SYNTHESIS OF THE ESTERS OF β-BENZYL-α,γ-DICYANOGLUTACONIC ACID.

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The formation of the sodium derivative of diethyl β-methyl-α, γ-dicyanoglutaconate $C_2H_5OCO(CN)C{:}C(CH_3){\cdot}CNa(CN)COOC_2H_5$ in the condensation of ethyl ethoxy-ethylidene-cyanoacetate $C_2H_5OC(CH_3){:}C(CN)COOC_2H_5$ with ethyl sodio-cyanoacetate $CHNa(CN)COOC_2H_5$ let the author suppose that any compound with the general formula $C_2H_5OCR : C(CN)COOC_2H_5$ will condense with ethyl sodio-cyanoacetate, yielding the following product:

$$C_2H_5OCO(CN)C{:}CR{\cdot}CNa(CN)COOC_2H_5.^{(2)}$$

Subsequently the author carried out experiments on the synthesis of the esters of β-benzyl-α, γ-dicyanoglutaconic acid,

$$ROCO(CN)C : C(CH_2C_6H_5) \cdot CH(CN)COOR.$$

Diethyl β-Benzyl-α,γ-dicyanoglutaconate. The sodium derivative of this ester, $C_2H_5OCO(CN)C : C(CH_2C_6H_5) \cdot CNa(CN)COOC_2H_5$, must be given by the condensation of ethyl α-cyano-β-ethoxy-γ-phenyl-crotonate $C_2H_5OC(CH_2C_6H_5) : C(CN)COOC_2H_5$ and ethyl sodio-cyanoacetate. Ethyl α-cyano-β-ethoxy-γ-phenyl-crotonate has been already obtained by Smith and

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(2) See p. 102 and 261 of this volume.

Thorpe.⁽¹⁾ It seems difficult to obtain a sufficient amount of this compound in the pure crystalline state, for these authors describe that the ethylation product of the silver derivative of ethyl α-cyano-γ-phenyl-acetoacetate was a mixture of two isomerides, ethyl α-cyano-β-ethoxy-γ-phenyl-crotonate and ethyl α-cyano-α-ethyl-γ-phenyl-acetoacetate, which could not be separated by distillation. The present author gave up the idea to obtain the pure ethyl α-cyano-β-ethoxy-γ-phenyl-crotonate, and used it without separating from its isomeride.

The method of preparation of ethyl α-cyano-γ-phenyl-acetoacetate was improved as follows: Powdered sodium (2 atoms) was covered with a large amount of pure benzene and an excess of ethyl cyanoacetate (over 2 mols) was introduced gradually. On several hours' standing, the mixture was converted into a white thick paste. Phenacetyl chloride (1 mol) was then added in small portions under constant stirring and cooling. The mixture was heated on the water bath for a while, and cooled. The sodium derivative of ethyl α-cyano-γ-phenyl-acetoacetate formed in this way was extracted with water. The aqueous solution was acidified with dilute sulphuric acid and the oily substance was extracted with ether. After dehydrating the ethereal solution with calcium chloride and evaporating away the ether, the ester was distilled under diminished pressure. Ethyl α-cyano-γ-phenyl-acetoacetate was transformed into the silver derivative by dissolving it in an aqueous solution of the calculated amount of sodium hydroxide and adding to this solution the calculated amount of a silver nitrate solution. The silver compound was washed with water and completely dried in vacuum in a dark place.

A mixture of the dried silver compound, an excess of ethyl iodide, and absolute alcohol, was boiled for a while with a reflux condenser. The alcoholic solution was filtered from silver iodide and evaporated. The residue was dissolved in ether and the ethereal solution was shaken with an aqueous solution of sodium carbonate until the latter remained alkaline. Then it was washed with water, dried with calcium chloride and evaporated. The ether was removed in vacuum over sulphuric acid as much as possible. The oily substance obtained in this way and containing ethyl α-cyano-β-ethoxy-γ-phenyl-crotonate was used for the condensation without further treatments.

Sodium (1 gram atom) was dissolved in absolute ethyl alcohol and ethyl cyanoacetate (1 mol) was added. Then ethyl α-cyano-β-ethoxy-γ-phenyl-crotonate (1 mol) was introduced, the above-described oily substance being assumed to consist of this compound alone. The alcoholic solution was evaporated to dryness in vacuum, and the residue was dissolved in water.

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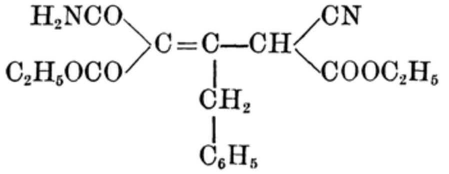
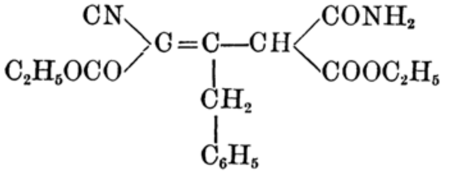
(1) *J. Chem. Soc.*, 91 (1907), 1905.

The insoluble oily substance might be the ethyl α-cyano-α-ethyl-γ-phenylacetoacetate which was indifferent in the reaction. This was removed by shaking the aqueous solution with ether. On adding dilute hydrochloric acid to the aqueous solution an oily substance separated out, which was extracted with ether. Some amount of the sodium derivative of ethyl cyanoacetate might be left intact, for the ethyl α-cyano-β-ethoxy-γ-phenylcrotonate had contained its isomeride indifferent in the reaction. On dissolving the condensation product in water, the ethyl sodio-cyanoacetate is at once transformed into sodium cyanoacetate and alcohol. Therefore, on acidifying the aqueous solution the ethyl cyanoacetate was not to be regenerated, and this fact facilitated the subsequent treatment.

The ethereal solution was washed with water. After a while, colourless crystals began to separate from the ethereal solution not yet dried. When the increase of the crystals ceased, they were collected, washed with ether and then with water. This crystalline substance was recrystallised from alcohol. It melted at 131°. By analysis it was found to be diethyl β-benzylcyano-carbamyl-glutaconate, and not the diethyl β-benzyl-α,γ-dicyanoglutaconate. 0.1943, 0.2022 Gr. of the substance gave 0.4465, 0.4622 gr. of CO_2 and 0.1001, 0.1044 gr. of H_2O respectively: 0.2462, 0.2727 gr. of the substance gave 18.3 c.c. (26.5°, 759.5 mm.), 20.15 c.c. (26.5°, 761. 9 mm.) of nitrogen respectively. (Found: C=62.69, 62.36; H=5.77, 5.78; N=8.18, 8.15. $C_{18}H_{20}O_5N_2$ requires C=62.75; H=5.86; N=8.14%.) On heating at about 90° or dehydrating in vacuum, it lost no water. This compound must be either of the following:



diethyl β-benzyl-α-cyano-α-carbamyl-glutaconate;



diethyl β-benzyl-γ-cyano-α-carbamyl - glutaconate.

The oily substance which was afterwards changed in the crystalline monohydrate must be diethyl β-benzyl-α,γ-dicyanoglutaconate, $C_2H_5OCO(CN)C:C(CH_2C_6H_5)\cdot CH(CN)COOC_2H_5$. Inspite of the impureness of the ethyl α-cyano-β-ethoxy-γ-phenyl-crotonate the condensation proceeded successfully as follows:

$$NaOC_2H_5 + CNCH_2COOC_2H_5 + C_2H_5OC(CH_2C_6H_5) : C(CN)COOC_2H_5$$
$$= C_2H_5OCO(CN)C : C(CH_2C_6H_5) \cdot CNa(CN)COOC_2H_5 + 2\ C_2H_5OH.$$

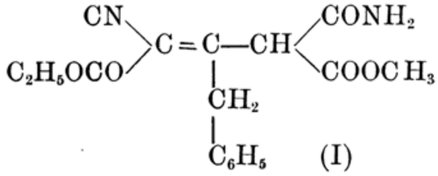
Although the sodium compound was not isolated, it was contained in the aqueous solution of the condensation product and it gave the free cyano-ester on acidifying, and the latter was then transformed into the monohydrate in the ethereal solution.

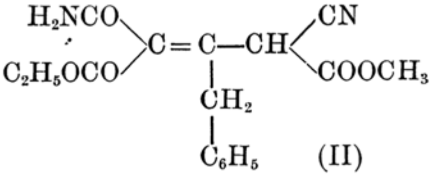
Methyl Ethyl Esters. Following the similar procedure the author carried out the experiment on the condensation of ethyl α-cyano-β-ethoxy-γ-phenyl-crotonate with methyl cyanoacetate in the presence of sodium methylate. The final product was the monohydrate of methyl ethyl β-benzyl-α, γ-dicyanoglutaconate melting at about 115°. 0.1930 Gr. of the substance gave 0.4351 gr. of CO_2 and 0.0946 gr. of H_2O; 0.2547 gr. of the substance gave 19.3c.c. of nitrogen at 22.5°, 761.8 mm. (Found: $C = 61.50$; $H = 5.49$; $N = 8.54$. $C_{17}H_{18}O_5N_2$ requires $C = 61.79$; $H = 5.50$; $N = 8.48$ %.) (Specimen A)

The condensation must be represented by the following equation:

$$C_2H_5OCO(CN)C:C(CH_2C_6H_5)OC_2H_5 + CH_2(CN)COOCH_3 + NaOCH_3$$
$$= C_2H_5OCO(CN)C : C(CH_2C_6H_5)\ CNa(CN)COOCH_3 + CH_3OH + C_2H_5OH.$$

The monohydrate $C_{17}H_{18}O_5N_2$, in which the sodium atom is replaced by hydrogen and either of the two cyano-groups is hydrated into a carbamyl-group, must be represented by either of the following formulas:


(I)


(II)

By starting from methyl α-cyano-β-ethoxy-γ-phenyl-crotonate(1), ethyl cyanoacetate, and sodium ethylate, another specimen of methyl ethyl β-benzyl-cyano-carbamyl-glutaconate was obtained. It melted at about 115°.

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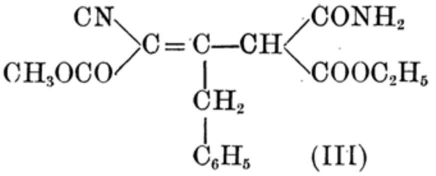
(1) This compound was prepared by a similar method as the ethyl ester. The sodium derivative of methyl cyanoacetate formed in benzene covered so compactly the surface of sodium grains that the transformation of methyl cyanoacetate into its sodium derivative was completed only by using a large excess of powdered sodium (about twice as much as necessary) and rubbing mechanically the sodium grains. On adding phenacetyl chloride and standing over night the metallic sodium disappeared. Then the mixture was worked on similarly as in the case of the ethyl ester. Methyl α-cyano-γ-phenyl-acetoacetate is a crystalline substance. This ester was transformed into methyl α-cyano-β-ethoxy-γ-phenyl-crotonate, which was used also without separating from its possible isomeride.

0.1889 Gr. of the substance gave 0.4261 gr. of CO_2 and 0.0928 gr. of H_2O; 0.2501 gr. of the substance gave 18.9 c.c. of nitrogen at 23°, 760.7 mm. (Found: $C=61.54$; $H=5.50$; $N=8.48$. $C_{17}H_{18}O_5N_2$ requires $C=61.79$; $H=5.50$; $N=8.48$ %.) (Specimen B)

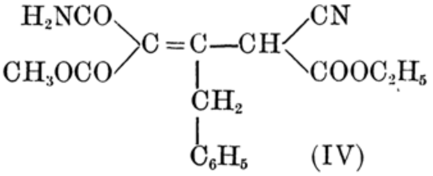
The condensation must be represented by the following equation:

$$CH_3OCO(CN)C:C(CH_2C_6H_5)OC_2H_5+CH_2(CN)COOC_2H_5+NaOC_2H_5$$
$$=CH_3OCO(CN)C:C(CH_2C_6H_5)\cdot CNa(CN)COOC_2H_5+2C_2H_5OH,$$

and the monohydrate by either of the following:



(III)



(IV)

The four formulas, (I), (II), (III), and (IV), are different from one another, and, therefore, the two specimens, A and B, must be different; but according to the example of the β-methyl compounds⁽¹⁾, they may be expected to be identical. Really the mixture of the two specimens showed no depression of the melting point, but both the pure specimens and the mixture did not melt sharply. Each of the specimens A and B is not the direct product of the condensation but the compound derived from it by a secondary change which can admit two formulas for it, for instance, (I) and (II). These specimens must be, therefore, examined in their purity. Besides, the greatest care must be exercised with regards to the identification of them, because, if they are not identical, they have a great resemblance in the constitutions. For the present the author will reserve the conclusion that the specimens A and B are identical.

The auther expresses his hearty thanks to Prof. K. Matsubara for his kind inspection of this paper.

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(1) See p. 261 of this volume.