner from 13.3 g. (0.55 mole) of magnesium turnings and 61.5 g. (0.50 mole) of *n*-propyl bromide (n_D^{25} 1.4326). For formation of the cadmium reagent, this reaction mixture was heated under reflux with 55.0 g. (0.30 mole) of finely ground anhydrous cadmium chloride until a negative Gilman test for Grignard reagent was obtained.

The reaction mixture was cooled to room temperature, then there was added with vigorous stirring during 1.5 hr. a solution in 30 ml. of benzene of 43.4 g. (0.35 mole) of 2-octanone (b.p. 172–173°, n_D^{25} 1.4136) and 63.3 g. (0.35 mole) of ethyl α-bromopropionate. After addition had been completed, the reaction mixture was stirred under reflux for an additional 2 hr. The reaction mixture was decomposed with ice and sulfuric acid, then worked up in the usual manner. Distillation of the product yielded, after a small fore-run, 60.4 g. (74%) of β-hydroxy ester, b.p. 120–122°/5.5 mm., n_D^{25} 1.4374. The infrared spectrum showed hydroxyl absorption at 2.85 μ and the doublet carbonyl band at 5.80 μ and 5.85 μ. A center cut, b.p. 122°/5.5 mm., was used for analysis.[36]

Anal. Calcd. for $C_{13}H_{26}O_3$: C, 67.82; H, 11.30. Found: C, 67.73; H, 11.01.

In a run carried out similarly except that the cadmium reagent was made from 0.75 mole of *n*-propyl bromide, the yield was the same. In a third run carried out as the first run, except that the quantity of ketone was reduced to 0.12 mole, the yield based on ketone was only 55%.

B. Reformatsky condensation. The Reformatsky reaction

was carried out essentially as has been described in *Organic Syntheses*,[13] using benzene as solvent, except that 0.20 mole of each reactant was used (zinc, ethyl α-bromopropionate, and 2-octanone). Distillation of the product yielded 36.2 g. (79%) of the β-hydroxy ester, b.p. 127–131°/7.0 mm., n_D^{25} 1.4377.

In a similar run in benzene, except that a threefold excess of zinc and α-bromo ester was used, the yield was essentially the same, 82%, of product with n_D^{25} 1.4373. In another similar run using an equimolar ratio of reactants, but with a solvent consisting of 150 ml. of benzene and 150 ml. of ether, the yield was again similar, 76%, of product with n_D^{25} 1.4378.

Dehydration of ethyl 2,3-dimethyl-3-hydroxynonanoate. A 9.4-g. sample of the hydroxy ester was mixed with a few crystals of iodine and heated at 150° for 3 hr. Distillation of the product at 3.7 mm. yielded 0.5 g. of fore-run followed by 2.6 g. of a fraction consisting largely of the unsaturated ester, b.p. 92–100°, n_D^{25} 1.4380–1.4400; and finally there was collected 2.5 g. of a fraction consisting largely of recovered hydroxy ester, b.p. 100–113°, n_D^{25} 1.4390. The infrared spectrum of the unsaturated ester fraction showed a very weak hydroxyl band at 2.85 μ and a single carbonyl band at 5.75 μ. The ultraviolet spectrum of this fraction (Fig. 1) showed presence of only a trace of α,β-unsaturated ester, which has a maximum near 220 mμ. Quantitative hydrogenation of this fraction gave absorption of hydrogen equivalent to 98% of the theoretical amount for one double bond.

Ethyl 2,2,3-trimethyl-3-hydroxynonanoate. A. Cadmium condensation. The cadmium reagent was prepared from 48.0 g. (0.39 mole) of *n*-propyl bromide and allowed to react in benzene-ether solution with 24.8 g. (0.20 mole) of 2-octanone and 53.6 g. (0.26 mole) of ethyl α-bromoisobutyrate (n_D^{25} 1.4430). Distillation of the product yielded a fore-run of 6.1 g., which consisted chiefly of ethyl 2,2,4-trimethyl-3-oxopentanoate, and 40.5 g. (83%) of β-hydroxy ester, b.p. 112–116°/3.3 mm., n_D^{25} 1.4404. The infrared spectrum showed characteristic bands for hydroxyl at 2.79 μ and for carbonyl a doublet at 5.80 μ and 5.85 μ. For analysis, there was used a center cut of b.p. 115°/3.3 mm.

Anal. Calcd. for $C_{14}H_{28}O_3$: C, 68.85; H, 11.47. Found: C, 68.83; H, 11.58.

B. Reformatsky condensation. In benzene solution, condensation was carried out with 0.30 mole of zinc, 0.10 mole of 2-octanone and 0.30 mole of ethyl α-bromoisobutyrate. Distillation of the product yielded 19.1 g. (78.4%) of the β-hydroxy ester, b.p. 118–121°/4.1 mm., n_D^{25} 1.4406.

Ethyl 2,5-dimethyl-3-isobutyl-3-hydroxyhexanoate. A. Cadmium condensation. The cadmium reagent was prepared from 0.43 mole of *n*-propyl bromide and allowed to react with 0.10 mole of distilled diisobutyl ketone (b.p. 166–168°, n_D^{25} 1.4102) and 0.30 mole of ethyl α-bromopropionate. On distillation, there was a fore-run of 16.2 g. which contained β-keto ester, and 12.6 g. (52%) of β-hydroxy ester which was collected in two fractions: (*a*) 1.0 g., b.p. 104–106°/4.5 mm., n_D^{25} 1.4376; (*b*) 11.6 g., b.p. 106–108°/4.5 mm., n_D^{25} 1.4368. The infrared spectrum showed a hydroxyl band at 2.75 μ and a carbonyl band at 5.80 μ, with a shoulder at 5.75 μ.

Anal. Calcd. for $C_{14}H_{28}O_3$: C, 68.85; H, 11.47. Found: C, 68.81; H, 11.61.

In a similar run in which the cadmium reagent from 0.29 mole of *n*-propyl bromide was allowed to react with 0.20 mole each of ketone and α-bromo ester, the yield of β-hydroxy ester was 20.3 g. (41.3%), b.p. 103–105°/3.5 mm., n_D^{25} 1.4377.

B. Reformatsky condensation. In a run carried out in benzene in which there were used 0.20 mole each of zinc, bromo ester, and ketone, the yield of β-hydroxy ester was 12.0 g. (24.6%), b.p. 109–113°/4.5 mm., n_D^{25} 1.4383. In a second run in which there was used a threefold excess of zinc and α-bromo ester, the yield of β-hydroxy ester was 12.8 g. (26%), b.p. 106–109°/4.5 mm., n_D^{25} 1.4379. In both these

(35) F. Kraft, *Ber.*, **15**, 1718 (1882).

(36) In combustion analysis of the β-hydroxy esters and unsaturated esters obtained in this investigation, there was persistent difficulty with low values for carbon. Use of a high furnace temperature and slow burning usually gave results near theory.

runs, substantial amounts of unreacted ketone were recovered.

In a run carried out in benzene-ether solvent, using 0.20 mole each of zinc, α-bromo ester, and ketone, the yield of β-hydroxy ester was 33.5 g. (68.5%), b.p. 105–107°/4.5 mm., n_D^{25} 1.4377.

When the Reformatsky reaction was carried out in purified tetrahydrofuran as solvent the zinc reacted completely, but 74% of starting ketone was recovered, and there could be isolated neither β-hydroxy ester nor unsaturated ester. Similarly, in a mixture of anisole and benzene, the zinc reacted readily; however, neither β-hydroxy ester nor unsaturated ester could be isolated from the reaction. None of the products of either of these reactions were identified.

Ethyl 2,5-dimethyl-3-isobutyl-3-hexenoate. In one run of the Reformatsky reaction with 0.20 mole each of zinc, ethyl α-bromopropionate, and diisobutyl ketone, essentially complete dehydration of the β-hydroxy ester occurred during work-up. This was unexpected since considerable difficulty was usually experienced in deliberate attempts at dehydration of these β-hydroxy esters. Presumably, this behavior should be ascribed to presence of an unidentified impurity acting as catalyst. Distillation of the product yielded, after a small fore-run, 28.9 g. (64%) of unsaturated ester, b.p. 87–91°/4.7 mm., n_D^{25} 1.4351. The infrared spectrum showed no hydroxyl band and a single carbonyl band at 5.75 μ. The ultraviolet spectrum (cf. Fig. 1) showed absence of α,β-unsaturated ester. A center cut was used for analysis.

Anal. Calcd. for $C_{14}H_{26}O_2$: C, 74.33; H, 11.50. Found: C, 74.27; H, 11.59.

The ester was saponified by heating under reflux overnight a solution of 10 g. of the ester and 4 g. of sodium hydroxide in a mixture of 100 ml. of ethanol and 100 ml. of water. Work-up of the reaction mixture and distillation yielded 6 g. (70%) of *2,5-dimethyl-3-isobutyl-3-hexenoic acid,* b.p. 127–128°/4.2 mm., n_D^{25} 1.4471. A center cut, having the same index of refraction as the main fraction, was used for analysis.

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.73; H, 11.11; Equiv. wt., 198. Found: C, 72.80; H, 10.90; Equiv. wt., 195.

Ethyl 2-methyl-3-n-propyl-3-hydroxyhexanoate. The Reformatsky reaction was carried out in benzene solution with 0.20 mole each of zinc, ethyl α-bromopropionate, and distilled 4-heptanone (b.p. 142–143°, n_D^{25} 1.4040). Distillation yielded, after a small fore-run, 28.6 g. (66.4%) of β-hydroxy ester, b.p. 116–118°/16 mm., n_D^{25} 1.4348.

A similar run in benzene-ether solvent yielded 34.8 g. (80.5%) of β-hydroxy ester, b.p. 107–110°/6.0 mm., n_D^{25} 1.4340–1.4342. The infrared spectrum showed the hydroxyl band at 2.75 μ and the carbonyl band at 5.80 μ, with a shoulder at 5.70 μ. For analysis, there was used a center cut with n_D^{25} 1.4342.

Anal. Calcd. for $C_{12}H_{24}O_3$: C, 66.66; H, 11.11. Found: C, 66.80; H, 10.96.

Ethyl 2-methyl-3-hydroxynonanoate. In the Reformatsky reaction in benzene, using 0.20 mole each of zinc, ethyl α-bromopropionate, and distilled n-heptaldehyde (b.p. 149–

150°), there was obtained 27.5 g. (64%) of β-hydroxy ester, b.p. 138–140°/14 mm., n_D^{25} 1.4360.

In a similar run in benzene-ether, the yield of β-hydroxy ester was 31.3 g. (73%), b.p. 122–125°/5.0 mm., n_D^{25} 1.4363 (literature[37] b.p. 124–128°/6 mm.). The infrared spectrum showed the hydroxyl band at 2.75 μ and a broad carbonyl band at 5.75 μ.

Reformatsky reaction between 2-heptadecanone and ethyl α-bromopropionate. A reaction carried out in benzene-ether solution utilized 0.03 mole of zinc, 0.03 mole of ethyl α-bromopropionate, and 0.016 mole of 2-heptadecanone (m.p. 45–46°). Distillation of the product yielded: (a) 1.09 g. of fore-run; (b) 1.38 g., b.p. 185–195°/2.0 mm., n_D^{25} 1.4491; (c) 1.53 g., b.p. 195–197°/2.0 mm., n_D^{25} 1.4491. The ultraviolet spectrum (cf. Fig. 1) shows that Fraction (b) consists largely of β,γ-unsaturated ester containing no more than traces of the α,β-unsaturated ester, while Fraction (c) contains a low percentage of unsaturated ester. The infrared spectrum of (b) shows a very weak hydroxyl band at 2.75 μ, while (c) shows a strong hydroxyl band at 2.75 μ; thus, (c) consists largely of the β-hydroxy ester. The infrared spectra of both Fractions (b) and (c) show a doublet carbonyl band at 5.75 μ and 5.80 μ; however, in (b) the band at 5.80 μ is barely detectable on the shoulder of the 5.75 μ band, whereas in (c) it is stronger than the band at 5.75 μ. This is consistent with the view that doubling of the carbonyl band in the β-hydroxy esters should be ascribed to chelation of the carbonyl with β-hydroxyl. The principal contributor to the carbonyl band in (b) is the carbonyl in the unsaturated ester.

The total yield of unsaturated ester and hydroxy ester is 2.9 g. (52%).

Ethyl 2-methyl-3-oxodecanoate. A Blaise reaction was carried out as has been previously described[17] except that the copper catalyst was not used and the solvent was a 1:1 mixture of benzene and ether. Reactants were 9.7 g. (0.15 mole) of zinc, 27.2 g. (0.15 mole) of ethyl α-bromopropionate, and 12.5 g. (0.10 mole) of distilled octanenitrile (b.p. 93–95°/17 mm.). Distillation of the product at 13 mm. yielded 6.2 g. of fore-run, b.p. 72–105°, n_D^{25} 1.4184; 0.8 g. of intermediate fraction; and 13.0 g. (57%) of β-keto ester, b.p. 143–145°, n_D^{25} 1.4339–1.4344. The infrared spectrum showed carbonyl bands at 5.70 μ and 5.80 μ.

Anal. Calcd. for $C_{13}H_{24}O_3$: C, 68.42; H, 10.53. Found: C, 68.49; H, 10.10.

In a second run using the same conditions as described above, the yield was 53% of β-keto ester with n_D^{25} 1.4338.

In a run using the same conditions except that only benzene was used as solvent, the yield was 44% of β-keto ester of b.p. 145–149°/12 mm., n_D^{25} 1.4341. This yield is slightly higher than that previously reported[17] for a similar preparation when a copper catalyst was employed and benzene alone was used as solvent.

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(37) S. Obata, *J. Pharm. Soc. Japan,* **73,** 1295 (1953); *Chem. Abstr.,* **49,** 175 (1955).