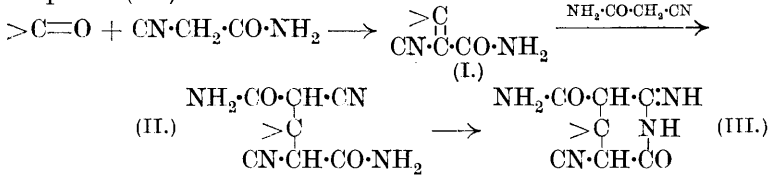
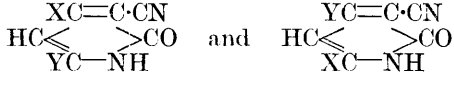
CCLXXXV.—*The Chemistry of* 1 : 3-*Dicarbonyl Compounds. Part I. The Mechanism of the Cyanoacetamide and Cyanoacetic Ester Condensations.*

By JOGENDRA CHANDRA BARDHAN.

WITHIN recent years a number of experiments have been placed on record dealing with the condensation of cyanoacetamide with ketonic compounds (Thole and Thorpe, J., 1911, **99**, 422; Wood and Thorpe, J., 1913, **103**, 1586; Kon and Thorpe, J., 1919, **115**, 686). The initial product of the condensation is an unsaturated amide (I), which usually reacts with a further molecule of cyanoacetamide to form a glutaric acid derivative (II), and this under the customary experimental conditions is converted into a cyclic imino-compound (III):



In extending these investigations to β-diketones it seemed probable that new complications might arise owing to the occurrence of keto-enolic tautomerism. An unsymmetrical β-diketone, X·C(OH):CH·COY, where X is an electronegative group, would give rise to two different pyridine derivatives,



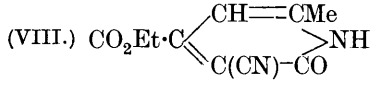
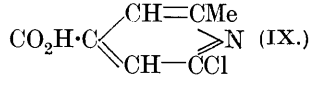
according as the molecule of cyanoacetamide reacts at the enolic double bond or with the carbonyl group.

The condensation of ethyl acetylpyruvate (IV), benzoylacetone (V), ω-propionylacetophenone (VI), and propionylacetone (VII) with cyanoacetamide has now been studied and the evidence

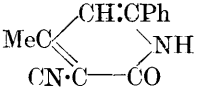
(IV.) $CO_2Et{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CH_3$ $C_6H_5{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CH_3$ (V.)

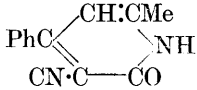
(VI.) $C_2H_5{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}C_6H_5$ $C_2H_5{\cdot}CO{\cdot}CH_2{\cdot}CO{\cdot}CH_3$ (VII.)

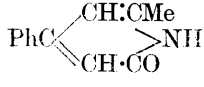
obtained strongly suggests that in each case the β-diketone reacts mainly in the keto-phase. When, for instance, cyanoacetamide and ethyl acetylpyruvate were condensed together under the conditions described later, the sole product was a crystalline substance (VIII). This was converted in the usual way into 2-chloro-6-methylpyridine-4-carboxylic acid (IX), the identity of which was established by direct comparison with a specimen prepared by the oxidation of

(VIII.)   (IX.)

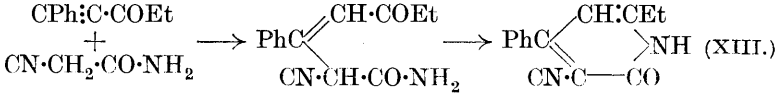
2-chloro-4 : 6-dimethylpyridine (Collie and Aston, J., 1897, **71**, 656). It follows, therefore, that the methylene group of cyanoacetamide has reacted with the keto-group adjacent to the carbethoxyl group of the ester. That the condensation product is not derived from the enolic form, $CO_2Et{\cdot}C(OH){:}CH{\cdot}CO{\cdot}CH_3$, through the occurrence of Michael's reaction is evident from the behaviour of other negatively substituted β-diketones. For instance, benzoylacetone condenses with cyanoacetamide with the production of a considerable quantity of 3-cyano-6-phenyl-4-methyl-2-pyridone (X) and a small quantity of 3-cyano-4-phenyl-6-methyl-2-pyridone (XI). The latter on hydrolysis yields 4-phenyl-6-methyl-2-pyridone (XII), the constitution of which is known (Ruhemann, J., 1899, **75**, 413).


(X.)

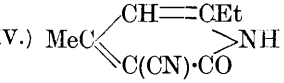

(XI.)

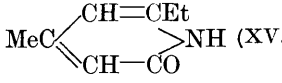

(XII.)

In the case of propionylacetophenone also the main product (X with Et in place of Me) is formed through the action of the methylene group of cyanoacetamide on the carbonyl group adjacent to the ethyl group. The structure of the pyridine derivative was indirectly ascertained by a synthesis of the isomeric compound (XIII), from cyanoacetamide and propionylphenylacetylene, which differed markedly from it.

 (XIII.)

In order to establish still further that the enolic forms of β-diketones do not take part in cyanoacetamide condensations, propionylacetone (VII) was next studied. A mixture of isomeric pyridine derivatives was obtained, in which one largely predominated. Were the enolic form of the β-diketone responsible for the production of these substances, they should be obtained in almost equal quantities, since there should not be any large difference in the relative proportions of the two forms, $CH_3{\cdot}C(OH){:}CH{\cdot}CO{\cdot}C_2H_5$ and $CH_3{\cdot}CO{\cdot}CH{:}C(OH){\cdot}C_2H_5$, into which propionylacetone could enolise. The principal product (XIV) of the above condensation gave on hydrolysis *4-methyl-6-ethyl-2-pyridone* (XV). This was converted, through the corresponding *chloro*-compound, into 4-methyl-6-ethylpyridine, the identity of which was established by the preparation of the picrate (Tschitschibabin, *J. Russ. Phys. Chem. Soc.*, 1924, **54**, 607; Eckert and Loria, *Monatsh.*, 1917, **38**, 226).

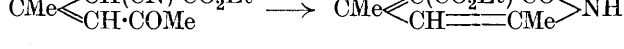
(XIV.) 

 (XV.)

It follows from the above that the carbonyl group adjacent to the positive alkyl group of the β-diketone is mainly reponsible for the reaction with cyanoacetamide, the actual proportion in which the two isomeric pyridine derivatives are produced being, however, determined by the relative activity of the two carbonyl groups. The behaviour of ethyl acetylpyruvate (IV) is different, but this is to be expected, because the presence of a carbethoxyl group adjacent to a carbonyl group greatly enhances its ketonic properties (compare Stewart, J., 1906, **89**, 905; Kohler and Corson, *J. Amer. Chem. Soc.*, 1923, **45**, 1976).

By condensing ethyl cyanoacetate with acetylacetone in presence of diethylamine, Simonsen and Naik (J., 1915, **107**, 793) obtained ethyl 4 : 6-dimethyl-2-pyridone-3-carboxylate :

$$OH{\cdot}CMe{:}CH{\cdot}COMe + CN{\cdot}CH_2{\cdot}CO_2Et \longrightarrow$$



According to them, the first phase of the reaction consists in the action of the cyanoacetic ester on the enolic form of acetylacetone, an intermediate compound being produced which then undergoes molecular rearrangement with the formation of the pyridone derivative. Ingold (J., 1921, **119**, 330), who has broadly discussed the mechanism of the action of ethyl cyanoacetate on keto-enolic compounds, considers that in all cases the unsaturated linking is responsible for the initial condensation, and that the elimination of

water is a subsequent effect. From this point of view, the experiment of Simonsen and Naik would seem to contradict the principle developed in this paper. The experiments of Kohler and Corson (*J. Amer. Chem. Soc.*, 1923, **45**, 1975) and of Lapworth and McRae (J., 1922, **121**, 2741) have, however, shown that Ingold's interpretation of the mechanism of the action of cyanoacetic ester on ketones is unnecessary, ketones to which no enolic form can be assigned reacting with ethyl cyanoacetate and malonate equally readily. Furthermore, a satisfactory explanation of the occurrence of $\beta\gamma$-unsaturated cyano-esters during the condensation of certain ketones with cyanoacetic ester has been advanced as a result of an examination of the action of these unsaturated substances on potassium cyanide (Kon and collaborators, J., 1923, **123**, 1361 and subsequent papers). Although the relative ease with which ketones react with cyanoacetic ester is dependent on their capacity to pass into the enolic form, this does not mean, as Ingold supposes, that the reactive feature is the enolic double bond : the great activity of keto-enolic compounds may also be attributed to the *nascent* carbonyl group that is generated during each successive phase of the tautomeric interchange (compare Stewart and Baly, J., 1906, **89**, 489).

From the above considerations it appears probable that in the experiment of Simonsen and Naik the β-diketone reacted in the ketonic form. If so, the condensation of acetylacetone with ethyl cyanoacetate would come into line with the reactions forming the subject of the present paper. Finally, in support of the mechanism suggested above, regarding the action of cyanoacetamide on β-diketones, it may be mentioned that acetylacetone does not condense with α-cyanopropionamide, although the latter reacts with αβ-unsaturated ketones in the expected way (Errera, *Ber.*, 1901, **34**, 3691).

Experimental.

Condensation of β-Diketones with Cyanoacetamide. General Method.—The β-diketone (0·1 g.-mol.) and cyanoacetamide (8·4 g.) were dissolved in just sufficient warm alcohol so that cyanoacetamide did not crystallise on cooling. When the solution, at 40—50°, was treated with diethylamine (4 c.c.), it became distinctly warmer and within a few minutes solidified to a crystalline mass. After cooling, the crystals were collected and washed with a little cold alcohol. A further quantity of diethylamine (2 g.) was added to the filtrate and the product was collected after 24 hours. The process was repeated until no further solid could be obtained. The yields were good, reaching 95% in some cases.

The cyanoacetamide was prepared by the method of Thole and

Thorpe (*loc. cit.*, p. 429) and after crystallising from alcohol was dried in the steam-oven for several hours before being used.

Condensation of Ethyl Acetylpyruvate with Cyanoacetamide : Ethyl 3-Cyano-6-methyl-2-pyridone-4-carboxylate (VIII).—The ethyl acetylpyruvate was prepared by the method of Claisen and Stylos (*Ber.*, 1887, **20**, 2188), the fraction, b. p. 114—115°/20 mm., being used. The sole product of the condensation, m. p. 217—218°, crystallised from 80% acetic acid (charcoal) in pale yellow needles, m. p. 219° (Found : C, 57·9; H, 5·0; N, 13·7. $C_{10}H_{10}O_3N_2$ requires C, 58·3; H, 4·9; N, 13·6%). It was insoluble in water, ethyl acetate, and light petroleum, sparingly soluble in chloroform and hot benzene, and readily soluble in hot glacial acetic acid and alcohol. It dissolved in alkali and in concentrated hydrochloric acid and was precipitated unchanged on acidification and on dilution with water, respectively.

This ester could not be prepared from ethyl acetylpyruvate, cyanoacetic ester, and alcoholic ammonia (Guareschi's method), but was obtained in almost quantitative yield when an aqueous solution of the ammonium derivative of ethyl acetylpyruvate (Mumm and Bergell, *Ber.*, 1912, **45**, 3040) and cyanoacetamide were mixed together.

Ethyl 5-bromo-3-cyano-6-methyl-2-pyridone-4-carboxylate was obtained by treating the preceding ester (0·8 g.) with bromine (0·5 c.c.) in acetic acid and diluting the solution with water after 12 hours. It crystallised from alcohol in prisms, decomp. 232—233° (Found : Br, 28·4. $C_{10}H_9O_3N_2Br$ requires Br, 28·1%).

Methylation. To a solution of sodium (0·23 g.) in methyl alcohol (10 c.c.), ethyl 3-cyano-6-methyl-2-pyridone-4-carboxylate (2 g.) was added, followed by methyl iodide (2 c.c.). After 12 hours, the clear solution was evaporated to dryness on the water-bath and the viscous product was extracted with chloroform, filtered, dried, and evaporated. The oily methylation product solidified when rubbed with ether, and on crystallisation from alcohol *ethyl 3-cyano-1 : 6-dimethyl-2-pyridone-4-carboxylate* was obtained in slender yellow needles, m. p. 177—179° (Found : N, 13·2. $C_{11}H_{12}O_3N_2$ requires N, 12·7%). This dissolved in water and in dilute acids, the solutions exhibiting a violet fluorescence.

6-Methyl-2-pyridone-4-carboxylic acid. The condensation product (VIII) (5 g.) was heated with 35 c.c. of concentrated hydrochloric acid at 150—160° for 3½ hours. The *acid* produced crystallised from much water in minute prisms, m. p. 314° (Found : C, 54·6; H, 4·7; N, 9·3. $C_7H_7O_3N$ requires C, 54·9; H, 4·6; N, 9·2%). It was easily soluble in concentrated hydrochloric acid, and gave a faint yellow coloration with ferrous sulphate solution. (The elimination of the cyano-group from the condensation product under the influence

of concentrated hydrochloric acid is typical of the decomposition undergone by all the 3-cyanopyridones described in this paper.)

The *methyl* ester, obtained by boiling the acid with methyl-alcoholic hydrochloric acid for 2 hours, separated from dilute alcohol in tufts of colourless needles, m. p. 228° (Found : C, 56·9; H, 5·5. $C_8H_9O_3N$ requires C, 57·4; H, 5·4%). It was easily soluble in hot alcohol, sparingly soluble in cold, and fairly readily soluble in chloroform, benzene, or ethyl acetate.

2-*Chloro*-6-*methylpyridine*-4-*carboxylic acid* (IX). Well-dried 6-methyl-2-pyridone-4-carboxylic acid (5 g.) was moistened with freshly distilled phosphoryl chloride and heated to 100°, phosphorus pentachloride (15 g.) was then gradually added, and the temperature allowed to rise during ¾ hour to 140°. The excess of phosphoryl chloride having been distilled off under reduced pressure, the residue was digested with water and crystallised from dilute acetic acid, 2-chloro-6-methylpyridine-4-carboxylic acid being obtained in colourless needles, m. p. 212° (Found : Cl, 20·3; N, 8·4. Calc. : Cl, 20·8; N, 8·2%).

Condensation of Benzoylacetone with Cyanoacetamide : 3-Cyano-6-phenyl-4-methyl-2-pyridone and 3-Cyano-4-phenyl-6-methyl-2-pyridone.—Benzoylacetone was prepared by Claisen's method (*Annalen*, 1898, **291**, 51).

The condensation product, obtained by heating for ½ hour on the steam-bath, melted at 270—286° and consisted of a mixture of isomeric pyridine derivatives, which were separated by fractional crystallisation from glacial acetic acid. 3-Cyano-6-phenyl-4-methyl-2-pyridone (X), the chief product, was very sparingly soluble and on recrystallisation was obtained in nacreous plates, exhibiting a slight blue fluorescence, m. p. 310° (decomp.) (Found : C, 74·3; H, 4·9. Calc. : C, 74·2; H, 4·8%) (Issoglio, *Atti R. Accad. Sci. Torino*, 1905, **40**, 495). The *methyl* derivative, prepared by heating the condensation product with sodium methoxide and methyl iodide at 100°, separated from glacial acetic acid in plates, m. p. 267° (Found : C, 74·7; H, 5·3. $C_{14}H_{12}ON_2$ requires C, 75·0; H, 5·4%).

6-*Phenyl*-4-*methyl*-2-*pyridone.* 3-Cyano-6-phenyl-4-methyl-2-pyridone was boiled with 80% sulphuric acid for 1 hour, and the cooled mixture poured into water. The product slowly separated in clusters of long colourless needles, which after recrystallisation from alcohol or water melted at 182—183° (Found : C, 77·5; H, 6·2. $C_{12}H_{11}ON$ requires C, 77·8; H, 5·9%). The *pyridone* is easily soluble in benzene and acetone, moderately soluble in alcohol, chloroform, and ether, and sparingly soluble in cold water but easily soluble in warm. Ferric chloride imparts to its aqueous solution a crimson colour. It also dissolves in alkali.

3-*Cyano*-4-*phenyl*-6-*methyl*-2-*pyridone* (XI). The mother-liquor from the crystallisation of the main condensation product (described above) on dilution with water yielded an isomeric substance which after repeated crystallisation from dilute acetic acid was obtained in minute needles, m. p. 249° (Issoglio, *loc. cit.*, gives 266—267°) (Found : C, 74·0; H, 4·8. Calc. : C, 74·2; H, 4·8%). Its constitution was proved by heating it with concentrated hydrochloric acid, removing the excess of acid on the water-bath, and nearly neutralising the residue with sodium carbonate. The 4-phenyl-6-methyl-2-pyridone obtained crystallised from alcohol in colourless needles and was identified by its m. p. 209° (Ruhemann, *loc. cit.*), analysis (Found : N, 7·7. Calc. : N, 7·6%), and by comparison with a specimen prepared by the hydrolysis of ethyl 4-phenyl-6-methyl-2-pyridone-5-carboxylate with concentrated hydrochloric acid (compare Ruhemann, J., 1899, **75**, 251).

Condensation of Propionylacetophenone with Cyanoacetamide : 3-*Cyano*-6-*phenyl*-4-*ethyl*-2-*pyridone*.—The condensation was brought about as in the case of benzoylacetone. The product after repeated crystallisation from acetic acid yielded chiefly 3-*cyano*-6-*phenyl*-4-*ethyl*-2-*pyridone*, m. p. 240° (decomp.) (Found : C, 75·2; H, 5·7; N, 12·8. $C_{14}H_{12}ON_2$ requires C, 75·0; H, 5·4; N, 12·5%), easily soluble in chloroform, amyl alcohol, and acetic acid.

Condensation of Propionylphenylacetylene with Ethyl Malonate and with Cyanoacetamide.—(1) Propionylphenylacetylene (Moureu and Brachin, *Bull. Soc. chim.*, 1904, **31**, 343; b. p. 140—142°/20 mm.) readily condensed with ethyl malonate (compare Kohler, *J. Amer. Chem. Soc.*, 1922, **44**, 384) when equimolecular quantities, dissolved in a little alcohol, were gently warmed on the steam-bath and treated with a few drops of sodium ethoxide solution. After cooling, the blood-red solution was acidified with dilute acetic acid and extracted with ether. The extract was washed with dilute sodium carbonate solution, dried, and evaporated. The residual *ethyl* 4-*phenyl*-6-*ethyl*-α-*pyrone*-3-*carboxylate* crystallised from dilute alcohol in pale yellow needles, m. p. 72—73° (Found : C, 71·2; H, 5·8. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%).

(2) To the white paste of the sodio-derivative obtained by adding 0·23 g. of sodium, dissolved in absolute alcohol, to a cooling solution of 0·84 g. of cyanoacetamide in 12 c.c. of boiling absolute alcohol, 1·6 g. of propionylphenylacetylene, dissolved in alcohol, were gradually added with vigorous shaking. The mixture, which became deep red and then yellow, was left for 12 hours at room temperature with occasional shaking. The alcohol was then removed, and the condensation product isolated in the usual way. 3-*Cyano*-4-*phenyl*-6-*ethyl*-2-*pyridone* separated from dilute acetic

acid (charcoal) in plates, m. p. 260° (Found : C, 75·5; H, 5·7. $C_{14}H_{12}ON_2$ requires C, 75·0; H, 5·4%).

Condensation of Propionylacetone with Cyanoacetamide : 3-Cyano-4-methyl-6-ethyl-2-pyridone (XIV).—Cyanoacetamide and propionylacetone (b. p. 159°/atm.; Morgan and Reeves, J., 1923, **123**, 447) reacted smoothly under the usual conditions, no external heat being necessary. The product, after being washed with a little alcohol and dried, melted at 210—220°. By repeated crystallisation from acetic acid, *3-cyano-4-methyl-6-ethyl-2-pyridone* was obtained in hard oblique prisms, m. p. 240—241°, having a curious bluish appearance due to the reflected light. This property becomes noticeable after many crystallisations and is apparently a good indication of the purity of the specimen (Found : C, 66·4; H, 6·2; N, 17·5. $C_9H_{10}ON_2$ requires C, 66·6; H, 6·2; N, 17·3%). The cyanopyridone is almost insoluble in water, acetone, or benzene, sparingly soluble in alcohol, and readily soluble in chloroform, boiling amyl alcohol, or acetic acid. It has a bitter taste.

4-Methyl-6-ethyl-2-pyridone (XV). The foregoing cyanopyridone (5 g.) was heated with concentrated hydrochloric acid (35 c.c.) at 140—150° for 3 hours. The excess of acid was then removed, the residue dissolved in water and treated with a solution of sodium carbonate, and the liberated base collected in chloroform. The solid remaining after evaporation of the chloroform crystallised from water in colourless needles, m. p. 144° (Found : C, 69·8; H, 8·0. $C_8H_{11}ON$ requires C, 70·1; H, 8·0%), which in aqueous solution gave a red colour with ferric chloride.

2-Chloro-4-methyl-6-ethylpyridine. Phosphorus pentachloride (15 g.) was gradually added to 4-methyl-6-ethyl-2-pyridone (10 g.) at 140°. After 2 hours the excess of phosphoryl chloride was distilled off under reduced pressure and the residue was carefully decomposed with ice-water, basified with a moderately concentrated solution of potash, and distilled in steam. An ethereal extract of the distillate, after being dried over caustic potash, gave a colourless, refractive oil, b. p. 124°/35 mm. and 224°/765 mm. (Found : Cl, 22·5. $C_8H_{10}NCl$ requires Cl, 22·8%). This readily dissolved in strong acids on warming and was reprecipitated on dilution. It did not form a double salt with platinic chloride.

4-Methyl-6-ethylpyridine was obtained when a mixture of 2-chloro-4-methyl-6-ethylpyridine (5 g.), hydriodic acid (12 c.c.; *d* 1·94), and red phosphorus (1 g.) was heated at 175—180° for 24 hours. The product was diluted with water, saturated with caustic potash, and extracted ten times with ether. The dried ethereal solution on distillation gave 4-methyl-6-ethylpyridine, b. p. 172—173°, as a colourless oil having a disagreeable smell recalling that of picoline

(Found : C, 78·9; H, 9·2. Calc.: C, 79·3; H, 9·1%). The picrate formed hard yellow prisms; after being purified from acetone and then from alcohol, it melted at 122—123° (Eckert and Loria, *loc. cit.*, give m. p. 115—116°; Tschitschibabin, *loc. cit.*, gives m. p. 120—121°) (Found : N, 16·2. Calc.: N, 16·0%). The reduction of the chloropyridine can also be effected by passing its vapour in a current of hydrogen over a layer of zinc dust heated to dull redness (compare Collie, P., 1897, **13**, 44).

Condensation of C-Ethylacetylacetone with Cyanoacetamide : 3-Cyano-4 : 6-dimethyl-5-ethyl-2-pyridone.—The condensation took place quite easily and the presence of a secondary carbon atom adjacent to the carbonyl group apparently had no marked effect on the course of the reaction. When the product was crystallised from acetic acid with the addition of a few drops of water, *3-cyano-4 : 6-dimethyl-5-ethyl-2-pyridone* was obtained in needles, m. p. 272° (decomp. and previous darkening) (Found : C, 68·1; H, 7·0; N, 16·0. $C_{10}H_{12}ON_2$ requires C, 68·1; H, 6·8; N, 15·9%).

4 : 6-Dimethyl-5-ethyl-2-pyridone was obtained when the above compound was hydrolysed with concentrated hydrochloric acid in the usual way. It crystallised from boiling water in colourless needles, m. p. 150° (Found : C, 71·2; H, 8·7. $C_9H_{13}ON$ requires C, 71·5; H, 8·6%).

Condensation of Acetylacetone with Cyanoacetamide : 3-Cyano-ψ-lutidocarbostyril.—The vigorous reaction was moderated by cooling in running water. The product (yield, almost quantitative) crystallised from alcohol in soft colourless needles, m. p. 289° (Found : C, 64·8; H, 5·5. Calc.: C, 64·9; H, 5·4%) (compare Guareschi, *Atti R. Accad. Sci. Torino*, 1893, **28**, 330, 836; Moir, J., 1902, **81**, 105).

A very good yield of ψ-lutidocarbostyril was obtained by hydrolysing the above cyano-compound with concentrated hydrochloric acid in the usual way. It was obtained by sublimation in long colourless needles, m. p. 180—181° (Found : N, 11·3. Calc.: N, 11·4%). Its identity was also established by the formation of the hydrochloride, m. p. 127—128°, and the picrate, m. p. 157° (compare Simonsen and Naik, *loc. cit.*).

Attempt to condense α-Cyanopropionamide with Acetylacetone.—The amide was prepared by the action of concentrated aqueous ammonia on ethyl α-cyanopropionate (compare Thole and Thorpe, *loc. cit.*), which was itself prepared by the method of Bone and Perkin (J., 1895, **67**, 421). The amide separated from alcohol in magnificent prismatic needles, m. p. 100—101° (Found : C, 49·0, 49·0; H, 5·9, 6·1. Calc.: C, 49·0; H, 6·1%). Henry (*Bull. Acad. roy. Belg.*, 1889, **25**, 680) gives m. p. 81°, and Beccari

(*Atti R. Accad. Sci. Torino*, 1903, **38**, 548) gives m. p. 105°. It could not be induced to react with acetylacetone under the usual conditions; even after prolonged heating, it remained practically unchanged.

In conclusion, my best thanks are due to Professor J. F. Thorpe, C.B.E., F.R.S., for reading the manuscript and to Professor P. C. Mitter, M.A., Ph.D., for the facilities which he placed at my disposal at the commencement of this research. My thanks are also due to the Trustees of the Palit Fund of the Calcutta University for a scholarship which enabled me to undertake this investigation.

UNIVERSITY COLLEGE OF SCIENCE, CALCUTTA.
IMPERIAL COLLEGE, LONDON, S.W.7. [*Received, August 20th*, 1928.]