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.

NEW YORK, N. Y. RECEIVED FEBRUARY 23, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

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

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

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.

(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).

TABLE I

ETHYL MONOALKYLCYANOACETATES, $RCH(CN)COOC_2H_5$

Alkyl group, R	Ketone or aldehyde used in preparation[a]	Time of condensation–reduction, hours	Yield,[b] %	B. p. °C.	Mm.	$n^{25}D$	d^{25}_4	Molecular refraction Calcd.[c]	Found
Ethyl[e]	Acetaldehyde	2.5	80–85 A	84–85	7	1.4163	0.9836	36.01	36.02
n-Propyl[f]	Propionaldehyde	3	94 A	95–96	8	1.4200	.9650	40.63	40.70
n-Butyl[g]	Butyraldehyde	1.3	94–96 A	108–109	8	1.4242	.9537	45.25	45.27
Isobutyl[h]	Isobutyraldehyde	4	98 B	98–99	7	1.4232	.9499	45.25	45.35
Isoamyl[f]	Isovaleraldehyde	4	95 B	113–114	7	1.4279	.9427	49.87	49.97
n-Heptyl[i]	Heptaldehyde	4	71 B	111–113	1	1.4337	.9284	59.11	59.24
Benzyl[e]	Benzaldehyde	16[d]	63 B	118–122	0.4	1.5033	1.0762	55.89	55.50
Isopropyl[h]	Acetone	5–6	90–93 C	89–91	8	1.4203	0.9662	40.63	40.67
s-Butyl[h]	Methyl ethyl ketone	4.5–6	79–81 C	99–100	7	1.4267	.9615	45.25	45.11
1-Methylbutyl[h]	Methyl propyl ketone	11	63 C	111–112	8	1.4300	.9496	49.87	49.85
Cyclohexyl[h]	Cyclohexanone	4–6	91–98 C	138–139	8	1.4574	1.0154	52.29	52.41
1,3-Dimethylbutyl[j]	Methyl isobutyl ketone	8–11	41–63 C	117–119	8	1.4316	0.9360	54.49	54.62
1-Methylhexyl[k]	Methyl amyl ketone	9	71 C	135–137	8	1.4340	.9305	59.11	59.14
4-Heptyl[h]	Dipropyl ketone	7–22	39 C	131–132	7	1.4378	.9407	59.11	58.94
1-Methylhexyl[l]	Methyl hexyl ketone	5–6	73–81 C	112–115	1.0	1.4359	.9286	63.73	63.43

[a] Freshly distilled commercial products were used. [b] Capital letters refer to condensation–reduction methods designated by these letters in the Experimental Part. [c] The value 3.12 was used for the atomic refraction of nitrogen; see Eisenlohr, *Z. physik. Chem.*, **79**, 142 (1912). [d] Heated to 60° during the hydrogenation. [e] Hessler, *Am. Chem. J.*, **22**, 175 (1889). [f] Darapsky, *J. prakt. Chem.*, **146**, 253 (1936). [g] Ref. 4. [h] Ref. 2. [i] Calcd. for $C_{12}H_{21}O_2N$: C, 68.26; H, 10.00; N, 6.7. Found: C, 68.60; H, 10.00; N, 6.8. [j] Calcd. for $C_{11}H_{19}O_2N$: C, 67.10; H, 9.70. Found: C, 67.20; H, 9.71. [k] Calcd. for $C_{12}H_{21}O_2N$: C, 68.26; H, 10.00. Found: C, 68.32; H, 10.19. [l] Calcd. for $C_{13}H_{23}O_2N$: C, 69.40; H, 10.30. Found: C, 69.16; H, 10.45.

In the alkylation procedure it is impossible to prevent dialkylation, and the lower molecular weight monoalkylcyanoacetates are difficult to separate from the dialkylcyanoacetates by distillation.[4] Pure products have been obtained in good yield by the condensation–reduction method described in this paper. All of the reactants are commercially available and it is unnecessary to prepare intermediate halides or nitriles, or to work in an anhydrous medium with sodium ethoxide or metallic sodium.

The optimum experimental conditions for the reaction vary slightly according to the type of carbonyl compound used. Piperidine acetate and acetic acid were employed as the condensing agents with aldehydes, and ammonium acetate and acetic acid with ketones. Alcohol was found to be the most satisfactory solvent for the condensation–reduction of ethyl cyanoacetate and ketones; dioxane for higher aldehydes (isobutyraldehyde, isovaleraldehyde, heptaldehyde and benzaldehyde); and glacial acetic acid for low molecular weight aldehydes (acetaldehyde, propionaldehyde, and butyraldehyde). The preferred procedure for carrying out the reaction for each of the three classes is given in the Experimental Part. Palladinized charcoal was found to be a suitable hydrogenation catalyst under these conditions. In the presence of platinum oxide partial reduction of the nitrile group occurred, while Raney nickel was deactivated by the acetic acid present in the reaction mixture. The properties and yields of ethyl monoalkylcyanoacetates prepared by the condensation–reduction procedure are listed in Table I.

(4) Hessler, *Am. Chem. J.*, **22**, 169 (1899).

The method seems particularly well adapted for use with aldehydes and methyl ketones not branched at the α-carbon atom, which gave yields ranging from 63 to 98% of ethyl monoalkylcyanoacetates. When dipropyl ketone was used the yield dropped to 39%, and a pure product could not be isolated from the reaction with diisobutyl ketone.

Condensation–reduction of acetophenone and propiophenone with ethyl cyanoacetate in alcohol or dioxane solution at temperatures up to 90° in the presence of ammonium acetate, acetic acid, and palladinized charcoal yielded mixtures, apparently due to incomplete hydrogenation of the condensation products. Under similar conditions, a pure sample of ethyl (1-phenylethylidene)-cyanoacetate[1] was not completely hydrogenated. When aldol was employed in the reaction, the product proved to be ethyl *n*-butylcyanoacetate.

Ethyl alkylmalonates could not be prepared by the condensation–reduction of butyraldehyde, isobutyraldehyde, or benzaldehyde with ethyl malonate in dioxane solution in the presence of ammonium acetate, acetic acid, and palladinized charcoal at temperatures up to 100°. No hydrogen was absorbed and the starting materials were recovered. Similar results were obtained with butyraldehyde and ethyl malonate in glacial acetic acid.

Experimental[5]

The following methods were used to prepare the compounds listed in Table I:

(5) All melting and boiling points are uncorrected. We are indebted to Mr. Saul Gottlieb for microanalyses.

A. Lower Molecular Weight Aliphatic Aldehydes with Ethyl Cyanoacetate.—A mixture of ethyl cyanoacetate[6] (56.6 g., 0.5 mole), the freshly distilled aldehyde (0.6 mole), 1.0 g. of palladinized charcoal[7] and 80 ml. of glacial acetic acid was placed in a 500-ml. Pyrex bottle later to be used for the reduction. To this was added a solution of piperidine (2.0 ml., 0.02 mole) in 20 ml. of glacial acetic acid and hydrogenation at a pressure of 1 to 2 atmospheres was begun immediately.[8] Reduction was rapid and exothermic. In one to three hours the theoretical amount of hydrogen (0.5 mole) was taken up, and absorption ceased.

The ethyl alkylcyanoacetates were purified readily by distillation. The reaction mixture was filtered, 50 ml. of benzene was added, and the solution was washed with two 50-ml. portions of 10% sodium chloride solution followed by three 25-ml. portions of water. If emulsions were formed at this point, they were broken by the addition of a few ml. of ether. The washings were extracted with two small portions of benzene and the combined benzene solutions were distilled through a Widmer column under reduced pressure. No ethyl cyanoacetate was recovered in the forerun, and only a small distillation residue remained.

When aldol was the aldehyde used, 0.7 mole of hydrogen was absorbed (calcd., 0.5 mole) and 55.5 g. (66%) of ethyl *n*-butylcyanoacetate was obtained. The identity of this ester was established by analysis (*Anal.* Calcd. for $C_9H_{15}O_2N$: C, 63.98; H, 8.94. Found: C, 64.29; H, 8.88), and conversion into the amide, m. p. and mixed m p. with a known sample 125.5–126.5°.[9]

(6) Obtained from the Dow Chemical Company, Midland, Michigan.

(7) Hartung, THIS JOURNAL, **50**, 3372 (1928), subsequently modified by Dr. Hartung as follows. Ten ml. of a commercial palladium chloride solution containing 0.1 g. of palladium and approximately 0.05 g. of hydrogen chloride per ml. (obtained from the J. Bishop Company, Malvern, Pennsylvania) is added to a solution of 27 g. of sodium acetate trihydrate in 100 ml. of water. Norite (9 g.) is added and the mixture is hydrogenated until absorption ceases. The catalyst (10 g.) is filtered on a Büchner funnel, washed with water, dried by drawing air through the funnel for about thirty minutes and stored in a desiccator over calcium chloride.

(8) With propionaldehyde the yield of ethyl *n*-propylcyanoacetate dropped from 94 to 61% when the solution was allowed to stand for one hour before reduction was commenced. The yield of ethyl *n*-butylcyanoacetate was 87% when the reaction mixture stood for three hours before hydrogenating.

(9) Guareschi, *Atti Accad. sci. Torino*, **37**, 15 (1901); *Chem. Zentr.*, **73**, II, 700 (1902).

B. Branched Chain, Higher Molecular Weight Aliphatic Aldehydes, and Benzaldehyde.—A mixture of ethyl cyanoacetate (56.6 g., 0.5 mole), the aldehyde (0.6 mole), glacial acetic acid (6.0 g., 0.05 mole) and 150 ml. of dioxane[10] was placed in a 500-ml. Pyrex bottle later to be used for the reduction and cooled in an ice–salt mixture to 4°. Piperidine (2.0 ml., 0.02 mole) was added dropwise to this solution during approximately ten minutes with occasional swirling. The temperature rose to 20° and the solution became turbid. When the addition was complete, 1.0 g. of palladinized charcoal was added and the mixture was hydrogenated as before. With the aliphatic aldehydes, heat was evolved and reduction was complete in about four hours. With benzaldehyde, hydrogen absorption was very slow even when the reaction was carried out at 60°. The esters were purified as in method A. In the reactions employing aliphatic aldehydes, no ethyl cyanoacetate was recovered and only small distillation residues were left. With benzaldehyde there was a forerun of ethyl cyanoacetate (8.0 g.) and considerable residue (35 g.).

C. Aliphatic Ketones with Ethyl Cyanoacetate.—Ethyl cyanoacetate (56.6 g., 0.5 mole), the ketone (0.55 mole), ammonium acetate (3.9 g., 0.05 mole), glacial acetic acid (6.0 g., 0.1 mole), 100 ml. of 95% ethanol and 1.0 g. of palladinized charcoal were placed in a 500-ml. Pyrex bottle and hydrogenated as before. These reductions were exothermic but to a lesser degree than those mentioned under methods A and B. The esters were purified as in method A.

Summary

Experimental conditions are described whereby a number of aldehydes and aliphatic ketones can be condensed with ethyl cyanoacetate and simultaneously hydrogenated in the presence of palladinized charcoal to obtain pure ethyl monoalkylcyanoacetates in good yield. Ammonium acetate and acetic acid were employed as the condensing agents with ketones, and piperidine acetate and acetic acid with aldehydes.

(10) Purified by boiling over sodium for forty-eight hours and redistilling.

NEW YORK, N. Y. RECEIVED FEBRUARY 23, 1944

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Some Derivatives of Phenothiazine

BY HENRY GILMAN AND DAVID A. SHIRLEY

The first attempt to apply a phenothiazine derivative as an antimalarial agent was made by Guttman and Ehrlich[1] in 1891, when they showed that methylene blue was an active chemotherapeutic agent against human malaria, and later work[2,3] substantiated this claim. As a part of the extensive antimalarial research carried out by the I. G. Farbenindustrie, Schuleman[4] modified the structure of methylene blue by replacing an N-methyl group with alkylaminoalkyl groupings. More recently Holcomb and Hamilton[5] prepared 3,7-di-(6′-methoxy-2′-methyl-4′-quinolyl)-thionine as a possible antimalarial, but no report is available of its pharmacological value.

These prior studies have been concerned with the oxidized or methylene blue types of phenothiazine. It seemed of interest to prepare some appropriately substituted, non-oxidized phenothiazines for testing in avian malaria. Phenothiazine and some of its simple derivatives have a significantly low toxicity for animals. The toxicity is still further reduced by the introduction of

(1) Guttman and Ehrlich, *Berlin klin. Wochschr.*, **28**, 953 (1891).

(2) Couto, *Arch. Schiffs- u. Tropen-Hyg.*, **30**, 275 (1926).

(3) Fourneau, Trefouel, Bovet and Benoit, *Ann. inst. Pasteur*, **46**, 520 (1931).

(4) Schuleman, *Proc. Roy. Soc. Med.*, **25**, 897 (1932); German Patent 688,945 [*C. A.*, **24**, 2242 (1930)]; German Patent 490,275 [*C. A.*, **24**, 2241 (1930)].

(5) Holcomb and Hamilton, THIS JOURNAL, **64**, 1309 (1942).