Reactions of 2-Aminopyridine with Picryl Halides (1)

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2-Aminopyridine reacts with picryl halides to give mixtures of 1-picryl-2-(*N*-picrylimino)-1,2-dihydropyridine and 2-(*N*-picrylamino)pyridine. When picryl fluoride is treated with an excess of 2-aminopyridine, the 1-picryl-2-(*N*-picrylimino)-1,2-dihydropyridine reacts further with 2-aminopyridine to yield two molecules of 2-(*N*-picrylamino)pyridine in a reaction catalyzed by the by-product, hydrogen fluoride. In contrast, the compositions of the mixtures obtained from the reactions of picryl chloride and picryl bromide with excess 2-aminopyridine are stable in their reaction media.

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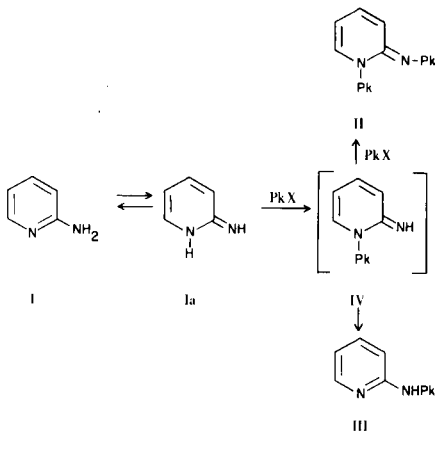
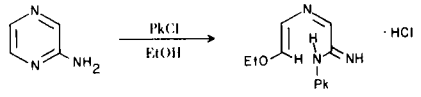
A previous communication from this laboratory (3) reported that 2-aminopyridine (I) reacts rapidly with two molar equivalents of picryl fluoride in DMF at 25° to yield 1-picryl-2-(*N*-picrylimino)-1,2-dihydropyridine (II) as the only product, but that a mixture of II and 2-(*N*-picrylamino)pyridine (III) is obtained when picryl fluoride is treated with two equivalents of I in DMF. However, when picryl chloride was treated with two equivalents of I in ethanol, III was the exclusive product. Furthermore, it was shown that III does not react with picryl fluoride under the conditions of the reaction of I with picryl fluoride.

Scheme I



In an attempt to account for these results, it was suggested that picryl halides react initially with the imino tautomer of I to give 2-imino-1-picryl-1,2-dihydropyridine (IV) as an intermediate, which may react further with picryl halides to give II or rearrange to III. It was further suggested that if the rate of reaction of IV with picryl fluoride to give II was much greater than that of IV with less reactive picryl chloride, then all the results could be rationalized (Scheme I).

The possibility that IV could undergo an amidine (Dimroth) rearrangement was strengthened by the report that the analogous 2-aminopyrazine (V) reacts with picryl chloride in ethanol to give the stable Dimroth intermediate as the hydrochloride (VI) (4).



V VI

In order to test the possibility that III may result from an amidine rearrangement of IV, the reactions of picryl fluoride and picryl chloride with 2-aminopyridine-1-^{15}N (VII) were studied. The labelled compound (VII) was obtained from the amination of pyridine-^{15}N (5) with sodium amide in *N,N*-dimethylaniline (6). Treatment of VII with picryl chloride in refluxing ethanol gave ^{15}N-labelled 2-(*N*-picrylamino)pyridine (VIII). On the other hand, picryl fluoride reacted with VII in DMF at 25° to give a mixture of VIII and ^{15}N-labelled 1-picryl-2-(*N*-

picrylimino)-1,2-dihydropyridine (IX). The mass spectrum of the VIII obtained from both reactions showed parent ion and pyridinium ion fragments with the same ratio of ^{15}N to ^{14}N as that of the original VII. Thus, VIII is 2-(*N*-picrylamino)pyridine-1-^{15}N and no amidine rearrangement occurs during the reaction of 2-aminopyridine (I) with picryl halides to give 2-(*N*-picrylamino)pyridine (III).

Scheme 2

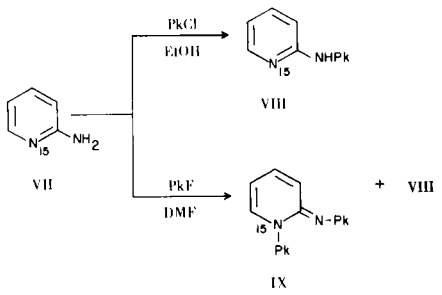


Table I

Reaction of 2-Aminopyridine (I, 0.04 mole) with Picryl Fluoride (0.02 mole) in DMF (60 ml.) at 25° C.

Time (minutes)	I (mole)	II (mole)	III (mole)
1.5	0.0271	0.0071	0.0058
30	0.0268	0.0068	0.0064
60	0.0267	0.0067	0.0066
120	0.0263	0.0063	0.0074
180	0.0255	0.0055	0.0090
240	0.0247	0.0047	0.0106
360	0.0241	0.0041	0.0118
480	0.0236	0.0036	0.0128
1440	0.0200	0	0.0200

Table II

Reaction of 1-Picryl-2-(*N*-picrylimino)-1,2-dihydropyridine (II, 0.01 mole) with 2-Aminopyridine (I, 0.02 mole) in the Presence of Hydrogen Fluoride (0.02 mole) in DMF (60 ml.) at 25° C.

Time (minutes)	I (mole)	II (mole)	III (mole)
15	0.0196	0.0096	0.0008
30	0.0193	0.0093	0.0014
60	0.0191	0.0091	0.0018
90	0.0187	0.0087	0.0026
120	0.0184	0.0084	0.0032
180	0.0178	0.0078	0.0044
240	0.0170	0.0070	0.0060
300	0.0169	0.0069	0.0062
360	0.0163	0.0063	0.0074
420	0.0161	0.0061	0.0078
480	0.0159	0.0059	0.0082

Treatment of picryl fluoride with an excess of 2-aminopyridine (I) in DMF at 25° gave a quantitative yield of a mixture containing 1-picryl-2-(*N*-picrylimino)-1,2-dihydropyridine (II) and 2-(*N*-picrylamino)pyridine (III) within 30 seconds; however, the ratio of III to II increased with time until III was the exclusive product (Table I). An obvious conclusion to be drawn from this change in the composition of the reaction products upon standing is that II reacts further with I to yield III, although no reaction occurred when a solution of II and I in DMF was let stand at 25° for 24 hours. Thus, the by-product of the initial reaction, hydrogen fluoride, must be present in order for the subsequent reaction of I with II to proceed. This conclusion is substantiated by the data in Table II.

In general, weak acids, such as hydrogen fluoride and phenol, and their salts will catalyze the reaction of I with II to give III; however, acetic acid and its salts will not catalyze the reaction. In the latter case equimolar amounts of III and 2-aminopyridine picrate (X) are formed. Strong acids and neutral bases, such as triethylamine and quinuclidine, are ineffective as catalysts for the reaction. The tetraethylammonium fluoride catalyzed reaction (Table III) is somewhat faster than the hydrogen fluoride catalyzed reaction, but the general course of the reactions is the same. In contrast, when equimolar amounts of I, II and sodium phenoxide were dissolved in DMF, equal amounts of the salt of III (XI) and 2,4,6-trinitrophenoxybenzene (XII) were formed immediately. This very rapid reaction was followed by the much slower reaction of I with XII to give III (Table IV). Authentic XII was prepared (7) and its reaction with I proceeded at essentially the same rate (Table V) as that of I with XII generated *in situ* from the reaction of II and sodium phenoxide. The reaction of I with XII was found to be second order, first order in I and first order in XII. When a very small amount of sodium phenoxide was used to catalyze the reaction of I with II, the reaction appeared to be first order in I (Table VI), whereas a small amount of potassium acetate would not catalyze the reaction of I with II.

Table III

Reaction of 1-Picryl-2-(*N*-picrylimino)-1,2-dihydropyridine (II, 0.01 mole) with 2-Aminopyridine (I, 0.02 mole) in the Presence of Tetraethylammonium Fluoride (0.02 mole) in DMF (60 ml.) at 25° C.

Time (minutes)	I (mole)	II (mole)	III (mole)
30	0.01576	0.00576	0.00848
60	0.01494	0.00494	0.01012
90	0.01428	0.00428	0.01144
123	0.01408	0.00408	0.01184
180	0.01352	0.00352	0.01296
240	0.01304	0.00304	0.01392
360	0.01270	0.00270	0.01460

Table IV

Reaction of 1-Picryl-2-(*N*-picrylimino)-1,2-dihydropyridine (II, 0.01 mole) with 2-Aminopyridine (I, 0.01 mole) in the Presence of Sodium Phenoxide (0.01 mole) in DMF (60 ml.) at 25° C.

Time (minutes)	I (mole)	II (mole)	III (mole)	XII (mole)	k_2 (ml. mole^{-1} sec^{-1})
0	0.0100	0	0.0100	0.0100	----
15	0.0095	0	0.0105	0.0095	0.351
30	0.0087	0	0.0113	0.0087	0.498
45	0.0080	0	0.0120	0.0080	0.556
60	0.0076	0	0.0124	0.0076	0.526
120	0.0063	0	0.0137	0.0063	0.489
180	0.0053	0	0.0147	0.0053	0.493
240	0.0047	0	0.0153	0.0047	0.470

Table V

Reaction of 2-Aminopyridine (I, 0.02 mole) with 1-Phenoxy-2,4,6-trinitrobenzene (XII, 0.02 mole) in DMF (60 ml.) at 25° C.

Time (minutes)	I (mole)	III (mole)	XII (mole)	k_2 (ml. mole^{-1} sec^{-1})
15	0.0166	0.0034	0.0166	0.683
30	0.0149	0.0051	0.0149	0.570
90	0.0091	0.0109	0.0091	0.665
120	0.0075	0.0125	0.0075	0.694
180	0.0058	0.0142	0.0058	0.680

None of the weak acids mentioned would react with II in the absence of I, but their anions displaced the 1-picryl group of II to give the anion of III (XI) and the picryl derivative of the acid, P*k*A. The reaction of tetraethylammonium fluoride with II reached equilibrium (K_{eq} = 0.151) at a measurable rate (Table VII), whereas that of potassium acetate with II reached equilibrium (K_{eq} = 37.6) at a rate too rapid to measure. However, the reaction of sodium phenoxide with II went to completion within two minutes.

A mechanism for the catalyzed reaction of I with II to yield III that is consistent with all the data obtained in this study is given in Scheme 3.

Scheme 3

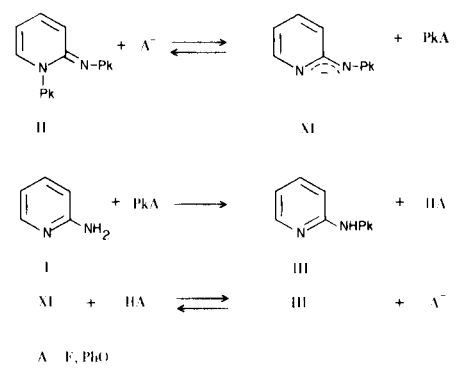


Table VI

Reaction of 1-Picryl-2-(*N*-picrylimino)-1,2-dihydropyridine (II, 0.02 mole) with 2-Aminopyridine (I, 0.04 mole) in the Presence of Sodium Phenoxide (0.004 mole) in DMF (60 ml.) at 25° C.

Time (minutes)	I (mole)	II (mole)	III (mole)	k_1 (sec^{-1})
240	0.0381	0.0181	0.0038	2.03×10^{-4}
360	0.0362	0.0162	0.0076	2.77×10^{-4}
480	0.0358	0.0158	0.0084	2.31×10^{-4}
1440	0.0284	0.0084	0.0232	2.37×10^{-4}
1860	0.0261	0.0061	0.0278	2.30×10^{-4}

Table VII

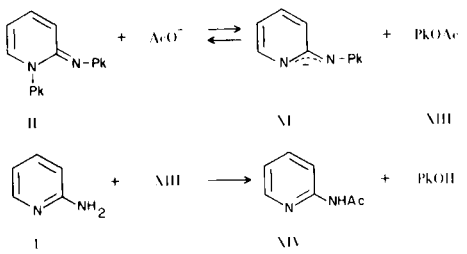
Reaction of 1-Picryl-2-(*N*-picrylimino)-1,2-dihydropyridine (II, 0.005 mole) with Tetraethylammonium Fluoride (0.005 mole) in DMF (120 ml.) at 25° C.

Time (minutes)	II (mole)	III (mole)	k_2 (ml. mole^{-1} sec^{-1})
2	0.0048	0.0002	8.36
5	0.0045	0.0005	9.14
11	0.0041	0.0009	9.04
15	0.0039	0.0011	9.52
30	0.0037	0.0013	
180	0.0036	0.0014	

The phenoxide catalyzed reaction clearly follows the mechanism given in Scheme 3. In this case the phenoxide ion reacts with II to give XI and XII in a very rapid reaction, which is followed by the rate controlling reaction of I with XII to give III and phenol. A rapid reaction of phenol with XI gives the second molecule of III and phenoxide ion for a subsequent reaction with II. The observation that the reaction of I with II catalyzed by a small amount of sodium phenoxide appears to be first order in I is consistent with Scheme 3 because, under these conditions, the concentration of XII is a small, constant value through most of the reaction. In contrast to the phenoxide catalyzed reaction, the reaction of fluoride ion with II is slower than the subsequent reaction of I with the product, picryl fluoride. The kinetics of the overall reaction are complicated because the reaction of I with the picryl fluoride formed in the initial reaction of II with fluoride ion gives II back as the major product.

Although acetate ion will react rapidly with II to yield XI and picryl acetate (XIII), small quantities of acetate ion would not catalyze the reaction of I with II. These observations suggested that I attacks the carbonyl carbon of XIII to give 2-(*N*-acetylamino)pyridine (XIV) and picric acid rather than III and acetic acid (Scheme 4). This interpretation, which accounts for the formation of equal amounts of 2-aminopyridine picrate (X) and III in the reaction of I with II in the presence of acetic acid or potassium acetate, was strengthened when authentic XIII (8) was found to react with I to yield XIV and picric acid.

Scheme 4



Treatment of 2-aminopyridine (I) with picryl chloride and picryl bromide under various reaction conditions gave 2-(*N*-picrylamino)pyridine (III) as the major product along with lesser amounts of 1-picryl-2-(*N*-picrylimino)-1,2-dihydropyridine (II) (Table VIII). The latter compound was formed in significantly greater quantities when the reactions of I and picryl chloride occurred in HMPA than when they occurred in DMF or DMSO. The reactions of I with picryl bromide gave essentially the same ratio of II to III in HMPA and DMSO, but in DMF the ratio was significantly smaller.

The III formed in these reactions is probably the result of a direct nucleophilic attack of I on the picryl halide rather than a subsequent catalyzed reaction of II with I because neither chloride nor bromide ions would catalyze the latter reaction.

The formation of III as the predominant product when two molar equivalents of picryl chloride or picryl bromide were used, as contrasted with the predominant formation of II in the case of picryl fluoride, may well be due to steric factors. A nucleophilic substitution reaction on a picryl halide involving the ring nitrogen of I as the attacking nucleophilic center would be expected to be more sensitive to steric interactions than the reaction in which the exocyclic nitrogen is the attacking nucleophile. In the case of picryl fluoride, where steric interference by the halogen atom is at a miminum, nucleophilic attack involves the ring nitrogen of I, which is more nucleophilic than that of the exocyclic amino group (9,10). With picryl chloride

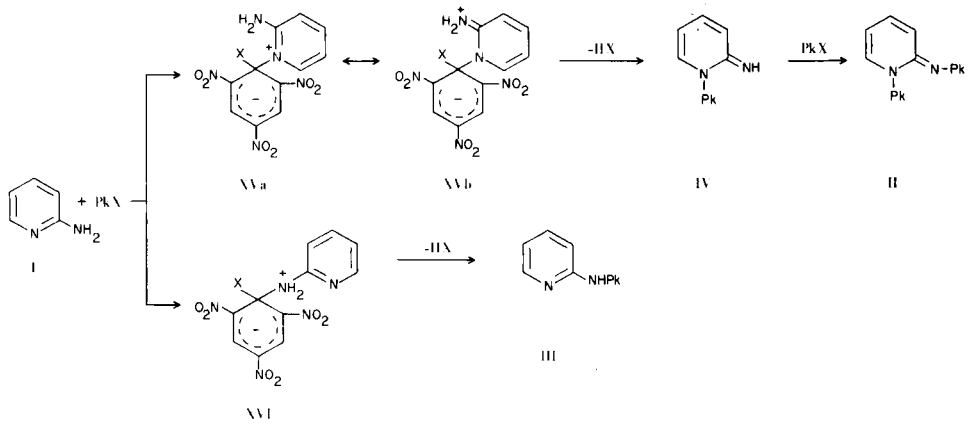
Table VIII

Reactions of 2-Aminopyridine (I) with Picryl Halides (PkX) in Various Solvents at 25° C.

I (mole)	PkX (mole, X)	Solvent (ml.)	Time (hours)	Product Distribution (a) II (%)	III (%)
0.01	0.02, Cl	DMF (10)	1.0	3.7	26.1
0.01	0.02, Cl	DMSO (10)	1.0	8.0	18.6
0.01	0.02, Cl	HMPA (10)	1.0	18.0	25.0
0.02	0.01, Cl	DMF (10)	2.0	4.5	92.1
0.02	0.01, Cl	DMSO (10)	2.0	4.3	92.0
0.02	0.01, Cl	HMPA (10)	2.0	33.0	65.0
0.01	0.02, Br	DMF (10)	6.0	5.1	45.4
0.01	0.02, Br	DMSO (10)	6.0	5.0	25.6
0.01	0.02, Br	HMPA (10)	6.0	4.6	25.7
0.02	0.01, Br	DMF (10)	6.0	3.9	83.0
0.02	0.01, Br	DMSO (10)	6.0	15.4	84.6
0.02	0.01, Br	HMPA (10)	6.0	15.6	84.4

(a) The remainder of the product was unreacted PkX.

Scheme 5

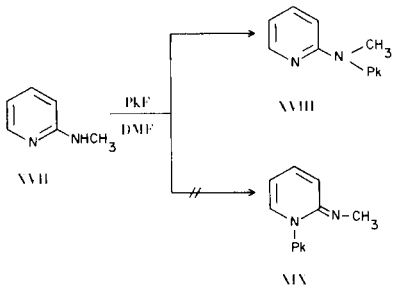


and picryl bromide, steric interactions with the halogen atom become serious and the reaction prefers the less hindered route involving the less nucleophilic exocyclic amino group (Scheme 5).

The higher percentage of II formed by these reactions in HMPA and DMSO compared to DMF may be due to enhanced stabilization of intermediate XV over intermediate XVI by HMPA and DMSO, the more polar of the three solvents studied, since the charge separation of the former is greater than that of the latter.

In order to determine whether the reaction of 2-aminopyridine (I) with picryl fluoride to give a picryl derivative of the imino form is general in scope, 2-(*N*-methylamino)pyridine (XVII) (11) was prepared and treated with picryl fluoride in DMF. The product was assigned the structure of 2-(*N*-methyl-*N*-picrylamino)pyridine (XVIII) on the basis of its pmr spectrum. The chemical shift of the picryl protons of XVIII is 9.02 δ compared to 9.03 δ determined for those of 2-(*N*-picrylamino)pyridine (III).

Scheme 6



It has been established that the chemical shifts of the picryl protons of 1-picrylpyrazoles and 1-picrylimidazoles are in the region of 9.23-9.45 δ and those of the corresponding *N*-picrylamino derivatives are in the region of 8.86-9.14 δ (12,13). Thus, if 1-picryl-2-(*N*-methylimino)-1,2-dihydropyridine (XIX) had been formed in the reaction of XVII with picryl fluoride, the chemical shift of the

Table IX

PMR Chemical Shifts (a)

Compound	Picryl Protons	δ (ppm) Pyridine Protons C-3	C-4	C-5	C-6	Other
I		6.55	7.32	6.43	7.93	
II	8.80, 9.28	6.73	7.55	6.53	7.83	
III	9.03	7.33	7.80	7.07	8.07	
XII	9.24					7.33 (Ph)
XIII	9.17					2.45 (CH_3)
XIV		8.17	7.67	7.00	8.23	2.22 (CH_3)
XVII		6.48	7.30	6.37	8.03	2.88, 2.80 (CH_3)
XVIII	9.02	6.92	7.65	6.78	7.93	3.40 (CH_3)
PkCl	9.07					
PkBr	9.00					

(a) Determined with a Varian A-60A spectrometer as acetone-d_6 solutions using tetramethylsilane as an internal standard.

picryl protons would be expected in the region of 9.2-9.5 δ, especially since the chemical shift of the 1-picryl protons of the analogous 1-picryl-2-(*N*-picrylimino)-1,2-dihydropyridine (II) is 9.29 δ. The pmr chemical shifts of the compounds prepared in this study are given in Table IX.

Apparently, the inductive electron donation of the methyl group of XVII causes the exocyclic amino nitrogen in this case to be more nucleophilic than the ring nitrogen.

EXPERIMENTAL

Reaction of 2-Aminopyridine-1-^{15}N (VII) with Picryl Chloride.

2-Aminopyridine-1-^{15}N (VII) (6) (3.80 g., 0.04 mole) in 25 ml. of absolute ethanol was stirred for five minutes. Following the addition of picryl chloride (4.96 g., 0.02 mole), the mixture was heated under reflux for five hours. It was then allowed to cool to room temperature and poured into 100 ml. of cold water. The precipitate was collected and vacuum dried. Recrystallization from absolute ethanol yielded 5.98 g. (98%) of 2-(*N*-picrylamino)-pyridine-1-^{15}N (VIII), m.p. 128-130°.

Anal. Calcd. for $C_{11}H_7N_4{}^{15}NO_6$: C, 43.15; H, 2.30; N, 23.20. Found: C, 42.86; H, 2.66; N, 22.97.

Reaction of 2-Aminopyridine-1-^{15}N (VII) with Picryl Fluoride.

A solution of 2-aminopyridine-1-^{15}N (VII) (6) (3.80 g., 0.04 mole) in dry *N,N*-dimethylformamide (15 ml.) was stirred for five minutes. After picryl fluoride (9.24 g., 0.04 mole) had been added, the reaction mixture was stirred for one hour and then poured into 100 ml. of cold water. The solid was removed by filtration, washed several times with cold water, air dried (4.42 g.), and transferred to 25 ml. of acetone. The resulting mixture was heated and acetone was added until all of the solid dissolved. Following concentration of the solution, small quantities of absolute ethanol were added until an orange-red solid began to separate. The mixture was allowed to cool to room temperature, then placed into a refrigerator for 30 minutes. Filtration yielded 2.34 g. (22%) of 1-picryl-2-(*N*-picrylimino)-1,2-dihydropyridine-1-^{15}N (IX), m.p. 218°.

Anal. Calcd. for $C_{17}H_{18}N_7{}^{15}NO_{12}$: C, 39.47; H, 1.56; N, 21.85. Found: C, 39.32; H, 1.67; N, 21.76.

The filtrate was concentrated until 2-(*N*-picrylamino)pyridine-1-^{15}N (VIII) began to crystallize, then it was chilled in the freezer. The yield of VIII was 2.08 g. (17%), m.p. 129-130°.

Reactions of 2-Aminopyridine (I) with Picryl Halides and 2,4,6-Trinitrophenoxybenzene (XII).

The amounts of 2-aminopyridine (I) and solvent, indicated in the appropriate table, were placed in a jacketed, round-bottom flask connected to a constant temperature bath maintained at 25 ± 0.1°. The resulting solution was stirred until thermal equilibrium had been established, then the quantity of picryl halide or 2,4,6-trinitrophenoxybenzene (XII) given in the table was added. Samples were withdrawn at the indicated time intervals, weighed, and quenched by adding them to an ice-water mixture. The resulting mixtures were acidified with dilute hydrochloric acid and the precipitated solids were collected by filtration, washed repeatedly with water and dried. After they had been weighed the products were analyzed by pmr spectroscopy. As shown in Table IX the difference between the chemical shifts of the picryl protons of II and III in acetone is large enough to allow accurate integration of these peaks. The ratio of the integrals of the 1-picryl protons of II (9.28 δ) and the picryl protons of III (9.03 δ) was taken as the mole ratio of II to III in the mixture. Likewise, the relative amounts of unreacted picryl chloride, picryl bromide, or 2,4,6-trinitrophenoxybenzene present were determined by integrating their picryl protons at 9.07 δ, 9.00 δ, and 9.24 δ, respectively. When picryl chloride or picryl bromide was present in a mixture with II and III (Table VIII), it was necessary to integrate the combined pyridine protons of II and III in addition to the picryl protons because the picryl protons of III and the picryl halides were not well resolved. Since the portion of the integral of the pyridine protons due to II is twice that of the integral of the 1-picryl protons of II, the remainder of the integral of the pyridine protons is due to III. One-half of the latter value is therefore the portion of the integral of the picryl protons at 9.00-9.07 δ due to III and the remainder of the latter integral is due to the unreacted picryl halide.

Reactions of 1-Picryl-2-(*N*-picrylimino)-1,2-dihydropyridine (II) with 2-Aminopyridine (I) and Various Nucleophiles.

The amounts of 1-picryl-2-(*N*-picrylimino)-1,2-dihydropyridine (II) (3), 2-aminopyridine (I, if used), and solvent indicated in the appropriate table were placed in a jacketed, round-bottom flask connected to a constant temperature bath controlled at 25 ± 0.1°. The resulting solution was stirred until thermal equilibrium had been established, then the catalyst or other species indicated in the table was added. Samples were withdrawn and quenched at the times given in the table and analyzed as described for the reactions of I with picryl halides.

The reactions of II with acetic acid, potassium acetate, and sodium hydroxide in the presence of I gave III and 2-aminopyridine picrate (X) as products. These products were easily separated since III is very soluble in acetone and X is practically insoluble in this solvent at room temperature. Thus, the mixture was stirred in acetone for 30 minutes, then the X was collected by filtration. The filtrate was evaporated to dryness to yield III together with any unreacted II. This mixture was analyzed by pmr spectroscopy. 2-Aminopyridine picrate (X) was identified by comparing its infrared spectrum with that of an authentic sample from I and picric acid.

Reaction of 2-Aminopyridine (I) with Picryl Acetate (XIII).

2-Aminopyridine (I, 0.45 g., 0.005 mole) and picryl acetate (XIII, 1.35 g., 0.005 mole) (8) were dissolved in 15 ml. of DMSO-d_6. The resulting solution was stirred for ten minutes and an aliquot was analyzed by pmr spectroscopy. A comparison of the spectrum of the above solution with that of an equimolar mixture of picric acid and 2-(*N*-acetylamino)pyridine (XIV) (14) in DMSO-d_6 revealed that the chemical shifts of the picryl protons of both solutions were identical (8.55 δ), but significantly different from that of 2-(*N*-picrylamino)pyridine (III) (3) in DMSO-d_6 (8.95 δ). The spectra of both solutions contained a singlet at 2.25 δ corresponding to the acetyl methyl group of XIV, but the reaction mixture contained an additional peak at 1.92 δ. The latter singlet was shown to be due to acetic acid when the addition of a small quantity of this compound caused the peak to increase in magnitude.

2-(*N*-Methyl-*N*-picrylamino)pyridine (XVIII).

2-(*N*-Methylamino)pyridine (XVII, 1.08 g., 0.01 mole) (11) was added to dry *N,N*-dimethylformamide (15 ml.) and the solution was stirred for five minutes. Following addition of picryl fluoride (2.77 g., 0.012 mole) the mixture was stirred for one hour, then it was poured over crushed ice. The precipitate was

removed by filtration, air dried and recrystallized from ethanol-acetone (4:1) to give 2.74 g. (90.7%) of 2-(*N*-methyl-*N*-picryl-amino)pyridine (XVIII), m.p. 147-148°.

Anal. Calcd. for $C_{12}H_9N_5O_6$: C, 42.99; H, 2.71; N, 20.89. Found: C, 42.86; H, 2.91; N, 20.67.

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REFERENCES AND NOTES

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