TABLE I

POLYHYDROXYAMINE HYDROHALIDES

Compounds	Empirical formula	M. p., °C. uncor.	Halogen analyses, % Calcd.	Found[b]
$(HOCH_2)_3CNH_2 \cdot HCl$[a]	$C_4H_{12}O_3ClN$	149–150	22.50	22.58
$(HOCH_2)_3CNH_2 \cdot HBr$[a]	$C_4H_{12}O_3BrN$	133–134	39.55	39.52
$(HOCH_2)_3CNHCH_2CH_2NHC(CH_2OH_3) \cdot 2HBr$	$C_{10}H_{26}O_6Br_2N_2$	205–206	37.16	37.09
$(HOCH_2)_3CNH(CH_2)_3NHC(CH_2OH)_3 \cdot 2HBr$	$C_{11}H_{28}O_6Br_2N_2$	170–171	35.98	35.25
$(HOCH_2)_3CNH(CH_2)_6NHC(CH_2OH)_3 \cdot 2HBr$	$C_{14}H_{34}O_6Br_2N_2$	160.5–162	32.87	32.10
$(HOCH_2)_3CNHCH_2CHOHCH_2NHC(CH_2OH)_3 \cdot 2HCl$	$C_{11}H_{28}O_7Cl_2N_2$	186–188	19.10	19.07
$(HOCH_2)_3CNHCH_2CHOHCH_2NHC(CH_2OH)_3 \cdot 2HBr$	$C_{11}H_{28}O_7Br_2N_2$	160–162	34.73	34.67
$(HOCH_2CH_2)_2NCH_2CHOHCH_2N(CH_2CH_2OH)_2 \cdot 2HCl$	$C_{11}H_{28}O_5Cl_2N_2$	98–100	20.90	20.97
$(HOCH_2CH_2)_2NCH_2CHOHCH_2NHC(CH_2OH)_3 \cdot 2HCl$	$C_{11}H_{28}O_6Cl_2N_2$	139–141	19.96	19.55
$(HOCH_2CH_2)(C_2H_5)NCH_2CHOHCH_2NH(CH_2OH)_3 \cdot 2HCl$	$C_{11}H_{28}O_5Cl_2N_2$	Sirup	20.90	19.74
$HOCH_2CHOHCH_2NHC(CH_2OH)_3 \cdot HCl$	$C_7H_{18}O_5ClN$	Sirup	15.31	14.90
$HOCH_2CH_2NHC(CH_2OH)_3 \cdot HCl$	$C_6H_{16}O_4ClN$	Sirup	17.58	17.30
$HOCH_2CH_2CH_2NHC(CH_2OH)_3 \cdot HBr$	$C_7H_{18}O_4BrN$	Sirup	30.72	30.18
$(HOCH_2)_3CNH(CH_2)_3O(CH_2)_3NHC(CH_2OH)_3 \cdot 2HCl$	$C_{14}H_{34}O_7Cl_2N_2$	Sirup	17.16	16.30

[a] Compounds given for reference. [b] We are indebted to E. E. Bowden and Walter W. Haden for most of the halogen analyses in this work.

from the melting points. No β,β'-bis-[tris-(hydroxymethyl)-methylamino]-ethyl ether was isolated.

1,2-Dihydroxy-3-tris-(hydroxymethyl)-methylaminopropane Hydrochloride, $HOCH_2CHOHCH_2NHC(CH_2OH)_3 \cdot HCl$.—A mixture of 24 g. of (A) (0.2 mole) and 11 g. of glycerol monochlorohydrin (0.1 mole) was heated under reflux with 50 ml. of alcohol for five hours. The resulting liquid was acidified with hydrochloric acid, while hot. On cooling, crystals of (A)·HCl were obtained and filtered off. More (A)·HCl was obtained by concentration of the filtrate and treatment with dry acetone. This process was repeated until no crystals were obtained. The solution then was concentrated to a sirup which was completely miscible with absolute alcohol and dry acetone. The sirup, while hot, was placed in a vacuum desiccator. After two days of drying, a satisfactory analysis for chloride was obtained.

Similar procedures were used for the reaction of ethylene chlorohydrin and trimethylene bromohydrin with (A) and for purification of the products formed.

Summary

A series of highly polar polyhydroxyamines have been made from tris-(hydroxymethyl)-aminomethane.

RICHMOND, VA.

RECEIVED JANUARY 18, 1944

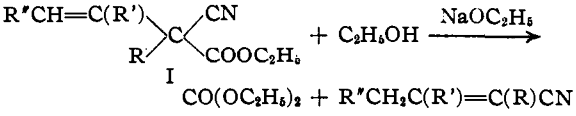
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

The Cleavage of (Dialkylvinyl)-alkylcyanoacetic Esters by Sodium Alkoxides[1]

BY ELIZABETH M. OSMAN AND ARTHUR C. COPE

More or less extensive cleavage of (dialkylvinyl)-alkylcyanoacetic esters to unsaturated nitriles has been observed to occur as a side reaction during condensation of the esters with urea in the presence of sodium alkoxides.[2] This paper reports an investigation of the cleavage reaction, and its use in the preparation of certain α,β-unsaturated nitriles. The hydrolysis of the nitriles to acids has also been studied.

The products of cleavage are ethyl carbonate and an α,β-unsaturated nitrile


I

$$R''CH{=}C(R')(R)C(CN)(COOC_2H_5) + C_2H_5OH \xrightarrow{NaOC_2H_5} CO(OC_2H_5)_2 + R''CH_2C(R'){=}C(R)CN$$

Similar cleavage of other cyanoacetic and malonic ester derivatives has been observed by several investigators.[3] The reaction proceeds readily at moderate temperature with disubstituted esters such as I which contain an α,β-unsaturated (electron attracting, or negative) group. Malonic ester derivatives which are not labilized by electron attracting substituents are cleaved in a similar manner at higher temperatures.[3c]

Kandiah and Linstead[4] have proposed a reaction mechanism for the cleavage in which the carbethoxyl group is removed by combination with ethoxide ion as ethyl carbonate, forming the anion of the nitrile. This ion acquires a proton from the solvent alcohol, producing the nitrile and reforming ethoxide ion. α,β- and β,γ-unsaturated nitriles are equilibrated rapidly in the presence of sodium ethoxide,[4] so that

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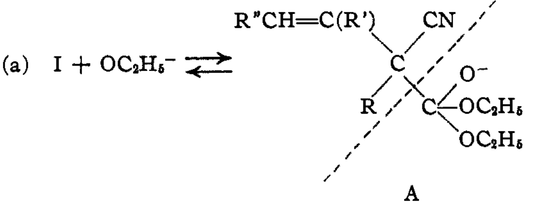
[1] Abstracted from a dissertation presented to the Faculty of the Graduate School of Bryn Mawr College by Elizabeth M. Osman in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] Cope and Hancock, THIS JOURNAL, **61**, 776 (1939).

[3] *Cf.* (a) Rogerson and Thorpe, *J. Chem. Soc.*, **87**, 1702 (1905); Thole and Thorpe, *ibid.*, **99**, 2191 (1911); Ingold and Thorpe, *ibid.*, **115**, 143 (1919); Birch, Kon and Norris, *ibid.*, **123**, 1369 (1923); Birch and Kon, *ibid.*, **123**, 2440 (1923); (b) Kon and Narayanan, *ibid.*, 1536 (1927); (c) Cope and McElvain, THIS JOURNAL, **54**, 4311, 4319 (1932).

[4] Kandiah and Linstead, *J. Chem. Soc.*, 2139 (1929).

either form or an equilibrium mixture can be the final product. Our results are in accord with this mechanism, which we would expand to include the addition of ethoxide ion as a discrete, reversible step.



A

$$\text{(b)}\quad \mathrm{A} \longrightarrow \mathrm{CO(OC_2H_5)_2} + \underbrace{[\mathrm{R''\underset{\cdot\cdot}{C}H{-}C(R'){=}C(R)CN}]^- \longleftrightarrow [\mathrm{R''CH{=}C(R')\underset{\cdot\cdot}{C}(R)CN}]^- \longleftrightarrow [\mathrm{R''CH{=}C(R'){-}C(R){=}C{=}N{:}}]^-}_{\mathrm{B}}$$

$$\text{(c)}\quad \mathrm{B} + \mathrm{C_2H_5OH} \longrightarrow \mathrm{OC_2H_5^-} + \mathrm{R''CH_2C(R'){=}C(R)CN}$$

The relative ease with which a number of ethyl (dialkylvinyl)-alkylcyanoacetates are cleaved was determined as follows. The esters (Table I, also ref. 5) were treated with a molecular equivalent of sodium ethoxide in absolute alcohol for one-half hour at a constant temperature. Temperatures were chosen at which partial cleavage occurred. The extent of the reaction was determined in each case by fractional distillation and determination of the yield of ethyl carbonate, unsaturated nitrile, and recovered ester. The data obtained are summarized in Table II.

The susceptibility to cleavage of four esters with the structure $C_2H_5CH{=}C(CH_3)C(R)(CN)$-$COOC_2H_5$ decreased in the following order: R = methyl > ethyl and *n*-propyl > isopropyl (esters 2, 7, 8 and 9, Table II). This is the order of increasing size and capacity for electron release of the alkyl groups. The relative rates of cleavage of six esters in which R in general formula I was methyl, while the substituted vinyl group was varied, were also determined (esters 1 to 6, Table II). All of these esters were cleaved to a similar extent, 35 to 49%, on treatment with one molar equivalent of alcoholic sodium ethoxide at 30° for thirty minutes.

The reason for the unusual ease with which (substituted vinyl)-alkylcyanoacetic esters are cleaved, according to the sequence of reactions outlined above, is the electron attraction of the substituted vinyl group. Esters are known to undergo ester interchange (step a) in the presence of sodium alkoxides. In this case the intermediate adduct, A, contains the electron attracting nitrile and substituted vinyl groups, while the carbethoxyl group has acquired an integral negative charge from the ethoxide ion and has become electron repelling. If the central methylene carbon atom acquires the electron pair corresponding to the bond at the point of the dotted line in formula A as a result of these forces, ethyl carbonate is formed and process (b) is completed. The normal reaction under mild conditions for esters in which the α-carbon atom is not attached to electron attracting groups is the reversal of (a). Large or branched alkyl groups on the central methylene carbon atom (R in formula I) would be expected to slow the cleavage by steric hindrance to the addition step (a), and by electron release opposed to the cleavage step (b). Modification of R and R″ would produce relatively minor effects, since the influence of the substituted vinyl group is due primarily to its unsaturation.

Much more drastic conditions were required to produce partial cleavage of similarly substituted malonic ester and malononitrile derivatives (10 and 11, Table II). Treatment with an equivalent quantity of alcoholic sodium ethoxide for thirty hours at 80° resulted in approximately 30% cleavage of the malonate, while the malononitrile was cleaved to the extent of 50% in one hundred and twenty hours at about 90°. The relatively slow cleavage of the malonate (10) compared to the corresponding cyanoacetate (1) is explained by the fact that the carbethoxyl is less electron attracting than the nitrile group. Consequently, there is less tendency for the cleavage step (b) to occur in the malonic ester series. The substituted malononitrile (11) apparently is converted by addition of an ethoxide ion into an iminoether derivative, $CH_3CH{=}C(C_2H_5)C(CH_3)$-$(CN)C(OC_2H_5){=}NH$, which resists cleavage.

The cleavage of alkyl (1-methyl-1-butenyl)-ethylcyanoacetates, $C_2H_5CH{=}C(CH_3)C(C_2H_5)$-$(CN)COOR$, by solutions of sodium in methyl, ethyl, isopropyl and *n*-butyl alcohols was also investigated, to determine the relation of the nature of the alkoxide ion to the rate of cleavage. The data obtained are listed in Table III. The cleavages proceeded at approximately equal rates in each of the alcohols except methanol. Cleavage was somewhat slower in methyl alcohol, and it was possible to convert the ethyl ester into the methyl ester by treatment with sodium methoxide in methyl alcohol at a temperature (50°) too low to produce cleavage. Previous investigation[5] of the alkylation of alkylidene cyanoacetic esters has shown that much poorer yields are obtained when the esters are converted into their enolates by sodium methoxide in methyl alcohol than when sodium ethoxide or sodium isopropoxide is employed. According to the present results, the defects of methanol as an alkylation medium cannot be explained by rapid cleavage of the products by methoxide ion. They probably are due to the higher acidity of methyl alcohol, which could lead to an unfavorable

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[5] Cope and Hancock, THIS JOURNAL, **60**, 2903 (1938).

TABLE I

SUBSTITUTED VINYLALKYLCYANOACETIC ESTERS[a]

Substituted vinyl group	Alkyl group	Yield, %	B. p., °C.	Mm.	$n^{25}\mathrm{D}$	d^{25}_{25}	Molecular refraction Calcd.	Molecular refraction Found	Formula[a]	Nitrogen, % Calcd.	Nitrogen, % Found
1-Methyl-1-propenyl	Methyl[d]	65	106–108	11	1.4450	0.9728	49.40	49.58	$C_{10}H_{15}O_2N$	7.73	7.60
1-Methyl-1-butenyl	Ethyl[b,e]	17	114–116	8	1.4519	.9780	54.02	54.01	$C_{11}H_{17}O_2N$[b]	7.17	7.21
1-Methyl-1-butenyl	Ethyl[c,f]	73	139–142	23	1.4414	.9332	63.26	63.38	$C_{13}H_{21}O_2N$[c]	6.28	6.35
1,3-Dimethyl-1-butenyl	Methyl[d]	79	129–133	20	1.4427	.9403	58.64	59.14	$C_{12}H_{19}O_2N$	6.69	6.54
1-Propyl-1-butenyl	Methyl[d]	81	128–129	12	1.4478	.9421	63.26	63.62	$C_{13}H_{21}O_2N$	6.28	6.39
1-Methyl-1-hexenyl	Methyl[d]	62	132–136	12	1.4477	.9403	63.26	63.37	$C_{13}H_{21}O_2N$	6.28	6.18

[a] Ethyl esters except for the following: [b] Methyl ester. [c] Isopropyl ester. [d] The alkylating agent was methyl iodide. [e] The alkylating agent was ethyl iodide. [f] The alkylating agent was ethyl sulfate.

equilibrium in the ester-ester enolate conversion.

$$\mathrm{RCH_2C(R){=}C(CN)COOR + RONa \rightleftharpoons [RCH{=}C(R)C(CN)COOR]^-Na^+ + ROH}$$

Completion of the cleavage of (substituted vinyl)-alkylcyanoacetic esters by refluxing with alcoholic sodium ethoxide affords a good synthesis for certain α,β-unsaturated nitriles. The properties of a number of nitriles which were prepared by this method are summarized in Table IV. An equilibrium mixture of α,β- and β,γ-unsaturated nitriles should be formed under the conditions of cleavage. The exaltation in molecular refraction of each of the nitriles, and the results of ozonization of two of them (outlined in the Experimental Part) indicate that they are very largely or completely in the α,β-unsaturated form.

The inert character and in particular the resistance to hydrolysis of conjugated unsaturated nitriles has been noted by many investigators.[3b,6] It was found to be possible to hydrolyze the nitriles listed in Table IV by employing drastic conditions. The nitriles were refluxed for forty-eight hours with a solution of potassium hydroxide in diethylene glycol containing a small amount of water. Unsaturated acids were obtained in this manner in yields of 49 to 81% (Table V). The available evidence (see the Experimental Part) indicates that the acids obtained were mixtures of the α,β- and β,γ-unsaturated isomers. The conditions of hydrolysis favor the establishment of equilibrium between the two forms.

One reaction in addition to hydrolysis which was completed successfully with 2-ethyl-3-methyl-2-hexenenitrile was conversion into the amidine by reaction with sodamide. The amidine was not very stable, and decomposed on standing into ammonia and the original nitrile. It was characterized by analysis and conversion into the picrate.

Experimental Part[7]

Substituted Vinylalkylcyanoacetic Esters.—Alkylidene cyanoacetic esters were prepared by the methods described recently.[8] They were alkylated in the alcohol corresponding to the ester alkoxyl group, to prevent ester interchange, by a general procedure previously employed for preparing homologous esters.[5] The yields and properties of esters not previously described in ref. 5 are recorded in Table I.

(1-Ethylpropenyl)-methylmalononitrile.—1-Ethylpropylidene malononitrile (40.2 g.) was added to a solution of 6.9 g. of sodium in 300 cc. of dry isopropyl alcohol and treated with 51 g. of methyl iodide under conditions used for synthesis of the ethyl homolog.[9] After purification by distillation, shaking with sodium bisulfite solution and redistillation, the alkylation product was obtained in yield of 41.6 g. (93%); b. p. 105–108° (17–18 mm.); $n^{25}\mathrm{D}$ 1.4458; d^{25}_{25} 0.9182; MD calcd. 42.95; found 43.15.

Anal. Calcd. for $C_9H_{12}N_2$: N, 18.90. Found: N. 18.83.

Cleavages in Ethyl Alcohol: Substituted Vinylalkylcyanoacetic Esters.—Each of the esters was treated with an equivalent quantity of sodium ethoxide in alcohol solution for exactly thirty minutes at 30, 50, or 80 ± 2°. The data in Table II show the extent of cleavage in each case. The following typical example is cited to illustrate the experimental procedure.

Sodium (4.6 g., 0.2 mole) was dissolved in 100 cc. of absolute alcohol in a 500-cc. three-necked flask equipped with a stirrer, a reflux condenser connected through a drying tube to a source of nitrogen, a dropping funnel and a thermometer. A nitrogen atmosphere under slight positive pressure was maintained throughout the reaction. The solution of sodium ethoxide was cooled to 30°, and ethyl (1-methyl-1-hexenyl)-methylcyanoacetate (44.7 g., 0.2 mole) was forced into the flask from the dropping funnel. The mixture was stirred at 30 ± 2° for thirty minutes, and then poured, with stirring, into a mixture of 40 cc. of 6 N hydrochloric acid and 100 g. of ice. The non-aqueous layer was removed, and the aqueous layer was extracted with three 50-cc. portions of benzene, which were combined with the non-aqueous layer and washed once with 30 cc. of water. The benzene was distilled through a small Widmer column at atmospheric pressure, and the residue was fractionated slowly and carefully through the column. The following fractions were separated: 3.5 g., b. p. 90–112°, $n^{25}\mathrm{D}$ 1.4080; 2.2 g. (9.3%) of ethyl carbonate, b. p. 112–115°, $n^{25}\mathrm{D}$ 1.3842; 1.3 g. of intermediate (5.5% calculated as ethyl carbonate), b. p. 115 (atm. p.)–100° (14 mm.), $n^{25}\mathrm{D}$ 1.3969; 9.9 g. (32.7%) of 2,3-dimethyl-2-octenenitrile, b. p. 100–110° (14 mm.), $n^{25}\mathrm{D}$ 1.4521; 1.3 g. intermediate (4.3% calculated as nitrile), b. p. 110–125° (13 mm.), $n^{25}\mathrm{D}$ 1.4510; 23.9 g. (53.7%) of the original ester, b. p. 125–133° (11 mm.), $n^{25}\mathrm{D}$ 1.4484; 3.0 g. (6.7% calculated as recovered ester) obtained by evacuating the column to a pressure of 1 mm., $n^{25}\mathrm{D}$ 1.4512. The object of the distillation was to provide as accurate an analysis as possible of the reaction mixture; physical properties of the pure esters and nitriles are recorded elsewhere (ref. 5 and Table I and IV). The same molar concentrations of reactants were employed in each cleavage.

Ethyl (1-Methyl-1-propenyl)-methylmalonate.—This ester[10] was treated with a molecular equivalent of alcoholic sodium ethoxide for thirty minutes in the manner outlined

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[6] *Cf.* Heyl and Meyer, *Ber.*, **28**, 1798 (1895); Meyer, *ibid.*, **28**, 3197 (1895); Kohler and Corson, THIS JOURNAL, **45**, 1975 (1923).

[7] All melting and boiling points are uncorrected.

[8] Cope, Hofmann, Wyckoff and Hardenbergh, THIS JOURNAL, **63**, 3452 (1941).

[9] Cope and Hoyle, *ibid.*, **63**, 733 (1941).

[10] Cope and Hancock, *ibid.*, **60**, 2902 (1938).

TABLE II

CLEAVAGE OF (DIALKYLVINYL)-ALKYLCYANOACETIC ESTERS[a] BY ALCOHOLIC SODIUM ETHOXIDE

No.	Ester	Formula	Conditions of cleavage Time, hours	Conditions of cleavage Temp., °C.	Ethyl carbonate yield, %[b]	Nitrile formed by cleavage, yield, %[b]	Ester recovered, %[b]
1	Ethyl (1-methyl-1-propenyl)-methylcyanoacetate	$CH_3CH{=}C(CH_3)C(CH_3)(CN)COOC_2H_5$	0.5	30	31	42 (43)	41 (54)
2	Ethyl (1-methyl-1-butenyl)-methylcyanoacetate	$C_2H_5CH{=}C(CH_3)C(CH_3)(CN)COOC_2H_5$	.5	30	29[c]	41 (44)[c]	47 (55)[c]
			.5	50	46 (59)	73 (90)	0
3	Ethyl (1-ethyl-1-propenyl)-methylcyanoacetate	$CH_3CH{=}C(C_2H_5)C(CH_3)(CN)COOC_2H_5$	.5	30	23 (25)	34 (35)	55 (65)
			.5	50	78 (79)	91 (104)	0
4	Ethyl (1,3-dimethyl-1-butenyl)-methylcyanoacetate	$i\text{-}C_3H_7CH{=}C(CH_3)C(CH_3)(CN)COOC_2H_5$	.5	30	19 (25)	46 (49)	44 (49)
5	Ethyl (1-methyl-1-hexenyl)-methylcyanoacetate	$n\text{-}C_4H_9CH{=}C(CH_3)C(CH_3)(CN)COOC_2H_5$	.5	30	9 (15)	33 (37)	54 (61)
6	Ethyl (1-propyl-1-butenyl)-methylcyanoacetate	$C_2H_5CH{=}C(n\text{-}C_3H_7)C(CH_3)(CN)COOC_2H_5$	.5	30	23 (27)[c]	41 (45)[c]	51 (57)[c]
7	Ethyl (1-methyl-1-butenyl)-ethylcyanoacetate	$C_2H_5CH{=}C(CH_3)C(C_2H_5)(CN)COOC_2H_5$	.5	50	25	38 (46)	36 (45)
8	Ethyl (1-methyl-1-butenyl)-propylcyanoacetate	$C_2H_5CH{=}C(CH_3)C(n\text{-}C_3H_7)(CN)COOC_2H_5$	.5	50	40 (44)	54 (60)	27 (37)
9	Ethyl (1-methyl-1-butenyl)-isopropylcyanoacetate	$C_2H_5CH{=}C(CH_3)C(i\text{-}C_3H_7)(CN)COOC_2H_5$	.5	50	0	0	87 (98)
			.5	80	42 (45)	71 (72)	17 (25)
10	Ethyl (1-methyl-1-propenyl)-methylmalonate	$CH_3CH{=}C(CH_3)C(CH_3)(COOC_2H_5)_2$	30	80	14	22 (32)	52 (64)
11	(1-Ethyl-1-propenyl)-methylmalononitrile	$CH_3CH{=}C(C_2H_5)C(CH_3)(CN)_2$	120	94–87		50 (51)	0

[a] A related malonic ester and malononitrile derivative are included in the table. [b] The first figures in each case represent the purest fraction, while the figures in parentheses include the intermediate fractions in the manner indicated in the detailed example in the Experimental Part. [c] Average from two similar cleavages in which the deviation in yield averaged 4% and the extreme deviation was 7%.

above at temperatures of 30, 50 and 80°, and also for five hours at 80°. In each case no monocarboxylic ester could be isolated, and 84 to 98% of the original ester was recovered. When the reaction mixture was kept at 80° for thirty hours, partial cleavage occurred as indicated in Table II. In order to identify the cleavage product, the fractions resulting from partial cleavage were combined and refluxed with alcoholic sodium ethoxide for seven days. This treatment resulted in complete cleavage. The properties of the monocarboxylic ester fraction were: b. p. 69–75° (16 mm.); $n^{25}D$ 1.4355. This index of refraction lies between the values ($n^{20}D$) of 1.4453 and 1.4298 given by Kon, Linstead and Maclennan[11] for ethyl 2,3-dimethyl-2-pentenoate and ethyl 2,3-dimethyl-3-pentenoate, respectively. An equilibrium mixture of these two esters should be formed in the presence of sodium ethoxide.

(1-Ethyl-1-propenyl)-methylmalononitrile.—No appreciable cleavage resulted from treatment of this malononitrile derivative (0.2 mole) with an equivalent quantity of alcoholic sodium ethoxide for thirty hours at 80°. Approximately 25% of the malononitrile derivative was recovered, while a higher boiling fraction was obtained, which according to analytical evidence was composed principally of $CH_3CH{=}C(C_2H_5)C(CH_3)(CN)C(OC_2H_5){=}NH$, the corresponding imino-ether (25 g., 64% calculated as the imino-ether, b. p. 120–129° (16 mm.), $n^{25}D$ 1.4560). Repetition of this experiment with a reaction time of one hundred and twenty hours at the boiling point (which dropped from 94 to 87° during this time) gave 50% cleavage to 3-ethyl-2-methyl-2-pentenenitrile, as indicated in Table II. Nitrogen and ethoxyl determinations on the higher boiling fraction were in accord with values for a mixture of the malononitrile derivative, the imino-ether formulated above, and the cyanoacetic ester derivative which could be formed from the latter in the process of isolation.[12]

Cleavages in Methyl, Isopropyl and *n*-Butyl Alcohols.—Ethyl (1-methyl-1-butenyl)-ethylcyanoacetate (0.2 mole) was added to a solution of 4.6 g. of sodium in 200 cc. of each of the anhydrous alcohols named above, and allowed to react for exactly thirty minutes at a constant temperature. More dilute solutions were employed than in the cleavages in ethyl alcohol in order to avoid crystallization of the least soluble sodium alkoxides. The cleavage of

TABLE III

CLEAVAGE BY SODIUM ALKOXIDES OF ALKYL (1-METHYL-1-BUTENYL)-ETHYLCYANOACETATES,

$C_2H_5CH{=}C(CH_3)C(C_2H_5)(CN)COOR$

Alcohol[a]	R of ester alkoxyl group	Cleavage temp., °C.	Nitrile formed by cleavage, yield, %[b]	Ester recovered, %[b,d]
Ethyl	Ethyl	50	10 (13)[c]	71 (80)[c]
Ethyl	Ethyl	69	37	48 (58)
Ethyl	Ethyl	80	65 (70)[c]	23 (26)[c]
Ethyl	Isopropyl	50	14 (16)	68 (76)
Isopropyl	Ethyl	80	67 (70)	19 (24)
Isopropyl	Isopropyl	80	55	28 (35)
n-Butyl	Ethyl	50	26	70 (74)
Methyl	Ethyl	50	0	82 (94)[e]
Methyl	Ethyl	69	7 (12)	62 (80)[e]
Methyl	Methyl	69	11 (16)	71 (79)

[a] The alcohol used as the medium for cleavage. [b] The first figures in each case represent the purest fraction, while the figures in parentheses include the intermediate fractions. [c] Average from two similar cleavages in which the deviation in yield averaged 3% and the extreme deviation was 8%. [d] The recovered ester is calculated as the original ester except where otherwise indicated. Mixed esters were actually produced in the reaction mixtures in which the ester and alcohol alkoxyl groups were dissimilar. [e] The ester recovered was practically pure methyl ester formed by ester interchange; $n^{25}D$ 1.4516 to 1.4512, b. p. 112–116° (8 mm.).

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(11) Kon, Linstead and Maclennan, *J. Chem. Soc.*, 2459 (1932).

(12) Similar mixtures have been obtained previously by reaction of malononitrile derivatives with sodium alkoxides; see ref. 9 and references cited therein.

TABLE IV

UNSATURATED NITRILES

Compound	B. p., °C.	B. p., Mm.	n^{25}_D	d^{25}_{25}	Molecular refraction Calcd.	Molecular refraction Found	Exaltation	Formula	Nitrogen, % Calcd.	Nitrogen, % Found[a]
2,3-Dimethyl-2-pentenenitrile	64	17	1.4469	0.8427	33.96	34.71	0.75	$C_7H_{11}N$	12.83	12.76
3-Ethyl-2-methyl-2-pentenenitrile	74–76	17	1.4500	.8442	38.58	39.33	.75	$C_8H_{13}N$	11.37	11.18
2,3-Dimethyl-2-hexenenitrile	73–77	14–16	1.4491	.8413	38.58	39.40	.82	$C_8H_{13}N$	11.37	11.35[b]
2-Ethyl-3-methyl-2-hexenenitrile	76–78	8	1.4512	.8394	43.20	44.16	.96	$C_9H_{15}N$	10.21	10.15
3-Methyl-2-propyl-2-hexenitrile	98	14	1.4531	.8404	47.82	48.80	.98	$C_{10}H_{17}N$	9.26	9.12
2-Isopropyl-3-methyl-2-hexenenitrile	81–84	9	1.4494	.8366	47.82	48.67	.85	$C_{10}H_{17}N$	9.26	9.04
2,3,5-Trimethyl-2-hexenenitrile	74–76	9	1.4503	.8371	43.20	44.21	1.01	$C_9H_{15}N$	10.21	10.03
2-Methyl-3-propyl-2-hexenenitrile	88–90	8	1.4542	.8415	47.82	48.84	1.02	$C_{10}H_{17}N$	9.26	9.12
2,3-Dimethyl-2-octenenitrile	96–98	9	1.4532	.8405	47.82	48.80	0.98	$C_{10}H_{17}N$	9.26	9.26[b]

[a] By the semi-micro Kjeldahl method unless otherwise indicated. The reason for the consistently low values is believed to be the stability and volatility of the compounds. [b] Micro-Dumas analysis by the Arlington Laboratories. Kjeldahl analyses were low.

this ester with sodium ethoxide in ethyl alcohol was repeated at the same concentration in order to obtain directly comparable data. In isolating the products, the reaction mixtures were poured into 40 cc. of 6 *N* hydrochloric acid and 200 g. of ice. After adding 200 cc. of water, the non-aqueous layer was separated and the aqueous layer was extracted with three 80-cc. portions of benzene. Two 40-cc. portions of sodium chloride solution were used to wash the combined extracts. Otherwise, the conditions of reaction and the method of separating the products corresponded to the procedure outlined for cleavages in ethyl alcohol. The corresponding isopropyl ester was also subjected to cleavage in ethyl and isopropyl alcohol under these conditions, and the methyl ester was treated with sodium methoxide in methyl alcohol, in order to determine the effect of the ester alkoxyl group on the rate of cleavage. Table III contains the data obtained. The yields of alkyl carbonates are not included, since mixtures were formed in the instances where the ester and alcohol alkoxyl groups were different.

A cleavage of the ethyl ester in methyl alcohol in which the quantities and concentrations of the reactants cited above were used was completed by refluxing the mixture for eight hours. The yield of 2-ethyl-3-methyl-2-hexenenitrile was 24.1 g. (88%).

Preparation and Characterization of Nitriles Produced by Cleavage.—The nitriles which are described in Table IV were prepared by completing the cleavages summarized in Table II. The products of partial cleavage were combined with any of the ester which was available and refluxed with an equivalent quantity or slight excess of sodium ethoxide in absolute alcohol for one to five hours. For example: sodium (10 g., 0.43 mole) was dissolved in 200 cc. of absolute alcohol. Ethyl (1,3-dimethyl-1-butenyl)-methylcyanoacetate (44 g., 0.2 mole) and the products from partial cleavage of 0.2 mole of this ester were added, and the solution was refluxed for one hour. The mixture was cooled, poured into ice and hydrochloric acid, extracted and distilled as described above. The yield of 2,3,5-trimethyl-2-hexenenitrile (Table IV) was 50.3 g. (89%). Yields were approximately 90% in the case of each nitrile prepared.

The carbon skeleton of 2-ethyl-3-methyl-2-hexenenitrile, chosen as representative of the nitriles listed in Table IV, was confirmed by hydrogenation followed by hydrolysis to a known derivative. The nitrile (27.4 g.) in alcohol solution absorbed a molar equivalent of hydrogen on shaking at room temperature in the presence of 1 g. of palladinized charcoal for sixty hours. After removal of the solvent, the product was washed with dilute hydrochloric acid to remove basic by-products and distilled through a small Widmer column. The yield of 2-ethyl-3-methylhexanenitrile was 16 g., b. p. 71–72° (7 mm.); n^{25}_D 1.4232; d^{25}_{25} 0.8181; MD calcd. 43.60, found 43.48.

Anal. Calcd. for $C_9H_{17}N$: N, 10.06. Found: N, 9.95.

The above nitrile (6.5 g.) was hydrolyzed by refluxing for twelve hours with a solution of 2.8 g. of potassium hydroxide in 40 cc. of ethylene glycol and approximately 1 cc. of water. The mixture was poured into water, extracted with ether, and separated into acidic and neutral fractions by reëxtraction with sodium hydroxide. The acid fraction on distillation yielded 1.9 g. of 2-ethyl-3-methylhexanoic acid,[3c] b. p. 230°, n^{25}_D 1.4332. The neutral fraction was steam distilled, and yielded as a volatile fraction 0.5 g. of the original nitrile. A solid (3.6 g.) was obtained from the residue, and on recrystallization yielded 3.4 g. of 2-ethyl-3-methylhexaneamide, m. p 96–97°.[13]

The exaltation in molecular refraction exhibited by the group of nitriles in Table IV (0.75 to 1.02 units) is good evidence that each of the compounds is α,β-unsaturated, although small amounts of the β,γ-unsaturated isomers could be present. von Auwers[14] observed exaltations of 0.9 to 1.0 for conjugated unsaturated nitriles. Two of the unsaturated nitriles were cleaved by ozonization, following a procedure outlined previously.[10] The volatile product obtained by hydrolysis of the ozonide from 2-ethyl-3-methyl-2-hexenenitrile was methyl propyl ketone, identified as the 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. with a known sample 143–144°. 2,3-Dimethyl-2-pentenenitrile yielded methyl ethyl ketone, m. p. and mixed m. p. of the 2,4-dinitrophenylhydrazone with a known sample 114–115°. These ketones are the products expected from the α,β-unsaturated structures in each case.

Hydrolysis of Unsaturated Nitriles.—The nitriles listed in Table IV were hydrolyzed by a general procedure which is illustrated by the following example. 2,3-Dimethyl-2-octenenitrile (17.8 g., 0.12 mole) was added to a solution of potassium hydroxide pellets (13.4 g.) and water (2.4 cc.) in 60 cc. of diethylene glycol. The solution was boiled under reflux for forty-eight hours, cooled and diluted with 120 cc. of water. The solution was extracted three times with benzene, acidified with 60 cc. of 6 *N* hydrochloric acid, and again extracted with three 50-cc. portions of benzene. The benzene extracts of the acid solution were washed with dilute sodium chloride solution and distilled through a small Widmer column, yielding 12 g. of 2,3-dimethyloctenoic acid (Table V). The acids obtained by hydrolysis have the properties of mixtures of the α,β- and β,γ-unsaturated isomers. The indices of refraction of 2,3-dimethylpentenoic acid, 3-ethyl-2-methylpentenoic acid and 2-ethyl-3-methylhexenoic acid lie between the values reported by Kon, Linstead, *et al.*, for the pure α,β- and β,γ-unsaturated forms (see footnotes to Table V). Two of the acids, 2-methyl-3-propylhexenoic acid and 2,3,5-trimethylhexenoic acid, were ozonized. Only products derived from the β,γ-unsaturated forms of these acids could be isolated, indicating that this form probably predominated in each case. From the former the 2,4-dinitrophenylhydrazone of ethyl propyl ketone was isolated, m. p. 145–146°, and from the latter the 2,4-dinitrophenylhydrazone of methyl ethyl ketone, m. p. 110–111°.

Ethyl (1-Methylbutylidene)-acetamidine.—2-Ethyl-3-methyl-2-hexenenitrile (41.9 g.) was added slowly to a

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[13] Volwiler and Tabern, THIS JOURNAL, 58, 1352 (1936).

[14] von Auwers, *Ber.*, 56, 1172 (1923).

TABLE V

UNSATURATED ACIDS

Acid	Yield, %	B. p., °C.	Mm.	n^{25}_D	d^{25}_{25}	Molecular refraction, Calcd.	Observed	Exaltation	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
2,3-Dimethylpentenoic[a]	50	118–120	20	1.4529	0.9681	35.60	35.88	0.28	$C_7H_{12}O_2$	65.59	65.63	9.44	9.41
3-Ethyl-2-methylpentenoic[b]	62	116–117.5	10	1.4548	.9571	40.22	40.41	.19	$C_8H_{14}O_2$	67.57	67.41	9.92	9.88
2,3-Dimethylhexenoic	53	115–118	10	1.4540	.9497	40.22	40.67	.45	$C_8H_{14}O_2$	67.57	67.52	9.92	9.96
2-Ethyl-3-methylhexenoic[c]	56	120–123	9	1.4514	.9358	44.84	45.11	.27	$C_9H_{16}O_2$	69.19	69.05	10.32	10.26
3-Methyl-2-propylhexenoic	49	131–133	10	1.4520	.9271	49.46	49.68	.22	$C_{10}H_{18}O_2$	70.55	70.52	10.66	10.72
2,3,5-Trimethylhexenoic	79	132–140	20	1.4520	.9274	44.84	45.58	.74	$C_9H_{16}O_2$	69.19	69.33	10.32	10.25
2-Methyl-3-propylhexenoic	81	129–133	9	1.4568	.9299	49.46	49.99	.53	$C_{10}H_{18}O_2$	70.55	70.43	10.66	10.84
2,3-Dimethyloctenoic	59	137–140	10	1.4560	.9289	49.46	49.96	.50	$C_{10}H_{18}O_2$	70.55	70.40	10.66	10.69

[a] Pure α,β- and β,γ-forms prepared by Abbott, Kon and Satchell, *J. Chem. Soc.*, 2519 (1928); α,β-unsaturated acid, b. p. 116° (18 mm.), $n^{17.5}_D$ 1.45952; β,γ-unsaturated acid, b. p. 116° (20 mm.), $n^{18.2}_D$ 1.4498. [b] Pure α,β- and β,γ-forms prepared by Kon, Leton, Linstead and Parsons, *J. Chem. Soc.*, 1416 (1931); α,β-unsaturated acid, b. p. 122° (12 mm.), $n^{20.5}_D$ 1.47183; β,γ-unsaturated acid, b. p. 116–117° (14 mm.), $n^{20.3}_D$ 1.45003. [c] α,β-unsaturated acid, b. p. 127° (12 mm.), n^{20}_D 1.46916; β,γ-unsaturated acid, b. p. 90° (14 mm.), $n^{19.5}_D$ 1.43568 (same ref. as footnote *b*).

suspension of sodamide (freshly prepared from 6.9 g. of sodium) in 100 cc. of dry boiling benzene in a 500-cc. three-necked flask, with stirring. After the exothermic reaction subsided, the mixture was refluxed for one-half hour. It was cooled to room temperature, and poured, with stirring, into 100 cc. of concd. hydrochloric acid and 100 g. of ice. The benzene layer was separated and washed with a little water, and the combined aqueous layers were washed twice with ether. The aqueous solution was covered with ether, cooled in an ice-bath and made alkaline by the slow addition from a dropping funnel of 180 cc. of 25% sodium hydroxide, with stirring. The ether layer was separated and the aqueous layer was extracted twice with small volumes of ether. The combined ether layers were washed once with water and distilled through a small Widmer column. Ethyl (1-methylbutylidene)-acetamidine was obtained in yield of 12.5–24.4 g. (27–53%); b. p. 99–101° (1 mm.); n^{25}_D 1.4932; d^{25}_{25} 0.9050; MD calcd. 48.68; found 49.70 (exaltation 1.02).

Anal. Calcd. for $C_9H_{18}N_2$: N, 18.16. Found: N, 18.09.

It was necessary to analyze the amidine derivative immediately after distillation, because of fairly rapid decomposition into the original nitrile and ammonia, each of which could be detected by odor. Nitrogen analyses made after three hours or more were approximately 0.5% low.

Ethyl (1-methylbutylidene)-acetamidine was converted into the picrate by reaction with an equivalent quantity of picric acid in boiling alcohol. It was precipitated by the addition of water and recrystallized from dilute alcohol; m. p. 136.5–137.5°.

Anal. Calcd. for $C_{15}H_{21}O_7N_5$: N, 18.27. Found: N, 18.14.

Summary

The cleavage of a number of (dialkylvinyl)-alkylcyanoacetic esters by sodium alkoxides has been investigated from the standpoint of the relation of structure to ease of cleavage, and also as a synthetic method for α,β-unsaturated nitriles. The hydrolysis of these nitriles to acids also has been studied.

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A Simultaneous Condensation–Reduction Method for the Preparation of Ethyl Monoalkylcyanoacetates

BY ELLIOT R. ALEXANDER AND ARTHUR C. COPE

A method for condensing aliphatic and aromatic ketones with ethyl cyanoacetate was described recently[1] in which the reactants are refluxed in benzene solution with an ammonium acetate and acetic acid catalyst. The equilibrium reaction

$$R_2CO + CH_2(CN)COOC_2H_5 \rightleftarrows R_2C{=}C(CN)COOC_2H_5 + H_2O$$

is displaced to the right by removing the water formed during the condensation with a constant water separator. Another possible method of displacing this equilibrium is to remove the unsaturated ester as it is formed by catalytic hydrogenation. This possibility has been investigated and experimental conditions have been developed for a practical synthetic method for condensing a number of aldehydes and ketones with ethyl cyanoacetate and simultaneously reducing the products to the corresponding ethyl monoalkylcyanoacetates.

In addition to the reduction of alkylidene cyanoacetic esters in the presence of palladinized charcoal[1] and with aluminum amalgam,[2] there are two general methods of preparing ethyl alkylcyanoacetates directly: the sodium enolate of ethyl cyanoacetate may be alkylated with alkyl halides, or ethyl carbonate may be condensed with nitriles in the presence of sodium ethoxide.[3] Both of these methods give poor yields of the lower members of the series of monoalkylcyanoacetates.

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

(2) Cowan and Vogel, *J. Chem. Soc.*, 1529 (1940).

(3) Wallingford, Jones and Homeyer, THIS JOURNAL, **64**, 576 (1942).