CLXXV.—*The Formation and Reactions of Imino-compounds. Part I. Condensation of Ethyl Cyanoacetate with its Sodium Derivative.*

By HAROLD BARON, FREDERICK GEORGE PERCY REMFRY, and JOCELYN FIELD THORPE.

THIS work originated in a desire to obtain evidence of the existence of the sodium compound of ethyl cyanoacetate in an "enol" form, this substance having been shown by one of us to exhibit properties very different from the corresponding sodium derivative of ethyl malonate (Trans., 1900, **77**, 923).

Baeyer (*Ber.*, 1885, **13**, 3454), on treating ethyl malonate with an equivalent quantity of its sodium derivative in alcoholic solution, obtained ethyl phloroglucinoltricarboxylate, and concluded from this that the sodium atom in the sodium derivative was undoubtedly attached to carbon (see also Moore, this vol., p. 165).

On applying a similar reaction to ethyl cyanoacetate, it was at once apparent that the condensation between this substance and its sodium derivative proceeded in quite a different way.

After heating only a short time on the water-bath, a large quantity of a sodium compound was obtained, which ultimately proved to be the sodium derivative of ethyl β-imino-α-cyanoglutarate, the condensation evidently having proceeded according to the equation :

$$\begin{matrix} CO_2Et\cdot CHNa \\ | \\ CN \end{matrix} + HCH(CN)\cdot CO_2Et \longrightarrow \begin{matrix} CO_2Et\cdot CHNa \\ | \\ C(:NH)\cdot CH(CN)\cdot CO_2Et. \end{matrix}$$

The proof of the constitution of this sodium compound is as follows.

With dilute mineral acids, it is converted into ethyl β-imino-α-cyanoglutarate, $CO_2Et\cdot CH_2\cdot C(:NH)\cdot CH(CN)\cdot CO_2Et$, which, on boiling with dilute sodium carbonate solution, is transformed into ethyl hydrogen β-imino-α-cyanoglutarate, $CO_2H\cdot CH_2\cdot C(:NH)\cdot CH(CN)\cdot CO_2Et$. On distilling the ammonium salt of this substance, it yields ethyl β-imino-α-cyanobutyrate, $MeC(:NH)\cdot CH(CN)\cdot CO_2Et$, which passes into ethyl cyanoacetoacetate, $MeCO\cdot CH(CN)\cdot CO_2Et$, on distillation with dilute sulphuric acid.

Ethyl cyanoacetoacetate prepared in this way is identical with the substance prepared by Haller and Held (*Ann. Chim. Phys.*, 1889, [vi], 17, 204) by the interaction of cyanogen chloride and ethyl acetoacetate, or by the condensation of acetyl chloride with ethyl sodiocyanoacetate.

The position of the sodium atom in the sodium compound of ethyl β-imino-α-cyanoglutarate is shown by the following considerations. It reacts with methyl iodide to form ethyl β-imino-α-cyano-α'-methylglutarate, $CO_2Et\cdot CHMe\cdot C(:NH)\cdot CH(CN)\cdot CO_2Et$; on hydrolysis with sodium carbonate, this substance yields ethyl hydrogen β-imino-α-cyano-α'-methylglutarate, $CO_2H\cdot CHMe\cdot C(:NH)\cdot CH(CN)\cdot CO_2Et$, the ammonium salt of which, on distillation, gives ethyl β-imino-α-cyanovalerate, $EtC(:NH)\cdot CH(CN)\cdot CO_2Et$, this in turn, when distilled with dilute sulphuric acid, yielding ethyl cyanopropionylacetate,

$$EtCO\cdot CH(CN)\cdot CO_2Et.$$

The final product is identical with that prepared by Haller (*Ber.*, 1888, 21, 354) by the interaction of ethyl sodiocyanoacetate and propionyl chloride.

In the same way, ethyl β-imino-α-cyano-α'-ethylglutarate,

$$CO_2Et\cdot CHEt\cdot C(:NH)\cdot CH(CN)\cdot CO_2Et,$$

prepared by the action of ethyl iodide on the sodium derivative, gives ethyl hydrogen β-imino-α-cyano-α'-ethylglutarate,

$$CO_2H\cdot CHEt\cdot C(:NH)\cdot CH(CN)\cdot CO_2Et,$$

ethyl β-imino-α-cyanocaprolate, $Pr^{\alpha}C(:NH)\cdot CH(CN)\cdot CO_2Et$, and ethyl *n*-butyrylcyanoacetate, $Pr^{\alpha}CO\cdot CH(CN)\cdot CO_2Et$, the latter being identical with the compound prepared by Haller from ethyl sodiocyanoacetate and butyryl chloride.

The formation of ethyl β-imino-α-cyanoglutarate in the foregoing condensation is evidently analogous to the production of the dimolecular nitriles which E. von Meyer (*J. pr. Chem.*, 1889, [ii], **39**, 189) and Riess and E. von Meyer (*ibid.*, 1885, [ii], **31**, 112) prepared by the action of sodium on a solution of the nitrile in dry ether. They represent this reaction as occurring in the following way:

$$\begin{matrix}\mathrm{MeC{:}N}\\ \mathrm{MeCHNa{\cdot}CN}\end{matrix} + \longrightarrow \begin{matrix}\mathrm{MeC{:}NNa}\\ \mathrm{MeCH{\cdot}CN}\end{matrix} \quad \text{or} \quad \begin{matrix}\mathrm{MeC{:}NH}\\ \mathrm{MeCNa{\cdot}CN}\end{matrix}.$$

From our experiments, however, it would appear that the nitrile group of the sodium derivative passes into the imino-group in accordance with the equation given on the previous page.

The greatest yield of the condensation product is formed when the reacting substances are in the proportion of one molecule of ethyl cyanoacetate to one molecule of its sodium derivative. A greater or less amount of sodium than this proportionately diminishes the yield.

The similarity between the reactions of substances containing the groups C:NH and CO is clearly shown by the behaviour of ethyl β-imino-α-cyanoglutarate towards reagents. Thus with strong alkaline hydrolytic agents it is completely decomposed into the alkali salt of malonic acid in accordance with the equation:

$$\mathrm{CO_2Et{\cdot}CH_2{\cdot}C(:NH){\cdot}CH(CN){\cdot}CO_2Et} + 4\mathrm{NaOH} + 2\mathrm{H_2O} = 2\mathrm{CH_2(CO_2Na)_2} + 2\mathrm{NH_3} + 2\mathrm{EtOH},$$

behaving therefore in the same way as would a compound having the formula $\mathrm{CO_2Et{\cdot}CH_2{\cdot}CO{\cdot}CH(CN){\cdot}CO_2Et}$. Again, the hydrogen atoms marked 1, 2, and 3 in ethyl β-imino-α-cyanoglutarate,

$$\underset{(1)\ (3)}{\mathrm{CO_2Et{\cdot}CHH{\cdot}C(:NH){\cdot}CH}}\underset{(2)}{\mathrm{(CN){\cdot}CO_2Et}},$$

are replaceable by sodium in the order indicated by the numerals.

The proof of this is as follows:—

Ethyl β-imino-α-cyanoglutarate,

$$\mathrm{CO_2Et{\cdot}CH_2{\cdot}C(:NH){\cdot}CH(CN){\cdot}CO_2Et},$$

gives ethyl β-imino-α-cyano-αα′-dimethylglutarate,

$$\mathrm{CO_2Et{\cdot}CHMe{\cdot}C(:NH){\cdot}CMe(CN){\cdot}CO_2Et},$$

on treatment with sodium ethoxide and methyl iodide, and this substance is identical with the compound prepared by the condensation of ethyl cyanomethylacetate with its sodium derivative, which evidently takes place in accordance with the equation:

$$\begin{matrix}\mathrm{CO_2Et{\cdot}CMeNa{\cdot}CN}\\ +\mathrm{CO_2Et{\cdot}CHMe{\cdot}CN}\end{matrix} \longrightarrow \begin{matrix}\mathrm{CO_2Et{\cdot}CMeNa{\cdot}C{:}NH}\\ \mathrm{CO_2Et{\cdot}CMe{\cdot}CN}\end{matrix} \longrightarrow \begin{matrix}\mathrm{CO_2Et{\cdot}CHMe{\cdot}C{:}NH}\\ \mathrm{CO_2Et{\cdot}CMe{\cdot}CN}\end{matrix}.$$

The sodium derivative, on direct treatment with methyl iodide, yields ethyl β-imino-α-cyano-αα′α′-trimethylglutarate,

$$CO_2Et\cdot CMe_2\cdot C(:NH)\cdot CMe(CN)\cdot CO_2Et,$$

identical with the compound prepared by the complete methylation of ethyl β-imino-α-cyanoglutarate with sodium ethoxide and methyl iodide.

The constitution of these substances is further shown by the products they yield on hydrolysis; thus ethyl β-imino-α-cyano-αα′-dimethylglutarate gives with sodium carbonate solution ethyl β-imino-α-cyano-α-methylvalerate, $EtC(:NH)\cdot CMe(CN)\cdot CO_2Et$, which, on distillation with dilute sulphuric acid, is converted into ethyl propionylcyanoacetate, $EtCO\cdot CMe(CN)\cdot CO_2Et$; it also gives methylmalonic acid as sole product on complete hydrolysis with sodium hydroxide.

In the same way, ethyl β-imino-α-cyano-αα′α′-trimethylglutarate yields ethyl β-imino-α-cyano-α-methyl*iso*butyrylacetate,

$$Pr^{\beta}C(:NH)\cdot CMe(CN)\cdot CO_2Et,$$

and ethyl *iso*butyrylcyanomethylacetate,

$$Pr^{\beta}CO\cdot CMe(CN)\cdot CO_2Et,$$

and gives on complete hydrolysis with sodium hydroxide solution a mixture of methylmalonic and dimethylmalonic acids.

Compounds of the type $CO_2Et\cdot CH_2\cdot C(:NH)\cdot CH(CN)\cdot CO_2Et$ do not give colorations with ferric chloride, neither do they react with nitrous acid to form nitrosoamines, but yield oximes where the formulæ permit or otherwise remain unacted on. Thus the ethyl hydrogen salt, $CO_2H\cdot CH_2\cdot C(:NH)\cdot CH(CN)\cdot CO_2Et$, gives with nitrous acid the oxime $HON:CH\cdot C(:NH)\cdot CH(CN)\cdot CO_2Et$, whereas the ethyl salt, $MeC(:NH)\cdot CH(CN)\cdot CO_2Et$, is, under ordinary conditions, unaffected.

These oximes are well defined crystalline solids which give coloured salts with alkalis and are characterised by giving in neutral solution intense blue to green colorations with ferrous sulphate.

A comparison of ethyl β-imino-α-cyanobutyrate,

$$MeC(:NH)\cdot CH(CN)\cdot CO_2Et,$$

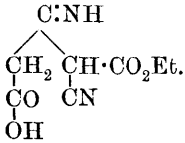
with ethyl cyanoacetoacetate, $MeCO\cdot CH(CN)\cdot CO_2Et$, shows that the substitution of NH for oxygen raises the boiling point of the compound about 100°. Thus the former substance boils at 210°/30 mm., the latter at 119°/30 mm.

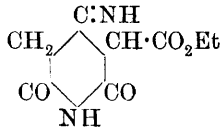
Ethyl hydrogen β-imino-α-cyanoglutarate,

$$CO_2H\cdot CH_2\cdot C(:NH)\cdot CH(CN)\cdot CO_2Et,$$

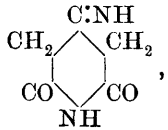
melts at 142° and at 160° gives off carbon dioxide, becoming converted into ethyl β-imino-α-cyanobutyrate. If, however, the ethyl hydrogen salt is kept one or two degrees above its melting point for ten minutes, it again becomes solid, being transformed into ethyl glutazinecarboxylate. This conversion, which takes place when the hydrogen

salt has been carefully dried, is evidently due to a molecular rearrangement:

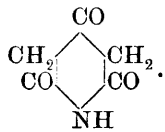




The constitution of this substance is shown by its behaviour on hydrolysis; thus with sodium hydroxide solution it is converted into glutazine:



which, on boiling for a few minutes with concentrated hydrochloric acid, yields 2 : 4 : 6-trioxypyridine:



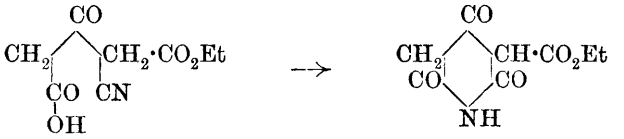
Ethyl glutazinecarboxylate is, however, best prepared by the action of cold concentrated sulphuric acid on ethyl β-imino-α-cyanoglutarate, $CO_2Et\cdot CH_2\cdot C(:NH)\cdot CH(CN)\cdot CO_2Et$, under which conditions the conversion into the cyclic compound is quantitative. This method has been adopted in the case of the various alkylated derivatives of ethyl β-imino-α-cyanoglutarate, described in this communication, and in most cases a quantitative yield of the corresponding glutazine derivative has been obtained. In the same way, the various alkylated ethyl hydrogen salts of ethyl β-imino-α-cyanoglutarate of the type:

$$CO_2H\cdot CHR\cdot C(:NH)\cdot CR(CN)\cdot CO_2Et$$

(where R = alkyl or hydrogen), give, on heating a few degrees above their melting points, the corresponding alkylated ethyl glutazinecarboxylate derivatives, which on hydrolysis with caustic alkali give the corresponding alkylated glutazines.

That other γ-cyano-acids undergo the same intermolecular change on heating, is shown by the similar behaviour of ethyl hydrogen cyanoacetonedicarboxylate, $CO_2H\cdot CH_2\cdot CO\cdot CH(CN)\cdot CO_2Et$, which is prepared by methods given in the experimental portion of this paper;

this acid, when heated a few degrees above its melting point, is transformed into ethyl 2 : 4 : 6-trioxypyridine-3-carboxylate:



Another instance of the same kind of change is exhibited by the oxime, $CH(:NOH)\cdot C(:NH)\cdot CH(CN)\cdot CO_2Et$; this substance melts, but instantly decomposes with separation of carbon. If, however, it is slowly added to concentrated sulphuric acid, it is transformed into a pyridazine derivative in accordance with the equation:

this and similar compounds are still under investigation.

Glutazine was originally prepared by Stokes and von Pechmann (*Ber.*, 1886, **19**, 2696) by acting on ethyl amino-β-hydroxyglutamate, $CONH_2\cdot CH_2\cdot C(OH)(NH_2)\cdot CH_2\cdot CO_2Et$, obtained from ethyl acetonedicarboxylate and ammonia, with alkaline carbonates. They considered that its constitution must be represented by one of the two following formulæ:

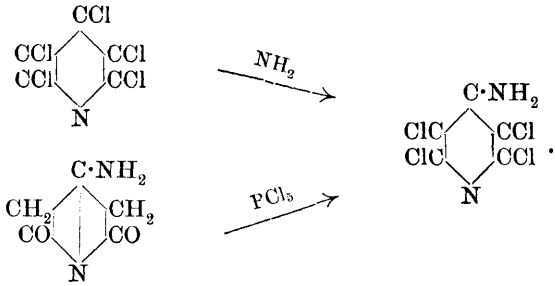
I. II.

but thought formula II the more probable owing to the analogy between the action of ammonia on ethyl acetonedicarboxylate and its action on ethyl acetoacetate which, as Collie (*Annalen*, 1884, **226**, 298) had shown, forms first an aminohydroxy-compound which by loss of water passes into ethyl aminocrotonate,

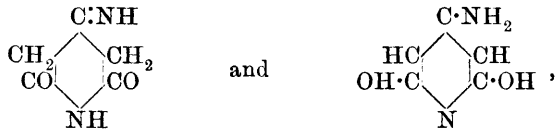
$MeC(OH)(NH_2)\cdot CH_2\cdot CO_2Et \longrightarrow MeC(NH_2):CH\cdot CO_2Et + H_2O$;

later, von Pechmann (*Ber.*, 1887, **20**, 2655), as a result of the study of the action of nitrous acid on glutazine definitely decided in favour of formula I. In spite of this opinion, Sell and Dootson (Trans., 1898, **73**, 777) considered that formula II best represented the constitution of glutazine and based their conclusion on the identity of a tetrachloroaminopyridine, prepared by the action of ammonia on penta-

chloropyridine, with a substance obtained by Stokes and von Pechmann by the interaction of phosphorus pentachloride and glutazine :



From the methods of synthesis described by us, there can be no doubt that glutazine possesses a constitution represented by formula I. The production of the tetrachloroaminopyridine described by Sell and Dootson can be readily understood if the probability of glutazine reacting in the two forms :



is taken into consideration.

The view that glutazine is capable of reacting in both forms receives support not only from the acid and basic character of the many derivatives of glutazine that we have investigated, but also from the close analogy between this substance and 2:4:6-trioxypyridine, which, as Stokes and von Pechmann showed, reacts both as a phenol and a base.

The chief fact which led von Pechmann to the conclusion that the imino-group was present in glutazine was the formation of nitroso-nitroglutazine by the action of nitrous acid. His method consisted in dissolving glutazine in alkali, adding the requisite quantity of sodium nitrite solution, and then pouring the mixture into dilute acetic acid. A sodium salt, $NaC_5H_3O_5N_4,xH_2O$, slowly separated, which gave the Liebermann reaction, and on warming with dilute sulphuric acid gave off nitrous acid. We have repeated this reaction by applying it to the glutazine prepared by us, with results which confirm von Pechmann's conclusions.

Glutazine also, as von Pechmann showed, is very quickly hydrolysed to the corresponding trioxypyridine on boiling with concentrated hydrochloric acid.

It is remarkable that all the substituted derivatives of glutazine

described by us react quite differently from glutazine itself. They may be divided into three classes :

1. The mono-substitution derivatives :

Ethyl glutazinecarboxylate, $NH<^{CO\text{———}CH_2}_{CO\cdot CH(CO_2Et)}>C{:}NH$, methylglutazine, $NH<^{CO\cdot CHMe}_{CO\text{---}CH_2}>C{:}NH$, ethylglutazine, $NH<^{CO\cdot CHEt}_{CO\text{—}CH_2}>C{:}NH$, and glutazine cyanide, $NH<^{CO\text{——}CH_2}_{CO\cdot CH(CN)}>C{:}NH$.

These compounds react with nitrous acid to form oximes of the type $NH<^{CO\text{——}CHR}_{CO\cdot C(:NOH)}>C{:}NH$, which are acid substances, forming coloured salts with alkalis, and are characterised by giving, in neutral solution, intense colours with ferrous sulphate. These mono-substitution products of glutazine are unattacked by strong mineral acids even on prolonged boiling.

II. The di-substitution products :

Ethyl methylglutazinecarboxylate, $NH<^{CO\text{——}CHMe}_{CO\cdot CH(CO_2Et)}>C{:}NH$, ethyl ethylglutazinecarboxylate, $NH<^{CO\text{———}CHEt}_{CO\cdot CH(CO_2Et)}>C{:}NH$, and dimethylglutazine, $NH<^{CO\cdot CHMe}_{CO\cdot CHMe}>C{:}NH$.

These compounds react with nitrous acid to form the corresponding pyridine derivatives with the evolution of free nitrogen. They are not hydrolysed by mineral acids.

III. The tri-substitution products :

Ethyl dimethylglutazinecarboxylate, $NH<^{CO\text{———}CHMe}_{CO\cdot CMe(CO_2Et)}>C{:}NH$.

This compound is unacted on by nitrous acid, and on boiling with mineral acids is hydrolysed partially to dimethylglutazine and partially to the corresponding pyridine derivative, whilst on treatment with caustic potash solution the former substance is alone produced.

Incidentally it may be mentioned that ethyl β-imino-α-cyano-$\alpha\alpha'\alpha'$-trimethylglutarate, $CO_2Et\cdot CMe_2\cdot C(:NH)\cdot CMe(CN)\cdot CO_2Et$, shows no tendency to pass into a ring compound, but on treatment with concentrated sulphuric acid is hydrolysed to straight chain degradation products.

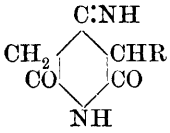
There seems to have been no work done on the nature of the interaction of the group C·NH with nitrous acid. And although von Pechmann concluded that this group was present in glutazine from the fact that on treatment with nitrous acid it yielded a nitrosoamine, yet from an examination of the many substances prepared by us, and

which undoubtedly contain this group, not one has been found to react in this way.

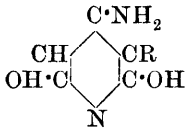
We have still under investigation a number of compounds containing this group which have been prepared by the interaction of ethyl sodiocyanoacetate with ethyl malonate, ethyl acetonedicarboxylate, and ethyl acetoacetate, and hope by their help to obtain some further insight into this question.

Meanwhile, from the experimental evidence at hand, it is possible to surmise the probable nature of the difference between glutazine and its di- and tri-substitution derivatives.

In the first place, it is evident that the mono-substitution products react in the two forms :



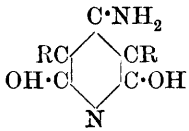
I.



II.

The behaviour towards nitrous acid is best accounted for by formula I, whereas the stability of the compounds towards acid hydrolysing agents is best explained by formula II.

In the second place, it is certain that di-substitution products react only in the form



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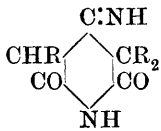
since this alone explains the formation of the pyridine derivative with nitrous acid and the stability of the compound towards acid hydrolysing agents. In the third place, it follows that the tri-substi tution derivatives react only in the form



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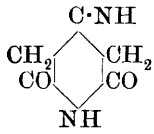
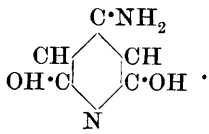
since they are unacted on by nitrous acid and are readily hydrolysed to the corresponding pyridine on treatment with acid hydrolysing agents.

With regard to the constitution of glutazine itself, it is difficult to suggest any formula which adequately explains its reactions.

The formation of the nitrosoamine with nitrous acid would indicate

the grouping $\begin{matrix}C\\C\end{matrix}>NH$, whereas the formation of trioxypyridine by the action of acids, and the formation of tetrachloroaminopyridine by the action of phosphorus pentachloride would seem to show that it can react in the forms





We hope, as the result of the future study of similarly constituted compounds, to arrive at some definite conclusion as to the nature of this substance.

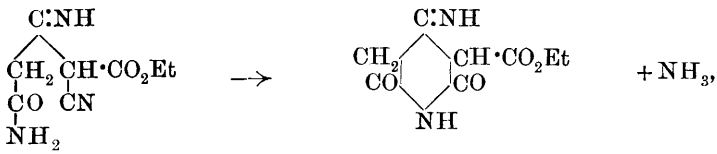
As already mentioned, Stokes and von Pechmann prepared glutazine by the action of alkali carbonates on ethyl amino-β-hydroxyglutamate, $CONH_2{\cdot}CH_2{\cdot}C(OH)(NH_2){\cdot}CH_2{\cdot}CO_2Et$.

A similar compound, namely, ethyl β-imino-α-cyanoglutamate,

$$CONH_2{\cdot}CH_2{\cdot}C(NH){\cdot}CH(CN){\cdot}CO_2Et,$$

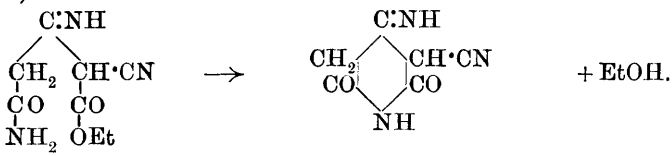
can be prepared by the action of alcoholic ammonia on ethyl β-imino-α-cyanoglutarate. From this substance, a glutazine derivative can be prepared in two ways.

1. By the action of concentrated sulphuric acid forming ethyl glutazinecarboxylate,



and

2. By the action of sodium carbonate solution forming glutazine cyanide,



Both these compounds yield glutazine on hydrolysis with caustic potash.

Experimental.

Preparation of Ethyl β-Imino-α-cyanoglutarate,
$CO_2Et \cdot CH_2 \cdot C(:NH) \cdot CH(CN) \cdot CO_2Et$.

In order to prepare this substance, 11·5 grams of sodium were dissolved in 122 grams of alcohol, and the solution, after being mixed with 113 grams of ethyl cyanoacetate, was heated on the water-bath for 2 hours. The white sodium compound of ethyl cyanoacetate which is in the first instance precipitated, rapidly passes into solution, and after heating for the requisite time the contents of the flask will be observed to consist of a viscid, brown liquid, which sets to a jelly-like mass on cooling. On adding water, this jelly forms a clear solution, showing a slightly alkaline reaction; after some time, an oil begins to separate and the solution then becomes markedly alkaline.

The separation of this oil, which is due to the gradual decomposition of the sodium compound of ethyl β-imino-α-cyanoglutarate by the action of the water, can be hastened by rendering the solution strongly acid by means of hydrochloric acid. The acidified solution was then extracted with ether, the ethereal extract washed successively with water and dilute aqueous sodium carbonate, dried, and distilled until free from ether. The residue consisted of a viscid syrup, which gradually solidified to a hard, crystalline cake, the yield being about 80 per cent. of the theory.

When recrystallised from dilute alcohol, ethyl β-imino-α-cyanoglutarate is obtained in well-defined needles melting at 53°.

0·2057 gave 0·4168 CO_2 and 0·1066 H_2O. C = 55·26; H = 5·76.
0·2165 ,, 0·4390 CO_2 ,, 0·1130 H_2O. C = 55·3; H = 5·8.
0·2064 ,, 19·6 c.c. nitrogen at 15° and 780 mm. N = 11·6.
$C_{10}H_{14}O_4N_2$ requires C = 55·4; H = 5·9; N = 11·8 per cent.

Ethyl β-imino-α-cyanoglutarate undergoes rapid decomposition when distilled in large quantities under diminished pressure, but when a small quantity is rapidly distilled, the pure substance passes over at 237°/25 mm.; it is easily soluble in most of the usual organic solvents excepting light petroleum, and instantly dissolves in a cold, strong aqueous sodium hydroxide without undergoing hydrolysis, since on acidifying the ethereal salt is recovered unchanged. In alcoholic solution, it gives no coloration with ferric chloride.

Ethyl β-imino-α-cyanoglutanilide,
$CONHPh \cdot CH_2 \cdot C(:NH) \cdot CH(CN) \cdot CO_2Et$,
is prepared by boiling ethyl β-imino-α-cyanoglutarate with excess of aniline and pouring the product into dilute hydrochloric acid; it

crystallises from absolute alcohol in fine, lustrous plates melting at 180°.

0·2047 gave 0·4625 CO_2 and 0·1076 H_2O. C = 61·62; H = 5·7.
$C_{14}H_{15}O_3N_3$ requires C = 61·54; H = 5·5 per cent.

Action of Hydrolytic Agents on Ethyl β-Imino-α-cyanoglutarate.

I. *Action of Sodium Carbonate Solution. Formation of Ethyl Hydrogen β-Imino-α-cyanoglutarate,*
$CO_2H{\cdot}CH_2{\cdot}C(:NH){\cdot}CH(CN){\cdot}CO_2Et$.

Ethyl β-imino-α-cyanoglutarate rapidly dissolves when boiled with a dilute solution of sodium carbonate, and if, when it has completely dissolved, the solution is acidified, a copious precipitate of the ethyl hydrogen ester is formed. This compound crystallises from hot water, in which it is readily soluble, in the form of large, transparent prisms, which, when dry, melt at 140°, giving off carbon dioxide at about 160°, and between these temperatures being slowly transformed into ethyl glutazinecarboxylate.

0·2534 gave 0·4497 CO_2 and 0·1190 H_2O. C = 48·4; H = 5·22.
0·2378 ,, 28·3 c.c. nitrogen at 16° and 770 mm. N = 13·9.
$C_8H_{10}O_4N_2$ requires C = 48·5; H = 5·00; N = 14·1 per cent.

This ethyl hydrogen salt appears to crystallise with 1 mol. of water of crystallisation, but as no definite results could be obtained on analysis the above figures refer to the substance dried at 100°.

The *silver* salt is formed as a white, gelatinous precipitate, when the calculated quantity of a silver nitrate solution is added to a solution of the ammonium salt of the acid which should be produced by neutralising a solution of the acid with ammonia in the cold.

0·2671 gave 0·1399 Ag. Ag = 52·4.
$C_8H_9O_4N_2Ag$ requires Ag = 52·6 per cent.

Esterification of Ethyl Hydrogen β-Imino-α-cyanoglutarate.—Ethyl hydrogen β-imino-α-cyanoglutarate (25 grams) was dissolved in 70 grams of absolute alcohol and 25 grams of concentrated sulphuric acid added, the whole being left for 12 hours. On adding water, a quantity of oil separated, the ethereal extract of which, when washed with aqueous sodium carbonate and distilled, yielded a product boiling at 197° under ordinary pressure, and giving on analysis numbers corresponding with ethyl malonate.

0·596 gave 0·5027 CO_2 and 0·1831 H_2O. C = 52·8; H = 7·4.
$C_7H_{12}O_4$ requires C = 52·5; H = 7·5 per cent.

The sodium carbonate washings of the above extract gave an oil on acidifying which slowly became solid, and was crystallised from dilute alcohol, from which solvent it separated in large prisms which melted at 43°. It is probably *ethyl cyanoacetonedicarboxylate*,

$$CO_2Et\cdot CH_2\cdot CO\cdot CH(CN)\cdot CO_2Et.$$

0·2148 gave 0·4173 CO_2 and 0·1166 H_2O. C = 52·98 ; H = 6·03.
$C_{10}H_{13}O_5N$ requires C = 52·9 ; H = 5·7 per cent.

This substance is soluble in sodium carbonate solution and gives a deep red coloration with ferric chloride.

On adding alkali to the mother liquors of the foregoing esterification until the solution is only slightly acid, a copious precipitate of ethyl glutazinecarboxylate is produced.

The following quantities were obtained in the foregoing experiment from 25 grams of ethyl hydrogen β-imino-α-cyanoglutarate.

Ethyl malonate, 10 grams; ethyl cyanoacetonedicarboxylate, 1 gram ; and ethyl glutazinecarboxylate, 12 grams.

Formation of Ethyl β-Imino-α-cyano-γ-isonitrosobutyrate,

$$CH(:NOH)\cdot C(:NH)\cdot CH(CN)\cdot CO_2Et.$$

This oxime is best prepared by dissolving the ethyl hydrogen salt in sodium hydroxide solution, and after mixing with this the requisite quantity of aqueous sodium nitrite, the mixture is poured into a 50 per cent. solution of acetic acid. After a short time, a crystalline substance is deposited which separates from absolute alcohol in well-defined prisms melting at 156° and instantly charring.

0·1652 gave 0·2804 CO_2 and 0·0744 H_2O. C = 46·29 ; H = 5·00.
0·1701 „ 34·1 c.c. nitrogen at 14·5° and 749 mm. N = 23·6.
$C_7H_9O_3N_3$ requires C = 45·9 ; H = 4·9 ; N = 22·09 per cent.

The oxime dissolves in aqueous sodium carbonate forming a yellow solution.

Formation of Ethyl 4-Imino-6-keto-1 : 5-dihydropyridazine-5-carboxylate,

$$NH\begin{cases} N=\!=\!=\!=CH \\ CO\cdot CH(CO_2Et) \end{cases}C:NH.$$

When the oxime is heated with concentrated sulphuric acid, considerable heat is generated and usually the whole mass chars, but if the solid is added in small quantities to the concentrated acid and the mixture is kept well cooled, the compound rapidly dissolves, forming a clear solution, which, when diluted with water and rendered alkaline with aqueous sodium carbonate, deposits a large quantity of an amorphous basic substance.

An analysis of the air-dried product showed it to have the formula of an ammonium base, $C_7H_{10}O_3N_3\cdot OH$.

0·2133 gave 0·3248 CO_2 and 0·1098 H_2O. C = 41·53 ; H = 5·46.
$C_7H_{11}O_4N_3$ requires C = 41·8 ; H = 5·5 per cent.

When dried in a vacuum desiccator for 5 days, the substance gave numbers corresponding with the free base.

0·2517 gave 0·4217 CO_2 and 0·1088 H_2O. C = 45·69 ; H = 4·8 per cent.

0·2153 gave 41·6 c.c. nitrogen at 15° and 763 mm. N = 23·1.
$C_7H_9O_3N_3$ requires C = 45·9 ; H = 4·9 ; N = 22·9 per cent.

Neither the anhydrous nor the hydrated base has any definite melting point, but both forms deflagrate at about 170°. On mixing with water, the anhydrous base becomes very hot and passes into its hydrated form.

The *hydrochloride*, $C_7H_9O_3N_3$,HCl, was made by dissolving the base in dilute hydrochloric acid, filtering, and evaporating nearly to dryness ; the solid which separated was then spread on a porous plate and dried in a desiccator over potassium hydroxide. It was analysed by weighing a quantity into a beaker, dissolving in water, and adding silver nitrate solution acidified with nitric acid.

0·2210 gave 0·1421 AgCl. Cl = 15·9.
$C_7H_{10}O_3N_3Cl$ requires Cl = 16·1 per cent.

The base undergoes a curious decomposition when boiled with a strong aqueous solution of sodium hydroxide, eliminating two of its nitrogen atoms in the form of free nitrogen. The products which are formed under these circumstances are still under investigation. The *hydrazone*, prepared by dissolving the base in dilute acetic acid, adding a solution of phenylhydrazine acetate, and boiling for a short time, is precipitated on cooling as an oil which slowly solidifies, and separates from hot absolute alcohol in the form of small, yellow needles melting at 173°.

0·1714 gave 0·3389 CO_2 and 0·0931 H_2O. C = 53·92 ; H = 6·03.
$C_{13}H_{17}O_5N_3$ requires C = 53·6 ; H = 5·8 per cent.

Ethyl β-imino-α-cyanobutyrate, $MeC(:NH)\cdot CH(CN)\cdot CO_2Et$, is formed in small quantities when ethyl hydrogen β-imino-α-cyanoglutarate is rapidly distilled ; it is, however, produced quantitatively when the ammonium salt of this acid is distilled under diminished pressure. It crystallises from absolute alcohol in large, transparent prisms, which melt at 181° and boil at 210°/30 mm.

0·2030 gave 0·4050 CO_2 and 0·1210 H_2O. C = 54·38 ; H = 6·6.
0·2157 „ 32·3 c.c. nitrogen at 18° and 780 mm. N = 18·4.
$C_7H_{10}O_2N_2$ requires C = 54·5 ; H = 6·5 ; N = 18·2 per cent.

Ethyl β-imino-α-cyanobutyrate is slowly formed when either the sodium or ammonium salt of ethyl hydrogen β-imino-α-cyanoglutarate is boiled with water.

Ethyl cyanoacetoacetate, $MeCO{\cdot}CH(CN){\cdot}CO_2Et$, is formed by the hydrolysis of ethyl β-imino-α-cyanobutyrate with dilute sulphuric acid. In order that the hydrolysis may not proceed too far, it is necessary to remove the first product as soon as it is formed. This can be readily done by passing a current of steam through the flask containing the hydrolysing mixture, which causes the ethyl cyanoacetoacetate to pass over into a receiver and prevents it from being further hydrolysed by the action of the sulphuric acid. Ethyl cyanoacetoacetate prepared in this way melts at 26° and boils at 119°/20 mm., it is in all respects identical with the substance prepared by Haller and Held.

0·2833 gave 0·5573 CO_2 and 0·1525 H_2O. C = 53·65; H = 5·98.
$C_7H_9O_3N$ requires C = 54·2; H = 5·8 per cent.

II. *Action of Sodium Hydroxide Solution. Formation of Malonic Acid.*

As already mentioned, ethyl β-imino-α-cyanoglutarate is dissolved by cold aqueous sodium hydroxide without undergoing hydrolysis. If, however, the solution is boiled, rapid hydrolysis ensues, and if the boiling is continued until the evolution of ammonia has ceased, the product on acidifying and extracting will be found to yield only malonic acid melting at 132°.

A decomposition of the same nature is undergone by ethyl hydrogen β-imino-α-cyanoglutarate and ethyl β-imino-α-cyanobutyrate, the former yielding, on prolonged boiling with sodium hydroxide solution, malonic acid, and the latter a mixture of malonic and acetic acids.

III. *Action of Concentrated Sulphuric Acid. Formation of Pyridine Derivatives.*

Ethyl Glutazinecarboxylate.

$$NH\begin{cases}CO\text{———}CH_2\\CO{\cdot}CH(CO_2Et)\end{cases}C{:}NH.$$

When ethyl β-imino-α-cyanoglutarate is dissolved in cold concentrated sulphuric acid and the solution left for 3 hours, a copious precipitate of this substance is produced on the addition of water. It crystallises from glacial acetic acid in lustrous plates, sometimes possessing a faint green tinge, and does not appear to melt when heated.

0·2590 gave 0·4603 CO_2 and 0·1260 H_2O. C = 48·47 ; H = 5·41.
0·2336 „ 28·4 c.c. nitrogen at 13·5° and 754 mm. N = 14·5.
$C_8H_{10}O_4N_2$ requires C = 48·5 ; H = 5·1 ; N = 14·1 per cent.

This substance is sparingly soluble in hot water, and its solution gives a deep red colour with ferric chloride. It forms salts with both acids and alkalis, but the former are unstable in solution.

The *hydrochloride*, $C_8H_{10}O_4N_2$,HCl, crystallises from concentrated hydrochloric acid in small prisms.

0·2357 gave 0·1423 AgCl. HCl = 15·4.
$C_8H_{10}O_4N_2$,HCl requires 15·56 per cent.

It is readily soluble in water, but is almost immediately decomposed with formation of the insoluble base.

The *oxime*, $HN<\begin{matrix}CO\text{---}C(:NOH)\\CO\cdot CH(CO_2Et)\end{matrix}>C:NH$, is best prepared by dissolving ethyl glutazinecarboxylate in caustic soda solution containing the requisite quantity of sodium nitrite, and pouring the mixture into dilute acetic acid ; a precipitate is immediately formed which can be recrystallised from dilute acetic acid, from which solvent it separates in the form of fine yellow needles.

0·1640 gave 0·2557 CO_2 and 0·0648 H_2O. C = 42·47 ; H = 4·38.
0·1746 „ 30·7 c.c. nitrogen at 14·5° and 748 mm. N = 18·7.
$C_8H_9O_5N_3$ requires C = 42·3 ; H = 4·0 ; N = 18·5 per cent.

This substance is an acid and dissolves in aqueous sodium carbonate to form a deep red solution, which, on concentrating, deposits the sodium salt in the form of a brick-red powder. A neutral solution of either the ammonium or sodium salt gives a characteristic deep blue coloration with ferrous sulphate, which on boiling is converted into a deep indigo-blue precipitate. The free acid dissolves in concentrated sulphuric acid and is precipitated unchanged on adding water. After prolonged boiling with dilute sulphuric acid, it passes into solution and on cooling straw-coloured needles are deposited. These are still under investigation.

The *dibenzoyl* derivative, $PhCO\cdot N<\begin{matrix}CO\text{---------}CH_2\\CO\cdot CH(CO_2Et)\end{matrix}>C:N\cdot COPh$, can be prepared by boiling ethyl glutazinecarboxylate with excess of benzoyl chloride in a Geissler flask for 3 hours.

On cooling, a crystalline precipitate slowly separates, which can be recrystallised from hot glacial acetic acid and obtained in small needles melting at 220°.

0·2230 gave 0·5290 CO_2 and 0·0863 H_2O. C = 64·70 ; H = 4·3.
$C_{22}H_{18}O_6N_2$ requires C = 65·0 ; H = 4·4 per cent.

Preparation of Glutazine from Ethyl Glutazinecarboxylate.

Glutazine can be prepared from the ethyl salt of its carboxylic acid by hydrolysis with caustic soda solution. The stability of the ethyl salt, however, is such that it is necessary almost to fuse it with caustic soda before hydrolysis ensues.

It was found most convenient to dissolve about one gram of the ethyl salt in potassium hydroxide solution contained in a wide-mouthed tube, and boil over the free flame until the odour of ammonia became perceptible at the mouth of the tube. On acidifying with acetic acid, a crystalline substance separated on cooling; this was recrystallised from water, from which solvent it separated in the form of rectangular plates.

0·2207 gave 0·3867 CO_2 and 0·1031 H_2O. C = 47·78; H = 5·19.
$C_5H_6O_2N_2$ requires C = 47·6; H = 4·8 per cent.

Glutazine obtained in this way is identical with the compound prepared by Stokes and Pechmann; it melts with decomposition at about 300° and gives in aqueous solution a red coloration with ferric chloride, which changes to green on boiling. The dibenzoyl derivative melts at 215—216°.

2 : 4 : 6-Trioxypyridine, produced from glutazine by the action of concentrated hydrochloric acid, as described by Stokes and Pechmann, is a heavy, yellow, sandy powder which decomposes at about 220°, without melting, and gives with ferric chloride in aqueous solution a deep red coloration.

0·2236 gave 0·3868 CO_2 and 0·0745 H_2O. C = 47·18; H = 3·72.
$C_5H_5O_3N$ requires C = 47·24; H = 3·94 per cent.

IV. *Action of Dilute Sulphuric Acid. Formation of the Sulphate of* 2 : 4 : 6-*Trioxypyridine Anhydride*, $C_{10}H_8O_5N_2,H_2SO_4,3H_2O$.

When ethyl β-imino-α-cyanoglutarate is boiled with a solution containing 1 part of sulphuric acid to three parts of water, it gradually dissolves, and if, after heating for three hours, the solution is cooled, well defined crystals of the above sulphate separate. It is a fairly stable substance and can be recrystallised from water, separating in the form of lustrous plates which melt at 115°; it is, however, decomposed on prolonged boiling.

0·4836 gave 0·3113 $BaSO_4$. S = 8·84.
0·2140 ,, 12·55 c.c. of nitrogen at 15·5° and 742 mm. N = 6·82.
0·1995 ,, 0·2302 CO_2 and 0·0790 H_2O. C = 31·42; H = 4·4.
$C_{10}H_8O_5N_2,H_2SO_4,3H_2O$ requires C = 31·74; H = 4·2; S = 8·46; N = 7·4 per cent.

The three molecules of water are expelled if the hydrated sulphate is heated at 100° for 4 or 5 hours.

0·2102 gave 0·1441 $BaSO_4$. S = 9·42.

$C_{10}H_8O_5N_2 \cdot H_2SO_4$ requires S = 9·5 per cent.

The same substance is produced in the form of fine needles when the hydrated sulphate is recrystallised from concentrated sulphuric acid; it however, readily takes up water from the air and passes into the hydrated condition.

If the aqueous solution of the sulphate is made alkaline with ammonia and then acidified with acetic acid, the *acid ammonium* salt is precipitated as a yellow powder.

0·1427 gave 0·2486 CO_2 and 0·0581 H_2O. C = 47·51; H = 4·53.

$C_{10}H_8O_5N_2,NH_3$ requires C = 47·4; H = 4·3 per cent.

2 : 4 : 6-*Trioxypyridine Anhydride*, $C_{10}H_8O_5N_2$.—As Stokes and von Pechmann showed, trioxypyridine anhydride is a dibasic acid. The free acid was therefore prepared from the sulphate in the following way. A weighed quantity of the hydrated sulphate was dissolved in cold water, neutralised with ammonia, and an equivalent quantity of hydrated sulphate dissolved in cold water was added to it. On mixing the two solutions, trioxypyridine anhydride was at once precipitated as a yellow solid.

0·1972 gave 0·3673 CO_2 and 0·0639 H_2O. C = 50·61; H = 3·62.

$C_{10}H_8O_5N_2$ requires C = 50·8; H = 3·4 per cent.

Trioxypyridine anhydride is converted into trioxypyridine by evaporating its aqueous solution and extracting the residue with alcohol.

V. *Action of Hydrochloric Acid. Formation of* 2 : 4 : 6-*Trioxypyridine.*

Ethyl β-imino-α-cyanoglutarate, when boiled with concentrated hydrochloric acid, rapidly passes into solution, and if, when all has dissolved, the solution is cooled, it deposits a considerable quantity of a crystalline substance: this was found to consist of a mixture of two compounds which could be separated by recrystallisation from water. The more insoluble proved to be ethyl hydrogen β-imino-α-cyanoglutarate, $CO_2H \cdot CH_2 \cdot C(:NH) \cdot CH(CN) \cdot CO_2Et$, and the more soluble to be *ethyl hydrogen α-cyanoacetonedicarboxylate*,

$$CO_2H \cdot CH_2 \cdot CO \cdot CH(CN) \cdot CO_2Et;$$

the latter crystallises from water in long, colourless needles which melt at 145° and at 170° give off carbon dioxide, being converted between these temperatures into ethyl 2 : 4 : 6-trioxypyridine-3-carboxylate.

0·2135 gave 0·3755 CO_2 and 0·0830 H_2O. C = 47·97; H = 4·32.
$C_8H_9O_5N$ requires C = 48·2; H = 4·5 per cent.

The dicarboxylate gives a red coloration in aqueous solution with ferric chloride.

On addition of water, ethyl glutazinecarboxylate is precipitated from the mother liquors. If, however, the hydrochloric acid solution is heated for five to six hours on the sand-bath, and the resulting solution evaporated to dryness on the water-bath, a residue is obtained which consists of a hydrochloride. After a rough estimation of the quantity of hydrochloric acid had been made, the calculated quantity of sodium carbonate solution was added to neutralise the hydrochloric acid present, when a white precipitate was at once formed which, on collecting, proved to be 2 : 4 : 6-trioxypyridine.

0·2154 gave 0·3712 CO_2 and 0·0756 H_2O. C = 47·01; H = 3·9.
$C_5H_5O_3N$ requires C = 47·2; H = 3·9 per cent.

When fused with ammonium acetate for from two to three minutes and then extracted with hot alcohol, the alcoholic solution on evaporation yielded a residue which crystallised from water in small plates, and gave in aqueous solution a deep red coloration with ferric chloride, changing to green on boiling. The substance was evidently therefore glutazine.

Action of Ammonia. Formation of Ethyl β-Imino-α-cyanoglutamate, $CONH_2 \cdot CH_2 \cdot C(:NH) \cdot CH(CN) \cdot CO_2Et$.

Ethyl β-imino-α-cyanoglutarate dissolves when warmed with concentrated ammonia solution, and on cooling the above substance separates out in the form of a white, crystalline powder. It is best prepared, however, by dissolving the ethyl salt in alcohol and saturating the solution with ammonia gas, or by dissolving it in alcohol (3 vols.) and adding 1 vol. of 0·880 ammonia solution. By either method, a practically quantitative yield of the glutamate separates on standing.

It is readily soluble in hot water, sparingly in cold, and separates from its hot aqueous solution in small needles which melt at 195° with decomposition.

0·2431 gave 45·3 c.c nitrogen at 19° and 755 mm. N = 21·8.
$C_8H_{11}O_3N_3$ requires N = 21·3 per cent.

Action of Concentrated Sulphuric Acid on the Amide. Formation of Ethyl Glutazinecarboxylate.—One gram of the pure, finely-ground amide was added gradually to 5 c.c. of concentrated sulphuric acid, the solution being kept cool under the tap. When all had dissolved, water

was added and the heavy, white precipitate which formed collected and recrystallised from glacial acetic acid. An analysis proved it to be ethyl glutazinecarboxylate.

0·1563 gave 0·2796 CO_2 and 0·0769 H_2O. C = 48·82; H = 5·47.
$C_8H_{10}O_4N_2$ requires C = 48·5; H = 5·1 per cent.

Action of Sodium Carbonate Solution on the Amide. Formation of Glutazine Cyanide, $NH<^{CO\text{——}CH_2}_{CO\cdot CH(CN)}>C{:}NH$.—Five grams of the amide were dissolved in sodium carbonate solution and boiled for 1 hour; alcohol and ammonia were eliminated, and the solution on cooling deposited a small quantity of ethyl *β*-imino-*α*-cyanobutyrate, melting at 181°. On acidifying the filtered solution with hydrochloric acid, a heavy precipitate of the above cyanide was formed. It can be recrystallised from a large quantity of water, but is more easily obtained pure by dissolving in sodium carbonate solution (in which it dissolves with effervescence) and acidifying hot with acetic acid; on cooling, the pure cyanide separates in the form of colourless needles.

0·2419 gave 0·4249 CO_2 and 0·0802 H_2O. C = 47·90; H = 3·68.
$C_6H_5O_2N_3$ requires C = 47·7; H = 3·3 per cent.

The aqueous solution gives with ferric chloride a reddish-violet coloration changing to brown on boiling. Glutazine cyanide is insoluble in concentrated hydrochloric acid, but dissolves in concentrated sulphuric acid, being reprecipitated on the addition of water; with caustic soda solution, it first forms a sparingly soluble acid salt which dissolves on addition of more alkali.

The *dibenzoyl* derivative is prepared by boiling the cyanide with benzoyl chloride until the evolution of hydrochloric acid ceases; on cooling, a crystalline substance slowly separates, which can be recrystallised from absolute alcohol yielding small plates melting at 193°.

0·2173 gave 0·5317 CO_2 and 0·0688 H_2O. C = 66·73; H = 3·52.
$C_{20}H_{13}O_4N_3$ requires C = 66·9; H = 3·6 per cent.

The *oxime*, $HN<^{CO\cdot C(:NOH)}_{CO-CH(CN)}>C{:}NH$, is formed by dissolving the cyanide in aqueous caustic soda, adding a solution of the calculated quantity of sodium nitrite, and pouring the mixture into dilute acetic acid. A red solution is formed which quickly deposits red crystals of a sodium salt. These do not give the Liebermann reaction, and on warming with dilute hydrochloric acid yield the free acid having the above formula as a yellow, microcrystalline powder.

The oxime is not decomposed on boiling for a short time with hydro-

chloric acid, and gives with ferrous sulphate in neutral solution a deep indigo-blue coloration.

0·2213 gave 0·3235 CO_2 and 0·0422 H_2O. C = 39·87; H = 2·12.
$C_6H_4O_3N_4$ requires C = 40·0; H = 2·2 per cent.

The substance deflagrates when heated, and does not possess a definite melting point.

Hydrolysis of the Cyanide. Formation of 2 : 4 : 6-Trioxypyridine.

The cyanide is not readily hydrolysed by hydrochloric acid, and even on prolonged boiling is little changed; it was therefore found advantageous to heat 1 gram with concentrated hydrochloric acid in a sealed tube at 180° for 4 hours. The contents of the tube on evaporating to dryness yielded a residue which, on treatment with sodium carbonate in the manner already described, yielded trioxypyridine, which, on fusion with ammonium acetate, yielded glutazine.

Conversion of Ethyl Hydrogen β-Imino-α-cyanoglutarate into Ethyl Glutazinecarboxylate.

In order to show that this molecular change takes place without the presence of water, 5 grams of the finely powdered and carefully purified ethyl hydrogen salt were dried at 100° for 8 hours. The slightly brown substance was then heated to 145° in a tube surrounded by sulphuric acid, and the temperature maintained at this point for 10 minutes.

The solid melted and gradually became yellow, a small quantity of carbon dioxide being eliminated at the same time; it then became solid, and after being heated for the requisite time was extracted with hot absolute alcohol and filtered. The residue weighing 4·2 grams was found to be pure ethyl glutazinecarboxylate, crystallising from glacial acetic acid in characteristic plates.

0·2217 gave 0·3959 CO_2 and 0·1031 H_2O. C = 48·7; H = 5·17.
$C_8H_{10}O_4N_2$ requires C = 48·5; H = 5·0 per cent.

The alcoholic solution on cooling deposited a small quantity of ethyl β-imino-α-cyanobutyrate melting at 181°.

Conversion of Ethyl Hydrogen Cyanoacetonedicarboxylate into Ethyl 2 : 4 : 6-Trioxypyridine-3-carboxylate, $NH\langle^{CO\text{———}CH_2}_{CO\cdot CH(CO_2Et)}\rangle CO$.

The carefully dried ethyl hydrogen salt was heated at 147° for from 10 to 15 minutes. A small quantity of carbon dioxide was eliminated from the melted mass, which subsequently set to a crystal-

line cake. This was purified by rubbing with cold absolute alcohol, filtering, and recrystallising from glacial acetic acid.

Ethyl 2 : 4 : 6-trioxypyridine-3-carboxylate is obtained in this way in small plates which melt at a high temperature and give in dilute alcoholic solution a red coloration with ferric chloride. It is soluble in alkalis and in acids.

0·1793 gave 0·3162 CO_2 and 0·0692 H_2O. C = 48·10; H = 4·29.
$C_8H_9O_5N$ requires C = 48·2; H = 4·5 per cent.

2 : 4 : 6-Trioxypyridine, prepared from the ethyl salt on hydrolysis with caustic potash, was extracted and purified by the method already given on page 1744, and was identified by conversion into glutazine on fusion with ammonium acetate.

Action of Methyl Iodide on the Sodium Compound of Ethyl β-Imino-α-cyanoglutarate. Formation of Ethyl β-Imino-α-cyano-α′-methylglutarate,
$CO_2Et{\cdot}CHMe{\cdot}C(:NH){\cdot}CH(CN){\cdot}CO_2Et$.

As already mentioned, after heating molecular proportions of ethyl sodiocyanoacetate and ethyl cyanoacetate in alcoholic solution for 2 hours on the water-bath, a jelly-like mass is obtained: this is the sodium compound, $CO_2Et{\cdot}CHNa{\cdot}C(:NH){\cdot}CH(CN){\cdot}CO_2Et$. On adding excess of methyl iodide and boiling, this sodium compound gradually dissolves, and, when all has passed into solution, the above ethyl salt is precipitated on adding water; it distils without decomposition at 220°/20 mm. and solidifies on cooling, forming small prisms from dilute alcohol which melt at 63°.

0·2164 gave 0·4356 CO_2 and 0·1287 H_2O. C = 54·80; H = 6·61.
$C_{11}H_{16}O_4N_2$ requires C = 55·0; H = 6·7 per cent.

Ethyl β-imino-α-cyano-α′-methylglutarate is not nearly so readily soluble in sodium carbonate solution as the unmethylated product, and it is necessary to boil the mixture for some time, using a 30 per cent. solution of the alkali, before complete solution is effected. On cooling, a quantity of crystals separated; these, on collecting, proved to be *ethyl α-cyano-β-aminovalerate*, $EtC(:NH){\cdot}CH(CN){\cdot}CO_2Et$, which crystallises from absolute alcohol in small prisms melting at 121°.

0·2071 gave 0·4352 CO_2 and 0·1308 H_2O. C = 57·31; H = 7·02.
$C_8H_{12}O_2N_2$ requires C = 57·1; H = 7·1 per cent.

On acidifying the sodium carbonate mother liquors, a copious precipitate of *ethyl hydrogen β-imino-α-cyano-α′-methylglutarate*,
$CO_2H{\cdot}CHMe{\cdot}C(:NH){\cdot}CH(CN){\cdot}CO_2Et$,
separated; this substance crystallises from hot water in glistening

plates, which melt at 145°, giving off carbon dioxide at 160°, and between these temperatures being gradually transformed into ethyl methylglutazinecarboxylate (see p. 1749).

0·2164 gave 0·4025 CO_2 and 0·1079 H_2O. C = 50·73 ; H = 5·54.
$C_9H_{12}O_4N_2$ requires C = 50·9 ; H = 5·7 per cent.

The *silver* salt separates as a white, gelatinous precipitate when a neutral solution of the ammonium salt is mixed with a solution containing the calculated quantity of silver nitrate.

0·2153 gave 0·0724 Ag. Ag = 33·62.
$C_9H_{11}O_4N_2Ag$ requires Ag = 33·77 per cent.

The ammonium salt, prepared by evaporating to dryness a solution of the hydrogen salt neutralised with ammonia, is quantitatively converted into ethyl β-imino-α-cyanovalerate on distillation under diminished pressure.

Ethyl cyanopropionylacetate, $EtCO{\cdot}CH(CN){\cdot}CO_2Et$, is prepared by hydrolysing ethyl β-imino-α-cyanovalerate with dilute sulphuric acid, passing at the same time a current of steam through the hydrolysing mixture. The steam carries with it the new ethyl salt, which can be extracted from the steam distillate by means of ether. It is a clear, mobile liquid boiling at 220—225° under the ordinary pressure.

0·2645 gave 0·5504 CO_2 and 0·1634 H_2O. C = 56·75 ; H = 6·86.
$C_8H_{11}O_3N$ requires C = 56·8 ; H = 6·5 per cent.

Ethyl β-imino-α-cyano-α′-methylglutarate dissolved slowly in aqueous caustic soda, and, on boiling, ammonia and alcohol were evolved. When the odour of ammonia ceased to be apparent, the product was acidified, saturated with ammonium sulphate, and extracted.

The extract was found to consist of methylmalonic acid melting at 130°.

0·2321 gave 0·3675 CO_2 and 0·1069 H_2O. C = 43·18 ; H = 5·12.
$C_4H_6O_4$ requires C = 43·6 ; H = 5·4 per cent.

The extracted mother liquors were evaporated to dryness and extracted with ether in a Soxhlet apparatus ; the extract in this case was malonic acid melting at 132°.

Ethyl hydrogen β imino-α-cyano-α′-methylglutarate is hydrolysed in the same way with caustic soda, whereas ethyl cyanopropionylacetate yields a mixture of malonic and propionic acids.

Ethyl Methylglutazinecarboxylate, $NH<^{CO\text{---}CHMe}_{CO\cdot CH(CO_2Et)}>C{:}NH$.

Eight grams of ethyl β-imino-α-cyano-α′-methylglutarate were dissolved in cold concentrated sulphuric acid and the well-cooled solution left for 10 minutes; on pouring into water, a copious, white precipitate was formed, which was collected and recrystallised from glacial acetic acid.

Ethyl methylglutazinecarboxylate consists of large needles, which melt and decompose at 213° and which give in dilute alcoholic solution a deep purple coloration with ferric chloride, disappearing on heating.

0·1874 gave 0·3487 CO_2 and 0·1014 H_2O. C = 50·76; H = 6·01.
$C_9H_{12}O_4N_2$ requires C = 50·9; H = 5·7 per cent.

This substance is not soluble in cold alkalis, but readily dissolves on warming; it is very soluble in cold mineral acids. The *dibenzoyl* derivative, prepared in the usual way, crystallises from absolute alcohol in the form of small needles and melts at 210°.

0·2002 gave 0·4803 CO_2 and 0·776 H_2O. C = 65·43; H = 4·31.
$C_{23}H_{19}O_6N_2$ requires C = 65·8; H = 4·5 per cent.

When the carefully dried and purified ethyl hydrogen β-imino-α-cyano-α′-methylglutarate, $CO_2H\cdot CHMe\cdot C(:NH)\cdot CH(CN)\cdot CO_2Et$, is heated for 5—10 minutes at 147°, that is, at a few degrees above its melting point, no appreciable amount of carbon dioxide is eliminated, but the melted compound slowly solidifies. The product on investigation proved to be a mixture of a small quantity of ethyl β-imino-α-cyanovalerate with ethyl methylglutazinecarboxylate; these were separated by treatment with hot absolute alcohol, in which the former is readily soluble.

Ethyl 2 : 4 : 6-*Trioxypyridine*-5-*methyl*-3-*carboxylate*,
$NH<^{CO\text{---}CHMe}_{CO\cdot CH(CO_2Et)}>CO$.

When a solution of ethyl methylglutazinecarboxylate in caustic soda is mixed with an aqueous solution of sodium nitrite and the mixture poured into acetic acid, a considerable quantity of nitrogen is evolved, and the solution becomes dark green; after evaporating, the pyridine derivative slowly separates and can be recrystallised from dilute acetic acid. It melts and decomposes at a high temperature, and gives in dilute alcoholic solution a red coloration with ferric chloride; it is soluble in acids and alkalis.

0·1927 gave 0·3567 CO_2 and 0·0869 H_2O. C = 50·48; H = 5·01.
$C_9H_{11}O_5N$ requires C = 50·7; H = 5·1 per cent.

2 : 4 : 6-*Trioxy*-5-*methylpyridine*, $NH<^{CO\cdot CHMe}_{CO\,-\,CH_2}>CO$, is prepared from the ethyl salt of its carboxylic acid by boiling it for a short time with aqueous caustic potash. On acidifying with hydrochloric acid and evaporating to dryness, the hydrochloride can be extracted from the residue by means of alcohol, and the free base derived from this on treating it with the calculated quantity of sodium hydroxide solution. It crystallises from a little water, in which it is fairly soluble in the cold, in the form of microscopic prisms, which, in aqueous solution, give a deep red coloration with ferric chloride. It melts at about 240° with evolution of gas.

0·2104 gave 0·3942 CO_2 and 0·0896 H_2O. C = 51·12 ; H = 4·73.
$C_6H_7O_3N$ requires C = 51·1 ; H = 4·9 per cent.

Preparation of Methylglutazine, $NH<^{CO\cdot CHMe}_{CO\,-\,CH_2}>C:NH$, *from Ethyl Methylglutazinecarboxylate.*

The ethyl salt dissolves in a large excess of sodium hydroxide solution, but a sodium salt is slowly deposited. This, however, dissolves when boiled, and if the heating be continued in a wide-mouthed tube until ammonia begins to be evolved, the residue, on acidifying with acetic acid, will give a crystalline precipitate of methylglutazine.

As in the case of glutazine itself, however, the solution has to be nearly evaporated to dryness before the hydrolysis is complete. Methylglutazine separates from water in needles, which have usually a bright red colour ; it melts about 260° and gives in aqueous solution a red coloration with ferric chloride, which disappears again almost instantly.

0·2084 gave 0·3913 CO_2 and 0·1115 H_2O. C = 51·22 ; H = 5·94.
$C_6H_8O_2N_2$ requires C = 51·4 ; H = 5·7 per cent.

The *hydrochloride* separates in fine needles from concentrated hydrochloric acid ; it is unstable in the presence of water. The *dibenzoyl* derivative, prepared from benzoyl chloride and methylglutazine, separates from hot glacial acetic acid in small plates which melt at 214°.

0·1690 gave 0·4259 CO_2 and 0·0717 H_2O. C = 68·73 ; H = 4·72.
$C_6H_7O_3N_3$ requires C = 69·0 ; H = 4·6 per cent.

Action of Nitrous Acid on Methylglutazine. Formation of the Oxime, $NH<^{CO\text{---}CHMe}_{CO\cdot C(:NOH)}>C:NH$.

This substance was prepared in the manner previously described, namely, by dissolving methylglutazine in water, adding caustic soda and sodium nitrite solution, and pouring the mixture into dilute acetic acid. A deep red solution is formed, which gradually deposits a red, crystalline substance containing sodium. When treated with dilute hydrochloric acid, this product is transformed into the free acid, which can be obtained in yellowish-white crystals from a large quantity of water.

Neither the sodium salt nor the free acid gives the Liebermann reaction, and the former, or the latter when neutralised, gives a deep green coloration with ferrous sulphate. Solutions of the free acid are reddened with alkalis.

0·1224 gave 0·1919 CO_2 and 0·0422 H_2O. C = 42·76 ; H = 3·83.
$C_6H_7O_3N_3$ requires C = 42·6 ; H = 4·14 per cent.

Prolonged boiling with concentrated hydrochloric or dilute (1:4) sulphuric acid fails to hydrolyse methylglutazine to the corresponding pyridine derivative, and in each case the methyl base was recovered unchanged. Hence by the action of dilute sulphuric or hydrochloric acid on ethyl β-imino-α-cyano-α′-methylglutarate, methylglutazine only is produced.

Ethyl β-imino-α-cyano-αα′-dimethylglutarate,
$CO_2Et\cdot CHMe\cdot C(:NH)\cdot CMe(CN)\cdot CO_2Et$.

The preparation of this substance was effected in two ways.

I. From the sodium derivative of ethyl β-imino-α-cyano-α′-methylglutarate and methyl iodide:

Ethyl β-imino-α-cyano-α′-methylglutarate (17·5 grams) was heated with a solution containing 1·7 grams of sodium dissolved in alcohol and excess of methyl iodide immediately added; after heating for from 4 to 5 hours, water was added and the precipitated oil extracted by ether. On fractionation, the larger portion distilled at 200—225°/25 mm., and slowly deposited crystals, which proved to be this dimethyl compound, and after recrystallisation from dilute alcohol formed small needles, melted at 64°, and boiled at 215°/22 mm. pressure.

0·1407 gave 0·2913 CO_2 and 0·0914 H_2O. C = 56·47 ; H = 7·2.
$C_{12}H_{18}O_4N_2$ requires C = 56·7 ; H = 7·1 per cent.

II. From the condensation of ethyl cyanomethylacetate with its sodium derivative:

Two molecular proportions of ethyl cyanomethylacetate were heated on the water-bath with 1 molecule of sodium dissolved in alcohol. At the end of 5 hours, the dark brown product was poured into dilute hydrochloric acid, and the oil which separated extracted with ether. Only a small yield of a high boiling oil was obtained on fractionation, which passed over at 215°/22 mm., and, on cooling, solidified to crystals which separated from dilute alcohol in small prisms and melted at 64°. The yield of the substance is not more than 20 per cent. of the theory. A comparison of its properties with those of the compound prepared by the first method proved the two to be identical.

0·3008 gave 0·6435 CO_2 and 0·1940 H_2O. C = 56·81; H = 7·00.
$C_{12}H_{18}O_4N_2$ requires C = 56·7; H = 7·1 per cent.

Formation of Ethyl β-Imino-α-cyano-α-methylvalerate, EtC(:NH)·CMe(CN)·CO_2Et.

Ethyl β-imino-α-cyano-αα′-dimethylglutarate does not readily dissolve in 30 per cent. aqueous sodium carbonate, and prolonged boiling is necessary before complete solution is effected. On cooling, a considerable quantity of the above compound crystallises out; when recrystallised from absolute alcohol, it forms small needles which melt at 119°.

0·2157 gave 0·5457 CO_2 and 0·1737 H_2O. C = 59·13; H = 7·67.
$C_9H_{14}O_2N_2$ requires C = 59·3; H = 7·7 per cent.

On acidifying the sodium carbonate mother liquors, no precipitate of the ethyl hydrogen salt took place, and, therefore, under the conditions of the experiment, the whole of the ethyl β-imino-α-cyano-αα′-dimethylglutarate had been converted into ethyl β-imino-α-cyano-α-methylvalerate.

Action of Dilute Sulphuric Acid on Ethyl β-Imino-α-cyano-α-methylvalerate. Formation of Ethyl Cyanopropionylmethylacetate, EtCO·CMe(CN)·CO_2Et.

This substance was prepared by boiling the ethyl salt with dilute (1 : 4) sulphuric acid, at the same time passing a current of steam through the hydrolysing solution; it passes over with the steam, and can be extracted from the distillate by means of ether. It is a mobile oil boiling at 230—235° under the ordinary pressure.

0·2137 gave 0·4606 CO_2 and 0·1391 H_2O. C = 58·79; H = 7·23.
$C_9H_{13}O_3N$ requires C = 59·0; H = 7·1 per cent.

Ethyl β-imino-α-cyano-αα′-dimethylglutarate dissolves on boiling with strong caustic potash solution, and if, after ammonia has ceased to be evolved, the product is acidified, saturated with ammonium sulphate, and extracted with ether, methylmalonic acid (m. p. 130°) is obtained as sole product.

0·2013 gave 0·2991 CO_2 and 0 0906 H_2O. C = 40·52 ; H = 5·00.
$C_4H_6O_4$ requires C = 40·7 ; H = 5·1 per cent.

Formation of Ethyl Dimethylglutazinecarboxylate,

$$NH\begin{cases}CO\text{———}CHMe\\CO\cdot CMe(CO_2Et)\end{cases}C{:}NH.$$

Ethyl β-imino-α-cyano-αα′-dimethylglutarate dissolves readily in twice its volume of concentrated sulphuric acid, and if after 5 hours the solution is poured into water, a large quantity of the above compound is precipitated on partially neutralising. The yield is about 50 per cent. of the theory, the filtrate furnishing methylmalonic acid. Ethyl dimethylglutazinecarboxylate crystallises from glacial acetic acid in small, colourless leaflets, which melt and decompose at 225°. It is appreciably soluble in hot water and dissolves in a mixture of one part of water to one part of alcohol ; its neutral solutions give a deep violet colour with ferric chloride. It is insoluble in cold alkalis, but dissolves on warming ; with acids it forms salts which are dissociated by water.

0·2213 gave 0·4293 CO_2 and 0·1219 H_2O. C = 52·91 ; H = 6·12.
$C_{10}H_{14}O_4N_2$ requires C = 53·1 ; H = 6·2 per cent.

The *hydrochloride* separates from concentrated hydrochloric acid in small, transparent prisms.

The *dibenzoyl* derivative is prepared by boiling the ethyl salt with benzoyl chloride until the evolution of hydrogen chloride ceases ; it separates on cooling, and can be crystallised from glacial acetic acid, when it is obtained in small prisms which melt at 235°.

0·2122 gave 0·5137 CO_2 and 0·1003 H_2O. C = 66·09 ; H = 5·26.
$C_{24}H_{22}O_6N_2$ requires C = 66·3 ; H = 5·1 per cent.

No definite products were isolated when ethyl dimethylglutazinecarboxylate was treated with nitrous acid, the majority of the ethyl salt being recovered unaltered.

Dimethylglutazine, $NH<\begin{matrix}CO\cdot CHMe\\CO\cdot CHMe\end{matrix}>C:NH$.

This base can be prepared by heating the foregoing ethyl salt with strong potassium hydroxide solution in a wide-mouthed tube until the odour of ammonia becomes apparent. In this case also it is necessary to evaporate the solution until nearly all the water has been driven off before complete hydrolysis is effected. On acidifying with acetic acid, dimethylglutazine separates, and can be recrystallised from water forming yellow plates, which melt at a high temperature. It gives in aqueous solution a permanent red colour with ferric chloride.

0·2128 gave 0·4238 CO_2 and 0·1228 H_2O. C = 54·32 ; H = 6·42.
$C_7H_{10}O_2N_2$ requires C = 54·5 ; H = 6·5 per cent.

The yield of this substance is small, a quantity of methylmalonic acid being recovered from the filtrate.

The *dibenzoyl* derivative is prepared by boiling dimethylglutazine with benzoyl chloride until hydrogen chloride ceases to be evolved ; it crystallises from the solution on cooling and when recrystallised from glacial acetic acid it forms small, glistening, yellow plates which melt at 205°.

0·2005 gave 0·5104 CO_2 and 0·0897 H_2O. C = 69·43 ; H = 4 97.
$C_{21}H_{18}O_4N_2$ requires C = 69·6 ; H = 5·0 per cent.

Formation of 2 : 4 : 6-*Trioxy*-3 : 5-*dimethylpyridine*,

$$NH<\begin{matrix}CO\cdot CHMe\\CO\cdot CHMe\end{matrix}>CO.$$

This substance was prepared by dissolving dimethylglutazine in a little alkali, adding a solution of the requisite quantity of sodium nitrite, and pouring the mixture into dilute acetic acid; a considerable quantity of nitrogen was evolved, and as no crystalline compound separated, the solution was therefore evaporated to dryness, hydrochloric acid being added and again evaporated. The solid residue was then extracted with alcohol, which dissolved out the hydrochloride of the above pyridine derivative. This was transformed into the free base by dissolving it in a little water and adding a solution of the calculated quantity of sodium hydroxide, when the trioxypyridine separated in the form of a brown precipitate. When recrystallised from water, it forms slender needles which are usually slightly coloured, and which give in aqueous solution a red coloration with ferric chloride.

0·1911 gave 0·3778 CO_2 and 0·0944 H_2O. C = 53·92 ; H = 5·49.
$C_7H_9O_3N$ requires C = 54·2 ; H = 5·8 per cent.

Prolonged action of concentrated hydrochloric acid or dilute (1 : 4) sulphuric acid does not hydrolyse dimethylglutazine to the corresponding pyridine derivatives.

On prolonged boiling of ethyl β-imino-α-cyano-αα′-dimethylglutarate with dilute mineral acids, dimethylglutazine is the sole product.

Ethyl β-Imino-α-cyano-αα′α′-trimethylglutarate, $CO_2Et{\cdot}CMe_2{\cdot}C(:NH){\cdot}CMe(CN){\cdot}CO_2Et$.

This substance may be prepared by two methods:

I. Treatment of ethyl β-imino-α-cyanoglutarate with sodium ethoxide and methyl iodide. In order to obtain a pure product by this method, it is necessary to repeat the process three times, on each occasion using an excess of sodium ethoxide and methyl iodide, since the introduction of the last methyl group seems to take place with some difficulty. The ultimate product boils at 200°/30 mm. and sets to a solid mass on cooling; when recrystallised from dilute alcohol, it is obtained in small prisms melting at 113°.

0·1927 gave 0·4099 CO_2 and 0·1252 H_2O. C = 58·01; H = 7·22.
$C_{13}H_{20}O_4N_2$ requires C = 58·2; H = 7·4 per cent.

II. By the action of methyl iodide on the sodium compound formed in the condensation of ethyl cyanomethylacetate with its sodium derivative. In this case, the product of the condensation, prepared as described on page 1736, was treated with excess of methyl iodide and boiled on the water-bath until the gelatinous sodium compound had completely dissolved. Water was then added and the oil which separated extracted with ether. The boiling and melting points of the substances were found to be the same as those given above.

0·2013 gave 0·4276 CO_2 and 0·1324 H_2O. C = 57·93; H = 7·31.
$C_{13}H_{20}O_4N_2$ requires C = 58·2; H = 7·4 per cent.

Ethyl β-Imino-α-cyano-α-methylisobutylacetate, $Pr^{\beta}C(:NH){\cdot}CMe(CN){\cdot}CO_2Et$.

Ethyl β-imino-α-cyano-αα′α′-trimethylglutarate only dissolves in a 30 per cent. aqueous sodium carbonate after prolonged boiling, and when all has dissolved the solution on cooling deposits the above compound. It crystallises from absolute alcohol in large, transparent prisms which melt at 135°.

0·2091 gave 0·4686 CO_2 and 0·1507 H_2O. C = 61·12; H = 8·01.
$C_{10}H_{16}O_2N_2$ requires C = 61·2; H = 8·2 per cent.

On acidifying the sodium carbonate mother liquors, no ethyl hydrogen salt was precipitated, the conditions of the experiment being such that only the above compound was formed.

Ethyl Cyanoisobutyrylmethylacetate, $Pr^{\beta}CO\cdot CMe(CN)\cdot CO_2Et$.

The conditions of the experiment were the same as those indicated in the previous cases.

The ethyl salt was boiled with dilute (1 : 4) sulphuric acid and a current of steam passed through the hydrolysing mixture. Ethyl cyano*iso*butyrylmethylacetate, which passed over with the steam and was extracted from the distillate by means of ether, is a mobile liquid boiling at 240° under the ordinary pressure.

0·2125 gave 0·4732 CO_2 and 0·1419 H_2O. C = 60·73 ; H = 7·42.
$C_{10}H_{15}O_3N$ requires C = 60·9 ; H = 7·6 per cent.

Ethyl β-imino-α-cyano-αα′α′-trimethylglutarate dissolves slowly on boiling in aqueous sodium hydroxide, and if the heating is continued until no more ammonia is evolved, the solution, on acidifying, saturating with ammonium sulphate, and extracting with ether, yields a solid which was found to consist of a mixture of methylmalonic and dimethylmalonic acids. These acids were separated by recrystallisation from concentrated hydrochloric acid, from which solvent dimethylmalonic acid crystallises, leaving methylmalonic acid in solution.

Three recrystallisations sufficed to cause the former acid to show the correct melting point (185°).

0·2129 gave 0·3529 CO_2 and 0·1153 H_2O. C = 45·21 ; H = 6·02.
$C_5H_8O_4$ requires C = 45·4 ; H = 6·1 per cent.

The methylmalonic acid was extracted from the mother liquors and found to melt at 130°.

When ethyl β-amino-α-cyano-αα′α′-trimethylglutarate is dissolved in cold concentrated sulphuric acid, and the solution, after 2 hours, is poured into water, no precipitation takes place, but the solution smells strongly of *iso*butyric acid.

When neutralised with ammonia and again acidified with hydrochloric acid, the solution gave, on extraction with ether, a crystalline substance which proved to be a mixture of methylmalonic and dimethylmalonic acids.

Evidently, therefore, the glutazine derivative is not formed from ethyl β-imino-α-cyano-αα′α′-trimethylglutarate under these conditions, the ethyl salt breaking down into straight chain degradation products.

Ethyl β-Imino-α-cyano-α′-ethylglutarate, $CO_2Et{\cdot}CHEt{\cdot}C(:NH){\cdot}CH(CN){\cdot}CO_2Et$.

If the gelatinous sodium compound produced in the condensation of ethyl cyanoacetate with its sodium derivative is treated with excess of ethyl iodide and heated on the water-bath until the sodium compound has dissolved, the above ethyl salt is obtained on adding water, extracting with ether, and fractionating. It boils at 215°/20 mm. and crystallises from dilute alcohol in prisms which melt at 68°.

0·2019 gave 0·4183 CO_2 and 0·1275 H_2O. C = 56·51; H = 7·02.
$C_{12}H_{18}O_4N_2$ requires C = 56·7; H = 7·1 per cent.

*Ethyl β-Imino-α-cyano-*n*-caprolate*, $Pr^{\alpha}C(:NH){\cdot}CH(CN){\cdot}CO_2Et$, *and Ethyl Hydrogen β-Imino-α-cyano α′-ethylglutarate*, $CO_2H{\cdot}CHEt{\cdot}C(:NH){\cdot}CH(CN){\cdot}CO_2Et$.

Ethyl β-imino-α-cyano-α′-ethylglutarate does not readily dissolve in 30 per cent. aqueous sodium carbonate, and it is necessary to boil for some time before complete solution is effected. On cooling, a crystalline substance separates, which was found to be ethyl β-imino-α-cyano-*n*-caprolate. It separates from absolute alcohol in small plates which melt at 115°.

0·2199 gave 0·4774 CO_2 and 0·1488 H_2O. C = 59·21; H = 7·52.
$C_9H_{14}O_2N_2$ requires C = 59·3; H = 7·7 per cent.

On acidifying the sodium carbonate solution, a quantity of crystals separated. These were collected and found to consist of ethyl hydrogen β-imino-α-cyano-α′-ethylglutarate. When recrystallised from hot water, this substance forms transparent prisms which melt at 153°, giving off carbon dioxide at 170°, and between these temperatures being converted into ethyl ethylglutazinecarboxylate.

0·2357 gave 0·4573 CO_2 and 0·1308 H_2O. C = 52·92; H = 6·17.
$C_{10}H_{14}O_4N_2$ requires C = 53·1; H = 6·2 per cent.

Ethyl Cyanobutyrylacetate, $Pr^{\alpha}CO{\cdot}CH(CN){\cdot}CO_2Et$.

When ethyl β-imino-α-cyano-*n*-caprolate is boiled with dilute sulphuric acid and steam is passed through the solution, the above compound passes over with the steam, and can be extracted with ether from the aqueous distillate. It is a mobile liquid, boiling at 235° under the ordinary pressure.

0·2009 gave 0·4326 CO_2 and 0·1269 H_2O. C = 58·73 ; H = 7·02.
$C_9H_{13}O_3N$ requires C = 59·0 ; H = 7·1 per cent.

Ethyl β-imino-α-cyano-α′-ethylglutarate dissolves on boiling with aqueous caustic soda, and if the heating is continued until ammonia ceases to be evolved, the product, on acidifying, saturating with ammonium sulphate, and extracting, yields ethylmalonic acid, crystallising from concentrated hydrochloric acid in small plates which melt at 112°.

0·1799 gave 0·2982 CO_2 and 0·0976 H_2O. C = 45·21 ; H = 6·03.
$C_5H_8O_4$ requires C = 45·4 ; H = 6·1 per cent.

Malonic acid (m. p. 132°) was obtained from the mother liquors on evaporating to dryness and extracting with ether in a Soxhlet apparatus.

Formation of Ethyl Ethylglutazinecarboxylate,

$$NH\begin{cases}CO\text{———}CHEt\\ CO\cdot CH(CO_2Et)\end{cases}C{:}NH.$$

This compound is best prepared by dissolving the ethyl salt in twice its volume of concentrated sulphuric acid and leaving the mixture for 12 hours. On pouring into water, no precipitation of the base immediately takes place owing to the stability of its sulphate ; if, however, ammonia is cautiously added, a white precipitate is produced.

When recrystallised from glacial acetic acid, ethyl glutazinecarboxylate forms small, colourless prisms, which melt at 212° to a red liquid. It is soluble in caustic potash solution in the cold, from which a bulky potassium salt slowly separates. It also dissolves in hot concentrated hydrochloric acid, and the solution on cooling deposits the hydrochloride in the form of small, colourless prisms.

Ethyl ethylglutazinecarboxylate gives in alcoholic solution a greenish-blue coloration with ferric chloride.

0·1566 gave 0·3076 CO_2 and 0·0954 H_2O. C = 53·57 ; H = 6·13.
0·1207 ,, 14 c.c. nitrogen at 20° and 757 mm. N = 12·7.
$C_{10}H_{14}O_4N_2$ requires C = 53·1 ; H = 6·2 ; N = 12·4 per cent.

The *dibenzoyl* derivative, prepared in the usual way, separates from glacial acetic acid in lustrous plates which melt at 229°.

0·1725 gave 0·1488 CO_2 and 0·0763 H_2O. C = 66·21 ; H = 4·91.
$C_{24}H_{22}O_6N_2$ requires C = 66·3 ; H = 5·1 per cent.

In one experiment, the sulphuric acid solution, when left for only 3 hours, was poured into water and the mixture allowed to get hot ; on cooling and partially neutralising with ammonia, a white precipitate separated, which was found to consist of ethyl ethylglutazine-

carboxylate and another substance. The latter was extracted by means of warm absolute alcohol and recrystallised by dilute alcohol. In this way, it was obtained in the form of long, slender needles which melted at 83°. It proved to be an acid soluble in sodium carbonate solution with effervescence, and analysis showed that it had the formula $C_9H_{15}O_4N$.

0·1428 gave 0·2821 CO_2 and 0·1007 H_2O. C = 53·88 ; H = 7·83.
0·1803 ,, 0·3538 CO_2 ,, 0·1236 H_2O. C = 53·52 ; H = 7·61.
$C_9H_{15}O_4N$ requires C = 53·7 ; H = 7·5 per cent.

In all probability this substance is *ethyl hydrogen β-imino-α′-ethylglutarate*, $CO_2Et{\cdot}CHEt{\cdot}C(:NH){\cdot}CH_2{\cdot}CO_2H$.

Ethyl 2 : 4 : 6-*Trioxy*-5-*ethylpyridine*-3-*carboxylate*,

$$NH\begin{<}CO\text{——}CHEt\\ CO{\cdot}CH(CO_2Et)\end{>}CO.$$

When a solution of ethyl ethylglutazinecarboxylate dissolved in warm aqueous caustic soda is mixed with a solution containing the calculated quantity of sodium nitrite and the mixture poured into dilute acetic acid, a considerable volume of nitrogen is evolved and the dark green solution slowly deposits crystals of the above substance. The product crystallises from absolute alcohol in the form of small prisms which melt above 260° and give in alcoholic solution a deep purple coloration with ferric chloride. It is soluble both in acids and alkalis.

0·2001 gave 0·3869 CO_2 and 0·1010 H_2O. C = 52·73 ; H = 5·61.
$C_{10}H_{13}O_5N$ requires C = 52·9 ; H = 5·7 per cent.

2 : 4 : 6-*Trioxy*-5-*ethylpyridine*, $NH\begin{<}CO{\cdot}CHEt\\ CO\text{—}CH_2\end{>}CO$.

This base is prepared by the hydrolysis of the preceding ethyl salt with aqueous caustic potash. After boiling for 2 hours, the dark product was acidified with hydrochloric acid and evaporated to dryness, the residue being extracted with alcohol.

The hydrochloride of 2 : 4 : 6-trioxy-5-ethylpyridine dissolves in the alcohol and can be recovered on evaporation. It was then dissolved in water and the calculated quantity of sodium carbonate solution added, when the base separated a a brown, crystalline precipitate. When recrystallised from water, in which it is fairly soluble, the base is obtained in the form of pale yellow leaflets which melt and decompose at about 245° and give in aqueous solution a reddish-violet coloration with ferric chloride.

0·1992 gave 0·3945 CO_2 and 0·1006 H_2O. C = 54·02; H = 5·61.
$C_7H_9O_3N$ requires C = 54·2; H = 5·8 per cent.

Conversion of Ethyl Hydrogen β-Imino-α-cyano-α'-ethylglutarate into Ethyl Ethylglutazinecarboxylate.

This conversion is brought about by heating the carefully dried and powdered ethyl hydrogen salt at 155° for from 10 to 15 minutes. The substance first melts and gives off a small quantity of gas; it then resolidifies to a yellow mass. When extracted with absolute alcohol, this product proved to be a mixture of a small quantity of ethyl β-imino-α-cyano-*n*-caprolate with ethyl ethylglutazinecarboxylate, the latter being present to the extent of about 80 per cent.

Ethylglutazine, $NH<\begin{matrix}CO\cdot CHEt\\CO—CH_2\end{matrix}>C:NH$.

This substance is prepared by heating ethyl ethylglutazinecarboxylate with strong caustic potash solution and boiling in a wide-mouthed tube until the odour of ammonia becomes apparent. On acidifying with acetic acid, ethylglutazine separates and can be collected and recrystallised from water. In this way it is obtained in the form of lemon-yellow plates which melt at about 260° and give in aqueous solution a red coloration with ferric chloride.

0·1954 gave 0·3012 CO_2 and 0·1174 H_2O. C = 54·62; H = 6·67.
$C_7H_{10}O_2N_2$ requires C = 54·55; H = 6·5 per cent.

The *dibenzoyl* derivative, prepared in the usual way, crystallises from glacial acetic acid in the form of glistening plates which melt at 209°.

0·2017 gave 0·5130 CO_2 and 0·0875 H_2O. C = 69·37; H = 4·82.
$C_{21}H_{18}O_4N_2$ requires C = 69·6; H = 5·0 per cent.

The *oxime*, $NH<\begin{matrix}CO——CHEt\\CO\cdot C(:NOH)\end{matrix}>C:NH$, is prepared by mixing an aqueous solution of ethylglutazine with an aqueous solution of sodium nitrite and pouring the mixture into a 50 per cent. solution of acetic acid. The solution at first becomes red, but gradually changes to yellow, and slowly deposits a yellow, crystalline compound.

This substance, which is the free oxime, crystallises from dilute alcohol in small, light yellow needles, dissolving in alkali to form a red solution which, when neutral, gives a deep bluish-green coloration with ferrous sulphate.

0·1921 gave 0·3214 CO_2 and 0·0816 H_2O. C = 45·63; H = 4·72.
$C_7H_9O_3N_3$ requires C = 45·9; H = 4·9 per cent.

Strong mineral acids are, under the ordinary conditions, without action on ethylglutazine, and we have been unable as yet to prepare the corresponding trioxypyridine derivative in this way.

Experiments having for their object the preparation and investigation of these substances are in progress, as well as the study of similar condensation products formed by the interaction of ethyl cyanoacetate and other compounds containing negative hydrogen atoms.

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CHEMICAL LABORATORY,
THE UNIVERSITY,
MANCHESTER.