

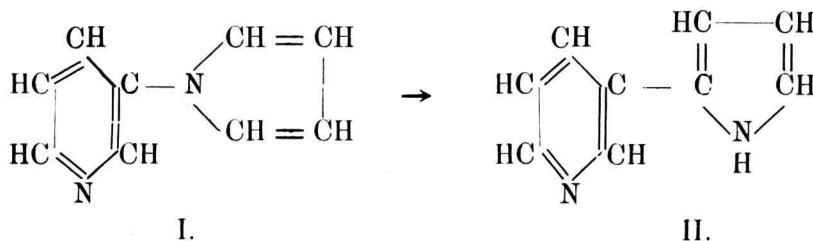
**Chemistry.** — "*The Synthesis of some Pyridylpyrroles.*" By Dr. J. P. WIBAUT and Miss ELISABETH DINGEMANSE. (Communicated by Prof. P. VAN ROMBURGH.)

(Communicated at the meeting of March 24, 1923.)

In the course of the researches on the structure of the natural alkaloids, several of these vegetable bases have been prepared by synthesis. In other groups of vegetable substances, investigators have not only succeeded in building up the substances occurring in nature, but also closely allied bodies were obtained synthetically. In the group of the sugars, e.g., a number of monoses have been obtained which do not occur in the vegetable kingdom, but which are isomeric with or closely related to the sugars found in nature. Our knowledge of the chemical and biochemical properties of the monoses has been greatly improved by these synthetic researches. It seems not devoid of interest to try and build up an isomer of a natural alkaloid, in order to examine afterwards in what respect the isomeric substance is distinguished from the natural alkaloid, especially with regard of physiological and biochemical properties.

Keeping this end in view we will try to build up an isomer of nicotine.

In his synthesis of nicotine PICTET started from  $\beta$ -amino-pyridine; this substance was heated with mucic acid, through which N ( $\beta$ -pyridyl)-pyrrole (I) was obtained. At high temperature N ( $\beta$ -pyridyl) pyrrole undergoes an isomerisation, in which C ( $\beta$ -pyridyl)-pyrrole (II) is formed:

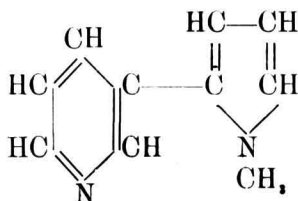


PICTET and CRÉPIEUX<sup>1)</sup> give the above structure to this C ( $\beta$ -pyridyl)

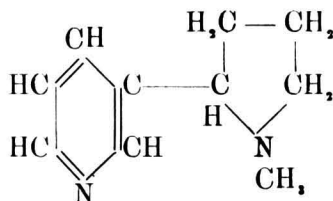
<sup>1)</sup> Ber. d. deutsch. chem. Ges. **28**, 1904 (1895).

pyrrole, in which it is, therefore, assumed that the pyridine nucleus is united at the  $\alpha$  C atom of the pyrrole nucleus.

In how far this assumption is justified, will be discussed afterwards. The preparation of these substances did not offer any special difficulty; on the other hand, the conversion of C(pyridyl) pyrrole (II) into the methyl derivative, nicotine (III), was difficult to realize:



III.



IV.

When it is tried to methylate the pyrrol derivative at the nitrogen atom by treating the potassium-compound with methyl-iodide, there is also a molecule of methyl iodide combined with the nitrogen atom of the pyridine nucleus, so that the iodine methylate of nicotine is formed, from which afterwards methyl iodide must be split off.

PICTET and ROTSCHY<sup>1)</sup> have obtained but very little of the nicotine by this method. For the continuation of his experiments PICTET has, therefore, made use of a nicotine preparation which was prepared by oxidation from nicotine (IV) by BLAU's method.

A similar procedure is of course impossible in our case. In the end PICTET and ROTSCHY have succeeded in reducing nicotine to nicotine by an indirect way through making use of iodine and bromine substitution products.

Hence if this synthesis is repeated, starting from  $\alpha$ -amino-pyridine, an isomer of the nicotine can be built up, in which the pyridine nucleus is substituted at the  $\alpha$ -place.

As  $\alpha$ -amino-pyridine is at present an easily accessible substance, it seemed not impossible to obtain sufficient quantities of all the intermediate products, so that it may also be expected that it will be possible to prepare so much of the final product that its properties can be properly studied.

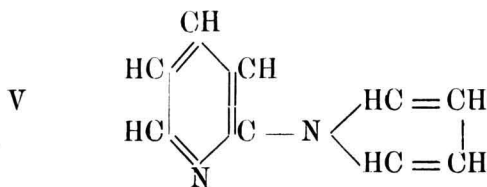
## § 2. The preparation of *N*-( $\alpha$ -pyridyl)-pyrrole.

For the preparation of *N*-( $\alpha$ -pyridyl)-pyrrole we have heated 25 gr. of  $\alpha$ -amino-pyridine with 28 gr. of mucic acid. First the salt of

<sup>1)</sup> Ber. d. deutsch. chem. Ges. **37**, 1225 (1904).

mucic acid with 2 mol.  $\alpha$ -amino-pyridine is formed. At a temperature of about  $140^\circ$  this salt begins to decompose: with separation of water and carbon dioxide the pyrrole derivative is formed while 1 mol. amino pyridine is split off. Hence a distillate is obtained which contains besides water, the required pyrrole derivative and amino pyridine. We have subjected the reaction product to fractionated distillation at 15 m.m. pressure. The first fraction of  $104\text{--}130^\circ$  is chiefly  $\alpha$ -amino pyridine. At  $140\text{--}145^\circ$  distills a liquid, of a slight yellow colour, which solidifies to a white crystalline mass on being cooled in ice. The melting-point of these crystals is  $17^\circ\text{C}$ .

This substance is N- $\alpha$ (pyridyl)-pyrrole, to which the following structure formula (V) applies.



The freshly distilled N- $\alpha$ (pyridyl)-pyrrole is a colourless liquid, which, however, assumes a dark colour after some time. The boiling-point at 760 mm. lies at  $260\text{--}261^\circ$ .

This substance is sparingly soluble in cold water, volatile with water vapour, and readily soluble in all organic solvents. A pine-chip moistened with hydrochloric acid is coloured red-violet by the vapour of N- $\alpha$ (pyridyl)-pyrrole; with a hydrochloric acid solution of dimethylaminobenzaldehyde there arises a red-violet colour, which later on changes into a dirty green. These colour reactions are considered as characteristic of pyrrol derivatives. By potassium permanganate this compound is rapidly oxidized already at the ordinary temperature.

The values of 19.58% N and 19.34% N were found for the nitrogen percentage of this preparation, the calculated percentage for  $\text{C}_9\text{H}_8\text{N}_2$  being 19.44%. We have prepared a picrate of this substance which melts at  $143^\circ$ . We obtained the iodine methylete of the N- $\alpha$ (pyridyl)-pyrrole by heating it in a sealed tube at  $100^\circ$  with the calculated quantity of methyl iodide. The reaction product was recrystallised from alcohol: yellowish white prisms, melting-point  $141^\circ\text{--}142^\circ$ .

The isomeric N- $\beta$ (pyridyl)-pyrrole prepared by PICTET and CRÉPIEUX has been described by these investigators as a liquid with

a boiling-point of 250.5—251° at 730 mm., which does not solidify at —10°.

The yield of N( $\alpha$ -pyridyl) pyrrole was in our experiments from 7 to 8 gr. out of 25 gr. of  $\alpha$ -aminopyridine.

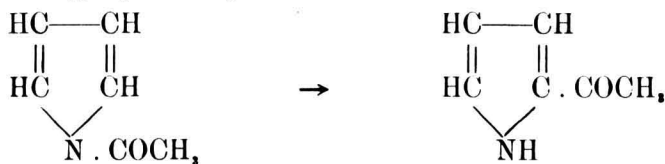
We found, however, that there is formed another substance besides this pyrrole derivative in the reaction between mucic acid and amino pyridine. During the distillation of the reaction product a liquid went over at 170°—190° and 15 mm., which crystallized at room temperature. After recrystallisation from alcohol this substance had a melting-point of 95°, and appeared to be  $\alpha$ - $\alpha'$ -dipyridyl amine. The formation of this compound during the heating of the mucic acid salt of amino pyridine seems to be analogous to the formation of diphenylamine from aniline and hydrochloric aniline.

We have actually obtained  $\alpha$ - $\alpha'$ -dipyridyl amine by heating equivalent quantities of  $\alpha$ -amino pyridine and the hydrochloric acid salt of this base in a sealed tube for two hours at 300°. We hope to return to this reaction on another occasion.

§ 3. *The conversion of N( $\alpha$ -pyridyl)-pyrrole into two isomeric C( $\alpha$ -pyridyl)-pyrroles.*

It was found long ago by CIAMICIAN<sup>1)</sup> and his collaborators that the N-derivatives of pyrrole can be transformed into C-derivatives by the action of high temperatures.

CIAMICIAN and MAGNAGHI<sup>2)</sup> heated N-acetyl pyrrole in a sealed tube at 250—280° and found that part of the starting material was changed into pyrrol methyl ketone:



That the acetyl rest actually occupies the  $\alpha$ -position in the pyrrole nucleus, results from the observation that the bromation product of this pyrrol methyl ketone yields the imide of di-bromomaleic acid by oxidation with nitric acid<sup>3)</sup>. Also some other pyrrole derivatives, in which an acylrest is combined with the nitrogen atom, were transformed into  $\alpha$ -pyrrolketones on heating.

It was found later by PICTET and his collaborators that N-methyl pyrrole, N-phenyl-pyrrole, and similar substituted derivatives of

<sup>1)</sup> Cf. CIAMICIAN. Ber. d. deutsch. chem. Ges. **37**, 4200 (1904).

<sup>2)</sup> Ibid. **18**, 1828 (1885).

<sup>3)</sup> CIAMICIAN and SILBER. ibid. **20**, 2594 (1887).

pyrrole can be transformed into C-derivatives by distillation through a red-hot tube.

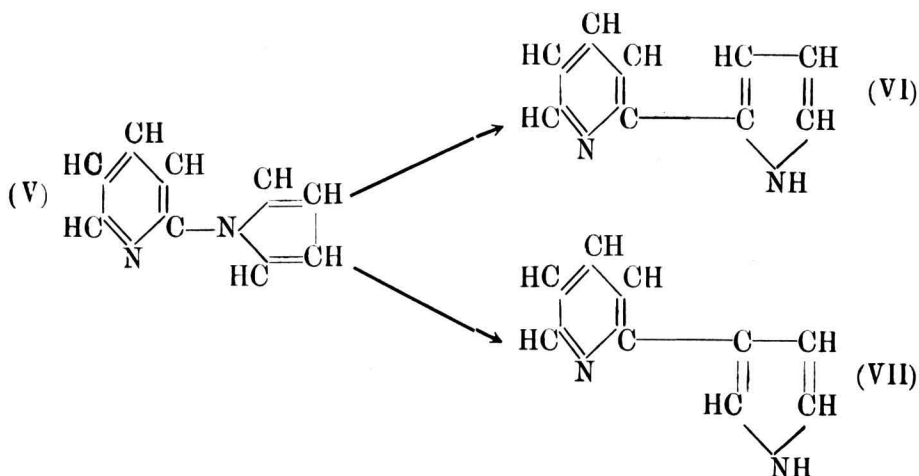
In all these intra-molecular arrangements only one C-derivative was found, whereas it would be theoretically possible that two isomeric pyrroles would be formed, since the hydrocarbon rest might be united at the  $\alpha$ - or at the  $\beta$ -carbon atom of the pyrrole nucleus.

From N-methyl pyrrole the  $\alpha$ -C-methyl pyrrole was obtained by PICTET. The structure of  $\alpha$ -C-methyl pyrrole had already been determined by ZANETTI, by converting this substance into the dioxime of levulic aldehyde.

PICTET and CRÉPIEUX assume on grounds of analogy that in the C-phenyl pyrrole which they obtained from N-phenyl-pyrrole, the phenylgroup is united at the  $\alpha$ -carbon atom of the pyrrole nucleus, and that the same thing holds for the C-pyridyl pyrrole (II), which they obtained from N- $\beta$ (pyridyl)-pyrrole (I). A direct experimental evidence, for this view was not given.

As regards PICTET and CRÉPIEUX'  $\beta$ -pyridyl- $\alpha$ -pyrrole, the structure which these investigators assign to it, is undoubtedly supported by the fact that they have obtained nicotyrine (III) from this  $\beta$ -pyridyl pyrrole, as the structural formula (IV) of nicotine has been made very probable by PINNER's researches.

We found however that two isomeric C-pyridyl-pyrroles are formed in the transformation of N( $\alpha$ -pyridyl) pyrrole, one of which melts at  $93^\circ$  and the other at  $132$ — $132.5^\circ$ . This reaction must be represented by the following scheme:



To which of our isomers formula VI applies and to which formula VII should be assigned, has not yet been established. It

will not be very easy to decide this point. In former researches it has been tacitly understood that in the transformation of a N-derivative of pyrrole in a C-derivative, it is always the  $\alpha$ -compound that is formed. In consequence of our observations the validity of these conclusion has become doubtful.

We shall now give a short description of our experiments on these reactions.

In the first place we have determined the most favourable temperature for the transformation of N( $\alpha$ -pyridyl) pyrrole into the C( $\alpha$ -pyridyl) pyrroles, as in PICTET's papers the reaction temperature is only vaguely indicated as "heated to redness" or "faintly red-hot". The best procedure appeared to be as follows:

25 gr. of N( $\alpha$ -pyridyl)pyrrole are distilled through a glass tube filled with pieces of pumice, which is heated at 670°—690° C. in an electrical oven. Part of the substance is decomposed, which shows itself in the formation of dense white vapours. The distillate consists of a black liquid, which soon solidifies at room temperature. This reaction product was distilled with steam, in which a white crystalline substance passed over, which was filtered off. This substance appeared to be very sparingly soluble in cold water. The crude product melted at 84°; after recrystallisation from a mixture of benzene and ligroine the melting-point is 90°. The yield of this substance was about 12 gr. The aqueous distillate contained only very little unchanged N( $\alpha$ -pyridyl) pyrrole. A second substance remained behind in the distillation flask, which is not volatile with water-vapour, and which after recrystallisation from hot water melts at 132—132.5°.

*Properties of the pyrridyl-pyrrole melting at 90°.*

This substance is obtained from benzene, to which some ligroine has been added, in hard, very shiny, colourless octohedrical crystals. We found 19,41 % for the nitrogen content; 19,44 % was calculated for  $C_8H_8N_2$ .

This substance is readily soluble in alcohol, ether, chloroform acetone and benzene; less easily in hot water and ligroine, very little in petroleum ether. These solutions exhibit a blue fluorescence, except the aqueous and alcoholic solution. A solution of  $\beta$ -pyridyl  $\alpha$ -pyrrole also shows fluorescence according to PICTET and CRÉPIEUX.

Our pyrrole derivative does not give a colour reaction with a pine-chip moistened with hydrochloric acid; with a hydrochloric acid

solution of dimethyl-aminobenzaldehyde there appears, however, a red-violet colour.

Metallic potassium acts on this substance: a potassium compound is formed, as is to be expected. For this purpose we dissolved the substance in toluene, and let the potassium act at the boiling temperature of the solution. At first the action proceeds pretty rapidly, but it soon slows down, so that the heating must be prolonged. The potassium compound was deposited as an insoluble yellow-brown powder.

In order to ascertain the structure of the C-( $\alpha$ -pyridyl)-pyrrole, we have oxidized two grammes of this substance with potassium permanganate in sulphuric acid solution. The oxidation takes place very readily at the ordinary temperature. Out of the reaction product we have isolated the characteristic violet copper salt of picolinic acid, and from this salt we freed the picolinic acid itself by addition of sulphuretted hydrogen. The picolinic acid thus obtained was sublimated in order to purify it. The sublimated preparation melted at  $134^{\circ}.2$ , while we found  $136^{\circ}.8$  for the melting-point of picolinic acid obtained by oxidation of picoline. The melting-point of the mixture of these two preparations was  $132.5^{\circ}$ — $133^{\circ}$ . The nitrogen percentage of our preparation that melted at  $134.2$ , was 11.25 % (calculated for picolinic acid 11.38 %). In spite of the slightly too low melting-point there is no doubt of the identity of our preparation; the characteristically crystallizing platinum salt had exactly the same appearance as the platinum salt of the picolinic acid prepared from picoline. It appears from this that in the pyrrole derivative melting at  $90^{\circ}$  the pyrrole nucleus is united to the  $\alpha$ -C-atom of the pyridine nucleus.

We have prepared a picrate from this pyridyl pyrrole, which was obtained after recrystallisation from alcohol as fine, yellow needles of the melting-point  $227$ — $228^{\circ}$ .

We have prepared the iodine methylate of the pyridyl pyrrole melting at  $90^{\circ}$  by heating this pyrrole derivative in methyl alcoholic solution with an excess of methyl iodide at  $100^{\circ}$  for three hours. After evaporation of the solvent and of the superfluous methyl iodide the reaction product was recrystallized from methyl alcohol; in this way yellow-brown hard prism-shaped crystals were obtained, which melt at  $148^{\circ}$ . We found 9.6 % for the nitrogen content, and 44.7 % for the iodine content. The calculated values for  $C_{10}H_{11}N$ , J are N: 9.73 %; J: 44.37 %. This substance has, therefore, been formed by the addition of one molecule of methyl iodide; the group  $CH_3J$  is combined with the nitrogen atom of the pyridine nucleus.

*Properties of the pyridyl-pyrrole melting at 132° 5.*

This substance, which as we already remarked, is not volatile with water vapour, and is separated in this way from the isomer melting at 90°, crystallizes from alcohol or benzene in leaves joined to rosettes; from hot water long needles are obtained.

This base is readily soluble in alcohol, ether, acetone, chloroform, and benzene; not so easily in ligroine and hot water, very little soluble in low-boiling petroleum ether. As far as the solubility properties are concerned, there is, therefore, a close agreement with the isomer melting at 90°. The ethereal solution shows a blue fluorescence.

We found 19,34 % and 19,62 % for the nitrogen content (calculated for  $C_9H_8N_2$ : 19,44 % N). This base does not give a colour reaction with a pine-chip moistened with hydrochloric acid; with a hydrochloric acid solution of dimethylamino-benzaldehyde there appears, however, a cherry-red colour, which has changed into blueviolet after a day.

That this substance, too, possesses a pyrrole nucleus, appears again from the behaviour towards metallic potassium. The base was dissolved in toluene and the calculated quantity of potassium was added. The potassium dissolves with vigorous generation of hydrogen; the reaction is much more rapid than with the isomer of melting-point of 90°. The potassium compound is deposited as a white powder.

We have oxidized the pyridyl pyrrole of melting-point 132.5 in the same way with potassium permanganate in an acid solution, as we already described for the isomer of melting-point of 90°. From the pyridyl pyrrole melting at 132°.5 we likewise obtained picolinic acid, which melted at 136°.8 after sublimation, and was identical with the picolinic acid from picoline.

It results from these experiments that the two substances that are formed from N-( $\alpha$ -pyridyl)-pyrrole, are two isomeric C-( $\alpha$ -pyridyl)-pyrroles, which are distinguished in this that the pyrrole-nucleus in one substance is substituted at the  $\alpha$ -place, and in the other substance at the  $\beta$ -place, as is expressed in formulae (VI) and (VII).

We may also mention that in this reaction chiefly the isomer melting at 90° is formed; the quantity of the isomer melting at 132°.5 is small.

§ 4. *The methylation of the C-( $\alpha$ -pyridyl)-pyrrole of melting-point 90°.*

The next step in the synthesis of a substance isomeric with nicotine is that the hydrogen atom of the imide group of the pyrrole-nucleus is replaced by the methyl rest.



The difficulties experienced by PICTET and CRÉPIEUX when they endeavoured to realize the reaction, were already pointed out in the introduction. We met with the same difficulties in our case. The potassium compound of the pyridyl pyrrole melting at  $90^{\circ}$  was heated with an excess of methyl iodide in a sealed tube at  $100^{\circ}$  for three hours. The reaction product was freed from superfluous excess of methyl iodide and solved in water. On evaporation of the aqueous solution crystals were separated, while potassium iodide was present in the mother liquor. These crystals were purified by recrystallisation from a small quantity of water. Yellow-brown crystals were obtained, melting at  $186^{\circ}$ . Analysis gave 8.95 for the nitrogen percentage, and 42.55 for the iodine percentage. Calculated for  $C_{11}H_{11}N_2I$ : Nitrogen 9.34 %, iodine 42.30 %.

This substance is, therefore, the iodine methylete of C ( $\alpha$ -pyridyl)-N-methyl-pyrrole:  $(CH_3I)N-C_5H_4 \cdot C_4H_4N \cdot CH_3$ .

Just as in PICTET and CRÉPIEUX' experiments not only was the nitrogen atom of the pyrrole nucleus methylated, but also a molecule of methyl iodide had combined with the nitrogen atom of the pyridine-nucleus.

This iodine methylete is easily soluble in water, sparingly in alcohol, very little soluble in the other usual organic solvents.

In order to split off the group  $CH_3I$  out of this compound, we have followed the method which PICTET and ROTSCHY<sup>1)</sup> already applied, i.e. heating with quick lime.

The iodine-methylete was mixed with quick lime, and slowly heated in a retort. Soon a liquid distilled over, which was received in ether, in order to separate it from a little of the unchanged methyl iodide compound, which had also been distilled over in a small quantity. After evaporation of the ethereal solution there was left a light yellow liquid; we have converted this base into the picrate, which melted at  $143^{\circ}$  after a double recrystallisation from alcohol. We found 18.19 for the nitrogen percentage of this substance, while 18.09 % of nitrogen is calculated for the monopicrate of C ( $\alpha$ -pyridyl)-N-methyl-pyrrole,

We have, accordingly, very probably obtained the required methyl derivative, which must, therefore, be an isomer of nicotine.

It seems, however, possible to carry out the methylation of the C ( $\alpha$ -pyridyl) pyrrole in such a way that the C ( $\alpha$ -pyridyl) N-methyl-pyrrole is obtained without the necessity of following the indirect way over the iodine methylete.

<sup>1)</sup> L. c.

It had, indeed, already appeared that the addition of methyl iodide to the pyridyl pyrrole of melting point  $90^{\circ}$  only takes place at a higher temperature, whereas PICTET and CRÉPIEUX' pyridyl pyrrole combines with methyl iodide already at the ordinary temperature.

For this reason we have heated a mixture of pyridyl pyrrole potassium with methyl iodide in molecular quantities in a sealed tube at  $50^{\circ}$ . The reaction mixture was a solid mass, in which pyridyl pyrrole potassium and the above mentioned methyl iodide compound of C-(pyridyl)-N-methyl-pyrrole were present. It was, however, possible to extract by means of ether a little of a yellow oil from this reaction mixture. This liquid was received in alcohol, and picric acid was added; a picrate crystallized out, which melted at  $142^{\circ}$  when it had been recrystallized out of alcohol, and appeared to be identical with the picrate of the C ( $\alpha$ -pyridyl)-N-methyl-pyrrole described above, as appeared from the melting point of the mixture of both preparations.

We shall first of all set ourselves the task of preparing a larger quantity of this C( $\alpha$ -pyridyl)-N-methyl-pyrrole, and examining its properties closely. We shall further try to determine the structure of the two isomeric pyridyl pyrroles more exactly.

A full communication of this investigation will appear in the *Recueil des Travaux chimiques des Pays Bas*.

*Organic-chemical Laboratory of the University.*

*Amsterdam, March 1923.*

---