XXVIII.—*Formation of Ethylic Dihydroxydinicotinate from Ethylic Cyanacetate.*

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THE experiments described in this paper have been undertaken with the view of investigating more closely the action of chloroform on ethylic malonate in presence of sodium ethoxide, as the yield of the sodium derivative of ethylic dicarboxyglutaconate thus obtained was found to be far from satisfactory, and in fact never reached that stated by Conrad and Guthzeit (*Annalen*, 1884, **222**, 249), although this compound had been frequently prepared by one of us and his pupils. The mother liquor of this substance which had accumulated in the course of their researches served as material for this study.

The red-brown alcoholic filtrate from ethylic sodiodicarboxyglutaconate which, after concentration, did not yield any further crop of this substance, even when left for several weeks, deposited an oil when diluted with water; this was separated by the use of ether, and distilled under diminished pressure. Although the examination of this oil is not yet complete, it has been ascertained that it consists to a large extent of ethylic malonate. Excess of hydrochloric acid was added to the aqueous layer left after treatment with ether, and the solution again repeatedly shaken with ether; on distilling off the ether, a red

oil was left which did not deposit any solid on standing. When heated under diminished pressure, only a small quantity of a colourless liquid distilled at about 150° , but at 160° a reaction took place which resulted in the contents of the flask becoming a semi-solid mass of crystals; these were freed from the mother liquor by washing with dilute alcohol. The dark coloured product thus obtained contained inorganic matter and was only sparingly soluble in water or alcohol, but dissolved in cold concentrated hydrochloric acid. On adding water to this solution, an almost colourless, crystalline product was obtained which readily dissolved in alcohol, and crystallised from it in transparent needles melting at 202° to a red liquid. The compound, on examination, was found to contain nitrogen and to be the ethylic salt of dihydroxydinicotinic acid,

0.2040 gave 0.3855 CO_2 and 0.1000 H_2O . C = 51.53; H = 5.44.

0.2400 „ 0.4510 CO_2 „ 0.1130 H_2O . C = 51.25; H = 5.23.

0.2285 „ 0.4318 CO_2 „ 0.1045 H_2O . C = 51.54; H = 5.08.

0.3084 „ 14.8 c.c. nitrogen at 19° and 769 mm.; N = 5.58.

$\text{C}_{11}\text{H}_{13}\text{NO}_6$ requires C = 51.76; H = 5.10; N = 5.49 per cent.

The compound is identical with that obtained by Guthzeit (*Ber.*, 1893, **26**, 2795) from ethylic ethoxy- α -pyronedicarboxylate and with the substance formed by heating ethylic dicarboxyglutaconate with formamide (Ruhemann and Sedgwick, *Ber.*, 1895, **28**, 825). Guthzeit gives the melting point of this ethereal salt as 199° , whilst we found it to be 202° (as compared with 201° stated before, *loc. cit.*).

The formation of this pyridine derivative by the interaction of chloroform and ethylic disodiummalonate could only be explained by assuming that the ethylic malonate contained ethylic cyanacetate. Its presence might easily be accounted for by the circumstance that, in the preparation of ethylic malonate from chloroacetic acid and potassium cyanide, and the subsequent action of alcohol and hydrogen chloride, a small quantity of the first formed ethylic cyanacetate remained unaltered.

With the view of verifying this explanation, we undertook the study of the action of chloroform on ethylic cyanacetate in the presence of sodium ethoxide. It was to be expected that this reaction would take place according to the equation $2\text{CN} \cdot \text{CNa}_2 \cdot \text{COOC}_2\text{H}_5 + \text{CHCl}_3 = \text{COOC}_2\text{H}_5 \cdot \text{C}(\text{CN}) : \text{CH} \cdot \text{CNa}(\text{CN}) \cdot \text{COOC}_2\text{H}_5 + 3\text{NaCl}$, and lead to the formation of the sodium compound of ethylic dicyanoglutaconate,

which in turn might be transformed into ethylic dihydroxydinicotinate. These reactions actually take place.

We had completed this enquiry when we noticed Errera's paper (*Gazzetta*, 1897, 27, ii, 393), which deals with the formation of ethylic dicyanoglutaconate and some of its derivatives.

Ethylic Dicyanoglutaconate.

The sodium derivative of this ethylic salt is prepared by a method similar to that used for ethylic dicarboxyglutaconate. To a solution of 9.2 grams of sodium in 150 grams of alcohol, 22.6 grams of ethylic cyanacetate and then 12 grams of chloroform are added; on heating the mixture on the water bath, the white precipitate of ethylic sodio-cyanacetate, first formed, becomes yellow, and after an hour's digestion the liquid is no longer alkaline to litmus. As the alcoholic solution can only with difficulty be freed by filtration from the gelatinous solid, the alcohol is distilled off, and water added to the residue, when the sodium derivative of ethylic dicyanoglutaconate remains undissolved. It is filtered from the dark coloured mother liquor, washed with water in which, in the cold, it is not very soluble, and twice recrystallised from boiling water; the long, yellow needles thus obtained, which, when dried in the air, contain $2\text{H}_2\text{O}$ (as was also found by Errera, *loc. cit.*), have the formula

0.2460 (air dried) lost 0.0300 at 100° . $\text{H}_2\text{O} = 12.19$.

$\text{C}_{11}\text{H}_{11}\text{NaN}_2\text{O}_4 + 2\text{H}_2\text{O}$ requires $\text{H}_2\text{O} = 12.24$ per cent.

0.2405 (dried at 100°) gave 0.0652 Na_2SO_4 . $\text{Na} = 8.78$.

0.2143 " " " 20.8 c.c. nitrogen at 19° and 753 mm. $\text{N} = 11.05$.

$\text{C}_{11}\text{H}_{11}\text{NaN}_2\text{O}_4$ requires $\text{Na} = 8.91$; $\text{N} = 10.85$ per cent.

On adding silver nitrate to the aqueous solution of this substance, a yellowish precipitate of the corresponding silver compound, $\text{C}_{11}\text{H}_{11}\text{AgN}_2\text{O}_4$, is thrown down, which dissolves in water with great difficulty.

0.2745 (dried at 100°) gave 0.0865 Ag. $\text{Ag} = 31.51$.

$\text{C}_{11}\text{H}_{11}\text{AgN}_2\text{O}_4$ requires $\text{Ag} = 31.48$ per cent.

Most characteristic is the copper derivative of ethylic dicyanoglutaconate, which is precipitated in red-brown glistening needles on mixing aqueous solutions of the sodium compound and copper sulphate. It dissolves in boiling water and, on cooling, crystallises unchanged. The air-dried crystals have the composition $(\text{C}_{11}\text{H}_{11}\text{N}_2\text{O}_4)_2\text{Cu} + 4\text{H}_2\text{O}$. They slowly lose their water of crystallisation at 100° , and turn pale brown.

0.3190 (air-dried) lost 0.0385 at 100°. $H_2O = 12.06$.

$(C_{11}H_{11}N_2O_4)_2Cu, 4H_2O$ requires $H_2O = 11.90$ per cent.

0.2635 (dried at 100°) gave 22.5 c.c. nitrogen at 10° and 766 mm. $N = 10.3$.

0.2800 " " " 0.0412 CuO. $Cu = 11.73$.

$(C_{11}H_{11}N_2O_4)_2Cu$ requires $N = 10.50$; $Cu = 11.82$ per cent.

In order to isolate ethylic dicyanoglutaconate, the sodium compound is dissolved in warm water, an excess of hydrochloric acid gradually added to the solution, and the yellow ethylic salt which soon separates is collected and washed with water until the washings are no longer acid. The pale yellow filtrate, after some days, loses its colour and acquires a beautiful blue fluorescence, whilst colourless needles are deposited; the small amount of the latter precluded us from examining it further.

Ethylic dicyanoglutaconate dissolves readily in hot acetone, and crystallises from it in yellow, glittering plates which melt and decompose at 187—188°. It was found to contain a small quantity of another substance which was not removed by repeated recrystallisation. The following analytical results show that the percentage of carbon in different specimens of the product varies from the theoretical number by one to two per cent.

0.2179 gave 0.4320 CO_2 and 0.1090 H_2O . $C = 54.07$; $H = 5.55$.

0.2012 " 0.4015 CO_2 " 0.0975 H_2O . $C = 54.42$; $H = 5.38$.

0.2073 " 0.4198 CO_2 " 0.1020 H_2O . $C = 55.22$; $H = 5.46$.

0.2258 " 0.4525 CO_2 " 0.1103 H_2O . $C = 54.65$; $H = 5.42$.

0.1980 " 19.5 c.c. nitrogen at 17° and 765 mm. $N = 11.50$.

0.2050 " 20.5 " " 16° " 763 mm. $N = 11.70$.

$C_{11}H_{12}N_2O_4$ requires $C = 55.93$; $H = 5.08$; $N = 11.86$ per cent.

A similar observation was made by Errera (*loc. cit.*), who was also unable to obtain the ethylic salt in a pure state by crystallising it from alcohol, although he states that he succeeded in removing the impurity by benzene, and that the compound thus purified melts at 178—179°.

The question arose whether ethylic dicyanoglutaconate under the influence of ammonia undergoes a decomposition analogous to that of ethylic dicarboxyglutaconate (Ruhemann and Morrell, *Trans.*, 1891, 59, 743). Experiment, however, showed that such a reaction does not take place either on leaving the ethereal salt in contact with aqueous ammonia at the ordinary temperature or on heating it with the reagent at 100°. The ethereal salt dissolves, and on concentrating the yellow solution, almost colourless, silky needles of the ammonium compound of ethylic dicyanoglutaconate crystallise; this dissolves fairly easily in cold water, and with the greatest ease on boiling; it melts and decomposes at 162—163°.

The following analytical data point to the view than this substance, when dried at 100° , contains $\frac{1}{2}\text{H}_2\text{O}$.

0.2397 (dried at 100°) gave 0.4455 CO_2 and 0.1132 H_2O . C = 50.71; H = 6.17.

0.2396 " " 33.5 c.c. nitrogen at 22° and 772 mm. N = 16.08.

0.2267 " " 31 c.c. " 20° " 775 mm. N = 15.95.

$\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_4, \text{NH}_3 + \frac{1}{2}\text{H}_2\text{O}$ requires C = 50.38; H = 6.10; N = 16.03 per cent.

On heating the ammonium compound to 110° , it turns yellow, and most probably suffers partial dissociation into ammonia and the ethylic salt.

We have, as stated above, undertaken the preparation of ethylic dicyanoglutaconate with a view of ascertaining whether it can readily be transformed into ethylic dihydroxydinicotinate. This change may indeed be effected, and this fact affords an explanation of the formation of the pyridine derivative from the product contained in the mother liquor of ethylic sodiodicarboxyglutaconate.

Ethylic Dihydroxydinicotinate.

If ethylic dicyanoglutaconate, or the sodium compound of the ethereal salt, is boiled with dilute hydrochloric acid, the substance after a short time enters into solution, and in the course of a few minutes a solid separates, which rapidly increases in quantity. When cold, this is collected, washed, and dried, and then treated with cold concentrated hydrochloric acid, which dissolves most of it; on adding water, a precipitate is thrown down which readily dissolves in chloroform, and crystallises from alcohol in colourless needles. This compound is characterised as ethylic dihydroxydinicotinate by the melting point (202°), the reddish-violet coloration produced on adding ferric chloride to its alcoholic solution, and by a nitrogen determination.

0.2025 gave 10 c.c. nitrogen at 20° and 772 mm. N = 5.73.

$\text{C}_{11}\text{H}_{13}\text{NO}_6$ requires N = 5.49 per cent.

The formation of ethylic dihydroxydinicotinate is undoubtedly preceded by that of the diamide of ethylic dicarboxyglutaconate, which then loses ammonia and condenses to the pyridine derivative, as illustrated by the following symbols.

Ethylic dihydroxydinicotinate.

On prolonged boiling with hydrochloric acid, ethylic dihydroxydinicotinate decomposes, losing carbon dioxide, and on evaporating the solution on the water bath, the residue gives a reddish-violet coloration with ferric chloride, and strongly reduces silver nitrate and potassium permanganate. The investigation of this compound is not yet complete; there can, however, be no doubt that it is *aa'*-dihydroxypyridine, which could not be isolated from the product of the interaction of ammonia and ethylic glutaconate, on account of the rapidity with which the dihydroxypyridine is oxidised by the oxygen of the air in ammoniacal solution (*see* Ruhemann and Morrell, *Trans.*, 1891, 59, 745).

Ethylic dihydroxydinicotinate not only forms a sodium and an ammonium derivative, but with phenylhydrazine also yields a compound which is thrown down on adding the hydrazine to a warm alcoholic solution of the ethylic salt. It dissolves but sparingly in boiling alcohol, and, on cooling, crystallises in groups of slender, colourless needles which decompose at 198°.

0.2130 gave 0.4365 CO₂ and 0.1112 H₂O. C=55.89; H=5.80.

0.2278 „ 22.5 c.c. nitrogen at 19° and 769 mm. N=11.49

C₁₁H₁₃NO₆, NH₂·NH·C₆H₅ requires C=56.19; H=5.78; N=11.57 p. c.

The hydroxyl groups in ethylic dihydroxydinicotinate have the same relative position in the pyridine ring as in citrazinamide; the latter, as shown some time ago (Ruhemann, *Ber.*, 1887, 20, 3369), may be transformed into trichlorocitrazinamide and the corresponding bromo-derivative, by the action of chlorine or bromine on the solution of the amide in hydrochloric acid. It seemed to be of some interest to subject ethylic dihydroxydinicotinate to a similar treatment with the view of arriving at analogous halogen derivatives. The ethylic salt, as has been stated before (Ruhemann and Sedgwick, *Ber.*, 1895, 28, 825), and as mentioned in this paper, has feeble acid properties; it dissolves in concentrated hydrochloric acid, but the hydrochloride thus formed dissociates on adding water. This behaviour of ethylic dihydroxydinicotinate has been made use of for its purification. On adding bromine to the solution of the ethylic salt in hydrochloric acid, an unstable additive product is formed (Ruhemann and Sedgwick, *loc. cit.*); chlorine however, we find, behaves differently. ¶

Ethylc Dihydroxydichloronicotinate.

On saturating the solution of ethylc dihydroxydinicotinate in concentrated hydrochloric acid with chlorine, a viscid mass separates and adheres to the sides of the vessel; this is washed, dissolved in dilute potash, and the solution acidified with hydrochloric acid, when a white precipitate is obtained which is sparingly soluble in boiling alcohol, and on cooling crystallises in colourless, shiny plates. These begin to darken at about 238° , and are completely decomposed at 248° ; ferric chloride gives a reddish-violet coloration with their alcoholic solution.

On analysis, numbers were obtained corresponding with the formula $C_8H_7NO_4Cl_2$.

0.2090 gave 0.2930 CO_2 and 0.0528 H_2O . $C = 38.23$; $H = 2.80$.

0.2318 „, 0.2636 $AgCl$. $Cl = 28.14$.

$C_8H_7NO_4Cl_2$ requires $C = 38.10$; $H = 2.78$; $Cl = 28.17$ per cent.

The mode of formation of the compound and the analytical results indicate that it is ethylc dichlorodihydroxynicotinate; its constitution may, *a priori*, be expressed by one of the formulæ.

The first formula, I, would correspond with the structure of trichlorocitrazinamide and to that of the dichloro-derivative formed from methyl dihydroxypyridine (Ruhemann, *Ber.*, 1894, 27, 1271), but the stability of ethylc dichlorodihydroxynicotinate compared with that of the others would indicate that the formula II has to be assigned to it. This formula is, moreover, supported by the behaviour of the substance towards phenylhydrazine. Whilst the former chloro-derivatives, on treatment with the base, are transformed into phenylhydrazones, with removal of halogen, the latter yields merely an additive product. This readily dissolves in alcohol, and on treatment with dilute hydrochloric acid the chloro-derivative is precipitated unchanged.

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