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INVESTIGATION ON THE BY-PRODUCT OBTAINED IN THE COPE-KNOEVENAGEL CONDENSATION OF ETHYL α-ACETOGLUTARATE WITH ETHYL CYANOACETATE

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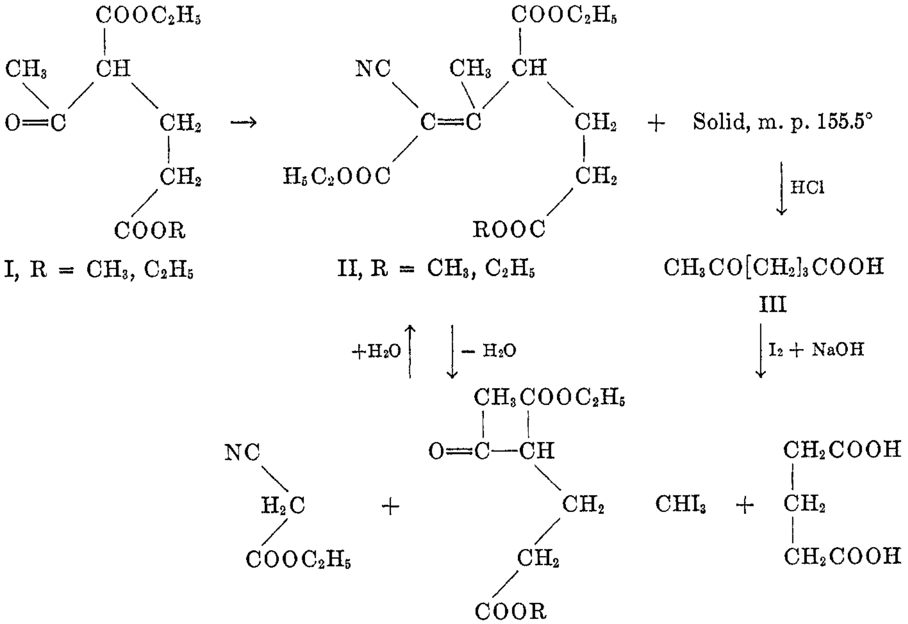
The isolation of a by-product, m.p. 155.5°, during the condensation of ethyl α-acetoglutarate (I, R = C_2H_5) with ethyl cyanoacetate was previously reported (1). The neutral nitrogenous product is not affected by cold dilute acid or alkali, does not produce any coloration with alcoholic ferric chloride or form any derivative on treatment with semicarbazide hydrochloride or 2,4-dinitrophenylhydrazine, and has U.V. λ_{max} at 279 mμ (Fig. 1). The product on refluxing with hydrochloric acid formed a keto acid in 70% yield. The latter on treatment with iodine and alkali yielded iodoform and glutaric acid. This proved the keto acid to be γ-acetobutyric acid (III), which was thoroughly confirmed by direct comparison with an authentic specimen. Evidently a geometrical isomer of the unsaturated cyano ester (II, R = C_2H_5) might have produced γ-acetobutyric acid by the acid hydrolysis, through the reversal of the Knoevenagel condensation (2), but this possibility had to be ruled out on account of the differences observed in the percentage of nitrogen, molecular weight and the U.V. data (Fig. 1).



Next the usual condensation mixture, consisting of ethyl α-acetoglutarate,

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[1] From the doctoral dissertation of S. K. Das Gupta of the University of Calcutta.

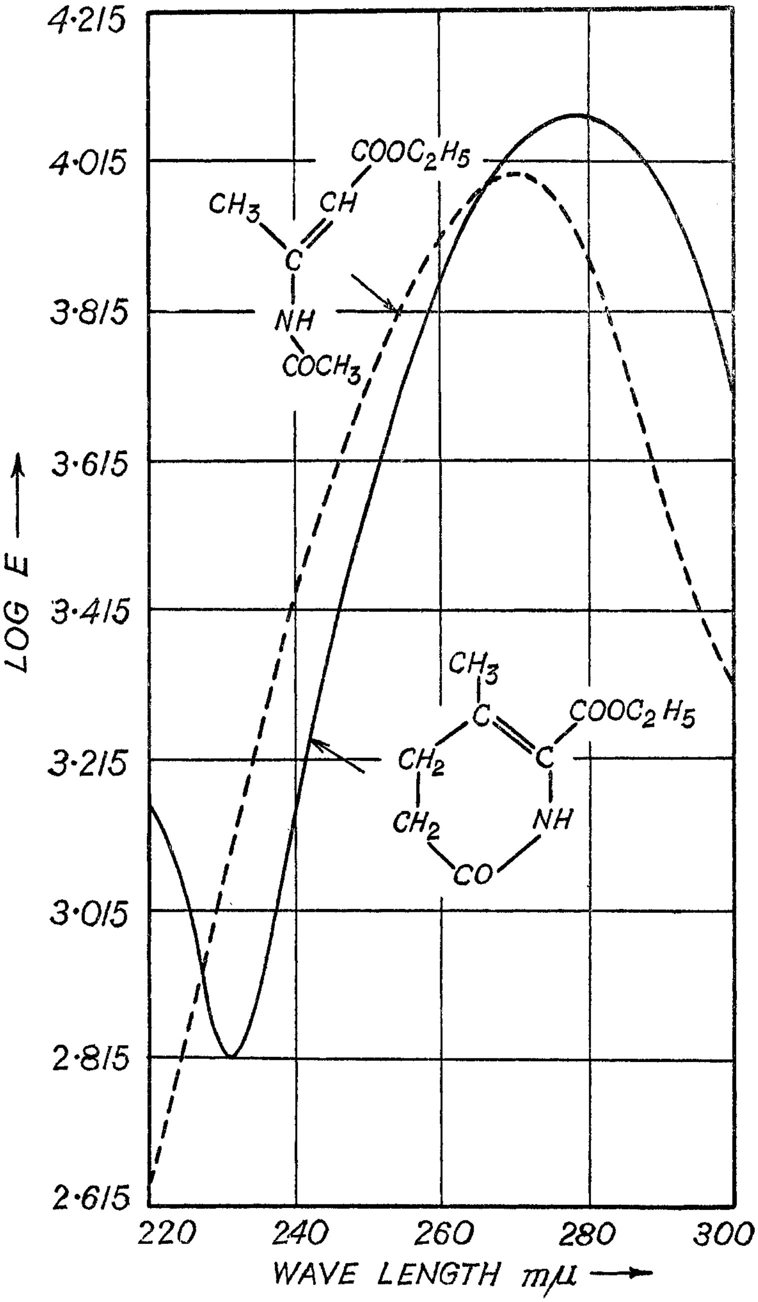
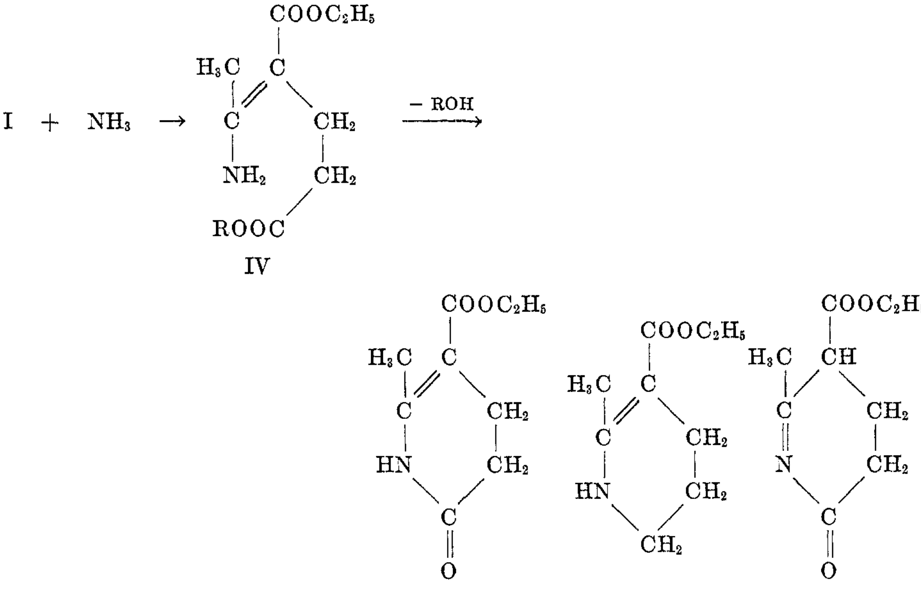


FIG. 1. THE ULTRAVIOLET ABSORPTION SPECTRA OF COMPOUND V (————) AND OF ETHYL β-ACETYLAMINOCROTONATE (— — — —).

ammonium acetate, acetic acid, and benzene, with the exclusion of ethyl cyanoacetate, was heated in the usual manner and the solid, m.p. 155.5°, was obtained in 76% yield. This conclusively proved that ethyl cyanoacetate did not play any part in the formation of the by-product.

In one of the condensation experiments, it was observed that the replacement of ethyl α-acetoglutarate (I, R = C_2H_5) by methyl γ-aceto-γ-carbethoxybutyrate (I, R = CH_3) led to the formation of the identical solid derivative, m.p. 155.5°. This showed that the formation of the by-product involved the elimination of the alkoxyl group, either $-OCH_3$ or $-OC_2H_5$, from the ester group of the propionic ester chain of I, (R = CH_3 or C_2H_5).

The influence of other condensing agents on the same reaction was also studied. The use of substituted amine acetates, such as diethylamine and piperazine acetates, prevented the formation of the by-product, and the normal condensation product (II, R = C_2H_5) was obtained along with the unchanged materials; but when acetamide was used as the condensing agent neither the normal condensation product nor the by-product was formed.



IV

V VI VII

From these evidences it seemed that the ammonia of ammonium acetate might have been responsible for the production of the by-product. Weiss (3) has also shown that the active form of ammonium acetate is the free ammonia base in the condensation of various carbonyl compounds with ammonium acetate in acetic acid to give a number of nitrogen heterocycles. Furthermore, in view of the fact that the β-ketonic esters are known to react with ammonia (4) to form the substituted β-aminoacrylic esters, it was concluded[2] that the ethyl α-acetogluta-

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[2] We are indebted to Mr. J. Datta of our laboratory for suggesting the structure (V) as representing the by-product.

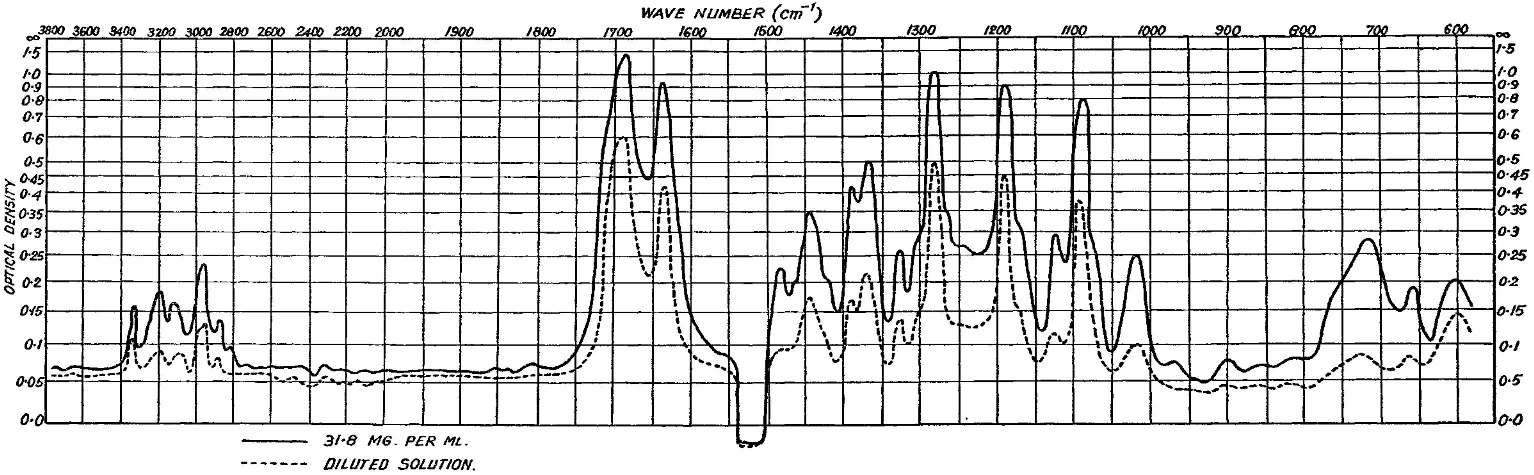

FIG. 2. THE INFRARED ABSORPTION SPECTRA OF COMPOUND V

rate first reacted with ammonia to yield ethyl α-(α′-aminoethylidene)glutarate (IV) and this was followed by the elimination of alcohol to give ethyl 1,4,5,6-tetrahydro-2-methyl-6-oxonicotinate (V); the latter representing the structure of the by-product. The observed analytical data and molecular weight also agrees with this formula.

A search of the literature showed that Emery (5) and later Clemo and Welch (6) had prepared ethyl 1,4,5,6-tetrahydro-2-methyl-6-oxonicotinate (V) by heating ethyl α-(α′-aminoethylidene)glutarate (IV) and the latter compound by continuously passing gaseous ammonia into ethyl α-acetoglutarate. Recently Albertson (7) also has prepared V by the careful hydrolysis of ethyl (2-cyanoethyl)acetoacetate. An authentic specimen of V was prepared by the last method and this was found to be identical with the solid by-product.

The examination of the constitution of the by-product in the light of absorption spectra also appeared to be interesting. Albertson (7) had recorded a U.V. λ_{max} 290 mμ for the corresponding desketo derivative (VI), which is 11 mμ higher than that of V. A similar difference in the U.V. absorption maxima of ethyl β-aminocrotonate (λ_{max} 274 mμ) (4) and its acetyl derivative (λ_{max} 269 mμ) (Fig. 1) was observed, when the U.V. data of the latter were studied by us. At this stage the possibility of the structure of the by-product being represented by the imino ketone structure (VII) was considerered. The I.R. absorption data,[3] however, shows two bands at 1688 cm^{-1} and 1635 cm^{-1}, strongly suggesting the presence of an α,β-unsaturated ester carbonyl and a ketone carbonyl respectively. Further it shows narrow bands at 3350 cm^{-1} and 3200 cm^{-1} indicating the presence of non-associated and associated N—H stretching vibrations respectively and this view is substantiated by the fact that at the lower concentration the 3350 cm^{-1} band is stronger, relative to the 3200 cm^{-1} band, than at higher concentration. Thus the consideration of the I.R. spectra definitely excludes the structure VII (See Figure 2).

EXPERIMENTAL[4]

Ethyl 1,4,5,6-tetrahydro-2-methyl-6-oxonicotinate (V). A mixture of 9.4 g. (0.04 mole) of ethyl α-acetoglutarate (I, R = C_2H_5), 3 g. (0.04 mole) of ammonium acetate, 4 ml. of glacial acetic acid, and 15 ml. of benzene was refluxed for four hours. On cooling, the separated crystals were filtered and washed thoroughly with water. The crude product weighed 5.6 g. (76%), m.p. 155–156° (shrinking at 151°), and on recrystallization from ethanol melted sharply at 155.5°. The melting point was not depressed on admixture with the by-product obtained during the Cope-Knoevenagel condensation of ethyl α-acetoglutarate with ethyl cyanoacetate (1).

Anal. Calc'd for $C_9H_{13}NO_3$: C, 59.02; H, 7.10; N, 7.65; Mol. wt., 183.

Found: C, 59.18; H, 6.85; N, 7.90; Mol. wt. (Rast's method), 168.

U. V. spectra in 95% ethanol, λ_{max} 279 mμ (log ε 4.01).

The authentic specimen of ethyl 1,4,5,6-tetrahydro-2-methyl-6-oxonicotinate, required for direct comparison, was prepared from ethyl (2-cyanoethyl)acetoacetate (8) by Albertson's procedure (6). The mixture melting point with the by-product remained undepressed.

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[3] We are indebted to Dr. R. Norman Jones of the National Research Council, Ottawa, Canada, for the I. R. data and the interpretation.

[4] All melting points are uncorrected.

The formation of V *from methyl γ-aceto-γ-carbethoxybutyrate* (I, R = CH_3) *and ethyl cyanoacetate.* By the following modification of the proportion of the reagents used in the previously described (1) Cope-Knoevenagel condensation a slightly better yield of the unsaturated cyano ester (II, R = CH_3) and a smaller formation of the by-product was realized. From a mixture of 108 g. (0.5 mole) of methyl γ-aceto-γ-carbethoxybutyrate (9), 67 g. (0.5 mole) of ethyl cyanoacetate, 7.7 g. (0.1 mole) of ammonium acetate, 24 ml. of glacial acetic acid, and 120 ml. of benzene, 85 g. (55%) of the unsaturated cyano ester (II, R = CH_3) and 9.5 g. of V were obtained.

Anal. Calc'd for $C_{15}H_{21}NO_6$: C, 57.88; H, 6.75.
Found: C, 58.02; H, 6.67.

The Cope-Knoevenagel condensation of ethyl α-acetoglutarate (I, R = C_2H_5) *with ethyl cyanoacetate using diethylamine and piperazine.* From a mixture of 23 g. of ethyl α-acetoglutarate, 11.5 g. of ethyl cyanoacetate, 5 ml. of diethylamine, 15 ml. of acetic acid, and 50 ml. of benzene, 13.4 g. (68% on the basis of the recovered keto ester) of the unsaturated cyano ester (II, R = C_2H_5) and 9.1 g. of unreacted I (R = C_2H_5) were obtained.

Similarly from a mixture of 92.39 g. of I (R = C_2H_5), 49 g. of ethyl cyanoacetate, 26 ml. of acetic acid, 5.6 g. of piperazine, and 110 ml. of benzene, 15.15 g. of II (R = C_2H_5) was obtained along with unreacted materials.

Hydrolysis of the solid by-product, m.p. 155.5°. A mixture of 20 g. of the by-product and 50 ml. of concentrated hydrochloric acid was refluxed for 15 hours. The cooled solution, after saturation with ammonium sulfate, was repeatedly extracted with ether and the ether solution was dried with sodium sulfate. The solvent was removed and the residue was distilled in a vacuum, b.p. 114°/1 mm.; yield, 9.6 g.

Anal. Calc'd for $C_{16}H_{10}O_3$: C, 55.38; H, 7.70; Neut. equiv., 130.
Found: C, 54.68; H, 8.13; Neut. equiv., 130.9.

The rather large difference in the analytical value may be explained by the hygroscopic nature of the keto acid, which solidified on exposure to the atmospheric air, m.p. 35–36°. The melting point of γ-acetobutyric acid monohydrate, as reported by Bentley and Perkin (10), is 35°. The mixture melting point with an authentic specimen remained undepressed.

The *semicarbazone* was prepared, m.p. 173°, from water. The mixture melting point with an authentic specimen remained undepressed.

The *oxime* was prepared, m.p. 103–104°, from benzene. The mixture melting point with an authentic specimen remained undepressed.

Oxidation of the keto acid (III) *with sodium hypoiodite.* To a stirred solution of 5 g. of the keto acid in 10 ml. of water and 120 ml. of 10% sodium hydroxide solution was added an iodine solution (prepared in the ratio $KI:I_2:H_2O::2:1:4$) until a dark red color persisted. The color of iodine was discharged by the addition of a few drops of sodium hydroxide solution. The separated solid, m.p. 119–120°, after filtration, was identified as iodoform. The filtrate, after being extracted with ether, was acidified and the color of the liberated iodine was discharged by passing in sulfur dioxide. The solution was evaporated to dryness on a steam-bath and the residue was extracted four times with 30-ml. portions of hot benzene. After the removal of benzene the gummy solid was spread over a porous plate. The solid product thus obtained, after two crystallizations from dry benzene, melted at 97°, which remained undepressed on admixture with an authentic specimen of glutaric acid.

Ethyl β-acetylaminocrotonate was prepared by the method of Collie (11) by refluxing a mixture of 6.4 g. of ethyl β-aminocrotonate (4) and 2.6 g. of acetic anhydride for four hours and then pouring the mixture into ice and water. The separated crystals, after crystallization from 50% aqueous ethanol, melted at 63° (recorded m.p. 63°). The U. V. spectra in 95% ethanol, λ_{max} 269 mμ (log ε 4.1).

SUMMARY

The solid by-product, m.p. 155.5°, obtained in the Cope-Knoevenagel condensation of ethyl α-acetoglutarate with ethyl cyanoacetate has been identified

as ethyl 1,4,5,6-tetrahydro-2-methyl-6-oxonicotinate (V). This has been formed by the reaction of ammonia, produced by the dissociation of ammonium acetate, with ethyl α-acetoglutarate followed by the elimination of a molecule of ethyl alcohol.

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