[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, DUKE UNIVERSITY]

# Claisen Acylations and Carbethoxylations of Ketones and Esters by Means of Sodium Hydride[1]

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Claisen acylations and carbethoxylations of ketones and esters to form β-diketones, β-keto esters and substituted malonic esters have generally been effected by means of sodium alkoxides, sodium or sodium amide.[2] Except in acylations with especially reactive esters like ethyl oxalate or ethyl formate, the usefulness of sodium alkoxides is limited since these reagents are often not sufficiently strong bases to produce satisfactory yields. Sodium amide is a much stronger base, but it frequently attacks the carbonyl group of esters to form amides.[3] The applicability of sodium in the self-condensation of esters is correspondingly limited by the tendency for bimolecular reduction with the formation of acyloins. Hansley[4] has shown that sodium hydride, which is available commercially, produces better yields than these other common reagents in certain acylations of ketones and especially self condensations of esters. We[5] have shown that sodium hydride effects the self-condensation of ethyl isovalerate which is not condensed by sodium ethoxide even under forcing conditions. In contrast to sodium amide, sodium hydride apparently does not attack the carbonyl group of esters under the conditions of these reactions.[5] Since sodium hydride appears to be about as effective as sodium amide and yet often produces fewer side-reaction products, a more thorough study of this reagent seemed desirable.

In the present investigation the use of sodium hydride in Claisen acylations and carbethoxylations of ketones and esters has been developed and evaluated. As with other basic reagents,[6] Claisen condensations with sodium hydride may be considered to involve the following three steps, in which the component to be acylated or carbethoxylated, $RCH_2COY$, is a ketone or an ester, and the acylating or carbethoxylating component, $R'COOR''$, an ordinary ester or ethyl carbonate.

$$RCH_2COY + NaH \longrightarrow Na(RCHCOY) + H_2 \quad (1)$$

$$R'COOR'' + Na(RCHCOY) \longrightarrow R'COCHRCOY + NaOR'' \quad (2)$$

$$R'COCHRCOY + NaH \longrightarrow Na(R'COCRCOY) + H_2 \quad (3)$$

Although only one molecular equivalent of sodium hydride is required to convert the component to be acylated to its sodio-derivative (step 1), a second equivalent of sodium hydride is neutralized in converting the product to its sodio-derivative (step 3). Of course, the sodium alkoxide formed as a by-product in step 2 should also be capable of effecting certain of these condensations but, under the conditions usually employed, this base does not appear to exert much effect. Thus the most efficient use of all the reactants appears to require two equivalents of sodium hydride to one each of the component to be acylated and the acylating ester. However, in order to obtain maximum yields based on the component to be acylated, we have usually employed an extra equivalent of the acylating ester (Method A).[7] In the acylation of ketones it has sometimes been advantageous to employ an extra equivalent of the ketone (Method B). The proportions of reactants corresponding to Method A have been employed in all cases of carbethoxylations of ketones and esters and for mixed ester condensations. These two different proportions of reactants have previously been employed advantageously in the acylations of ketones with esters by means of sodium amide.[8]

The procedure of first converting the ketone or ester to be acylated to its sodio-derivative (step 1) and then adding the acylating ester, employed previously with sodium amide,[8] has generally not been satisfactory with sodium hydride since, under the conditions required to effect step 1, considerable self-condensation of the ketone or ester usually takes place.[5] The general method adopted in this investigation for "mixed" condensations by sodium hydride consists in slowly adding the component to be acylated to a stirred suspension of sodium hydride in the acylating ester, usually in the presence of an inert solvent. Generally the suspension of sodium hydride in the acylating ester was heated to the temperature required to ionize the component to be acylated (step 1). The condensation (step 2) thus proceeds continually as the component to be acylated is converted to its sodio-derivative. The progress of the reaction was conveniently followed by means of a wet test meter which measured the evolved hydrogen. Since sodium hydride is practically

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(1) Paper XLV on Condensations. This work was carried out under contract N7-onr-455 with the Office of Naval Research.

(2) Sodium triphenylmethide and potassium triphenylmethide are generally applicable but they are somewhat less convenient to use; see Abramovitch and Hauser, THIS JOURNAL, **64**, 2271 (1942); Levine, Baumgarten and Hauser, *ibid.*, **66**, 1230 (1944).

(3) See Levine, Kibler and Hauser, *ibid.*, **68**, 26 (1946).

(4) (a) Hansley, U. S. Patent 2,158,071, May 16, 1939; (b) Hansley, U. S. Patent 2,218,026, Oct. 15, 1940; (c) Hansley and Carlisle, *Chem. Eng. News*, **23**, 1332 (1945).

(5) Swamer and Hauser, THIS JOURNAL, **68**, 2647 (1946).

(6) See especially Hauser and Hudson, "Organic Reactions," Vol. I, Ed., Roger Adams, John Wiley and Sons, Inc., New York, N. Y., 1942; Chapter 9, p. 266.

(7) The extra equivalent of the acylating ester appears to increase the yield by about 10% and to minimize self-condensation of the acylated component.

(8) (a) Adams and Hauser, THIS JOURNAL, **66**, 1220 (1944) (b) Levine, Conroy, Adams and Hauser, *ibid.*, **67**, 1510 (1945).

insoluble in organic solvents, it is sometimes desirable to reduce the particle size in order to bring about reaction at a reasonable rate. This has been accomplished, in the case of sluggish reactions, by means of a ball mill. Certain of the acylations of ketones and esters and all of the

TABLE I

ACYLATIONS OF KETONES WITH ESTERS USING SODIUM HYDRIDE

| Ester | Ketone | Method | Time reqd., hr. | Product | B. p., °C. | Mm. | Yield, % |
|---|---|---|---|---|---|---|---|
| Ethyl laurate | Acetone | B | 3[a] | Lauroylacetone[b] | 148–150[c] | 3 | 83 |
| Methyl benzoate | Acetone | B | 3[a] | Benzoylacetone | 60–61 (m. p.) | .. | 66[d] |
| Ethyl *n*-caproate | Acetone | A | 5[e] | Caproylacetone | 101–103[f] | 19 | 80 |
| Ethyl *n*-caproate | Acetone | B | 3 | Caproylacetone | 101–103 | 19 | 65 |
| Ethyl isobutyrate | Acetone | B | 3 | Isobutyrylacetone[b] | 63–64 | 19 | 41 |
| Ethyl propionate | Methyl ethyl | A | 5 | Dipropionylmethane | 78–80 | 30 | 51[g] |
| | | | | Methylpropionylacetone | 90–100 | 30 | 9[h] |
| Methyl benzoate | Methyl *n*-propyl | A | 5[e] | Benzoyl-*n*-butyrylmethane[b] | 168–171 | 20 | 31[g] |
| Methyl benzoate | Methyl *n*-propyl | A[j] | 1 | Benzoyl-*n*-butyrylmethane | 167–170 | 20 | 61 |
| Ethyl acetate | Diethyl | A | 8 | Methylpropionylacetone[b] | 181–184 | Atm. | 60 |
| Ethyl propionate | Methyl isobutyl | A | 6[e] | Propionyl-isovalerylmethane | 91–93 | 19 | 75 |
| Ethyl propionate | Methyl isobutyl | A[k] | 6[e] | Propionyl-isovalerylmethane | 89–91 | 17 | 68 |
| Ethyl isovalerate | Methyl isobutyl | A | 4[e] | Diisovalerylmethane[b] | 113–115 | 20 | 45[g,p] |
| Ethyl acetate | Pinacolone | A | 10[n] | Pivaloylacetone[m] | 70–71 | 20 | 32[g,l] |
| Ethyl *n*-valerate | Pinacolone | A | 11[e] | *n*-Valeryl-pivaloylmethane[m] | 114–118 | 20 | 22 |
| Ethyl propionate | Cyclohexanone | A | 4 | α-Propionylcyclohexanone[b] | 124–125 | 20 | 29 |

[a] Stood an additional four hours at room temperature. [b] See ref. 8b. [c] M. p. 31–32° after recrystallization from ethanol. [d] Isolated by distillation through a von Braun system followed by recrystallization from dilute ethanol. [e] Stood overnight at room temperature. [f] Green and LaForge (ref. 14c) give b. p. 94–98° (11 mm.). [g] Isolated by the copper salt method; see ref. 8a. [h] Obtained from the filtrate and washings from the preparation of the copper salt of dipropionylmethane; see ref. 8a. [j] Reaction carried out in laboratory ball mill. [k] 1 ester:1 ketone:2 sodium hydride. [l] The same yield was obtained when the reaction was carried out in the ball mill, but the reaction required only two hours. [m] See ref. 8a. [n] With a sample of very finely powdered sodium hydride, which was kindly sent to us by the Ethyl Corporation Research Laboratories, Detroit, Michigan, this reaction was effected in the same yield in four hours. [p] When the reaction was carried out in the ball mill, the yield of β-diketone was 22%. The reaction gave also an unidentified by-product which distilled along with the β-diketone.

TABLE II

MIXED ESTER CONDENSATIONS USING SODIUM HYDRIDE[j]

| Acylating ester | Ester acylated | Temp., °C. | Time reqd., hr. | Product | B. p., °C. | Mm. | Yield, % |
|---|---|---|---|---|---|---|---|
| Me benzoate | Me *n*-butyrate | 110 | 6 | Me α-benzoyl *n*-butyrate[a] | 132–134[b] | 4 | 65 |
| Et nicotinate | Et *n*-butyrate | 110 | 4 | Et α-nicotinyl *n*-butyrate[c] | 138–140 | 2.5 | 68 |
| Et benzoate | Et laurate | 120 | 7 | Et α-benzoyl laurate[d] | ..... | | 68[e] |
| Et benzoate | Et isovalerate | 110 | 14 | Et α-benzoyl isovalerate[f] | 130–132 | 3 | 34 |
| Et benzoate | Et isovalerate | 110 | 3.5[g] | Et α-benzoyl isovalerate | 130–131 | 2.5 | 56 |
| Et oxalate | Et isovalerate | 70–80 | 2 | Et α-oxalyl isovalerate[h] | 134–135 | 15 | 36 |
| Et nicotinate | Et isovalerate | 125 | 10 | Et α-nicotinyl isovalerate[i] | 138–140 | 3 | 34 |
| Et nicotinate | Et isovalerate | 110 | 5[g] | Et α-nicotinyl isovalerate | 137–140 | 3 | 24 |

[a] Hydrolyzed to butyrophenone (b. p. 128–130° (30 mm.)) in 95% yield; see ref. 11. [b] Royals, THIS JOURNAL, **70**, 489 (1948), gives b. p. 115–120° (1 mm.). [c] *Anal.* Calcd. for $C_{12}H_{15}O_3N$: C, 65.12; H, 6.84; N, 6.33. Found: C, 64.86; H, 6.88; N, 6.45. [d] The β-keto ester distilled with considerable decomposition and could not be induced to crystallize. It was hydrolyzed to the known ketone, laurophenone, m. p. 45°; see ref. 11. [e] Yield of crude β-keto ester. [f] *Anal.* Calcd. for $C_{14}H_{18}O_3$: C, 71.75; H, 7.75. Found: C, 71.48; H, 7.44. [g] Reaction carried out in laboratory ball mill. [h] *Anal.* Calcd. for $C_{11}H_{18}O_5$: C, 57.36; H, 7.88. Found: C, 57.11; H, 7.82. [i] *Anal.* Calcd. for $C_{13}H_{17}O_3N$: C, 66.34; H, 7.29; N, 5.95. Found: C, 65.95; H, 7.25; N, 6.00. [j] Analyses by Clark Microanalytical Laboratories, Urbana, Ill.

TABLE III

CARBETHOXYLATIONS OF ESTERS AND KETONES WITH ETHYL CARBONATE USING SODIUM HYDRIDE

| Ester or ketone | Reaction temp., °C. | Product | B. p., °C. | Mm. | Yield, % |
|---|---|---|---|---|---|
| Acetophenone | 30–35 | Et benzoylacetate[a] | 150–152 | 12 | 81 |
| Cyclohexanone | 28–33 | 2-Carbethoxycyclohexanone[a] | 104–108 | 10.5 | 37 |
| Pinacolone | 48–53 | Et γ,γ,γ-trimethylacetyl acetate[a] | 96–100 | 15 | 45 |
| Et *n*-butyrate | 100 | Diethyl ethylmalonate[b] | 93–96 | 10 | 48 |
| Et isovalerate | 90 | Diethyl isopropylmalonate[c] | 103–107 | 15 | 29 |

[a] Levine and Hauser, THIS JOURNAL, **66**, 1769 (1944). [b] Eijkman, *Chem. Zentr.*, **78**, II, 1210 (1907). Wallingford and co-workers (see ref. 17) give b. p. 94–96° (13 mm.). [c] Perkin, *J. Chem. Soc.*, **45**, 515 (1884), gives b. p. 216–217°, 188–188.5° (330 mm.); Wallingford and co-workers (see ref. 17) give b. p. 106–109° (18 mm.).

carbethoxylations have been effected in the ball mill. The results are summarized in Tables I, II and III.

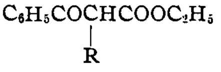
Hansley[4] has shown that sodium hydride produces good yields of β-diketones in the acylation of tetralone with ethyl acetate and in the acylation of acetone with various aliphatic esters. We have shown previously[5] that sodium hydride produces a fairly good yield in the benzoylation of cyclohexanone with methyl benzoate. We have now obtained fair to good yields in various acylations of both methyl and methylene ketones with aliphatic and aromatic esters (Table I). In previous acylations of acetone by means of sodium hydride it has been customary to employ from one to twenty equivalents of ester in excess of that required. Although a good deal of the excess ester may be recovered in such cases, we prefer our Method B, in which a one-equivalent excess of acetone is employed, except of course when the yield is considerably lower. Actually we have obtained a better yield of lauroylacetone by this method than was previously obtained[4a] using excess ester although very high yields have been reported in other cases where excess ester was used in acylations of acetone. In the acylation of acetone with ethyl caproate we have obtained a somewhat higher yield (80%) by Method A than that (65%) by Method B (Table I) but the latter method may still be preferred in view of the relative availabilities of the ketone and ester.[9] The advantageous application of the laboratory ball mill in these ketone acylations is noted in the benzoylation of methyl *n*-propyl ketone with methyl benzoate. In this case the use of the ball mill allowed the reaction to be effected in one-fifth the time and gave a yield which was twice that obtained in the conventional glass apparatus. With methyl ethyl ketone and ethyl propionate, some of the methylene derivative (II) was obtained along with the larger yield of the methyl derivative (I); however, the latter compound was readily isolated in essentially pure condition by the copper salt procedure.[8a] With methyl *n*-propyl or methyl isobutyl ketone, apparently only the methyl derivative was formed. Similar results have been obtained in the acylation of these methyl-methylene ketones by means of sodium amide.[8]

$C_2H_5COCH_2COC_2H_5$ (I) $C_2H_5COCH(CH_3)COCH_3$ (II)

In general, sodium hydride produces considerably better yields in the acylations of ketones with esters than sodium ethoxide or sodium, and equally good yields as sodium amide which has been regarded as one of the best reagents for this purpose.[8] In certain acylations of methylene ketones, the yields have been highest with sodium hydride. Since sodium hydride usually produces few side-reaction products, the β-diketones can often be isolated directly by distillation or recrystallization of the crude material instead of by the copper salt procedure which is generally required in acylations by sodium amide.[10] In certain cases, however, the presence of high boiling residues (presumably aldol condensation products of the ketone) makes necessary the use of the copper salt procedure of isolation. In the acylation of methyl isobutyl ketone with ethyl isovalerate, sodium hydride has produced a considerable amount of an unidentified by-product (see Table I) which has not been observed with sodium amide.[8]

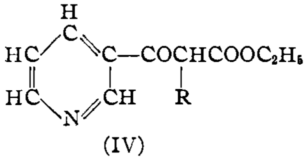
Hansley[4] has shown that sodium hydride produces good yields of the β-keto esters in the self-condensation of various straight chain aliphatic esters up to and including methyl stearate. Although many of these esters may be self-condensed by means of sodium alkoxides under forcing conditions the use of sodium hydride is probably preferable. Sodium hydride is definitely superior to sodium amide[11] or sodium for self-condensations of aliphatic methyl or ethyl esters.[12]

We have found that sodium hydride produces fair to good yields of mixed β-keto esters in the acylations of methyl or ethyl *n*-butyrate, ethyl laurate or ethyl isovalerate with methyl or ethyl benzoate, ethyl nicotinate or ethyl oxalate (Table II). Examples of the types of mixed β-keto esters formed are represented by III, IV and V. The use of the ball mill reactor in these ester acylations has been quite advantageous in several cases, generally resulting in higher yields of the products in less reaction time. Method A was employed in these condensations in order to minimize self-condensation of the acylated ester.

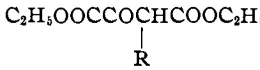


$C_6H_5CO\underset{R}{\underset{|}{C}}HCOOC_2H_5$

(III)



(IV)



$C_2H_5OOCCO\underset{R}{\underset{|}{C}}HCOOC_2H_5$

(V)

β-keto esters of types (III) and (IV) in which R is methyl or ethyl (from ethyl propionate and ethyl *n*-butyrate) have been obtained in only poor yields from mixed ester condensations employing sodium ethoxide, and the condensation

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(9) Green and LaForge (see ref. 14c) have reported a 54% yield of caproylacetone from approximately one molecular equivalent each of sodium hydride, acetone and ethyl caproate.

(10) In spite of this additional procedure, however, the sodium amide method for the acylation of ketones (ref. 8) might be considered somewhat more convenient, where liquid ammonia is available, than the sodium hydride method in which certain precautions are required (see Experimental).

(11) See Shivers, Dillon and Hauser, THIS JOURNAL, **69**, 119 (1947).

(12) It should be mentioned that diisopropylaminomagnesium bromide, which is readily prepared from ethylmagnesium bromide and diisopropylamine, has recently been found particularly suitable for self-condensations of esters: Frostick and Hauser, THIS JOURNAL, **71**, 1350 (1949).

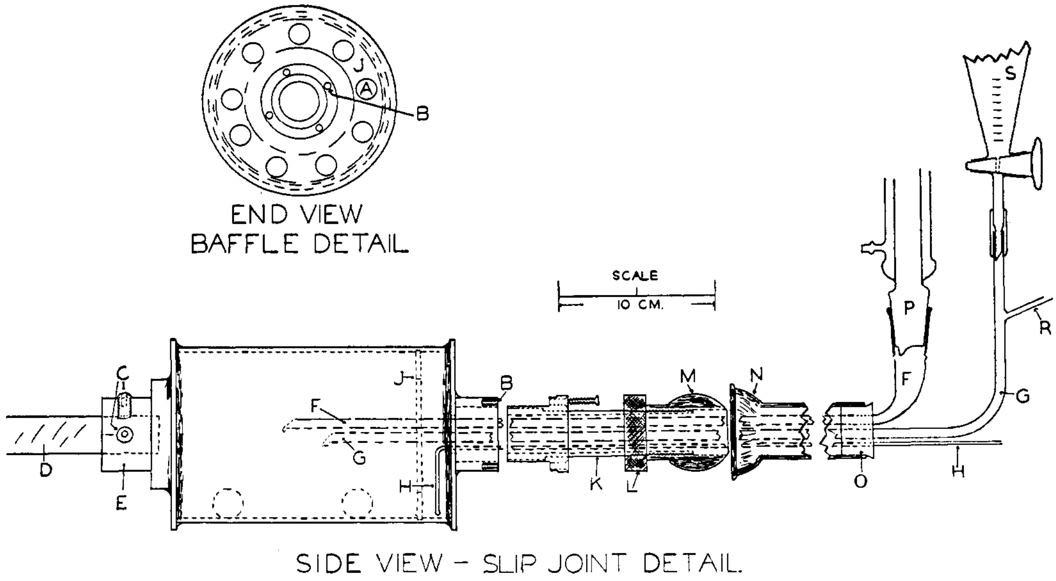

Fig. 1.—Laboratory ball mill: (A), baffle perforations; (B), threaded screw slots for attaching slip-joint to reactor; (C), $^3/_8$ inch set screw; (D), steel rotor shaft; (E), brass block; (F), gas outlet tube; (G), gas and liquid inlet tube; (H), copper thermowell; (J), baffle; (K), stainless steel pipe; (L), aluminum nut; (M), brass 50/30 spherical joint; (N), Pyrex 50/30 spherical joint; (O), rubber stopper; (P), reflux condenser; (R), gas inlet; (S), graduated dropping funnel.

would presumably fail completely with this reagent when R is isopropyl.[13]

During the progress of the present investigation several papers have been published on the carbethoxylations of ketones and esters[14] to form β-keto esters and substituted malonic esters. In order to evaluate the method we have carried out several additional reactions of these types (Table III).

In carbethoxylations of ketones, sodium hydride has generally produced higher yields than sodium ethoxide[15] or sodium and even somewhat better yields than sodium amide.[16] In carbethoxylations of esters, sodium hydride has given yields equal to those with sodium ethoxide.[17] The use of sodium hydride obviates the forcing procedures which are required in carbethoxylations of both ketones and esters by means of sodium ethoxide.

It should be mentioned that sodium hydride may be considered somewhat more hazardous to handle[4c] than sodium ethoxide but, with the simple precautions given in the experimental section, we have handled sodium hydride without incident on the laboratory scale.

## Experimental

Reactions with sodium hydride[18] were carried out either in a three-necked, one-liter, round-bottomed flask or in a stainless steel cylindrical ball mill (11.5-cm. diameter by 17-cm. length) of approximately 1.5 liters volume. The flask was equipped with an efficient stirrer, thermometer, dropping funnel, gas inlet tube and a reflux condenser to the outlet end of which was attached a tube leading through a Dry Ice-acetone-trap to a wet test meter. The ball mill which is a modification of the semi-conical ball mill employed by Hansley[19] in certain condensations is represented in Fig. 1. It is equipped with a perforated baffle which provides a free space in the reactor in which a thermocouple dips into the reaction mixture so that temperatures can be measured continually during a reaction. The outlet end of the condenser is provided with a tube passing to a wet test meter. The rotating reactor is equipped with a slip joint of the type described by Hansley[19] and is rotated at a speed of approximately thirty revolutions per minute by an electric motor operating through a speed reduction gear.

The apparatus was assembled and thoroughly purged with nitrogen. In general, the sodium hydride[20] was weighed out rapidly, charged to the reactor, and covered immediately with a small amount of dry solvent (or with one of the reactants in cases where no solvent was used). The system was then reassembled and reactions were carried out as described below.

In reactions in which the ball mill was used, the reaction mixture, after neutralization, was milled for twenty

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[13] Recently in this Laboratory certain isopropyl and *t*-butyl β-keto esters corresponding to III and IV have been prepared by means of sodium amide (see ref. 11). However, the sodium hydride method is probably to be preferred since the required aliphatic methyl and ethyl esters are more available.

[14] (a) Soloway and LaForge, THIS JOURNAL, **69**, 2677 (1947); (b) LaForge and Soloway, *ibid.*, **69**, 2932 (1947); (c) Green and LaForge, *ibid.*, **70**, 2287 (1948); (d) Jackburn, Klenk, Fishburn, Tullar and Archer, *ibid.*, **70**, 2884 (1948).

[15] Wallingford, Homeyer and Jones, *ibid.*, **63**, 2252 (1941).

[16] Levine and Hauser, *ibid.*, **66**, 1768 (1944).

[17] Wallingford, Homeyer and Jones, *ibid.*, **63**, 2056 (1941).

[18] We are indebted to the Electrochemicals Department, E. I. du Pont de Nemours and Co., Niagara Falls, N. Y., for samples of sodium hydride.

[19] Private communication from V. L. Hansley, Electrochemicals Department, E. I. du Pont de Nemours and Co., Niagara Falls, N. Y.

[20] Generally the same precautions are to be observed in handling sodium hydride as are observed with sodium (see ref. 4c). The operator should always be provided with eye protection. If the humidity is high, the sodium hydride should be handled in an atmosphere of nitrogen. Mixing with any volatile solvent or reactant should always be carried out under nitrogen.

minutes and then poured carefully into a metal pan. The balls and reactor were rinsed with a solvent and water, the rinsings being added to the reaction mixture which was then transferred to a separatory funnel. Before using again, the ball mill was steamed out, washed with acetone, and dried in an oven at 100°.

**Acylations of Ketones with Esters** (Table I).—To a stirred mixture of 9.6 g. (0.4 mole) of sodium hydride and the acylating ester (0.4 mole in Method A, 0.2 mole in Method B) was added the ketone (0.2 mole in Method A, 0.4 mole in Method B) in 50 ml. of dry ether during thirty to sixty minutes so as to maintain a convenient rate of reaction. In acylations of acetone the temperature of the reaction mixture was kept at 30–40° by occasional cooling in a Dry Ice–xylene-bath. In acylations of higher ketones the temperature was kept at 40–55° by gentle warming in an oil-bath. If the reaction did not start after the addition of a few ml. of the ketone solution, the addition was stopped and a little alcohol added. The reaction should definitely begin, as evidenced by the evolution of hydrogen, before much of the ketone, especially acetone, is added; otherwise the reaction may become too vigorous. After all the ketone had been added the mixture was stirred at 40–55° until at least 80% of the hydrogen had been evolved. About 150–200 ml. of dry ether was added during this time to maintain a fluid reaction mixture. The reaction mixture was cooled to room temperature and sufficient ether added to bring the total volume to about 400 ml. Most of the unreacted sodium hydride was destroyed by the addition of 20–30 ml. of ethanol and stirring for about twenty minutes. The mixture was then cooled to 10°, and while stirring and passing nitrogen through the reactor, a mixture of 300 g. of ice-water and a slight excess of concentrated hydrochloric acid or glacial acetic acid was added, keeping the temperature below 20° during the neutralization. Stirring was continued until all the solid had dissolved (or for twenty minutes in the ball mill). The ether phase was separated and the aqueous phase was extracted with an additional 100 ml. of ether. The combined ether extracts were washed with sodium bicarbonate solution, then with water and dried over Drierite. The solvent was removed and the residue was either fractionated through a 25-cm. Vigreux column or the diketone was isolated by the copper salt procedure described previously.[8a] In some cases it was found desirable to collect a fairly wide cut on the first fractionation and refractionate this material to obtain relatively pure β-diketone boiling over a range of 2–3°.

**Mixed Ester Condensations** (Table II).—To a stirred mixture of 9.6 g. (0.4 mole) of sodium hydride in 0.4 mole of the acylating ester, heated to 100° by means of an oil-bath, was added dropwise over a period of thirty to sixty minutes the ester to be acylated (0.2 mole) in 50 ml. of dibutyl ether. The reaction mixture was then stirred and heated at 100–110° until gas evolution stopped and for one hour thereafter. About 150–200 ml. of dibutyl ether was added gradually during this period to keep the reaction mixture fluid. After completion of the reaction, the mixture was cooled to about 10° and 100 ml. of ethyl ether added. With the exception of acylations with ethyl nicotinate, the reaction mixture was neutralized and worked up in the same manner as described for the acylations of ketones, the product being fractionated through a 20-cm. Vigreux column. In acylations with ethyl nicotinate, the procedure for working up the reaction product was modified as follows[11]: after cooling the reaction mixture to 10° and adding 100 ml. of ether, 200 g. of ice-water was run in slowly, keeping the temperature below 20°. Stirring was continued until all the solid was dissolved and all sodium hydride was destroyed. The reaction product was transferred to a separatory funnel and the aqueous phase containing the β-keto ester as its sodium derivative, was separated. While adding ice to the aqueous phase, concd. hydrochloric acid was added until the mixture was just acid. The solution was then saturated with sodium bicarbonate and the separated oil extracted with ether. The ether extract was dried over Drierite, the solvent removed and the residue fractionated through a 20-cm. Vigreux column.

**Carbethoxylations of Esters and Ketones** (Table III).—These reactions were all carried out in the laboratory ball mill. Carbethoxylations of ketones (with the exception of pinacolone) were effected at room temperature to 35° using ether as solvent. Pinacolone was carbethoxylated at 50–60° using dibutyl ether as solvent. The procedure was the same as that used for acylations of ketones. Carbethoxylations of esters were effected at 100–110° according to the procedure for mixed ester condensations.

## Summary

1. The use of sodium hydride in Claisen acylations and carbethoxylations of ketones and esters has been extended and the results compared with those obtained with sodium alkoxides, sodium and sodium amide.

2. In acylations and carbethoxylations of ketones, sodium hydride generally produces as good yields as sodium amide and usually better yields than sodium ethoxide or sodium.

3. In the self-condensation of methyl and ethyl esters and especially in certain mixed ester condensations, sodium hydride is superior to sodium ethoxide, sodium or sodium amide.

4. In the carbethoxylation of esters, sodium hydride produces as good yields as sodium ethoxide.

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