overlooked the fact that Ullmann's technique was the reverse of that used in the Sandmeyer reaction.

Summary

1. When suitable experimental techniques are employed, ammoniacal suspensions of hydrated cuprous oxide or solutions of cupro-ammonia ion are excellent reducing agents for the conversion of diazotized anthranilic acid to diphenic acid; yields as high as 90% are obtained.

2. The initial value of the ratio Cu^+/RN_2X should be unity or higher with all reducing agents. Concentration of cuprous ion in the reducing solution is not a critical factor.

3. The use of a solution of cuprous chloride in hydrochloric acid as recommended by Ullmann gives little or no biaryl but large yields of the Sandmeyer type product.

4. Cupri-ammonia solutions do not convert diazotized anthranilic acid to the biaryl.

DURHAM, N. H. RECEIVED NOVEMBER 20, 1940

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

The Introduction of Substituted Vinyl Groups. VII. Alkylidene and Substituted Vinyl Alkylmalononitriles

BY ARTHUR C. COPE AND KATHRYN E. HOYLE

The practicality with which a variety of substituted vinyl alkylmalonic and cyanoacetic esters can be prepared by the alkylation of alkylidene esters[1] has led us to investigate the application of this synthetic method in the malononitrile series.

Alkylidene Malononitriles.—Although a number of aromatic aldehydes have been condensed with malononitrile to form arylidene derivatives,[2] $ArCH{=}C(CN)_2$, the corresponding reaction of certain aliphatic aldehydes[3] and ketones[4] has been reported to produce alkylidene bismalononitriles, dimeric alkylidene malononitriles or other complex substances. Cyclohexanone,[2] acetone[5] and diethyl ketone[4] have been reported to form simple alkylidene malononitriles, $R_2C{=}C(CN)_2$, all of which were said to be crystalline solids melting between 165 and 175°.

We have condensed cyclohexanone with malononitrile in the presence of piperidine, acetic acid, piperidine acetate and ammonium acetate, and in each case obtained a liquid product, b. p. 137–138° (10 mm.). This product was proved to be cyclohexylidene malononitrile by ozonization, which produced cyclohexanone, and by its alkylation to 1-cyclohexenyl ethylmalononitrile, described below. The crystalline solid of m. p. 173.5–174.5° previously described as cyclohexylidene malononitrile[2] may have been a dimer or polymer of this substance.

Acetone, diethyl ketone and methyl propyl ketone were also condensed with malononitrile in the presence of piperidine acetate or ammonium acetate to give alkylidene derivatives, all of which are liquids. The liquid, monomeric isopropylidene malononitrile was obtained by condensing acetone with malononitrile in the presence of piperidine acetate and a large excess of acetic acid. It is very sensitive to traces of piperidine, in the presence of which it polymerizes to a crystalline dimer, m. p. 168–170°, which corresponds in properties to the product obtained by Schenck and Finken[5] from the reaction of acetone with malononitrile in the presence of potassium ethoxide. On the basis of molecular weight determinations in acetic acid, they concluded that their freshly prepared solid, m. p. 171.5°, was monomeric isopropylidene malononitrile, which on standing for two years changed into a dimer. Only very approximate molecular weight determinations supported this conclusion, however, for the solid is quite insoluble in acetic acid, and their observed freezing point depressions were small and variable. Cryoscopic molecular weight determinations on our solid product in dioxane and acetophenone solution proved it to be dimeric.

While monomeric alkylidene malononitriles were obtained from aliphatic ketones, the condensation of isovaleraldehyde with malononitrile gave a colorless liquid product which changed rapidly on standing into a red, viscous polymer, and was not investigated further.

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[1] THIS JOURNAL, **62**, 314 (1940), and preceding papers.

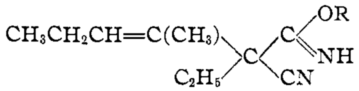
[2] *Cf.* Corson and Stoughton, *ibid.*, **50**, 2825 (1928).

[3] Diels, Gärtner and Kaack, *Ber.*, **55**, 3439 (1922).

[4] Östling, *Oeversikt Finska Vetenskaps-Soc. Forh.*, **57A**, No. 11 (1915); *Chem. Abstr.*, **15**, 2829 (1921).

[5] Schenck and Finken, *Ann.*, **462**, 267 (1928).

Alkylations.—The reaction of cyclohexylidene and 1-ethyl propylidene malononitrile with sodium isopropoxide in isopropyl alcohol gave sodium derivatives, which were alkylated in good yield on treatment with ethyl iodide. The alkylation products were proved to be 1-cyclohexenyl ethylmalononitrile and 1-ethyl propenyl ethylmalononitrile, respectively, by condensation with urea, which produced the corresponding known 5,5-disubstituted barbituric acids. The alkylation of the sodium derivative obtained from 1-methyl butylidene malononitrile with ethyl iodide, ethyl bromide or ethyl sulfate in isopropyl alcohol or ethyl alcohol solution gave a mixture of 1-methyl 1-butenyl ethylmalononitrile and the corresponding imino ether


$$CH_3CH_2CH{=}C(CH_3)(C_2H_5)C(CN)C({=}NH)OR$$

The mixture was characterized by condensation with urea, which produced the known 5-(1-methyl-1-butenyl)-5-ethylbarbituric acid (Delvinal), and by Zeisel determinations, which showed that the higher boiling fractions were composed principally of the imino ether. The addition of alcohol to a nitrile group during this alkylation, in contrast to the two normal alkylations mentioned above, is presumably due to the smaller steric hindrance afforded by the 1-methyl-1-butenyl group. The partial[6] or complete[7] conversion of malononitriles into imino ethers during alkylation in alcohol solution has been observed previously. It is noteworthy that while alcohol adds to one of the nitrile groups of this disubstituted malononitrile in the presence of alcoholic sodium ethoxide, under the same conditions the corresponding cyanoacetic ester is cleaved very rapidly to the nitrile, $C_3H_7C(CH_3){=}C(C_2H_5)CN$, and ethyl carbonate.[8]

Experimental Part[9]

Cyclohexylidene Malononitrile.—Following the procedure of Corson and Stoughton,[2] 20 g. of malononitrile was dissolved in 30 g. of cyclohexanone and treated with 0.5 cc. of piperidine. The mixture became hot immediately, and soon became orange in color. No solid was formed in two hours. On cooling with dry-ice the mixture solidified, but melted below room temperature. It was dissolved in benzene, washed with very dilute hydrochloric acid and water to remove the piperidine, and distilled in vacuum; yield 35.5 g. (80%); b. p. 137–138° (10 mm.); n^{25}_{D} 1.5110; d^{25}_{25} 1.0183; M_D calcd. 40.75, found 43.13; exaltation +2.33.

Anal. Calcd. for $C_9H_{10}N_2$: N, 19.17. Found: N, 18.97.

The same product was obtained in 70% yield from 0.1 mole of malononitrile and 0.11 mole of cyclohexanone in 25 cc. of benzene containing 0.34 g. of piperidine and 1.22 g. of acetic acid on refluxing for forty minutes under a constant water separator, and in 75% yield under similar conditions using 0.77 g. of ammonium acetate and 1.22 g. of acetic acid as the catalyst. Cyclohexylidene malononitrile was also obtained in 50% yield on heating 0.075 mole of malononitrile and an equivalent quantity of cyclohexanone in 25 cc. of glacial acetic acid on the steam-bath for seventeen hours.

Cyclohexylidene malononitrile (2 g.) in 40 cc. of pentane was ozonized under conditions previously employed for unsaturated esters.[10] The volatile cleavage product was steam distilled out of the mixture obtained on decomposing the ozonide by distilling 150 cc. of water, and concentrated by redistilling a total volume of 20 cc. It was proved to be cyclohexanone by preparing the 2,4-dinitrophenylhydrazone, m. p. 157–158°; mixed m. p. with a known sample of m. p. 159–160° was 158–159°. No other product could be isolated, but the aqueous solution contained hydrocyanic acid. The other cleavage product would be $CO(CN)_2$, which is known to react rapidly with water, producing carbon dioxide and hydrocyanic acid.[11]

Cyclohexylidene malononitrile (8 g.) dissolved in 25 cc. of 20% sodium bisulfite solution on shaking for three hours. On extraction of the bisulfite solution 0.9 g. of cyclohexylidene malononitrile was recovered. When the bisulfite solution was made alkaline with sodium carbonate and again extracted with ether, 2.2 g. of cyclohexylidene malononitrile was recovered. Cyclohexlidene malononitrile therefore forms a sodium bisulfite addition product, but cannot be recovered from it in good yield. Shaking with sodium bisulfite solution was consequently employed to remove any unalkylated material in the alkylations described below, but was not used in purifying the alkylidene malononitriles.

1-Ethyl Propylidene Malonitrile.—Malononitrile (26.4 g., 0.4 mole) and diethyl ketone (38 g., 0.44 mole) were dissolved in 50 cc. of benzene to which was added 3.08 g. (0.04 mole) of ammonium acetate and 4.8 g. (0.08 mole) of acetic acid. The mixture was refluxed under a constant water separator for forty minutes, while 8.5 cc. of water collected. The mixture was cooled, washed with water and distilled in vacuum; yield 46 g. (85%), b. p. 122–125° (23 mm.); n^{25}_{D} 1.4692; d^{25}_{25} 0.9311; M_D calcd. 38.33, found 40.26, exaltation +1.93.

Anal. Calcd. for $C_8H_{10}N_2$: N, 20.88. Found: N, 20.88.

Both 1-ethylpropylidene and cyclohexylidene malonotrile gave dark, viscous polymers on heating or standing in the presence of piperidine. Cursory attempts to isolate crystalline dimers or polymers were unsuccessful.

1-Methylbutylidene Malononitrile.—Malononitrile (1.72 mole, 113.5 g.), methyl propyl ketone (176 g., 10% excess), ammonium acetate (13.2 g.) and acetic acid (20.6

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[6] Hesse, *Am. Chem. J.*, **18**, 744 (1896).

[7] Hessler, *ibid.*, **22**, 169 (1899).

[8] Cope and Hancock, THIS JOURNAL, **61**, 776 (1939), and unpublished work of Elizabeth M. Osman.

[9] All melting and boiling points are uncorrected.

[10] Cope and Hancock, THIS JOURNAL, **60**, 2901 (1938).

[11] Malachowski, Jurkiewicz and Wojtowicz, *Ber.*, **70**, 1012 (1937).

g.) in 50 cc. of benzene were refluxed under a constant water separator for one hour, when 34 cc. of water had collected. The mixture was cooled, washed twice with water, and distilled in vacuum through a Widmer column; yield 175 g. (76%); b. p. 110–113° (12 mm.); $n^{25}\text{D}$ 1.4690; d^{25}_{25} 0.9294; M_D calcd. 38.33, found 40.32, exaltation +1.99.

Anal. Calcd. for $C_8H_{10}N_2$: N, 20.88. Found: N, 20.77.

Longer heating of the reaction mixture should be avoided, because high boiling material is formed and the yield is diminished.

Isopropylidene Malononitrile.—Malononitrile (26.4 g., 0.4 mole), 40 cc. of acetone, 100 cc. of 99.8% acetic acid and 0.5 cc. of piperidine were heated on the steam-bath under a reflux condenser for four hours. The solvent was then distilled in vacuum and the residue distilled directly from a modified Claisen flask. The crude product, b. p. 110–112° (22 mm.), $n^{25}\text{D}$ 1.4452, weighed 31 g. It was dissolved in 100 cc. of benzene, washed with five 50-cc. portions of cold water to remove malononitrile, and redistilled, yielding 18.3 g., b. p. 109–111° (23 mm.), $n^{25}\text{D}$ 1.4615. Repetition of the washing and redistilling gave 15 g. (35%) of pure isopropylidene malononitrile, b. p. 107–108° (23 mm.); $n^{25}\text{D}$ 1.4662. The purity of this product was verified by again repeating the process of washing with water and redistilling, which produced no change in physical properties. The recovery was 14 g., b. p. 107–108° (23 mm.); $n^{25}\text{D}$ 1.4662; d^{25}_{25} 0.9541; M_D calcd. 29.09, found 30.91, exaltation +1.82.

Anal. Calcd. for $C_6H_6N_2$: N, 26.40. Found: N, 26.53.

Attempts to alkylate isopropylidene malononitrile were unsuccessful. This was anticipated because of the sensitivity of the compound to bases (see below), and the fact that isopropylidene cyanoacetic ester cannot be alkylated.[12]

Isopropylidene malononitrile (3 g.) treated with 0.2 cc. of piperidine became very hot due to rapid polymerization, and on cooling set to a glass from which the crystalline dimer could be obtained by crystallization from alcohol. The dimer was prepared more successfully by treating a solution of 3 g. of isopropylidene malononitrile in 10 cc. of benzene with 0.1 cc. of piperidine. The yellowish-white crystals which separated while the solution stood for two hours were filtered and recrystallized twice from alcohol; yield 2 g., m. p. 168–170° (softens at 158°). The m. p. of the dimer varies with the rate of heating, and the melt does not completely resolidify. One preparation of isopropylidene malononitrile in which piperidine and a small amount of acetic acid were the condensing agents solidified to the dimer after distillation, probably because of the presence of a trace of piperidine in the distillate.

Anal. Calcd. for $C_{12}H_{12}N_4$: N, 26.40; mol. wt., 212. Found: N, 26.33; mol. wt., 197 (f. p. in dioxane), 190 (f. p. in acetophenone).

1 - Cyclohexenylethylmalononitrile.—Cyclohexylidene malononitrile (29.2 g., 0.2 mole) was added through a dropping funnel with stirring to a solution of 4.6 g. of sodium in 250 cc. of dry isopropyl alcohol in a 500-cc. three-necked flask. The sodium isopropoxide solution was at 50° when the addition was started, and was cooled in an ice-bath during the addition, which required two minutes. Ethyl iodide (37.5 g., 0.24 mole) was added in one portion to the orange solution of the sodium derivative, which was then heated rapidly to the boiling point. The solution became neutral after refluxing for one hour. It was cooled, diluted with two volumes of water and extracted three times with 100-cc. portions of benzene. The solvent was removed and the product distilled in vacuum. The slightly impure alkylation product was obtained in a yield of 30.9 g. (88%); b. p. 145–155° (24 mm.); $n^{25}\text{D}$ 1.4735. This material was purified by shaking for five hours with 75 cc. of 20% sodium bisulfite solution and redistilling through a Widmer column; the recovery was 22.2 g.; b. p. 153–154° (20 mm.); $n^{25}\text{D}$ 1.4734; d^{25}_{25} 0.9799; M_D calcd. 49.99, found 50.07.

Anal. Calcd. for $C_{11}H_{14}N_2$: N, 16.08. Found: N, 16.22.

The alkylation product was identified as 1-cyclohexenyl ethylmalononitrile by condensing 5.22 g. with 2.88 g. of urea in a solution of 2.07 g. of sodium in 100 cc. of dry isopropyl alcohol, under the conditions used in similar condensations of substituted cyanoacetic esters.[8] The imino derivative obtained was hydrolyzed directly by refluxing with 20% hydrochloric acid for two hours. The filtrate from the crystals which separated was refluxed for an additional four hours to complete the hydrolysis. After recrystallization from hot water the product had m. p. 171–172°; yield 5.4 g. (76%). It was identified as 5-ethyl 5-(1-cyclohexenyl) barbituric acid[13] by the mixed m. p. with a known sample.

1-Ethylpropenyl Ethylmalononitrile.—Following the procedure outlined above, 26.8 g. of 1-ethylpropylidene malononitrile gave 28.7 g. (88%) of slightly impure 1-ethyl propenyl ethylmalononitrile, b. p. 123–133° (27 mm.), $n^{25}\text{D}$ 1.4489. After purification by shaking with sodium bisulfite and redistilling the recovery was 22 g., b. p. 128–130° (29 mm.); $n^{25}\text{D}$ 1.4490; d^{25}_{25} 0.9180; M_D calcd. 47.57, found 47.54.

Anal. Calcd. for $C_{10}H_{14}N_2$: N, 17.27. Found: N, 17.06.

On condensation with urea 6.5 g. of the above nitrile gave 5.6 g. (63%) of 5-ethyl-5-(1-ethyl propenyl)-barbituric acid, m. p. 174.5°,[8] identified by the mixed m. p. with a known sample.

Alkylation of 1-Methyl-butylidene Malononitrile.—Again following the procedure outlined above, 22.5 g. of 1-methyl-butylidene malononitrile on alkylation with ethyl iodide gave 23 g. of a product b. p. 120–140° (22 mm.). After shaking with 70 cc. of 20% sodium bisulfite solution for four hours and redistilling, three fractions were separated: (1) 4.2 g., b. p. 121–124° (24 mm.), $n^{25}\text{D}$ 1.4432, N analysis 16.0%; (2) 5.4 g., b. p. 127–130° (22 mm.), $n^{25}\text{D}$ 1.4461, N analysis 15.3%; (3) 6.1 g., b. p. 130–137° (22 mm.), $n^{25}\text{D}$ 1.4488, N analysis 12.0%. N calcd. for 1-methyl-1-butenylethyl malononitrile, $C_{10}H_{14}N_2$, is 17.27%. Repetitions of the procedure, and similar alkylations with diethyl sulfate, gave exactly similar results. Both the low and high boiling fractions gave positive tests for isopropoxyl groups by the Zeisel method, and yet both fractions gave pure 5-ethyl 5-(1-methyl-1-butenyl)-barbi-

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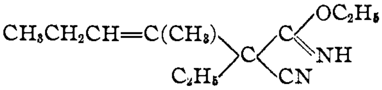
[12] Birch and Kon, *J. Chem. Soc.*, **123**, 2442 (1923).

[13] U. S. Patent 1,690,796; *Chem. Abstr.*, **23**, 483 (1929).

turic acid in yields of 40 to 60% on condensation with urea. Consequently the alkoxyl groups are introduced by addition to the nitrile rather than the alkenyl group, as otherwise a substituted barbituric acid containing alkoxy groups would be produced with urea. Evidence that addition of alcohol to the alkylation product could occur during the alkylation was obtained by refluxing 5.6 g. of relatively pure 1-methyl-1-butenyl ethylmalononitrile (b. p. 119–120° (22 mm.), $n^{25}\text{D}$ 1.4448, N analysis 17.0%) with a solution of 0.8 g. of sodium in 30 cc. of absolute ethyl alcohol for twelve hours. The product (5 g.) corresponded in properties to the higher boiling fractions obtained from the alkylations; b. p. 135–148° (28 mm.), $n^{25}\text{D}$ 1.4558. N analysis of the middle portion, b. p. 144–146° (28 mm.), 12.2%. A similar experiment in which isopropyl alcohol was employed likewise resulted in addition of the alcohol, giving 4 g. of a mixture, b. p. 120–140° (23 mm.), $n^{25}\text{D}$ 1.4508.

The product containing alkoxyl groups was most completely characterized as isolated from an alkylation carried out in ethyl alcohol. 1-Methylbutylidene malononitrile (134 g.) was converted into the sodium derivative by addition to a solution of 23 g. of sodium in 800 cc. of absolute ethyl alcohol at −15° during ten minutes. Ethyl bromide (130 g.) was added in one portion, and the solution was heated to boiling. The reaction was vigorous. After refluxing for thirty minutes the mixture was cooled, poured into ice water containing enough hydrochloric acid to make the mixture slightly acid, extracted and distilled in the usual manner. The crude distillate (78.8 g., b. p. 120–160° (29 mm.)) was shaken overnight with 300 cc. of 20% sodium bisulfite solution and redistilled through a Widmer column. The product (57.1 g.) was separated into four fractions, boiling between 130 and 150° (27 mm.) and having $n^{25}\text{D}$ between 1.4440 and 1.4560. Three refractionations partially separated the mixture into a low and high boiling fraction. The middle portion of the high boiling fraction (12 g.) had b. p. 142.5–143° (26 mm.), $n^{25}\text{D}$ 1.4541. Analysis showed this fraction to be the impure imino ether



Calcd. for $C_{12}H_{20}ON_2$: N, 13.45; OC_2H_5, 21.63. Found: N, 10.80; OC_2H_5, 20.50. Since both the ethoxyl and nitrogen values on this fraction were low, it contained some impurity other than the corresponding malononitrile. The most likely contaminant is the corresponding cyanoacetic ester, which would be formed by partial hydrolysis of the imino ether during the purification with sodium bisulfite. This impurity would lower the nitrogen without appreciably affecting the ethoxyl content. Indirect evidence that this fraction actually contained the imino ether was obtained in an attempt to prepare a picrate from it. The above product (1.2 g.) and picric acid (1.2 g.) in warm ether gave a bright yellow solid (1.1 g.), which was proved to be ammonium picrate by nitrogen analysis and the liberation of ammonia with sodium hydroxide. Ammonium picrate could be formed under these mild conditions only from a structure very readily cleaved by acids, such as an imino ether.

Summary

Malononitrile has been condensed with four aliphatic ketones to give alkylidene derivatives, $R_2C{=}C(CN)_2$, all of which are liquids. Three of them have been reported previously to be rather high melting solids, which may have been dimers or polymers of the simple compounds. The alkylidene malononitriles form sodium derivatives which can be alkylated to produce substituted vinyl alkylmalononitriles.

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RECEIVED DECEMBER 16, 1940

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA, AND THE NATIONAL INSTITUTE OF HEALTH]

Amino Alcohols Derived from Carbazole. II[1]

BY LEONE RUBERG AND LYNDON SMALL

Preliminary investigations of the simple aminocarbazoles and amino-9-methylcarbazoles have shown that some compounds of the series exert definite and prolonged analgesic action, and are of relatively low toxicity. Among the many phenanthrene and dibenzofuran compounds that have been synthesized in our laboratory for analgesia studies, those derivatives carrying an amino group and an alcoholic hydroxyl, attached directly to the nucleus, or in a side chain, are particularly active.[2] These facts led to the selection of amino alcohols derived from carbazole for further study.

In a recent communication[3] we described the preparation of several amino alcohols of types I and II.

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(1) The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, The U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan. Publication authorized by the Surgeon General, U. S. P. H. S.

(2) Small, Eddy, Mosettig and Himmelsbach, "Studies on Drug Addiction," Supplement No. 138 to the Public Health Reports.

(3) Ruberg and Small, THIS JOURNAL, **60**, 1591 (1938).