Reactivity of Conjugated Systems. Part III. Condensation of $\alpha:\beta$-Unsaturated Esters with Cyanoacetamide.

By Chittaranjan Barat.

The present work deals with the reactivity of the ethylenic bond in the system R·CH=CH·CO·OEt and strictly speaking falls under the category of Part I of this series which deals with the reactivity of the corresponding double bond in the system R·CH=CH·CO·R′. (Barat, *J. Indian Chem. Soc.*, 1930, **7**, 321). The following reasons, however, sufficiently justify its treatment in a separate paper, namely,

(1) the products obtained with the present set of compounds are fundamentally different from those obtained from the former series, and

(2) there seems to be a marked difference in the activity of the above-mentioned double-bond in these two series, due, no doubt, to the replacement of the carbethoxy group $-CO\cdot OEt$ in place of the acyl group $-COR$ as present in the previous set of starting compounds.

It is well-known that in a system of the type $>C=CH\cdot X$ (where X is a so-called negative group, *e.g.* $-COR$, $-CO\cdot OEt$, $-CO\cdot NH_2$, etc.) or in other words, where an ethylenic bond exists in the $\alpha:\beta-$ position to a negative group X, the activity of that double-bond towards additive reactions in particular, is greatly influenced by the nature of the group X, *i.e.*, the activity increases with an increase in the negative character of X and *vice versa*. It is quite natural to expect therefore that the replacement of the rather strongly negative grouping $-CO\cdot R$ by the less negative one $-CO\cdot OEt$, the activity of the double-bond in the α-position to it will be greatly impaired, and this anticipation has been borne out by facts. When, however, the carbethoxy group is replaced by a slightly more negative carbonamide group $-CO\cdot NH_2$, the reaction takes place more readily than in the previous case. Quite a parallel case has been recently cited by Basu (*J. Indian Chem. Soc.*, 1930, **7**, 481 ; *cf.* also Meyer, *Ber.*, 1912, **45**, 2843).

The products of condensation described in the present work, belong to the glutarimide type. Such compounds do not appear to have been prepared by the present method, and advantage has been taken of this reaction to attempt the synthesis of 2:6-dihydroxy-pyridines, by dehydrogenating these compounds.

Although several methods of condensing these esters with acetoacetic, malonic and cyanoacetic esters are placed on record (Auwers, *Ber.*, 1891, **24**. 308 ; Auwers and Köbner, *ibid*, p. 1929 ; Auwers, Köbner and Meyenburg, *ibid*, p. 2888; Perkin and Thorpe, *J. Chem. Soc.*, 1899, **75**, 49 ; Thorpe, *ibid*. 1900, **77**, 923 ; also Ingold and others, *ibid*. 1926, **128**, 1868) no attempt has yet been made to condense them with cyanoacetamide, when, no doubt, the following reaction takes place—

$$\begin{matrix} R\cdot CH=CH\cdot CO\cdot OEt \\ + \\ CN\cdot CH_2-CO\cdot NH_2 \end{matrix} \longrightarrow \left[\begin{matrix} R\cdot CH-CH_2\cdot CO\cdot OEt \\ | \\ CN\cdot CH-CO\cdot NH_2 \end{matrix} \right]$$

(I)

$$\longrightarrow \begin{matrix} R\cdot CH-CH_2\cdot CO \\ | \quad\quad | \\ CN\cdot CH-CO\cdot NH \end{matrix} \quad \ldots \quad (1)$$

(II)

leading to the formation of a 2:6-diketo-3-cyano-4-(R)-piperidine. The other probability, namely that of the ester reacting as a ketonic ether is expressed as follows :—

$$\begin{matrix} R\cdot CH\cdot CH_2\cdot CO\cdot OEt \\ | \\ CN\cdot CH-CO\cdot NH_2 \end{matrix} \longrightarrow \left[\begin{matrix} R\cdot CH\cdot CH_2\cdot C\cdot OEt \\ | \quad\quad \| \\ CN\cdot CH\cdot CO\cdot N \end{matrix} \right]$$

(I) (III)

$$\longrightarrow \left[\begin{matrix} R\cdot CH\cdot CH=C \\ | \quad\quad \| \\ CN\cdot CH\cdot CO\cdot N \end{matrix} \right] \longrightarrow \begin{matrix} R\cdot C=CH-CH \\ | \quad\quad \| \\ CN\cdot CH\cdot CO\cdot N \end{matrix} \quad \ldots \quad (2)$$

(IV) (V)

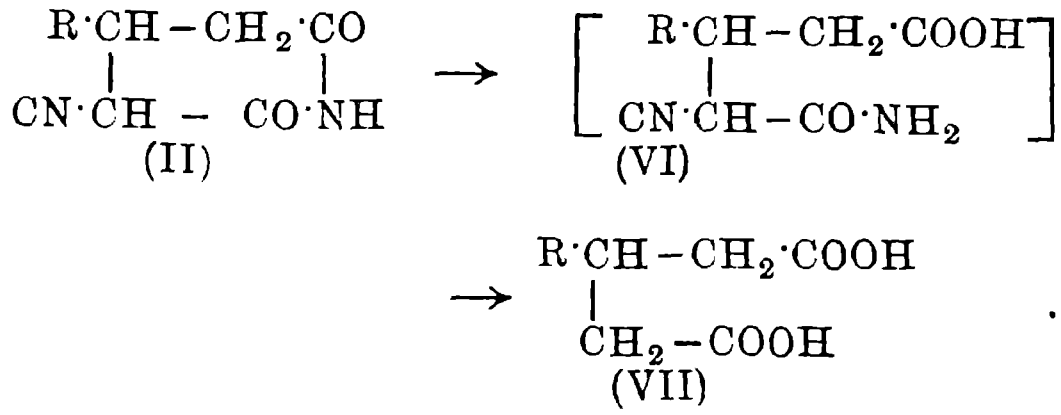
But this latter scheme had to be discarded on the grounds that—

(1) the analytical figures of the condensation products correspond to a composition (II) and not to (V), and

(2) on hydrolysis the condensation products give rise to open-chain dibasic acids containing no nitrogen, which is only possible to compounds of type (II), whereas a compound (V) on hydrolysis would have given rise to 2-hydroxy-4-(R)-pyridines (*cf.* Barat, *loc. cit.*,

also *J. Indian Chem. Soc.*, 1930, 7, 851).

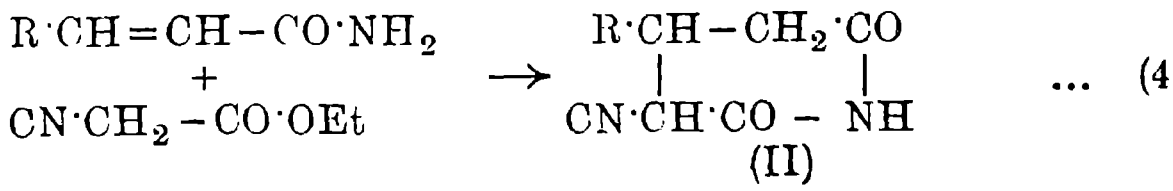
It is thus clearly established that the reaction takes place according to the scheme (1) ; the resulting products, belonging to glutarimide derivatives, suffer ring-fissure on hydrolysis and form β substituted glutaric acids (VII) possibly through the intermediary of an amido-acid (VI) as shown below.



The constitutions of these acids (VII) have been finally established by synthesising them from the appropriate aldehydes and ethyl malonate according to the method of Knoevenagel (*Ber.*, 1894, **27**, 2346).

Up till the present time it has not been possible to isolate compounds (I) and (VI) described above. The formation of (I) is precluded in a Michael's medium, where the elimination of alcohol is extremely easy. It would, however, have been possible to obtain it by Knoevenagel's method, but unfortunately these esters did not enter into combination with cyanoacetamide in the presence of Knoevenagel's reagent under ordinary circumstances. On the other hand, the free existence of a compound (VI) is rendered improbable between the two extreme tendencies of formation of the compounds (II) and (VII).

The amides of the corresponding acids have been condensed with ethyl cyanoacetate when products identical with (II) have been obtained according to the scheme—



This reaction affords a further confirmation of the structure as given to these compounds. The reaction takes place with greater ease than with the esters of the corresponding acids and this further strengthens the theory that the more negative nature of the

$-CO\cdot NH_2$ group (than $-CO\cdot OEt$) enhances the reactivity of the double-bond in the α-position to it towards additive reactions.

Attempts are in progress to convert these compounds into 2;6-dihydroxypyridines by oxidation.

Experimental.

General Procedure.

As has already been indicated in the theoretical part, the condensation failed to take place by Knoevenagel's method and recourse had therefore to be taken to Michael's reaction alone to effect the condensations. To the usual suspension of sodiocyanoacetamide in absolute alcohol, the equivalent quantity of the ester was added, the mixture well shaken from time to time and left over till the odour of the ester completely disappeared. During this process of condensation the mixture usually developed a characteristic coloration which disappeared on the final acidulation of the mixture. The reaction was usually over in 3 or 4 days, but the isolation of the free condensation product was taken up usually after a week. The sodium salt was filtered off, washed with alcohol, dissolved in the minimum quantity of water, and acidulated with glacial acetic acid. The mixture was then cooled in ice, and the separated product filtered, washed with cold water, dried and crystallised. The cyanopiperidones that were thus formed were soluble both in alkalis and alkali carbonates, from which they were obtained unchanged on acidulation, excepting where it was also soluble in water. Their alcoholic or aqueous solutions did not give any coloration with ferric chloride, showing the absence of a hydroxyl group.

These compounds could be easily hydrolysed both by acids and alkalis but it was best achieved by means of 75% sulphuric acid as detailed in the previous works (*locc. cit.*). Where the dibasic acid formed did not separate on cooling and diluting the solution it was extracted by ether, and isolated by evaporation of the ethereal solution.

The dibasic acids so obtained were compared with identical specimens prepared by condensing the appropriate aldehyde with two molecular proportions of ethyl malonate according to the method of Knoevenagel (*loc. cit.*). The aldehyde and the ester were mixed together and left aside after the addition of a little piperidine. Next

day, the separation of a little water was observed and the mixture was heated under reflux for about half an hour; as the intermediate product (the tetra-carboxylic ester) was not required an equal volume of concentrated hydrochloric acid (*d*, 1.14) and another equal volume of water were added and the mixture heated under reflux till the evolution of carbon dioxide ceased. This usually took 6 to 8 hours, the mixture was then cooled, neutralised with sodium carbonate, the solution washed with ether (to remove any oily matter) and acidulated. The glutaric acid usually separated out, but was better extracted with ether, and the acid isolated therefrom. It was then purified by crystallisation and compared with the corresponding specimen.

Ethyl Acrylate and Cyanoacetamide.

The ester was prepared by the method of Münder and Tollens (*Annalen*, 1873, **167**, 222) and Caspary and Tollens (*ibid*, 248) from allyl alcohol. The yield was poor, on account of its tendency to polymerise and form a characteristic resinous matter on distillation (*cf.* Weger, *Annalen*, 1884, **221**, 80).

Formation of 2:6-*Diketo*-3-*cyanopiperidine*.—On mixing the components the mixture became blood red in colour, and shortly afterwards deposited a pink solid. After the usual time the mixture was carefully neutralised by dry hydrogen chloride, when the colour changed sharply into yellow; the sodium chloride was filtered off and the condensation product obtained by evaporation of the alcoholic solution (yield about 40%). It was soluble in almost all solvents (including water) excepting petroleum ether. Crystallised from alcohol it was obtained in short prisms, m.p. 206-7°. Its alcoholic solution turned violet on exposure to air, probably due to oxidation and consequent formation of the dihydroxypyridine which has been known to impart similar colorations (*cf.* Ruhemann, *J. Chem. Soc.*, 1898, **73**, 350). (Found: N, 20·10. $C_6H_6O_2N_2$ requires N, 20·29 per cent.).

Formation of Glutaric Acid.—The above compound was hydrolysed by sulphuric acid as usual, but the glutaric acid formed did not separate on cooling and diluting the solution. It was therefore extracted with ether, and isolated by evaporating the solvent. Crystallised from benzene it was obtained in colourless prisms, m.p. 97-98°. (Found: C, 45·24; H, 6·83; equiv. wt., 67·19. $C_5H_8O_4$ requires C, 45·45; H, 6·66 per cent.; equiv. wt., 66).

This was also synthesised from formaldehyde and ethyl malonate by Knoevenagel's method (*loc. cit.*). The purified product melted at 97-98°, and was identical with the specimen obtained above.

Ethyl Crotonate and Cyanoacetamide.

The ester was obtained according to the method of Michael (*Ber.*, 1900, **33**, 3766).

Formation of 2:6-Diketo-3-cyano-4-methylpiperidine.—Immediately on mixing the reactants the colour became reddish-violet and the sodium salt of the condensation product separated gradually. The free condensation product was separated as in the previous case, or by dissolving the sodium salt in the minimum quantity of water, neutralising the solution carefully with acetic acid, and cooling the solution with ice, when the product crystallised out. On crystallising from water it was obtained in colourless prismatic plates melting at 140-42°. It was very soluble in all solvents excepting petroleum ether and benzene (sparingly). (Found: N, 18·68. $C_7H_8O_2N_2$ requires N, 18·42 per cent.).

Formation of β-Methylglutaric Acid.—It was obtained by hydrolysing the above compound in an exactly similar way as in the previous case. It resembled its lower homologue in all its properties and crystallised from water in short prisms that melted at 85-86°. (Found: C, 49·58; H, 7·02; equiv. wt., 75·23. $C_6H_{10}O_4$ requires C, 49·31; H, 6·85 per cent.; equiv. wt., 73).

The acid could be directly obtained by treating acetaldehyde with ethyl malonate in alcoholic solution in presence of piperidine, and hydrolysing the product as before. It was found advisable however, to remove the alcohol before hydrolysis, as its presence appreciably hinders hydrolysis. The acid isolated as before and crystallised from water, melted at 85-86°, and was identical with the one obtained above.

Ethyl Cinnamate and Cyanoacetamide.

Formation of 2:6-Diketo-3-cyano-4-phenylpiperidine.—The reaction mixture exhibited a green coloration and the condensation took place more slowly than in the previous cases, as the odour of the ester was perceptible even after a week. But as the product

was insoluble in water it could be isolated with greater ease. (Yield about 65% .) Crystallised from alcohol, it was obtained in fine white scaly flakes melting at 224-25°, and but for its lesser solubility, resembled the other homologues in all its properties (Found: N, 13·38. $C_{12}H_{10}O_2N_2$ requires N, 13·08 per cent.).

The above compound was also obtained in a still better yield* (about 75%) when the amide of cinnamic acid, m.p. 145-47°, (prepared by the method of Autenrieth, *Ber.*, 1904, **34**, 184) was condensed in the usual way with ethyl cyanoacetate.

Formation of β-Phenylglutaric Acid.—When the above compound was hydrolysed by 75% sulphuric acid, and the reaction mixture diluted after being cooled, the acid separated as a thick oil which was extracted with ether. Crystallised from 40% alcohol it was obtained in fine white scales, m.p. 137-38°. (Found: C, 63·74; H, 6·01; equiv. wt., 108. $C_{11}H_{12}O_4$ requires C, 63·46; H, 5·77 per cent.; equiv. wt., 104).

The acid was directly obtained from benzaldehyde and ethyl malonate in the usual way. No solvent was employed, and the product melted at 137-38°, and was identical with the other specimen.

Ethyl p-*Nitrocinnamate and Cyanocetamide.*

Formation of 2:6-*Diketo*-3-*cyano*-4-p-*nitrophenylpiperidine.*—The condensation was carried out as usual and the condensation product separated as in the previous case. The product was almost insoluble in all solvents excepting glacial acetic acid and pyridine. Crystallised from either of these solvents it was obtained in yellow prisms, m.p. 279-80°. (Found: N, 16·51. $C_{12}H_9O_4N_3$ requires N, 16·22 per cent.) This compound was obtained in a far better yield when the amide of *p*-nitrocinnamic acid (m.p. 155°) was condensed with ethyl cyanoacetate ester as in the previous case.

Formation of β-p-Nitrophenylglutaric Acid.—The above compound was readily hydrolysed by 75% sulphuric acid, and the resulting acid easily separated on diluting the acid solution. The substance was fairly soluble in ether, alcohol, benzene and acetic acid, sparingly so

* This superiority in yield confirms the statement (*vide supra*) that the —CO·NH_2 group being more negative than the—CO·OEt group enhances the reactivity of the α : β-double bond.

in water and insoluble in petroleum ether. It crystallised in very pale yellow prismatic needles m. p. 238-40°. (Found: N, 5·36; equiv. wt., 128·05. $C_{11}H_{11}O_6N$ requires N, 5·62 per cent., equiv. wt., 126·5).

The acid was directly obtained from *p*-nitrobenzaldehyde and ethyl malonate in the usual way. The acid separated on diluting the hydrochloric acid solution and was filtered off, washed and crystallised from alcohol. It had m.p. 238-40° and was identical with the previously obtained sample.

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Department of Applied Chemistry,
University College of Science and Technology,
Calcutta.

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