468.6); I. V., Rosenmund-Kuhnhenn 117.7, three hours (300% excess reagent) (calcd. 117.4).

Spectrophotometric Analysis of Cholesteryl Linoleate for Preformed Conjugation.—A Beckmann spectrophotometer was used in all spectral absorption measurements.

Absorption measurements of a solution of cholesteryl linoleate in iso-octane solution showed a total diene conjugation of less than 0.1% and the triene conjugation was negligible. Corrections for preformed conjugation were therefore not made in the final $E^{1\%}_{1\,\text{cm.}}$ values given in Table I.

TABLE I

$E^{1\%}_{1\,\text{cm.}}$ VALUES FOR ALKALI ISOMERIZED CHOLESTERYL LINOLEATE

$E^{1\%}_{1\,\text{cm.}}$ 234 mμ	
Direct isomerization, Mitchell, *et al.*[3]	Modified method
29	363
49	369
59	388
63	373
43	
33	
Av. 46	Av. 373

Alkali Isomerization of Cholesteryl Linoleate.—Since direct isomerization of cholesteryl linoleate in alkaline glycol solution was not feasible, the following modification of the method developed by Mitchell, *et al.*, was used.

The alkaline glycol used in the isomerization was prepared by dissolving in redistilled ethylene glycol 7.5 g. of potassium hydroxide in 100 ml. of glycol. The solution was heated before use to 190°, cooled to room temperature, and made up to 100 ml. with ethylene glycol.

Approximately 0.1 g. of cholesteryl linoleate was weighed into the bottom of a 1" × 6" Pyrex test-tube. One ml. of alcoholic potassium hydroxide (55 g. to 100 ml. of 99% ethyl alcohol) was added to the sample and to a blank from a pipet. The tubes were warmed in a water-bath at 55–60° for ninety minutes. Ten ml. of alkaline ethylene glycol was added by pipet to the sample and blank and the tubes were placed in a constant temperature bath at 180° for thirty minutes under nitrogen. At three successive one-minute intervals, the tubes were removed and shaken thoroughly for proper mixture of ester and reagent. The slight foaming which occurred during the heating process did not interfere with the isomerization. After exactly thirty minutes of total heating time the tubes were removed from the bath and immediately cooled in water. The isomerized soaps and excess reagent were transferred with 99% ethyl alcohol to volumetric flasks and further diluted to optical densities suitable for measurement in the spectrophotometer. Typical results are shown in Table I.

The $E^{1\%}_{1\,\text{cm.}}$ value for linoleic acid from which the cholesteryl linoleate was prepared was 867. Comparison of the calculated theoretical $E^{1\%}_{1\,\text{cm.}}$ of 374 for cholesteryl linoleate with the average experimental value of 373 indicates a purity of the compound of 99.7%, within the limits of experimental error.

The purity of cholesteryl linoleate in terms of the linoleic acid content determined by this method is more reliable than that based on iodine value. The method should be equally applicable for the determination of the purity of cholesteryl linolenate.

Summary

A modified spectrophotometric procedure for the determination of the linoleic acid in cholesteryl linoleate is reported.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

The Acylation of Ketones with Esters to Form β-Diketones by the Sodium Amide Method[1]

BY ROBERT LEVINE, JOSEPH A. CONROY, JOE T. ADAMS AND CHARLES R. HAUSER

It was shown recently[2] that, in the acylation of ketones with esters by means of sodium amide, it is advantageous to use two equivalents of the base to one of the ketone and two of the ester. This method produced much better yields of certain β-diketones than were obtained with sodium or sodium ethoxide. The scope of the sodium amide method has now been extended considerably. Various acylations have been effected using the proportions of reactants given above, designated Method A, or the proportions of two equivalents each of sodium amide and ketone to one of ester, designated Method B. The reactions were carried out by first converting the ketone to its sodium derivative by means of sodium amide in ether suspension and, after five to ten minutes,[3] adding the ester and refluxing the mixture two hours.[2] The β-diketone was generally isolated as its copper salt from which the β-diketone was regenerated. The new results are summarized in Table I.

From these results and those reported previously,[2] it may be concluded that sodium amide is satisfactory[4] for the acylation of various methyl

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(1) Paper XXX on "Condensations"; paper XXIX, THIS JOURNAL, 67, 284 (1945).

(2) Adams and Hauser, *ibid.*, 66, 1220 (1944).

(3) Evidently no appreciable amount of self-condensation of the ketone occurs within five or ten minutes. It has been found that with two equivalents of sodium amide to one of acetone less than 5% of the self-condensation product is formed even after one hour at the reflux temperature of ether. However, with equivalents of sodium amide and acetone, these conditions produced mesityl oxide (11%) and other products.

(4) Although Method A, in which the yield is based on the ketone, has been used most frequently, Method B, in which the yield is based on the ester, is to be preferred when the ester is relatively expensive or when the β-diketone fails to form a copper salt. When both the ketone and ester are expensive, it may be advantageous to use two equivalents of sodium amide to one of ketone and one (or slightly more) of ester, since these proportions have produced only an 8% lower yield than that obtained by Method A. The use of equivalents of all three reactants is not advantageous from the standpoint of either the ketone or ester. Although only an equivalent of sodium amide is required to convert the ketone to its sodium derivative, half of the ketone is regenerated during the acylation leaving half of the ester.

TABLE I

ACYLATION OF KETONES WITH ESTERS BY MEANS OF SODIUM AMIDE

				B. p.,		Yield,
Ether, ethyl	Ketone	Method[a]	Product	°C.	Mm.	%
Propionate	Acetone	A	Propionylacetone[b]	155 –158	atm.	60
Isobutyrate	Acetone	B	Isobutyrylacetone[c]	65 – 67	20	30
Laurate	Acetone	A	Lauroylacetone[d]	31.5– 32 (m. p.)		76
Laurate	Acetone	B	Lauroylacetone[d]	31.5– 32 (m. p.)		75
Hexahydrobenzoate	Acetone	A	Hexahydrobenzoylacetone[e]	130	20	62
Cinnamate	Acetone	A	Cinnamoylacetone			6[f]
Acetate	Methyl ethyl	A	Propionylacetone[g]	155 –158	atm.	40
Phenylacetate	Methyl ethyl	A	Phenylacetylpropionylmethane[h]	160	20	54
Benzoate	Methyl ethyl	A	Propionylacetophenone[i]	124.5–127	5	42
Acetate	Methyl *n*-propyl	A	*n*-Butyrylacetone[j]	67.5– 70	20	47
Benzoate	Methyl *n*-propyl	A	*n*-Butyrylacetophenone[k]	166 –171	20	38
n-Butyrate	Methyl isopropyl	A	*n*-Butyrylisobutyrylmethane[l]	89 –90.5	20	59
Acetate	Methyl isobutyl	A	Isovalerylacetone[m]	76 – 77	19	59
Isovalerate	Methyl isobutyl	B	Diisovalerylmethane[n]	115 –116	20	75
Formate	Methyl *t*-butyl	A	Pivaloylacetaldehyde[o]	43.5– 45	13	50
Acetate	Methyl *n*-amyl	A	Caproylacetone[p]	103.5–105.5	20	61
n-Caproate	Methyl *n*-amyl	B	Dicaproylmethane[q]	162 –164	20	60
Propionate	Acetophenone	A	Propionylacetophenone[i]	124 –127	5	55
n-Butyrate	Acetophenone	A	*n*-Butyrylacetophenone[k]	166 –171	20	42
n-Valerate	Acetophenone	A	*n*-Valerylacetophenone[r]	183 –186	30	40
Benzoate	Acetophenone	A	Dibenzoylmethane[s]	77 – 78 (m. p.)		70
Anisate	Acetophenone	B	4-Methoxydibenzoylmethane[t]	132 (m. p.)		45
Acetate	Diethyl	A	Methylpropionylacetone[u]	181 –183	atm.	45
Propionate	Diethyl	A	Methyldipropionylmethane[v]	95 – 97	20	28
Acetate	Cyclohexanone	A	2-Acetylcyclohexanone[w]	110 –115	20	35
Propionate	Cyclohexanone	A	2-Propionylcyclohexanone[w]	125	20	4
n-Butyrate	Cyclohexanone	A	2-*n*-Butyrylcyclohexanone[w]	130 –135	20	6–12
Acetate	Diisobutyl	A	Ethyl acetoacetate[x]	77.5– 80	20	44

[a] In Method A, 0.6 mole of sodium amide to 0.3 mole of ketone to 0.6 mole of ester are used; in Method B, 0.6 mole of sodium amide to 0.6 mole of ketone to 0.3 mole of ester are used. [b] Blue copper salt, m. p. 197–198°; Griner, *Ann., chim. phys.*, [6] **26**, 362 (1892). [c] Blue copper salt, m. p. 171–172°; Conrad and Geist, *Ber.*, **31**, 1339 (1898). [d] Blue copper salt, m. p. 112–112.5°; Morgan and Holmes, *J. Chem. Soc.*, **127**, 2891 (1925). [e] Sprague, Beckham and Adkins, THIS JOURNAL, **56**, 2665 (1934). [f] Isolated as the crude copper salt; Ryan and Dunlea, *Proc. Irish Acad.*, **32B**, 1 (1913). [g] See note *b*. There was also obtained methylacetylacetone (10%), b. p. 77–84° at 30 mm.; its gray copper salt gave no sharp melting point or decomposition point; Hauser and Adams, THIS JOURNAL, **66**, 345 (1944). [h] Copper salt, m. p. 185–187°. Calcd. for $C_{12}H_{14}O_2$: C, 75.84; H, 7.37. Found: C, 75.63; H, 7.33. [i] Copper salt, m. p. 148–149°; Leser, *Bull. soc. chim.*, [3] **27**, 64 (1902). [j] Blue copper salt, m. p. 164–165°; Morgan and Drew, *J. Chem. Soc.*, **125**, 731 (1924). There was also obtained ethylacetylacetone (2%) isolated as its gray copper salt, m. p. 209–211°; Curtiss, *Am. Chem. J.*, **17**, 436 (1895). [k] Blue-green copper salt, m. p. 135°; Beyer and Claisen, *Ber.*, **20**, 2178 (1887). [l] Blue copper salt, m. p. 122–123°; Bouveault and Bongert, *Bull. soc. chim.*, [3] **27**, 1094 (1902). [m] Blue copper salt, m. p. 154–155° (ref. given in note *j*). [n] Blue copper salt, m. p. 157–158°; Adams and Hauser, THIS JOURNAL, **66**, 1220 (1944). [o] Blue copper salt m. p. 125–126°; Couturier and Vignon, *Compt. rend.*, 140, 1695 (1905). [p] Blue copper salt, m. p. 137–138°; Morgan and Holmes, *J. Chem. Soc.*, **125**, 760 (1924). There was also obtained *n*-butylacetylacetone (0.4%) isolated as its gray copper salt, m. p. 185–186 (ref. given in note *g*). [q] Blue copper salt, m. p. 119–120° (ref. given in note *n*). [r] Claisen, *Ber.*, **20**, 2178 (1887). [s] Allen, Abell and Normington, "Organic Syntheses," Col. Vol. I, John Wiley and Sons, New York, N. Y., 1941, p. 205. [t] Blue-green copper salt, m. p. 239–241°; Bradley and Robinson, *J. Chem. Soc.*, **129**, 2356 (1926). [u] Gray copper salt, m. p. 176–177°; Morgan, Drew and Porter, *Ber.*, **58**, 333 (1925). This reaction using sodium amide was carried out at 0° for two hours. When the reaction was carried out in the usual manner, a mixture of products appeared to be formed, similar to that reported by Morgan and co-workers using sodium. [v] Gray copper salt, m. p. 176–178° (ref. given in note *u*). [w] Adams and Hauser, THIS JOURNAL, **67**, 284 (1945). [x] Semicarbazone, m. p. 128–129° Thiele and Stange, *Ann.*, **238**, 29 (1894).

ketones with various aliphatic or aromatic esters to form β-diketones of the type $RCOCH_2COR$. However, the yield has been low with ethyl cinnamate and acetone, while unsuccessful attempts have been made to acylate acetophenone with ethyl *m*-nitrobenzoate and benzalacetone with ethyl *n*-butyrate. With diethyl ketone the results were fairly satisfactory but with cyclohexanone the yield was fairly good only with ethyl acetate. An attempt to acetylate diisobutyl ketone with ethyl acetate by means of sodium amide or sodium triphenylmethide resulted in the self-condensation of the ester. It should be pointed out that, not only would acylations that fail with sodium amide probably also fail with sodium or sodium ethoxide, but that a number of acylations which are unsatisfactory with sodium and sodium ethoxide are quite satisfactory with sodium amide. For example, the acylation of acetone with ethyl hexahydrobenzoate fails with sodium ethoxide[5] but gives a good yield with sodium amide.

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(5) Sprague, Beckham and Adkins, THIS JOURNAL, **56**, 2665 (1934).

Similar to the propionylation of methyl ethyl ketone reported previously,[2] the acetylation of this ketone by the means of sodium amide forms an appreciable amount of the methylene derivative in addition to the higher yield of the methyl derivative[6]; however, the acylation of methyl *n*-propyl or methyl *n*-amyl ketone forms only little of the methylene derivative. It has been found that not all basic reagents produce both the methyl and methylene derivatives with methyl ethyl ketone. In Table II are given the yields of methyl and methylene derivatives (propionylacetone and methyl acetylacetone, respectively) that have been obtained on acetylation of methyl ethyl ketone with ethyl acetate by means of four different basic reagents. It can be seen that the proportion of methyl to methylene derivative is about the same with sodium amide and metallic sodium, but relatively much greater with sodium triphenylmethide and sodium ethoxide. Actually none of the methylene derivative was found in the experiment with sodium ethoxide. The reason for the variation in the proportions of methyl and methylene derivatives with these different basic reagents is not clear.[7]

TABLE II

METHYL AND METHYLENE DERIVATIVES ON ACETYLATION OF METHYL ETHYL KETONE WITH VARIOUS BASIC REAGENTS

Basic reagent	Methyl derivative, yield, %	Methylene derivative, yield, %
Sodium amide	40	10
Sodium[a]	33	8
Sodium triphenylmethide[b]	40	2
Sodium ethoxide[c]	40	0

[a] The reaction of 1.0 moles of sodium, 0.5 mole of methyl ethyl ketone and 3.0 moles of ethyl acetate was carried out according to the method of Sprague, Beckham and Adkins, THIS JOURNAL, **56**, 2665 (1934). [b] An ether solution of 0.645 mole of methyl ethyl ketone was added to 0.645 mole of sodium triphenylmethide at 0° and, after the color of the base was discharged, 0.645 mole of ethyl acetate in absolute ether was added. After one hour the reaction was worked up as described previously (Baumgarten, Levine and Hauser, THIS JOURNAL, **66**, 862 (1944)). [c] The reaction of 1.0 mole of sodium ethoxide, 1.0 mole of methyl ethyl ketone and 5.0 moles of ethyl acetate was carried out as described previously for acetylacetone; Adkins and Rainey, "Organic Syntheses," Vol. XX, John Wiley and Sons, New York, N. Y., 1940, p. 6.

In each of these experiments the ether solution containing the product was dried, the solvent distilled and a methanol solution of the residue poured into hot saturated copper acetate solution. The precipitate of the blue copper salt of the methyl derivative (from which the propionylacetone was regenerated[2]) was filtered off, washed with ligroin, and the methylene derivative isolated from the filtrate by shaking with 100 cc. of 10% sulfuric acid and 200 cc. of ether, distilling the ether, and fractionating the residue *in vacuo*. For the properties of the methyl and methylene derivatives see notes of Table I.

Summary

1. Various ketones have been acylated with various esters by means of sodium amide to form β-diketones (or β-ketoaldehyde). Certain of the reactions have been effected satisfactorily only by means of this reagent, while others failed even with this reagent.

2. A study has been made of the proportions of the methyl and methylene derivatives of methyl ethyl ketone produced on acetylation in the presence of four different basic reagents.

DURHAM, N. C. RECEIVED FEBRUARY 17, 1945

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(6) Although there has been no difficulty in isolating the methyl derivative of methyl ethyl ketone in the pure condition, that ester-ketone combination which does not employ methyl ethyl ketone is generally to be preferred in the synthesis of β-diketones of the type, $RCOCH_2COC_2H_5$, since the yields are usually better. This may be illustrated by the synthesis of propionylacetone, which is obtained in 60% yield from ethyl propionate and acetone but only in 40% yield from ethyl acetate and methyl ethyl ketone, and by the synthesis of propionylacetophenone, which is obtained in 55% yield from ethyl propionate and acetophenone but only in 43% yield from ethyl benzoate and methyl ethyl ketone.

(7) It should be pointed out that the sodium amide was suspended in ether whereas the sodium triphenylmethide was in ether solution and that, with sodium amide and sodium, two equivalents of the reagent to one of the ketone were used while, with sodium triphenylmethide and sodium ethoxide, equivalents of the reagent and ketone were employed. Similar proportions of the corresponding methyl (32%) and methylene (8%) derivative have been obtained with ethyl propionate and methyl ethyl ketone using equivalents of sodium amide and ketone.