[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

The Introduction of Substituted Vinyl Groups. III. (Dialkylvinyl)-alkylcyanoacetic Esters

BY ARTHUR C. COPE AND EVELYN M. HANCOCK

Indirect methods similar to those previously described for introducing isopropenyl and 1-methylpropenyl groups into malonic ester[1] are not equally practical for synthesizing higher (1-alkylvinyl)-alkylmalonic esters. Such syntheses would require as intermediates higher 1-alkylalkylidenemalonic esters, $RCH_2C(R')=C(COOEt)_2$. Esters of the latter type are difficult to prepare because ketones higher in molecular weight than methyl ethyl ketone do not condense easily with malonic ester. Higher ketones do condense readily with cyanoacetic ester to give excellent yields of alkylidene cyanoacetic esters.[2] This paper reports an investigation of the alkylation of these cyanoacetic ester derivatives.

Aralkylidene cyanoacetic esters, which are activated by an aryl group in addition to the nitrile and ester groups, have been alkylated previously.[3] However, an attempt to alkylate an alkylidene derivative not similarly activated by an aryl group, ethyl isopropylidenecyanoacetate, was reported to be unsuccessful.[4] We have found that alkylidenecyanoacetic esters can be alkylated, and that (dialkylvinyl)-alkylcyanoacetic esters are produced in good yields if the conditions of synthesis minimize destruction of the products by alcoholysis.

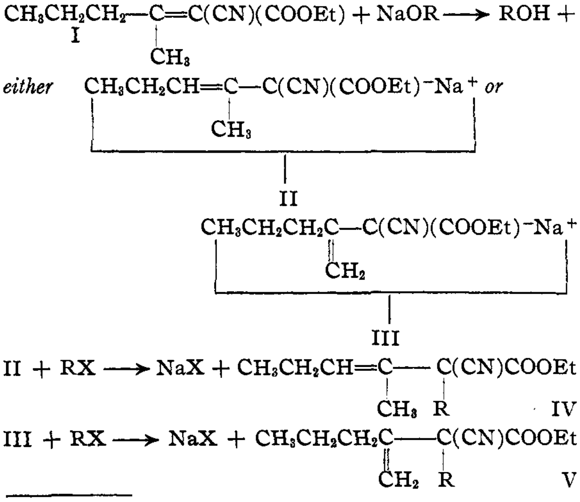
Sodium derivatives can be prepared from the alkylidenecyanoacetic esters by reaction with sodamide, metallic sodium, or sodium alkoxides. Sodamide is the reagent of choice in the malonic ester series,[1] but it produces both cleavage and polymerization of the cyanoacetic esters. The use of powdered sodium in inert solvents causes partial reduction of the unsaturated esters, and partially reduced products are formed when the enolates are alkylated. Sodium alkoxides react with the alkylidene esters to give good yields of the sodium derivatives, which can be alkylated satisfactorily in alcohol solution under proper conditions.

The (dialkylvinyl)-alkylcyanoacetic esters which are produced in the alkylations undergo alcoholysis even more readily than do the corresponding malonic esters, so that the success of their synthesis in alcohol solution is rather surprising. The alkylations of the cyanoacetic esters proceed very rapidly, however, so that the products are in contact with the alcohol and sodium alkoxide for only a short time, and there is little opportunity for alcoholysis.

Yields in the alkylation reactions are poorest in methyl alcohol solution, better in ethyl alcohol, and highest in isopropyl alcohol. This is the order of decreasing effectiveness of the three alcohols in producing alcoholysis in ester–alcohol interchange reactions.[5]

As would be expected, the rapid alkylations obtained with the most active alkylating agents give highest yields. The syntheses of 1-ethylpropenyl and 1-propyl-1-butenyl substituted esters, containing the groups $CH_3CH=C(C_2H_5)$- and $CH_3CH_2CH=C(C_3H_7)$-, gave excellent yields. The yields of 1-methyl-1-alkenyl substituted esters, containing $RCH=C(CH_3)$- groups, were lower regardless of the size of the group R. This is attributed to the hindrance to alcoholysis afforded by the presence of a group larger than methyl in the 1-position of the alkenyl residue in the former esters.

Alkylidenecyanoacetic esters prepared from unsymmetrical ketones can lead to two structural types, as the following equations with the methyl propyl ketone condensation product illustrate.



$$\underset{\text{I}}{CH_3CH_2CH_2}-\underset{\underset{CH_3}{|}}{C}=C(CN)(COOEt) + NaOR \longrightarrow ROH +$$

$$\text{either}\quad \underbrace{CH_3CH_2CH=\underset{\underset{CH_3}{|}}{C}-C(CN)(COOEt)^-Na^+}_{\text{II}} \quad \text{or}$$

$$\underbrace{CH_3CH_2CH_2\underset{\underset{CH_2}{\|}}{C}-C(CN)(COOEt)^-Na^+}_{\text{III}}$$

$$\text{II} + RX \longrightarrow NaX + CH_3CH_2CH=\underset{\underset{CH_3}{|}}{C}-\underset{\underset{R}{|}}{C}(CN)COOEt \qquad \text{IV}$$

$$\text{III} + RX \longrightarrow NaX + CH_3CH_2CH_2\underset{\underset{CH_2}{\|}}{C}-\underset{\underset{R}{|}}{C}(CN)COOEt \qquad \text{V}$$

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(1) (a) Cope and Hancock, THIS JOURNAL, **60**, 2644 (1938); (b) *ibid.*, **60**, 2901 (1938).

(2) *Cf.* Cope, *ibid.*, **59**, 2327 (1937).

(3) Hugh and Kon, *J. Chem. Soc.*, 780 (1930).

(4) Birch and Kon, *ibid.*, **123**, 2443 (1923).

(5) Fehlandt and Adkins, THIS JOURNAL, **57**, 193 (1935); Hatch and Adkins, *ibid.*, **59**, 1694 (1937).

Ozonization of the alkylation products gave propionaldehyde but only traces of formaldehyde, so that formula IV is correct rather than V. The alkylation products of alkylidenecyanoacetic esters derived from four other methyl ketones were ozonized, and the higher aldehydes to be expected on cleavage of molecules having the structures indicated in Table I were formed, while only traces of formaldehyde were produced. Consequently, in this series as well as in the malonic ester series,[1b] the formation of a sodium derivative involves the loss of hydrogen from the methylene of an alkyl group higher than methyl, rather than from the methyl group.

When the various alkylated esters were purified by distillation alone, they were found to contain the corresponding alkylidene esters as impurities. Alkylidenecyanoacetic esters form sodium bisulfite addition compounds,[6] so that it was possible to remove any unalkylated ester present by shaking the crude product with 20% sodium bisulfite solution. Addition of an excess of sodium carbonate solution to the sodium bisulfite extract liberates the alkylidenecyanoacetic esters, which can be recovered in this manner.

Experimental Part

Both methyl and ethyl alkylidenecyanoacetates were alkylated in methyl, ethyl and isopropyl alcohols. Analytically pure esters result only when the alkyl of the ester is the same as that of the alcohol used as a solvent, for otherwise ester interchange results during the alkylation, and mixed esters are produced. Although the mixed esters do not have constant boiling points, they are perfectly satisfactory for use as intermediates in syntheses in which the alkyl of the ester group is removed. The yields of methyl esters obtained in methyl alcohol were poor, and they were prepared in this manner only to obtain pure samples for analyses and physical constants. Methyl esters alkylated in ethyl alcohol usually gave as good yields as did the ethyl esters, however, and both classes gave highest yields when alkylated in isopropyl alcohol.

An additional advantage of using isopropyl alcohol as a solvent is the fact that it permits the use of dialkyl sulfates, particularly diethyl sulfate, as alkylating agents. The dialkyl sulfates are poorly adapted to alkylating esters in ethyl alcohol solution, because of the rapid side reaction which occurs with the alcohol. The hydrogen of the hydroxyl group in isopropyl alcohol is less reactive, so that the competing reaction of the alcohol with the dialkyl sulfate is diminished, and the ester alkylation becomes the principal reaction.

Alkylations in Alcohol Solution.—The ethylation of ethyl (1-methylbutylidene)-cyanoacetate (I) in isopropyl alcohol will be described as a typical example. A solution of 13.8 g. (0.6 mole) of sodium in 600 cc. of dry isopropyl alcohol was prepared in a one-liter three-necked flask. The solution was cooled to 60°, at which temperature sodium isopropoxide started to crystallize out. Ethyl (1-methylbutylidene)-cyanoacetate, 108.6 g. (0.6 mole), was added during four minutes, with stirring. The mixture was cooled in ice during the addition, and the solution was at 25° when the addition was completed. Diethyl sulfate, 94 g. (0.61 mole), was added in one portion and the solution quickly heated to the boiling point. The reaction was vigorous, and after one-half to one hour of refluxing, the solution was neutral to litmus. The mixture was cooled in ice, diluted with 1400 cc. of water, and the ester layer separated. The water layer was extracted four times with benzene, and the combined ester and benzene extracts washed twice with water. Distillation from a modified Claisen flask gave 118 g. of crude ester, b. p. 125–140° (16 mm.). After shaking the crude product for twelve hours with 200 cc. of 20% sodium bisulfite solution and redistilling through a Widmer column, the yield of a mixture of the ethyl and isopropyl esters of ethyl (1-methyl-1-butenyl)-cyanoacetic acid, b. p. 129–133° (14 mm.) was 100 g. (80%, calculated as the ethyl ester). Other alkylations in isopropyl alcohol were performed in a similar manner. When the less active alkyl halides are used in these alkylations, it is not essential to cool the solutions before adding the halides. With the dialkyl sulfates, the reactions are too vigorous unless this precaution is taken. Alkylations in methyl and ethyl alcohols were performed using 700 cc. of the anhydrous alcohols per mole of sodium, and cooling the sodium alkoxide solutions to −5° during the addition of the alkylidene esters. After the esters were added, the solutions were stirred for twenty minutes at −5 to −10° before adding the alkylating agent. The mixtures were then heated rapidly to the boiling point, and the reactions were usually vigorous. Small aliquot portions of those reaction mixtures which did not become neutral were titrated from time to time with standard acid, and refluxed until the alkalinity became constant. The properties of various (dialkylvinyl)-alkylcyanoacetic esters and data concerning the preparations are recorded in Table 1.

Sodamide in Inert Solvents.—A sodium derivative was prepared from methyl (1-methylhexylidene)-cyanoacetate by adding 0.5 mole of the ester to an equivalent quantity of sodamide in liquid ammonia solution. On replacing the ammonia with toluene containing a small amount of ether, according to the procedure used in other alkylations with sodamide,[1] a very insoluble sodium derivative was precipitated. Diethyl sulfate was added and the mixture refluxed until it became neutral (two hours), after which the ester was washed and distilled. The low boiling portion of the distillate contained methyl amyl ketone, a cleavage product of the alkylidene ester. The crude ester fraction weighed 21 g., and a large tarry residue remained. The impure product was shaken with sodium bisulfite solution and redistilled. The yield of pure methyl (1-methyl-1-hexenyl)-cyanoacetate, identical with the product described in Table I, was only 14 g. (13%).

Sodium in Inert Solvents.—Powdered sodium was used in several cases for preparing sodium derivatives of the alkylidenecyanoacetic esters. For example, 0.25 mole of methyl (1-propylbutylidene)-cyanoacetate was treated

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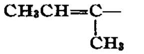
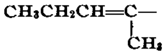
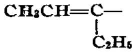
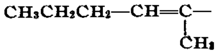
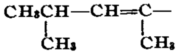
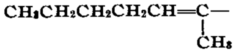
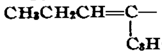
(6) Lapworth and McRae, *J. Chem. Soc.*, 121, 2745 (1922).

TABLE I

SUBSTITUTED VINYLALKYLCYANOACETIC ESTERS

Substituted vinyl group	Alkyl group	Ester	Alkylating agent	Hours refluxed	Yield, %	B. p. (uucorr.) °C.	Mm.	n^{25}_D	d^{25}_{25}	Molecular refraction Calcd.	Molecular refraction Found	Formula	Nitrogen, % Calcd.	Nitrogen, % Found[a]	Yield of mixed ethyl isopropyl ester, %
1-Methylpropenyl,  $CH_3CH{=}\underset{\substack{\vert\\CH_3}}{C}—$	Ethyl[l]	Ethyl	Ethyl iodide	1.0	55	117–117.5	12	1.4470	0.9665	53.95	54.11	$C_{11}H_{17}O_2N$	7.11	7.16	..
	Propyl	Ethyl	Propyl iodide	0.3	42	120–122.5	9	1.4481	.9560	58.57	58.68	$C_{12}H_{19}O_2N$	6.70	6.78	58
	Butyl	Ethyl	Butyl iodide	2.3	40	134–134.5	9	1.4500	.9478	63.19	63.47	$C_{13}H_{21}O_2N$	6.28	6.39	..
1-Methyl 1-butenyl,  $CH_3CH_2CH{=}\underset{\substack{\vert\\CH_3}}{C}—$	Methyl[l]	Ethyl	Methyl iodide	0.5	68	124–126	16	1.4445	.9589	53.95	54.26	$C_{11}H_{17}O_2N$	7.18	7.02	82[b]
	Ethyl[l]	Ethyl	Ethyl iodide	3.0	63[c]	135–136	17	1.4460	.9530	58.57	58.70	$C_{12}H_{19}O_2N$	6.70	6.71	80[d]
	Propyl	Ethyl	Propyl iodide	1.0	43	128–129	9	1.4480	.9436	63.19	63.50	$C_{13}H_{21}O_2N$	6.28	6.34	70[e]
	Isopropyl	Ethyl	Isopropyl iodide	3.0	42	133–134	13	1.4485	.9482	63.19	63.26	$C_{13}H_{21}O_2N$	6.28	6.30	73[f]
	Allyl	Ethyl	Allyl bromide	1.0	40	130–133	9	1.4602	.9622	62.72	63.16	$C_{13}H_{19}O_2N$	6.34	6.33	55[g]
1-Ethylpropenyl,  $CH_3CH{=}\underset{\substack{\vert\\C_2H_5}}{C}—$	Methyl	Ethyl	Methyl iodide	0.5	87	112–113	8	1.4490	.9703	53.95	54.10	$C_{11}H_{17}O_2N$	7.18	7.20	..
	Ethyl	Ethyl	Ethyl iodide	0.8	70	141–143	22	1.4500	.9637	58.57	58.50	$C_{12}H_{19}O_2N$	6.70	6.57	77[d]
	Propyl	Ethyl	Propyl bromide	1.0	57	132–133.5	10	1.4510	.9541	63.19	63.17	$C_{13}H_{21}O_2N$	6.28	6.33	91
	Isopropyl	Ethyl	Isopropyl iodide	1.5	63	129–130	12	1.4520	.9572	63.19	63.08	$C_{13}H_{21}O_2N$	6.28	6.31	87
1-Methyl-1-pentenyl,  $CH_3CH_2CH_2—CH{=}\underset{\substack{\vert\\CH_3}}{C}—$	Methyl[l]	Ethyl	Methyl iodide	1.0	78	138–139	17	1.4460	.9488	58.57	58.96	$C_{12}H_{19}O_2N$	6.70	6.77	..
	Ethyl[l]	Ethyl	Ethyl iodide	3.5	70	145–146	17	1.4480	.9445	63.19	63.44	$C_{13}H_{21}O_2N$	6.28	6.27	..
1,3-Dimethyl-1-butenyl,  $CH_3\underset{\substack{\vert\\CH_3}}{CH}—CH{=}\underset{\substack{\vert\\CH_3}}{C}—$	Methyl[l]	Methyl	Methyl iodide	2.5	46	130–133	22	1.4475	.9624	53.95	54.39	$C_{11}H_{17}O_2N$	7.18	7.14	..
	Ethyl[l]	Methyl	Ethyl iodide	2.5	32[h]	137–139	22	1.4483	.9561	58.57	58.77	$C_{12}H_{19}O_2N$	6.70	6.59	..
1-Methyl-1-hexenyl,  $CH_3CH_2CH_2CH_2CH{=}\underset{\substack{\vert\\CH_3}}{C}—$	Methyl	Methyl	Methyl iodide	4.0	23[i]	150–152	22	1.4500	.9556	58.57	58.99	$C_{12}H_{19}O_2N$	6.70	6.55	70
	Ethyl	Methyl	Ethyl iodide	4.0	18[j]	158–159	22	1.4524	.9510	63.19	63.54	$C_{13}H_{21}O_2N$	6.28	6.13	..
1-Propyl-1-butenyl,  $CH_3CH_2CH{=}\underset{\substack{\vert\\C_3H_7}}{C}—$	Ethyl[l]	Methyl	Ethyl iodide	3.0	78[k]	150–151.5	22	1.4560	.9596	63.19	63.40	$C_{13}H_{21}O_2N$	6.28	6.35	..

[a] We are indebted to Mr. C. S. Miller for semi-micro Kjeldahl analyses. [b] Dimethyl sulfate gave a 65% yield. [c] Diethyl sulfate gave a 45% yield, ethyl bromide 41%. [d] Using diethyl sulfate. [e] Using propyl bromide. [f] 55% with isopropyl bromide. [g] Using allyl chloride. [h] Yield in ethyl alcohol 83%, calculated as the methyl ester. [i] Yield in ethyl alcohol 77%. [j] Yield in ethyl alcohol 58%. [k] Yield in ethyl alcohol 93%. [l] Ozonized by the procedure described in the Experimental Part.

with 0.25 mole of powdered sodium under 250 cc. of dry ether. The sodium had all dissolved after three hours of refluxing, and the soluble sodium derivative was alkylated with diethyl sulfate approximately as in the similar alkylation of ethyl isopropylidenemalonate.[1a] A 58% yield of methyl (1-propyl-1-butenyl)-ethylcyanoacetate was obtained, b. p. 117–119° (4 mm.); $n^{25}\text{D}$ 1.4489, d^{25}_{25} 0.9482. This ester gave satisfactory nitrogen analyses (calcd. for $C_{13}H_{21}O_2N$: N, 6.28; found: N, 6.38), but the low index of refraction, compared with that of the pure ester prepared in methyl alcohol and described in Table I, indicates the presence of the corresponding reduced ester as an impurity.

Ozonizations.—The esters indicated by footnote *l* in Table I were ozonized by the procedure described previously.[1b] The aldehydes formed on decomposition of the ozonides were converted to the 2,4-dinitrophenylhydrazones as before, and color tests for formaldehyde were made. In each case, a trace of formaldehyde was present, as indicated by positive ring tests with both gallic acid and resorcinol, but in no case was there enough to give the moderately sensitive resorcinol test with sodium hydroxide. As in the previous work, the most volatile portion of each of the distillates was treated with 2,4-dinitrophenylhydrazine and hydrochloric acid in alcohol solution. The derivatives formed were nearly pure as precipitated, and one recrystallization brought them to constant melting point in each case. The respective 1-alkyl-alkenyl esters gave the following aldehydes, as shown by the melting points of their 2,4-dinitrophenylhydrazones and mixed melting points with known samples. The 1-methylpropenyl ester gave acetaldehyde, m. p. and mixed m. p. of the derivative 163–165°. The 1-methyl-1-butenyl esters gave propionaldehyde, m. p. and mixed m. p. of the derivative 153–154°. The 1-methyl-1-pentenyl esters gave butyraldehyde, m. p. and mixed m. p. of the derivative 121–122°. The 1,3-dimethyl-1-butenyl ester gave isobutyraldehyde, m. p. and mixed m. p. of the derivative 181–182°. The 1-methyl-1-hexenyl ester gave valeraldehyde, m. p. and mixed m. p. of the derivative 108–109°.[7] (These melting points are uncorrected.)

Summary

Alkylidenecyanoacetic esters derived from both symmetrical and unsymmetrical ketones give sodium derivatives when treated with sodium alkoxides in alcohol solution. Alkylation of these sodium derivatives with alkyl halides and dialkyl sulfates produces (dialkylvinyl)-alkylcyanoacetic esters, RCH=C(R′)C(R″)(CN)COOR‴. In the formation of a sodium derivative from five alkylidenecyanoacetic esters derived from a series of methyl ketones, hydrogen is lost from the methylene of an alkyl group higher than methyl, rather than from the methyl group. Yields in the alkylation reactions are highest when sodium isopropoxide and isopropyl alcohol are employed, presumably because of the relatively slow alcoholysis of the products in this solvent.

(7) The valeraldehyde derivatives had a higher melting point than the one previously recorded. All others are in agreement with those reported by Campbell, *Analyst*, **61**, 391 (1936).

BRYN MAWR, PENNA. RECEIVED SEPTEMBER 26, 1938

[CONTRIBUTION FROM THE WILLIAM H. CHANDLER CHEMISTRY LABORATORY, LEHIGH UNIVERSITY]

The Action of Bromine on Nitrothiophene

BY V. S. BABASINIAN

The literature has very little to reveal regarding the behavior of nitrothiophene toward bromine. Casual references to the changes involved merely imply that the halogen attacks the nitro group with avidity, converting the compound to tetrabromothiophene.[1] The reaction was studied more closely in this Laboratory. It was found that in direct contact with the theoretical amount of bromine, nitrothiophene yields mainly tetrabromothiophene, but the product invariably is contaminated with the unattacked nitro compound. On the other hand, when the amount of bromine is reduced to the required minimum for the replacement of a single hydrogen in the thiophene nucleus, brominated intermediates appear in the product along with tetrabromothiophene. The reaction is likewise modified if brominations are effected in neutral or alkaline aqueous suspensions, or in ordinary organic solvents. Small-scale experiments performed under these conditions[2] give every indication that in the direct bromination of nitrothiophene the nitro group offers a degree of resistance to replacement by bromine, permitting the formation of a number of substituted derivatives, and under proper control the reaction pursues a course that can be followed with reasonable certainty.

The author proposes to show that with bromine vapor at room temperature, nitrothiophene

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(1) (a) Meyer, "Die Thiophengruppe," Braunschweig, 1888, p. 102; (b) Steinkopf and co-workers, *Ann.*, **512**, 137 (1934).

(2) The author desires to record his gratitude to Messrs. John B. Fishel and Horace F. Ether who performed the preliminary experiments. The analytical data for tetrabromothiophene, given later, were secured by Mr. Ether.