napthoquinone (m. p. 102–103.5, mixed m. p. 103–104°) by the method described in "Organic Syntheses"[20] for oxidizing 1-naphthol.

The following results were obtained on heating other esters with acetamide: ethyl γ-phenylbutyrate (9.3 g.), was heated with 20 g. of acetamide for fifteen hours at 220°; 7.6 g. of the ester was recovered. γ-Phenylbutyric acid (6.4 g.), heated with 15 g. of acetamide at 220° for two hours, gave 2.9 g. of γ-phenylbutyramide, m. p. 83–84°. Ethyl 4-phenyl-2-butenoate[8] (5 g.) and 10 g. of acetamide, were heated for one and one-half hours at 220°; 3.8 g. of the ester was recovered. Ethyl (1-*o*-tolylethylidene)-cyanoacetate III (Table I) (10 g.) and acetamide (20 g.), were heated at 220° for one and one-half hours; 6.8 g. of the ester was recovered.

Summary

Experimental conditions are described under which both aliphatic and aromatic ketones, including benzophenone, can be condensed with ethyl cyanoacetate to give ethyl alkylidene cyanoacetates. The condensing agents are ammonium acetate and acetic acid. Piperidine acetate and acetic acid are used under similar conditions to condense certain aldehydes with ethyl malonate. Conditions suitable for the hydrogenation of these esters are described.

The condensation product of benzyl methyl ketone and ethyl cyanoacetate, ethyl (1-methyl-2-phenylethylidene)-cyanoacetate (I), loses alcohol when heated in acetamide solution, producing 2-cyano-3-methyl-1-naphthol (II).

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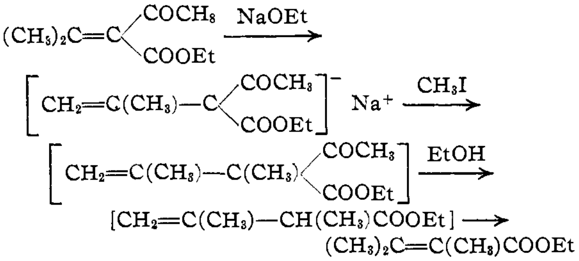
[20] "Organic Syntheses," Coll. Vol. I, 1932. p. 41, and p. 375.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

The Introduction of Substituted Vinyl Groups. VIII. Acetoacetic Ester Series[1]

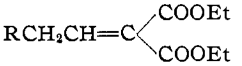
BY ARTHUR C. COPE AND CORRIS M. HOFMANN

When ethyl isopropylideneacetoacetate is treated with alcoholic sodium ethoxide and methyl iodide, ethyl trimethylacrylate is formed.[2] The sequence of reactions involved is the formation of a sodium enolate from the ester by three-carbon tautomerism, followed by alkylation, cleavage (alcoholysis) of the acetyl group, and migration of the double bond.



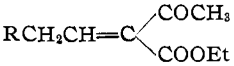
$$(CH_3)_2C{=}C\begin{smallmatrix}COCH_3\\COOEt\end{smallmatrix} \xrightarrow{NaOEt} \left[CH_2{=}C(CH_3){-}C\begin{smallmatrix}COCH_3\\COOEt\end{smallmatrix}\right]^- Na^+ \xrightarrow{CH_3I} \left[CH_2{=}C(CH_3){-}C(CH_3)\begin{smallmatrix}COCH_3\\COOEt\end{smallmatrix}\right] \xrightarrow{EtOH} [CH_2{=}C(CH_3){-}CH(CH_3)COOEt] \longrightarrow (CH_3)_2C{=}C(CH_3)COOEt$$

Although the alkylation of ethyl isopropylidenemalonate in alcohol solution is accompanied by partial cleavage,[3] primary alkylidene malonic esters (I) can be alkylated successfully under similar conditions.[4]



$$RCH_2CH{=}C\begin{smallmatrix}COOEt\\COOEt\end{smallmatrix}$$

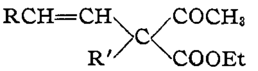
I



$$RCH_2CH{=}C\begin{smallmatrix}COCH_3\\COOEt\end{smallmatrix}$$

II

It consequently seemed possible that primary alkylidene acetoacetic esters (II) could be alkylated in alcohol solution without cleavage, producing alkyvinyl alkylacetoacetic esters (III).



$$\begin{smallmatrix}RCH{=}CH\\R'\end{smallmatrix}{>}C{<}\begin{smallmatrix}COCH_3\\COOEt\end{smallmatrix}$$

III

$RCH{=}CH{-}CH(CH_3)COOR'$

IV, R and R' = Et
V, R = Et; R' = *i*-Pr
VI, R = *i*-Pr; R' = Et
VII, R and R' = *i*-Pr

A number of primary alkylidene acetoacetic esters (Table I) were prepared by condensing aldehydes with ethyl and isopropyl acetoacetates. Two of them, ethyl butylideneacetoacetate and ethyl isopentylideneacetoacetate, were converted into sodium enolates with alcoholic sodium ethoxide and treated with methyl iodide. The products of the vigorous reactions which occurred were the β,γ-unsaturated monocarboxylic esters, IV and VI (Table II). Cleavage consequently had occurred just as in the ethyl isopropylideneacetoacetate methylation,[2] but the double bond had not migrated to the α,β-position. The double bond probably failed to shift in these cases because the alkylations proceeded very rapidly, removing the sodium enolates (and sodium ethoxide) which would catalyze isomerization of the products.

Methylation of the corresponding isopropyl alkylideneacetoacetates in isopropyl alcohol solu-

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[1] From a dissertation presented to the Faculty of the Graduate School of Bryn Mawr College by Corris M. Hofmann in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] Jupp, Kon and Lockton, *J. Chem. Soc.*, 1642 (1928).

[3] Cope and Hancock, THIS JOURNAL, **60**, 2644 (1938).

[4] Cope, Hartung, Hancock and Crossley, *ibid.*, **62**, 314 (1940).

tion gave similar results, producing the β,γ-unsaturated isopropyl esters V and VII (Table II). Evidently the acetyl group in substituted vinyl alkylacetoacetic esters is very readily cleaved by alcoholysis.

This type of synthesis is not capable of general application to the preparation of unsaturated esters. The alkylation of ethyl and isopropyl butylidene acetoacetates with butyl iodide gave impure α,β-unsaturated esters, $n\text{-}C_3H_7CH{=}C(C_4H_9)COOR$ (VIII). Ethyl and isopropyl isopentylideneacetoacetates on alkylation with propyl iodide reacted in the same way to give $i\text{-}C_4H_9CH{=}C(C_3H_7)COOR$ (IX). Higher boiling material which could not be separated completely from the esters VIII and IX was also formed in the alkylations. The different course taken by the reactions when higher alkyl iodides were used may be explained by the fact that the alkylations were slower. Consequently, the products were in contact with alcohol containing the sodium enolates (and sodium alkoxides in equilibrium with them) for a considerable length of time. As a result, migration of the double bond and partial addition of alcohol to the resulting α,β-unsaturated esters occurred.[5]

Experimental[6]

Condensation of Aldehydes with Acetoacetic Esters.—The conditions employed by Knoevenagel for condensing aldehydes with ethyl acetoacetate[7,8] proved to be more satisfactory than procedures in which piperidine acetate or acetamide and acetic acid were used as the condensing agents. The esters described in Table I were prepared by a procedure which may be illustrated by describing the synthesis of ethyl butylideneacetoacetate.

A mixture of ethyl acetoacetate (0.5 mole) and butyraldehyde (freshly distilled) (0.55 mole) was cooled to −5°. Piperidine (0.5 g.) in 1 g. of alcohol was added slowly (five to ten minutes), so that the heat of reaction did not cause the temperature to rise above +5 to +10°. The mixture was cooled to 0° and placed in an icebox for twelve to twenty-four hours, after which the ester was washed with three 100-cc. portions of water containing a few drops of acetic acid. The washings were extracted with ether, and the combined ether extract and ester layer were distilled in vacuum through a Widmer column. The yield of ethyl butylideneacetoacetate was 71.4 g. (81%) (Table I).

Butyraldehyde, isovaleraldehyde, 2-ethylbutanal and 2-ethylhexanal were also condensed with ethyl acetoacetate by treating the molar quantities of reactants listed above with 1.7 g. of piperidine, 6.1 g. of acetic acid and 25 cc. of

TABLE I

CONDENSATION PRODUCTS FROM ALDEHYDES AND ALKYL ACETOACETATES

Aldehyde	Alkyl alkylidene-acetoacetate	Yield, %	B. p., °C.	Mm.	n^{25}_D	d^{25}_{25}	Mol. refr. Calcd.	Mol. refr. Found	Exaltation	% Hydrogen abs. in quant. reduction	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Butyraldehyde	Butylidene[a]	81	118–120	18	1.4510	0.9780	49.59	50.81	1.22	99	$C_{10}H_{16}O_3$	65.19	64.99	8.75	8.79
Butyraldehyde	Butylidene[b]	75	125–128	24	1.4467	.9548	54.21	55.57	1.36	98	$C_{11}H_{18}O_3$	66.64	66.59	9.15	9.40
Isovaleraldehyde	Isopentylidene[a,c]	83	120–121	15	1.4492	.9615	54.21	55.41	1.20	102	$C_{11}H_{18}O_3$				
Isovaleraldehyde	Isopentylidene[b]	89	135–136	24	1.4448	.9423	58.83	60.07	1.24	97	$C_{12}H_{20}O_3$	67.89	67.73	9.50	9.58
2-Ethylbutanal	2-Ethylbutylidene[a]	71	122–123	11	1.4539	.9584	58.83	59.96	1.13	99	$C_{12}H_{20}O_3$	67.89	67.69	9.50	9.54
2-Ethylhexanal	2-Ethylhexylidene[a]	72	138–141	11	1.4559	.9423	68.07	69.43	1.36	103	$C_{14}H_{24}O_3$	69.96	69.84	10.07	10.07

[a] Ethyl ester, prepared from ethyl acetoacetate. [b] Isopropyl ester, prepared from isopropyl acetoacetate. [c] Previously prepared by Claisen and Matthews, *Ann.* **218**, 174 (1883), and Knoevenagel (ref. 8).

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(5) Alcohol adds to α,β-unsaturated esters (but not to β,γ-unsaturated esters) in the presence of sodium alkoxides; *cf.* Kon, Linstead and Maclennan, *J. Chem. Soc.*, 2454 (1932).

(6) All melting and boiling points are uncorrected.

(7) Knoevenagel, *Ber.*, **29**, 172 (1896).

(8) Knoevenagel, *ibid.*, **31**, 730 (1898).

TABLE II

METHYLATION PRODUCTS FROM ALKYLIDENE ACETOACETIC ESTERS

Alkyl alkylidene-acetoacetate	Product	Yield, %	B. p. °C.	B. p. Mm.	n^{25}_D	d^{25}_{25}	Mol. refr., M_D Calcd.	Mol. refr., M_D Found	% Hydrogen abs. in quant. reduction	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Ethyl butylidene	Ethyl 2-methyl-3-hexenoate[a] (IV)	45	65–66	13	1.4231	0.8919	44.96	44.72	98	$C_9H_{16}O_2$	69.19	69.26	10.32	10.50
Isopropyl butylidene	Isopropyl 2-methyl-3-hexenoate (V)	36	75–76	18	1.4191	.8700	49.58	49.54	99	$C_{10}H_{18}O_2$	70.55	70.50	10.66	10.58
Ethyl isopentylidene	Ethyl 2,5-dimethyl-3-hexenoate (VI)	69	73–74	15	1.4234	.8747	49.58	49.72	100	$C_{10}H_{18}O_2$	70.55	70.33	10.66	10.63
Isopropyl isopentylidene	Isopropyl 2,5-dimethyl-3-hexenoate (VII)	49	89–91	25	1.4192	.8595	54.20	54.27	99	$C_{11}H_{20}O_2$	71.69	71.71	10.94	10.89

[a] Previously described by Kon, Linstead and Maclennan (ref. 5). Analyzed to check the purity of the ester prepared in this manner.

benzene, and refluxing the mixture under a constant water separator[9] until the formation of water ceased (one to eight hours). The yields of alkylidene acetoacetic esters obtained by this method were 52, 68, 63 and 64%, respectively. The condensation products of butyraldehyde and isovaleraldehyde with ethyl acetoacetate were also prepared in 54 and 67% yield, respectively, by a similar procedure in which 10 g. of acetamide replaced the piperidine. Ethyl butylideneacetoacetate was obtained in 28% yield in a reaction similar to the above except that 4.8 g. of *p*-toluenesulfonic acid replaced the piperidine.

Efforts to condense either methyl ethyl ketone or methyl amyl ketone with ethyl acetoacetate by the procedures listed above were unsuccessful. No reaction occurred, and the starting materials were recovered in each case.

The purity of the alkylidene acetoacetic esters was determined by quantitative reduction (results are listed in Table I). Samples of 0.01 to 0.03 mole of each ester dissolved in 20 cc. of alcohol were hydrogenated at room temperature and atmospheric pressure in the presence of 1 g. of palladinized charcoal catalyst.[10]

The reduction product of ethyl butylideneacetoacetate was identified as ethyl butylacetoacetate by ketonic hydrolysis to methyl amyl ketone (57% over-all yield), which was characterized as the semicarbazone.

Alkylation of Alkylidene Acetoacetic Esters.—The alkylidene acetoacetic esters were alkylated under conditions similar to those used in alkylating primary alkylidene malonic esters.[4] The following example is typical.

A solution of sodium ethoxide was prepared by dissolving 11.5 g. of sodium in 500 cc. of absolute alcohol in a 1 l. three-necked flask. The solution was cooled to −5° and ethyl butylideneacetoacetate (92 g., 0.5 mole) was added slowly with stirring. After the solution had been stirred for one-half hour at −5°, methyl iodide (85.2 g., 0.6 mole) was added rapidly and the mixture was heated to boiling at once. After the exothermic reaction had ceased, the solution was refluxed for three-quarters of an hour, at which time it was nearly neutral. The reaction mixture was cooled and added to one liter of water containing 1 cc. of 20% hydrochloric acid. The ester was extracted with benzene and distilled in vacuum through a Widmer column; yield of (IV) 35 g. (45%). In the preparation of each of the esters described in Table II, there was little if any material boiling lower than the alkylation product, but there was a rather large high-boiling residue.

The isopropyl esters were alkylated by a procedure similar to the above, except that the sodium isopropoxide solution (600 cc.) was cooled to 56° rather than −5° before adding the isopropyl alkylideneacetoacetate and stirred at that temperature for five minutes before the methyl iodide was added.

Identification of the Alkylation Products.—The esters described in Table II were hydrogenated quantitatively in the manner described above.

Ethyl 2-methyl-3-hexenoate (Compound (IV), Table II) was identified by correspondence in physical properties to the recorded values for this ester,[5] and by saponification to

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(9) Cope, Hofmann, Wyckoff and Hardenbergh, THIS JOURNAL, 63, 3452 (1941).

(10) Hartung, *ibid.*, 50, 3372 (1928).

2-methyl-3-hexenoic acid, b. p. 121–122° (24 mm.); n^{25}_D 1.4382; d^{25}_{25} 0.9461; M_D calcd. 35.60; found, 35.66. These properties also are in agreement with recorded values.[11] The unsaturated acid was hydrogenated quantitatively, and the reduced acid was converted into 2-methylhexanamide through the acid chloride. After recrystallization from ether and pentane, the amide had m. p. 71–72°,[12] and was identical (mixed m. p.) with a known sample prepared from 2-methylhexanoic acid obtained from ethyl butylmethylmalonate. The same amide was obtained from isopropyl 2-methyl-3-hexenoate (V, Table II).

Isopropyl 2,5-dimethyl-3-hexenoate (VII, Table II) was identified similarly by hydrogenation followed by saponification to 2,5-dimethylhexanoic acid, from which the acid chloride and amide were prepared. After recrystallization from ether and pentane the amide melted at 100–101°,[13] and was identical with a sample prepared from 2,5-dimethylhexanoic acid obtained from ethyl isoamylmethylmalonate.

The position of the double bond in the esters described in Table II was established by ozonization of 0.01 mole samples under conditions previously described.[14] The ozonization of esters (IV) and (V) produced propionaldehyde, while (VI) and (VII) gave isobutyraldehyde. The aldehydes were identified as their 2,4-dinitrophenylhydrazones.

Attempts to Introduce Higher Alkyl Groups.—The alkylations of ethyl and isopropyl butylideneacetoacetates with butyl iodide and of ethyl and isopropyl isopentylideneacetoacetates with propyl iodide were carried out under conditions similar to those used in the methylations described above. Mixtures of products were formed, which were incompletely separated into two principal fractions by distillation in each case. The lower boiling fraction isolated from each alkylation was slightly impure, but was characterized as an α,β-unsaturated ester (VIII or IX) by ozonization, which produced butyraldehyde from (VIII) and isovaleraldehyde from (IX). The higher boiling fractions were mixtures which were not completely characterized. Enough data were obtained to show that the high boiling fraction formed in the alkylation of ethyl butylideneacetoacetate with butyl iodide was produced in part by addition of alcohol to the double bond. A quarter-mole alkylation gave (1) 12 g. of impure VIII (R = Et) and (2) 16.6 g. of higher boiling material, b. p. 88–125° (23 mm.). Redistillation of the latter fraction gave (3) 6.5 g., b. p. 95–97° (20 mm.). Quantitative reduction of (3) showed 15% unsaturation, calculated as (VIII), and Zeisel determinations showed 45% ethoxyl; calcd. for (VIII) 22.7%, and for the addition product of (VIII) and alcohol (n-$C_3H_7CH(OEt)CH(C_4H_9)COOEt$, X) 36.9%. From the high per cent. of ethoxyl found, reactions other than simple addition of alcohol are involved in the formation of the high boiling material. Saponification of fraction (3) gave an impure acid, b. p. 138–139° (18 mm.), with a neutral equivalent of 195.6, 15% unsaturation calculated as the acid corresponding to (VIII), and 25.1% OEt (calcd. for the acid from (VIII, neutr. eq. 170, OEt, none; for the acid from X, neutr. eq. 216, OEt, 20.8%).

Refluxing the ester IX (R = Et) for three hours with absolute alcohol containing one-third of a molar equivalent of sodium ethoxide converted approximately one-third of the ester into higher boiling material (resembling the fraction of similar boiling point obtained in the alkylation in which IX was prepared), which showed only 24% unsaturation (calcd. as IX) on hydrogenation. This reaction was carried out to verify the fact that alcohol will add to α,β-unsaturated esters of this type in the presence of alcoholic sodium ethoxide (see ref. 5).

Summary

Several primary alkylidene acetoacetic esters have been alkylated by treatment with sodium alkoxides and alkyl iodides in alcohol solution. When methyl iodide was used as the alkylating agent, the products isolated were the α-methyl β,γ-unsaturated esters produced by cleavage (alcoholysis) of the acetyl group from the substituted vinyl methylacetoacetic esters. Complex mixtures containing α-alkyl α,β-unsaturated esters were formed when higher alkyl iodides were used in the alkylation.

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[11] Von Auwers and Heyna, *Ann.*, **434**, 158 (1923); Kon, Linstead and Maclennan, *J. Chem. Soc.*, 2453 (1932).

[12] Rassetti, *Bull. soc. chim.*, **33**, 690 (1905).

[13] Barbier and Locquin, *Compt. rend.*, **156**, 1445 (1913).

[14] Cope and Hancock, THIS JOURNAL, **60**, 2902, 2906 (1938).