[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF LOYOLA UNIVERSITY]

SOME NOVEL COLOR REACTIONS OF SOME PYRIDINE DERIVATIVES

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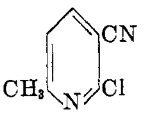
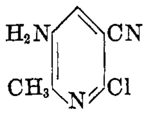
Considerable variation in the reactivity of substituted 2-chloropyridines with alkoxides has been reported (1) and further investigated (2).



I



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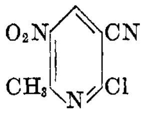
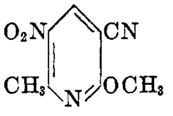
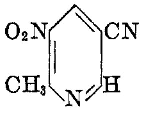


III

For example, I reacted smoothly with alkoxide to give the corresponding ether in high yield, II did not react, and III did react instantly in the cold to give an *intense purple solution.* Later, it was discovered that it was possible to discharge the purple color and to isolate the expected ether IV. It was interesting to note that V, produced from III by controlled reduction, did not produce an intense color when base was added to it.



IV



V

The purpose of this investigation was to study the conditions necessary to produce this color change and to determine the nature of the color species.

The similar 4,6-dimethyl-3-cyanopyridine series was investigated chiefly because of the ease in preparing the starting compounds, (Figure 1).

Improved nitrating techniques converted 4,6-dimethyl-3-cyano-2-pyridone in good yield to VI. VI was hydrolyzed into the corresponding acid VII, from which, by decarboxylation, X was obtained. Neither VI, VII, nor X, gave color reactions with base.

Chlorination of VI gave VIII, analogous in structure to III. When treated with sodium alkoxide, an alcoholic solution of VIII turned a deep purple, in-

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[1] Taken in part from the thesis of John J. Callahan in partial fulfillment of the degree of Master of Science.

[2] Taken in part from the thesis of Abbas O. Jibril in partial fulfillment of the degree of Master of Science. Eli Lilly and Company, Fellow, 1953–1954.

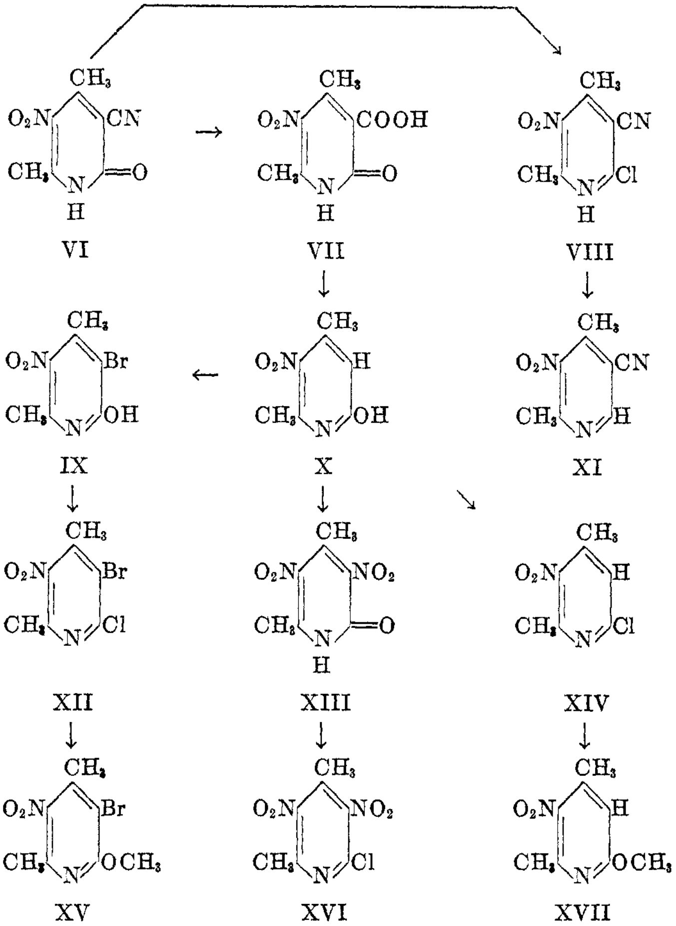
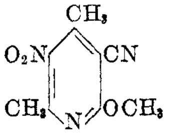
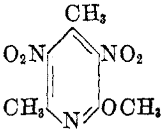


FIG. 1

stantly in the cold. This color then was discharged and the expected ether (XVIII) was isolated.



XVIII



XIX

The chlorination of X gave XIV, which reacted with alkoxide smoothly to give XVII, and without any accompanying color changes. This is similar to the reaction of I with base.

X was nitrated and the dinitropyridone (XIII) was obtained. Chlorination of XIII gave XVI, which, when treated with alkoxide, gave an intense brown-purple color. The color was discharged and the expected ether (XIX) was isolated. In this regard the nitro and nitrile groups have similar activating effects, (*Cf.* XVI and VIII) as would be expected.

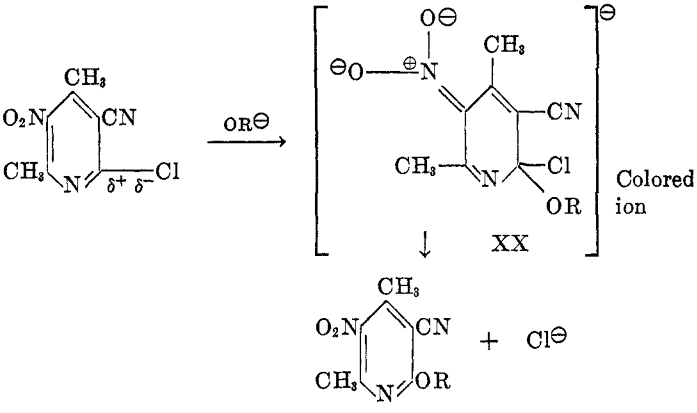
Bromination of X gave IX, which was easily converted into XII, by the use of PCl_5. Treatment of XII with alkoxide gave the corresponding ether XV. Although there was a little color change noted as the reaction proceeded, the intensity was considerably diminished as compared, for example, to the reaction of III with base. In this respect the bromo group has a somewhat different activating effect as compared to the nitro and cyano groups (*Cf.* XII with XVI and VIII), as would be expected.

From the foregoing, it would appear that a 2-chloropyridine, substituted in the 3- and 5- positions with powerful electron-attracting groups, capable of resonance with the ring, will react with bases to give intense colors.

The facile replacement of the 2-chloro group in pyridines substituted in *either* the 3- or 5- positions with nitro or cyano groups is well known (3–6). The activation of the halogen in these cases is similar to the activation of the halogen in the benzene series. In compound II, the amino group tends to offset the effect of the neighboring cyanide group, and the result is a deactivation of the 2-chloro group with respect to displacement.

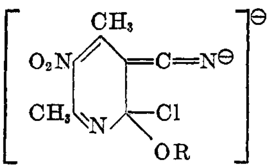
In compounds III, VIII, and XVI, we have situations somewhat similar to 2,4-dinitrochlorobenzene or picryl chloride, in that the halogen is extremely activated with respect to replacement.

A most logical explanation which would explain the color formation and the easy removal of color and the isolation of ethers would involve the formation of an unusually stable quinone-type ion such as XX.



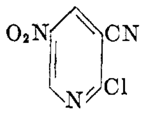
XVIII ($R = CH_3$)
XXI ($R = C_2H_5$)

This colored ion, XX, would be stabilized by other resonance structures such as

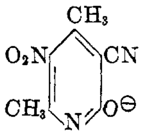


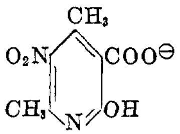
XXII

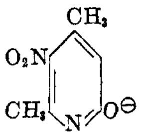
The 2-ethers themselves (IV, XVIII and XXI) also gave colored solutions when treated with alkoxides, giving additional evidence of the lability of the 2-position in these cases. In addition, the 2-methyl ether (XVIII) was converted into the 2-ethyl ether (XXI) by treatment with sodium ethoxide. Fanta and Stein (7) also noted that in the conversion of XXIII to the corresponding ether by means of sodium ethoxide, an intermediary red-brown solution was formed.


XXIII

It was clear why compounds, such as VI, VII and X gave no color in basic solution. In these cases the addition of bases simply removed a relatively available proton to yield stable ions such as XXIV, XXV, and XXVI, respectively which would resist further nucleophilic attack.


XXIV


XXV


XXVI

Analogous observations in the benzene series were made by Miller (8). Similar explanations were given for the enhanced activity of and the colors produced by some chlorobenzenes, activated in the 2, 4, and 6-positions, when treated with alkoxides. Picryl chloride itself turns deep red when treated with alkoxides.

Since McElvain (9) has shown that there is steric inhibition of resonance in trinitromesitylene, XXII would be the important colored intermediate and not XX, in cases where there is an R group in the 4-position.

Additional experiments in our laboratories were performed varying the solvents as well as the bases in the color-producing reactions. Solvents such as methanol, ethanol, and acetone were used, and with acetone (Table I) the absorption maxima occurred at shorter wavelengths. Bases such as sodium hydroxide, potassium acetate, ammonium hydroxide, as well as alkoxides all produced colors when mixed with VIII. Sodium hydroxide and the alkoxides produced colors of the same intensity, whereas potassium acetate and ammonium hydroxide gave colors of diminished intensity in that order.

An alcoholic solution of XVIII when treated with NaOH, KOH, and alkoxides also produced deep purple colors. However, potassium acetate and ammonium hydroxide in this case produced no color changes.

EXPERIMENTAL (10)

DIMETHYL SERIES

3-Cyano-4,6-dimethyl-5-nitro-2(1)-pyridone (VI). The following method uniformly gave the highest yields of pure product. A suspension of 11.6 g. of powdered and dry 3-cyano-4,6-

TABLE I

COLOR REACTIONS OF PYRIDINES WITH BASES

Compound	Solvent	Base	mμ	log ε
VIII	Acetone	$NaOCH_3$	525	2.368
VIII	Acetone	$NaOC_2H_5$	500	2.376
VIII	Acetone	NaOH	535	2.372
XVIII	Ethanol	NaOH	542	2.324
XVIII	Ethanol	$NaOC_2H_5$	540	2.324
XVIII	Acetone	NaOH	480	2.400
XVIII	Acetone	$NaOCH_3$	480	2.400
XVIII	Acetone	$NaOC_2H_5$	480	2.400
XXI	Ethanol	$NaOCH_3$	537	2.382
XXI	Ethanol	NaOH	540	2.350
XXI	Acetone	$NaOC_2H_5$	480	2.410
XXI	Acetone	NaOH	480	2.396

dimethyl-2(1)-pyridone (11) in 40 ml. of acetic anhydride was cooled to 0°. To this was added dropwise, a solution of 7 ml. of fuming nitric acid in 6 ml. of acetic anhydride, which previously had been prepared and kept at 0°. The solution was vigorously stirred during the addition and the addition was so regulated that the temperature of the reaction mixture did not exceed 5°. When the addition had been completed, the stirring was continued and the temperature was maintained at 5° for one-half hour. The ice-bath then was removed and stirring was continued for one-half hour, as the temperature of the reaction mixture rose to about 50°. The contents were poured on ice, filtered, washed with ice-cold water, and preferably crystallized as soon as possible from absolute ethanol. The purified product usually weighed about 4.8–5.2 g.; dark yellow needles, m.p. 268° (dec.) (12). This nitropyridone was insoluble in water and acid, and it dissolved very slowly in sodium hydroxide to form a yellow solution. The ferric chloride test was negative.

4,6-Dimethyl-5-nitro-2-oxo-nicotinamide. To a stirred mixture of 5 g. of nitropyridone (VI) in 12 ml. of concentrated sulfuric acid, kept at 80°, were added, dropwise, 12 ml. of fuming (30%) sulfuric acid. After the addition was completed the temperature was held at 80° for one-half hour. The solution then was poured over 100 g. of cracked ice, and the cold suspension then was filtered; 80% yield, yellow needles from 1:1 water-ethanol, m.p. 292°. The ferric chloride test was negative. The amide was immediately converted into the corresponding nicotinic acid (VII).

4,6-Dimethyl-5-nitro-2-oxo-nicotinic acid (VII). (*a*). *From the amide, using* HNO_2. To a solution of 3.1 g. of amide in 60 ml. of water was added 25 ml. of concentrated hydrochloric acid. This solution was cooled to 5°, and then 4.5 g. of sodium nitrite was added, portionwise, with stirring. After the addition had been completed, the contents were heated to 100° and maintained at that temperature for one hour. The solution then was cooled, and the crystals were collected by filtration; 2.0 g., m.p. 225°. The acid was soluble in sodium bicarbonate and it turned the solution yellow. The ferric chloride test was negative.

(*b*). *From the amide using NaOH.* A solution of 2.2 g. of amide and 9.0 g. of sodium hydroxide in 80 ml. of water was refluxed for 12 hours. After cooling, acidification with 1:1 hydrochloric acid, and filtration, the substituted nicotinic acid was obtained, 2.0 g., m.p. 222–225°. The samples prepared by methods (*a*) and (*b*) proved to be the same by mixture m.p.

Anal. Calc'd for $C_8H_8N_2O_5$: N, 13.21. Found: N, 13.40.

4,6-Dimethyl-5-nitro-2-pyridol (X). The acid VII (2.0 g.) was heated to slightly above the m.p. in a tube and maintained until decomposition was completed (15 minutes). The black residue then was sublimed in a vacuum to give yellow needles, 0.55 g., m.p. 251°. The sublimed product was not soluble in sodium bicarbonate. The ferric chloride test was weakly positive (orange color).

Anal. Calc'd for $C_7H_8N_2O_3$: N, 16.67. Found: N, 16.62.

4,6-Dimethyl-5-nitro-3-bromo-2-pyridol (IX). To a warm solution of 0.45 g. of X in 5 ml. of glacial acetic acid was added 1 ml. of liquid bromine, dropwise. The solution was shaken for five minutes and then was poured on cracked ice. The product then was recovered by filtration. The crude material was purified by sublimation in a vacuum to give 0.50 g. of pale yellow crystals, m.p. 273° (sealed tube). The ferric chloride test was weakly positive (orange color).

Anal. Calc'd for $C_7H_7BrN_2O_3$: N, 11.33. Found: N, 11.46.

4,6-Dimethyl-5-nitro-3-bromo-2-chloropyridine (XII). Compound IX (470 mg.) was mixed with 250 mg. of phosphorus pentachloride and the mixture was kept at 180° for four hours. The mixture then was cooled to room temperature and was mixed with 10 ml. of benzene. Then 2.0 ml. of water was added, slowly, with stirring. The benzene layer was separated and dried with calcium sulfate. The dried benzene solution was taken to dryness, and the colored residue was sublimed in a vacuum. Final recrystallization from absolute methanol gave 190 mg., m.p. 83°.

Anal. Calc'd for $C_7H_6BrClN_2O_2$: N, 10.55. Found: N, 10.65.

4,6-Dimethyl-3-bromo-5-nitro-2-methoxypyridine (XV). To a solution of 0.19 g. of XII in 5 ml. of methanol was added 0.10 g. of sodium methoxide. The light brown solution was refluxed for three hours, and then was taken to dryness in a vacuum, and the resulting brown residue was distilled at 150° and 1 mm. to give 0.11 g. of light yellow crystals, m.p. 90°. A mixture m.p. of XV and XII was depressed to 65°.

Anal. Calc'd for $C_8H_9BrN_2O_3$: N, 10.73. Found: N, 10.78.

4,6-Dimethyl-5-nitro-2-chloropyridine (XIV). Compound X (0.50 g.) was heated with 1.0 g. of phosphorus pentachloride for three hours at a temperature of 180°. The liquid was cooled to room temperature and mixed with 10 ml. of benzene. The mixture was cooled to 10° and 2.0 ml. of water was added, dropwise, with stirring. The benzene layer was separated, dried, and evaporated to dryness in a vacuum. The yellow solid was distilled at 120° and 1 mm. to give 0.24 g. of white crystals, m.p. 63°.

Anal. Calc'd for $C_7H_7ClN_2O_2$: N, 15.02. Found: N, 14.77.

4,6-Dimethyl-5-nitro-2-methoxypyridine (XVII). To a solution of 0.25 g. of XIV in 5.0 ml. of methanol was added 0.50 g. of sodium methoxide. The solution was refluxed for ten minutes and then was taken to dryness in a vacuum. The resulting yellow residue was distilled at 135° and 1 mm. to give 0.095 g. of white crystals, m.p. 60°. A mixture m.p. of XVII and XIV was depressed to 36°.

Anal. Calc'd for $C_8H_{10}N_2O_3$: N, 15.38. Found: N, 15.18.

4,6-Dimethyl-3,5-dinitro-2(1)-pyridone (XIII). A mixture of 0.40 g. of X in 1.3 ml. of acetic anhydride was cooled to −5° in an ice-salt bath. A nitrating solution was prepared as follows: to 0.6 ml. of acetic anhydride (0°) was added 0.3 ml. of fuming nitric acid (0°) slowly, with gentle agitation. The ice-cold nitrating mixture was added all at once to the reaction mixture at −5°, and the mixture was kept in the salt bath for about ten seconds. The cooling bath then was removed, and stirring was continued. The temperature rose to 40°, and the cooling bath was used again to reduce the temperature to 10°, as a granular yellow solid precipitated. The mixture was added to cracked ice, and 0.26 g. of a yellow solid was obtained by filtration, m.p. 232° (dec.). Recrystallization from 95% ethanol gave a solid m.p. 238° (dec.). The material darkens 10 degrees before the m.p. and finally decomposes to a black liquid. The purified material gave a negative ferric chloride test.

Anal. Calc'd for $C_7H_7N_3O_5$: N, 19.72. Found: N, 19.65.

4,6-Dimethyl-3,5-dinitro-2-chloropyridine (XVI). Compound XIII (0.30 g.) was heated with 1.0 g. of phosphorus pentachloride for four hours at 180°. The reaction mixture then was cooled to room temperature and was added to cracked ice, and a dark viscous liquid was formed which slowly solidified to a brown solid. Recrystallization from 95% ethanol gave 0.19 g. of a rust-colored solid. Distillation at 120° and 1 mm. gave 0.14 g. of white crystals, m.p. 84°.

Anal. Calc'd for $C_7H_6ClN_3O_4$: N, 18.15. Found: N, 18.17.

4,6-Dimethyl-3,5-dinitro-2-methoxypyridine (XIX). When 0.20 g. of sodium methoxide was added to a solution of 0.088 g. of XVI in 1 ml. of methanol a deep brown color developed immediately. Then 5.0 ml. of water was added, and a brown solid separated out which was removed by filtration. The solid was distilled at 120° and 1 mm. to give 0.036 g. of pale yellow crystals, m.p. 66°.

Anal. Calc'd for $C_8H_9N_3O_5$: N, 18.50. Found: N, 18.66.

4,6-Dimethyl-5-nitro-3-cyano-2-methoxypyridine (XVIII). When a solution of 1.0 g. of VIII (prepared from VI by method of Wagtendonk and Wibaut (11) in 40 ml. of methanol was mixed with 1.0 g. of sodium methoxide a deep purple color was formed immediately, in the cold. The color was identical to that of a concentrated $KMnO_4$ solution. The color was stable and not transient. When 40 ml. of water was added to the purple solution the color was discharged and a white solid was precipitated. The solid was separated by filtration and distilled at 140° and 1 mm. to give 0.60 g. of white crystals, m.p. 84°.

Anal. Calc'd for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.38; M.W., 207.
Found: C, 52.28; H, 4.31; N, 20.08; M.W., (camphor), 211.

4,6-Dimethyl-5-nitro-3-cyano-2-ethoxypyridine (XXI). To a solution of 1 g. of VIII in 20 ml. of absolute ethanol was added a solution prepared from 3.8 g. of freshly-cut metallic sodium in 50 ml. of absolute ethanol. An intense purple solution was formed immediately. When water was added the color was discharged and a fine-gray precipitate appeared. The solid was vacuum-sublimed to give an oil, which slowly solidified, 35% yield, m.p. 46°.

Anal. Calc'd for $C_{10}H_{11}N_3O_3$: N, 19.00. Found: N, 18.75.

The treatment of an ethanolic solution of XVIII (m.p. 84°) with sodium ethoxide gave a solid, m.p. 43–44°, which did not depress the m.p. of an authentic sample of XXI.

2,4-Dimethyl-3-nitro-5-cyanopyridine (XI). 4,6-Dimethyl-5-nitro-3-cyano-2-chloropyridine (0.50 g.) was dissolved in 100 ml. of absolute ethanol and 0.50 g. of 5% palladium-on-charcoal was added. The mixture was shaken in an atmosphere of hydrogen, 23 p.s.i., for three hours. The mixture was filtered, and the alcohol was removed in a vacuum. The residue was distilled at 170° and 1 mm. to give 0.12 g. of a white solid. This solid was recrystallized from 1 ml. of methanol to give 0.07 g. of a white crystals; m.p. 145°. The Beilstein halogen test was negative.

Anal. Calc'd for $C_8H_7N_3O_2$: N, 23.72. Found: N, 23.95.

When a solution of XI in methanol was treated with sodium methoxide, no color resulted.

MONO-METHYL SERIES

2-Methyl-3-nitro-5-cyanopyridine (V). 2-Methyl-3-nitro-5-cyano-6-chloropyridine (13, 14) (0.15 g.) was dissolved in 25 ml. of absolute ethanol and 0.15 g. of 5% palladium-on-charcoal was added. The mixture was shaken within an atmosphere of hydrogen, 25 p.s.i. for one-half hour. The mixture was filtered and the ethanol was removed in a vacuum. The brown solid was distilled at 250° and 1 mm. to give 0.032 g. of a yellow solid, m.p. 223° (dec.). The Beilstein test for halogen was negative.

Anal. Calc'd for $C_7H_5N_3O_2$: N, 25.77. Found: N, 26.02.

When a methanolic solution of V was treated with sodium methoxide no significant color change was noted.

6-Methyl-5-nitro-3-cyano-2-methoxypyridine (IV). When 0.30 g. of sodium methoxide was added to a solution of 0.071 g. of 6-methyl-5-nitro-3-cyano-2-chloropyridine (14) in 1 ml. of methanol, an intense purple color developed immediately. Then 3.0 ml. of water was added and a dark solid separated which was removed by filtration. Vacuum sublimation gave 0.016 g. of a white solid, m.p. 63°.

Anal. Calc'd for $C_8H_7N_3O_3$: N, 21.78. Found: N, 21.45.

Spectroscopic results. The ultraviolet spectra were determined with a Beckman Spectrophotometer, Model DU. The cells were of Pyrex and calculations were made as indicated before (15).

SUMMARY

2-Chloropyridines containing very powerful electron-attracting groups in the 3 and 5 positions react with bases to produce intense colors. The corresponding 2-ethers also give colors when treated with strong bases. A common intermediate responsible for color formation is probably a quinoid system, analogous to the benzene series.

CHICAGO 26, ILLINOIS

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