others. In presence of their sodium salts, however, these isomers are hydrogenated at the same rate.

When the cyclohexanols can exist in *cis–trans* forms, the ratio of the products is not appreciably altered by the presence of the sodium salts except at high temperatures.

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The Acylation of Methyl Ketones with Aliphatic Esters by Means of Sodium Amide. Synthesis of β-Diketones of the Type $RCOCH_2COR$[1]

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The acylation of methyl ketones with esters by means of sodium, sodium ethoxide or sodium amide is the common method for the preparation of β-diketones having the reactive methylenic group.

$$RCO_2C_2H_5 + CH_3COR \longrightarrow RCOCH_2COR + C_2H_5OH$$

While acetylations with ethyl acetate have generally been satisfactory,[2] acylations with higher aliphatic esters have previously given only fair yields of the β-diketones.[3,4] In the present investigation good yields of β-diketones have been obtained from various aliphatic esters and methyl ketones by means of sodium amide.

In preliminary experiments using molecular equivalents of ethyl *n*-butyrate, methyl isobutyl ketone and sodium amide the yield of the β-diketone was 44% when the sodium derivative of the ketone was first prepared and the ester added, but only 36% when a mixture of the ester and ketone was added to the sodium amide in accordance with the more common practice.[4] The former procedure was therefore adopted.

Although Claisen[5] reported a 77% yield in the acetylation of acetophenone with ethyl acetate using two equivalents of sodium amide to one of the ketone, later workers[4] used no appreciable excess of sodium amide in acylations of aliphatic ketones with higher aliphatic esters and obtained much lower yields. We have found that the presence of excess sodium amide has a very favorable influence on the yield of β-diketone, at least in the cases studied. Our results are summarized in Table I. With each of the first six ester–ketone combinations listed in the table, the acylations were carried out using molecular equivalents of sodium amide and ketone, and also using two equivalents of sodium amide to one of the ketone. It can be seen that the yields obtained in the presence of the extra equivalent of sodium amide are twice those obtained using only an equivalent of the base. The influence of excess ester on the yield is much less pronounced. This is shown by the fact that, in the acylation of methyl *n*-propyl ketone with ethyl *n*-butyrate, the yield was only slightly higher with two equivalents of ester to one of ketone than with equivalents of ester and ketone. To obtain optimum yields, however, excess of the ester was generally used.

Except possibly when the β-diketone fails to form a copper salt, the procedure using excess sodium amide is preferred. The β-diketone from ethyl *n*-valerate and methyl *t*-butyl ketone failed to form a copper salt, and when the reaction was carried out in the presence of excess sodium amide, it was rather difficult to isolate the β-diketone in the pure condition. Two products obtained from side reactions were isolated in this case, *n*-valeramide formed by the reaction of the sodium amide with the carbonyl group of the ester, and ethyl *n*-valeryl-*n*-valerate which is the self-condensation product of the ester. In the corresponding experiment using equivalents of reactants none of the amide was found, although some of the self-condensation product of the ester was isolated. These types of side reaction probably also accompanied the other acylations, especially when excess sodium amide was used, but the β-diketones were readily isolated in the form of their copper salts.

In addition to the good yield of the methyl derivative, $C_2H_5COCH_2COC_2H_5$, obtained from methyl ethyl ketone and ethyl propionate using excess sodium amide, a low yield (13%) of the methylene derivative, $C_2H_5COCH(CH_3)COCH_3$, was isolated. A very low yield (2%) of the corresponding methylene derivative was obtained from methyl *n*-propyl ketone and ethyl propionate. No attempt was made to isolate methylene derivatives in the experiments with methyl isobutyl or methyl *n*-amyl ketones. In all cases studied thus far, the methyl derivatives were readily isolated in good yields essentially free from the methylene derivatives.

For acylations with the esters higher than ethyl acetate listed in Table I, sodium amide is superior to sodium ethoxide or metallic sodium. Two of those listed, the acylations of methyl *t*-butyl ketone with ethyl *n*-valerate and with ethyl pivalate, have failed in the presence of sodium

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[1] Paper XXVI on "Condensations": paper XXV, THIS JOURNAL, **66**, 1037 (1944).

[2] See especially Sprague, Beckham and Adkins, *ibid.*, **56**, 2665 (1934).

[3] Morgan and Thomason, *J. Chem. Soc.*, **125**, 756 (1924).

[4] Fischer and Orth, "Die Chemie des Pyrrols," Akademische Verlagsgesellschaft, Leipzig, 1934, p. 402.

[5] Claisen, *Ber.*, **38**, 694 (1905).

ethoxide,[2] while a third, the acylation of methyl *n*-propyl ketone with ethyl *n*-butyrate, has given only an 11% yield[6] with this base. Several acylations with higher esters have been effected by means of metallic sodium,[3] but the best yield, that from ethyl *n*-butyrate and methyl ethyl or methyl *n*-propyl ketone, is only 22%. The acylation of acetone with ethyl isobutyrate by means of sodium has given only a 6% yield of the β-diketone.[7] Even for certain acetylations with ethyl acetate, sodium amide appears to be superior. Thus, the 43% yield of pivaloylacetone from ethyl acetate and methyl *t*-butyl ketone obtained with sodium amide is almost twice that (25%) reported with sodium.[8] It should be mentioned, also, that with sodium amide acylations can be effected in considerably less time than with sodium ethoxide or sodium.

The fact that the yield of β-diketone from ketone is less than 50% using equivalents of sodium amide and ketone and generally considerably greater than 50% using two equivalents of sodium amide to one of ketone is understandable on the basis of the following mechanism.

$$\text{(1)}\quad CH_3COR + {}^-NH_2 \longrightarrow (CH_2COR)^- + NH_3$$

$$\text{(2)}\quad RCO_2C_2H_5 + (CH_2COR)^- \longrightarrow RCOCH_2COR + {}^-OC_2H_5$$

$$\text{(3)}\quad RCOCH_2COR + (CH_2COR)^- \longrightarrow (RCOCHCOR)^- + CH_3COR$$

or

$$RCOCH_2COR + {}^-NH_2 \longrightarrow (RCOCHCOR)^- + NH_3$$

With an equivalent of amide ion, the ketone is converted in step (1) essentially completely to its anion. Part of the ketone anion condenses in step (2) with the carbonyl group of the ester to form the β-diketone, which reacts relatively rapidly in step (3)[9] with unchanged ketone anion to form the anion of the β-diketone and the original ketone. Theoretically one-half of the original ketone may be regenerated in this manner, the maximum yield of β-diketone based on the ketone being 50%.[10] When an extra equivalent of the amide ion is present, however, the regeneration of the ketone from the ketone anion is prevented and the maximum yield of β-diketone is 100%. Under these conditions, step (3) is considered to be effected by the amide ion, which is the strongest base present. It is interesting that the ester reacts mainly with the ketone anion instead of with the extra equivalent of amide ion.[11] With certain ester–ketone combinations, the ester might react mainly with the excess amide ion and the yields of β-diketones would accordingly be smaller.

Experimental

General Procedure.—In a 500-cc. three-necked round-bottomed flask having ground glass joints and equipped with a mercury-sealed stirrer, a removable glass plug, and a dry-ice condenser (with a drying tube), was placed 300 cc. of anhydrous liquid ammonia. To the stirred ammonia was added in small portions the calculated amount (and 10% excess)[12] of clean sodium and a small crystal of ferric nitrate[13] to catalyze the conversion of the sodium to sodium amide. After this conversion was complete, as indicated by the change of the blue solution to a dark gray suspension, the dry-ice condenser was replaced by a water condenser and the glass plug replaced by a dropping funnel. The ammonia was then evaporated by means of a steam-bath, sufficient anhydrous ether being added through the dropping funnel so that the volume of the liquid remained at approximately 300 cc. After practically all of the ammonia had evaporated (indicated by the refluxing of the ether) the suspension of sodium amide was stirred and refluxed for a few minutes and then cooled to room temperature. The procedure thus far requires only about one hour.

To the stirred suspension of sodium amide was added during five to ten minutes a solution of the calculated amount of ketone in 50 cc. of absolute ether. After five minutes (when the sodium derivative of the ketone was assumed to be formed) the calculated amount of ester in 50 cc. of absolute ether was added, and the stirring continued for two hours while the mixture was refluxed on a steam-bath. The mixture, containing a gelatinous precipitate of the sodium salt of the β-diketone, was poured into 300 cc. of water, neutralized with dilute hydrochloric acid and extracted with ether. The solvent was distilled from the ether solution and the residue dissolved in an equal volume of methanol. The β-diketone was precipitated from this methanol solution in the form of its copper salt, from which the free β-diketone was regenerated by treatment with acid. In the experiments with 0.6 mole of sodium amide, this was carried out as described below; in the experiments with 0.3 mole of sodium amide, half quantities of reagents were used.

To the methanol solution was added a hot filtered solution of 40 g. of copper acetate in 350 cc. of water and the mixture allowed to stand until it had cooled to room temperature. After filtering through a Buchner funnel, the copper salt of the β-diketone was sucked dry in air, washed with 100 cc. of ligroin (b. p. 30–60°), and again sucked dry. The yields of the copper salts thus obtained are given in Table I. In each case a small sample of the salt was recrystallized from methanol or 95% ethanol and the melting point determined; these melting points are recorded in the table. The bulk of the unrecrystallized salt, which melted only a few degrees lower than the recrystallized sample, was shaken with 500 cc. of 10% sulfuric acid and 200 cc. of ether until the ether layer was light yellow or colorless. The aqueous acid layer was again extracted with ether and the combined ether solution dried over sodium sulfate. The solvent was distilled and the residue fractionated *in vacuo* through a 30-cm. Vigreux column. The yields and boiling points of the β-diketones obtained are given in Table I.

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[6] This result was obtained by us using 0.3 mole each of sodium ethoxide and ketone and 0.6 mole of ester according to the general procedure of Sprague, Beckham and Adkins.[4]

[7] Powell and Seymour, This Journal, 53, 1049 (1931).

[8] See ref. *o* in Table I.

[9] Step (3) may be effected also by the ethoxide ion formed in step (2), but this need not be considered, since the alcohol that would be produced would be neutralized by the amide ion or ketone anion regenerating the ethoxide ion and ammonia or ketone.

[10] This is on the basis that the ethoxide ion formed in the second step does not effect the condensation under the conditions employed, which is apparently true in our experiments, since our yields were less than 50%, and, in certain cases, part of the original ketone was recovered.

[11] This seems rather remarkable, since the ketone anion is not only a weaker base than the amide ion but also the larger molecule. The sodium derivative of the ketone appears to be more soluble in ether (used as reaction medium) than does sodium amide and, perhaps on this account, the former reacts to the larger extent with the ester.

[12] This excess was used in order to ensure the formation of the amount of sodium amide given in Table I.

[13] See Vaughn, Vogt and Nieuwland, This Journal, 56, 2120 (1934).

TABLE I

YIELDS OF β-DIKETONES FROM ALIPHATIC ESTERS AND METHYL KETONES IN THE PRESENCE OF SODIUM AMIDE

Ester		Ketone (0.3 mole)	NaNH$_2$, moles	β-Diketone	B. p.,[a] °C.	Mm.	Yield, %	Copper salt	
Ethyl	Moles							Yield, %	M. p.,[a] °C.
Propionate	0.3	Methyl ethyl	0.3	Dipropionylmethane	78– 80	30	30	33	209–210[b]
Propionate	.6	Methyl ethyl	.6	Dipropionylmethane[c]	78– 80	30	57	61	209–210
n-Butyrate	.3	Methyl *n*-propyl	.3	Dibutyrylmethane	101–102	20	33	35	156–157[d]
n-Butyrate	.3	Methyl *n*-propyl	.6	Dibutyrylmethane	101–102	20	68	70	156–157
n-Butyrate	.6	Methyl *n*-propyl	.6	Dibutyrylmethane	101–102	20	76	78	156–157
n-Butyrate	.3	Methyl isobutyl	.3	Butyrylisovalerylmethane[e]	109–110	20	44	47	136–137
n-Butyrate	.6	Methyl isobutyl	.6	Butyrylisovalerylmethane	109–110	20	80	83	136–137
n-Valerate	.3	Methyl *t*-butyl	.3	*n*-Valerylpivaloylmethane	116–119	20	32	..	...
n-Valerate	.375	Methyl *t*-butyl	.6	*n*-Valerylpivaloylmethane[f,g]	116–119	20	52	[h]	..
Isovalerate	.3	Methyl isobutyl	.3	Diisovalerylmethane[i]	114–116	20	27	32	157–158[j]
Isovalerate	.6	Methyl isobutyl	.6	Diisovalerylmethane	115–116	20	76	79	157–158
n-Caproate	.3	Methyl *n*-amyl	.3	Dicaproylmethane[k]	162–164	20	28	32	119–120[j]
n-Caproate	.375	Methyl *n*-amyl	.6	Dicaproylmethane	162–164	20	68	73	119–120
Pivalate	.3	Methyl *t*-butyl	.3	Dipivaloylmethane[l]	96– 97	20	28	30	197–198[m]
Acetate	.6	Acetone	.6	Acetylacetone	139–141	758	54	62	dec.[n]
Acetate	.6	Methyl *t*-butyl	.6	Pivaloylacetone	70– 71	20	43	46	191–192[o]
Propionate	.6	Methyl *n*-propyl	.6	Propionylbutyrylmethane[p]	84– 86	20	70	74	157–168[q]
n-Butyrate	.6	Methyl ethyl	.6	Propionylbutyrylmethane[r]	..	..	..	60	157–158
Isobutyrate	.6	Acetone	.6	Isobutyrylacetone	66– 67	20	42	50	171–172[s]

[a] Boiling points and melting points are uncorrected. Analyses are by Dr. T. S. Ma, Microchemical Laboratory, Department of Chemistry, University of Chicago, Chicago, Illinois. [b] Fischer and Bartholomaus, *Ber.*, **45**, 1983 (1912). [c] The filtrate and washings of the copper salt of dipropionylmethane were extracted with ether; after washing the ether solution with 10% sulfuric acid and distilling the solvent, there was obtained 5 g. (13%) of methyl propionylacetone, b. p. 90–100° at 30 mm.; m. p. and mixed m. p. of copper salt 176–177° (see note *o*). [d] Fischer, Berg and Schormüller, *Ann.*, **480**, 151 (1930). [e] *Anal.* Calcd. for $C_{10}H_{18}O_2$: C, 70.56; H, 10.66. Found: C, 70.10; H, 10.30. [f] *Anal.* Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 72.10; H, 10.48. [g] In addition to the β-diketone there was also isolated 2.0 g. of *n*-valeramide, m. p. 104–105° [Mitchell and Reid, THIS JOURNAL, **53**, 1881 (1931)] and 6.0 g. of ethyl *n*-valeryl-*n*-valerate. *Anal.* Calcd. for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.23; H, 10.59. Cleavage of the β-keto ester with a mixture of sulfuric and acetic acids gave dibutyl ketone, b. p. 181–185°. [h] This β-diketone did not form a copper salt under the conditions used. The ether solution of the products was washed five times with 100-cc portions of water to remove the *n*-valeramide, dried and the solvent distilled. The β-keto ester and the β-diketone were separated by fractional distillation. [i] *Anal.* Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 72.20; H, 10.44. [j] These copper salts were blue, like most of the copper salts of β-diketones of the type $RCOCH_2COR$. [k] *Anal.* Calcd. for $C_{13}H_{24}O_2$: C, 73.53; H, 11.39. Found: C, 73.69; H, 10.95. [l] *Anal.* Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.63; H, 10.25. [m] This copper salt was purple, like the copper salts of other β-diketones of the type R_3C-$COCH_2COR$. [n] Claisen, *Ber.*, **22**, 1010 (1889). [o] Morgan and Drew, *J. Chem. Soc.*, **121**, 922 (1922). [p] From the filtrate and washings of the copper salt of this β-diketone there was isolated (see note *c*) 0.8 g. (2%) of ethyl propionylacetone b. p. 95–100° at 20 mm., m. p. of copper salt 175–176° (see ref. 3). [q] Morgan, Drew and Ackerman, *J. Chem. Soc.*, **125**, 740 (1924). [r] This experiment was carried out by Mr. Joseph A. Conroy of this Laboratory. [s] Conrad and Gast, *Ber.*, **31**, 1339 (1898).

Summary

1. The acylation of aliphatic methyl ketones with aliphatic esters by means of sodium amide has been studied under various conditions.

2. The yields of β-diketones with two equivalents of sodium amide to one of the ketone are twice those with equivalents of the base and ketone. This is accounted for on the basis of the mechanism of the reaction.

3. Methyl ethyl ketone is acylated mainly at the methyl group but also to a small extent at the methylene group. In certain cases the self-condensation of the ester and the formation of the amide have been observed as side reactions.

4. Sodium amide is superior to either metallic sodium or sodium ethoxide for the acylation of methyl ketones with aliphatic esters higher than ethyl acetate, and even for certain acetylations with the latter ester.

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