[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

STUDIES IN THE PYRIDINE SERIES. V. REACTIONS INVOLVING THE ORTHO EFFECT IN CERTAIN β,γ SUBSTITUTED PYRIDINES

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Received January 15, 1942

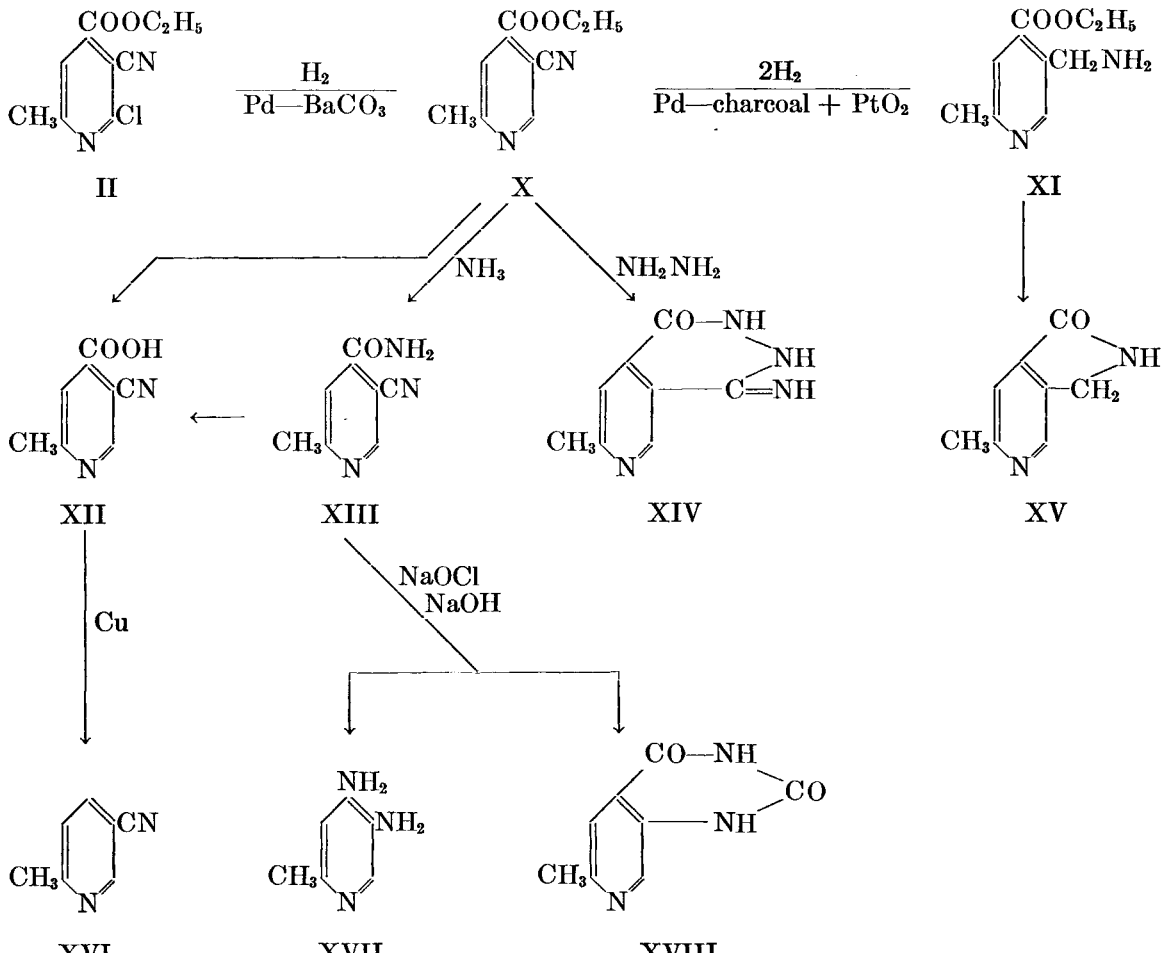
With the increasing importance which is being assumed by various derivatives of pyridine as a result of the recognition that these substances constitute integral parts of such physiologically important classes as the nucleic acids and the vitamin B complex, a fuller knowledge of the behavior of pyridine derivatives becomes desirable.

Most of the studies hitherto reported on pyridine derivatives are the result of work done some time ago, and frequently the observations on record leave considerable to be desired. Thus, in many cases insufficient data exist to enable one to predict the behavior of a given pyridine derivative under definite experimental conditions, except by analogy to corresponding benzene derivatives, a procedure often dangerous because of the difference in behavior of substituents in the α- and γ-positions of the pyridine nucleus compared with one in the β-position. Furthermore, the published data frequently omit yields, formation of by-products, etc., and are to a greater or less extent unsatisfactory. In order to clarify some of these points, it was felt that a study of certain transformations of pyridine derivatives containing substituents in the β- and γ-positions might be of help.

For this purpose, the 2-methyl-4-carbethoxy-5-cyano-6-pyridone described by Bardhan (1) forms a readily accessible substance. It carries two reactive groups in the desired β- and γ-positions, and possesses in addition a substituent in one of the α-positions which can be used to study the ortho effect on the adjacent group in the β-position. For the immediate purpose at hand this pyridone (I) was converted into the corresponding chloro derivative (II). Parallel experiments were then carried out on 2-methyl-4-carbethoxy-5-cyano-6-chloropyridine, in which the nitrile group in position 5 is sterically hindered by the chlorine atom in position 6 (hereafter designated as the hindered compound), and on the chlorine-free compound (X) in which the ortho effect is absent.

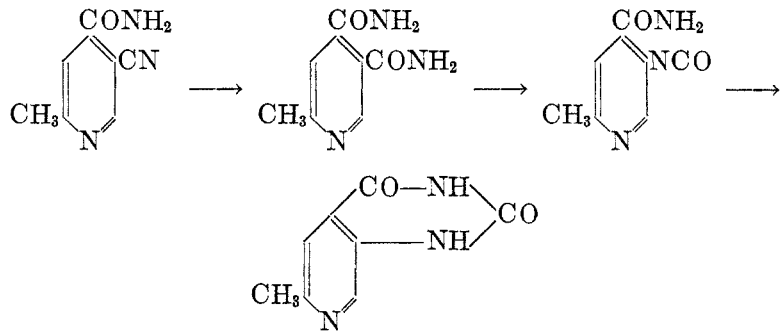
The first series of experiments dealt with the conventional Hofmann degradation of both the hindered and free cyano amides (III and XIII). These were readily prepared by treatment of the appropriate esters with ammonia. Hofmann degradations of isonicotinic acid amide and cinchomeronic acid 4-amide have been described in the literature (2, 3), with no yields reported. Dioxycopazoline has been obtained from the diamide of cinchomeronic acid by the same means (4, 5). In the benzene series, Hofmann degradation of the diamide

COOC2H5
CN
Cl
CH3
N
O
H
I
PCl5
POCl3
II
NH3
NH2—NH2
H+ or OH−
H2O
CONH2
III
CONHNH2
V
HNO2
C6H5CHO
CONHN=CHC6H5
VI
COOH
IV
H+
H2O
SOCl2
Cu
CH3OH
or
CH3ONa
Br
CH3ONa
CONHBr
VII
COOH
VIII
CN
IX
COCl
XIX


COOC2H5
CN
CH3
Cl
N
II
H2
Pd—BaCO3
X
2H2
Pd—charcoal + PtO2
CH2NH2
XI
NH3
NH2NH2
COOH
CONH2
CO—NH
NH
C=NH
CO
XII
XIII
XIV
XV
Cu
NaOCl
NaOH
NH2
CO
XVI
XVII
XVIII

of phthalic acid and of *o*-cyanobenzamide (6, 7) is reported as yielding benzoyleneurea by a reaction analogous to the formation of dioxycopazoline. It was of interest, therefore, to determine whether any differences between the benzene series, in which the positions are equivalent, and the pyridine series, in which the β- and γ-positions show differences in behavior, are apparent.

When the amide of 2-methyl-5-cyanoisonicotinic acid (XIII) was subjected to the Hofmann degradation using aqueous sodium hypochlorite solution (8), the products isolated were 2-methyldioxycopazoline (XVIII) and 2-methyl-4, 5-diaminopyridine (XVII) in the ratio of about 9 to 1. This contrasts with the degradation of *o*-cyanobenzamide which is reported as yielding no diamino derivative. We believe that the formation of 2-methyldioxycopazoline may be explained by the series of reactions:



The alternative scheme in which the nitrile is hydrated to the amide while the amide in the 4-position is converted to the isocyanate, seems unlikely on the basis of observations to be presented later on the stability of a haloamide in the γ-position of the pyridine ring. In any event, the formation of the dioxycopazoline arises by interaction of an amide group with an isocyanate group and parallels the observations of Jeffrys (9) on the formation of acyl-alkyl ureas as by-products of the Hofmann degradation in the aliphatic series.

When the degradation of the hindered amide of 2-methyl-5-cyano-6-chloroisonicotinic acid was investigated, a strikingly different behavior both of the amide and of the nitrile group was noted. As expected, the reactivity of the nitrile group was somewhat repressed in so far as hydration to an amide is concerned. However, the amide group in position 4 assumed an enhanced susceptibility to hydrolysis compared to the non-hindered compound discussed above. When the chloro derivative (III) was treated with cold aqueous alkaline hypobromite solution, the only product isolated was the sodium salt of 2-methyl-5-cyano-6-chloroisonicotinic acid, which obviously must arise by hydrolysis of the amide. As a result of the behavior of the free and hindered amides on acid hydrolysis, we believe that this apparent lability of the amide is due to the ortho effect of the chlorine atom on the nitrile group. When either amide is dissolved in cold dilute hydrochloric acid, the corresponding acid precipitates almost immediately. However, in the case of the free nitrile, under alkaline conditions, hydration of the nitrile to the amide apparently proceeds even faster than

hydrolysis of the amide in position 4. In the case of the hindered nitrile such hydration is repressed with the result that the nitrile continues to exert its activating influence on the amide in position 4. With the hydration of the nitrile in the unhindered compound, an amide results, which would not be expected to induce such rapid hydrolysis of a vicinal amide. A similar ease of hydrolysis of ester groups under alkaline conditions was noted in both series.

While the chlorine atom exerts an ortho effect on the nitrile sufficient to repress its hydration in the sense noted above, this is by no means as pronounced as might have been predicted. It is well known that di-ortho substituted nitriles in the benzene series are difficultly hydrolyzed, (10, 11, 12, 13), and to a lesser extent mono-ortho substituted nitriles, with the exception of those in which the ortho group is a carboxyl group (14). In the above chloronitrile acid, one would predict on the basis of recorded behavior of such compounds in the benzene series that the nitrile group would be moderately difficult to hydrolyze, in view of the hindering chlorine atom on one side and the activating carboxyl group on the other. Such is not the case, for merely recrystallizing the chloronitrile acid from acidulated water results in hydrolysis to the corresponding cinchomeronic acid derivative (VIII). Thus one is able to prepare at will 5-cyanoisonicotinic acids or cinchomeronic acids, by carrying out hydrolysis of the appropriate derivative under suitable conditions.

Decarboxylation of either of the above cyano acids by the copper method led to the corresponding nitriles (XVI and IX). However, when such decarboxylation was attempted in quantities larger than about one-half gram, the yield suffered markedly.

In view of the easy hydrolysis of the hindered amide when the Hofmann degradation was attempted in aqueous solution, the method of Jeffrys (9), based on the observation of Lengfeld and Stieglitz (16, 17) that sodium methoxide in anhydrous methanol converts bromo amides to urethans which can be subsequently hydrolyzed to amines, was applied to the hindered compound. When the general method of Jeffrys was applied, the amide was recovered unchanged. However, when the amide was treated with exactly one equivalent of bromine and sodium methoxide, a substantially quantitative yield of bromo amide (VII) was obtained. The bromine atom in the latter substance again displayed a remarkable lability. When the bromo amide was merely boiled with methyl or ethyl alcohol, bromine was rapidly liberated and the original amide was recovered. The bromo amide also resisted attempts to rearrange it to the urethan and decomposed to the original amide during all such experiments.

Attention was next directed to a study of the Curtius degradation as applied to both the free and hindered nitrile amides. Isonicotinic acid hydrazide is readily prepared, but available information is to the effect that conversion of the latter to the azide is accomplished only with poor yields (18). In the present case, the reactions of the two esters with hydrazine led to different products depending on whether the ortho effect of the chlorine atom in the 6-position was present or not. Ethyl 2-methyl-5-cyano-6-chloroisonicotinate reacted readily with hydrazine to yield the normal hydrazide (V). As such, a benzal derivative (VI) was readily

prepared. However, in the subsequent treatment of the hydrazide with nitrous acid, the same lability manifested itself as with the corresponding amide, and 2-methyl-5-cyano-6-chloroisonicotinic acid was formed by hydrolysis of the hydrazide. Amyl or butyl nitrite in non-aqueous solution were without effect on the hydrazide. Likewise, treatment of the acid chloride of IV with freshly crystallized sodium azide (19, 20, 21, 22) failed to yield the desired azide.

On the other hand, when ethyl 2-methyl-5-cyanoisonicotinate, in which the ortho chlorine substituent is absent was treated with hydrazine, a substance which furnished analytical figures corresponding to the expected hydrazide was obtained. However, this substance did not yield a benzal derivative when treated with benzaldehyde, and is accordingly assigned the structure XIV. Failure of the hydrazide of the hindered acid to react with the nitrile group may, therefore, be ascribed to the ortho effect of the chlorine substituent in the latter.

Finally, we wish to present some observations on the catalytic reduction of ethyl 2-methyl-5-cyano-6-chloroisonicotinate. The reduction of this compound proceeds smoothly in a stepwise manner in the presence of a palladium on barium carbonate catalyst, and one may stop at ethyl 2-methyl-5-cyanoisonicotinate if desired. However, if the reduction is carried farther in a sodium acetate-acetic acid medium, ethyl 2-methyl-5-aminomethylisonicotinate (XI) may be isolated as the picrate. If the reduction is carried out under strongly acid conditions as used by Kindler (23, 24), the reaction product consists of a mixture of the above amine (XI) and the lactam (XV) derived from it. The free amine when treated with cold dilute hydrochloric acid readily yields the hydrochloride of the lactam. Ring closure to the latter takes place so readily that it has not been possible to isolate the free amine. Treatment of the amine picrate with nitrous acid in the cold, in an attempt to obtain either the lactone or free alcohol, resulted in formation of the lactam.

EXPERIMENTAL

All melting points are corrected for stem exposure.

Ethyl 2-methyl-5-cyano-6-chloroisonicotinate (II). To 100 g. of ethyl 2-methyl-5-cyano-6-hydroxyisonicotinate, prepared according to Bardhan (1), was added 200 g. of phosphorus oxychloride. To the mixture was added, in small portions, 200 g. of finely pulverized phosphorus pentachloride. When the evolution of hydrogen chloride slowed down, the mixture was warmed on the steam-bath until the solution cleared (45 minutes) after which heating was continued 15 minutes longer. The flask was then removed from the steam-bath and allowed to stand two hours, after which the phosphorus oxychloride was removed at reduced pressure and the syrup was poured onto 400 g. of cracked ice. After refrigerating overnight, the granular precipitate was filtered off and dried. The chlorinated product was extracted from unreacted pyridone with petroleum ether. The compound was recrystallized from petroleum ether or dilute alcohol. A very pure material was obtained by subliming the product at 0.1 mm. pressure, and 70°. The compound can also be purified by distillation through an apparatus equipped with a steam-jacketed condenser. The chloro derivative boils at 135–136.5° at 0.5 mm. pressure and melts at 62°. The yield was 50–70%. The compound is insoluble in water and in 10% hydrochloric acid, and soluble in alcohol, ether, benzene, chloroform, hot petroleum ether, and concentrated hydrochloric acid.

Anal. Calc'd for $C_{10}H_9ClN_2O_2$: C, 53.4; H, 4.1; N, 12.5.
Found: C, 53.8; H, 4.3; N, 12.4.

Ethyl 2-methyl-5-cyanoisonicotinate (*X*). One gram of ethyl 2-methyl-5-cyano-6-chloroisonicotinate and two grams of catalyst (5% palladium on barium carbonate) were suspended in 100 cc. of commercial absolute alcohol and shaken with hydrogen gas at atmospheric pressure until the calculated amount of hydrogen was taken up. The catalyst was filtered off, washed with alcohol, and the filtrate was concentrated *in vacuo* to 2 cc. Fifteen cubic centimeters of water was added and an oil separated which soon set to a mass of crystals. The compound was purified by sublimation at 0.1 mm. pressure and 70°. The substance, obtained in 95% yield, may also be recrystallized from dilute alcohol, and melts at 58°.

Anal. Calc'd for $C_{10}H_{10}N_2O_2$: C, 63.2; H, 5.3; N, 14.7.
Found: C, 63.3; H, 5.5; N, 14.9.

Amide of 2-methyl-5-cyanoisonicotinic acid (*XIII*). Ten grams of ethyl 2-methyl-5-cyanoisonicotinate was shaken with 400 cc. of ice-cold concentrated ammonia, keeping the flask in an ice-bath. After an hour a flocculent precipitate appeared. After three hours the amide was filtered off. The yield was 6 g., or 70% of the theory. The compound melts with decomposition at 275°.

Anal. Calc'd for $C_8H_7N_3O$: C, 59.6; H, 4.4; N, 26.1.
Found: C, 59.9; H, 4.7; N, 26.0.

Amide of 2-methyl-5-cyano-6-chloroisonicotinic acid (*III*). Fifty grams of ethyl 2-methyl-5-cyano-6-chloroisonicotinate was shaken at room temperature with 500 cc. of concentrated ammonium hydroxide until no more ester dissolved. The mixture was filtered and the solid was shaken with another 500 cc. of concentrated ammonium hydroxide. The mixture was filtered and the combined filtrates were concentrated at reduced pressure to 300 cc. The amide precipitated and was filtered off. The yield was 28.5 g. of amide which, when recrystallized from benzene or alcohol, melted at 233°. By working up the mother liquors, the yield may be raised to 80%.

Anal. Calc'd for $C_8H_6ClN_3O$: C, 49.3; H, 3.1; N, 21.5.
Found: C, 49.5; H, 3.3; N, 20.3.

Hofmann degradation of the amide of 2-methyl-5-cyanoisonicotinic acid. Methyldioxycopazoline (*XVIII*) *and 2-methyl-4,5-diaminopyridine* (*XVII*). Two grams of the amide was treated with 30 cc. of 10% potassium hydroxide solution and 11 cc. of freshly prepared normal sodium hypochlorite solution. The clear yellow solution was heated on the steam-bath to 80° for 30 minutes. A small amount of gas was evolved. The solution was chilled and extracted with ether. The ether solution, when dried and saturated with dry hydrogen chloride, yielded 5–10% of 2-methyl-4,5-diaminopyridine dihydrochloride, which melted with decomposition above 250°.

Anal. Calc'd for $C_6H_{11}Cl_2N_3$: C, 36.7; H, 5.6.
Found: C, 36.2; H, 5.6.

The cold aqueous solution was neutralized with acetic acid and yielded a copious precipitate of fine yellow needles which were recrystallized from alcohol or pyridine. The yield was 70% of methyldioxycopazoline which did not melt up to 310°.

Anal. Calc'd for $C_8H_7N_3O_2$: C, 54.2; H, 4.0; N, 23.7.
Found: C, 53.9; H, 4.0; N, 24.0.

2-Methyl-5-cyano-6-chloroisonicotinic acid (*IV*). Two grams of the amide of 2-methyl-5-cyano-6-chloroisonicotinic acid was treated with 50 cc. of water and 10 cc. of 6 *N* hydrochloric acid at room temperature. Solution was prompt and the acid separated almost immediately. The acid was recrystallized from water and melted at 198.5°. The yield was quantitative.

Anal. Calc'd for $C_8H_5ClN_2O_2$: C, 48.9; H, 2.5; N, 14.3.
Found: C, 49.2; H, 2.9; N, 14.3.

Alkaline hydrolysis of the ethyl ester of 2-methyl-5-cyano-6-chloroisonicotinic acid was equally striking. The ester was dissolved in the minimum amount of alcohol at room temperature. The theoretical amount of sodium hydroxide in 50% aqueous alcoholic solution was added, and the sodium salt of the acid precipitated at once. It was filtered off and then dissolved in water. Hydrochloric acid was added, which precipitated the nearly pure acid. The compound was recrystallized from water, during which the solution was boiled as little as possible. The acid melted at 198.5°. The yield was nearly quantitative.

The *methyl ester* of the above acid, prepared by means of diazomethane, melts at 168.5°, after sublimation at 0.2 mm. at 100°.

Anal. Calc'd for $C_9H_7ClN_2O_2$: C, 51.3; H, 3.4.
Found: C, 51.6; H, 3.5.

2-Methyl-6-chlorocinchomeronic acid (VIII). 2-Methyl-5-cyano-6-chloroisonicotinic acid was refluxed in 5% hydrochloric acid for one hour. The mixture was chilled and filtered and the acid was recrystallized from water; it melted at 205°. The same compound was isolated from the mother liquors from the recrystallization of 2-methyl-5-cyano-6-chloroisonicotinic acid.

Anal. Calc'd for $C_8H_6ClNO_4$: C, 44.7; H, 2.8; N, 6.5.
Found: C, 45.0; H, 2.7; N, 6.3.

The *dimethyl ester* was prepared with diazomethane, and melted at 85° after recrystallization from dilute alcohol.

Anal. Calc'd for $C_{10}H_{10}ClNO_4$: C, 49.3; H, 4.1.
Found: C, 49.3; H, 4.2.

2-Methyl-5-cyanoisonicotinic acid (XII). The ester (X) was treated with the theoretical amount of sodium hydroxide in alcohol, whereupon the sodium salt precipitated in quantitative yield. The sodium salt was dissolved in water and the solution was acidified with dilute hydrochloric acid. The acid was recrystallized from acidulated dilute alcohol. In a like manner the amide (XIII) was treated with enough cold 0.1 *N* hydrochloric acid to dissolve it. In one minute the acid came out as long flexible needles looking like tufts of cotton. It was recrystallized as above. The acid from either source melted at 230°.

Anal. Calc'd for $C_8H_6N_2O_2$: C, 59.3; H, 3.7.
Found: C, 59.6; H, 3.9.

Decarboxylation of 2-methyl-5-cyanoisonicotinic acid to 2-methyl-5-cyanopyridine (XVI). Two hundred and fifty milligrams of the acid was mixed with 2.5 g. of freshly reduced copper powder and placed in the short side of a 10 mm. diameter Pyrex tube which was bent at an angle of 120° about 5 cm. from the closed end. The charge was heated with a yellow Bunsen flame until no more liquid distilled around the bend in the tube. The distillate crystallized on cooling, and a small amount of this material was sublimed *in vacuo*. The compound melts at 84–85°, as reported by Räth and Schiffman (15) for 2-methyl-5-cyanopyridine. It was impossible to secure satisfactory analytical data for the compound.

Anal. Calc'd for $C_7H_6N_2$: C, 71.1; H, 5.1.
Found: C, 70.5; H, 5.3.

2-Methyl-5-cyano-6-chloropyridine (IX). This was prepared by the same method used for 2-methyl-5-cyanopyridine. The nitrile melts at 114.5–115.5°.

Anal. Calc'd for $C_7H_5ClN_2$: C, 55.1; H, 3.3; N, 18.4.
Found: C, 55.4; H, 3.4; N, 18.3.

Bromo amide of 2-methyl-5-cyano-6-chloroisonicotinic acid (VII). One gram of the amide (III) was suspended in 30 cc. of methyl alcohol and to this was added 0.2 cc. of bromine. To the mixture was added a solution of 0.2 g. of sodium in 10 cc. of absolute methyl alcohol. Following this 0.3 cc. of bromine was added. Solution occurred followed by the precipitation of a solid. The mixture was warmed five minutes on the steam-bath, chilled, and filtered. The precipitate was recrystallized from methyl alcohol and melted at 199.8°. The yield was nearly quantitative. Boiling in alcohol or chloroform caused the formation of free bromine. The bromo amide released iodine from an acidified potassium iodide solution.

Anal. Calc'd for $C_8H_5BrClN_3O$: C, 35.0; H, 1.8; N, 15.3.
Found: C, 35.5; H, 1.9; N, 14.6.

Attempts to rearrange the above bromo amide. Four hundred seventy milligrams of the bromo amide (VII) was refluxed 1.5 hours with a solution of 0.04 g. of sodium in 27 cc. of absolute methyl alcohol. The solvent was removed and the residue was recrystallized from benzene. One-tenth of a gram of bromine-free material was isolated. It melted at 235°, and when it was mixed with the amide (III) the melting point showed no depression. No other product could be isolated from the reaction.

Attempts were also made to form the bromo amide and rearrange it at the same time, but the results were the same as above.

1-Hydroxy-4-amino-7-methyl-2,3,6-pyridopyridazine (XIV). To 0.7 g. of ethyl 2-methyl-5-cyanoisonicotinate, dissolved in a sufficient quantity of a mixture of alcohol and ether (1:1), was added with cooling 0.15 g. of anhydrous hydrazine. Yellow crystals soon precipitated and were filtered off and dried. The yield was 77% of a material which may be crystallized from alcohol, and melts at 324°.

Anal. Calc'd for $C_8H_8N_4O$: C, 54.6; H, 4.6.
Found: C, 54.7; H, 5.2.

The above compound is basic and forms a brilliant red *hydrochloride.* This could not be recrystallized and on heating with alcohol or water decomposition occurred, resulting in the precipitation of the free base.

Anal. Calc'd for $C_8H_9ClN_4O$: C, 45.2; H, 4.3; N, 26.4.
Found: C, 45.3; H, 4.5; N, 26.6.

This compound did not form a derivative with benzaldehyde and, therefore, has been assigned the keto structure XIV.

Hydrazide of 2-methyl-5-cyano-6-chloroisonicotinic acid (V). To 20 g. of ethyl 2-methyl-5-cyano-6-chloroisonicotinate dissolved in the minimum amount of cold ether-alcohol mixture (1:1) was added 4.3 g. of anhydrous hydrazine. The solution was chilled and the cream colored plates were filtered off, washed with alcohol, and dried *in vacuo.* No suitable solvent could be found for recrystallization of this compound. It sublimed above 360°.

Anal. Calc'd for the dihydrate $C_8H_7ClN_4O \cdot 2H_2O$: C, 39.1; H, 4.5.
Found: C, 39.6; H, 4.8.

The *benzal derivative* (VI) of the above hydrazide melted at 282.5°, after recrystallization from alcohol.

Anal. Calc'd for $C_{15}H_{11}ClN_4O$: C, 60.3; H, 3.7.
Found: C, 60.6; H, 4.2.

2-Methyl-5-cyano-6-chloroisonicotinic acid chloride (XIX). One and four-tenths grams of 2-methyl-5-cyano-6-chloroisonicotinic acid was refluxed 6 hours with 20 cc. of thionyl chloride in an apparatus protected from atmospheric moisture with a calcium chloride tube. The excess thionyl chloride was removed at reduced pressure and the acid chloride

crystallized in small rosettes. A small sample was pressed on a clay tile and washed with a small amount of benzene. The compound so treated melts at 98–103°.

That the nitrile group was not attacked by this treatment was shown by preparation of the amide and ethyl ester from the acid chloride. The former melted at 233°, the latter at 62°, and neither showed a depression in melting point when mixed with varying proportions of known amide and ester respectively.

Ethyl 2-methyl-5-aminomethylisonicotinate (XI) and the lactam, 2-methyl-4,5-pyrrolidonopyridine (XV). To 1 g. of ethyl 2-methyl-5-cyano-6-chloroisonicotinate was added 1 g. of 5% palladium metal supported on charcoal, 50 mg. of Adams' platinum oxide catalyst, 0.4 g. of fused sodium acetate, and 100 cc. of redistilled glacial acetic acid. The mixture was shaken with hydrogen at atmospheric pressure and room temperature until 3 molar equivalents of hydrogen had been taken up. The catalyst was filtered off, washed with acetic acid, and the filtrate was concentrated at reduced pressure and room temperature to a syrup. This was taken up in hot alcohol, the inorganic salts were filtered off, and the filtrate was reconcentrated to a syrup. This was taken up in water, treated with saturated aqueous picric acid, and the precipitated picrate was filtered off. The yield was 60% of a compound melting with decomposition at 170°. Analytical figures corresponded with those for the *picrate* of ethyl 2-methyl-5-aminomethylisonicotinate.

Anal. Calc'd for $C_{16}H_{17}N_5O_9$: C, 45.3; H, 4.0.
Found: C, 45.3; H, 3.9.

Reduction of 22 g. of the same nitrile in a solvent composed of 125 cc. of glacial acetic acid and 7 cc. of concentrated sulfuric acid, yielded a mixture of 12.5 g. of the lactam picrate and 22.5 g. of the amine picrate when worked up as above. This represents an over-all yield of 77%. The two compounds could be separated by recrystallization from water. The *lactam picrate* is the less soluble of the two and melts at 205.5°.

Anal. Calc'd for $C_{14}H_{11}N_5O_8$: C, 44.6; H, 2.9; N, 18.6.
Found: C, 44.8; H, 3.1; N, 18.9.

If either of the above reduction mixtures was allowed to become warm while working them up, ring closure always occurred and the lactam picrate was the only product isolated.

Conversion of the picrate to the hydrochloride in the usual manner always yielded the *hydrochloride of the lactam* which sublimes above 285°.

Anal. Calc'd for $C_8H_9ClN_2O$: C, 52.2; H, 4.9.
Found: C, 52.0; 52.2; H, 4.9; 5.0.

The free *lactam* was prepared from the hydrochloride by neutralization with sodium hydroxide. This compound may be recrystallized from benzene or toluene and melts at 250° in a sealed tube.

Anal. Calc'd for $C_8H_8N_2O$: C, 64.8; H, 5.4.
Found: C, 65.1; H, 5.7.

The microanalyses here reported were performed by Mr. Saul Gottlieb of these laboratories.

SUMMARY

1. Catalytic reduction of ethyl 2-methyl-5-cyano-6-chloroisonicotinate leads either to ethyl 2-methyl-5-cyanoisonicotinate or to ethyl 2-methyl-5-aminomethylisonicotinate. The latter substance readily lactamizes and can be isolated only as its salts.

2. The ortho effect of a chlorine atom in the 6-position of the pyridine ring on

the behavior of a nitrile group in the 5-position has been studied from the standpoint of partial and complete hydrolysis of the latter group.

3. The usefulness of the Hofmann and Curtius degradations applied to various isonicotinic and cinchomeronic acid derivatives has been indicated.

4. New methods for the preparation of nicotinic and isonicotinic acid derivatives have been described.

NEW YORK, N. Y.

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