

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JAMES MILLIKIN UNIVERSITY.]

## ALKYL CYANOACETIC ACIDS.

By JOHN C. HESSLER.

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This paper describes work done, under the writer's direction, by three students, Mr. Thomas B. Magath, Mr. Fred F. Joel, and Miss Margaret C. Hessler. It includes the preparation of several new alkyl cyanoacetic acids, their salts and other derivatives. In this work caustic potash dissolved in methyl alcohol has been used for the saponification of the dialkyl cyanoacetic esters, with excellent results. Finally there is given a description of the benzylation of cyanoacetic ethyl ester in methyl alcohol solution; the dibenzylated derivative is shown to be the methyl, rather than the ethyl ester.

**Dimethylcyanoacetic Acid**,  $(\text{CH}_3)_2\text{C}(\text{CN})\text{COOH}$ .—The acid was made from 8.7 g. of its ethyl ester<sup>1</sup> by treatment with a solution of 9 g. of potassium hydroxide in 100 cc. of absolute methyl alcohol. The mixture was kept cool by means of running water and was allowed to stand overnight. Water was then added and the solution was acidified with dilute sulfuric acid. The acid solution was extracted three times with ether and the ether solution was washed five times with water and dried, rapidly, three times with fused calcium chloride. Distillation of the ether left a thick, slightly yellow liquid; this distilled at 132–135° under 12 mm. The distillate weighed 2.5 g.; it crystallized at once when disturbed. The crystals melted at 57° after being dried *in vacuo* over concentrated sulfuric acid.

The **silver salt** of dimethylcyanoacetic acid was made from the aqueous solution of the acid and freshly precipitated silver carbonate. The mixture was heated with a reversed condenser for 4–5 hours on a boiling water bath; it was then filtered and the filtrate was concentrated on the water bath. The silver salt came out in long, fine crystals.

Calc. for  $\text{C}_6\text{H}_8\text{NO}_2\text{Ag}$ : Ag, 49.09. Found: Ag, 49.20.

The **barium salt** was made from the aqueous solution of the acid and powdered barium carbonate. The mixture was heated on the boiling water bath for 2 hours and filtered hot. It was concentrated and then allowed to evaporate in the open air. After 4 weeks the barium salt crystallized out as long prisms; these were very readily soluble in water.

Calc. for  $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_4\text{Ba}\cdot 18\text{H}_2\text{O}$ : Ba, 13.47. Found: Ba, 13.56.

**Diethylcyanoacetic Acid**,  $(\text{C}_2\text{H}_5)_2\text{C}(\text{CN})\text{COOH}$ .—The diethylcyanoacetic ethyl ester was made as already described.<sup>2</sup> Then 42.5 g. of it were treated with 28 g. caustic potash dissolved in 300 cc. of methyl

<sup>1</sup> THIS JOURNAL, 35, 990–994 (1913).

<sup>2</sup> *Am. Chem. J.*, 22, 171 (1899); also Hadley, THIS JOURNAL, 34, 925 (1912).

alcohol. The mixture stood overnight. It was treated with 2 liters of water and dilute sulfuric acid was added until the solution had an acid reaction. The acid was extracted with ether as in the case of dimethylcyanoacetic acid. It weighed 31 g. and melted at  $66^\circ$  after it had been dried on a clay plate. The melting point previously reported was  $57^\circ$ ,<sup>1</sup> but in this case the acid had been made by saponification with concentrated hydrochloric acid in a sealed tube.

The **silver salt** was made by the treatment of the acid with a slight excess of aqueous ammonia, removal of the excess of ammonia over sulfuric acid *in vacuo*, and addition of an excess of aqueous silver nitrate. It was a bulky, white precipitate.

Calc. for  $C_7H_{10}NO_2Ag$ : Ag, 43.55. Found: Ag, 43.41.

The **barium salt** resulted from the boiling of the acid with water and powdered barium carbonate. The mixture was filtered while hot and was concentrated on a boiling water bath. The salt came out in the form of fine needles; it was analyzed air dry.

Calc. for  $C_{14}H_{20}N_2O_4Ba$ : Ba, 32.85. Found: Ba, 32.39.

The **lead salt** was made from the acid and powdered lead carbonate; it crystallized out when its solution was concentrated on the water bath. The salt forms flat, flaky crystals that are somewhat soluble in cold water, and very soluble in hot water. The salt was dried on a clay plate for analysis.

Calc. for  $C_{14}H_{20}N_2O_4Pb$ : Pb, 42.50. Found: Pb, 42.36.

The **calcium salt** was made by the method used for the barium salt. It came out as long needles when its solution was concentrated to a small volume. It was analyzed air dry.

Calc. for  $C_{14}H_{20}N_2O_4Ca \cdot 3H_2O$ : Ca, 10.69. Found: Ca, 10.65.

The **strontium salt** was obtained as long, soluble prisms.

Calc. for  $C_{14}H_{20}N_2O_4Sr \cdot 3H_2O$ : Sr, 20.77. Found: Sr, 20.49.

The **cadmium salt** was formed as flat, irregular plates when its solution was concentrated.

Calc. for  $C_{14}H_{20}N_2O_4Cd \cdot 3H_2O$ : Cd, 25.17. Found: Cd, 24.84, 24.80.

The **copper salt** was made from freshly prepared basic copper carbonate and the acid. The copper carbonate was obtained from copper sulfate and sodium carbonate solutions; it was washed by decantation. The copper salt separated from its concentrated solution as rectangular, bright green crystals. It was dried on a clay plate.

Calc. for  $C_{14}H_{20}N_2O_4Cu \cdot 3H_2O$ : Cu, 15.99. Found: Cu, 16.05, 16.30.

**Preparation of Propylcyanoacetic Ethyl Ester,**

$$\begin{array}{c} C_3H_7 \\ \diagdown \\ C(CN)COOC_2H_5 \\ \diagup \\ H \end{array}$$

<sup>1</sup> Hesse, *Am. Chem. J.*, 18, 746 (1896).

—Propylcyanoacetic ester was made from 50 g. cyanoacetic ester in 100 cc. of absolute alcohol, 10.2 g. of sodium in 250 cc. of absolute alcohol, and 80 g. (one gram equivalent = 75 g.) of normal propyl iodide. The propyl iodide was added as soon as the sodium salt of the cyanoacetic ester began to be precipitated. The solution became hot; the final temperature was 65°.

The mixture was left overnight in a flask protected by a calcium chloride tube and became neutral to litmus. The alcohol and excess of propyl iodide were distilled off on a paraffin bath, the residue was dissolved in water, and the solution was extracted twice with ether. The ether solution was washed five times with water and dried with fused calcium chloride. When the ether was distilled, the crude ester was obtained; it boiled at 117–130° under 24 mm. Yield, 51.5 g.

**Propylcyanoacetic Acid and Its Salts.**—The crude ester, containing both the monopropyl- and the dipropylcyanoacetic esters, was shaken twice, in ether solution, with an excess of 10% sodium hydroxide solution. The alkaline solution was separated from the ether, acidified with dilute sulfuric acid and extracted three times with ether. The propylcyanoacetic acid obtained weighed 24.9 g. The ether solution neutral to sodium hydroxide contained the dipropylcyanoacetic ester. This will be described later.

*a. Silver Salt.*—The ammonium salt of the acid was made by treatment of the acid with ammonia water and the removal of the excess of ammonia over concentrated sulfuric acid, *in vacuo*. Silver nitrate in slight excess was then added. The heavy, white precipitate of silver salt was filtered off and dried. A silver determination by ignition resulted as follows:

Calc. for  $C_6H_9NO_2Ag$ : Ag, 45.95. Found: Ag, 46.52.

*b. Barium Salt.*—The barium salt was made from the acid, water, and powdered barium carbonate. This mixture was heated several hours on a boiling water bath; the excess of barium carbonate was then filtered off and the filtrate was allowed to stand *in vacuo* over sulfuric acid. The salt crystallized in almost white plates.

Calc. for  $C_{12}H_{18}N_2O_4Ba$ : Ba, 35.21. Found: Ba, 35.23.

*c. Pure propylcyanoacetic ester* was made from the silver salt and an excess of ethyl iodide. The mixture was heated gently under a reflux condenser and then distilled. Boiling point 218–219° under 755 mm. Sp. gr. 0.972 at 32°.

**Dipropylcyanoacetic Ethyl Ester.**—The ether solution neutral to 10% sodium hydroxide was distilled under 21–23 mm. and gave the dipropyl ester, boiling at 129–132°. The amount obtained was 17.8 g., out of the original 51.5 g. of crude ester. Sp. gr. (Westphal) 0.93 at 26°.

**Dipropylcyanoacetic Acid.**—Dipropylcyanoacetic ester was treated with three times the theoretical amount of potassium hydroxide dissolved in pure methyl alcohol. The mixture stood overnight; it was then poured into much water, acidified with dilute sulfuric acid, and extracted three times with ether. After the ether solution had been washed and dried, the ether was distilled; the acid remained. When left several days *in vacuo* over sulfuric acid it did not crystallize. However, when water was added the acid crystallized in rhombic prisms. When dried on a clay plate the crystals melted at 41°. Over sulfuric acid *in vacuo* the crystals lost water and left a syrupy liquid. After 5 days the results were as follows:

Calc. for  $C_9H_{18}NO_2 \cdot H_2O$ :  $H_2O$ , 9.62. Found:  $H_2O$ , 9.68

The **silver salt** was made from the ammonium salt, as in the case of the silver salt of monopropylcyanoacetic acid. A silver determination was first made in the case of the air dried salt.

Calc. for  $C_9H_{14}NO_2Ag \cdot H_2O$ : Ag, 36.70. Found: Ag, 36.69.

The salt lost its water of hydration when dried *in vacuo* over sulfuric acid.

Calc. for  $C_9H_{14}NO_2Ag$ : Ag, 39.13. Found: Ag, 38.82.

**Isobutylcyanoacetic Ethyl Ester,**  $\begin{matrix} C_4H_9 \\ \diagdown \\ C(CN)COOC_2H_5 \\ \diagup \\ H \end{matrix}$ .—The crude

ester was prepared by the Conrad-Limpach reaction, as in the case of the propyl derivative. The yield was 52.7 g. from 50 g. of cyanoacetic ester. It was distilled in three fractions under a pressure of 35–42 mm.

I. Up to 127°, 11.5 g. II. 127–132°, 36.9 g. III. 133–185°, 4.3 g.

**Isobutylcyanoacetic acid** was made by treatment of the crude ester once with 5% sodium hydroxide solution (no ether was used) and twice with 10% sodium hydroxide, the first time for one or two minutes, the second time for one and half hours. After the last treatment the unchanged diisobutylcyanoacetic ester was removed by means of ether. The sodium hydroxide solution was then acidified with dilute sulfuric acid, extracted with ether, and the ether solution dried rapidly with calcium chloride. The yield of acid was 20.5 g. This represents 24.6 g. of ester, or 46.6% of the total yield of crude ester.

The **silver salt** was made from 17 g. of the acid, by means of the ammonium salt. Yield, 23.7 g. It was an almost white powder after it had been dried on a clay plate.

Calc. for  $C_7H_{10}NO_2Ag$ : Ag, 43.54. Found: Ag, 43.11.

The **barium salt** was made when the acid, water and powdered barium carbonate were heated on a boiling water bath. It crystallized in long, white needles when its solution stood in a desiccator over sulfuric acid.

Calc. for  $C_{14}H_{20}N_2O_4Ba \cdot 2H_2O$ : Ba, 30.51. Found: Ba, 30.36.

**Pure isobutylcyanoacetic ethyl ester** was made from the silver salt of the acid and an excess of ethyl iodide. Boiling point 223–224° under 755 mm. Sp. gr. 0.958 at 35° C.

**Diisobutylcyanoacetic Ethyl Ester.**—The part of the crude isobutylcyanoacetic ester that was neutral to sodium hydroxide solution was taken up with ether and the ether solution was washed with water and dried with calcium chloride. The yield of the diisobutyl ester was 28.1 g., or 53.3% of the crude ester. The boiling point was 245–250° under 755 mm. Sp. gr. (Westphal) 0.915 at 31°.

**Diisobutylcyanoacetic acid** was made from its ester by the action of potassium hydroxide dissolved in methyl alcohol. After the acid had been dried *in vacuo* over sulfuric acid it melted at 82°. Yield, 20 g. from 23.7 g. of the distilled ester.

The **silver salt** was prepared through the ammonium salt. It formed a bulky, white precipitate.

Calc. for  $C_{11}H_{18}NO_2Ag$ : Ag, 35.52. Found: Ag, 35.71.

#### Derivatives of Isoamylcyanoacetic Acid.

**a. Copper Salt.**—Isoamylcyanoacetic acid was prepared as described in an earlier paper.<sup>1</sup> It was converted into the ammonium salt and the solution was treated with a solution of copper sulfate. The copper salt came out as a blue, crystalline precipitate. It was analyzed air dry.

Calc. for  $C_{10}H_{24}N_2O_4Cu \cdot 7H_2O$ : Cu, 12.78. Found: Cu, 12.39.

When the salt was dried *in vacuo* over sulfuric acid, it became green.

**b. Barium Salt.**—The barium salt resulted when the acid, water and powdered barium carbonate were heated together. The salt crystallized from its concentrated, aqueous solution as tufts of white needles.

Calc. for  $C_{10}H_{24}N_2O_4Ba \cdot 2H_2O$ : Ba, 28.48. Found: Ba, 28.06.

**c. Acid Chloride and Anilide.**—Isoamylcyanoacetic acid chloride resulted as a colorless liquid when the acid and phosphorus pentachloride (a slight excess) were heated together. The phosphorus oxychloride was distilled *in vacuo*. When the acid chloride was treated with an excess of concentrated ammonia water, the acid amide was produced. It melted at 142°.<sup>2</sup>

When the acid chloride was treated with aniline, the acid anilide was formed. This separated from alcohol as balls of needle-shaped crystals melting at 102°.

Calc. for  $C_{14}H_{18}ON_2$ : N, 12.17. Found: N, 12.47.

#### Diisoamylcyanoacetic Acid and Its Derivatives.

**a. Preparation of the Acid.**—The diisoamylcyanoacetic ester<sup>2</sup> that was used in the preparation of the acid boiled at 158–159° under 16 mm.

<sup>1</sup> THIS JOURNAL, 35, 993 (1913).

<sup>2</sup> *Ibid.*, *Loc. cit.*

It was saponified by means of potassium hydroxide dissolved in methyl alcohol. The acid crystallized from benzene in white needles; these melted at 74–75° after being dried over sulfuric acid *in vacuo*.

**b. Ammonium Salt.**—The ammonium salt was prepared from the acid and dilute ammonium hydroxide. It crystallized out as white flakes. Only about 2.9 g. of this salt were soluble in 100 cc. of water at 16°.

**c. The silver salt** was formed as a white precipitate when the solution of the ammonium salt was treated with silver nitrate solution.

Calc. for  $C_{13}H_{22}NO_2Ag$ : Ag, 32.53. Found: Ag, 32.19.

**d. The copper salt** was made by precipitation from the solution of the ammonium salt by means of copper sulfate solution. It was a green, flaky solid when dry.

Calc. for  $C_{20}H_{44}N_2O_4Cu.3H_2O$ : Cu, 11.23. Found: Cu, 11.09.

**e. The calcium salt** was prepared from the acid, water, and powdered calcium carbonate. It came out of solution as white, rhomboidal crystals.

Calc. for  $C_{22}H_{44}N_2O_4Ca.4H_2O$ : Ca, 7.14. Found: Ca, 7.18.

**f. Diisoamylcyanoacetamide.**—The acid chloride was prepared from the acid and phosphorus pentachloride. When it was treated with concentrated ammonia water, the amide was formed. This crystallized from hot alcohol in needles melting at 152°.

Calc. for  $C_{18}H_{34}ON_2$ : N, 12.50. Found: N, 13.11.

**Derivatives of Benzylcyanoacetic Acid.**—Benzylcyanoacetic acid was made by the method already described;<sup>1</sup> it was a white, crystalline solid melting at 101°.

**a. Lead Salt.**—The lead salt was made (1) by addition of a dilute solution of lead nitrate to an aqueous solution of the acid; (2) by addition of the lead nitrate solution to an aqueous solution of the ammonium salt. In each case the lead salt came down as a bulky, white, crystalline precipitate. An analysis of the air-dried salt gave the following figures:

Calc. for  $C_{20}H_{18}N_2O_4Pb.3H_2O$ : Pb, 33.97. Found: Pb, 33.83, 33.95.

After the salt had been dried for several hours *in vacuo* over sulfuric acid the figures were:

Calc. for  $C_{20}H_{18}N_2O_4Pb$ : Pb, 37.30. Found: Pb, 36.87.

The lead salt is soluble in hot water and in hot methyl and ethyl alcohols.

**b. Barium and Calcium Salts.**—The barium and calcium salts were made from the acid and water, with barium and calcium carbonates, respectively. Both salts were white and crystallized in needles. The anhydrous calcium salt was obtained when its hydrate stood *in vacuo* over sulfuric acid; the other salts were air-dried.

<sup>1</sup> *Am. Chem. J.*, 22, 176 (1899).

Calc. for  $C_{20}H_{16}N_2O_4Ca$ : Ca, 10.31. Found: 10.42.

Calc. for  $C_{20}H_{16}N_2O_4Ca \cdot 3H_2O$ : Ca, 9.05. Found: 9.06.

Calc. for  $C_{20}H_{16}N_2O_4Ba \cdot 6H_2O$ : Ba, 23.10. Found: 23.01.

The barium and calcium salts are soluble in hot alcohol and in hot water.

**c. Copper Salt.**—The cupric salt was prepared by the addition of a dilute solution of cupric sulfate to the solution of the ammonium salt. It came out as a deep blue precipitate, but turned green when it lost its water of hydration. The water was lost at about  $65^\circ$ ; the salt melted with decomposition and evolution of carbon dioxide at  $105-115^\circ$ . The percentage of copper was determined by ignition, that of water of hydration by the loss sustained *in vacuo* over sulfuric acid.

Calc. for  $C_{20}H_{16}N_2O_4Cu \cdot 5H_2O$ : Cu, 12.68. Found: 12.42;  $H_2O$ , 17.96. Found: 18.08; N, 5.58. Found: 5.45.

**d. Acid Chloride.**—The acid chloride of benzylcyanoacetic acid was made from the acid and phosphorus pentachloride. It was a slightly colored liquid that did not distil under 35 mm. when the outside temperature was  $290^\circ$ . When the chloride was treated with an excess of ammonia water it gave benzylcyanoacetamide, melting at  $130^\circ$ .<sup>1</sup>

**Salts of Dibenzylcyanoacetic Acid.**—The acid was made from its ester, boiling at  $225-235^\circ$  under 15 mm., and potassium hydroxide dissolved in methyl alcohol. After being recrystallized from benzene it melted at  $194-195^\circ$ . Cassirer<sup>2</sup> gives the melting point as  $188-189^\circ$ .

The silver salt was made from the ammonium salt and silver nitrate. It formed a white precipitate.

Calc. for  $C_{17}H_{14}NO_2Ag$ : Ag, 29.03. Found: Ag, 29.69.

The copper salt was made from the ammonium salt and cupric sulfate. It came out as a blue precipitate that turned green when dried.

Calc. for  $C_{24}H_{22}N_2O_4Cu \cdot H_2O$ : Cu, 10.43. Found: Cu, 10.21.

**Benzylation of Cyanoacetic Ethyl Ester in Methyl Alcohol Solution: Dibenzylcyanoacetic Methyl Ester.**—Twenty grams of cyanoacetic acid ethyl ester were dissolved in 125 cc. of Kahlbaum's anhydrous methyl alcohol and treated with a solution of 4.07 g. of sodium in 125 cc. of methyl alcohol. Benzyl chloride (22.4 g.) was then added and the mixture was allowed to stand for 14 hours. The alcohol was then distilled off and the residue was treated with water and extracted with ether. The ether solution was washed, dried and distilled. The product (19.5 g.) was fractionated under 15 mm. pressure. The fractions were:

I. Boiling up to $101^\circ$ .....	5.5 g.	III. $195-250^\circ$ .....	3.2 g.
II. $101-160^\circ$ .....	1.5 g.	IV. $250-260^\circ$ .....	6.7 g.

<sup>1</sup> *Am. Chem. J.*, 22, 180 (1899).

<sup>2</sup> *Ber.*, 25, 3027 (1892).

Fractions III and IV crystallized when cool. They were dissolved in ether and the ether solution was shaken with 10% sodium hydroxide. The sodium hydroxide solution yielded 1.6 g. of benzylcyanoacetic acid; the ether solution gave 4.9 g. of dibenzylcyanoacetic acid methyl ester, which crystallized when cold. It was recrystallized from an ether-ligroin mixture, coming out as large, six-sided, white plates melting at 78-79°.

Calc. for  $C_{18}H_{17}NO_2$ : C, 77.43; H, 6.09; N, 5.02. Found: C, 77.81 and 77.69; H, 6.83 and 6.42; N, 5.11.

The methyl ester was also prepared by treatment of the silver salt of dibenzylcyanoacetic acid (*q. v.*) with methyl iodide.

The study of the derivatives of cyanoacetic acid is being continued.

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[CONTRIBUTION FROM THE HARRIMAN RESEARCH LABORATORY, ROOSEVELT HOSPITAL, NEW YORK.]

## A COMPARATIVE STUDY OF AERATION AND HEAT DISTILLATION IN THE KJELDAHL METHOD FOR THE DETERMINATION OF NITROGEN.

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In 1903, Folin<sup>1</sup> described a method for the determination of ammonia in urine based upon its removal by passing a rapid current of air through the solution under suitable conditions, absorbing the ammonia in acid, and titrating the excess of acid.

P. A. Kober,<sup>2</sup> in 1908, proposed the use of aeration for the separation of ammonia in all Kjeldahl determinations in place of the ordinary heat distillation and described the apparatus and method to be employed. He quoted experiments made by Dr. Kristeller on the estimation of the ammonia in an ammonium chloride solution, three by aeration and two by heat distillation, with excellent agreement.

In the following year, Sebelien<sup>3</sup> suggested the same method for all Kjeldahl determinations. He worked with ammonium salts only and studied the conditions necessary for the removal and absorption of the ammonia.

Davis<sup>4</sup> found aeration to give unsatisfactory results in the determination of nitrogen in cottonseed meal and proposed to heat the solutions during aeration. Gill and Grindley<sup>5</sup> confirmed the work of Davis with cottonseed-meal, but obtained results agreeing with heat distillation for a number of other substances.

<sup>1</sup> *Z. physiol. Chem.*, **33**, 161 (1903).

<sup>2</sup> *THIS JOURNAL*, **30**, 1 (1908).

<sup>3</sup> *Chem. Zig.*, **33**, 795 (1909).

<sup>4</sup> *THIS JOURNAL*, **31**, 556 (1909).

<sup>5</sup> *Ibid.*, **31**, 1249 (1909).