SYNTHESES AND REACTIONS OF IMIDAZO[1,2-a]PYRIDINES

A Thesis

by

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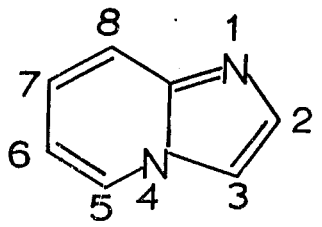
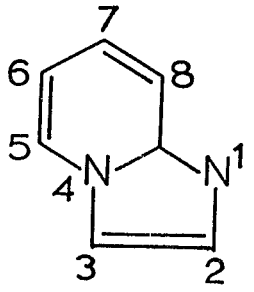
General Introduction

The imidazo[1,2-a]pyridine ring system consists of an imidazole ring fused to a pyridine ring with its nitrogen atom forming a bridgehead common to both rings. This name has been adopted by the Ring Index[1] and is numbered RI 765 or RRI 1197. The numbering in the imidazo-[1,2-a]pyridine system is as follows:

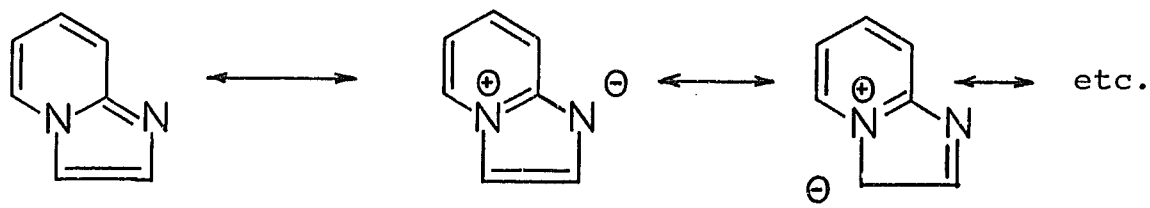


The letter "a" refers to that imidazole bond which is involved in the junction of the two rings, while the numbers 1 and 2 denote the two atoms of the pyridine ring which form the two bridgeheads. The orientation of imidazo[1,2-a]pyridine as shown above is the correct one according to the rules of the Commission on Nomenclature of IUPAC (1957). The appearance of the imidazo[1,2-a]pyridine even in the most recent publications is, however, in the following orientation:



This latter orientation appears to be convenient in representing syntheses of imidazo[1,2-a]pyridines from pyridine derivatives. In view of the contents of this thesis, and in conformity with the generally accepted representation of imidazo-[1,2-a]pyridines, the latter orientation has been adopted throughout this work.

Imidazo[1,2-a]pyridine is a heteroaromatic system with 10 π-electrons possessing a high resonance energy of 57.5 kcal/mole.[2] In addition to the above canonical structure I-A, further resonance structures can be drawn, involving charge separation:



I-A I-B I-C

Molecular orbital (M.O.) calculations indicate structure I-C to be a significant contributor to the π-electron density distribution in the imidazo[1,2-a]pyridine ring system. Consequently the 3-position carries a high electron density, which affects the reactivity of imidazo[1,2-a]pyridines towards electrophilic reagents and greatly influences the reactivity of any 3-position substituents.

In view of such an electron density distribution, imidazo[1,2-a]pyridines were expected to be acylated in the

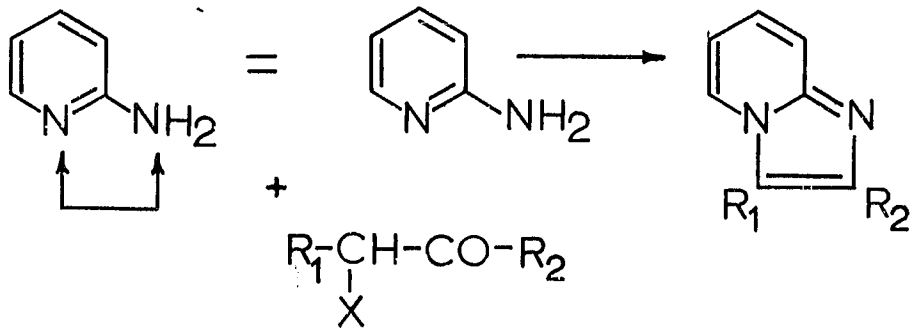
3-position, a reaction not reported so far. It seemed of further interest to examine the reactivity of 3-position acyl groups in intramolecular condensation reactions with the purpose of achieving a ring closure with suitable 6-position group.

The introduction of substituents other than methyl groups into the imidazo[1,2-a]pyridine system was expected to provide an evaluation of synthetic methods leading to imidazo-[1,2-a]pyridines. Kröhnke's synthesis, in particular, gave promise of further applications. Consequently, it was considered to be necessary to study the mechanism of Kröhnke's base catalyzed cyclization in greater detail and to approach further synthetic work with the knowledge gained by such a study. This mechanistic study was also expected to shed more light on the mode of reaction of carbanions influenced by steric and electronic factors.

Historical Introduction

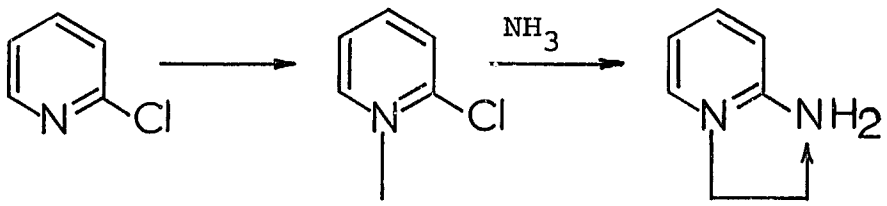
With the exception of a few syntheses commencing with an imidazole nucleus to which the six-membered ring is subsequently added[3,4], the largest majority of reported syntheses of imidazo[1,2-a]pyridines start from 2-aminopyridine. This starting material, although readily available since 1914 was employed for the first time in 1925 by Tschitschibabin for the synthesis of imidazo[1,2-a]pyridine.[5] 2-Aminopyridine was heated with bromo-acetaldehyde to 150-200° in a sealed tube; the yield of the desired product was rather low. In an improved synthesis, such drastic reaction conditions were no longer required and imidazo[1,2-a]-pyridine could be obtained in a higher yield from the same reactants in the presence of sodium bicarbonate.[6] In the years that followed Tschitschibabin's discovery, numerous workers explored alternate routes leading to imidazo[1,2-a]-pyridines and three modifications of Tschitschibabin's synthesis were eventually developed. In all three modifications, the pyridine derivatives were used. Tschitschibabin's approach makes use of bifunctional reagents, such as α-halo-carbonyl compounds which directly interact with both nitrogen atoms of 2-aminopyridine (Reaction scheme I).

Scheme I:

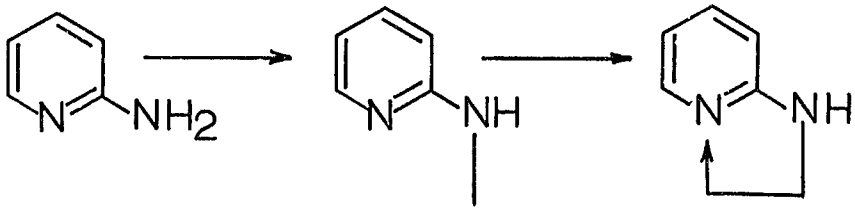


In the two other modifications, first a sidechain is attached, to only one of the nitrogen atoms, and subsequently in the second reaction, the side chain is annellated to the remaining nitrogen atom (reaction schemes A and B).

Scheme A

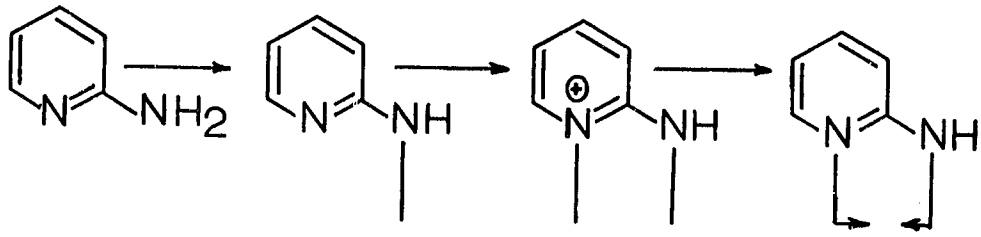


Scheme B

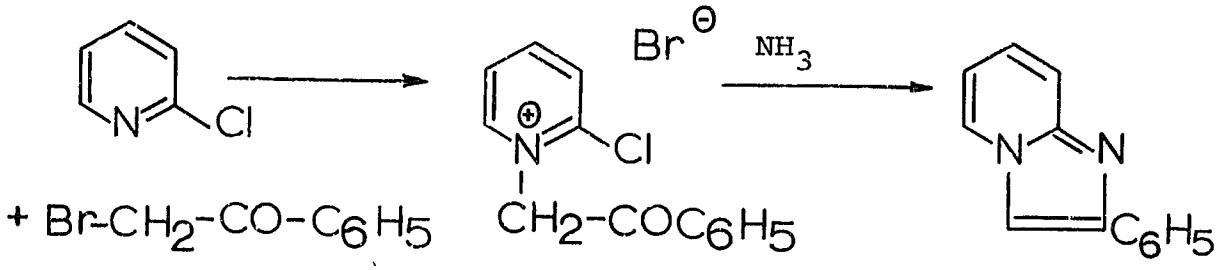


Finally, in a third scheme "C", also starting from 2-amino-pyridine, sidechains are attached to both nitrogen atoms (consecutively) and the five-membered ring is formed by annellation of two carbon atoms of each sidechain (reaction scheme C).

Scheme C:

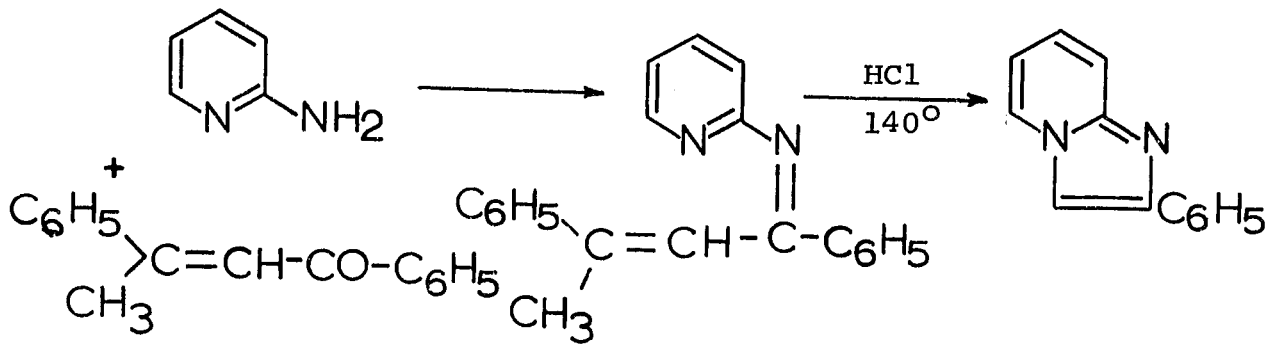


Kröhnke's synthesis of 2-phenylimidazo[1,2-a]-pyridine provides an example of a synthesis of the imidazo-[1,2-a]pyridine ring according to modification "A"[7]:



With only one nitrogen atom available for interaction with ω-bromoacetophenone, the above reactions represented an unambiguous synthesis of 2-phenylimidazo[1,2-a]-pyridine and thus provided proof for the assignment of the phenyl substituent to position 2.

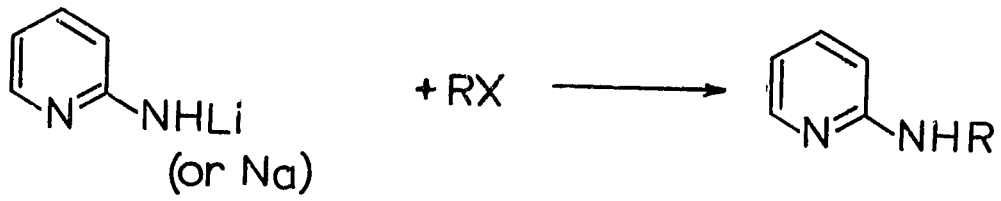
2-Phenylimidazo[1,2-a]pyridine can be obtained also (in quantitative yield) via modification "B" by treatment of 2-aminopyridine with 2,4-diphenyl-2-butene-4-one (dypnone).[8]



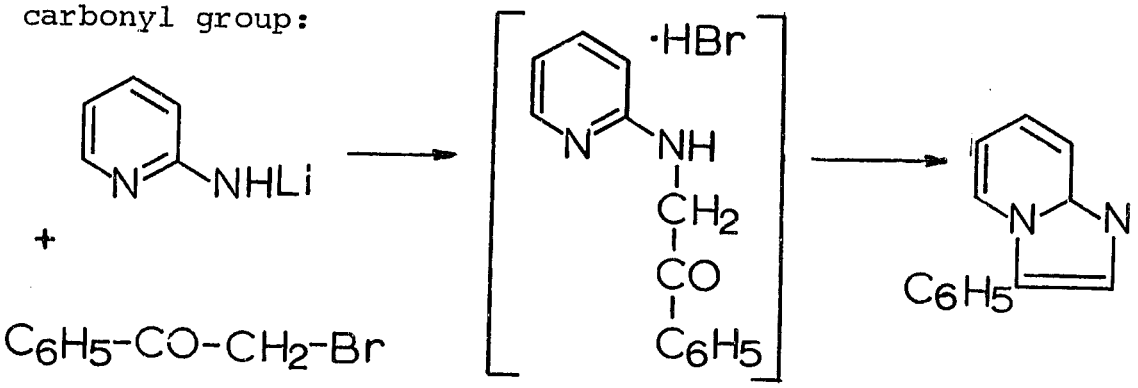
The most extensively used synthetic route to the imidazo[1,2-a]pyridine system involves the use of α-halocarbonyl compounds.[35] Although, in the end, both nitrogen atoms are attacked by the two functional groups of the halo-compound, all evidence, accumulated so far, strongly suggests that the amino group interacts <u>first</u> with the carbonyl group of the halide. The nucleophilic displacement of the halogen atom by the pyridine ring nitrogen follows next and, unlike other quaternisation reactions, is accelerated by virtue of being an intramolecular process. The reaction of 2-amino-pyridine with α-halocarbonyl compounds thus belongs to the scheme "B" class.

The orientation of the α-halocarbonyl compound with respect to 2-aminopyridine, however, posed a certain problem. As the sequence of (mechanistic) steps was not fully understood in earlier syntheses, the assignment of the substituents in the 2- and 3-positions of the di-substituted imidazo[1,2-a]pyridine remained ambiguous. In 1954 Djerassi

and Pettit[9] observed the formation of 2-alkylaminopyridines in the reaction of sodium or lithium derivatives of 2-aminopyridine with alkylhalides:



Turning now to the reaction of 2-aminopyridyllithium with -bromoacetophenone, Djerassi postulated that, in an analogous manner, the amino group nitrogen atom interacted with the halogen bearing carbon atom and not with the carbonyl group:

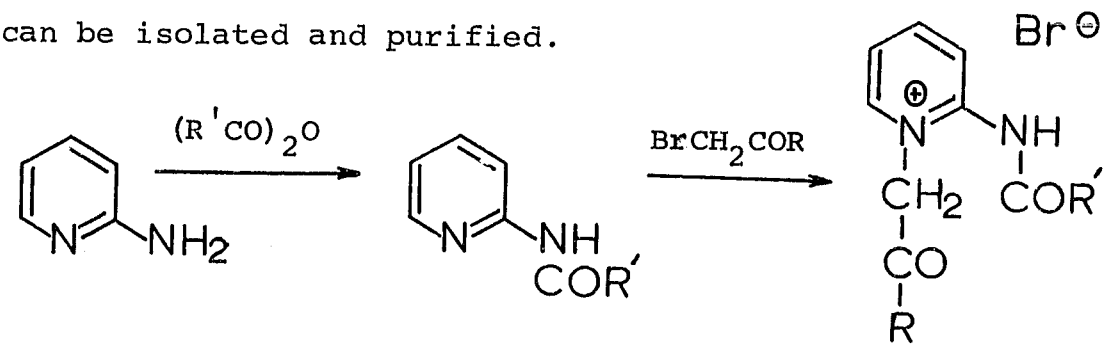


Thus, Djerassi claimed that, consequently, the final product of the reaction was not 2-phenyl derivative of imidazo[1,2-a]pyridine but rather 3-phenylimidazo[1,2-a]-pyridine. His reasoning was proved to be incorrect by Kröhnke,[7] who demonstrated the fact that water was formed in the above condensation reaction. As a result, the lithium

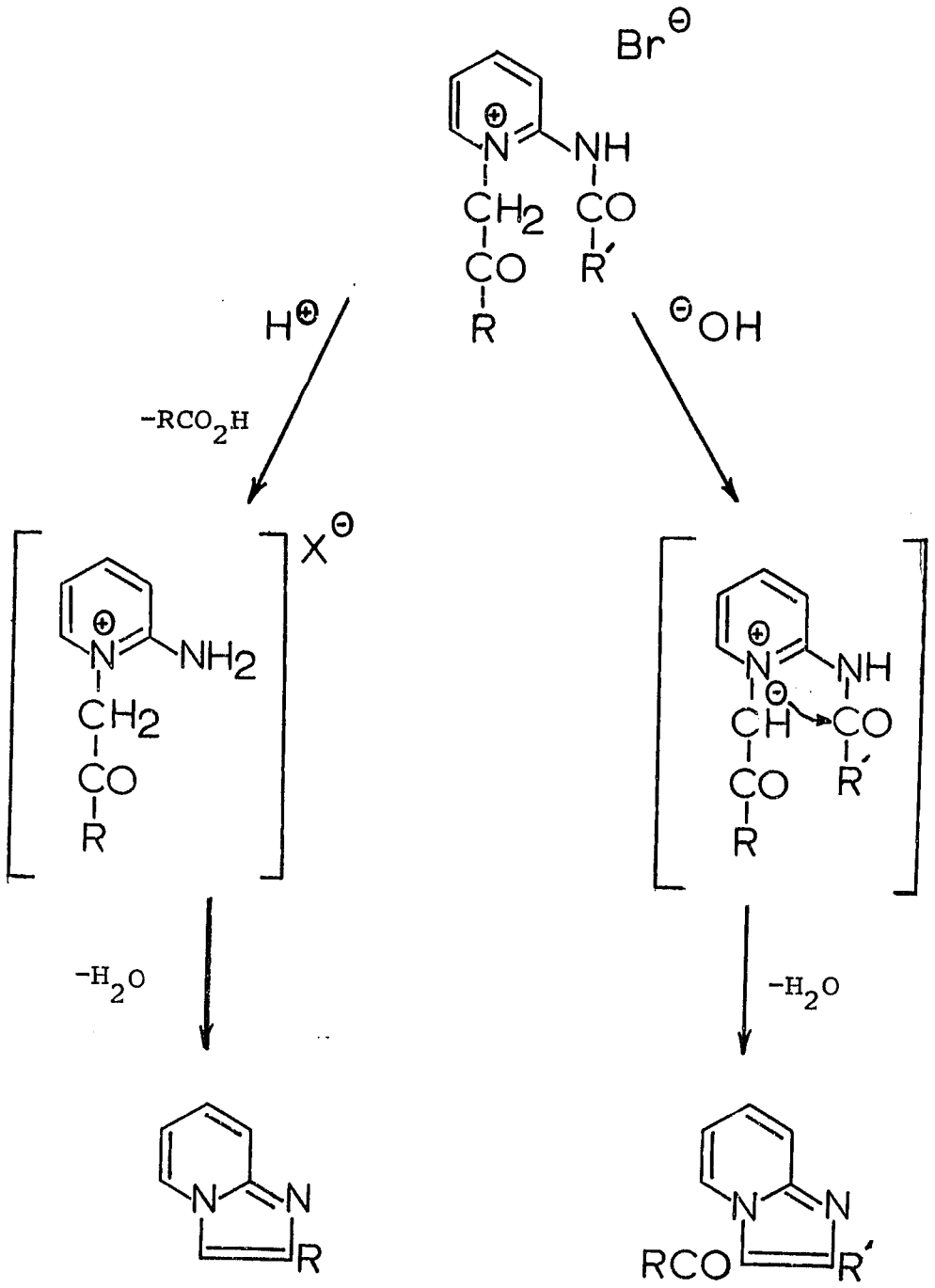
derivative of 2-aminopyridine decomposed to the free bse, which then reacted with ω-bromoacetophenone in the usual manner (as originally proposed by Tschitschibabin) to give 2-phenylimidazo[1,2-a]pyridine.

The use of bifunctional reagents, i.e. α-halocarbonyl compounds represents the most direct and simple approach to the imidazo[1,2-a]pyridine system. From the viewpoint of practical usefulness, this approach is limited by the availability of a specific α-halocarbonyl compound, which must contain <u>both</u> groups destined to become the 2- and 3-position substituents of the imidazo[1,2-a]pyridine.

To circumvent this limitation, a third scheme "C" has been devised by Schilling, Kröhnke and Kickhöfen.[10] It consists of the acylation of 2-aminopyridine, which is followed by the quaternization of the amide with a halide of the type $X-CH_2-CO-R$ to give a stable pyridinium salt which can be isolated and purified.



The cyclization of the above pyridinium salt can be accomplished with either acid or base catalysis:



R' = H, CH_3, C_6H_5

R = CH_3, C_6H_5

The acid catalyzed condensation leads to a product which could also be obtained directly from the halide and 2-aminopyridine. Kröhnke's synthesis, however, offers certain preparative advantages: the amides, as well as the pyridinium salts can be isolated and purified* Furthermore, the acid catalyzed cyclization is a "clean" reaction, giving no discoloured by-products and high yields of 2-substituted imidazo-[1,2-a]pyridines. The original acyl group of the amide bond is, however, lost and does not form a substituent in the heterocycle.

Treatment of the same pyridinium salt with base under mild conditions (2N $K_2CO_3/0^o$), results in another type of cyclization. The methylene group readily loses a proton to give a carbanion which is highly stabilized by the adjacent carbonyl group and the pyridine nitrogen atom (carrying a positive charge). This carbanion then attacks the amide carbonyl group and the (intramolecular) cyclization is then brought to completion by the elimination of water and aromatization of the five membered ring. Both side chains, attached to the two nitrogen atoms of the pyridinium salt are preserved and become the 2- and 3-position substituents of the imidazo[1,2-a]pyridine. 3-Acylimidazo[1,2-a]pyridines can thus be obtained directly without any need of further acylation of the 3-position.

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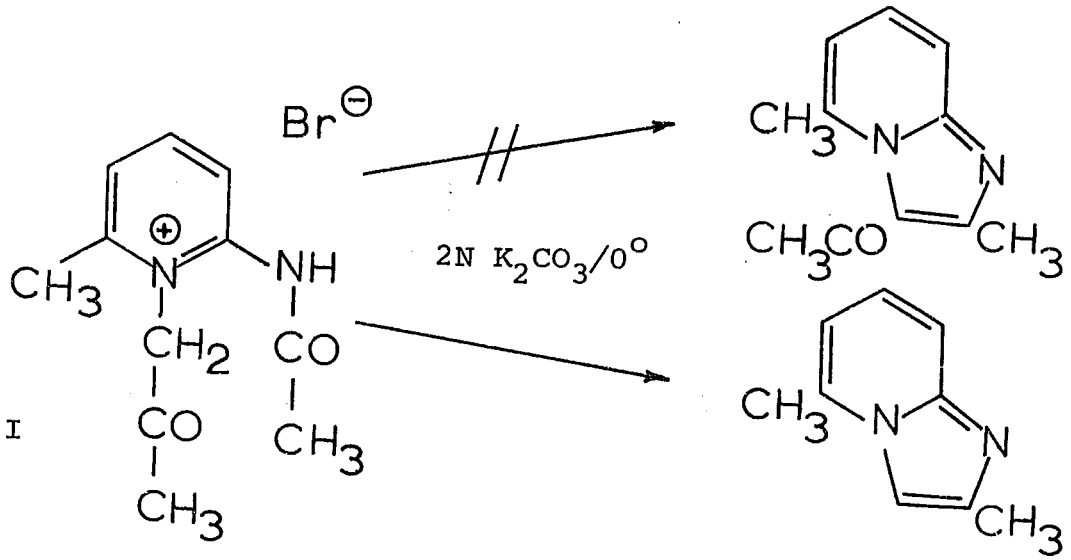
*In most of the direct syntheses, the intermediate pyridinium salts are not isolated.

In Kröhnke's synthesis, via modification "C", no attempt was made to prepare imidazo[1,2-a]pyridines with substituents in the six-membered ring. It was of interest to apply this synthetic route to 2-acylamidopyridine also possessing other substituent on the pyridine ring and to explore any possibilities of preparation of imidazo[1,2-a]pyridines with 2- and 3-position substituents other than -H, $-CH_3$ and $-C_6H_5$.

DISCUSSION

In an attempt to prepare 3-acetyl-2,5-dimethyl-imidazo[1,2-a]pyridine (III) from 2-acetamido-1-acetonyl-6-methylpyridinium hydrobromide (I), the latter was dissolved in water and an excess of a 2N potassium carbonate solution was added to it at 0°. The reaction proceeded rather slowly and, after several hours, an oil began to separate from the aqueous phase. Upon isolation and purification of the product, it was identified as 2,5-dimethylimidazo[1,2-a]-pyridine (II). This was not the expected product. In view of the types of products which were obtained by Kröhnke[10] by alkaline treatment of 2-acetamido-1-acetonylpyridinium salts, the reaction described above led actually to an "anomalous" cyclization, yielding a product which one would normally expect to be formed at elevated temperatures in an acidic medium. This unexpected result demanded further



I

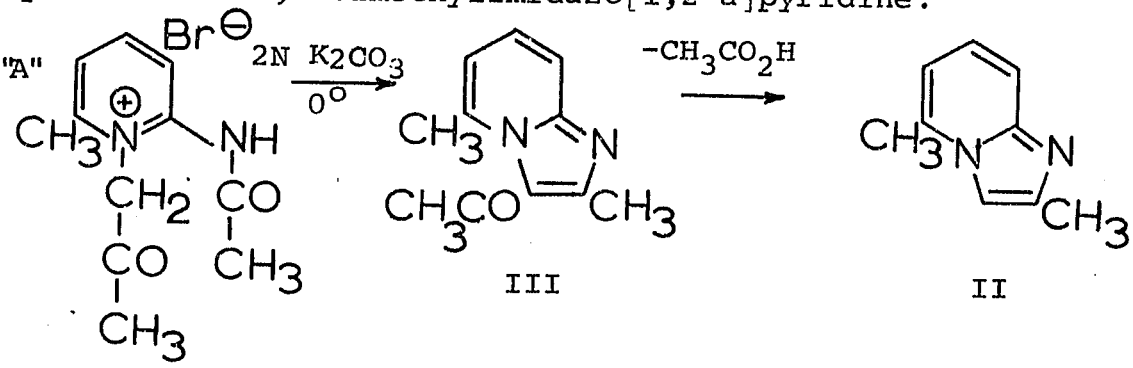
III

II

investigation and thus one of the objectives of the present work became the elucidation of the mechanism of cyclizations leading to the imidazo[1,2-a]pyridines, and, in particular, to account for the causes of the anomaly described above.

The formation of 2,5-dimethylimidazo[1,2-a]pyridine can proceed along two alternative routes. Considering one of these paths, 1-acetonyl-2-acetamido-6-methylpyridinium hydrobromide is at first transformed into 3-acetyl-2,5-dimethylimidazo[1,2-a]pyridine, which is subsequently deacetylated into 2,5-dimethylimidazo[1,2-a]pyridine.

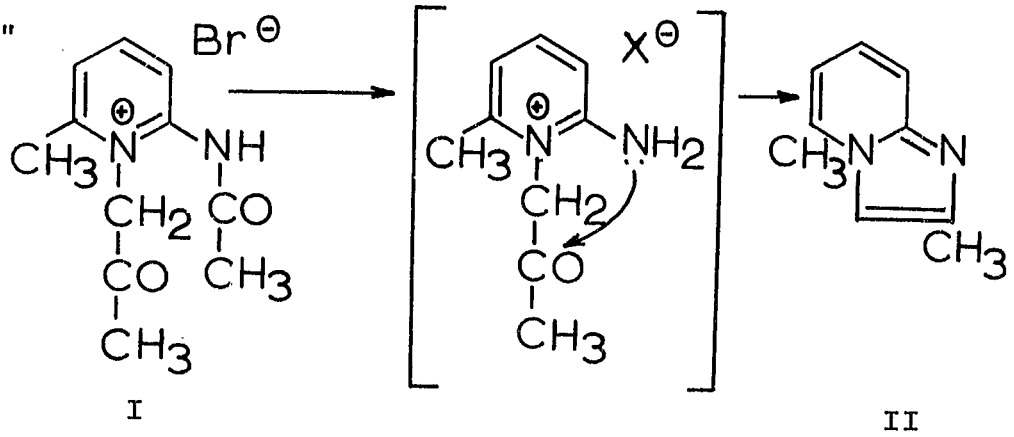
Route "A"



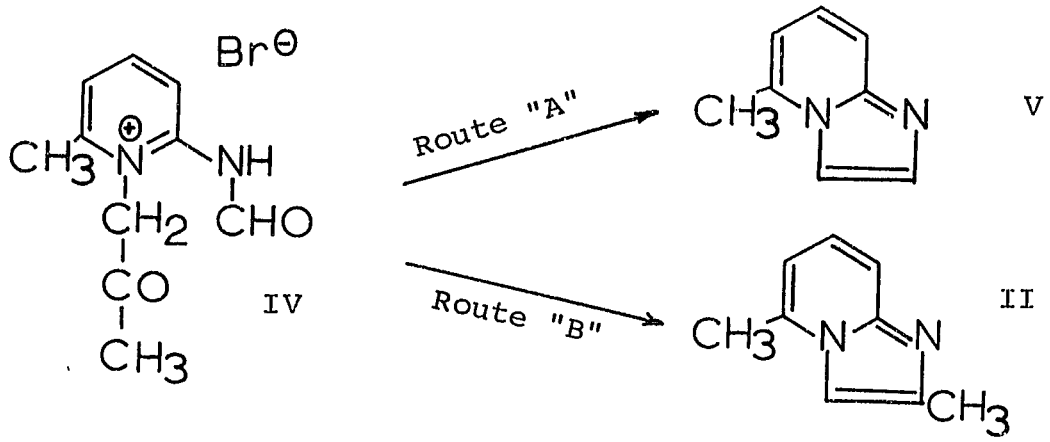
Although there exists some indirect evidence contradicting the deacetylation in the above step in the alkaline medium, there is some possibility that loss of the acetyl group may occur before the aromatization of the five membered ring.[11]

Another route to the 2,5-dimethylimidazo[1,2-a]-pyridine would involve the hydrolysis of the amide bond in 2-acetamido-1-acetonyl-6-methylpyridinium hydrobromide followed by the condensation of the free amino group with the acetonyl carbonyl group:

Route "B"

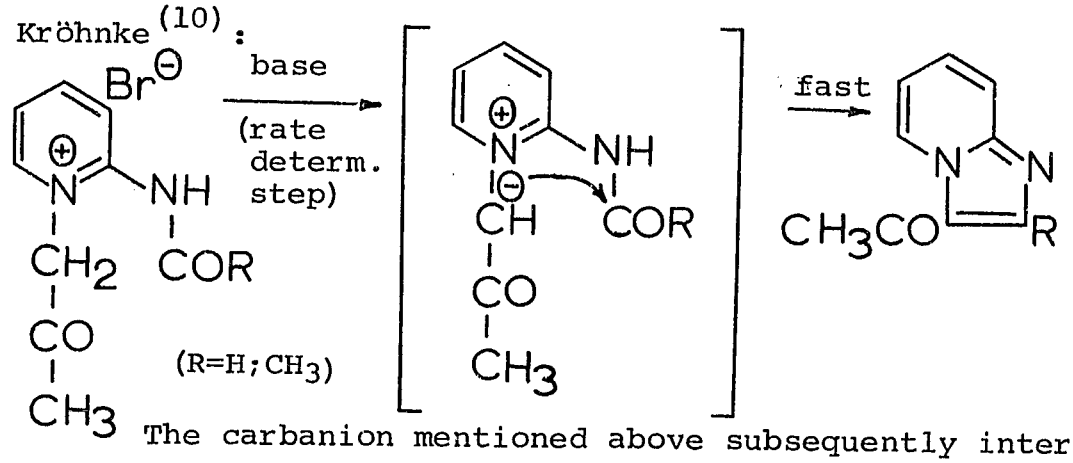


It is relatively easy to distinguish between the two routes, A and B, if the alkaline treatment at 0° is applied to the 1-acetonyl-2-formamido-6-methylpyridinium hydrobromide (IV). Route "A" should lead to the 5-methyl-imidazo[1,2-a]pyridine (V), whereas 2,5-dimethylimidazo-[1,2-a]pyridine (II) would be obtained along the path "B":



When the actual experiment was performed, 1-acetonyl-2-formamidopyridinium hydrobromide on treatment with 2N K_2CO_3 at room temperature gave a good yield of 2,5-dimethylimidazo-[1,2-a]pyridine. Thus path "B" was established as the one along which the salt changes into one of the final products. Hence, it became evident that Kröhnke's condensation of

1-acetonyl-2-acetylaminopyridinium salts can give two types of products even in an alkaline reaction medium, and the mechanism proposed by Kröhnke had to be supplemented to accommodate the new observations. The base-catalyzed cyclization reaction has to be visualized as follows: 1-acetonyl-2-acylamidopyridinium salt (without additional ring substituents) in aqueous solution reacts with a base which abstracts a proton from the methylene group, highly activated by an adjacent carbonyl group and a positively (quaternary) charged nitrogen atom. This is the rate determining step of the "normal" cyclization as described by Kröhnke[10]:



The carbanion mentioned above subsequently interacts also very rapidly with the carbonyl group of the amide and the ringclosure reaction is completed in a few minutes.

In another case, however, such as in the alkaline treatment of 1-acetonyl-2-acylamido-6-methylpyridinium hydrobromide, the rate of formation or the reactivity* of

---

* Subject of discussion in following pages.

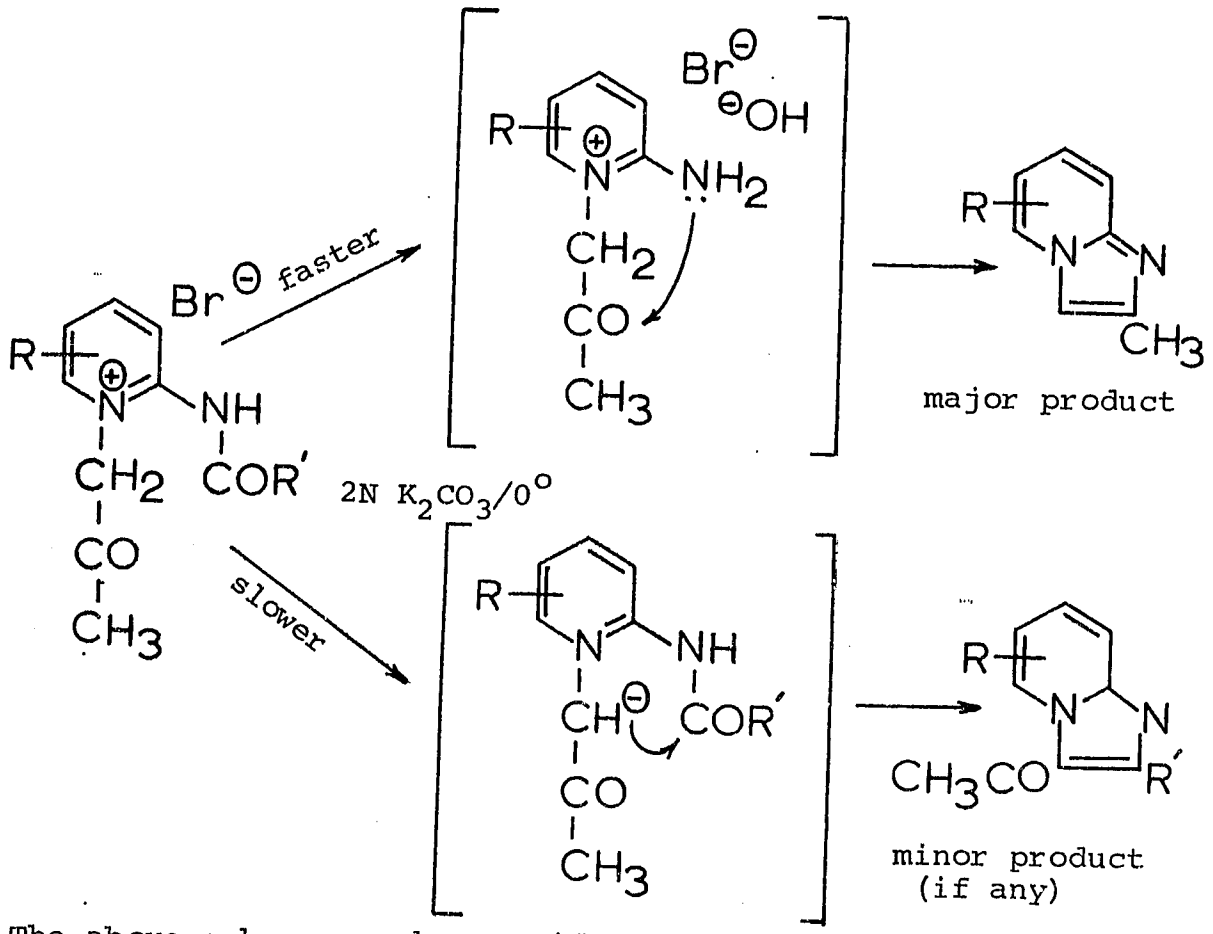
the carbanion is reduced so drastically that the relatively slow base-catalyzed hydrolysis of the amide bond proceeds at a higher rate than the attack of the carbanion.

Apart from the low reactivity at the carbanion centre, the hydrolysis of an amide bond under mild conditions is rather unexpected; usually the base hydrolysis of an amide requires rather drastic conditions, such as refluxing with a strong base. Two factors, however, have to be considered which accelerate the hydrolysis of the amide bond of the pyridinium salts in question:

a. Conjugation of the amide linkage with the pyridinium cation, and,

b. a strong electron withdrawing effect of the positive charge distributed over the pyridine ring.

Hence, even relatively mild reaction conditions are sufficient to hydrolyse the amide.[12] The free amine, which is so produced now determines the direction of the cyclization. Thus the distribution of the final cyclized products will depend on the outcome of the competition between the two reaction rates involved, or more precisely on the rate-determining steps of these rates, namely the reactivity of the carbanion and the rate of amide hydrolysis:



The above scheme can be considered to be a general one. Which of the initial steps will be the more rapid depends largely on the nature of the substituent R. Thus, indirectly, the substituent will determine the ratio of the two final products.

To sum up, Kröhnke observed the exclusive formation of 3-acetylimidazo[1,2-a]pyridines when the pyridine ring was carrying no other substituents (R = H, faster carbanion attack), while the introduction of an α-methyl group (R = CH_3) favored to a large extent the more rapid hydrolysis of the amide bond.

The problem can now be restated in the following way: Why does the methyl group on the α-position of the

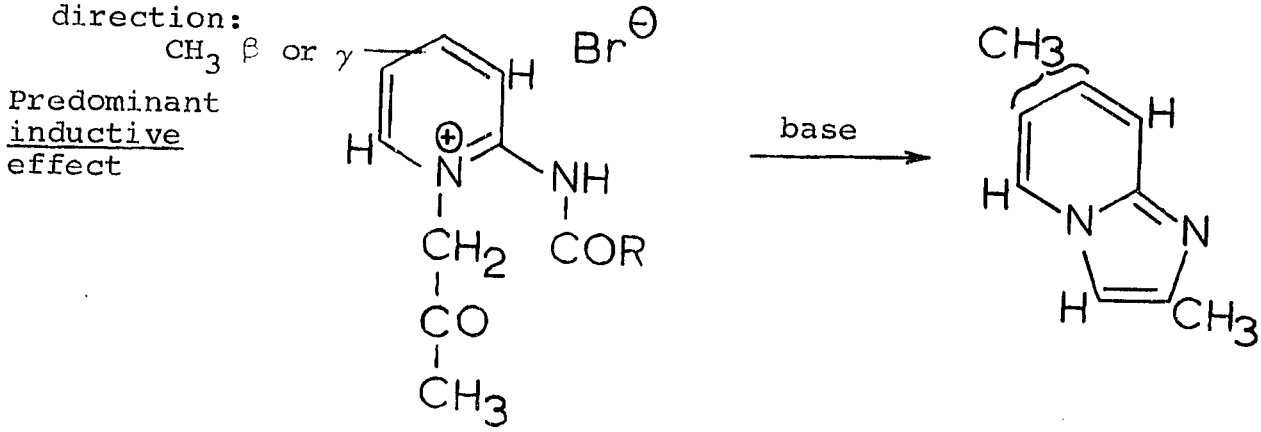
pyridine ring exert such an enormous influence on the reactivity or rate of formation of the carbanion?

In general terms, the reason for this can be found in both the steric and inductive effects of the methyl group. The inductive effect of the α-methyl group would tend to diminish the positive charge of the pyridine nitrogen atom and thereby decrease the stability of the carbanion. Its steric effect could be again visualized as a certain hindrance, influencing the formation of the carbanion by the base. One might, a priori, assume that both the inductive and steric effects are operative in the scheme discussed above.

Attention was now focussed on an effort to distinguish between the inductive and steric effects of the α-methyl group. A test was therefore required to determine which of the two effects is the dominating one or to what extent each one contributes to a possible combined effect. At first, it seemed that such a test might consist of replacing the α-methyl group by another substituent of equal steric requirements (van der Waals radius), but possessing an opposite, electron withdrawing, inductive effect. A substitutent which could satisfy this requirement would be the trifluoromethyl group. Since the synthesis of 1-acetonyl-2-acetylamido-6-trifluoromethylpyridinium hydrobromide would have required, as a

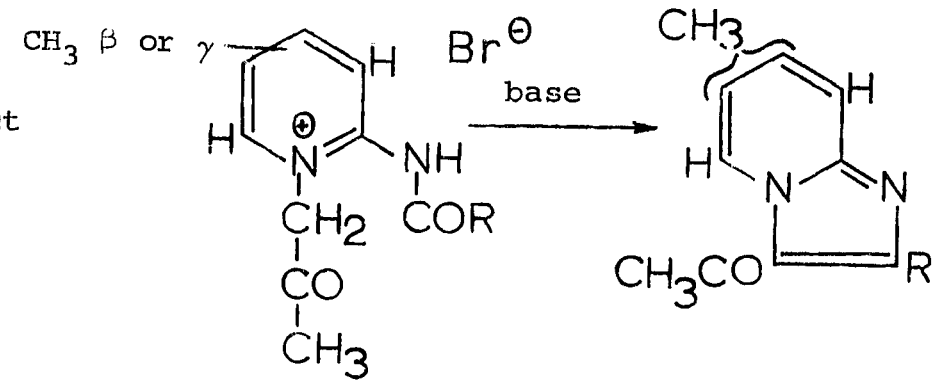
prerequisite, the preparation of 2-amino-6-trifluoromethyl-pyridine, not yet described in the literature, this approach was abandoned. In addition, an uncertainty would have remained concerning the outcome of the quaternisation reaction (with bromo acetone) of the pyridine ring, carrying a strong electron withdrawing group.[13]

A more convenient approach to the problem was found in the placement of the methyl group on the pyridine nucleus in the β- and γ-positions. If the effect is a purely inductive one, the methyl group in the β- or γ-positions may cause the cyclization reaction to proceed in the "anomalous" direction:



If, on the other hand, the effect of the α-methyl group is mainly a steric one, its removal from the α-position to the β- or γ-positions should result in an elimination of any hindrance from the region of the N-methylene group and the direction of the cyclization should return to the "normal" pathway, as observed by Kröhnke:

Predominant
steric effect



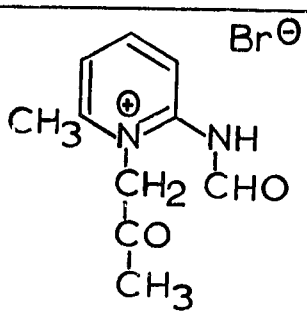
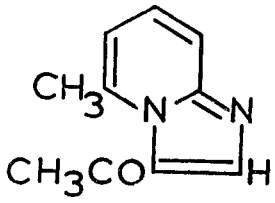
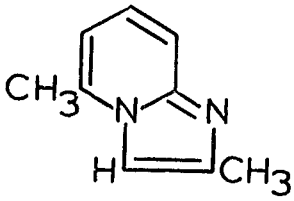
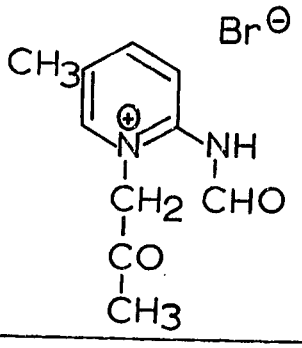
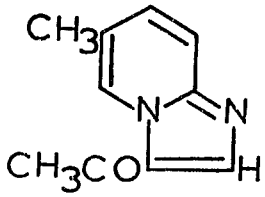
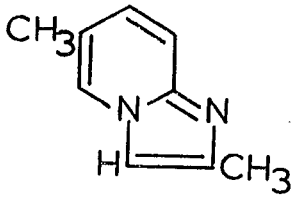
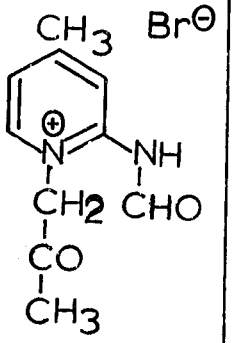
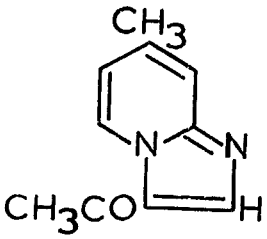
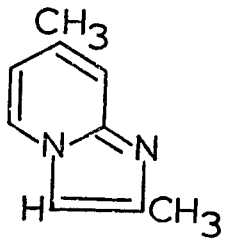
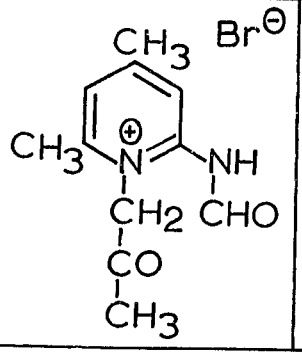
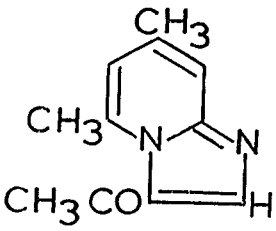
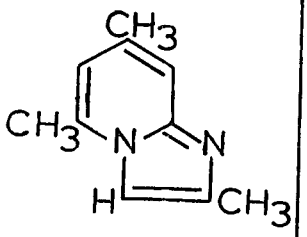
Any minor products might be expected to indicate the measure of that effect which is operative to a lesser degree and is kinetically less favourable. In order to accentuate the base-catalyzed hydrolysis of the amide bond and to make it more competitive with the reactivity of the carbanion, the acyl group in the pyridinium salts was a formyl group (formamides are known to hydrolyze more rapidly than acetamides[14]).

The test described above was performed with four 1-acetonyl-2-formamidopyridinium hydrobromides and the results are summarized in Table I. The analyses of the product mixtures were carried out by the integration of the n.m.r. spectra and are expressed in mole ratios of both reaction products.

As can be seen from Table I, the electron donating effect of the methyl group on the pyridine ring can and does definitely influence the acidity of the N-methylene proton to an appreciable extent: when the methyl group is either in the β- or γ-positions, 25 per cent of the product is formed via the "anomalous" cyclization, while only traces of "anomalous" products are formed when the pyridine ring is

Table I

Products obtained by alkaline treatment (2N $K_2CO_3/0^o$) of ring substituted 1-acetonyl-2-formamidopyridinium hydrobromide.

Starting material	Products of normal cyclization	Products of anomalous cyclization	Remarks
	 18.5 %	 81.5 %	Reaction very slow (several hours).
	 73.7 %	 26.3 %	Reaction fast (complete in few minutes).
	 69 %	 31 %	Reaction fast (complete in few minutes).
	 10 %	 90 %	Reaction very slow (several hours).

free of methyl groups. This inductive effect, transmitted through the pyridine nitrogen atom, is equally large with the methyl groups either in the β- or the γ-positions.

When the methyl group is in the α-position, 75 per cent of the ring closure compounds are of the "anomalous" type. The addition of a second methyl group to the γ-position is capable of decreasing still further the reactivity (or rate of formation) of the carbanion and the competitive amide hydrolysis now occurs to the extent of 90 per cent. Thus it can be concluded that the inductive effect of the methyl group is operative, electron donating, and the effect of two methyl groups is cumulative as would normally be expected.

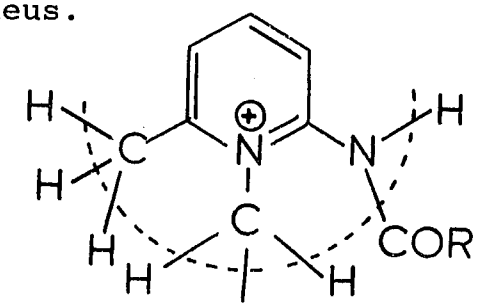
The contrast between the reaction path with a methyl group in the α-position and β- or γ-positions leaves no doubt that, of the two effects, the steric effect exerts the most profound influence on the course of the reaction.*

Having thus established the fact that a methyl group in the position α- to the pyridine nitrogen introduces mainly a steric factor into the course of the cyclization, there arises now the question concerning the exact nature of such a steric influence. This question becomes more

---

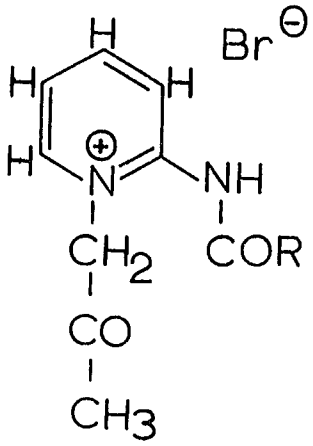
* It is customary to attribute small and gradual changes in reactivity to increasing or decreasing inductive effects of substituents; an abrupt change in reactivity is usually assigned to steric effects.

acute when one considers the fact that the pyridine ring is planar and all substituent atoms, including the N-methylene carbon atom are also located on the same plane as that of the pyridine nucleus.



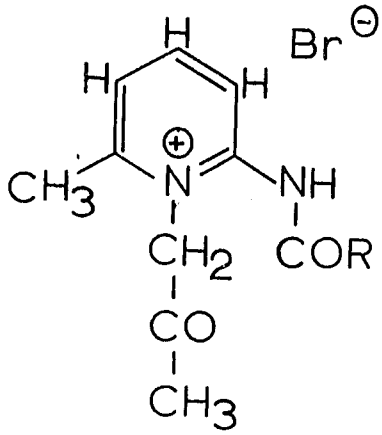
Hence, the approach of the base for the purpose of proton abstraction from the N-methylene group is not hindered (to any appreciable extent) if the base reacts along a direction perpendicular to the plane of the pyridine ring.

If one considers the following two salts (VI) and (VII)



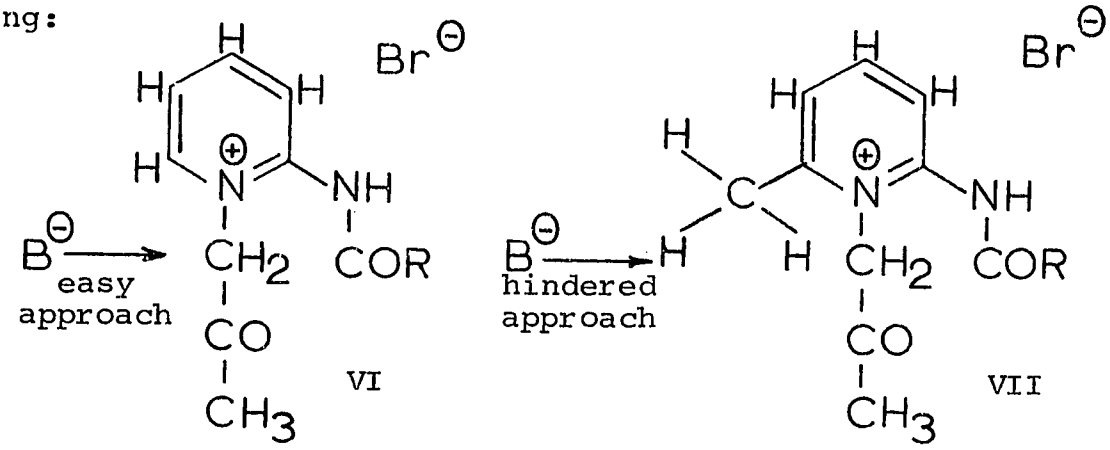
VI

and



VII

the approach of the base should be equally easy yet the results discussed above indicate that in salt (VII) the formation of the carbanion is considerably retarded and that the steric effect is mainly responsible for this with only a minor contribution from the inductive effect of the methyl group. Since it must be concluded that the steric bulk of the methyl group is capable of interfering with the reaction at the N-methylene carbon atom, a plausible explanation can be proposed in terms of a preferential approach of the base in the same plane as the pyridine ring:



If the base approaches in the plane of the ring towards salt (VI), the carbanion centre will be formed readily and the reaction will proceed towards 3-acetylimidazo[1,2-a]-pyridines. If, however, the base interacts with salt (VII), the reaction at the N-methylene group will be hindered and the competition of the amide bond hydrolysis will be favoured kinetically. The step of proton abstraction may

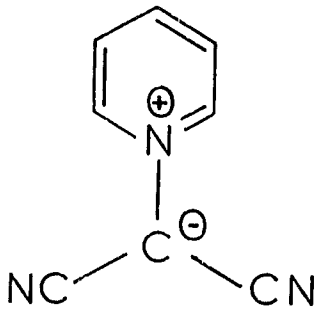
not even be a necessary prerequisite to initiate the attack of the carbanion if the base can induce, in this preferential direction of approach, sufficient electron density between the N-methylene carbon and the amide carbonyl group. Such a build up of electron density between the two centres may occur via electrostatic induction.

The steric effect of the α-methyl group can be interpreted also in terms of carbanion stability. It must be taken into consideration that the carbanion, formed from the N-methylene group derives its stability from both adjacent atoms:

a. from conjugation with the acetonyl carbonyl group with the enolate anion (as another resonance structure),

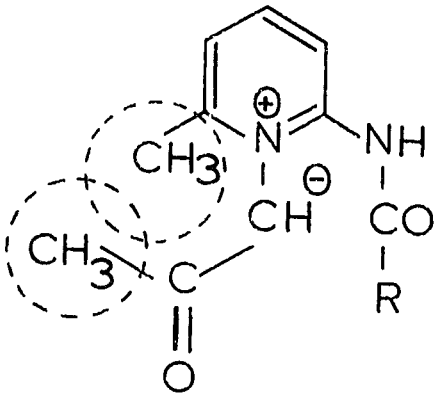
b. from the positive charge of the quaternary pyridine nitrogen atom, and,

c. from the coplanarity of the trigonal carbanion with the pyridine ring. This last stabilizing factor is based on the assumption of a trigonal structure (shape) of the carbanion and its coplanarity with the pyridine ring, as has been reported in the carbanion (VIII).[15]

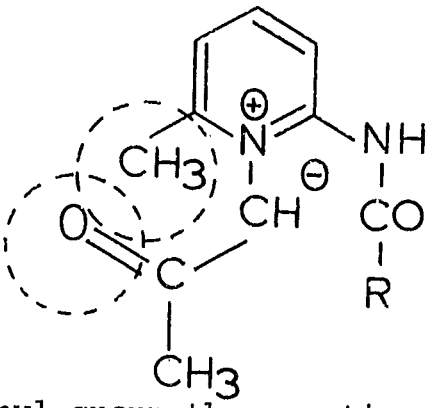


VIII

Assuming further, that the largest stabilizing effect on the carbanion is achieved by its coplanarity with the pyridine ring <u>and</u> the carbonyl group simultaneously, the whole acetonyl side chain must, of necessity, be fixed in a certain conformation, (see photograph - Fig. 1) in which all of its three atoms are located on one plane; this must also be the same plane as that of the pyridine ring. If a methyl group is now placed into a position α- to the pyridine nitrogen atom, the carbanion can become coplanar either with only the carbonyl group, or with only the pyridine ring, but not with both simultaneously:



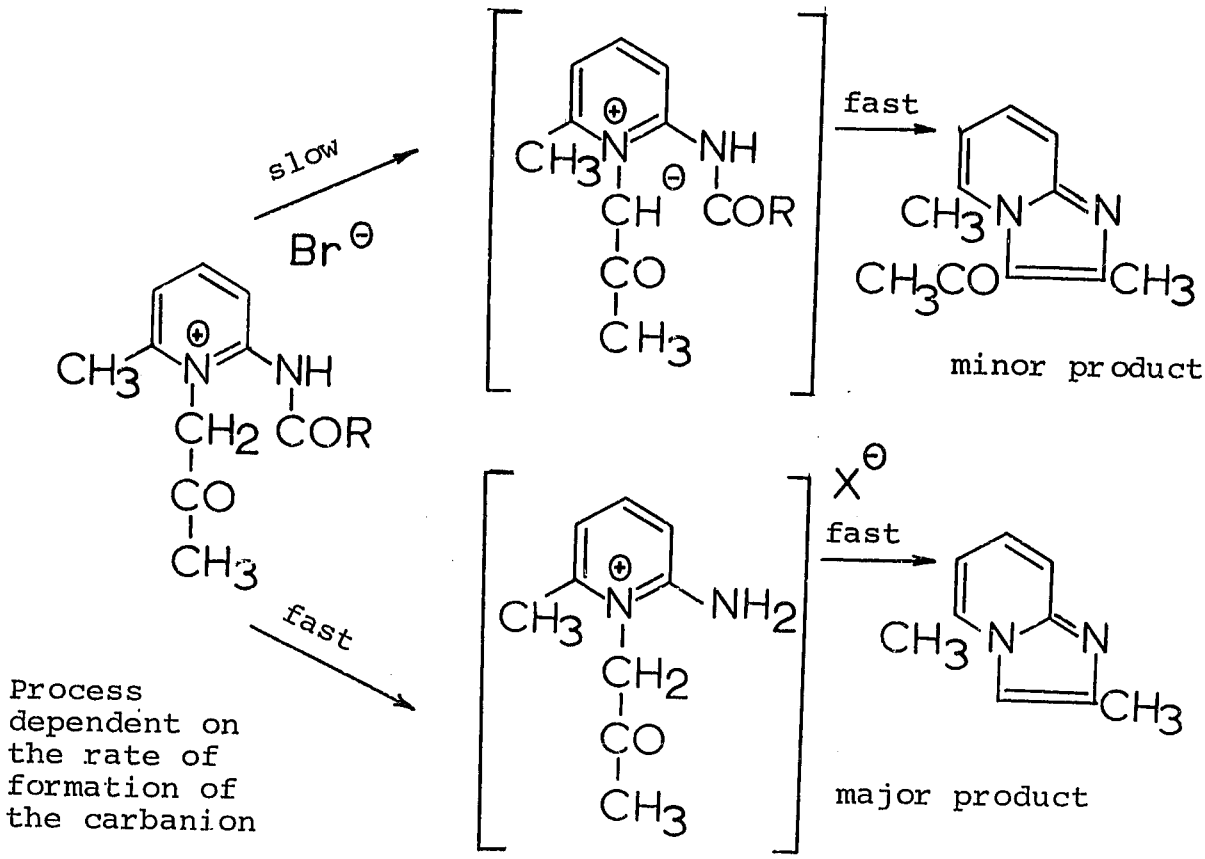
or



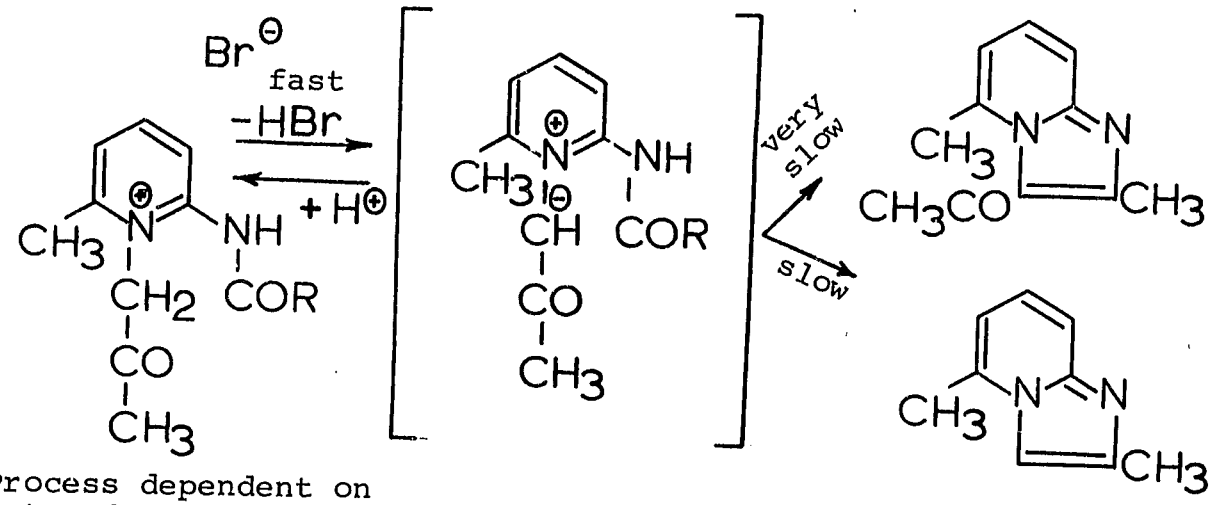
In the absence of the α-methyl group the negative charge of the carbanion is distributed over the two adjacent groups, the carbonyl group and the pyridinium cation; the carbanion becomes highly stabilized and the reaction proceeds rapidly towards the attack of the amide carbonyl group, while the amide bond hydrolysis is then too slow to affect the course of the reaction. However, should the carbanion

charge be spread over only one of the stabilizing centres, either over the carbonyl group or the pyridine ring, its stability will be diminished and the amide bond hydrolysis will become more competitive with the carbanion attack. The reactivity of the free amine (after hydrolysis) will then determine the direction of cyclization.

In the above discussion, an assumption has been made without any examination as to its validity: it was tacitly assumed that the rate of formation of a carbanion centre (at the N-methylene group) is the critical and rate determining step of the cyclization reactions. Such an assumption is often a reasonable one - carbanion is a very reactive species and once formed, it reacts rapidly with any substrate available to it, in particular with an intra-molecular substrate, as is the case in the cyclization reactions under discussion.[16] In other words, it was assumed that as soon as the carbanion is formed, it immediately reacts with the amide carbonyl group. This is, however, an oversimplification, which overlooks a possibility of a <u>rapid equilibrium</u> of proton abstraction and return at the N-methylene group, followed by a relatively <u>slow</u> carbanion attack on the amide carbonyl group. Thus, two possible routes can be formulated for the "anomalous" cyclization: one, in which the carbanion is formed rather slowly, but its attack, as well as all subsequent steps leading to the final products are fast;



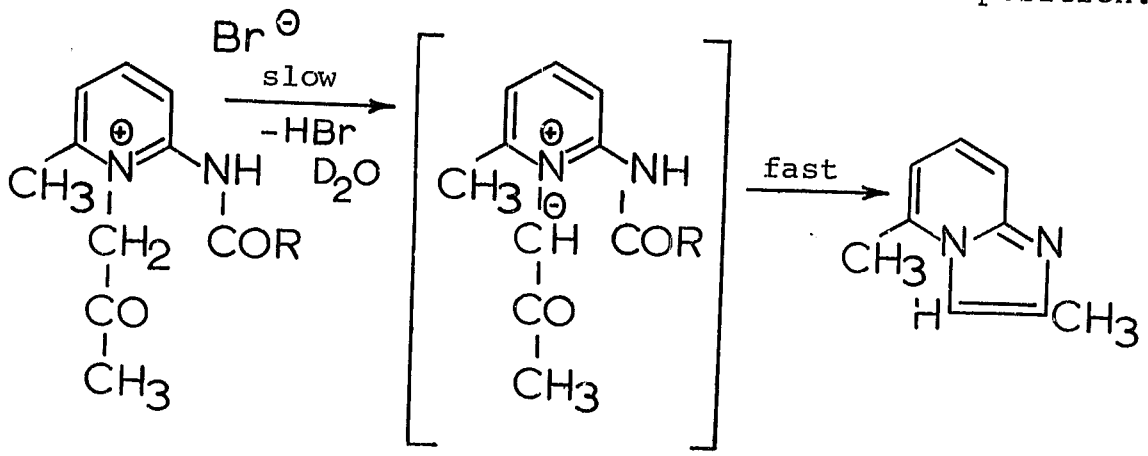
two, in which the carbanion is formed rapidly, it interacts, however, also rapidly with the solvent and the N-methylene group is restored in an equilibrium process. If now the rate of attack of the carbanion is slower than the amide bond hydrolysis (which could indeed be a slow process in comparison), then the -NH-CO- bond rupture takes place preferentially and the "anomalous" cyclization is observed:



Process dependent on rate of carbanion attack

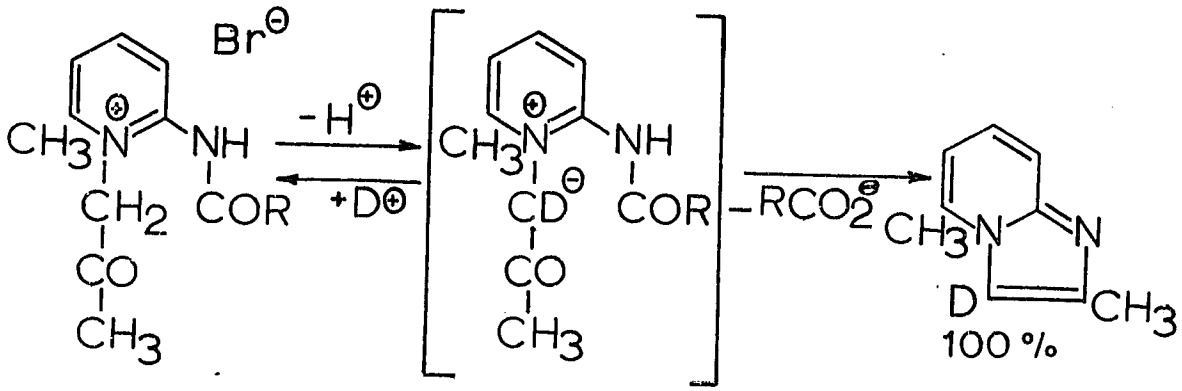
There is, fortunately, a possibility of distinguishing between the two routes mentioned above.

In the route involving a slow carbanion formation, followed by a fast attack, it is necessary to remove merely one proton from the N-methylene group (in order to proceed rapidly to final products). If now the reaction is carried out in deuterium oxide, the imidazo[1,2-a]pyridine will have very little, if any, deuterium incorporated at its 3-position:



VII IX

If, on the other hand, the attack of the carbanion is the rate determining step of the reaction but is preceded by a fast equilibrium of proton abstraction and return, a complete exchange of both N-methylene protons will take place in a deuterated solvent. Consequently, one would expect a high - if not complete - incorporation of deuterium into the imidazo[1,2-a]pyridine:



When the actual experiment was performed and 2-acetamido-1-acetonyl-6-methylpyridinium hydrobromide was treated with potassium carbonate (2N) in deuterium oxide, a full (~ 100 per cent) incorporation of deuterium was observed in the 3-position of the 2,6-dimethylimidazo[1,2-a]-pyridine. This result suggests therefore the latter route is the one actually followed by the salt in its progress towards ring closed products.

In view of the evidence discussed so far, the overall mechanism of imidazo[1,2-a]pyridine formation can be

summarized as follows: The treatment of 1-acetonyl-2-acylaminopyridinium salts with a base results in two types of reactions. Which of these routes a certain salt will follow depends largely on the substituent, or lack of it, at the position α- to the pyridine nitrogen atom. If no substituent is present, the base rapidly abstracts a proton from the N-methylene group and the carbanion rapidly attacks the amide carbonyl group; all subsequent steps are also very rapid. The observation that the reaction is complete within a few minutes corroborates the above statements. If, however, a methyl group is placed α- to the pyridine nitrogen, the interaction of the pyridinium salt with the base results, at first, in a rapid exchange of both N-methylene protons with the solvent. The carbanion, however, <u>does not</u> attack the amide carbonyl group at any rapid rate. In fact, its rate of attack is so diminished that the amide bond hydrolysis can now proceed at an appreciably higher rate and subsequently the free 2-amino group begins to interact with the acetonyl carbonyl group to give ring closed products.

Finally, there now remains the problem of the unexpected low reactivity of the carbanion (at the N-methylene group) caused by the presence of a methyl group in the α-position of the pyridine ring. The treatment of 1-acetonyl-2-acylamido-6-methylpyridinium hydrobromides with base does not yield coloured solutions, while other 1-acetonylpyridinium

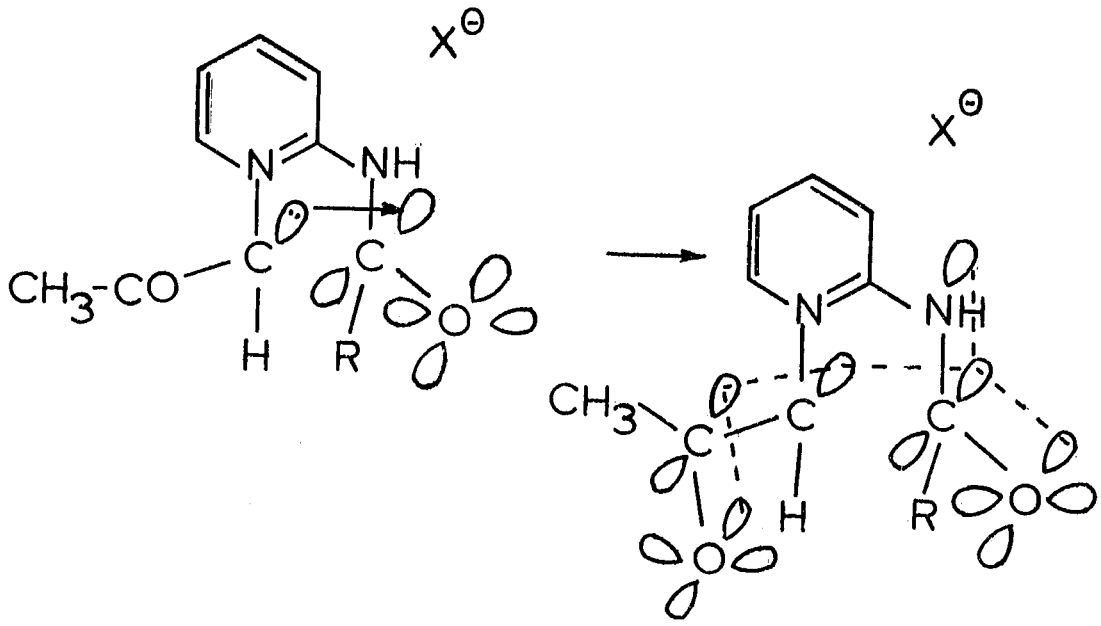
salts, which cannot proceed towards an intramolecular cyclization-condensation, normally produce (on treatment with base) yellow enol-betaines.[17]
Thus, it seems that the α-methyl group introduces some orientation factors into the structure (shape) of the long lived carbanion intermediate IX ; a highly probable structural feature of the carbanion-enol betaine could consist of an enolate anion, whose plane would be perpendicular to the plane of the pyridine ring, as shown in Fig. 2. The lack of any colour of such an enol betaine could be attributed to its insufficient conjugation with the pyridine ring. It might be deduced that such a configuration can and does cause the carbanion to be very unreactive toward its intramolecular substrate, the amide carbonyl group, but be normally reactive towards the solvent. It is obvious that the stability of the carbanion is enhanced by its coplanarity with the pyridine ring and, if present, the α-methyl group tends to twist the acetonyl group out of such a conformation, thus adversely affecting the stability of the N-methylene carbanion. If the rate of attack of the carbanion is proportional to its stability, the results observed can be accounted for by a lifetime-stability relationship.

It is, however, also possible that a carbanion, coplanar with the pyridine ring, is not only more stable

in terms of a longer lifetime but also in a more preferential orientation (conformation) to react with the amide carbonyl group. A carbanion, which has been forced to take up another conformation (due to steric hindrance of the methyl group) may not only be less stable but also less suitably oriented to attack the substrate.

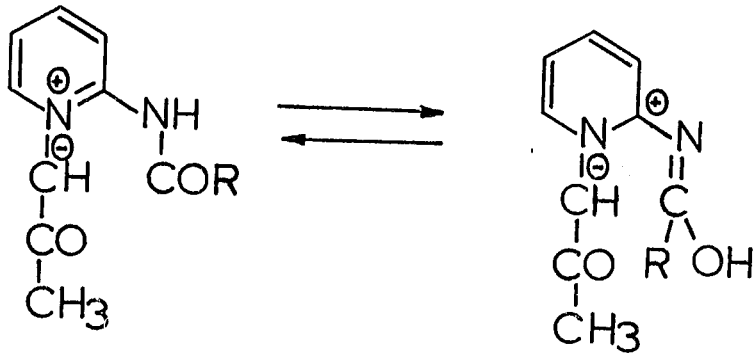
Unlike the carbonium ions which have been better explored, the structure and mode of reaction of carbanions are generally considered to be somewhat less understood and no appropriate analogies to the above "anomalous" carbanion reactivity have been reported. At present, one can offer only speculations concerning the relationship between orientation and reactivity of the carbanion at hand. Two such alternatives can be considered. In one, the carbanion (coplanar with the pyridine ring <u>and</u> the acetonyl-carbonyl group) extends its charge into the electron depleted* p-orbital of the amide carbonyl group, forming, at first, a π-bond in a manner analogous to the overlap of electrodensity of two p-orbitals (forming a π-bond). Such an extension of charge will occur readily in view of the fact that the newly formed π-bond will be (after the reaction) in conjugation with at least four more atoms, namely the oxygen and nitrogen atoms of the amide bond. The conjugation could extend further to the acetonyl carbonyl group, not counting the pyridine ring.

* It should be remembered that unlike other amide linkages, the amide bond in the compounds under discussion is extremely susceptible to attack by nucleophiles, e.g. bases. (See page 17)

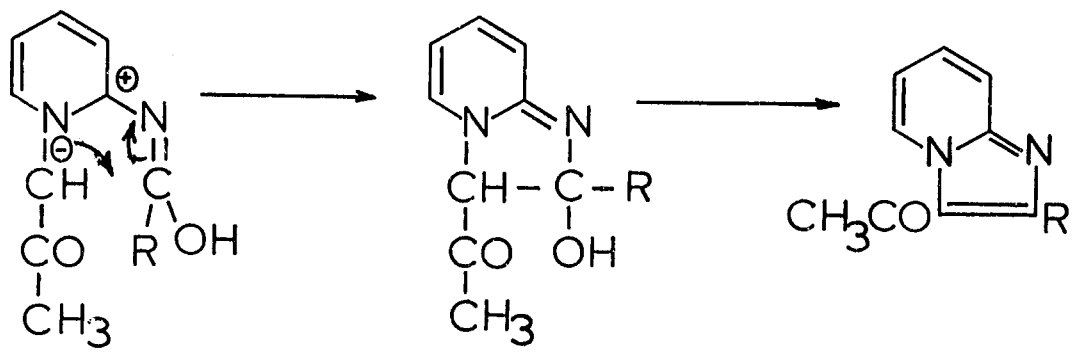


If the acetonyl group is forced to take up another conformation (due to steric hindrance) then the carbanion, even if sufficiently stable, will not be properly "lined up" for a rapid expansion of its charge towards the amide carbonyl group.

The other alternative suggests itself in the consideration of one of the tautomeric structures of the carbanion-enol betaine:



It can readily be seen that a 1,3-dipole is at hand, an azomethine ylide,[18] with one of the bonds to the dipolarophile, the amide group, already formed; further reaction leads to the intermediate carbinol, which, on dehydration, gives the final product:



Although the above carbanion might be sufficiently stable to react as a 1,3-dipole, insufficient data are available, at present, to classify an amide bond as dipolarophile. A weakness of this alternative, however, is the fact that insufficient information is available also about the steric requirements of the two reactants in a 1,3-dipolar cycloaddition. Consequently, the difficulty of interpreting the difference of reactivity of hindered and unhindered centres of negative charge would remain and therefore the former alternative, at present, seems to be the more satisfactory one.

The mechanistic studies described previously revealed certain limitations of Kröhnke's syntheses of imidazo[1,2-a]-pyridines. It became apparent that substituent effects cannot

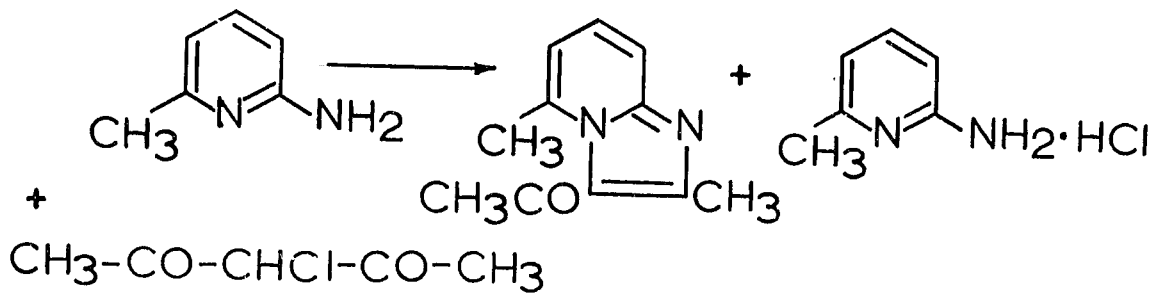
be neglected in the alkaline condensation reactions of 1-acetonyl-2-acylaminopyridinium salts. Further efforts were therefore directed toward the circumvention of difficulties, the synthesis of 3-acylimidazo[1,2-a]pyridines in better yields and, in general, towards the introduction of other substituents into the five-membered ring.

Cyclization of 2-acetamido-1-acetonyl-6-methylpyridinium hydrobromide into 3-acetyl-2,5-dimethylimidazo[1,2-a]pyridine with sodium bicarbonate solution.

As the original synthesis was aimed at the preparation of 3-acetyl-2,5-dimethylimidazo[1,2-a]pyridine and in view of the poor yields obtained under Kröhnke's reaction conditions, a modification of the alkaline condensation was devised. Since the 2N potassium carbonate solution was found to be capable of hydrolyzing the amide bond of 1-acetonyl-2-acylamidopyridinium salts more rapidly than it was possible for the carbanion to react, the obvious correction of such a situation appeared to be in the use of a basic medium of reduced hydrolytic capability, yet, not totally inhibiting the formation of a carbanion. A saturated solution of sodium bicarbonate was chosen as the reaction medium for the cyclization of 2-acetamido-1-acetonyl-6-methylpyridinium hydrobromide and a yield of 53 per cent of 3-acetyl-2,5-dimethylimidazo-[1,2-a]pyridine was obtained. This reaction is reminiscent of the Tschitschibabin synthesis in the pyrrocoline series[19],

where, it seems, sodium bicarbonate provides the optimal yields of conversion of 1-acetonyl-α-picolinium salts into cyclized products.

The same product, 3-acetyl-2,5-dimethylimidazo-[1,2-a]pyridine can be obtained also directly from 2-amino-6-methylpyridine and 3-chloroacetylacetone in moderate yield:



The excess of amine acts as a proton abstractor and the intermediate salt, which is formed by the quaternisation of the base with the halide is converted in the same reaction mixture to the final product. The reaction is carried out at room temperature and is very slow, requiring several weeks for completion.

Although the synthetic objective was achieved in the preparation of 2-acetyl-2,5-dimethylimidazo[1,2-a]pyridine, the use of sodium bicarbonate in the cyclization of 1-acetonyl-2-formamide-6-methylpyridinium hydrobromide resulted in only a moderate yield (3 per cent) of the desired compound, 3-acetyl-5-methylimidazo[1,2-a]pyridine. Thus, the use of a less basic medium (pH ~ 8 sat. $NaHCO_3$ solution) does not substantially

alter the competition between the "anomalous" and the "normal" cyclization. The yields of products formed via the normal cyclization are merely improved. Thus Kröhnke's synthesis has its limitations in the preparation of imidazo[1,2-a]-pyridine with electron donating substituents in the six-membered ring, particularly when substituents in the 2-position are not desired.

The same situation applies also to the reaction of 1-acetonyl-4,6-dimethyl-2-formamidopyridinium hydrobromide in a sodium bicarbonate solution: the desired 3-acetyl-5,7-dimethylimidazo[1,2-a]pyridine was obtained in only 19.3 per cent yield; the other ring closure product was 2,5,7-trimethylimidazo-[1,2-a]pyridine*, obtained via "anomalous" cyclization. It seems probable that with a more rigorous control of the basicity of the reaction mixture (i.e. by means of buffers) and of temperature, the yield of the desired 3-acetyl compounds could be improved.

Attempts to synthesize imidazo[1,2-a]pyridines with various substituents.

Following the assessment of substituent effects in Kröhnke's syntheses starting from 1-acetonyl-2-acylaminopyridinium salts, synthetic efforts were directed towards

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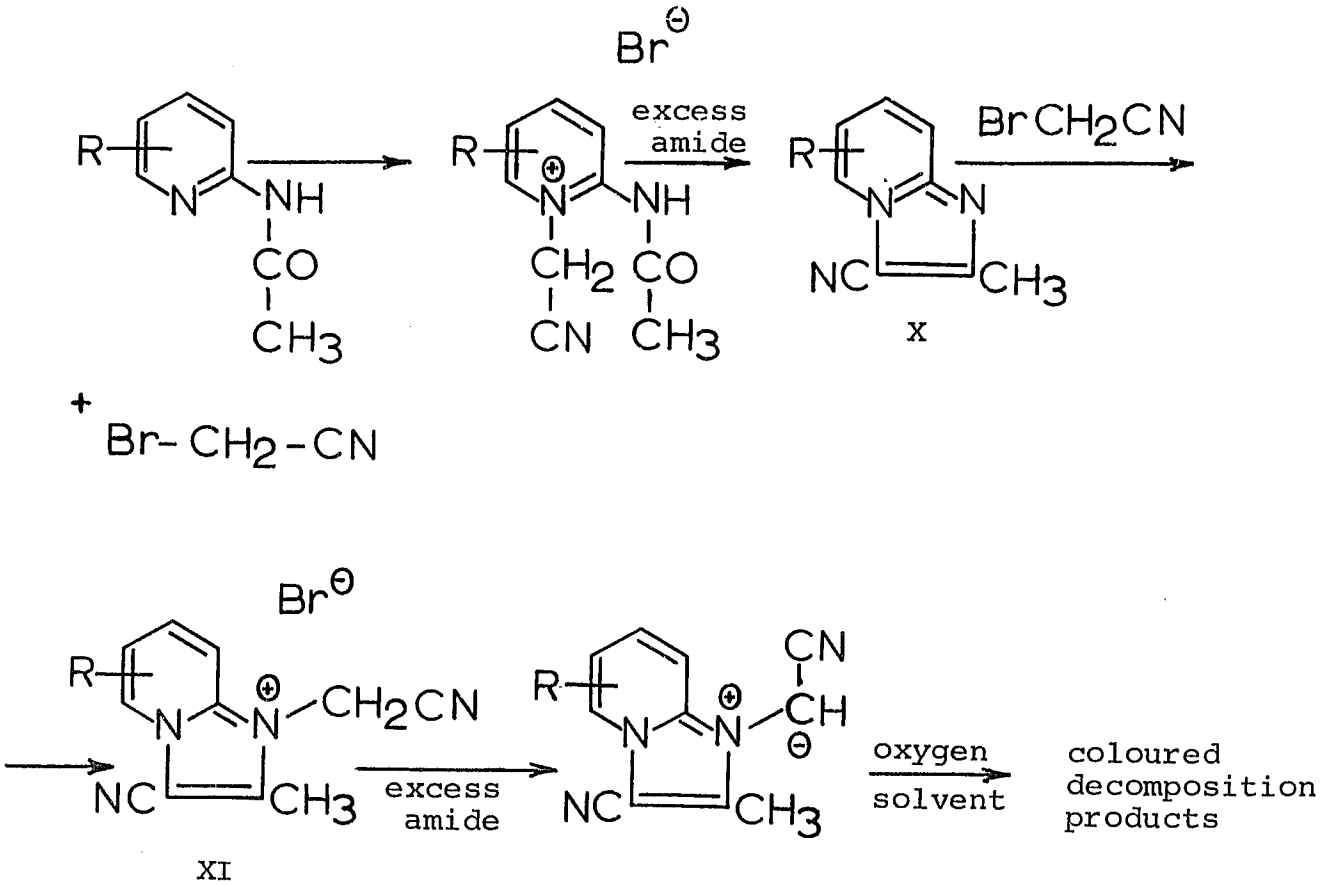
*The "anomalous" products, if desired, could be prepared in excellent yield and purity by the acid catalyzed condensation of the precursor salts.

the introduction of a variety of substituents into the imidazo[1,2-a]pyridine ring. In particular, it seemed desirable to replace the N-acetonyl group by other suitable groups, capable of producing a sufficiently stable carbanion centre adjacent to the pyridine nitrogen atom. To achieve a high degree of stabilization of the future carbanion only a certain type of halide was considered appropriate for the quaternisation of the 2-acylaminopyridines. These were halides of the type $X-CH_2-R$, where R would be a strongly electron withdrawing group. For one series of experiments, the nitrile group was chosen as a suitable substituent R. When 2-acetamidopyridine was treated with chloroacetonitrile under the conditions normally used for quaternisation of pyridines, no salt was precipitated from the solution. Upon evaporation of the solvent and chloroacetonitrile, the acetamidopyridine was recovered unreacted. Apparently the chlorine atom constitutes a poor leaving group in the quaternisation - S_N2 reaction, the pyridine nitrogen atom being an insufficiently reactive nucleophile. Since bromine is known to be a better leaving anion, the quaternisation of 2-acylamidopyridines was attempted with bromoacetonitrile.[33] The reaction did not yield the desired pyridinium salt, but resulted in the precipitation from the solution of a dark coloured tar which could not be characterized. It is possible that a quaternary pyridinium salt was formed as an intermediate,

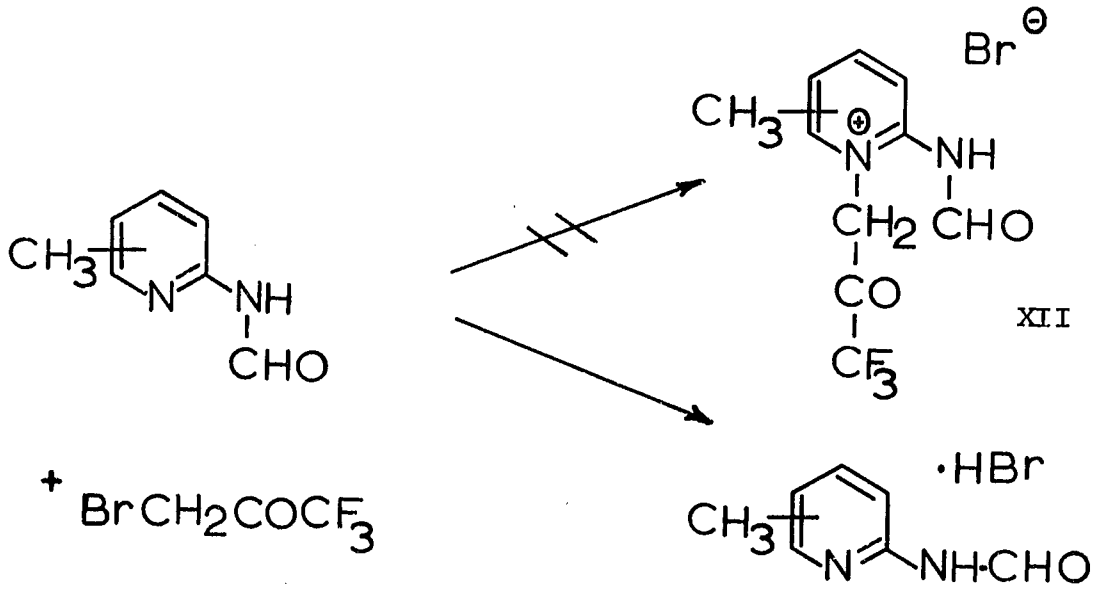
which then reacted further to give an imidazo[1,2-a]pyridine (X) in the presence of excess base, acting as a proton acceptor. The imidazo[1,2-a]pyridine probably reacted subsequently with the halide to give a salt of the structure XI. Since it is known that imidazo[1,2-a]pyridinium salts, on treatment with base yield, coloured enol-betaines of poor stability towards solvents and oxygen, the above mentioned formation of coloured tar can be attributed to an excessive reactivity of salt XI towards a relatively weak base:



As was correctly observed already by Kröhnke[10], complications, analogous to the above, arising from the high reactivity of 1-acetonylpyridinium salts, constitute another limiting factor in syntheses dependent on the isolation of the intermediate salts.

Experiments with 3-bromo-1,1,1-trifluoropropanone

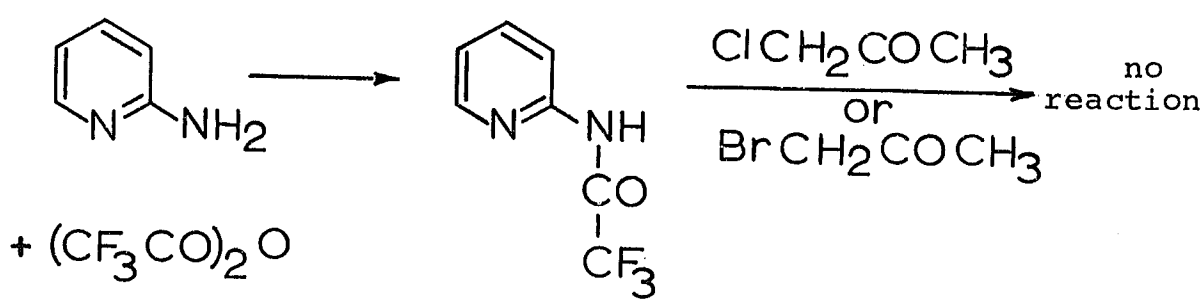
In the recent past, the availability of fluorinated reactive intermediates has prompted the introduction of fluorine into some heteroaromatic compounds[36] and sometimes unexpected results were obtained.[20] In an effort to extend the application of Kröhnke's syntheses to the preparation of fluorine containing imidazo[1,2-a]pyridines, the preliminary step consisted of an attempt to synthesize salt XII by quaternisation of 2-acylamidopyridines with 3-bromo-1,1,1-trifluoropropanone. The intention was to treat the resulting salt with acid or base to induce a cyclization reaction leading to imidazo[1,2-a]pyridines. In two of these experiments, 2-formamido-5-methylpyridine and 2-formamido-6-methylpyridine were treated with 3-bromo-1,1,1-trifluoropropanone, however, instead of the expected salt XII, only the hydrobromides of the 2-acylamidopyridines were recovered:



Since the hydrobromides of 2-formamidopyridines were obtained rapidly in good yield, the above reaction does not constitute a normal nucleophilic substitution of bromine by the pyridine nitrogen, but consists of a dehydrobromination-fragmentation of the reactive halide, possibly catalyzed by the pyridine base. At present, little is known about such a collapse of reactive halides; the observation that the precipitation of 2-formamidopyridinium hydrobromides proceeds somewhat more rapidly than the precipitation of the 6-methyl isomer seems to suggest some steric effect of the 6-methyl group and consequently the involvement of the pyridine nitrogen atom in the decomposition of 3-bromo-1,1,1-trifluoropropanone. An analogous fragmentation of a halide was observed when 2,5-dimethylimidazo[1,2-a]pyridine was treated with bromoacetone in refluxing ethanol. Again, instead of the expected 1-acetonyl-

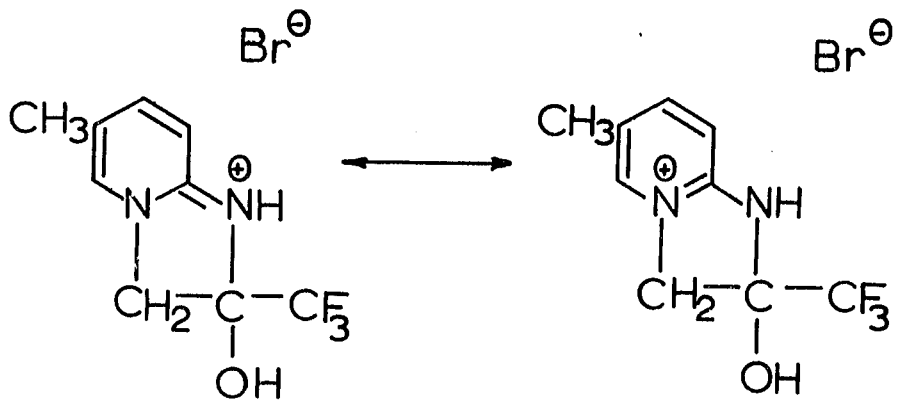
2,5-dimethylimidazo[1,2-a]pyridinium hydrobromide, the hydrobromide of 2,5-dimethylimidazo[1,2-a]pyridine was recovered in good yield. The above results emphasize further the limitations of Kröhnke's synthesis, and the difficulties encountered in the quaternisation reactions, which are known to be very sensitive to various influencing factors.[21]

The introduction of a trifluoromethyl group into the imidazo[1,2-a]pyridine ring was therefore attempted via the trifluoroacetyl amide. The prerequisite 2-trifluoroacetamidopyridine was prepared by treating 2-aminopyridine with trifluoroacetic anhydride (see appendix A). The amide was subsequently treated with bromoacetone under normal reaction conditions (in benzene solution at 50°C). No quaternary salt was obtained from the reaction mixture. When the attempt to obtain salt XII was repeated with chloroacetone, the results were equally fruitless:



It is possible that the strong electron withdrawing effect of the trifluoroacetyl group exerts its influence through to the pyridine nitrogen, affecting its basicity and thus preventing the quaternisation reaction.[37] It must be noted here that many quaternisations are reactions of rather large negative entropies of activation[38] and attempts to increase the rate of reaction by raising the temperature do not necessarily lead to better yields. The reactive halides also tend to decompose or polymerize more rapidly at elevated temperatures.

In view of the two unfruitful attempts to apply Kröhnke's synthesis to the preparation of imidazo[1,2-a]-pyridines, containing a trifluoromethyl substituent in the five-membered ring, the synthetic approach was changed to a direct reaction of 2-aminopyridine with 3-bromo-1,1,1-trifluoro-propanone. The experiment was performed with 2-amino-5-methyl-pyridine in a 1,2-dimethoxyethane solution, to which was added an equimolar quantity of 3-bromo-1,1,1-trifluoropropanone. Almost instantaneously, upon the mixing of the reactants, a crystalline precipitate separated, while noticeable heating of the solution was observed. The salt which was thus obtained was recrystallized from ethanol and its elementary analysis gave a formula of $C_9H_{10}BrF_3N_2O_2$ corresponding to a suggested structure:

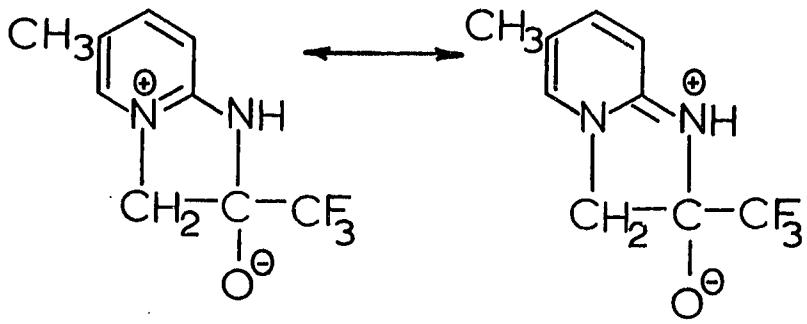


XIII

The i.r. spectrum of the salt XIII shows no significant absorption between 1700 cm^{-1} and 1800 cm^{-1}. The region characteristic of N-H or O-H stretching frequencies contains no absorption bands, thus indicating the absence of free amino- or hydroxyl-groups. Instead, a wide absorption band appeared between 2000-2600 cm^{-1} which was assigned to a $-\overset{+}{N}H$ group.[39] The n.m.r. spectrum revealed further information about the nature of the methylene group. Instead of a single absorption line, which could be expected to arise due to equivalence of both protons in a non-cyclic compound, four perturbed lines were observed.[22] This is in accordance with a cyclic structure, in which the two methylene protons have very similar chemical shifts, but are nevertheless non-equivalent in consequence of a restricted rotation.

Salt XIII was dissolved in water and treated with a solution of sodium carbonate. A yellow crystalline precipitate was obtained instantly, in almost theoretical yield; the com-

pound was, however, not the expected 6-methyl-2-trifluoromethylimidazo[1,2-a]pyridine. After recrystallization from a mixture of absolute ethanol and n-hexane, its analysis corresponded to a formula of $C_9H_9F_3N_2O$, indicating that salt XIII lost the elements of hydrogen bromide by the treatment with base and that the dehydration-aromatization had not as yet been achieved. It exhibited an intense bluish-white fluorescence, characteristic of partially aromatic compounds[23] and melted at a rather high temperature ($\sim 200^{o}$) with decomposition. Also, its solubility in a variety of polar and non-polar solvents was low. The n.m.r. spectrum, as in the case of its precursor, salt XIII, contained in addition to the absorption lines, due to the methyl group and the aromatic protons, also a band of four lines (centered around 4.1 δ), characteristic of an A-B system involving two geminal protons of nearly equal chemical shift and strong coupling. The total area of absorption lines at 4.1 was equivalent to two protons. Thus the absorption can be assigned to two non-equivalent methylene protons fixed in a rigid configuration of a cyclic compound. The i.r. spectrum contained two broad bands at 2500 cm^{-1} and 2700 cm^{-1}, characteristic of $\overset{\oplus}{N}H$ stretching frequency, a zwitterionic structure could be suggested for the partially aromatic compound XIV:

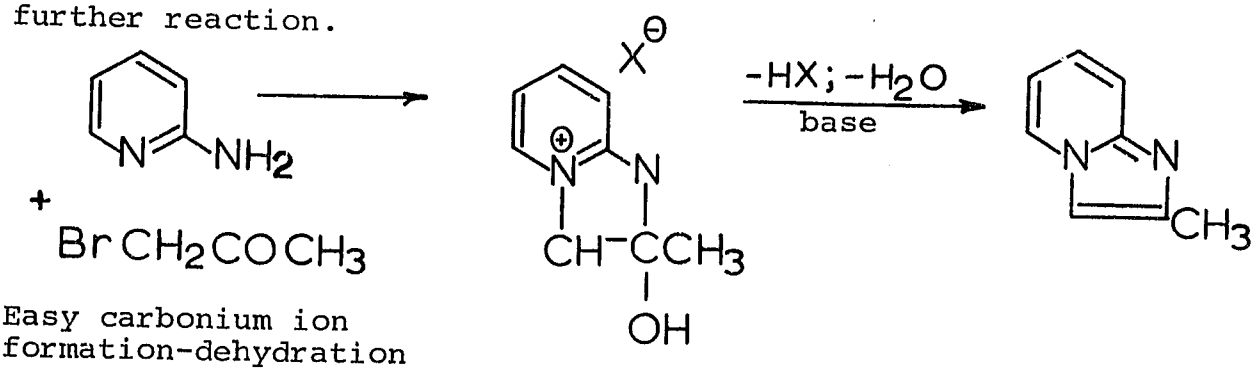


XIV

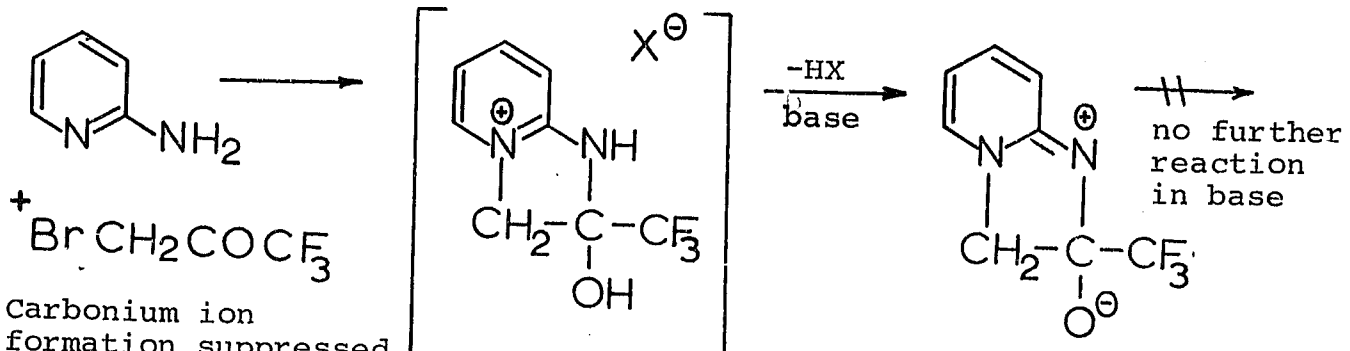
The presence of the strong electron withdrawing group might be expected to increase the acidity of the adjacent hydroxyl group and thus promote the transfer of the hydroxyl proton to the nitrogen atom to give a betaine. Since the oxygen function is now less prone to an elimination-dehydration reaction, the formation of the fully aromatic imidazo[1,2-a]pyridine is arrested at an intermediate stagee. The isolation of the stable intermediate compound has, therefore, certain mechanistic implications.

In all reported cases of imidazo[1,2-a]pyridine syntheses, starting from 2-aminopyridines, the reaction does not stop at an intermediate carbinol (similar to betaine XIV) but proceeds readily to the final product. Only in the case of the intermediate XIV does the dehydration fail to occur. If the aromatization (dehydration) of the five membered ring is initiated by the abstraction of one of the N-methylene group protons by base and it is then followed by a β-elimination of the oxygen function the betaine XIV should dehydrate readily

in a basic medium; in fact, its isolation from a basic solution should not be possible. Its failure to dehydrate must therefore be interpreted in terms of an aromatization-dehydration reaction dependent on the initial formation of a carbonium ion centre, which is then followed by the removal of one of the N-methylene group protons by the base. Should the formation of a carbonium ion centre be suppressed by a strongly electron withdrawing group, such as a trifluoromethyl group, attached to the carbon atom in question, the dehydration will not occur. The dehydration step will be blocked also on account of the oxygen function in the betaine XIV which is a poor leaving group. This will result in no further reaction.



Easy carbonium ion formation-dehydration

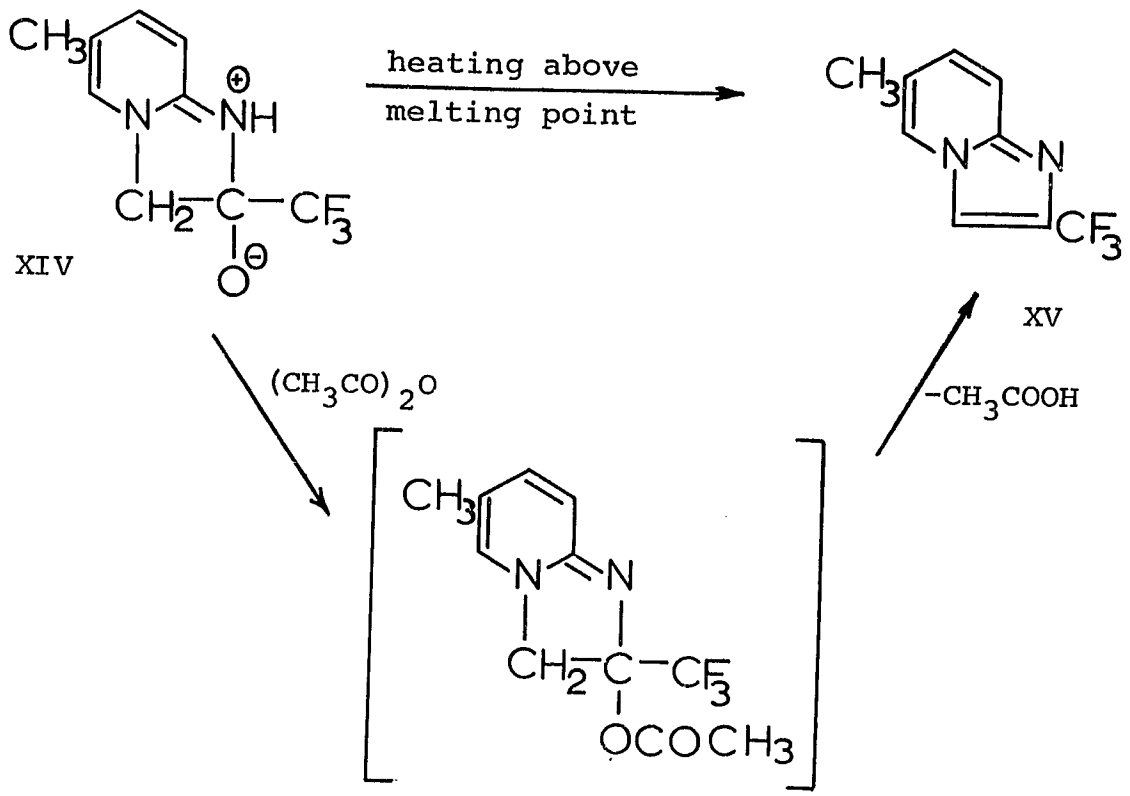


Carbonium ion formation suppressed, no dehydration

If the dehydration were dependent on the formation of a carbanion centre at the N-methylene carbon atom, in both the above reactions, the dehydration should be equally easy and lead to the fully aromatic imidazo[1,2-a]pyridine.

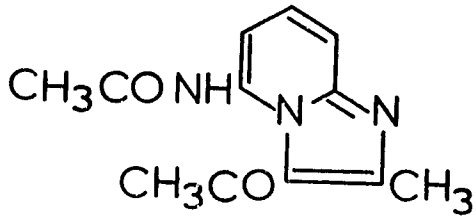
Synthesis of 6-methyl-2-trifluoromethylimidazo[1,2-a]-pyridine (XV)

The final step in the synthesis of 6-methyl-2-trifluoromethylimidazo[1,2-a]pyridine was accomplished by the application of two dehydration methods, both of them capable of overcoming the reluctance of betaine XIV to dehydrate. In one experiment, more rigorous reaction conditions were applied, such as heating above its melting point. This resulted in excellent yields of the desired imidazo[1,2-a]pyridine. The other approach was based on the mechanistic considerations of the failure to dehydrate the betaine XIV. As it was found that the oxygen function sonstitutes a poor leaving group, it was transformed into a better leaving group by esterification. When betaine XIV was treated with hot or cold acetic anhydride, an ester was formed, but it dehydrated so readily that only the final 6-methyl-2-trifluoromethylimidazo[1,2-a]pyridine could be isolated from the reaction mixture:



The preparation of some 5-aminoimidazo[1,2-a]pyridines from 2,6-diaminopyridine was reported for the first time in 1965.[24] However, the characterization of 5-aminoimidazo[1,2-a]pyridnes by preparation of their amide derivatives was omitted. Since the availability of the above amines gave rise to a hope of the introduction of further substituents into the imidazo[1,2-a]pyridine ring, it seemed appropriate to prepare the amide derivatives and thereby "protect" the amino group in reactions which it would be expected to be attacked readily. In view of the fact that methyl groups simplify n.m.r. spectra by replacing a proton capable of introducing additional spin coupling, and since they are detected with ease, it was decided to prepare the

acetyl derivative of 5-amino-2-methylimidazo[1,2-a]pyridine. The amine was refluxed for 45 minutes in acetic anhydride without any other solvent. The reaction mixture was poured on ice and neutralized with ammonium hydroxide solution. When the aqueous solution was extracted with ether for the purpose of isolating the acetamide, a yellow compound was isolated which analyzed for $C_{12}H_{13}N_3O_2$ indicating that the molecular weight of the original amine was increased by <u>two</u> acetyl groups. The n.m.r. spectrum showed the presence of three methyl groups, confirming the addition of two acetyl groups. The absorption of the NH group was observed at an unusually low field of 12.66 δ . It is possible that the amide proton suffers a deshielding effect which can be attributed to its proximity to the carbonyl group of the second acetyl substituent. In conjunction with the predicted position of electrophilic substitution, the additional acetyl group therefore occupied the 3-position of the heterocyclic ring. The three aromatic protons of the six-membered part of the imidazo[1,2-a] pyridine gave an n.m.r. absorption characteristic of an AMX system. Thus the structure of the diacetylcompound must be 5-acetamido-3-acetyl-2-methyl-imidazo[1,2-a]pyridine (XVI):



XVI

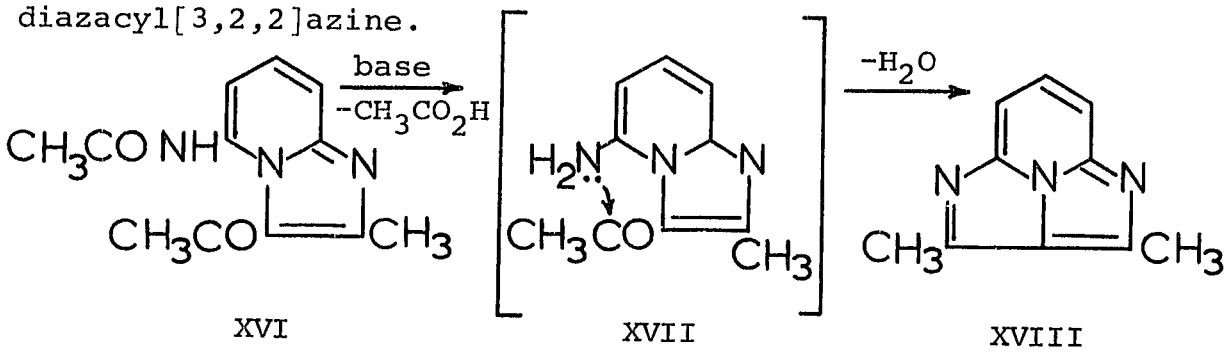
It is believed that the above compound XV was formed by acetylation at the 3-position in a Friedel-Crafts type of reaction. Such a reaction is not unexpected in view of the fact that the 3-position in the imidazo[1,2-a]pyridine ring carries a high electron density and is readily attacked by electrophilic reagents.[25]

The 5-acetylamino-2-methylimidazo[1,2-a]pyridine remained in the aqueous solution and was recovered from it in only median purity. Its further purification posed considerable difficulties as the amide was extremely hygroscopic and could not be separated efficiently from inorganic salts. Further acetylation of 5-acetamido-2-methylimidazo[1,2-a]pyridine led to the introduction of a second acetyl group in the 3-position and thus to additional amounts of compound XVI.

Synthesis of 2,3-dimethyl-1,4-diazacycl[3,2,2]azine (XVIII)

5-Acetamido-3-acetyl-2-methylimidazo[1,2-a]pyridine contains two chemically nonequivalent acetyl groups. The

amide acetyl group is susceptible to the base catalyzed hydrolysis while the acetyl group in the 3-position can be removed only in an acidic medium. When the diacetyl compound XVI was treated with aqueous alkali, the amide bond was hydrolyzed, as expected, while the other acetyl group remained in the 3-position. The free amine, 3-acetyl-5-amino-2-methylimidazo[1,2-a]pyridine XVII was, however, not isolated. The amino group reacted with the favourably placed intramolecular substrate - the 3-acetyl carbonyl group - giving rise to a new ring compound XVIII, a 2,3-dimethyl 1,4-diazacyl[3,2,2]azine.



The structure of 2,3-dimethyl-1,4-diazacyl[3,2,2]azine XVIII is evident from the following data:

1. The n.m.r. spectrum contains seven lines in the aromatic region, at 8.16, 8.07, 8.00, 7.91, 7.77 and 7.70 δ, forming a pattern characteristic of an AB_2 system with an overlap of lines 5(B) and 6(B) at 7.85 δ. The chemical shift of proton A, as given directly by line 3(A), is 8.00 δ, whereas protons B would absorb at 7.81 δ if not modified by spin coupling. The coupling constant, J_{AB}, was calculated to be 7.98.[26]

Preliminary molecular orbital calculations of electron densities in the 1,4-diazacycl[3,2,2]azine system indicate a lower electron density for position 6 than for positions 5 and 7, a result which is in accordance with the observed proton chemical shifts. A single absorption line with an area equivalent to six protons was observed at 2.95 δ indicating a symmetrical structure of XVII and magnetic equivalence of both methyl groups.

2. Mass spectrometric data indicate the correct molecular weight of 171, as well as the formula $C_{10}H_9N_3$.

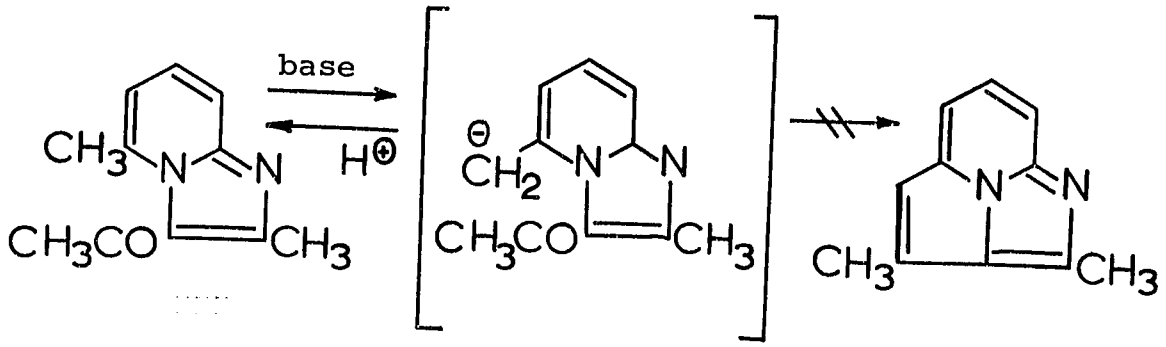
In an attempt to explore a possible synthetic route towards the unsubstituted 1,4-diazacyl[3,2,2]azine, via formylation of the known amine, 5-aminoimidazo[1,2-a]pyridine, the homologue, 5-amino-2-methylimidazo[1,2-a]pyridine was treated for 48 hours at room temperature with the mixed anhydride $CH_3COOCHO$, obtained by previous heating of 99 per cent formic acid with acetic anhydride. This formylating agent was used successfully in the preparation of 2-formamidopyridines. In the reaction with 5-amino-2-methylimidazo[1,2-a]pyridine, no formylation occurred , neither in the 3-position, nor, surprisingly on the amino group, and the amine was recovered unreacted.* Apparently more vigorous reaction conditions are required for

*In order to avoid substituents in the 3-position of 1,4-diazacyl[3,2,2]azine, it is imperative to introduce an aldehyde group into the 3-position of 5-aminoimidazo[1,2-a]pyridine, regardless of the nature of the acyl group involved in the amide bond which is lost on ring closure.

the electrophilic substitution at the 3-position and acylation of the 5-amino group.

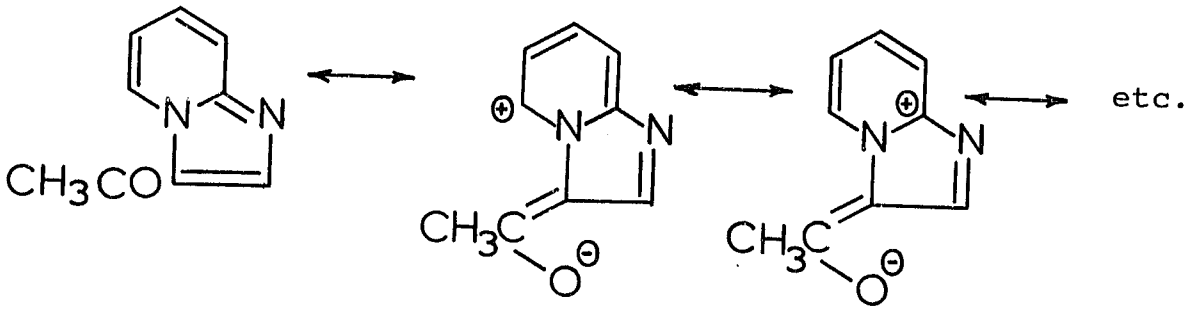
Attempted cyclization of 3-acetyl-2,5-dimethylimidazo-[1,2-a]pyridine (III)

The synthesis of the 1,4-diazacyl[3,2,2]azine ring also prompted an attempt to achieve a ring closure reaction between the carbonyl group and the 5-methyl group of 3-acetyl-2,5-dimethylimidazo[1,2-a]pyridine (III). It is well known that, in the pyridine series, the α-position carries the lowest electron density and, in consequence, stabilization is provided for carbanions formed at the 2-position. Numerous examples have been reported of condensations of the α-picolyl group with carbonyl groups via a carbanion intermediate.[27] By analogy, the position of lowest electron density occurs in the imidazo[1,2-a]pyridine system in the 5-position[40] also α-to the nitrogen atom of the six membered ring. With the hope of creating a stabilized carbanion centre from the 5-methyl group, which would be capable of attacking the carbonyl group in an intramolecular condensation reaction, 3-acetyl-2,5-dimethylimidazo[1,2-a]pyridine was treated with tert.-butoxide in tert.-butanol. After refluxing for several hours, the compound was recovered unchanged:



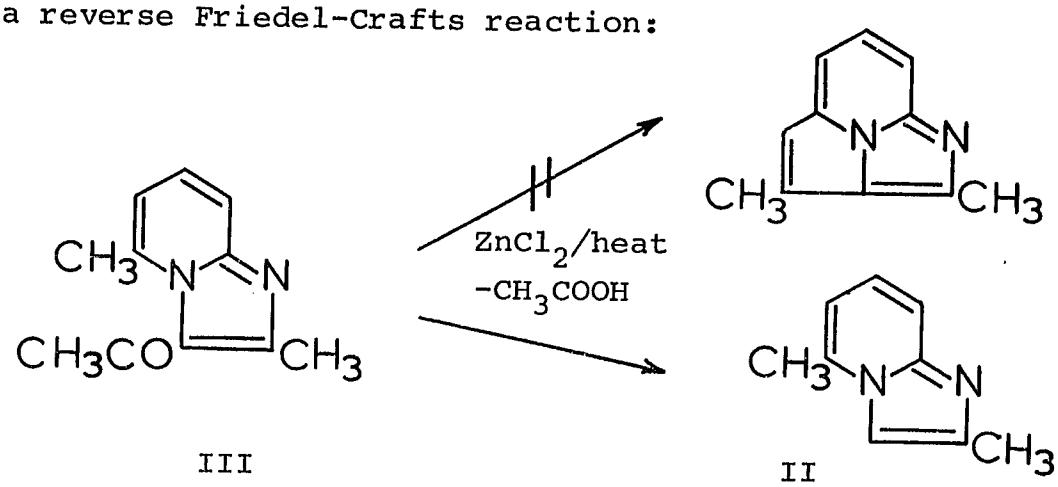
III

Apparently, the carbonyl group is strongly deactivated for nucleophilic attack by the high electron density located on the 3-position of the imidazo[1,2-a]pyridine ring. The i.r. absorption of the carbonyl group occurs at ~1650 cm^{-1} indicating a strong conjugation with a strong electron donor:[41]



The above experiment demonstrated that it is not through the lack of carbanion formation that the reaction failed, but rather on account of the inertness of the carbonyl group. A further ring closure attempt therefore seemed feasible via catalysis of the carbonyl group. An analogous activation

of an unreacting carbonyl group has been reported in the condensation reaction of p-dimethylaminobenzaldehyde with 2-methylpyrimidine.[28] Here, anhydrous zinc chloride acted as a catalyst. When 3-acetyl-2,5-dimethylimidazo[1,2-a]-pyridine was heated in the presence of anhydrous zinc chloride, no ring closure occurred; instead, the compound deacetylated in a reverse Friedel-Crafts reaction:



The above deacetylation reaction of the 3-position in imidazo-[1,2-a]pyridine has its analogy in the pyrrocoline series where a facile deacetylation of the 3-position has been observed.

<u>Nitration of 5-amino-2-methylimidazo[1,2-a]pyridine</u>

Since the nitration of 5-amino-2-methylimidazo[1,2-a]-pyridine has not been reported up to the present, it was of interest to prepare 2-methyl-5-nitraminoimidazo[1,2-a]pyridine and rearrange it to the nitro compound.[29]

When 5-amino-2-methylimidazo[1,2-a]pyridine was treated with nitric acid (at low temperature) the desired

product was not obtained. It is highly probable that initially a nitramine was formed, however, it rearranged immediately into a nitro compound. Subsequently further nitration of the imidazo[1,2-a]pyridine ring occurred and the final compound which was isolated in moderate yield was characterized as 5-amino-2-methyltrinitroimidazo[1,2-a]pyridine. The remaining ring proton possibly occupies the 7-position. The imidazo-[1,2-a]pyridine ring system is very susceptible to electrophilic attack and the possibility is not excluded that nitration of the 3-position occurred prior to the nitramine formation and rearrangement. The substitution by three nitro groups is not unusual in highly activated systems.[34]

EXPERIMENTAL

Infrared spectra were recorded on a Perkin-Elmer Infracord spectrophotometer; the compounds were pressed into KBr discs. Ultraviolet spectra were obtained on a Perkin-Elmer Model 350 spectrophotometer, with absolute ethanol as a solvent. Nuclear magnetic resonance spectra were determined by the author on a Varian high resolution spectrometer Model A-60. A variety of solvents was used, including chloroform-d ($DCCl_3$), dimethylsulphoxide - d_6, carbon tetrachloride and deuterium oxide. Where the solubility allowed, the samples had concentrations of the order of 0.1 g./ml. solvent. Tetramethylsilane was used as internal reference with the exception of the water solutions. All line positions are given in δ units with TMS as zero. Elemental analyses were carried out by Dr. C. Daessle, (Montreal) and by A. Bernhardt (Germany). Mass spectrometric analyses were performed by Morgan and Schaefer Corporation (Montreal) and S. Meyerson (American Oil Co.). Melting points reported herein are corrected; the melting points of most of the pyridinium salts were not reported or these are not true melting points and depend on the rate of heating as well as other variables.

Acetylation of 2-amino-6-methylpyridine

2-Amino-6-methylpyridine was purified by distillation under reduced pressure and subsequently refluxed with acetic anhydride (100 per cent excess) for two hours. The unreacted acetic anhydride acetic acid and the acetate of the base, all of which had lower boiling points than the amide, were removed by vacuum distillation. The residue was recrystallized from water, to which a small amount of ammonium hydroxide was added. 2-Acetamido-6-methylpyridine was obtained in 84 per cent yield, colourless needles, m.p. 90-91°, lit. value. 88°.[30]

Preparation of bromoacetone

The procedure outlined in Organic Syntheses was followed.[31] The yields of bromoacetone were lower than those reported in the literature; considerable losses occur in the purification by distillation under reduced pressure. B.p. 45-47° at 25 mm. Hg., lit. value: 40-42° at 13 mm. Hg.

Preparation of 2-acetamido-1-acetonyl-6-methylpyridinium hydrobromide (I)

For the preparation of 2-acetamido-1-acetonyl-6-methylpyridinium hydrobromide, as well as in most of the subsequent quaternisation reactions of pyridine amines, the procedure used by Kröhnke was followed.[10] The solvent used in these reactions was dry benzene. While both reactants, the amide and the halide, are soluble in benzene, the final product is an ionic salt and is practically insoluble in the

solvent and readily separates from the reaction mixture.

2-Acetamido-6-methylpyridine (40.7 g.; 0.27 mole) was dissolved in dry benzene (200 ml.) and bromoacetone (37.18 g., 0.27 mole) was added all at once. The clear solution was kept at a constant temperature of 50°. After several hours the quaternary salt began to precipitate. After 24 hours the first crop of crystals was filtered off. The reaction mixture was returned to the water bath and continued to produce additional quantities of the pyridinium salt. After one month when the concentration of reactants had decreased to low levels, the collection of the crystalline product was discontinued. The crude product (49.45 g.) was washed with dry benzene and recrystallized from ethanol-acetone-ether (decolourizing carbon. 2-Acetamido-1-acetonyl-6-methylpyridinium hydrobromide (II) crystallized in colourless needles (24.28 g., 31% yield). In the i.r. spectrum the acetonyl carbonyl group absorbed at 1720 cm^{-1} and the NH stretch was observed at 3200 cm^{-1} (KBr). The n.m.r. spectrum of this salt showed an incompletely resolved ABC-system in the region of 7.40-8.50 with an area equivalent to three protons (two β- and one γ-protons). The N-methylene group protons absorbed at 4.90 (single line with an area equivalent to two protons). The assignment of the methyl group absorptions is as follows: acetonyl methyl; 2.10 δ ; acetamide methyl group, 2.60 δ ; and 6-position methyl group, 2.72 δ . The NH

proton was exchanged in the deuterium oxide solvent. The melting point of 2-acetamido-1-acetonyl-6-methylpyridinium hydrobromide was not reproducible (approx. 160°); it depended on the rate of heating and traces of solvent used in the last recrystallization. On melting, another solid was formed, which darkened above 300° without melting.

Anal. calcd. for $C_{11}H_{15}BrN_2O_2$: C, 46.00; H, 4.88; N, 9.75.
Found: C, 45.91; H, 5.16; N, 9.89.

Alkaline treatment of 2-acetamido-1-acetonyl-6-methylpyridinium hydrobromide (I)

a) 2-Acetamido-1-acetonyl-6-methylpyridinium hydrobromide (0.62 g.) was dissolved in water (3 ml.), the solution cooled to 0° in an ice bath and treated with an equally cold solution of 2N potassium carbonate (5 ml.). The clear reaction mixture was kept overnight at 0°. An oil precipitated from the aqueous phase. It was separated and the water layer extracted three times with 20 ml. portions of chloroform. The oil was added to the combined chloroform extracts and the solution was dried over anhydrous sodium sulphate. Upon evaporation of the solvent, the waxy residue (0.259 g.) was dissolved in 1 ml. of chloroform-d for n.m.r. analysis.*

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* The n.m.r. spectra of the individual components of the mixture will be discussed later in greater detail.

Since the protons in the 6-positions of 3-acetyl-2,5-dimethylimidazo[1,2-a]pyridine and of 2,5-dimethylimidazo-[1,2-a]pyridine absorb at 6.76 and 6.51 p.p.m. respectively, the areas covered by the two absorption lines, as obtained by integration, gave the mole ratio of the two compounds present in the mixture. The product consisted of 21 per cent of 3-acetyl-2,5-dimethylimidazo[1,2-a]pyridine (III) and 79 per cent of 2,5-dimethylimidazo[1,2-a]pyridine (II).

b. Larger quantities of pure 2,5-dimethylimidazo-[1,2-a]pyridine were obtained by treatment of 72 g. of salt I with potassium carbonate at 0°, as described above. The resulting mixture (32.15 g.) was fractionated under reduced pressure at 11.5 mm Hg. The main fraction (12 g.), distilling between 151-153°, consisted of pure 2,5-dimethylimidazo[1,2-a]-pyridine. The distillate solidified to white hygroscopic needles, which, on exposure to air, oxidized to purple red products; m.p. 53-54°. The inefficient one theoretical plate distillation process is capable of providing only 30 per cent of pure 2,5-dimethylimidazo[1,2-a]pyridine; larger recoveries could be obtained by means of preparative v.p.c.

In the n.m.r. spectrum both methyl groups exhibit almost identical chemical shifts: one absorption line at 2.47δ was observed, with an area equivalent to six protons. In the region of 6.40-7.60 δ, the three aromatic protons of the six-membered ring form an AMX pattern with the 3-position

proton superimposed on one of the lines at 7.20 (Fig. 3). An analytical sample was prepared by recrystallization from benzene-n-hexane.

Anal. calcd. for $C_9H_{10}N_2$: C, 73.97; H, 6.85; N, 19.17.
Found: C, 73.88; H, 6.96; N, 19.04.

c. 2-Acetamido-1-acetonyl-6-methylpyridinium hydrobromide (0.125 g.) was dissolved in deuterium oxide (1 ml.). The solution was cooled to 0° and small portions of anhydrous potassium carbonate were added to it for the purpose of avoiding a large temperature increase. After standing overnight at 0°, the aqueous phase was extracted with chloroform. The combined extracts were dried and the solvent was evaporated to dryness. The residue was used directly for the n.m.r. analysis. The spectrum was almost identical with that of the 2,5-dimethylimidazo[1,2-a]pyridine prepared from a (light) water solution. The only difference between the spectrum of 3d-2,5-dimethylimidazo[1,2-a]pyridine and 2,5-dimethylimidazo[1,2-a]pyridine was the lack of the superimposed absorption line at 7.20 δ. The remaining aromatic protons formed the previously observed AMX pattern with a total area equivalent to three protons.

When (ordinary) 2,5-dimethylimidazo[1,2-a]pyridine, dissolved in carbon tetrachloride, was shaken with a small amount of deuterium oxide, to which some potassium carbonate had been added, the n.m.r. spectrum showed no exchange of the

3-position proton for deuterium.

Preparation of 2-formamido-6-methylpyridine (XIX)

Acetic anhydride (89.6 ml.) was mixed with 99 per cent formic acid (37.2 ml.). The mixture warmed up to about 50° by the exothermic reaction and was kept at this temperature for two hours. After cooling, it was added slowly to an ether solution of 2-amino-6-methylpyridine (94 g. in 438 ml. of anhydrous ether). This amine solution was cooled in an ice bath during the gradual addition of the formylating agent. The reaction mixture was left standing at room temperature for two days for the completion of the acylation reaction. After this period, the solvent and acetic acid were removed under reduced pressure. The residue was fractionated further to separate the amine acetate from the higher boiling formamide. 2-Formamido-6-methylpyridine (XIX) distilled at 139-140° at 6 mm Hg. and 85 grams were collected in the main fraction (88 per cent yield). After recrystallization from benzene-n-hexane 81 grams of the pure amide were obtained in colourless needles, m.p. 78-80°C.

The n.m.r. spectrum of 2-formamido-6-methylpyridine consists of an ABC system in the region of 6.90 to 9.50 δ with the formamide proton superimposed onto the pattern. The area was found to be equivalent to five protons. The NH absorbed at 10.60 δ (area equivalent to one proton) while the methyl group absorption was observed at 2.52δ.

Anal. calcd. for $C_7H_8N_2O$: C, 61.76; H, 5.88; N, 20.59.
Found: C, 61.85; H, 6.04; N, 20.78.

Preparation of 1-acetonyl-2-formamido-6-methylpyridinium hydrobromide (IV)

2-Formamido-6-methylpyridine (82.8 g.) was dissolved in dry chloroform (332 ml.) and bromoacetone (91.8 ml.) was added. The clear solution was left at 50° for three weeks. At the end of this period the crude salt separated from the dark solution (32.44 g.). After filtering and washing with chloroform, 1-acetonyl-2-formamido-6-methylpyridinium hydrobromide (IV) was recrystallized twice from 95 per cent ethanol. White needles were obtained (11.8 g., 7.1 per cent yield). This rather low yield of the desired salt was caused by the fragmentation of the halide into hydrogen bromide which then formed the hydrobromide salt 2-formamido-6-methylpyridine. The two salts which were obtained from the reaction mixture could be readily separated by recrystallization by virtue of the fact that salt IV is the less soluble one.

The n.m.r. spectrum of 1-acetonyl-2-formamido-6-methylpyridinium hydrobromide (0.147 g. in D_2O) shows the acetonyl methyl group and the 6-position methyl group at 2.10 δ and 2.77 δ respectively. The two N-methylene protons absorbed as a single line at 4.92 δ with an area equivalent to two protons. The three aromatic protons formed an ABX pattern between 7.50 and 8.60 δ while the formyl proton was found at

9.10 δ . The NH proton was exchanged in the solvent.

Anal. calcd. for $C_{10}H_{13}BrN_2O_2$: C, 43.95; H, 4.76; N, 10.25.

Found: C, 44.13; H, 4.93; N, 10.40.

Alkaline treatment of 1-acetonyl-2-formamido-6-methylpyridinium hydrobromide (IV)

a) 1-Acetonyl-2-formamido-6-methylpyridinium hydrobromide (46 g.) was dissolved in water, the solution cooled to 0° and to it was added an equally cold solution of potassium carbonate (2N, 368 ml.). After standing overnight at 0°, an oil separated. The aqueous layer was decanted from the oil and extracted with chloroform. The oil was added to the extracts. Upon drying and evaporation of the solvent 37 g. of mixed products were obtained. The n.m.r. analysis of this product showed that the mixture consisted of 81.5 per cent of 2,5-dimethylimidazo[1,2-a]pyridine and 18.5 per cent of 3-acetyl-5-methylimidazo[1,2-a]pyridine.

b. When 1-acetonyl-2-formamido-6-methylpyridinium hydrobromide was treated with a saturated solution of sodium bicarbonate at 100°, a different ratio of products was obtained. The n.m.r. analysis of the resulting mixture showed the following percentages: 2,5-dimethylimidazo[1,2-a]pyridine, 70 per cent; 3-acetyl-5-methylimidazo[1,2-a]pyridine, 30 per cent. The latter compound was not isolated, while 2,5-dimethylimidazo-[1,2-a]pyridine was readily purified by fractionation under reduced pressure (see page 64).

Preparation of 3-acetyl-2,5-dimethylimidazo[1,2-a]-pyridine (III).

a. 2-Acetamido-1-acetonyl-6-methylpyridinium hydrobromide (1.30 g.) was dissolved in water (10.4 ml.) to which was added sodium bicarbonate (0.8 g.). The clear solution was rapidly heated to boiling point and kept at that temperature for one half hour. On cooling, an oil separated which solidified into a yellowish crystalline mass. The yield of this crude product was 0.45 g. After recrystallization from absolute ethanol-n-hexane 3-acetyl-2,5-dimethylimidazo[1,2-a]-pyridine (III) was obtained in white flakes, m.p. 105°. In the i.r. spectrum, the carbonyl group absorption was superimposed on an aromatic band at 1650 cm^{-1}. The n.m.r. spectrum of the acetyl compound consists of an ABX-system in the region of 6.68-7.68 (total area equivalent to three protons); the lines at 6.68-6.88 are tentatively assigned to the 6-position proton. The three methyl groups absorb at 2.44, 2.62 and 2.75 δ (see Fig. 4). A mass spectrometric analysis confirmed the molecular weight corresponding to the formula of $C_{11}H_{12}N_2O$.

The presence of the acetyl group was detected by the appearance of a strong peak at mass number 145 (loss of the acetyl group of mass 43 in the cracking pattern).

Anal. calcd. for $C_{11}H_{12}N_2O$: C, 70.21; H, 6.38; N, 14.89.

Found: C, 70.17; H, 6.53; N, 14.52.

b. Acetylacetone (50 g.) was chlorinated by a gradual addition of sulphuryl chloride (62.5 g.) at room temperature.[32] The slow addition required three hours for completion, whereupon the clear reaction mixture was fractionated under reduced pressure. The distillate boiling between 50-57° (at 20 mm.Hg) was refractionated. 3-Chloroacetylacetone of two degree boiling range (52-54° at 20 mm. Hg) was used directly in the following reaction:

2-Amino-6-methylpyridine (36.1 g.) was dissolved in dry benzene (150 ml.) and was added 3-chloroacetylacetone (22.44 g.). From the clear solution a salt crystallized very slowly, consisting mainly of 2-amino-6-methyl pyridinium hydrobromide. After one month the brown solution was filtered off and the solvent was removed under reduced pressure. The crude, dark crystalline product (11.95 g.) was purified by recrystallization from absolute ethanol-n-hexane. The i.r. and n.m.r. spectra of an analytical sample were identical with the spectra of 3-acetyl-2,5-dimethylimidazo[1,2-a]-pyridine. A mixed melting point with the authentic sample of the acetyl compound III showed no depression.

<u>Reactions of 3-acetyl-2,5-dimethylimidazo[1,2-a]pyridine</u>

a. 3-Acetyl-2,5-dimethylimidazo[1,2-a]pyridine (1.0 g.) was dissolved in dry benzene (4 ml.), and chloroacetone (0.44 g.) was added to the solution. Crystals began

to precipitate after several hours; the reaction was allowed one month for completion (at room temperature). After this period, the crystalline product was filtered off and washed with acetone. The yield of 1-acetonyl-3-acetyl-2,5-dimethyl-imidazo[1,2-a]pyridinium hydrochloride (XX) amounted to 0.938 g. (62 per cent). An analytically pure sample was obtained by recrystallization from 95% ethanol-acetone-ether. In the n.m.r. spectrum of the above salt the following absorptions were observed: At 2.63 δ the superimposed lines of two methyl group protons were found (area equivalent to six protons); the other two methyl groups absorbed at 2.78 and 2.97 δ. The N-methylene group was observed at 5.81 δ (area equivalent to two protons) while the aromatic protons formed an ABX pattern between 7.47 and 8.35 δ (total area equivalent to three protons).

Anal. calcd. for $C_{14}H_{17}ClN_2O_2 \cdot 1H_2O$: C, 56.28; H, 6.36; N, 9.38.
Found: C, 56.40; H, 6.46; N, 9.65.

When 1-acetonyl-3-acetyl-2,5-dimethylimidazo[1,2-a]-pyridinium hydrochloride was treated with a variety of bases, ranging from aqueous sodium bicarbonate to tert.-butoxide, no stable product could be obtained.

b. 3-Acetyl-2,5-dimethylimidazo[1,2-a]pyridine (1.765 g.) was dissolved in t-butanol (25 ml.) in which metallic potassium (0.125 g.) was previously dissolved. The clear solution was refluxed for 90 minutes whereupon some water was added. The

precipitate which was formed by the dilution was filtered, washed with water and dried. It consisted of unchanged starting material (1.58 g.) slightly discoloured by impurities.

c. 3-Acetyl-2,5-dimethylimidazo[1,2-a]pyridine (5.00 g.) was dissolved in dry benzene (25 ml.); the solution was poured into pulverized (freshly fused) anhydrous zinc chloride (50 g.). After thorough mixing of the solution with the solid, benzene was evaporated and the zinc chloride, soaked with the acetyl compound, was heated (in an oil bath) to 165° for two hours. After cooling, the contents of the flask were dissolved in water and ammonium hydroxide was added until the initially formed precipitate redissolved. The clear basic solution was extracted with ether. The extract was dried with anhydrous sodium sulphate and the solvent was evaporated. The residue distilled at 152-154° at 11 mm. Hg. The distillate solidified to colourless waxy needles (1.892 g.; 49 per cent yield); its i.r. and n.m.r. spectra being identical with those of 2,5-dimethylimidazo[1,2-a]-pyridine.

Preparation of 2-formamido-5-methylpyridine (XXI)

2-Amino-5-methylpyridine (94 g.) was dissolved in dry ether (437 ml.), the solution cooled in an ice bath and gradually, with continuous stirring, a formylating agent was added prepared from acetic anhydride (89.63 ml.) and 99 per cent formic acid (37.16 ml.). After the solution had been left standing at room temperature for two days, the solvent

was evaporated and the residue was fractionated under reduced pressure. The foreruns consisted of acetic acid and acetate of the base. The last fraction, consisting of 2-formamido-5-methylpyridine distilled at 150-154° at 6 mm. Hg. The crude formamide was recrystallized from benzene-n-hexane; colourless needles were obtained (103 g.; 87 per cent) which melted at 117-119°. An analytical sample was prepared by two additional recrystallizations, m.p. 118-119°.

The n.m.r. spectrum of 2-formamido-5-methylpyridine consisted of the methyl group absorption at 2.28 δ, a group of aromatic proton bands with the formamide proton absorption superimposed into it in the region between 6.70 and 9.40 δ, and of the NH absorption which appeared at 10.16 .

Anal. calcd. for $C_7H_8N_2O$: C, 61.76; H, 5.88; N, 20.59.

Found: C, 62.10; H, 6.06; N, 20.69.

<u>Preparation of 1-acetonyl-2-formamido-5-methylpyridinium hydrobromide (XXII)</u>

2-Formamido-5-methylpyridine (45 g.) was dissolved in dry benzene (244 ml.) and bromoacetone (46 g.) was added at once. After one week of heating to 50°, the initially yellowish solution became dark and a crystalline precipitate was formed. The product was filtered off, washed with benzene and recrystallized from ethanol-ether. The yield of purified 1-acetonyl-2-formamido-5-methylpyridinium hydrobromide after

two recrystallizations amounted to 24 g. (26 per cent). The salt XXII crystallized in colourless needles. Its n.m.r. spectrum was obtained from a solution in deuterium oxide. The two methyl group absorptions occur at 2.10 and 2.48 δ; the one at higher field can be assigned to the acetonyl methyl group. The N-methylene group absorbs at 4.98 δ (single line with an area equivalent to two protons), while the three aromatic protons appear as two broadened lines at 8.25 and 8.50 δ (area equivalent to three protons). The formamide proton absorption occurs at 9.08 δ.

Anal. calcd. for $C_{10}H_{13}BrN_2O_2$: C, 43.95; H, 4.76; N, 10.25.
Found: C, 44.12; H, 4.92; N, 10.17.

Alkaline treatment of 1-acetonyl-2-formamido-5-methylpyridinium hydrobromide

1-Acetonyl-2-formamido-5-methylpyridinium hydrobromide (2 g.) was dissolved in water (10 ml.) and the solution was cooled to 0°. An equally cold solution of potassium carbonate was added (2N; 16 ml.). Within two minutes a white crystalline precipitate began to form. The reaction was allowed to run to completion overnight at 0°, whereupon all organic material was extracted with several portions of benzene. The combined extracts were dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure. The residue (0.967 g.) was analyzed by n.m.r. and was found to be composed of 3-acetyl-6-methylimidazo[1,2-a]pyridine (XXIII), 73.7 per

cent and of 2,6-dimethylimidazo[1,2-a]pyridine (XXIV) 26.3 per cent. From this mixture the acetyl compound was isolated in pure form by recrystallization from n-hexane. The yield of 3-acetyl-6-methylimidazo[1,2-a]pyridine was 0.362 grams; no doubt, somewhat better yields could be obtained by treatment of salt XXII with sodium bicarbonate. 3-Acetyl-6-methylimidazo[1,2-a]pyridine crystallizes in colourless plates; m.p. 72-74°. In its n.m.r. spectrum, the two methyl groups appear at 2.28 and 2.49 δ. This latter absorption line can be assigned to the 6-position methyl group, the former to the acetyl methyl group. Without spin coupling, the assignment of the aromatic absorption lines is as follows: H-2, 8.24δ; H-5, 9.33δ; H-7, 7.21 δ and H-8, 7.56 δ. The coupling constants between protons in the 7- and 8-position is 9.4 cps while the coupling constant between the protons in 5- and 7-positions amounts to only 1.6 c.p.s.

Anal. calcd. for $C_{10}H_{10}N_2O$: C, 68.96; H, 5.74; N, 16.09.
Found: C, 68.84; H, 5.94; N, 15.92.

<u>Preparation of 2,6-dimethylimidazo[1,2-a]pyridine (XXIV)</u>.

1-Acetonyl-2-formamido-5-methylpyridinium hydrobromide (10 g.) was dissolved in conc. hydrobromic acid (80 ml.). The solution was heated to boiling point for 20 minutes, whereupon all water and hydrogen bromide were evaporated under reduced pressure. When the residue attained a syrupy consistency, it was cooled and the residual acid was neutralized with excess of sodium carbonate (sat. solution; 100 ml.);

this treatment also liberated the imidazo[1,2-a]pyridine from its hydrobromide salt. The heterocyclic base was extracted with chloroform and the extract was dried over anhydrous sodium sulphate. When the solvent was evaporated, the crude 2,6-dimethylimidazo[1,2-a]pyridine (XXIV) was distilled under reduced pressure. Since the acid catalyzed cyclization is a "clean" reaction, giving no by-products, all of the heterocyclic base distilled within a 1° range at 132° at 6 mm. Hg. 4.3 grams were obtained (81.4 per cent). 2,6-Dimethylimidazo-[1,2-a]pyridine is a low melting hygroscopic solid (liquid at room temperature). In its n.m.r. spectrum the two methyl groups (in the 2- and 6-positions) absorb at 2.20 and 2.40 . The absorption lines in the region between 6.7 and 7.7 δ have been assigned to the aromatic protons: H-3, 7.20δ; H-5, 7.75δ; H-7, 6.88δ; H-8, 7.60δ; when not spin coupled. A coupling constant of 9.4 c.p.s. was observed between the protons H-7 and H-8; The former proton is coupled to H-5 by a constant of 1.6 c.p.s. The hydrochloride salt of 2,6-dimethylimidazo-[1,2-a]pyridine was prepared for the elemental analysis.

Anal. calcd. for $C_9H_{11}ClN_2$: C, 59.16; H, 6.03; N, 15.34.

Found: C, 59.03; H, 6.06; N, 15.20.

Preparation of 2-formamido-4-methylpyridine (XXV)

2-Amino-4-methylpyridine (94 g.) was dissolved in anhydrous ether and treated with a formylating agent prepared from acetic anhydride (89.63 ml.) and 99 per cent formic acid

(37.16 ml.). The reaction mixture was allowed to proceed to completion for two days at room temperature. Then the solvent, as well as the acetic acid were evaporated under reduced pressure and the residue was fractionated for the purpose of separating the lower boiling acetate of the base from the amide. 2-Formamido-4-methylpyridine (XXV) distilled at 155° at 6 mm. Hg. After recrystallization from benzene-hexane the amide was obtained in white needles (107 g.; 86.2 per cent); m.p. 86-88°. An analytical sample was obtained after additional two recrystallizations from the same solvent. The n.m.r. spectrum of 2-formamido-4-methylpyridine exhibited the following absorptions. The methyl groups absorbed at 2.28 δ; the aromatic protons were observed in the region of 6.75 to 8.20 δ while the formamide proton absorption appeared as a doublet (8.53 and 9.30 δ); the NH proton absorbed at 10.73 δ.

Anal. calcd. for $C_7H_8N_2O$: C, 61.76; H, 5.88; N, 20.59.
Found: C, 62.02; H, 5.77; N, 20.44.

<u>Preparation of 1-acetonyl-2-formamido-4-methylpyridinium hydrobromide (XXVI)</u>

2-Formamido-4-methylpyridine (45 g.) was dissolved in dry benzene (244 ml.) and an equimolal amount of bromoacetone (46 g.) was added to the solution. The reaction mixture was heated to 50° for six days, whereupon the crystalline precipitate was filtered off and washed with benzene. 62.5 grams of

crude 1-acetonyl-2-formamido-4-methylpyridinium hydrobromide (XXVI) were obtained (69 per cent yield). The salt was recrystallized from 70 per cent aqueous ethanol, to which some acetone had been added. An analytical sample was prepared by an additional recrystallization from 95 per cent ethanol; the n.m.r. spectrum was obtained from a deuterium oxide solution. The following absorptions were observed: The two methyl groups (acetonyl methyl and 4-position methyl) absorbed at 2.04 and 2.63 p.p.m. The N-methylene protons were found at 4.93 p.p.m. (single line with an area equivalent to two protons). The three aromatic protons were assigned the following absorption lines if not spin coupled: H-3, 8.24 δ ; H-5, 7.59 δ ; H-6, 8.48 δ . The coupling constants between the aromatic protons could not be evaluated accurately due to insufficient resolution. The formamide proton absorption occurred at 9.08 δ .

Anal. calcd. for $C_{10}H_{13}BrN_2O_2$: C, 43.95; H, 4.76; N, 10.25.
Found: C, 44.11; H, 4.91; N, 10.42.

<u>Alkaline treatment of 1-acetonyl-2-formamido-4-methylpyridinium hydrobromide (XXVI)</u>

1-Acetonyl-2-formamido-4-methylpyridinium hydrobromide (2 g.) was dissolved in water (10 ml.); the clear solution was cooled to 0°. An equally cold solution of potassium carbonate was added (2N; 16 ml.) at once. An oily precipitate began to form after one-half hour. The reaction mixture was left standing overnight at 0°. The precipitate, which eventually

solidified was filtered off and dissolved in benzene. The aqueous filtrate was extracted with benzene and the combined benzene solution was dried over anhydrous sodium sulphate. When the solvent was removed under reduced pressure, a waxy residue (1.077 g.) remained in the flask. When analyzed (by means of n.m.r.) for its composition, the mixture was found to consist of 2,7-dimethylimidazo[1,2-a]pyridine (XXVII); 31 per cent and of 3-acetyl-7-methylimidazo[1,2-a]pyridine (XXVIII) 69 per cent. The latter compound, being the less soluble of the two, was separated from the mixture and purified by recrystallization from absolute ethanol-hexane. 3-Acetyl-7-methylimidazo[1,2-a]pyridine (XXVIII) crystallized in colourless plates; m.p. 138-140° (0.503 g.). In its n.m.r. spectrum the 7-position methyl group appeared at 2.47 while the acetyl methyl group absorbed at higher field, at 2.36 δ . The four aromatic protons were correlated with the following absorption lines: H-6, 6.78 δ ; H-8, 7.41 δ ; H-2, 8.21 δ ; H-5, 9.36 δ when not spin coupled. The coupling constant between H-5 and H-6 was 7 c.p.s. and 1.5 c.p.s. for protons H-6 and H-8.

Anal. calcd. for $C_{10}H_{10}N_2O$: C, 68.96; H, 5.74; N, 16.09.
Found: C, 68.89; H, 5.56; N, 16.05.

<u>Preparation of 2,7-dimethylimidazo[1,2-a]pyridine (XXVII)</u>

1-Acetonyl-2-formamido-4-methylpyridine (10 g.) was dissolved in hydrobromic acid (2N; 80 ml.) and the solution was heated to boiling point for 20 minutes. After cooling, a

saturated solution of sodium carbonate was added (100 ml.) and the oil which precipitated was extracted with chloroform. The extract was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure. The remaining heterocyclic base was purified by vacuum distillation. The largest fraction was collected at 131-132° at 5.5 mm. Hg (4.16 g. 77.8 per cent). The n.m.r. spectrum of 2,7-dimethylimidazo-[1,2-a]pyridine prepared by the above route was identical with the spectrum of the (same) 2,7-dimethylimidazo[1,2-a]pyridine prepared directly from chloroacetone and 2-amino-4-methyl-pyridine[4].

Preparation of 2-formamido-4,6-dimethylpyridine (XXIX)

2-Amino-4,6-dimethylpyridine (97.15 g.) was treated in an anhydrous ether solution (450 ml.) with the formylating agent prepared from 99 per cent formic acid (34 ml.) and acetic anhydride (82 ml.). The reaction mixture was left standing for two days at room temperature. When the reaction had run to completion, the solvent was removed and the acetic acid was distilled off under reduced pressure. The fractionation (in vacuum) was continued and, as usual, the acetate of the amino distilled first, followed by the amide. 2-Formamido-4,6-dimethylpyridine (XXIX) distilled at 151° at 5 mm. Hg within a one degree range (95.3 g.; 79.8 per cent). After recrystallization from benzene-hexane 2-formamido-4,6-dimethyl obtained in colourless needles, m.p. 107-109°. In the n.m.r. spectrum

the 4- and 6-position methyl groups absorbed at 2.18 δ and 2.31 δ respectively. The two β-protons, the formyl proton and the NH proton were observed in the region of 6.25 δ to 9.83 δ (not completely resolved).

Anal. calcd. for $C_7H_{10}N_2O$: C, 64.00; H, 6.67; N, 18.67.
Found: C, 63.88; H, 6.78; N, 18.83.

Preparation of 1-acetonyl-2-formamido-4,6-dimethylpyridinium hydrobromide (XXX)

The same procedure was followed as was described in the treatment of the other amides with bromoacetone. 2-Formamido-4,6-dimethylpyridine (82 g.) was dissolved in dry benzene (407 ml.) and bromoacetone (75 g.) was added at once. After three weeks at 50°, the pyridinium salt formed a precipitate, which was filtered from the reaction mixture, and washed with benzene (40.3 g.; 25.6 per cent). The salt was recrystallized from 95 per cent ethanol. 1-Acetonyl-2-formamido-4,6-dimethylpyridinium hydrobromide crystallized in colourless needles (29.1 g.; 18.5 per cent). In its n.m.r. spectrum, the three methyl group absorptions were observed at 2.01, 2.55 and 2.61 δ. The N-methylene group protons gave a single absorption line at 4.78 δ while the aromatic protons absorbed at 7.41 and 8.03 δ; the formamide proton was found at 9.02 δ since salt XXX was dissolved in deuterium oxide (0.157 g./2 ml.) the N-H proton was exchanged.

Anal. calcd. for $C_{11}H_{15}BrN_2O_2$: C, 46.00; H, 4.88; N, 9.75.
Found: C, 45.94; H, 5.00; N, 9.75.

Alkaline treatment of 1-acetonyl-2-formamido-4,6-dimethylpyridinium hydrobromide

a. 1-Acetonyl-2-formamido-4,6-dimethylpyridinium hydrobromide (2.726 g.) was dissolved in water (6.5 ml.) and the solution cooled to 0°. Some of the salt crystallized out at this temperature, however, on addition of the cold potassium carbonate solution (2N) all precipitate redissolved. The reaction mixture was left standing at 0° and remained clear for at least one hour. After remaining at 0° overnight, all organic material was extracted with chloroform, the extract dried over anhydrous sodium sulphate and the solvent evaporated. An oily product was recovered (1.46 g.), which consisted of 2,5,7-trimethylimidazo[1,2-a]pyridine (XXXI) (90 per cent) and of 3-acetyl-5,7-dimethylimidazo[1,2-a]pyridine (XXXII) (10 per cent).

b. 1-Acetonyl-2-formamido-4,6-dimethylpyridinium hydrobromide (10 g.) was dissolved in a saturated solution of sodium bicarbonate (80 ml.) which was rapidly brought to boiling point and kept at that temperature for ten minutes. After cooling to room temperature, all basic material was extracted with chloroform. After the drying of the extract and evaporation of the solvent, an oil was obtained (5.178 g.) which was found to consist of 2,5,7-trimethylimidazo[1,2-a]pyridine (XXXI) (80.7 per cent) and 3-acetyl-5,7-dimethylimidazo[1,2-a]pyridine (XXXII) (19.3 per cent). The two products were separated by

fractionation under reduced pressure. 2,5,7-Trimethylimidazo-[1,2-a]pyridine distilled at 155-156° at 9 mm. Hg. (2.73 g.; 49 per cent). An analytical sample was prepared by recrystallization from cyclohexane; m.p. 74-76°. The n.m.r. spectrum of 2,5,7-trimethylimidazo[1,2-a]pyridine consists of the three methyl group absorptions, which occur at 2.23, 2.33 and 2.38 δ and of three aromatic proton absorptions at 6,22, 6.98 and 7.07 δ ; long range coupling can be observed between the methyl group protons and the aromatic protons in the order of 1-2 c.p.s.

Anal. calcd. for $C_{10}H_{12}N_2$: C, 75.00; H, 7.50; N, 17.50.
Found: C, 75.14; H, 7.30; N, 17.71.

The residue (0.784 g.) which remained in the distilling flask after the fractionation and removal of 2,5,7-trimethylimidazo[1,2-a]pyridine was recrystallized from absolute ethanol-hexane (decolourizing carbon) and for the second time from cyclohexane. 3-Acetyl-5,7-dimethylimidazo[1,2-a]pyridine crystallized in colourless plates; m.p. 103-104°. In its n.m.r. spectrum the aromatic methyl group absorptions were observed at 2.39 and 2.67 δ ; the acetyl methyl group absorbed at 2.60 δ and the three aromatic protons were observed at 6.67, 7.37 and 8.33 δ .

Anal. calcd. for $C_{11}H_{12}N_2O$: C, 70.21; H, 6.38; N, 14.89.
Found: C, 70.17; H, 6.49; N, 15.07.

Preparation of 3-bromo-1,1,1-trifluoropropanone

The procedure of McBee and Barton[42] was followed in the bromination of the ketone. 1,1,1-Trifluoroacetone (199.3 g.) was gradually stirred into concentrated sulphuric acid (473.6 ml.). Cooling was applied in order to avoid losses of the very volatile ketone. To the clear solution bromine (142.1 g.) was added dropwise. The addition of bromine required two hours, during which time the unchanged ketone was prevented from evaporating by a special reflux condenser using dry ice as coolant. Crude 3-bromo-1,1,1-trifluoropropanone, being insoluble in the acid was separated by decantation. Difficulties were experienced, however, in this stepL The two liquids exhibited almost identical specific gravities. After separation, the halide was purified further by distillation (at atmospheric pressure). The fraction boiling between 86 and 89° (lit. value 85-86.8^{o}) was used directly in the subsequent quaternisation reactions. The yield of 3-bromo-1,1,1-trifluoropropanone was 124 g. (36.5 per cent) only half of the recovery reported by McBee and Barton; this could be attributed to losses in the separation of the liquids and the unavoidable inefficiency of a simple distillation process.

Attempted quaternisation of 2-acylamidopyridines

2-Acetamido-5-methylpyridine (4.5 g.; 0.03 mole) was dissolved in dry benzene (18 ml.) and 3-bromo-1,1,1-trifluoropropanone (5.94 g.) was added. The clear solution

soon became cloudy and a crystalline precipitate began to separate. The reaction mixture was heated for three days to 50° whereupon the crystals were filtered off, washed with benzene, dried and recrystallized from absolute ethanol. The purified salt (6.16 g.) was treated with a solution of sodium bicarbonate at room temperature and gave a strong effervescence (evolution of carbon dioxide). When the aqueous solution was extracted with ether, upon removal of the solvent, a basic substance was obtained, the physical characteristics of which were identical with those of 2-acetamido-5-methylpyridine. Evidently, the salt isolated from the quaternisation attempt was 2-acetamido-5-methylpyridinium hydrobromide, obtained in a 88 per cent yield.

When 2-acetamido-6-methylpyridine was treated under identical reaction consitions with 3-bromo-1,1,1-trifluoropropanone, the corresponding hydrobromide salt was obtained in a 76% yield.

Preparation of 2-hydroxy-6-methyl-2-trifluoromethyl-3H-imidazo-[1,2-a]pyridinium hydrobromide (XIII)

2-Amino-5-methylpyridine (2.872 g.) was dissolved in 1,2-dimethoxyethane (25 ml.) and bromo-1,1,1-trifluoropropanone was added to the solution. Instantaneously a crystalline precipitate separated from the yellow solution and the reaction mixture became noticeably warm. The crystals were filtered off, washed with acetone and dried. The crude salt XIII (6.921. g.;

(87 per cent) was recrystallized twice from absolute ethanol. 2-Hydroxy-6-methyl-2-trifluoromethyl-3H-imidazo[1,2-a]pyridinium bromide crystallized in colourless needles (5.73 g.; 72 per cent). An analytical sample of salt XIII was dissolved in deuterium oxide and its n.m.r. spectrum was recorded. The methyl group absorption was observed at 2.30 δ . The two protons in the 3-position, being non-equivalent, formed an AB pattern in the region of 4.65-5.35 δ , partly obscured by the water absorption, the coupling constant J_{AB} was found to be 15 c.p.s. The three aromatic protons H-5, H-7, and H-8 absorbed in the region of 7.13-8.20 δ (area equivalent to three protons). The NH proton was exchanged by the solvent.

Anal. calcd. for $C_9H_{10}BrF_3N_2O$: C, 36.12; H, 3.34; F, 19.06; N,9.36.
Found: C, 36.13; H, 3.20; F, 19.26; N,9.50.

Preparation of 2-hydroxy-6-methyl-2-trifluoromethyl-3H-imidazo[1,2-a]pyridinium hydroxide betaine (XIV).

2-Hydroxy-6-methyl-2-trifluoromethyl-3H-imidazo-[1,2-a]pyridinium hydrobromide (3 g.) was dissolved in water (15 ml.) and an equal volume of a saturated sodium carbonate solution was added. Instantaneously, a pale yellow crystalline precipitate was formed. The precipitate was filtered off, washed with water and dried. 2-Hydroxy-6-methyl-2-trifluoro-methyl-3H-imidazo[1,2-a]pyridinium hydroxide betaine XIV was obtained in 79.5 per cent yield (1,738 g.). An analytical sample was prepared by recrystallization from absolute ethanol-

hexane. The betaine XIV forms pale yellow needles which exhibit intense bluish white fluorescence in u.v. light. Melting point is above 200° with decomposition. Betaine XIV was dissolved in dimethylsulphoxide-d_6 and its n.m.r. spectrum was recorded. The 6-position methyl group was found to absorb at 1.91 δ ; the two protons in the 3-position formed a doublet (not fully resolved AB system) with the principal lines at 3.97 and 4.03 δ. The assignment of the absorption observed in the 6-8 δ region is as follows: H-5, 7.21 δ ; H-7, 6.98 δ ; H-8, 6.27 δ , if not spin coupled. The coupling constant of proton H-5 to H-7 was found to be 2 c.p.s. while protons H-7 and H-8 showed a coupling constant of 9 c.p.s. Since N-H and OH groups interact with the water present in the solvent, only a broadened absorption could be observed at 3.28 δ . Since the water absorption and very possibly NH or OH protons fall under the same absorption line, the area and position* of the above absorption are of limited value.

Anal. calcd. for $C_9H_9F_3N_2O$: C, 49.54; H, 4.13; F, 26.14; N, 12.84.
Found: C, 49.53; H, 4.31; F, 25.89; N, 13.03.

<u>Preparation of 6-methyl-2-trifluoromethylimidazo[1,2-a]pyridine (XV)</u>

a. 2-Hydroxy-6-methyl-2-trifluoromethyl-3H-imidazo-[1,2-a]pyridinium hydroxide betaine (0.184 g.) was heated above

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*The position of the water absorption in dimethylsulphoxide is concentration dependent.

its melting point to 200-220° for ten minutes. Droplets of water were observed condensing on the cooler parts of the flask. The residue weighed 0.168 g., indicating a loss of 0.016 g. of water (theoretical loss of water, from 0.184 g. of betaine XIV should amount to 0.0153 g.). 6-Methyl-2-trifluoromethylimidazo[1,2-a]pyridine was recrystallized from n-hexane. Colourless needles were obtained, m.p. 106-107°. The substance does not exhibit any fluoroescence in u.v. light. It is sufficiently basic to be soluble in dilute hydrochloric acid.

b. 2-Hydroxy-6-methyl-2-trifluoromethylimidazo[1,2-a]-pyridinium hydroxide betaine (0.1 g.) was dissolved in acetic anhydride (2 ml.) and the solution was heated to boiling point for one hour. Thereupon the cooled reaction mixture was poured on crushed ice and all acid was neutralized with sodium bicarbonate. 6-Methyl-2-trifluoromethylimidazo[1,2-a]-pyridine was extracted from the aqueous solution with chloroform. The extract was dried with anhydrous sodium sulphate and the solvent was evaporated. The residue (0.087 g.; 94.7 per cent) was recrystallized from n-hexane.

When the above acetylation attempt was carried out at room temperature only 6-methyl-2-trifluoromethylimidazo-[1,2-a]pyridine could be recovered from the reaction mixture in good yield.

The assignment of n.m.r. spectral lines to the various protons of 6-methyl-2-trifluoromethylimidazo[1,2-a]-pyridine is as follows: The 6-position methyl group appears as a doublet at 2.31 δ; long range coupling to the H-5 proton amounting to 1 c.p.s. The 3-position proton forms a quartet, centered at 7.81 δ ; long range coupling to the three fluorine atoms also amounting to 1 c.p.s. The remaining aromatic protons around the six-membered ring are correlated with the observed absorption in the following manner: H-5, a multiplet, not completely resolved, centered at 7.94 δ; H-7, a quartet, centered at 7.10 δ; H-8, a doublet at 7.53 δ. The coupling constant between protons H-7 and H-8 is 9 c.p.s., while 2 c.p.s. is observed for protons H-5 and H-7 (Fig. 5). The trifluoromethyl group absorption was split into a doublet (fluorine resonance spectrum) by proton H-3. Spin decoupling experiments confirmed the above assignment.

Anal. calcd. for: $C_9H_7F_3N_2$: C, 54.00; H, 3.50; F, 28.50; N, 14.00.
Found: C, 54.20; H, 3.42; F, 28.36; N, 14.14.

Preparation of 5-amino-2-methylimidazo[1,2-a]pyridine

The procedure of Paolini and Robins was followed in this preparation of the amine.[24] 2,6-Diaminopyridine (80 g.) was dissolved in ethanol (1 l.) and chloroacetone (68 g.) was added. The solution, which soon became dark brown, was refluxed for four hours, whereupon all solvent was evaporated

to a syrupy consistency. The 5-amino-2-methylimidazo[1,2-a]-pyridnium hydrochloride salt was, however, not isolated. Instead, the aqueous alcoholic suspension was, without prior purification, converted to the free amine by addition of excess of sodium carbonate. 5-Amino-2-methylimidazo[1,2-a]pyridine precipitated in grey crystals. The precipitate was filtered off, washed with a small amount of water and recrystallized from aqueous ethanol (decolourizing carbon). The free base was obtained in the form of small grey crystals (22.65 g.; 21 per cent). Its n.m.r. spectrum was identical with that published by Paolini and Robins. These authors do not discuss the isolation and purification of the free base. It has been found that aqueous ethanol is the best solvent, among a variety of conventional solvents, giving optimal recoveries.

Acetylation of 5-amino-2-methylimidazo[1,2-a]pyridine

5-Amino-2-methylimidazo[1,2-a]pyridine (2 g.) was acetylated by refluxing with acetic anhydride (4 ml.) for 45 minutes. The reaction mixture was poured on crushed ice and neutralized with excess ammonium hydroxide. The dark coloured solution was extracted repeatedly with ether and the combined extracts were dried over anhydrous sodium sulphate. After evaporation of the solvent, 5-acetamido-3-acetyl-2-methyl-imidazo[1,2-a]pyridine crystallized in yellow needles, m.p. 145.5-146.5^{o}, (0.539 g.; 17 per cent). Its n.m.r. spectrum

(see Fig. 6) consisted of eleven absorption lines: an AMX-system with two overlapping lines in the region of 7-8 δ and three lines at 2.25 δ, 2.69 δ, and 2.78 δ, assigned to the methyl groups. The NH absorption was observed at unusually low field at 12.66 δ.

Anal. calcd. for $C_{12}H_{13}N_3O_2$: C, 62.34; H, 5.36; N, 18.18.
Found: C, 62.12; H, 5.76; N, 18.07.

The aqueous phase after the extraction of 5-acetamido-3-acetyl-2-methylimidazo[1,2-a]pyridine with ether was evaporated to dryness. The residue, which contained considerable quantities of ammonium acetate was extracted with ether. The extract upon evaporating gave 5-acetamido-2-methylimidazo[1,2-a]pyridine (XXXIII) (1.39 g.; 37 per cent). Its n.m.r. spectrum consists of two methyl group absorption at 2.23 and 2.33δ, and eight lines not completely resolved in the region of 6.6-7.6 δ which are assigned to aromatic protons (total area equivalent to four protons). The NH absorption occurs at 9.0 δ (see Fig. 7).

5-Acetamido-2-methylimidazo[1,2-a]pyridine (0.955 g.) was refluxed with acetic anhydride (4 ml.) for 45 minutes. The reaction mixture was poured on crushed ice and treated in the same manner as described above in the acetylation of 5-amino-2-methylimidazo[1,2-a]pyridine. When the ether extracts were evaporated, 5-acetamido-3-acetyl-2-methylimidazo[1,2-a]pyridine (0.103 g.) was obtained.

Attempted formylation of 5-amino-2-methylimidazo[1,2-a]-pyridine

A formylation mixture was prepared by heating acetic anhydride (2.06 ml.) with 99 per cent formic acid (0.86 ml.) for two hours at 50°.[43] The cooled mixed anhydride was added to a solution of 5-amino-2-methylimidazo[1,2-a]pyridine (2.66 g.) in 1,2-dimethoxyethane (12 ml.). The clear solution was left standing at room temperature for two days, whereupon the solvent and unreacted acids were evaporated under reduced pressure. The residue was dissolved in water (50 ml.) and sodium bicarbonate was added to neutralize the residual acidity. A greyish crystalline precipitate was obtained, which was filtered off, washed with a little water and dried. The product consisted of the unchanged amine (2.10 g.).

Preparation of 2,3-dimethyl-1,4-diazacycl[3,2,2]azine (XVIII)

5-Acetamido-3-acetyl-2-methylimidazo[1,2-a]pyridine (0.5 g.) was dissolved in 25% aqueous sodium hydroxide (10 ml.) and a sufficient quantity of ethanol was added to dissolve all of the solid. The clear solution was refluxed for one hour; then it was acidified with conc. hydrochloric acid and the small excess of acid was neutralized with a solution of ammonium hydroxide. A sufficient amount of the latter base was employed to liberate the heterocyclic base whereupon all solvents were evaporated to dryness under reduced pressure. The residue, containing inorganic salts (ammonium and sodium

chloride) and the heterocyclic base was extracted with carbon tetrachloride until the inorganic salts lost all yellow colour. Upon evaporation of the combined extracts, 2,5-dimethyl-1,4-diazacycl[3,2,2]azine (XVIII) crystallized in yellow needles (0.288 g.; 77 per cent). An analytical sample was prepared by recrystallization from cyclohexane, m.p. 113-114°. The base XVIII did not exhibit any fluorescence in u.v. light. Absorption in u.v.: λ_{max} (in mμ) and log ϵ (absolute ethanol) 377 (2.43); 343 (4.23); 337 (4.01); 320(sh) (3.81); 292 (4.02); 284 (4.01); 230 (5.00). (Fig. 8,9).

Anal. calcd. for $C_{10}H_9N_3$: C, 70.16; H, 5.30; N, 24.54.
Found: C, 70.16; H, 5.79; N, 24.49.

Nitration of 5-amino-2-methylimidazo[1,2-a]pyridine

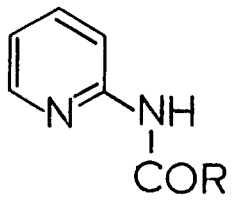
5-Amino-2-methylimidazo[1,2-a]pyridine (1.35 g.) was added in small portions to concentrated sulphuric acid (5 ml.); the temperature was maintained at 0° in spite of considerable heat being generated by the protonation of the base. When all amine had been dissolved, a nitration mixture was added, also dropwise.[45] This nitrating agent was preparedd by mixing at low temperature (-30°) 90 per cent nitric acid (4.6 ml.) with concentrated sulphuric acid (7.5 ml.). The nitration reaction generated additional heat which had to be dissipated into a cooling bath of dry ice in ethanol. The temperature was maintained at -10°; the addition of the nitrating agent required one hour. The reaction mixture, by now dark brown and viscous,

was poured on crushed ice and all acid was neutralized by an excess of sodium carbonate while cooling. A brown precipitate separated, was filtered off, washed with water and dried (1.576 g.). On recrystallization from absolute ethanol, 5-amino-2-methyl-trinitroimidazo[1,2-a]pyridine (XXXIV) was obtained in yellow needles (0.22 g.), m.p. 170° (decomposed). The n.m.r. spectrum of the nitrocompound consisted of three absorption lines: the methyl group absorption was observed at 2.57 δ, while the NH proton was found at 10.83 δ (area equivalent to two protons). A single absorption line with an area equivalent to one proton was found at 8.63 δ. The nitro-compound XXXIV is very reactive and tends to decompose on mere recrystallization from ethanol; intermolecular condensations probably occur, giving rise to less soluble brown material.

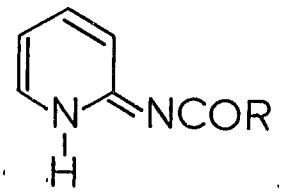
Anal. calcd. for $C_8H_6N_6O_6$: C, 34.04; H, 2.13; N, 29.79.
Found: C, 34.21; H, 2.31; N, 30.04.

APPENDIX A

Although the problem of tautomerism in 2-acylamidopyridines has been recognized for some time[45,46], it was not until 1957 when Sheinker[47] made an attempt to determine, by means of i.r. spectra, the actual tautomeric form in which some of these amides exist. Two tautomers are possible, in one the NH proton resides on the exocyclic nitrogen atom (structure A), and in the other, the proton is bonded to the pyridine ring nitrogen atom (structure B).



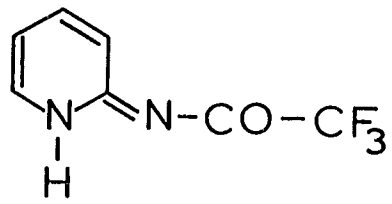
A



B

In Sheinker's approach, the absorptions observed in the i.r. region of 1500-2000 cm^{-1} served as a guide for the determination of the tautomeric structure. In particular, the position of the carbonyl absorption band was used as the criterion. Sheinker examined the spectra of some acylated N-methylpyridoneimines (in solid state) and found that the carbonyl absorption occurred in the region of 1606-1630 $cm.^{-1}$ In contrast, the carbonyl absorption bands of compounds of structure A were observed in the region of 1686-1718 $cm.^{-1}$

When Sheinker recorded the spectrum of 2-trifluoroacetamidopyridine, he found the carbonyl absorption band at 1630-1640 cm^{-1} and arrived at a conclusion that the amide exists mainly in the acylpyridone imine form:



This conclusion found further support in Sheinker's reasoning based on the "acidifying" ability of the acyl groups; presumably acyl groups of strong acidifying ability favour the acylimine tautomeric form. In the experimental section, the preparation of 2-trifluoroacetamidopyridine was described in limited detail; it was implied that 2-trifluoroacetamidopyridine was prepared by treatment of the "corresponding" amide with trifluoroacetic anhydride. Elementary analysis, showing only carbon and hydrogen percentages, seemed to be correct: C, 44.0; H, 2.49; m.p. 98-101°.

When 2-trifluoroacetamidopyridine was required as a potential starting material for various syntheses, the following procedure was employed:

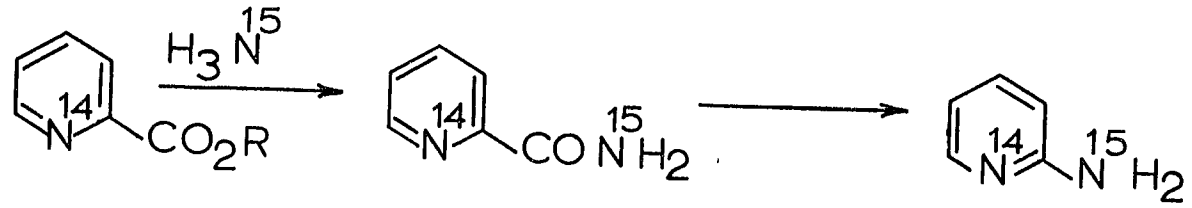
2-Aminopyridine (4.7 g.; 0.05 mole) was dissolved in anhydrous ether (30 ml.) and to the solution, cooled in an ice bath, was added dropwise trifluoroacetic anhydride (10.5 g.;

0.05 mole). After all the acid anhydride had been added, the solution was left standing overnight at room temperature, whereupon all solvent was evaporated to dryness. The residue, consisting of 2-trifluoroacetamidopyridinium trifluoroacetate crystallized in colourless plates, m.p. 67-73° (11.0 g.; 72.3 per cent). This salt was subsequently dissolved in benzene (50 ml.) and the solution was shaken with a saturated solution of sodium bicarbonate. Instantaneously, carbon dioxide was evolved. The benzene layer containing the free amide was dried over anhydrous sodium sulphate and the solvent was evaporated. The amide was recrystallized from benzene-hexane. 2-Trifluoroacetamidopyridine (XXXV) crystallized in colourless plates (3.5 g.; 41 per cent).

Anal. calcd. for $C_7H_5F_3N_2O$: C, 44.21; H, 2.63; F, 30.00; N, 14.74. The elemental analysis of 2-trifluoroacetamidopyridine prepared by the above procedure gave: C, 44.35; H, 2.68; which is essentially within the margin of error and is in the same range as the results of Sheinker. In addition, nitrogen and fluorine analyses gave the following values: F, 29.87; N, 14.56; in good agreement with the calculated values. The melting point, however, differs considerably from that given by Sheinker: it was found to be 76-77°. The n.m.r. spectrum of 2-trifluoroacetamidopyridine (XXXV) shows an ABMX pattern (not fully resolved) in the region of aromatic proton absorptions, area equivalent to four protons; the NH absorption occurs at 10.70 δ.

area equivalent to one proton (Fig. 11). Thus far, all evidence suggests that the compound prepared from 2-aminopyridine and trifluoroacetic anhydride (m.p. 76-77°) is the true 2-trifluoroacetamidopyridine; the compound of m.p. 98-101° has probably a different structure. Unlike Sheinker's compound, which exhibits the shortest wave length absorption at 1643 cm^{-1} (in the 1500-2000 cm^{-1} region), 2-trifluoroacetamidopyridine of m.p. 76-77° absorbs at 1740 cm^{-1} [48] (Fig. 12). Hence Sheinker's conclusions concerning the tautomeric form of 2-trifluoroacetamidopyridine are incorrect and doubt is thrown on the structure of the remaining amides included in that study.

It is therefore proposed to approach the question of tautomerism in 2-acylamidopyridines along different lines. The availability of N^{15} labelled compounds* makes the following synthesis feasible:



(R=Cl; OC_2H_5)

The required amides can be obtained subsequently from the labelled 2-aminopyridine and the respective acid anhydrides in very good yields.

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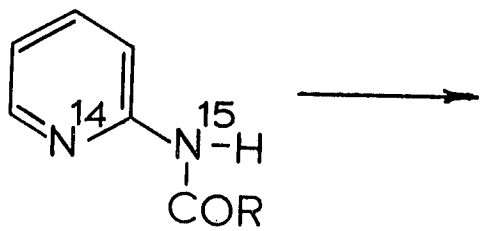
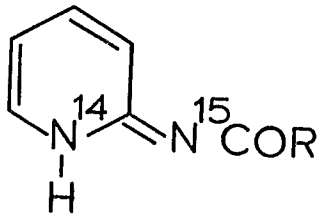
* N^{15} chemicals are available with 95 per cent isotopic purity.

Since the N^{15} isotope has a nuclear spin of 1/2 and no electrical quadrupole moment, the proton absorption (N^{15}-H proton) should appear as a well defined doublet with a line separation of 64 c.p.s., this being the coupling constant between a proton and an N^{15} nucleus.(49) Such would be the case of a 2-acylamidopyridine in the ordinary amide form:



doubet; J_{NH} 64 c.p.s.

if however the 2-acylamidopyridine exists in the acylimine form,



no characteristic doublet should be observed; instead the NH proton absorption would appear as a single broadened peak, characteristic of all N^{14} quadrupole interactions.

The approach to the study of tautomerism in 2-acylamidopyridines, as outlined above, is being proposed as one of the future research efforts planned in the field of heteroaromatic compounds.

APPENDIX B

When the n.m.r. spectrum of 2,5-dimethylimidazo-[1,2-a]pyridine was recorded at low concentrations (0.05 g./1 ml. deuterochloroform) it was noticed that both methyl groups exhibited the same chemical shift and consequently only a single absorption line was observed at 2.47 δ (area equivalent to six protons). At an increased concentration of the heterocyclic base (0.085 b./ml.) the position of one of the methyl group absorption lines began to shift towards higher field. Finally, at a concentration of 0.14 g./ml. a complete separation of the two methyl group absorption lines was observed. Apparently, the higher concentration increased the probability of association of the solute molecules (with each other) and this resulted in the increased shielding of one of the methyl group protons. A closer examination of the n.m.r. spectrum (at reduced sweep widths) revealed that the band of the methyl group which is affected by the association, and thus shifts to higher field, is actually an incompletely resolved quartet, whereas that methyl group absorption which is not affected by association forms a well defined doublet. In 2,5-dimethylimidazo[1,2-a]pyridine only the 2-position methyl group can be split into a doublet by the 3-position proton. The 5-position methyl group "sees" the 6-position and 7-position protons (long range coupling) and is thus split into four lines. Having thus established the identity and assignment of the

methyl group absorptions, the n.m.r. spectra of 2,5-dimethyl- and 2,5,7-trimethylimidazo[1,2-a]pyridine were recorded in various solvents. The objective of this study was to find a correlation between the chemical nature of the solvent and its power to associate with the solute. Table II shows the observed chemical shifts of the 2- and 5-position methyl group in 2,5-dimethylimidazo[1,2-a]pyridine.

TABLE II

Chemical shifts of methyl groups in 2,5-dimethylimidazo-[1,2-a]pyridine

Solvent	2-position CH_3	5-position CH_3
Chloroform-d	2.470	2.470
Benzene	2.490	1.891
Anisole	2.458	2.110
Nitrobenzene	2.516	2.40
Thiophene	2.483	2.025
Pyridine	2.525	2.325

Two observations become apparent immediately:

A. The positions of the 2-methyl group remain practically unchanged regardless of the nature of the solvent. It is exclusively the 5-position methyl group which is affected by complexing of the solvent with the solute. Consequently it appears that the solvent associates exclusively with the six-membered part of imidazo[1,2-a]pyridine.

B. The largest displacement of the 5-methyl group absorption from its position in chloroform occurs in benzene.[50] It became appropriate to investigate how electron donating and electron withdrawing substituents in benzene might influence its coordinating ability. Surprisingly enough, both anisole and nitrobenzene were found to coordinate with the heterocycle to a lesser extent than benzene. Since in anisole and nitrobenzene the substituents were expected to interfere with the coordination process, pyridine was chosen as another solvent, free of substituents, yet possessing sufficiently polar character. The coordination of the solute with pyridine was also rather weak as compared to that with benzene.

Thus, there exists no simple correlation between the nature of the solvent and the magnitude of the displacement of the 5-methyl group absorption. Finally, to probe into steric causes of the coordination, thiophene was used as a solvent. It was hoped that thiophene being a five-membered heterocycle might coordinate with the five-membered part of imidazo[1,2-a]pyridine and consequently shift the position of the 2-methyl group. This, however, was not the case and thiophene, like the other solvents also caused a shielding of the 5-methyl group.

When 2,5,7-trimethylimidazo[1,2-a]pyridine was dissolved in benzene, the absorptions of both of the six-membered ring methyl groups (5-CH_3 and 7-CH_3) were displaced

to higher field, whereas the position of the 2-methyl group remained unchanged at 2.5 δ . No doubt, the aromatic protons on the six-membered portion of imidazo[1,2-a]pyridine are also subjected to an increased shielding in benzene solvent.

In conclusion, the data presented above are not sufficiently complete to establish a predictable correlation between the degree of coordination and the nature of the solvent. The discriminating selectivity of the solvents to coordinate with only certain parts of heterocyclic molecules promises to evolve into a diagnostic tool, simplifying complex spectra by shifting certain absorption out of regions where superimposition renders assignment difficult.[51]

FIGURE 1

Molecular model of pyridinium betaine with the N-acetonyl side chain coplanar with the pyridine ring (no 6-position substituent).

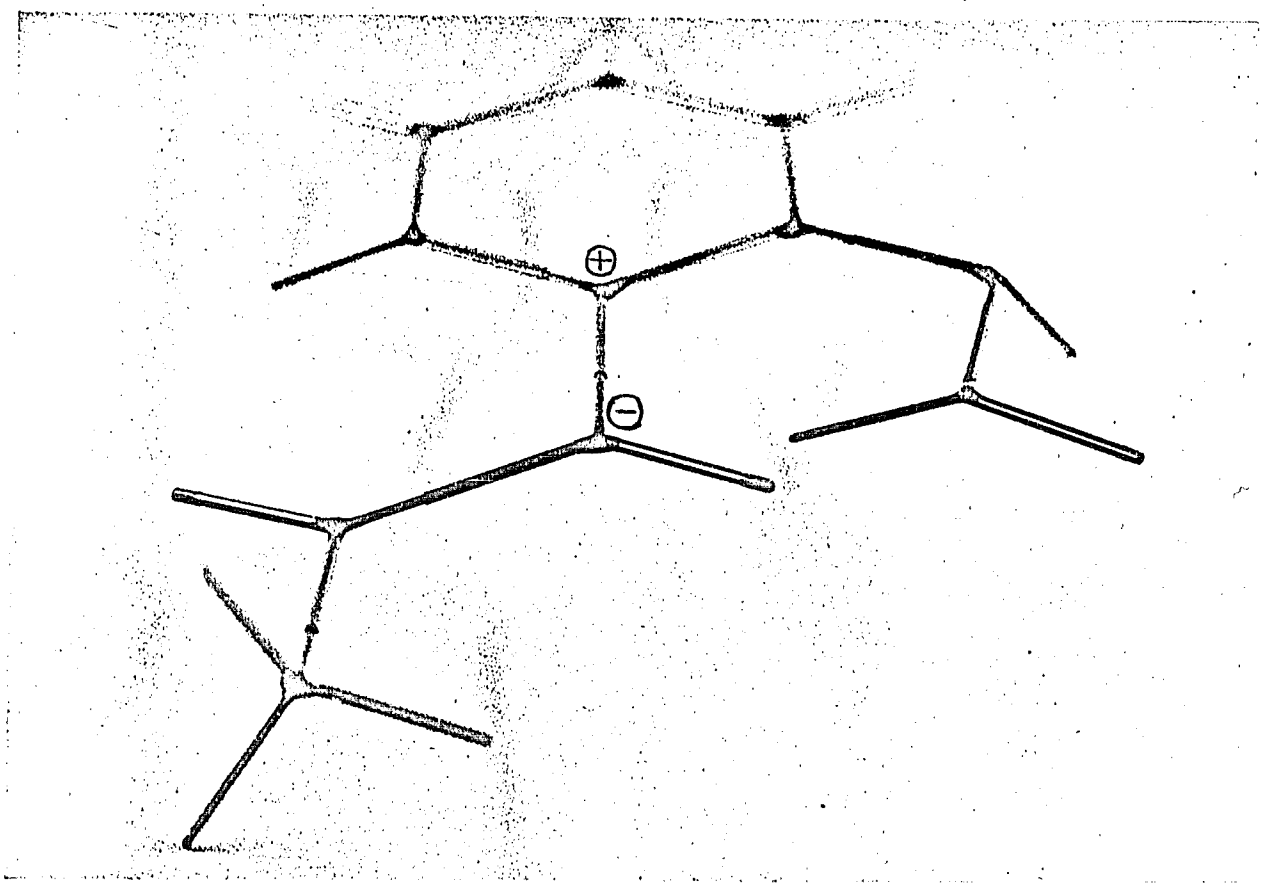


FIGURE 2

Molecular model of a pyridinium betaine in which the plane of the N-acetonyl side chain is perpendicular to the plane of the pyridine ring (6-position substituent present).

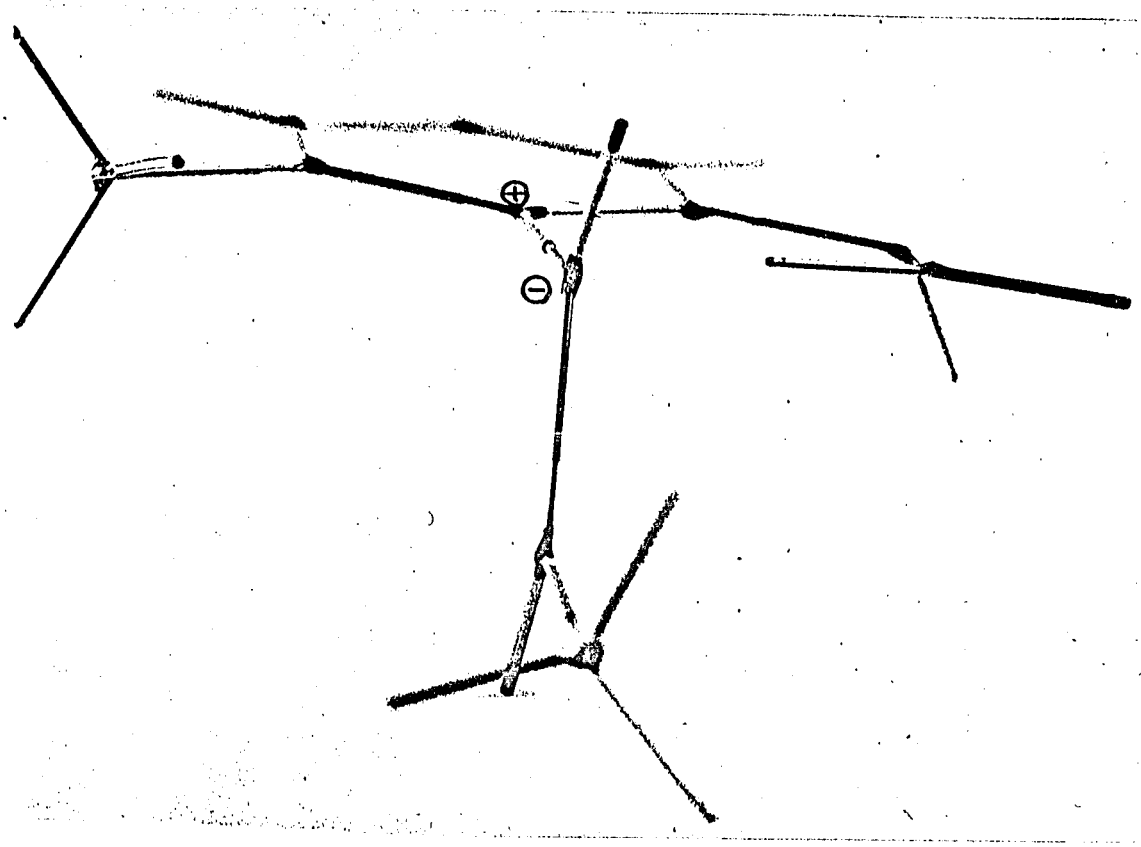


FIGURE 3

NMR Spectrum of 2,5-dimethylimidazo[1,2-a]-pyridine (II) in $DCCl_3$ (500 c.p.s. sweep width).

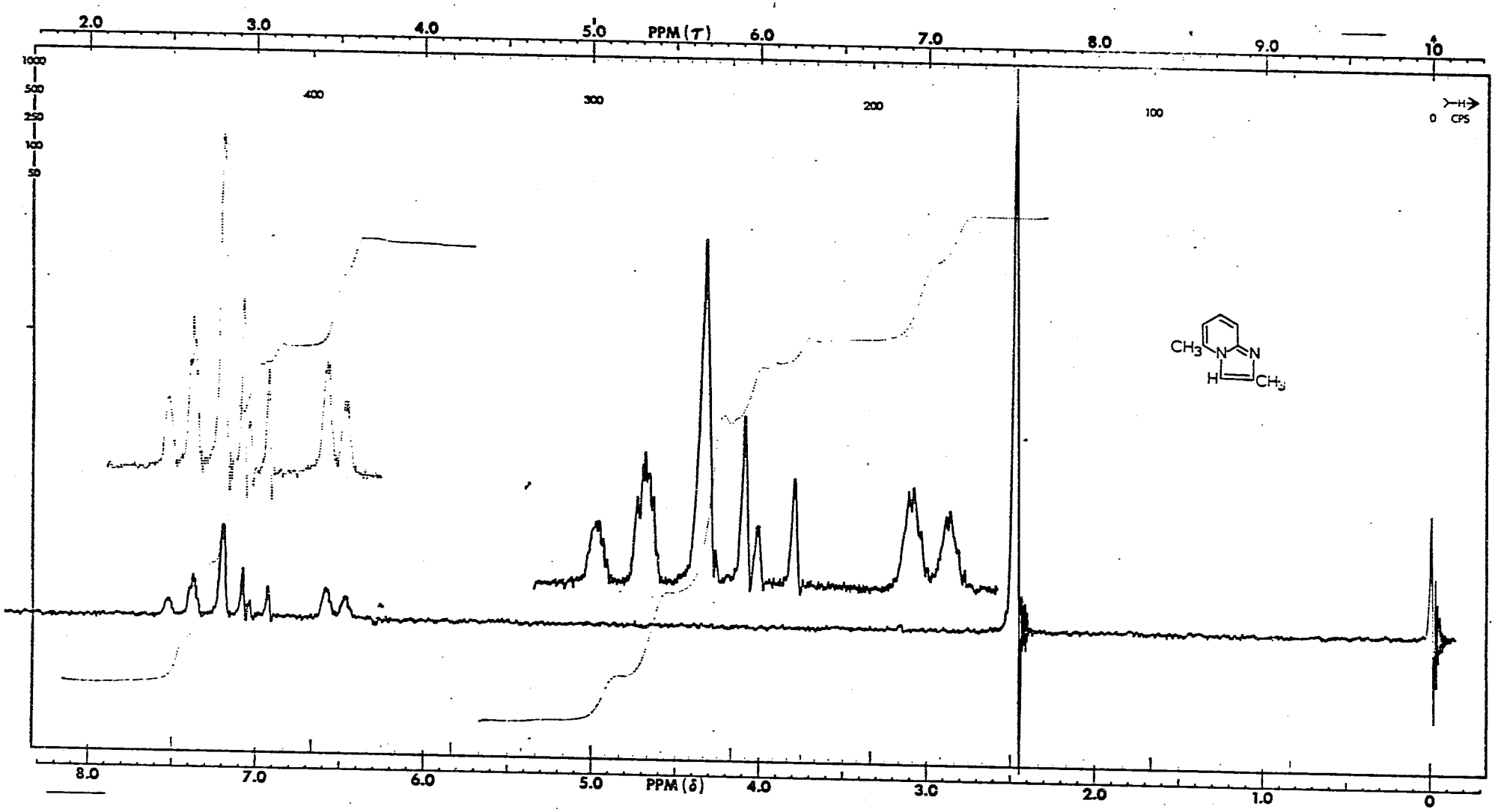

PPM (τ)
PPM (δ)
CPS
CH3
N
N
H
CH3

FIGURE 4

NMR Spectrum of 3-acetyl-2,5-dimethyl imidazo[1,2-a]pyridine (III) in $DCCl_3$ (500 c.p.s. sweep width).

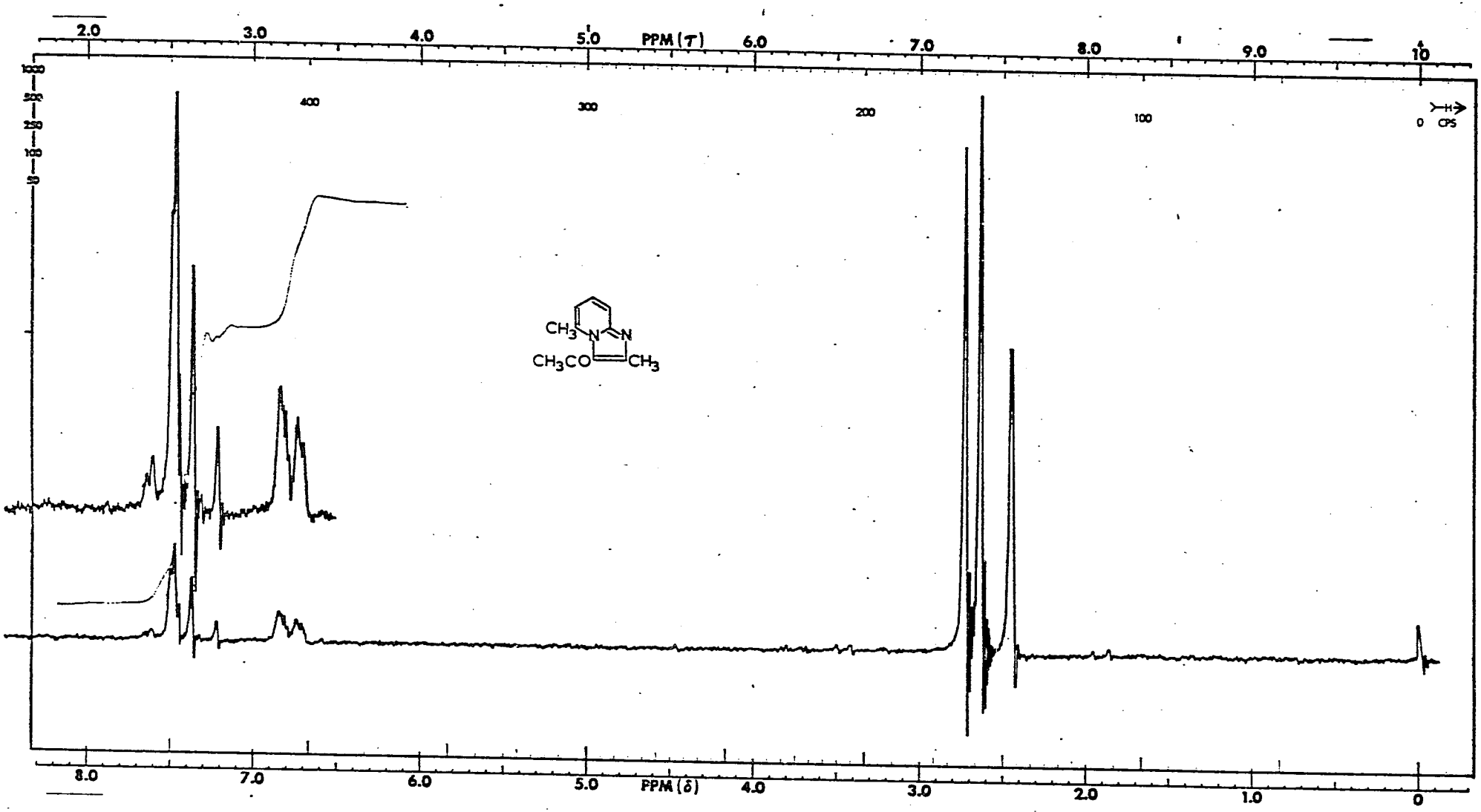

PPM (τ)
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10
400
300
200
100
0 CPS
CH3
N
N
CH3CO
CH3
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

FIGURE 5

NMR Spectrum of 6-methyl-2-trifluoromethyl imidazo[1,2-a]pyridine (XV) in $DCCl_3$ (500 c.p.s. sweep width).

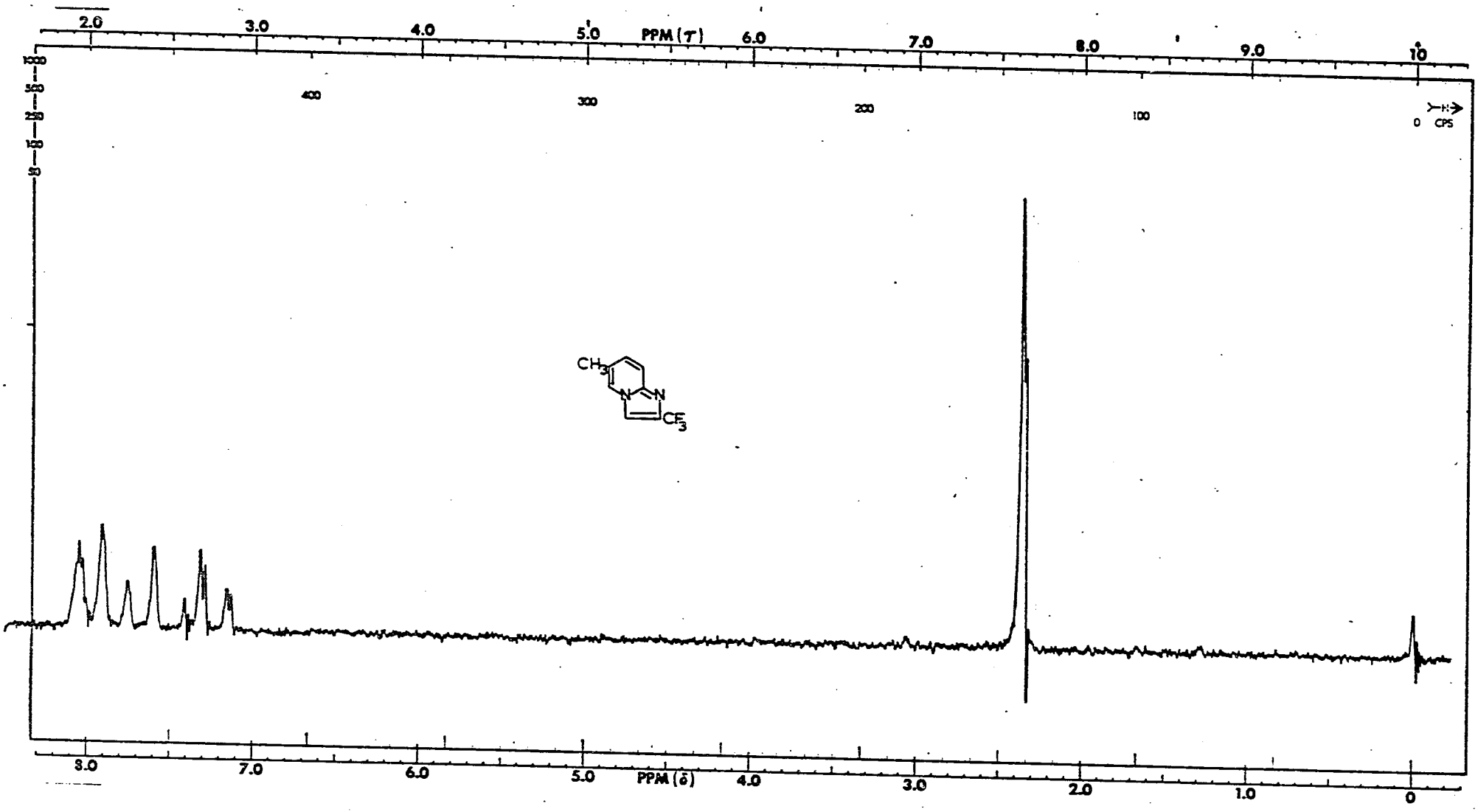

PPM (τ)
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10
400
300
200
100
0 CPS
CH3
N
N
CF3
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

FIGURE 6

NMR Spectrum of 5-acetamido-3-acetyl-2-methylimidazo[1,2-a]pyridine (XVI) in $DCCl_3$ (500 c.p.s. sweep width).

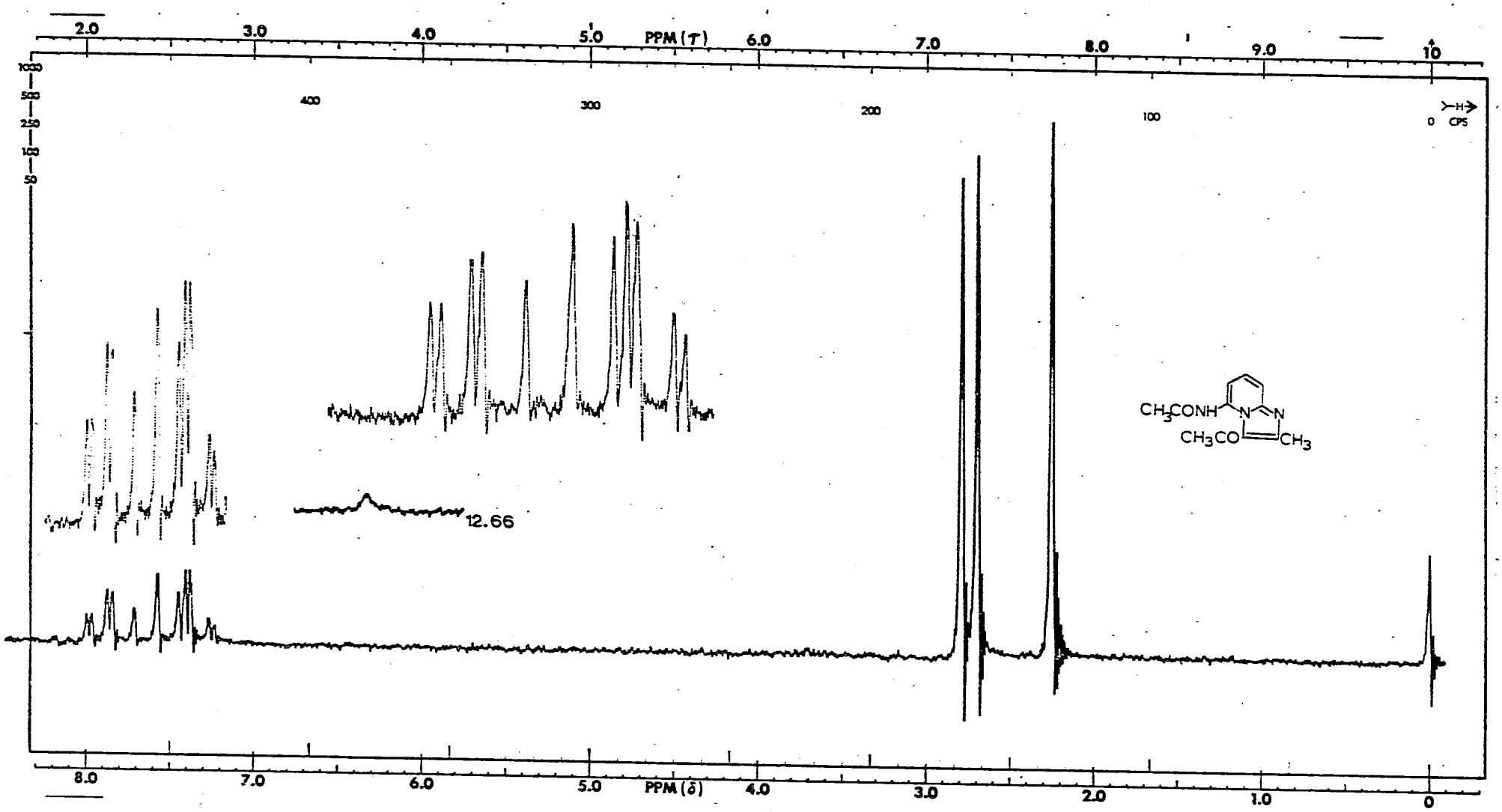

PPM (τ)
PPM (δ)
CPS
12.66
CH3CONH
CH3CO
CH3

FIGURE 7

NMR Spectrum of 5-acetamido-2-methyl-imidazo[1,2-a]pyridine (XXXIII) in $DCCl_3$ (1000 c.p.s. sweep width).

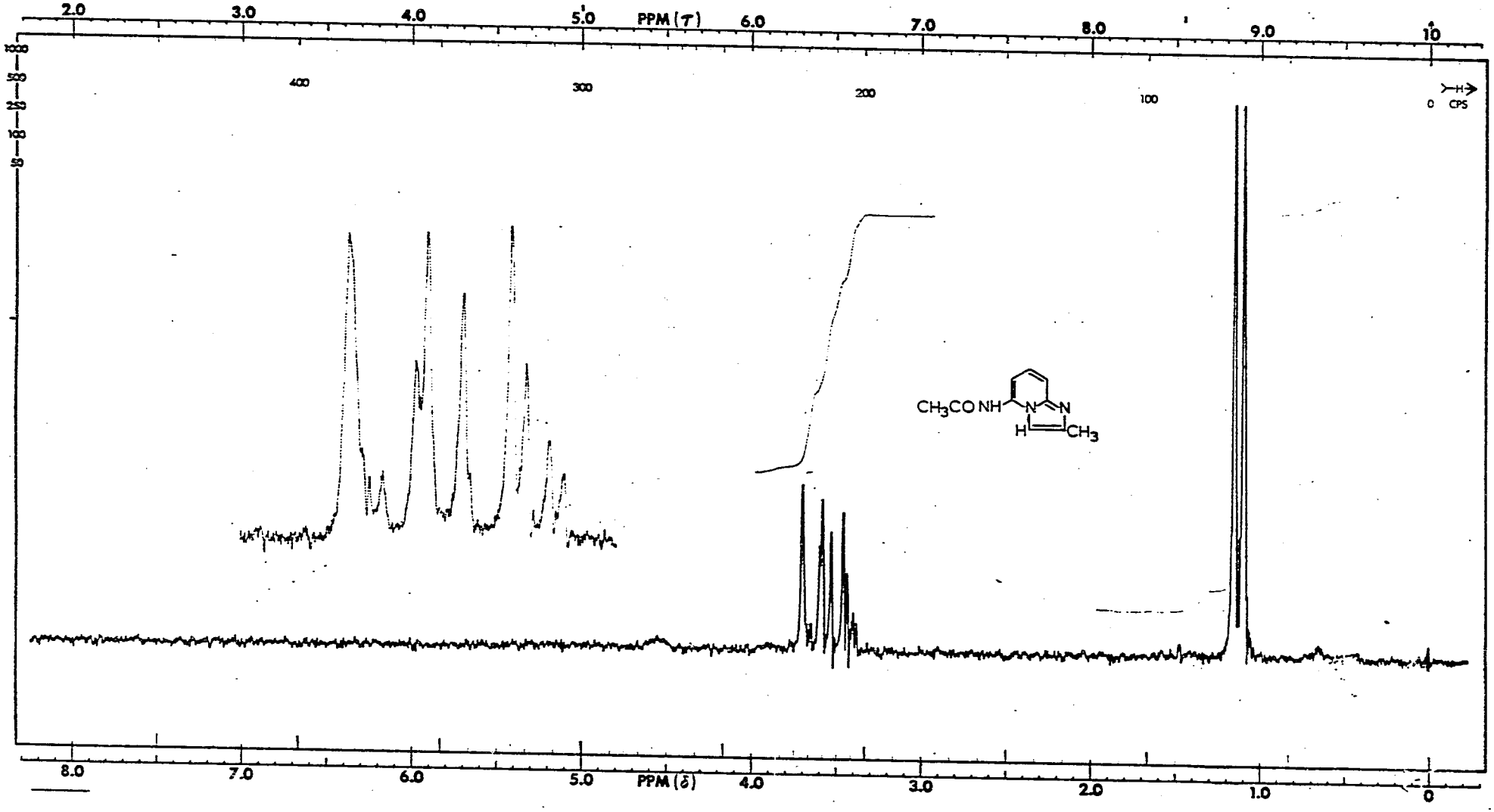

PPM (τ)
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10
400
300
200
100
0
CPS
CH3CO NH
N
N
H
CH3
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

FIGURE 8

U.V. Spectrum of 2,3-dimethyl-1,4-diaza-cycl[3.2.2]azine (XVIII) in absolute ethanol.

- · - · - · - · - (3.6 mg./10 ml.)

——————————— (0.014 mg./10 ml.)

---------- (0.00058 mg./10 ml.)

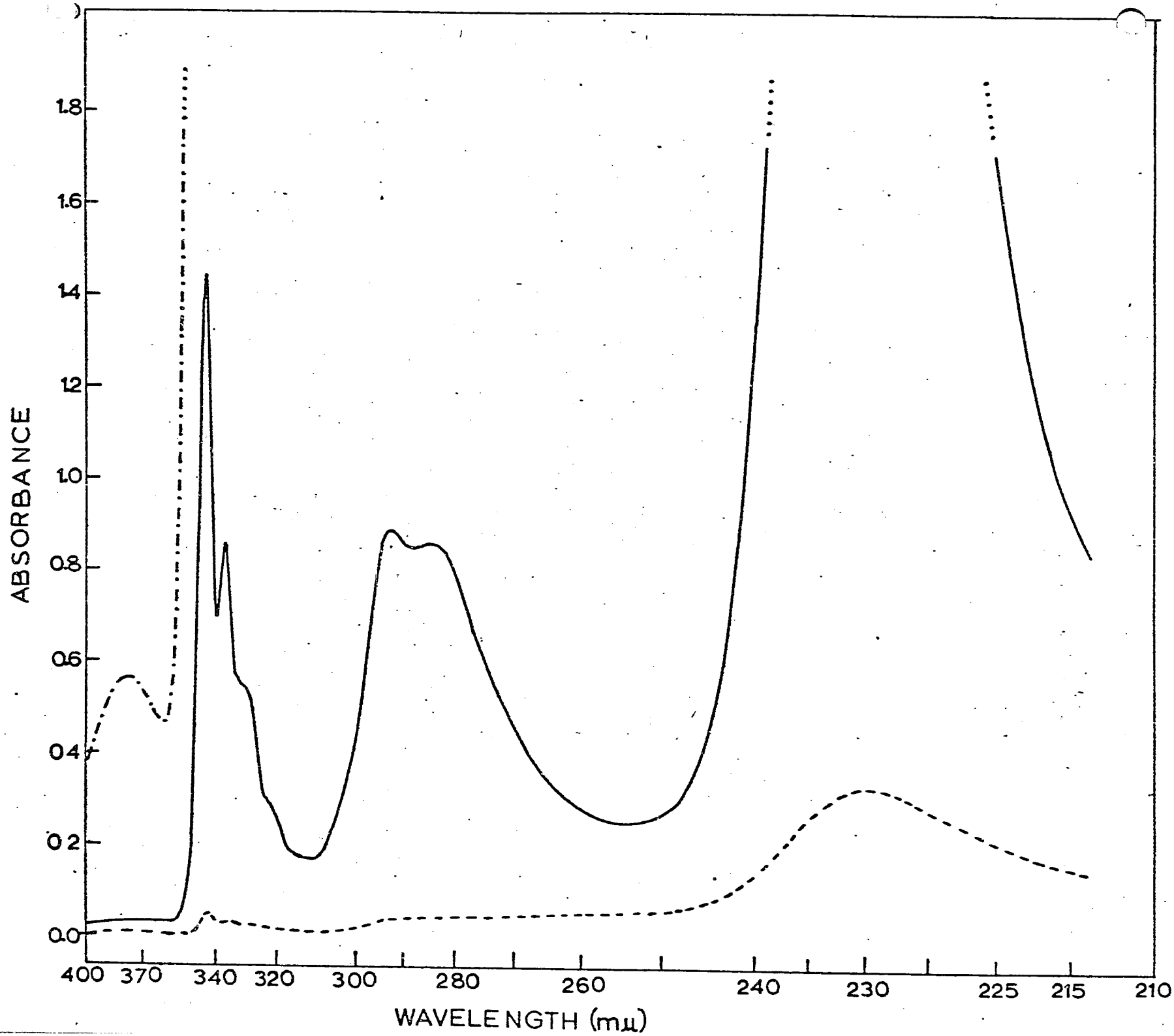

ABSORBANCE
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
400
370
340
320
300
280
260
240
230
225
215
210
WAVELENGTH (mμ)

FIGURE 9

I.R. Spectrum of 2,3-dimethyl-1,4-diaza-cycl[3.2.2]azine (XVIII) in KBr.

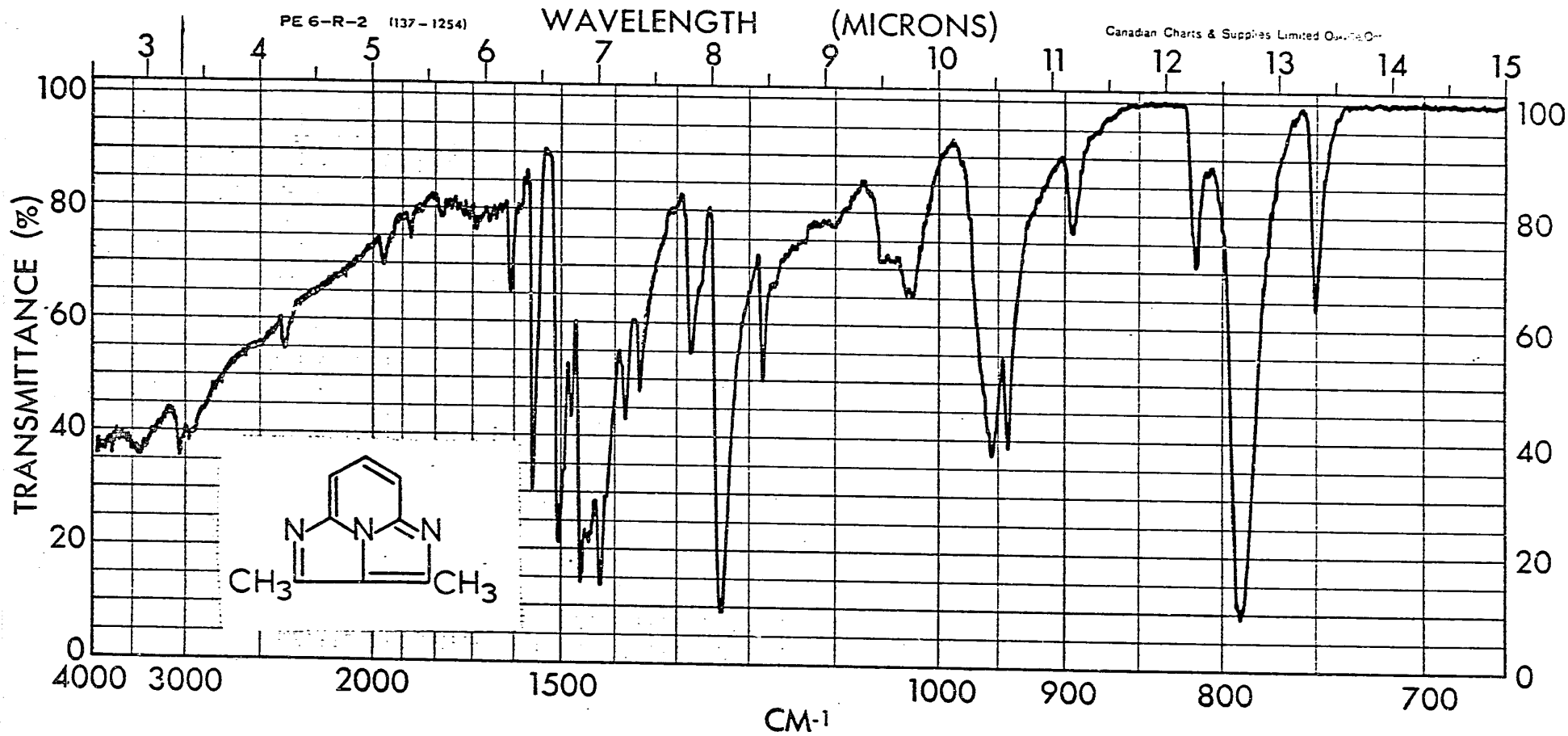

PE 6-R-2 (137-1254)
WAVELENGTH (MICRONS)
Canadian Charts & Supplies Limited
3
4
5
6
7
8
9
10
11
12
13
14
15
TRANSMITTANCE (%)
100
80
60
40
20
0
4000
3000
2000
1500
1000
900
800
700
CM-1
N
N
N
CH3
CH3

FIGURE 10

NMR Spectrum of 2,3-dimethyl-1,4-diaza-cycl[3.2.2]azine (XVIII) in $DCCl_3$ (500 c.p.s. sweep width).

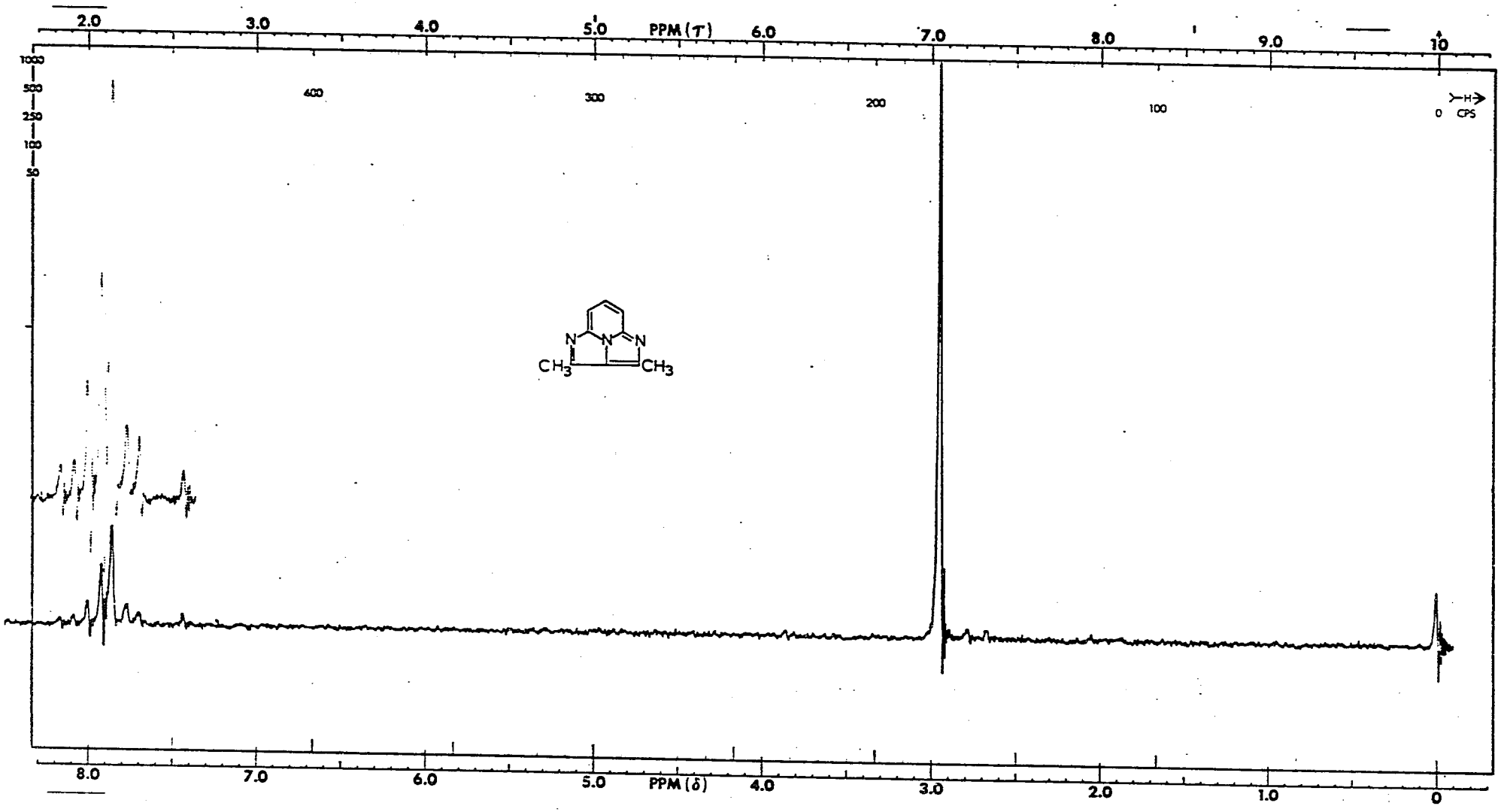

PPM (τ)
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10
1000
500
250
100
50
400
300
200
100
0
CPS
N
N
N
CH3
CH3
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
0

FIGURE 11

NMR Spectrum of 2-trifluoroacetamidopyridine (XXXV) in $DCCl_3$ (500 c.p.s. sweep width; 300 c.p.s. sweep offset).

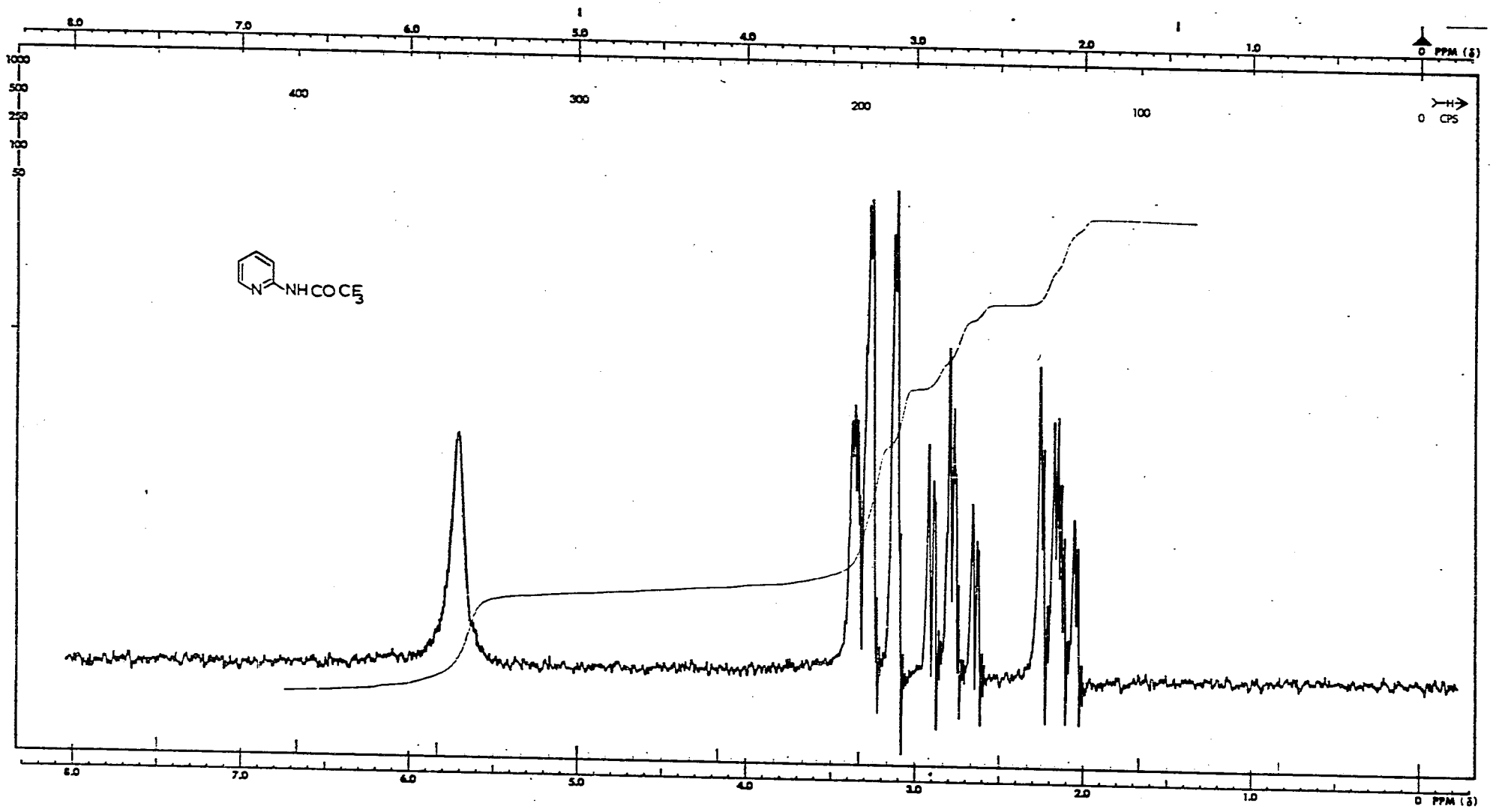
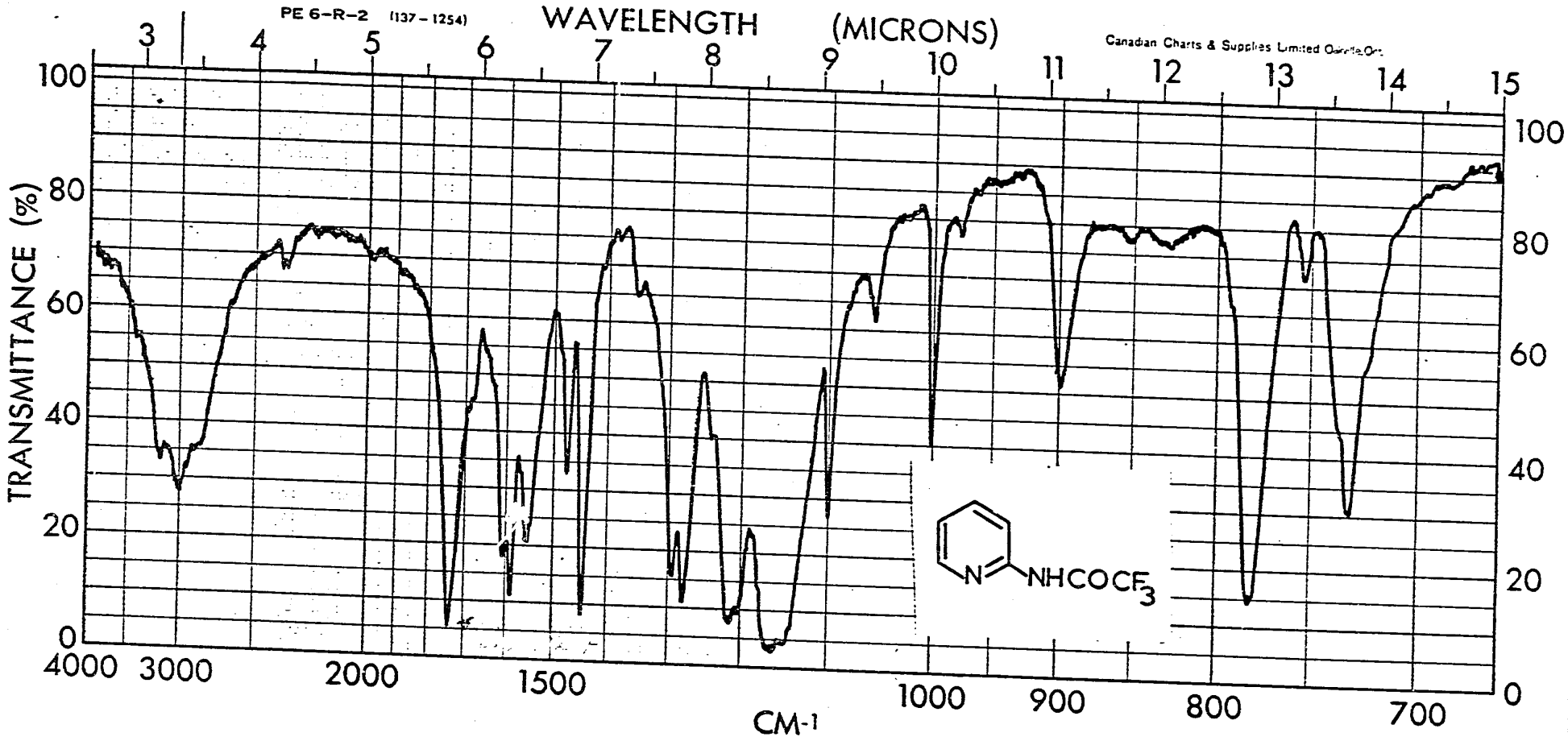

NHCOCF3
N
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0 PPM (δ)
1000
500
250
100
50
400
300
200
100
0 CPS

FIGURE 12

I.R. Spectrum of 2-trifluoroacetamidopyridine (XXXV) in KBr.


PE 6-R-2 (137-1254)
WAVELENGTH (MICRONS)
Canadian Charts & Supplies Limited
3
4
5
6
7
8
9
10
11
12
13
14
15
TRANSMITTANCE (%)
100
80
60
40
20
0
4000
3000
2000
1500
1000
900
800
700
CM-1
N
NHCOCF3

SUMMARY AND CONTRIBUTION TO KNOWLEDGE

1. 2-Acetamido-1-acetonyl-6-methylpyridinium hydrobromide was prepared and treated with base at 0°. The cyclization reaction did not give the expected 3-acetyl-2,5-dimethylimidazo[1,2-a]pyridine, but instead, 2,5-dimethylimidazo-[1,2-a]pyridine was obtained. It was expected that this latter product would form in an acid catalyzed cyclization of the above salt.

2. The above anomalous cyclization prompted a reinvestigation of Kröhnke's synthesis and further studies of its mechanism. A test was devised capable of distinguishing between steric and electronic effects of the 6-position methyl group on the course of the cyclization.

3. In compliance with the requirements of the above test, 1-acetonyl-2-formamidopyridinium hydrobromides were prepared, carrying methyl group substituents in the 4- and 5-positions of the pyridine ring; also 1-acetonyl-4,6-dimethyl-2-formamidopyridinium hydrobromide was prepared from the corresponding amide.

4. The above salts were cyclized in alkaline medium giving mixtures of imidazo[1,2-a]pyridines, with and without an acetyl group in the 3-position; each salt gave a characteristic percentage of the acetylated compound. This proportion was dependent on the position of the methyl group on the pyridine ring.

1-Acetonyl-2-formamido-6-methylpyridinium hydrobromide and 2-acetamido-1-acetonyl-6-methylpyridinium hydrobromide when treated with base, gave the same product - the 2,5-dimethylimidazo[1,2-a]pyridine.

The results, outlined above, led to the following conclusions:

a. The outcome of the cyclization is governed by the competition between the rate of amide bond hydrolysis and the rate of carbanion attack on the amide carbonyl group.

b. When the pyridine ring carries a substituent, such as a methyl group in the 6-position, the rate of amide bond hydrolysis is greater than that of the carbanion attack. The 6-position substituent is capable of influencing the stability of the carbanion formed at the N-methylene carbon atom, thus impairing the reactivity of this centre.

c. The preparation of 3d-2,5-dimethylimidazo[1,2-a]-pyridine from 2-acetamido-1-acetonyl-6-methylpyridinium hydrobromide in deuterium oxide solvent permitted further elucidation of the base catalyzed cyclization; the distinction being between the rate of carbanion formation and its rate of attack. It was found that the latter rate is considerably smaller than the rate of carbanion formation.

5. Additional information about the mechanism of the imidazo-[1,2-a]pyridine ring formation was obtained from the synthesis of 5-methyl-2-trifluoromethylimidazo[1,2-a]pyridine. On

treatment of 2-amino-5-methylpyridine with 1,1,1-trifluorobromoacetone, a partially aromatic betaine was obtained. The dehydration-aromatization of this betaine was suppressed by the failure of the oxygen function to undergo β-elimination. Only after the oxygen function has been transformed into a better leaving group (acetate), did dehydration occur, giving the (fully aromatic) 5-methyl-2-trifluoromethylimidazo[1,2-a]-pyridine. This observation suggests that the dehydration stop (which aromatizes the five-membered ring) depends on the formation of a carbonium ion centre at the 2-position.

Attempts to quaternize 2-trifluoroacetamidopyridine with bromo- or chloroacetone and to employ reactive halides other than bromoacetone in Kröhnke's approach lead to inconclusive results. It seems that Kröhnke's synthesis is not a general one; its scope is limited by substituent effects and by the availability of 2-acylamido-1-alkylpyridinium salts.

6. 5-Amino-2-methylimidazo[1,2-a]pyridine was treated with acetic anhydride. Two products were obtained - 5-acetamido-2-methylimidazo[1,2-a]pyridine and 5-acetamido-3-acetyl-2-methylimidazo[1,2-a]pyridine in 39 per cent and 17 per cent yields respectively.

7. 5-Acetamido-3-acetyl-2-methylimidazo[1,2-a]pyridine was treated with base, resulting in a cleavage of the amide bond. The free amino group condensed intramolecularly with the 3-position acetyl group giving a novel heteroaromatic system -

the 2,3-dimethyl-1,4-diazacycl[3.2.2]azine.

An attempt to induce a similar intramolecular condensation in 3-acetyl-2,5-dimethylimidazo[1,2-a]pyridine failed to give the desired 1-azacycl[3.2.2]azine derivative.

8. 5-Amino-2-methylimidazo[1,2-a]pyridine was nitrated by a nitration mixture consisting of 90 per cent nitric acid dissolved in conc. sulphuric acid. Multiple nitration of the aromatic ring resulted in the formation of 5-amino-2-methyltrinitroimidazo[1,2-a]pyridine.

9. 2-Trifluoroacetamidopyridine was prepared by acylation of 2-aminopyridine with trifluoroacetic anhydride. The i.r. spectrum of the amide shows the carbonyl group absorption band at 1740 cm^{-1}, which, according to Sheinker's study, rules out the acylimine tautomeric form. Additional data indicate that Sheinker's compound is not 2-trifluoroacetamido-pyridine, thus doubt is thrown on the validity of his conclusion concerning the tautomerism in 2-acylamidopyridines.

10. The n.m.r. spectra of 2,5-dimethylimidazo[1,2-a]pyridine and of 2,5,7-trimethylimidazo[1,2-a]pyridine were recorded by employing solvents of varying chemical and physical character. The solvents formed complexes exclusively with the six-membered ring of imidazo[1,2-a]pyridine. Consequently the 5- and 7-position methyl group absorption line were shifted to higher field. The 2-position methyl group

11. The following new compounds were prepared and characterized:

2-Acetamido-1-acetonyl-6-methylpyridinium hydrobromide (I)

2,5-Dimethylimidazo[1,2-a]pyridine (II)

3-Acetyl-2,5-dimethylimidazo[1,2-a]pyridine (III)

2-Hydroxy-6-methyl-2-trifluoromethyl-3H-imidazo[1,2-a]-pyridinium hydrobromide (XIII)

2-Hydroxy-6-methyl-2-trifluoromethyl-3H-imidazo[1,2-a]-pyridinium hydroxide betaine (XIV)

6-Methyl-2-trifluoromethylimidazo[1,2-a]pyridine (XV)

5-Acetamido-3-acetyl-2-methylimidazo[1,2-a]pyridine (XVI)

2,3-Dimethyl-1,4-diazacyl[3,2,2]azine (XVIII)

2-Formamido-6-methylpyridine (XIX)

1-Acetonyl-3-acetyl-2,5-dimethylimidazo[1,2-a]pyridinium hydrochloride (XX)

2-Formamido-5-methylpyridine (XXI)

1-Acetonyl-2-formamido-5-methylpyridinium hydrobromide (XXII)

3-Acetyl-6-methylimidazo[1,2-a]pyridine (XXIII)

2,6-Dimethylimidazo[1,2-a]pyridine (XXIV)

2-Formamido-4-methylpyridine (XXV)

1-Acetonyl-2-formamido-4-methylpyridinium hydrobromide (XXVI)

3-Acetyl-7-methylimidazo[1,2-a]pyridine

2-Formamido-4,6-dimethylpyridine (XXIX)

1-Acetonyl-4,6-dimethyl-2-formamidopyridinium hydrobromide (XXX)

2,5,7-Trimethylimidazo[1,2-a]pyridine (XXXI)

3-Acetyl-5,7-dimethylimidazo[1,2-a]pyridine (XXXII)

5-Acetamido-2-methylimidazo[1,2-a]pyridine (XXXIII)

5-Amino-2-methyltrinitroimidazo[1,2-a]pyridine (XXXIV).

2-Trifluoroacetamidopyridine (XXXV).

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