showed no absorption in the carbonyl region, but a sharp band at 2.83 μ. Chromatography of this material on 25 g. of alumina of activity 3 gave rather clean-cut separation of two components present in a ratio of about 1:1.3. The first component, *ethyltritylcarbinol*, which was present in the smaller amount, was eluted with hexane. After two crystallizations from hexane, the melting point was 92–93.6°, and there was a sharp absorption band at 2.83 μ.

Anal. Calcd. for $C_{22}H_{22}O$: C, 87.4; H, 7.3. Found: C, 87.0; H, 7.3.

The second component, *2,2,2-triphenylethanol* was eluted with 1:1 hexane-benzene. After two crystallizations from hexane, the melting point was 108.8–109.9°, and there was infrared absorption at 2.82 μ, but the spectrum differed substantially in other areas from that of ethyltritylcarbinol. Melting points reported for 2,2,2-triphenylethanol are 103–105°,[1] 104–105°,[14] 107°,[15] and 110.5°.[16]

Chromic acid oxidation of ethyltritylcarbinol. A solution of 32.4 mg. of the alcohol of m.p. 92–93.6°, and of 10.7 mg. of chromic anhydride, in 1 ml. of glacial acetic acid (distilled from permanganate) was allowed to stand at room temperature for about 14 hr. At the end of this period, clear needles had crystallized from the solution. After 10 ml. of water had been added to the reaction mixture the product was collected, washed with water, and dried: wt. 25 mg. (78%), m.p. 122.8–124°. The infrared spectrum of this product was identical with that of ethyl trityl ketone, m.p. 122.5–125° (*cf.* below).

Ethyl trityl ketone was prepared from diethylcadmium and triphenylacetyl chloride according to the procedure described for preparation of methyl trityl ketone. Yield data are recorded in Table I. The ketone, separated by chromatography on alumina of activity 3, was crystallized twice from ethanol to yield material of m.p. 122.5–125°.

Anal. Calcd. for $C_{22}H_{20}O$: C, 88.0; H, 6.7. Found: C, 87.9; H, 6.8.

The hydrocarbon mixture separated by chromatography on alumina was analyzed by gas chromatography and found to exhibit only the band for triphenylmethane and that assigned to triphenylpropane. At 257°, in a 1.6-m. column, under conditions giving retention times of 5.4 and 6.5 min. for triphenylmethane and -ethane respectively, the time for the band assigned to triphenylpropane was 7.8 min.

n-Butyl trityl ketone was prepared in a cadmium reaction carried out similarly to those described for its homologs. Separation of the ketone from the hydrocarbons by chromatography on alumina of activity 3 was somewhat less clean-cut than for the lower homologs, but was satisfactory. Chromatography of a reaction product weighing 765 mg. yielded an initial fraction of 397 mg. of a mixture of ketone and hydrocarbons. Succeeding fractions of ketone contained less than 1% hydrocarbons and weighed 362 mg. The mixture in the initial fraction was analyzed by gas chromatography and found to contain 92 mg. of triphenylmethane, 171 mg. of 1,1,1-triphenylpentane, and 132 mg. of butyl trityl ketone. In a 3-m. column, at 290° and with 21 cm. of helium pressure, retention times for the three compounds, in the order mentioned above, were 15.0, 28.5, and 43 min. For analysis, the ketone was crystallized from ethanol to yield material of m.p. 82.8–83.8°.

Anal. Calcd. for $C_{24}H_{24}O$: C, 87.8; H, 7.3. Found: C, 87.5; H, 7.3.

1,1,1-Triphenylpentane was separated by gas chromatography, in a 3 m. 15 mm. o.d. column, of the first fraction of material separated by chromatography on alumina. After crystallization from ethanol, there was obtained hydrocarbon of m.p. 60–61.2°.

Anal. Calcd. for $C_{23}H_{24}$: C, 92.0; H, 8.0. Found: C, 91.8; H, 8.0.

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(14) S. Weinstein, B. K. Morse, E. Grunwald, K. C. Schrieber, and J. Corse, *J. Am. Chem. Soc.*, **74**, 1119 (1952).
(15) W. Schenk and R. Ochs, *Ber.*, **49**, 610 (1916).
(16) J. Danilow, *J. Russ. Phys. Chem. Soc.*, **51**, 122 (1920).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Factors in Aldol Condensations of Alkyl Acetates with Benzophenone and Reversals by Sodium Amide Versus Lithium Amide. Metallic Cation Effects[1]

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The condensations of ethyl, isopropyl, and *t*-butyl acetates with benzophenone to form the corresponding β-hydroxy esters were effected by sodium amide in liquid ammonia, but controlled conditions were required with the first two alkyl acetates. Certain of these conditions were the same as those previously used with lithium amide, but certain of them were different. In contrast to lithium amide, sodium amide failed to effect the condensation of ethyl acetate with acetophenone. Four β-hydroxy esters were shown to undergo cleavages with catalytic amounts, and, in certain cases, with equivalent amounts of sodium amide in liquid ammonia but not with lithium amide. Possible reasons for these cleavages are discussed. Metallic cation effects and mechanisms are considered. The condensations are suggested to require the formation of a weaker base.

In a previous investigation[3] it was shown that ethyl and isopropyl acetates can be condensed with benzophenone by means of one equivalent of lithium amide in liquid ammonia to form the corresponding β-hydroxy esters, provided the ketone is added to the reaction mixture soon after the alkyl acetate. Otherwise the alkyl acetate undergoes self-condensation. In the present investigation it was found that these condensations can be effected similarly with one equivalent or slightly more of sodium amide in liquid ammonia provided that, not only is the ketone added immediately after the ester, but also that the reaction mixture is neutralized within a few minutes. Otherwise the

(1) Supported in part by the Office of Ordnance Research, U. S. Army.
(2) Allied Chemical and Dye Corporation Fellow, 1958–59.
(3) W. R. Dunnavant and C. R. Hauser, *J. Org. Chem.*, in press.

TABLE I

YIELDS OF β-HYDROXY ESTERS FROM ALKYL ACETATES WITH BENZOPHENONE BY SODIUM AMIDE IN LIQUID AMMONIA

Exp. No.	Alkyl Acetate	Equiv. $NaNH_2$	Ioniz. Time, min.[a]	Cond. Time, Min.	β-Hydroxy Ester	Yield, %
1	Ethyl	1.1	0[b]	5	I	71–73
2	Ethyl	1	0[b]	60	I	0[c]
3	Ethyl	2	0[b]	60	I	72
4	Ethyl	2	15	60	I	0[c]
5	Isopropyl	1	0[b]	5	II	56
6	Isopropyl	1	0[b]	60	II	0[c]
7	*t*-Butyl	1	20	60	III	55
8	*t*-Butyl	1	0[b]	60	III	54
9	*t*-Butyl	2	20	60	III	70

[a] Time allowed after adding the ester to the reagent before adding the ketone. [b] Although the ketone was added immediately after the ester, a few seconds probably elapsed. [c] Benzophenone was recovered in yields of 85–95%.

reaction undergoes reversion (see next section). These condensations, as well as that of *t*-butyl acetate which requires no special conditions with either lithium amide or sodium amide, may be represented by general Equation 1.

$$CH_3COOR \xrightarrow[\text{liq. } NH_3]{MNH_2} MCH_2COOR \xrightarrow[2.\ NH_4Cl]{1.\ (C_6H_5)_2C{=}O} (C_6H_5)_2C(OH)CH_2COOR \quad (1)$$

M = Li or Na

I. R = C_2H_5
II. R = $CH(CH_3)_2$
III. R = $C(CH_3)_3$

Certain of these condensations were also effected with two equivalents of sodium amide in liquid ammonia. The results are summarized in Table I. The ionization-time column in this Table designates the period allowed for the ionization of the α-hydrogen of the alkyl acetate before adding the ketone, and the condensation-time column the period after adding the ketone. The immediate addition of the ketone after the ester is signified by zero ionization time, although a few seconds probably elapsed in the procedure employed (see Experimental). The resulting reaction mixtures were poured into liquid ammonia solutions of ammonium chloride. This inverse neutralization procedure was employed to minimize the possible cleavages of the β-hydroxy esters.

It can be seen from Table I that good yields of β-hydroxy esters I and II were obtained with one or slightly more than one equivalent of sodium amide when the ionization time was zero and the condensation time only five minutes (exps. 1 and 5), whereas the benzophenone was recovered when the ionization time was again zero but the condensation time was one hour (exp. 2 and 6). Under both conditions the β-hydroxy esters were formed as their sodio salt, for example, I′, but under the latter condition this salt underwent cleavage to regenerate the ketone. Such cleavages are further considered in the next section.

$$(C_6H_5)_2C(ONa)—CH_2COOC_2H_5$$

I′

On the other hand, a good yield of β-hydroxy ester I was realized with two equivalents of the reagent when the ionization time was zero and the condensation time was even one hour (exp. 3). This lack of appreciable cleavage under these conditions may be ascribed to the conversion of monosodio β-hydroxy ester I′ to the disodio derivative I″, which might be expected to be more stable

$$(C_6H_5)_2C(ONa)—CHCOOC_2H_5 \quad (Na)$$

I″

towards cleavage. Although the formation of disodio salt I″ with two equivalents of sodium amide was not established, evidence has previously been obtained[3] that the corresponding condensation of ethyl acetate with benzophenone by two equivalents of lithium amide does produce the analogous dilithio salt.

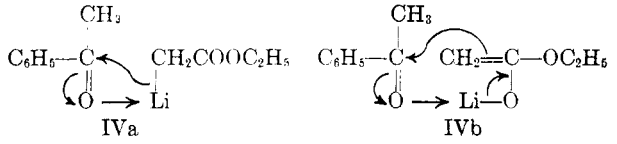
In contrast to β-hydroxy esters I and II, β-hydroxy ester III was obtained with one equivalent of sodium amide even when the ionization time was twenty minutes, and the condensation time one hour (exp. 7, Table I). This may be attributed to less tendency for the further reaction of sodio *t*-butyl acetate, a low concentration of which is presumably present in equilibrium (see next section). The somewhat better yield of β-hydroxy ester III with two equivalents of sodium amide than with one equivalent (compare exp. 9 with 7 and 8) may indicate that the additional driving force that should be furnished by the conversion of the monosodio β-hydroxy ester to its disodio derivative is required for maximum yield.

The fact that β-hydroxy ester I was obtained with two equivalents of sodium amide when the ionization time was zero but not when it was fifteen minutes (compare exps. 3 and 4) indicates that an extra equivalent of sodium amide did not exert the type of stabilizing effect on the intermediate sodio ethyl acetate observed previously[3] with an extra equivalent of lithium amide on the intermediate lithio ester. This was substantiated by

treating ethyl acetate alone with two equivalents of sodium amide in liquid ammonia for twenty minutes, after which a 12% yield of acetoacetic ester was obtained. Some acetamide might also have formed but none was isolated. Earlier workers have similarly reported only low yields (5–15%) of acetoacetic ester or acetamide from ethyl acetate and sodium amide[4,5] in liquid ammonia[5] or ether.[4]

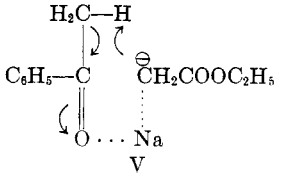
Since ethyl acetate has now been condensed with benzophenone in 71–73% yields by one or two equivalents of sodium amide in liquid ammonia and converted to acetamide in 10% yield by two equivalents of this reagent,[5] the ratio of attack of this reagent at the α-hydrogen of this ester versus the carbonyl carbon appears to be about 7:1. The ratio might even be higher since the ionization of the α-hydrogen should be reversible, whereas that of acetamide formation would presumably be irreversible.

Although sodium amide effected the aldol type of condensation of ethyl acetate with benzophenone, this reagent (one or two equivalents) failed to bring about the corresponding condensation of this ester with acetophenone, even when the ketone was added immediately after the ester. Instead the intermediate sodio ester evidently effected the ionization of an α-hydrogen of acetophenone to form the sodio ketone, since the ketone was recovered on acidification. The recovered material gave an enol test with ferric chloride indicating the presence of acetoacetic ester or benzoylacetone. Previously[3] ethyl acetate has been condensed in good yield with acetophenone by means of two equivalents of lithium amide, and one equivalent of this reagent would probably be equally satisfactory. This metallic cation effect appears to be attributable to the greater nucleophilic nature of the lithio ester to add to the carbonyl group of the ketone, presumably through coordination at the carbonyl oxygen, as indicated in IVa or IVb.



IVa IVb

The sodio ester, which should coordinate to a smaller degree, functions as the stronger base ionizing the α-hydrogen of the ketone as indicated in V.



V

(4) A. W. Titherly, *J. Chem. Soc.*, **81**, 1520 (1902).

(5) C. R. Hauser, R. Levine, and R. F. Kibler, *J. Am. Chem. Soc.*, **68**, 26 (1946).

A similar metallic cation effect has been previously observed in the reactions of lithio and sodio *t*-butyl acetates with acetophenone.[6]

Cleavage of β-hydroxy esters. Although ethyl, isopropyl, and *t*-butyl acetates can be condensed with benzophenone by means of one to two equivalents of sodium amide in liquid ammonia (see Table I), the resulting β-hydroxy esters can be cleaved again by catalytic amounts of this reagent and, in certain cases, even by equivalent amounts. These and certain related results are summarized in Table II. In all of these experiments the reaction mixtures were neutralized inversely to ensure that the cleavage observed had occurred during the four hour period allowed, not during the neutralization.

TABLE II

CLEAVAGE OF β-HYDROXY ESTERS BY ALKALI AMIDES IN LIQUID AMMONIA DURING FOUR HOURS

Exp. No.	β-Hydroxy Ester	Alkali Amide	Equiv.	Benzophenone Yield, %	Recov. β-Hydroxy Ester, %
1	I	Sodium	0.2[a]	26	42
2	I	Sodium	1.25	89	0
3	I	Sodium	2.0	0	94
4	I	Potassium	1.0	71	0
5	I	Potassium	1.2	67	0
6	I	Lithium	0.1	0	96
7	I	Lithium	1.0	0	96
8	I	Lithium	2.0	0	93
9	II	Sodium	0.15	86	0
10	III	Sodium	0.15	82	0
11	III	Sodium	0.5	21	69
12	III	Sodium	1.0	0	91

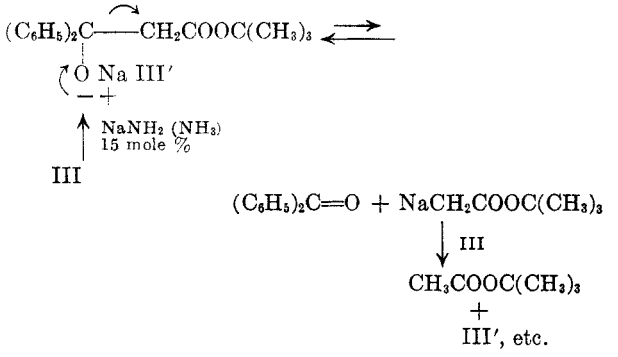
[a] Neutralized after only five minutes.

First, consideration will be given to the use of catalytic amounts of sodium amide, which effected the cleavages of all three of the β-hydroxy esters studied, I, II, and III, to form benzophenone and presumably the corresponding alkyl acetate (exps. 1, 9, and 10). While only the ketone was isolated, the appropriate fraction of the reaction product from β-hydroxy ester I was indicated by its infrared spectrum to contain ethyl acetate. All of the β-hydroxy esters were probably cleaved completely within much less time than the four hours allowed, since appreciable cleavage of I was observed within five minutes (exp. 1). These reactions are brought about presumably because the neutral ketone and alkyl acetate molecules are more stable thermodynamically than the neutral β-hydroxy ester. The mechanism may be considered to involve a β-elimination of the sodio salt of the β-hydroxy ester, for example, III′, but only that amount of the β-hydroxy ester corresponding to the mole percent of the catalyst employed is first converted to this intermediate. The remainder of the free β-

(6) C. R. Hauser and W. H. Puterbaugh, *J. Am. Chem. Soc.*, **75**, 4756 (1953).

hydroxy ester is gradually converted to this intermediate as it neutralizes the sodio alkyl acetate, a low concentration of which is present in equilibrium (Scheme A).

SCHEME A



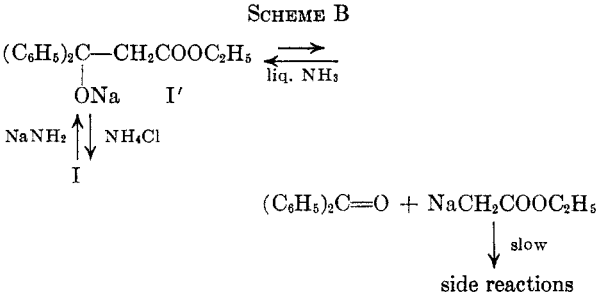
In agreement with Scheme A, less than half of β-hydroxy ester III underwent cleavage with 0.5 mole % of sodium amide (exp. 11), and essentially none of β-hydroxy ester III was cleaved by one equivalent of the reagent (exp. 12). In this last experiment essentially all of the β-hydroxy ester was immediately converted to its sodio salt III′, leaving none to serve as an acid in the last step.

One of the β-hydroxy esters, I, was also cleaved with a catalytic amount of sodium ethoxide in ethanol. A number of β-hydroxy esters have previously been cleaved with alcoholic alkali alkoxides but an equivalent or more of the reagent has generally been employed.[7] The mechanism would presumably be similar to that shown in Scheme A. However, even with an equivalent of an alkoxide ion, which is a much weaker base than the amide ion, the β-hydroxy ester would probably be converted only gradually to its anion, and the last step may be considered to be effected mainly by the alcohol used as solvent.

Next, consideration will be given to the use of an equivalent or slightly more of sodium amide or potassium amide, which effected the cleavage of β-hydroxy ester I (exps. 2, 4, and 5, Table II) but not that of β-hydroxy ester III under similar conditions (exp. 12). Since both sodio ethyl acetate and sodio *t*-butyl acetate can be condensed in high yield with benzophenone (see Table I), this difference in the relative ease of cleavage of the two resulting sodio β-hydroxy esters I and III appears to be due to the relative tendencies towards side-reactions of the sodio ethyl and sodio *t*-butyl acetates, low concentrations of which are presumably present in equilibrium. In agreement with this, ethyl acetate is known to be converted by sodium amide in liquid ammonia through the sodio ester to its self-condensation product or corresponding acid amide much more readily than *t*-butyl acetate (see previous section). The relationship between the formation and cleavage of sodio β-hydroxy ester I′ may be represented tentatively by Scheme B.

(7) See H. E. Zaugg, *J. Am. Chem. Soc.*, **72**, 3001 (1952).

SCHEME B

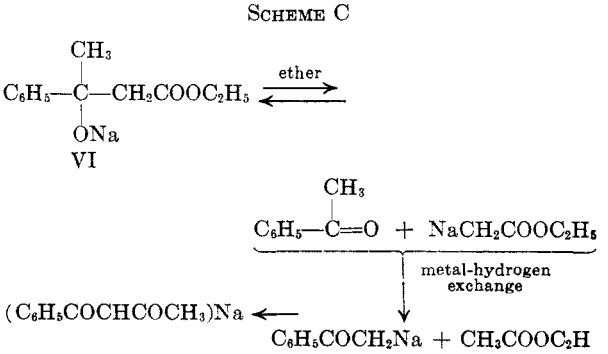


However, an attempt to isolate acetoacetic ester or acetamide from the cleavage product of β-hydroxy ester I was unsuccessful. Perhaps these products were converted to derivatives that escaped detection. Actually, only low yields of the β-keto ester and amide have previously been obtained from ethyl acetate and sodium amide[4,5] (see previous section).

The possibility that the β-hydroxy ester I was cleaved by an equivalent of sodium amide because the benzophenone was removed from the equilibrium seems unlikely, since III was not cleaved. In line with this, evidence was obtained that the ketone was not converted to the addition compound $(C_6H_5)_2C(ONa)NH_2$ by reaction with sodium amide, a low concentration of which might have been present in equilibrium. Thus, the suspension resulting from the replacement of the ammonia by ether appeared to contain none of this salt-like product, which should be insoluble in ether (see Experimental).

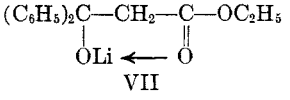
A better established example of a cleavage by an equivalent of sodium amide brought about because of further reaction of one or both of the products was observed previously[6] with sodio-β-hydroxy ester VI in ether. In this cleavage the ketone and sodio ethyl acetate present in the equilibrium underwent hydrogen-metal exchange followed by Claisen acylation of the resulting sodio ketone (Scheme C). Sodio salt VI was formed from the corresponding β-hydroxy ester and an equivalent of sodium amide.

SCHEME C



It can be seen from Table II that, whereas β-hydroxy ester I was cleaved with one equivalent or slightly more of sodium amide or potassium amide, the β-hydroxy ester was recovered after standing with two equivalents of sodium amide under similar conditions (exp. 3). This lack of appreciable cleavage with two equivalents of reagent, which is in agreement with the observation in the previous section concerning the condensation of ethyl acetate with benzophenone (see Table I), may be ascribed to the formation of the relatively stable disodio β-hydroxy ester I″.

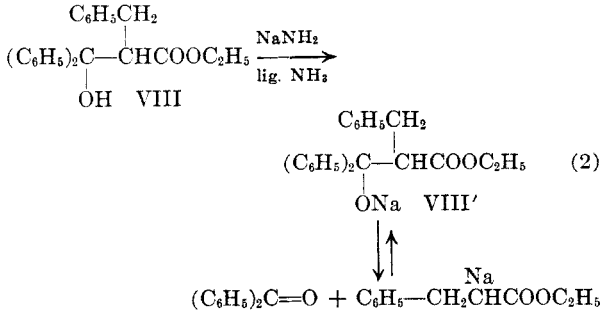
It can be seen further from Table II that, in contrast to sodium amide, a catalytic or equivalent amount of lithium amide failed to effect appreciable cleavage of β-hydroxy ester I during four hours, although longer time or more drastic conditions might possibly produce some cleavage. This metallic cation effect appears to be ascribable to less ionization of the lithium-oxygen bond and more chelation in the lithio-β-hydroxy ester VII than in the corresponding sodio-β-hydroxy ester I′.



VII

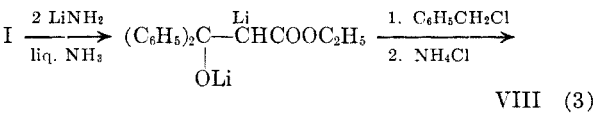
A similar metallic cation effect has previously been observed[6] in ether with sodio-β-hydroxy ester VI and the corresponding lithio-β-hydroxy ester. Although the lithio-β-hydroxy ester failed to cleave appreciably in refluxing ether it was cleaved in refluxing toluene to form benzoylacetone and the self-condensation product of acetophenone.[6]

It should be mentioned that β-hydroxy ester VIII has recently[3] been cleaved by means of 1.25 equivalents of sodium amide in liquid ammonia to form, after inverse neutralization, benzophenone and ethyl hydrocinnamate in high yields. This β-hydroxy ester has now been cleaved similarly with one equivalent of potassium amide. In contrast to sodio β-hydroxy ester III which was stable for at least four hours (see Table II), the sodio or potassio β-hydroxy ester VIII′ establishes an equilibrium with benzophenone and the alkali ethyl hydrocinnamate apparently on the side of the two latter components (Equation 2).



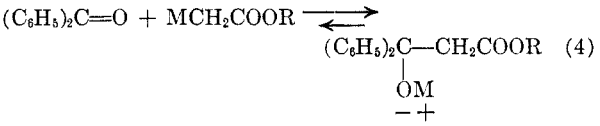
(2)

If this position of equilibrium is later established, it could presumably be ascribed to steric factors. Indirect support for this position of equilibrium is our observation that sodio ethyl hydrocinnamate, prepared from the ester and sodium triphenylmethide in ether, failed to yield β-hydroxy ester VIII with benzophenone in this medium even though the reaction mixture was neutralized inversely. The ketone and ester were largely recovered. Actually β-hydroxy ester VIII was obtained, not by an aldol type of condensation,[8] but through the benzylation of the dilithio derivative of β-hydroxy ester I (Equation 3).[3]



VIII (3)

Factors in condensation. The greater thermodynamic stability of the neutral ester and ketone molecules than the neutral β-hydroxy ester (see above) suggests that the addition of the sodio or lithio alkyl acetate to the carbonyl group of benzophenone to form the metallo β-hydroxy ester is dependent on the formation of the more weakly basic anion of this product (Equation 4).[9] Contributing



(4)

factors may be chelation, especially with the lithio derivative as indicated in VII, and precipitation of the product.

In line with this hypothesis, lithio malonic ester, the anion of which is a weaker base than an alkoxide ion such as that shown in Equation 4, failed to add to the carbonyl group of benzophenone in liquid ammonia during one hour, and the starting compounds were recovered. The lithio malonic ester was prepared by means of an equivalent of lithium amide in liquid ammonia. The condensation failed even in the presence of excess lithium amide, which was employed to effect ionization of the α-hydrogen of the possible condensation product.

Similar observations have been reported by earlier workers. Thus, sodio and lithio malonic esters,[10] prepared by means of sodium and lithium triphenylmethides in ether, failed to add to the carbonyl group of benzaldehyde in this solvent and the malonic ester was recovered. Malonic ester was condensed with benzaldehyde by sodium ethoxide

(8) The possibility of effecting the aldol type condensation of lithio- or magnesium-bromo ethyl hydrocinnamate with benzophenone seems worthy of consideration. Although the Reformatsky reaction of ethyl α-bromohydrocinnamate with this ketone has apparently not been reported, that with 2-methylcyclohexanone has been achieved; R. Grewe, *Ber.*, **76B**, 1076 (1943).

(9) For similar suggestions in the condensations of sodium diphenylmethide and dialkali phenylacetates with benzophenone see P. J. Hamrick, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, **81**, 3146 (1956); P. J. Hamrick, Jr., and C. R. Hauser, *J. Am. Chem. Soc.*, **82**, 1957 (1960).

(10) G. Wittig, U. Todt, and K. Nagel, *Ber.*, **83**, 110 (1950).

or amines in refluxing ethanol, but the product was benzalmalonic ester (22%).[10] Apparently the dehydration of the intermediate aldol furnished the needed driving force.

Finally, it should be pointed out that the present addition reaction illustrated by Equation 4 is analogous to those of the common organometallic compounds such as sodium diphenylmethide,[9] phenyllithium, and the Grignard reagent with ketones or aldehydes, at least most of which form more weakly basic anions.

EXPERIMENTAL[11]

Condensations of alkyl acetates with benzophenone by sodium amide. Ethyl, isopropyl, and *t*-butyl acetates were condensed with benzophenone by 1–2 equivalents of sodium amide in liquid ammonia[12] to form β-hydroxy esters I, II, and III respectively. The results including failures are summarized in Table I. Some experiments are described in detail below.

A. Experiments with ethyl acetate. In Experiment 1, a solution of 17.6 g. (0.2 mole) of ethyl acetate in an equal volume of ether was added through the addition funnel as rapidly as possible to a stirred suspension of 0.22 mole of sodium amide in 400 ml. of commercial anhydrous liquid ammonia. Since frothing occurred, a reaction vessel having a volume twice that of the amide suspension was used. As the last of the ester passed through the stopcock, a solution of 36.4 g. (0.2 mole) of benzophenone in 70 ml. of anhydrous ether was poured immediately into the addition funnel and allowed to run into the reaction flask as rapidly as possible, the addition funnel being rinsed with a little ether. The resulting white suspension was stirred for 5 min. and was then inversely neutralized by pouring it into a solution of ammonium chloride in liquid ammonia.The ammonia was evaporated to dryness. The residue was stirred with cold water and filtered to yield a white solid, which crystallized from petroleum ether (b.p. 60–90°) to give 38.1 g. (71%) of ethyl β-hydroxy-β,β-diphenylpropionate (I), m.p. 86–87°, reported[13] m.p. 87°.

In Experiment 3, a solution of 17.6 g. (0.2 mole) of ethyl acetate in an equal volume of ether was added rapidly to a stirred solution of 0.4 mole of sodium amide in 400 ml. of liquid ammonia followed immediately by 36.4 g. (0.2 mole) of benzophenone in 70 ml. of ether (see previous experiment). The resulting black solution was stirred for 1 hr. and was inversely neutralized with ammonium chloride. The ammonia was evaporated on the steam bath as 300 ml. of ether was added. Water was added and the aqueous layer was thoroughly extracted with ether. The combined ethereal solution was dried and evaporated to a residue which, upon crystallization from petroleum ether (b.p. 60–90°) gave 38.7 g. (72%) of β-hydroxy ester I, m.p. 85–86°.

B. Experiments with isopropyl acetate. In Experiment 5, a solution of 16.5 g. (0.16 mole) of isopropyl acetate in an equal volume of ether was added rapidly to a stirred suspension of 0.16 mole of sodium amide in 400 ml. of liquid ammonia, followed immediately by 30 g. (0.16 mole) of benzophenone in 70 ml. of ether (see experiment 2 with ethyl acetate). The suspension was stirred for 5 min. and was inversely neutralized with ammonium chloride. The ammonia was replaced by ether. Water was added and the aqueous layer was thoroughly extracted with ether. The combined ethereal solution was evaporated and the residue was crystallized from petroleum ether (b.p. 60–90°) to give 26.1 g. (56%) of isopropyl-β-hydroxy-β,β-diphenylpropionate (II), m.p. 101–102°.

Following removal of II, the filtrate was concentrated and cooled to yield 10.2 g. (34%) of crystalline benzophenone, m.p. 46–47°, reported[14] m.p. 48–48.5°.

C. Experiment with t-butyl acetate. In Experiment 9, a solution of 23.3 g. (0.2 mole) of *t*-butyl acetate in an equal volume of ether was added to a stirred suspension of 0.4 mole of sodium amide in 400 ml. of liquid ammonia. After stirring for 20 min., 36 g. (0.2 mole) of benzophenone in 75 ml. of ether was added. The reaction mixture was stirred for 1 hr. and was inversely neutralized with ammonium chloride. The ammonia was replaced by 300 ml. of ether. Water was added and the aqueous layer was thoroughly extracted with ether. The combined ethereal solution was dried and evaporated. The residue was crystallized from ethanol to give 41.5 g. (70%) of *t*-butyl β-hydroxy-β,β-diphenylpropionate (III), m.p. 92–93°, reported[15] m.p. 92–93°.

Treatment of sodio ethyl acetate with acetophenone. A reaction identical to Exp. 1, Table I (above), with ethyl acetate was carried out, but using 0.2 mole of acetophenone in place of benzophenone. The ethereal residue at the end of the reaction workup was vacuum distilled to give 20.1 g. (84%) of recovered acetophenone, b.p. 88–90°/16 mm, reported[16] b.p. 88.5° at 16 mm. Neither the combined ethereal solution, nor the orange residue obtained upon its evaporation gave a positive enol test.

Repeating this experiment, but using 2 equivalents of sodium amide gave a similar result.

Attempted condensation of ethyl hydrocinnamate with benzophenone. To a stirred suspension of 0.07 mole of sodium amide in 300 ml. of anhydrous liquid ammonia was added 16.8 g. (0.07 mole) of solid triphenylmethane. The deep red solution was stirred for 15 min. and 12.2 g. (0.07 mole) of ethyl acetate in an equal volume of ether was added. The red triphenylmethide color was discharged at the end of the addition and a gray suspension formed. After stirring for 5 min., 12.5 g. (0.07 mole) of benzophenone in 25 ml. of ether was added. The gray suspension was stirred for 1 hr. and was then inversely neutralized with ammonium chloride. The ammonia was replaced by ether and water was added. The aqueous layer was thoroughly extracted by ether. The combined ethereal solution was dried and the solvent was removed. The resulting orange residue was crystallized from petroleum ether (b.p. 60–90°) to give 15.6 g. (93%) of recovered triphenylmethane, m.p. 92–93°, reported[17] m.p. 93–94°. Concentrating and cooling the filtrate precipitated 10.2 g. (82%) of benzophenone, m.p. 46–47°. The remaining filtrate was distilled to give 10.65 g. (85%) of recovered ethyl hydrocinnamate, b.p. 246–248° at 750 mm, reported[18] 247° at 760 mm.

General procedure for cleavages of β-hydroxy esters I, II, *and* III *by alkali amides.* The yields of benzophenone obtained by the cleavage of the β-hydroxy esters and/or the per cent recovery of the β-hydroxy esters upon noncleavage are summarized in Table II.

To a stirred suspension of the appropriate quantity of the alkali amide (see Table II) in 400 ml. of anhydrous liquid ammonia were added 0.05–0.08 mole of the β-hydroxy ester in sufficient ether to effect their solutions. The resulting suspensions were stirred for 4 hr. and were then inversely neutralized by pouring them with stirring into solutions of ammonium chloride in liquid ammonia. The ammonia was then

(11) The melting points were taken on a Fisher-Johns melting point apparatus.

(12) For the preparation of the reagent see C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, VIII, 122 (1954).

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eplaced by 300 ml. of ether and water was added. The aqueous layers were extracted thoroughly with ether. The combined ethereal solutions were dried and then evaporated. The resulting residues were then fractionally crystallized from petroleum ether (b.p. 60–90°) to give recovered β-hydroxy ester and/or benzophenone. Since the β-hydroxy ester is only slightly soluble in this solvent, it crystallizes first, reduction of the solvent volume and cooling being required for recovery of the ketone. In each case the identities of the β-hydroxy ester and ketone were verified by comparison of their infrared spectra with those of the respective authentic substances.

In a repetition of Experiment 2, Table II, involving β-hydroxy ester I and one equivalent of sodium amide, the ammonia was replaced by ether at the end of 4 hr. and the ethereal suspension, without being neutralized, was filtered through a fritted-glass funnel. Benzophenone (86%) was obtained from the ethereal filtrate in the usual manner following acidification with aqueous hydrochloric acid. The solid on the funnel was shown not to contain a benzophenone–sodium amide addition complex by its noninflammability, and by the fact that its acidification produced no benzophenone.

Cleavage of β-hydroxy ester I by sodium ethoxide. To a solution of 0.0008 mole of sodium ethoxide in 50 ml. of absolute ethanol was added 2.0 g. (0.007 mole) of β-hydroxy ester I. The mixture was allowed to stand at room temperature with occasional shaking for 48 hr. when complete solution was achieved. The solution was poured with stirring into a solution of 5 ml. of concd. hydrochloric acid and 25 ml. of water. Much (50 ml.) of the solvent was removed, and the residue extracted with ether. There was isolated 2.6 g. (85%) of the 2,4-dinitrophenylhydrazone of benzophenone, m.p. 236–238°, reported[19] m.p. 238°.

In a blank experiment with β-hydroxy ester I and absolute ethanol, essentially complete recovery of this compound was realized.

Attempted condensation of malonic ester and benzophenone by lithium amide. To a stirred suspension of 0.1 mole of lithium amide in 400 ml. of anhydrous liquid ammonia was added 16 g. (0.1 mole) of diethyl malonate in an equal volume of ether. The suspension was stirred for 5 min. and 18.2 g. (0.1 mole) of benzophenone in 40 ml. of anhydrous ether was added. After stirring for 1 hr. the suspension was inversely neutralized with ammonium chloride. The ammonia was replaced by 300 ml. of ether. The combined ethereal solution was then evaporated. The resulting residue was vacuum distilled to give 14.8 g. (92%) of recovered diethyl malonate, b.p. 94–98° at 18 mm, reported[20] b.p. 88–89° at 13 mm. Also, 15.9 g. (88%) of benzophenone was recovered, b.p. 186–189° at 15 mm. The benzophenone reaction, after solidification, was crystallized from petroleum ether (b.p. 60–90°) to give crystals of the ketone, m.p. 46–47°.

Repetition of this reaction, but using 2, 3 or 4 equivalents of lithium amide, gave comparable recoveries of the ketone and diester in each case.

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[CONTRIBUTION FROM THE CHEMICAL RESEARCH AND DEVELOPMENT CENTER OF THE FOOD MACHINERY AND CHEMICAL CORPORATION]

α-Oximinoketones. VII. Synthesis of Alkyl 5-Cyano-2-oximinovalerates and DL-Lysine from 2,6-Dioximinocyclohexanone[1]

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DL-Lysine monohydrochloride has been prepared in 63% over-all yield from cyclohexanone by a three-step synthesis which involves: (1) nitrosation of cyclohexanone to give 2,6-dioximinocyclohexanone (75%), (2) reaction of 2,6-dioximinocyclohexanone in ethanolic sodium ethoxide with acetic anhydride to give ethyl 5-cyano-2-oximinovalerate (92%), and (3) hydrogenation of ethyl 5-cyano-2-oximinovalerate over Raney nickel in acetic anhydride containing a basic co-catalyst followed by hydrolysis with hydrochloric acid to give DL-lysine monohydrochloride (92%). Discovery that ethanol could be used as solvent for step (2) and Raney nickel as catalyst for step (3) more than doubled the overall yield obtained in previous versions of this synthesis.[3,4]

In two previous papers[3,4] the two similar syntheses of DL-lysine from cyclohexanone outlined below as routes (A) and (B) (p. 1303) were described.

In both syntheses the key reaction was the "partial cleavage" of 2,6-dioximinocyclohexanone to 5-cyano-2-oximinovaleric acid or a derivative. It is readily apparent that conversion of cyclohexanone to lysine *via* this key reaction offers an extremely facile synthesis of this important amino acid, quite possibly more direct than any previously reported. Neither of the previous versions of this synthesis realized its full potential, however, since both suffered from unsatisfactory yields in the steps following the relatively satisfactory initial nitrosation (75% yield). Thus in the first version of the synthesis (route A),[3] the yield in the partial cleavage step was 62% and in the reduction step only 43%, giving an over-all yield of 20%. In the second version (route B),[4] the excellent 88% yield of the partial cleavage was in part offset by the necessity for introducing a separate acylation step (76% yield), so that the over-all conversion of 2,6-dioximinocyclohexanone to ethyl 5-cyano-2-oximinovalerate was 67%.

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