XXVI.—*Production of Pyridine Derivatives from Ethylic β -Amidocrotonate.*

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AMONGST compounds from which pyridine derivatives can be obtained, ethylic acetoacetate stands out prominently, and since Hantzsch (*Ann.*, 1882, 215, 10) showed that, by warming this compound with aldehyde-ammonia, diethylic dihydrocollidinecarboxylate was formed, almost every year has seen some addition to the ever-increasing number of

closed ring nitrogen compounds which can be produced either from ethylic acetoacetate or its condensation derivatives.

I have already called attention to the fact that when ethylic β -amidocrotonate is destructively distilled, various pyridine derivatives are formed (*Ann.*, 1884, 226, 297; *Trans.*, 1891, 59, 172; also *Trans.*, 1895, 67, 215), the chief product being ethylic lutidonemonocarboxylate.

I have also shown how pyridine derivatives could be produced by the same kind of reaction from dehydracetic acid and from triacetic lactone, both condensation products of ethylic acetoacetate.

Some years ago, during attempts to obtain larger quantities of ethylic lutidonemonocarboxylate, I prepared the hydrochloride of ethylic β -amidocrotonate in the hope that, when it was heated, it would condense at a lower temperature, according to the following equation: $C_6H_{11}NO_2 \cdot HCl + C_6H_{11}NO_2 = C_{10}H_{13}NO_3 + NH_4Cl + C_2H_5 \cdot OH$. The reaction took place at once, and a large quantity of a pyridine compound was obtained, but I was astonished to find that, not only was the product of the action a mixture of two substances, but that they both had the formula $C_{10}H_{13}NO_3$, and also that they were both entirely distinct in properties from ethylic lutidonemonocarboxylate; their melting points were as follows.

Compound A.	Compound B.	Ethylic lutidonemonocarboxylate.
138—139°*	166—167°	163—164°

A short note of the reaction was published in 1887 (*Ber.*, 20, 445), and, since then, from time to time I have investigated the properties of these two substances and their compounds. They are both ethylic salts, and yield alcohol and the sodium salts of acids when warmed with caustic soda solution. The melting points of the acids are—

Compound A.	Compound B.	Lutidonemonocarboxylic acid.
300—304°	190—191°	254—256°

When heated above their melting points, they both decompose quantitatively into pseudolutidostyryl, a substance first obtained by Hantzsch (*Ber.*, 1884, 17, 2904). Now lutidonemonocarboxylic acid, when heated, yields lutidone,

* All the melting and boiling points given have been determined by means of a set of Auchütz thermometers, and are therefore corrected temperatures.

and as both the acids from compounds A and B gave pseudolutidostyryl, it seemed possible that the difference between them might lie in some stereochemical molecular arrangement. After further study of their properties, however, I have abandoned this idea, as it is quite possible to explain their various differences and the production of pseudolutidostyryl by ordinary graphic formulæ. The interesting fact still remains that, if ethylic β -amidocrotonate is heated alone, it yields lutidone derivatives, whilst its hydrochloride yields two isomeric compounds which are derivatives of pseudolutidostyryl.

The formation of these two compounds may be explained as follows.

whilst the tautomeric modification of ethylic β -amidocrotonate would give

This reaction is precisely similar to that which takes place when ethylic lutidonemonocarboxylate is formed (compare Trans., 1895, 67, 401), when dehydracetic acid is heated with strong ammonia, or when dehydracetic acid is produced by the distillation of ethylic acetoacetate.

The production of pseudolutidostyryl from the free acids of either of the two compounds A and B is easily accounted for—

These compounds are, therefore, derivatives of isodehydracetic acid,

the connection of that acid with pseudolutidostyryl was first pointed out by Hantzsch (*Ann.*, 1884, **222**, 46).

A great deal of the work that has been done with these nitrogen compounds has been with the object of attempting to arrive possibly at reactions by which it would be possible to follow, step by step, the formation of true pyridine compounds. These oxy-derivatives are hardly true pyridine derivatives, being almost devoid of basic properties, but yet are as closely allied to pyridine as phloroglucinol is to benzene. When treated with chlorinating agents, they give chloro-derivatives which, without doubt, contain the atomic linking present in pyridine itself. One is, therefore, able to follow the gradual change from an open chain compound, such as ethylic β -amidocrotonate, through a series of reactions, none of which need a high temperature, until, finally, true pyridine derivatives are obtained.

These oxypyridine compounds, therefore, supply excellent material for the investigation. From their formation and properties, the evidence seems to be more in favour of the linking in the pyridine ring resembling that of benzene, than that it should be represented by the formula suggested first by Lieben and Haitinger. For, although the formation of γ -chlorolutidine by treating lutidone with phosphorus pentachloride seems to favour Lieben and Haitinger's formula,

still the production of α -chlorolutidine from pseudolutidostyryl is in direct opposition to such an atomic grouping,

The explanation which agrees best with all these reactions is that the internal linking of the pyridine ring resembles that of benzene, and therefore it may be expressed either by the original formula for pyridine that Körner first suggested, or by what is practically identical with it, the centric formula.

Action of Heat on the Hydrochloride of Ethylic β -Amidocrotonate.

When perfectly dry hydrogen chloride is passed into a dry ethereal solution of ethylic β -amidocrotonate, a precipitate begins to form almost at once, and settles to the bottom of the flask as a semi-crystalline mass. This crystalline compound is at once decomposed by water into ammonium chloride and ethylic acetoacetate, but if collected carefully and analysed, it is found to contain 21.6 per cent. Cl, 43.4 per cent. C, and 7.8 per cent. H. $C_6H_{11}NO_2 \cdot HCl$ requires 22.3 per cent. Cl, 43.5 per cent. C, and 7.3 per cent. H. When the crystals are heated they partially melt, and an action at once occurs with evolution of heat, the mass becoming almost solid from separation of ammonium chloride. By treating the product with a small quantity of water, the ammonium chloride can be washed away, leaving a solid, crystalline residue, which dissolves almost entirely in boiling water; after filtering from the small quantity of undissolved resinous matter, the filtrate, on cooling, sets to an almost solid mass of long, silky needles. When purified by several recrystallisations from hot water, the compound melts at 138—139°. The mean of a large number of analyses gave the following result.

	C.	H.	N.
Found	61.6	6.9	7.3
Calculated for $C_{10}H_{13}NO_3$...	61.5	6.6	7.2

The molecular weight was determined by the Raoult method, using acetic acid as the solvent.

Found, 194. M.W. of $C_{10}H_{13}NO_3$ = 195.

The reaction, therefore, occurs according to the equation

As hydrogen chloride was evolved during the action, it was thought that time might be saved by only half-saturating the ethylic β -amidocrotonate with the gas. An experiment was made, using 100 grams of the amidocrotonate dissolved in ether, the solution being divided into two equal portions, one of which was treated with excess of gaseous hydrogen chloride, the other half added, and the ether evaporated off on a water bath. The flask was now transferred to an oil bath and heated to 120°, when a vigorous reaction occurred; on cooling, the contents of the flask were treated with a small quantity of water to remove ammonium chloride, and the residue recrystallised from water. These crystals were found to be very different from those obtained before; ultimately they proved to be a mixture of two compounds, one, A, melting at 138—139°, the other, B, melting at 166—167° (the chief product).

The new compound, B, was analysed; the mean of several analyses gave,

	C.	H.	N.
Found	61.8	6.8	7.4
Calculated for $C_{10}H_{13}NO_3$...	61.5	6.6	7.2

The molecular weight was determined by the Raoult method, using glacial acetic acid as the solvent. Found, 195. $C_{10}H_{13}NO_3$ requires M.W. = 195.

From these analyses, it appears that the compounds A and B are isomeric, and at first it seemed that the change in the conditions of the experiment had determined the formation of the new compound, and that the semi-saturation of the amidocrotonate with hydrogen chloride was the reason for the production of B. This, however, was not found to be the case, for, on attempting to prepare compound A, using crude benzene (b.p. 80—120°) instead of ether, and fully saturating with hydrogen chloride, the compound B again seemed to be the chief product. This, however, was not always the case, for in another experiment with benzene, A was formed in considerably larger quantities than in the first trial; ultimately, after many different methods had been tried, it was found that, if the solvent used was evaporated off at a low temperature, so as to leave the hydrochloride in a pure condition, then, on further heating to a temperature of about 120°, compound A alone was produced, whereas, if crude benzene was used or excess of amidocrotonate, a varying mixture of A and B was the result.

The yield of either of these compounds was never as much as 50 per cent., much resin being always formed at the same time. In one experiment, 400 grams of pure amidocrotonate was saturated with hydrogen chloride in ethereal solution, and 140 grams of A was obtained; whilst, in another experiment, 200 grams that had been semi-saturated with the gas gave 60 grams of B mixed with 5 grams of A. Compound A is easily purified by recrystallisation, but compound B is more difficult to separate from the resin formed at the same time; of the two, A is also the least soluble in water. Sometimes the separation was effected by warming with dilute solution of soda for a few minutes; under these conditions, B was at once hydrolysed, whilst A remained undecomposed, and crystallised out again on cooling the solution. The acid, of which B is the ethylic salt, was recovered by acidifying the soda solution. To sum up,—(1) When 100 grams of ethylic β -amidocrotonate was dissolved in ether, and saturated with dry gaseous hydrogen chloride, and the ether evaporated, the residue, on heating, gave 30 grams of A melting at 138—139°. (2) When 100 grams of ethylic β -amidocrotonate was semi-saturated with the gas and heated under similar conditions, 25 grams of B was obtained mixed with small quantities of A; the yield of B, however, often varied in different experiments.

The theoretical amount that ought to be produced is 71 grams, the yield, therefore, is only 40 per cent.

Of the various experiments tried, it may be mentioned that B was also produced in small quantities when ethylic β -amidocrotonate was treated with acetyl chloride.

Both A and B are ethereal salts of acids, and yield alcohol and a sodium salt when boiled with caustic soda. But A has to be persistently boiled with strong soda solution before the decomposition is complete, whilst B, as has been already mentioned, is hydrolysed at once. Many attempts were made to convert the one into the other, but boiling with acids, heating with water alone in sealed tubes, or with acid did not effect the change. The compound A crystallises from hot water in long silky needles, but these become granular by stirring or standing when it is quite pure, and settle down to a thin layer at the bottom of the crystallising vessel. When boiled with acetyl chloride, no change occurs, and the substance may be heated with acetic anhydride at 140° for 6 hours with no result. Hydroxylamine does not seem to form any compound, and nitrous acid or boiling hydrochloric acid is without action on it. If it is heated at 100° with strong sulphuric acid and the mixture then poured into water, the unchanged compound separates out again. The action of heated soda lime was also tried. 10 grams was mixed with and distilled over excess of heated soda lime; traces of ammonia were produced, but the chief product was an oil boiling at $280\text{--}285^\circ$. This gave a well crystallised platinochloride, containing no water of crystallisation; the mean of four analyses gave 25.9 per cent. Pt. Theory for $(C_9H_{13}NO)_2, H_2PtCl_4$ is 26.2 per cent.

When the compound A is dissolved in glacial acetic acid, and bromine is added in excess, a bromine compound is produced which can be precipitated by pouring the mixture into water; it recrystallises from alcohol in long, glistening needles, melts at $158\text{--}159^\circ$, and on analysis proved to be a monobromo-substitution product. The mean of several analyses gave C = 44.0; H = 4.5; N = 5.3; Br = 29.1. Calc. for $C_{10}H_{12}NO_3Br$: C = 43.8; H = 4.4; N = 5.1; Br = 29.2.

Compound A also reacts with pentachloride of phosphorus. It is best not to dilute the substance with any solvent, but to add the pentachloride in small quantities, keeping the flask heated in an oil bath at 180° .

The reaction is as follows:—

The action is not violent, and after the oxychloride of phosphorus has been distilled off, the residue can be added to water and steam distilled. The oil which passes over when purified boils at $288\text{--}290^\circ$. Its analyses gave the following numbers. C = 56.6; H = 6.0

N = 7.0 ; Cl = 16.6. Calc. for $C_{10}H_{12}NO_2Cl$: C = 56.2 ; H = 5.6 ; N = 6.5 ; Cl = 16.6.

The chloride is a very stable substance, and is only decomposed slowly by boiling with potash. Some of it was treated for a week with tin and strong hydrochloric acid warmed on a water bath. By blowing steam through the neutralised product of the reaction, an oil boiling at 246—248° was obtained, which, unlike the original chloride, had basic properties and formed a platinum salt melting at 208—210°. When this oil is boiled with aqueous soda and an acid added to the solution, a pyridine acid melting at 158—160° is precipitated. The platinum salt contained 25.4 per cent. of Pt, and the ether and acid were both free from chlorine.

The substance which had been produced was, therefore, an ethylic α -dimethyl pyridine β -carboxylate, and is probably identical with a compound produced by Michael (*Ber.*, 1885, 18, 2020) from ethylic acepoacetate. He found that the ether, $C_5H_2N(CH_3)_3 \cdot COOC_2H_5$, boiled at 246—247°, the platinochloride melted at 191°, and the acid had a melting point of 166°. This reduction of the chloro-derivative by tin and hydrochloric acid is of interest, because many of the chloropyridines are not acted on by nascent hydrogen produced in this manner. The compound A needs prolonged treatment with boiling and moderately concentrated soda to effect its decomposition. The sodium salt produced is decomposed on the addition of hydrochloric acid, and the free acid is at once precipitated. It is very insoluble in most solvents, but can be recrystallised from boiling water. When pure, it melts at a little above 300°, about 304°, and decomposes at once at that temperature, carbon dioxide and pseudolutidostyryl being produced. It crystallises with 1 mol. H_2O , and has the formula $C_8H_9NO_3 \cdot H_2O$. Auchütz, Bendix, and Kerp (*Ann.*, 1890, 259, p. 174) obtained an acid melting at 275° by heating isodehydracetic acid with ammonia; although they give the melting point as 275°, it probably is the same acid, for, on heating, it yields carbon dioxide and pseudolutidostyryl.

Several salts of this acid were prepared and analysed. The *silver* salt is thrown down as a white precipitate from neutral solutions. The *copper* salt is a light green precipitate. The *lead* salt crystallises from concentrated solutions in small tufts composed of microscopical needles. The *barium* salt is also soluble, but crystallises from concentrated solutions.

Several analyses of the acids were made which gave results agreeing with the formula $C_8H_9NO_3 \cdot H_2O$.

As already stated, when it is heated it decomposes at its melting point, giving carbon dioxide and pseudolutidostyryl

This reaction appears to be nearly quantitative. Five grams of the dried acid yielded 660 c.c. of carbon dioxide, and 3.6 grams of residue, the amount required by theory being 670 c.c. and 3.7 grams. The residue agreed in every respect with pseudolutidostyryl; it melted at 180—181°, and boiled at 306—307°.

The analyses that were made also agreed with the formula C_7H_9NO . This substance was first prepared by Hantzsch (*Ber.*, 1884, 17, 1026) by the action of sulphuric acid on

The methylpseudolutidostyryl was then converted into pseudolutidostyryl by heating with hydriodic acid. As very considerable molecular change must have occurred during the production of methylpseudolutidostyryl, it is of interest to be able to confirm the formula which Hantzsch suggested for pseudolutidostyryl from the formation of that substance by a totally different set of reactions.

According to Hantzsch, pseudolutidostyryl, when heated with zinc dust, gave α -dimethylpyridine. Before I had seen Hantzsch's paper, I had tried the experiment, and as the results were slightly different, and the amounts used very much larger, they are worth recording.

In one experiment, where 25 grams of the substance was heated with zinc dust, 12 grams of pyridine bases were obtained boiling between 150 and 170°; these, on fractional distillation, gave, at 150—160°, 2 grams; 160—165°, 6 grams; 165—170°, 4 grams. The portion boiling from 150—160° was converted into platinochloride and recrystallised; it contained 31.0 per cent. Pt, and was without doubt the substance $[C_5H_3N(CH_3)_2]_2H_2PtCl_6$, which contains 31.2 per cent. Pt and has no water of crystallisation. α -Dimethylpyridine boils at 156—157°.

The larger portion of the pyridine bases, however, boiled between 160° and 170° , and gave a platinochloride less soluble in water than the former one. After many crystallisations, the salt, which melted at 217° , was repeatedly analysed. (1) C = 29.4; H = 3.9. (2) C = 29.5; H = 4.0. (3) Cl = 33.1. (4) Six determinations of platinum, varying from 29.7 to 29.9.

The substance is, therefore, a trimethylpyridine or a collidine.

Lutidine.	Collidine.	Found.
$[\text{C}_5\text{H}_3\text{N}(\text{CH}_3)_2]_2, \text{H}_2\text{PtCl}_6.$	$[\text{C}_5\text{H}_2\text{N}(\text{CH}_3)_3]_2, \text{H}_2\text{PtCl}_6.$	
C 26.9	29.4	29.4
H 3.2	3.7	3.9
Cl 34.1	32.7	33.1
Pt 31.2	29.9	29.9

Some of the platinochloride was decomposed with hydrogen sulphide, and the free base obtained from the filtrate; its boiling point was $167-168^{\circ}$.

It gave C = 79.2; H = 9.1; N (by diff.) = 11.7.

	C.	H.	N.
Lutidine, $\text{C}_7\text{H}_9\text{N}$	78.5	8.4	13.1
Collidine, $\text{C}_8\text{H}_{11}\text{N}$	79.3	9.1	11.6
Found	79.2	9.1	11.7

From the boiling point, probably, this collidine is the symmetrical trimethylpyridine.

According to Hantzsch (*Ann.*, 1882, 215, 13), this collidine boils at $171-172^{\circ}$, whilst Durkopf (*Ber.*, 1888, 21, 2713) gives the boiling point $167-168^{\circ}$.

The remainder of the base was submitted to oxidation by permanganate of potash—for, according to Durkopf, uvitonic acid is produced (pyridine- α -methyl- $\alpha'\gamma$ -dicarboxylic acid), but the products were formed in such small quantity that no definite results were obtained.

That it is a trimethylpyridine is of considerable interest; and it is a curious fact that a substance like pseudolutidostyryl should be thus changed into a collidine derivative when heated with zinc dust, and that Hantzsch's collidine compound with strong sulphuric acid should yield pseudolutidostyryl. Moreover, the chlorolutidine obtained by the action of pentachloride of phosphorus on pseudolutidostyryl seems

to give nothing but lutidine (b. p. 156—158°) when heated with zinc dust.

This chlorolutidine is produced almost quantitatively, 25 grams of pseudolutidostyryl yielding about 22 grams of the chloro-compound.

α -Chloro- α' - γ -dimethylpyridine, $C_5NH_2(CH_3)_2Cl$.

When pure, it boils at 212—214°. An analysis gave C=59.0, H=5.7, whilst C_7H_8NCl requires C=59.3, H=5.6. It combines feebly with hydrochloric acid, and forms a stable platinochloride, which, when analysed, gave 28.1 per cent. Pt. Theory for $(C_7H_8NCl)_2, H_2PtCl_6$ = 28.1 per cent. The only way to prepare the hydrochloride is to saturate the oil with hydrogen chloride. The white solid hydrochloride thus formed was weighed, and it was found that the chlorolutidine had taken up 12.2 per cent. of hydrogen chloride, which is almost the amount necessary if 2 molecules of the chlorolutidine react with 1 molecule of hydrogen chloride—12.8 per cent.

The platinochloride seems, however, to be the normal compound, for it gave 28.0 per cent. Pt, and $(C_7H_8NCl)_2, H_2PtCl_6$ contains 28.1 per cent. Pt.

The analysis and methods for the preparation of this substance have already been given (p. 304).

When it is boiled with strong hydrochloric acid, it slowly decomposes into the free acid (m. p. 190—191°), carbon dioxide, ethylic chloride, and pseudolutidostyryl. It does not give an acetyl derivative when heated with acetic chloride or acetic anhydride, but, as already stated, it is hydrolysed at once by alkalis (difference from compound A), and on adding an acid to the alkaline solution, the free acid crystallises out.

Unlike the compound A, it does not react in a simple manner with pentachloride of phosphorus. Even when it is dissolved in various solvents, and the pentachloride of phosphorus is added carefully, considerable decomposition occurs, blackening, evolution of carbon dioxide and other gases being amongst the most noticeable results, whilst no pure substance could be obtained from the product of the action. With bromine, however, it forms a definite compound. When the compound

B is dissolved in glacial acetic acid, and bromine is added carefully, two molecular proportions of bromine have to be added before it remains in excess. The pure bromine compound melts at 168—170°.

The mean of three bromine determinations gave 44.7 per cent. Br., and on combustion C = 34.5 per cent., H = 3.3 per cent.

$C_{10}H_{11}NO_3Br_2$ requires C = 34.0; H = 3.1; Br = 45.3 per cent.

The bromide is hydrolysed at once on treatment with soda; the free acid crystallises in small needles, and when heated to 256—258°, melts and chars, giving off carbon dioxide, bromacetone, and hydrogen bromide. Although the compound A gives no hydrazone with phenylhydrazine, the compound B, when heated in a sealed tube with that reagent, enters at once into combination with it. It was found, however, that, even after many crystallisations, the substance was not pure.

Results of analysis: C = 65.0; H = 6.3; N = 15.0 per cent.

Calculated $C_{16}H_{19}N_3O_2$: C = 67.4; H = 6.6; N = 14.7. „

This compound, when heated, melted at 227—228°, blackening considerably, and gave a strong smell of aniline compounds, so that, although it had not been obtained in a pure condition, still there was no doubt that a hydrazone had been produced.

When the compound B is treated even with dilute alkalis, it dissolves, and on warming at once hydrolyses. The free acid, which is obtained by adding hydrochloric acid to the solution of the sodium salt, crystallises from water, either in needles or flat, needle-shaped plates, containing no water of crystallisation. It melts at 190—191°, and on analysis gave results agreeing with the formula $C_8H_9NO_3$.

The *sodium* salt crystallises in large plates; the *barium* salt seems to be less soluble in boiling than in cold water; the *lead* salt separates in leaflets from strong solutions; the *silver* salt is thrown down as a flocculent precipitate in neutral solutions, and is moderately soluble in hot water, from which it can be crystallised. It contains no water of crystallisation, and gave on analysis 56.0 per cent. Ag. Theory for $C_8H_7NO_3Ag_2$: Ag = 56.0 per cent.

Probably the hydrogen atom that is attached to the nitrogen atom, has been replaced by the silver as well as the hydrogen in the carboxyl group. The same result was obtained on analysing the silver salt of the isomeric acid (m. p. 300—304°) from the compound A. 54.1 and 55.0 per cent. Ag. On heating this acid (m. p. 190—191°), it is noticed that copious effervescence of carbon dioxide occurs the moment it melts; 10 grams lost 2.5 grams.

According to the equation, $C_8H_9NO_3 = C_7H_9NO + CO_2$, it should lose 26 per cent.

The residue in the flask is almost pure pseudolutidostyryl, identical in

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That it is a substituted acetic acid also receives additional support from its behaviour with ferric chloride. In neutral solutions, it gives at first a reddish coloration, but on boiling, the yellow ferric salt is at once precipitated.