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Rearrangements of Tertiary Amine Oxide. XVIII.[1] The Reaction of 4-Substituted Pyridine *N*-Oxides with *p*-Nitrobenzenesulfenyl Chloride and *p*-Nitrobenzenesulfinyl Chloride

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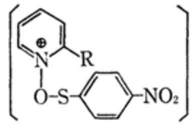
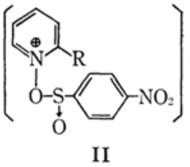
When 4-nitropyridine *N*-oxide was allowed to react with *p*-nitrobenzenesulfenyl chloride, 4-pyridyl 4′-chloropyridinium chloride (V) and 4-(4′-pyridol)pyridine (IV) were obtained, along with *p*, *p*′-dinitrodiphenyl disulfide, *p*-nitrobenzenesulfonic acid, and a salt, presumed to have a VI structure. Similar products were formed in the reaction between 4-chloropyridine *N*-oxide with *p*-nitrobenzenesulfenyl chloride. In the case of 4-methoxypyridine *N*-oxide, however, a simple reduction was the main reaction; thus 4-methoxypyridine was obtained, while the other products were the same. As in the case of pyridine- and α-picoline *N*-oxide, no ring-substituted product was isolated in the reactions of these *N*-oxides. Apparently, the reaction of these *N*-oxides with *p*-nitrobenzenesulfenyl chloride involves the initial formation of the salt, which has a *N*-sulfenoxy bond, ^{+}N–O–S–, which presumably cleaves homolytically in the succeeding step to give the final products.

In a previous paper of this series, it was reported that the reactions of pyridine or α-picoline *N*-oxides with *p*-nitrobenzenesulfenyl chloride[2] and *p*-nitrobenzenesulfinyl chloride[3] gave as major products deoxygenated pyridine or α-picoline, along with *p*, *p*′-dinitrodiphenyl disulfide, *p*-nitrobenzenesulfonic acid, and *p*-nitrophenyl *p*-nitrobenzenethiolsulfonate. It was suggested that those reactions involved the initial formation of such salts as I or II, which, upon heating, presumably undergo a homolytic fission of the N–O bond to give the final products.



I



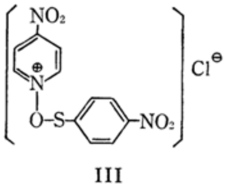
II

R=H, CH_3

However, when *p*-toluenesulfonyl chloride[4] was used as the acylating agent in the reaction with pyridine *N*-oxide, the over-all reaction is entirely different. Namely, it involves a prior formation of a neutral addition intermediate with the chloride ion, a portion of which, upon intramolecular allylic-type rearrangement, is presumed to give a ring-substituted ester, *i. e.*, β-tosyloxypyridine. Thus, the mode of the reaction of these *N*-oxides is affected considerably by the electronic environment of the acylating agent. When the acyl group is changed to that of another strong acid, *i. e.*, *p*-nitrobenzoyl, a similar rearrangement was observed in the reaction with pyridine *N*-oxide.[5] It seemed of interest in this connection to investigate the effects of a few typical substituents on the pyridine ring on the nature of the reactions between 4-substituted pyridine *N*-oxides and both *p*-nitrobenzenesulfenyl and *p*-nitrobenzenesulfinyl chlorides. Thus, 4-nitro-, 4-chloro-, and 4-methoxypyridine *N*-oxides were chosen and subjected to reaction either with *p*-nitrobenzenesulfenyl chloride or *p*-nitrobenzenesulfinyl chloride, or both.

Results and Discussion

When equimolar amounts of *p*-nitropyridine *N*-oxide and *p*-nitrobenzenesulfenyl chloride were mixed in a chloroform solution, light yellow crystalline precipitates were formed immediately. These crystals were rather unstable, and slowly decomposed at room temperature, evolving NO_2 gas; therefore, the analytical data deviate considerably from those based on the calculated value for the presumed structure of the salt, III, as is shown below:



III

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[1] Part XVII: S. Oae, S. Tamagaki and S. Kozuka, *Tetrahedron Letters,* **1966**, 1513.

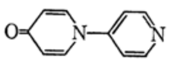
[2] S. Oae and K. Ikura, This Bulletin, **38**, 58 (1965).

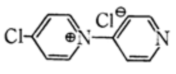
[3] S. Oae and K. Ikura, *ibid.*, **39**, 1306 (1966).

[4] S. Oae, T. Kitao and Y. Kitaoka, *Tetrahedron,* **19**, 827 (1963).

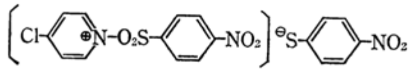
[5] Unpublished results.

However, because of its similarity to the intermediate salts from pyridine- and α-picoline *N*-oxide with the sulfenyl chloride, this salt is also considered to have the above structure. The III salt obtained after the through removal of the solvent chloroform in vacuo started to evolve NO_2 gas markedly at around 80°C. We kept heating it at 80°C until no NO_2 gas evolution was recognized, and then heated it at 180—200°C for five hours. Among the reaction products isolated were *p*-nitrobenzene-sulfonic acid, *p, p′*-dinitrodiphenyl disulfide, 4-(4′-pyridol)pyridine(IV), 4-pyridiyl-4′-chloropyridinium chloride(V), and VI salt, which accounts for more than 93% of the products.

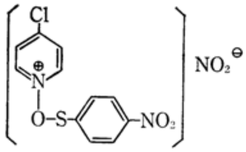

IV


V

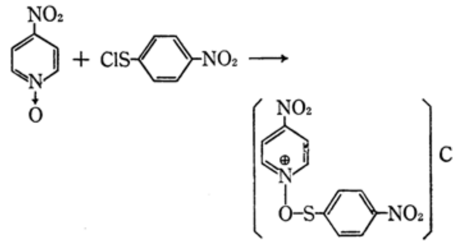
The major product, a salt presumed to have the VI structure, was sparingly soluble in both common organic solvents and water, but was found to hydrolyze readily to give the compound IV, *p*-nitrobenzenesulfonic acid, and *p, p′*-dinitrodiphenyl disulfide. These results and the analytical data seem to suggest that the salt has the VI structure shown bellow:

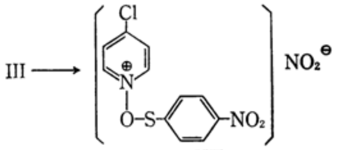

VI

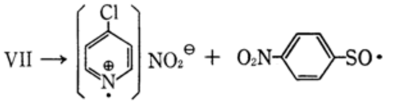
Here again neither a ring-substituted rearrangement product nor unreacted pyridine *N*-oxide was isolated among the products; the reduced product of the *N*-oxide, *i. e.,* 4-nitropyridine, was not obtained either. On the basis of these reaction products and their distribution, one can theorize that this reaction is initiated first by the replacement of the nitro group with chloride to form the salt, VII, and that then the N–O bond of the VII salt cleaves homolytically as in the reactions of pyridine and α-picoline *N*-oxides with *p*-nitrobenzenesulfenyl chloride.2)


VII

The replacement of the nitro group by chloride would be more facile in the III salt, since the nitro group is readily replaced by an anion from 4-nitropyridine *N*-oxide than from 4-nitropyridine, while the 4-chloropyridine thus produced is known to dimerize to the compound V, which then undergoes a facile hydrolysis to afford IV. Therefore, there would be no chance to obtain 4-nitropyridine in the reaction. The over-all reaction scheme may thus be formulated as:


III (1)


VII (2)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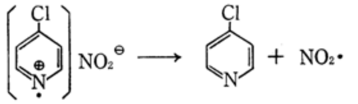
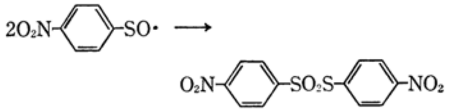
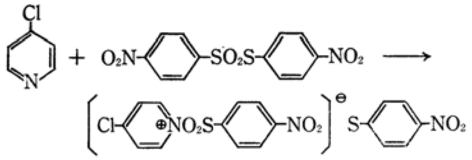
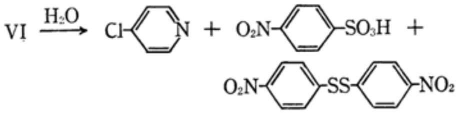

(4)


(5)


VI (6)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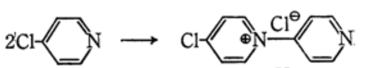
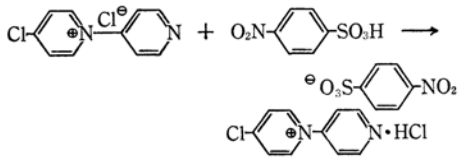

V (8)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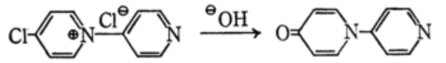
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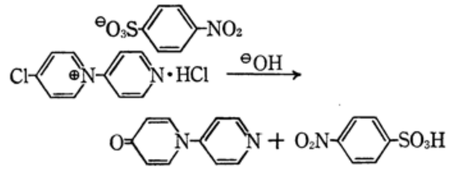
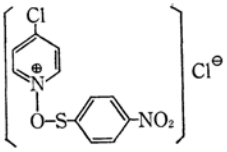
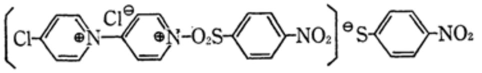

(11)

The same reaction was applied to 4-chloropyridine *N*-oxide. Here, too, when equimolar amounts of 4-chloropyridine *N*-oxide and *p*-chlorobenzenesulfenyl chloride were mixed in a chloroform solution, colorless crystalline precipitates were formed immediately, with an evolution of heat. This salt changed to its perchlorate, which was found by analysis to have the correct composition as derived from the VIII salt:



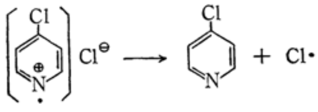
VIII

The salt was heated at around 190°C for ten hours after the removal of the solvent chloroform under a vacuum. Although this salt did not melt at around the reaction temperature, it gradually turned light red. After a usual work-up, the reaction products isolated were 4-(4′-pyridol)pyridine, *p, p*′-dinitrodiphenyl disulfide, *p*-nitrophenyl *p*-nitrobenzenethiolsulfonate, *p*-nitrobenzenesulfonic acid, 4-pyridyl-4′-chloropyridinium chloride, and a salt, presumed to have a IX structure. The total yield of all the products isolated was 86%. In this case, however, the VI salt was not isolated, unlike as in the case of 4-nitropyridine *N*-oxide, and the amount of the IX salt obtained was much less than that of the VI salt formed in the reaction with 4-nitropyridine *N*-oxide. This IX salt has the same infrared spectrum as the insoluble product formed from the reaction of the compound V with *p*-nitrophenyl *p*-nitrobenzenethiolsulfonate. It was readily hydrolyzed to give the compound IV, *p*-nitrobenzenesulfonic acid, and *p, p*′-dinitrodiphenyl disulfide. This chemical behvior and the spectral data seem to suggest that the salt composition is:



IX

The formation of the small amount of the IX salt may be explained by assuming that the IX salt reacted further with the chlorine produced by the charge-transfer step 13 and so formed the X salt, as is shown below:



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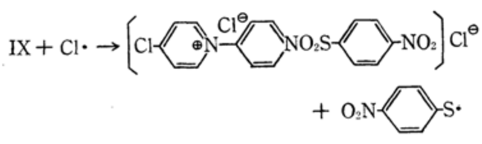
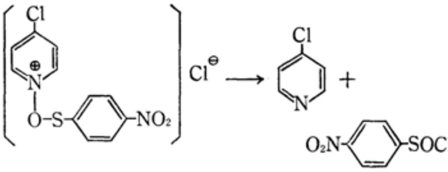


(13)

This assumption may be supported by the fact that the amount of *p, p*′-dinitrodiphenyl disulfide extracted with chloroform from the reaction products before the hydrolysis was larger in this case than in the case of 4-nitropyridine *N*-oxide. In the case of 4-nitropyridine *N*-oxide, the $NO_2\cdot$ radical presumed to be formed by the charge transfer readily escapes from the reaction system as NO_2 gas; therefore, the same reaction leading to the step 13 may not take place. Here again the reaction seems to be explainable by assuming a similar homolytic cleavage of the N–O bond of the VIII salt; hence, the over-all reaction scheme may be considered to be analogous to the one previously postulated for the reaction with 4-nitropyridine *N*-oxide excepting steps 2 and 13.

If one assumes the following heterolytic N–O bond as an alternative process, the mechanism may be written in either one of two ways:



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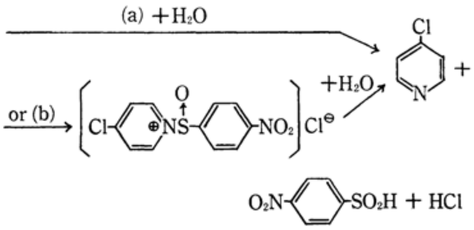

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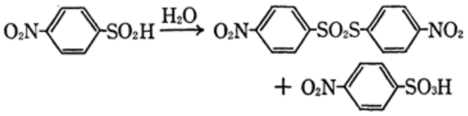
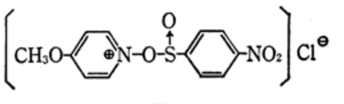


(16)

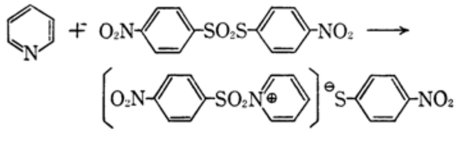
However, the formation of *p, p*′-dinitrodiphenyl disulfide before the hydrolysis can not be explained by this mechanism, sicne the disulfide can be formed only after the formation of *p*-nitrophenyl *p*-nitrobenzenethiolsulfonate by the hydrolysis, according to this mechanism, while the contrary was actually observed.

We have extended the reaction to 4-methoxypyridine *N*-oxide with *p*-nitrobenzenesulfinyl chloride. When equimolar amounts of 4-methoxypyridine *N*-oxide and *p*-nitrobenzenesulfinyl chloride were mixed in a chloroform solution, colorless crystalline precipitates were formed gradually, with the evolution of heat. This salt was not very hygroscopic and was rather stable; it was found by analysis to give the correct value represented by the X structure:



X

When this salt was heated in chloroform for ten hours, the evolution of hydrogen chloride was noticed during the refluxing. The reaction products isolated were 4-methoxypyridine, *p*-nitrophenyl *p*-nitrobenzenethiolsulfonate, *p*-nitrobenzenesulfonic acid, and an unreacted salt, 1-*p*-nitrobenzene sulfinoxy-4-methoxypyridinium chloride, X (which accounted for 86% of the products). Here again, neither a ring-substituted rearrangement product nor unreacted 4-methoxypyridine *N*-oxide was isolated among the products. *p, p'*-Dinitrodiphenyl disulfide was not isolated among the reaction products, unlike as in the cases of pyridine- and *α*-picoline *N*-oxide with *p*-nitrobenzenesulfinyl chloride. In the previous case, the formation of the disulfide was assumed to proceed through the following pathway:



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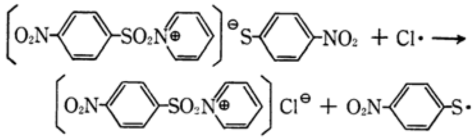

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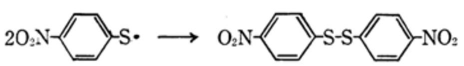
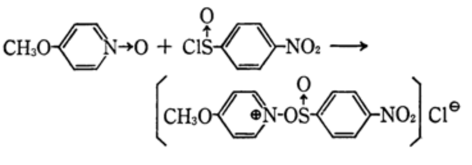


(19)

Unlike the previous cases, however, the reaction of this compound took place under much milder conditions, such as in refluxing chloroform, instead of being heating at about 180°C; probably, then, the steps shown above did not occur in this case. In fact, the disulfide was obtained only when the X salt was heated at around 180°C after the solvent had been removed.

Thus the over-all scheme of the reaction may be formulated as:



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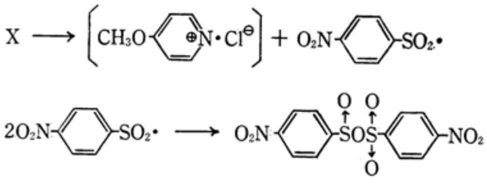
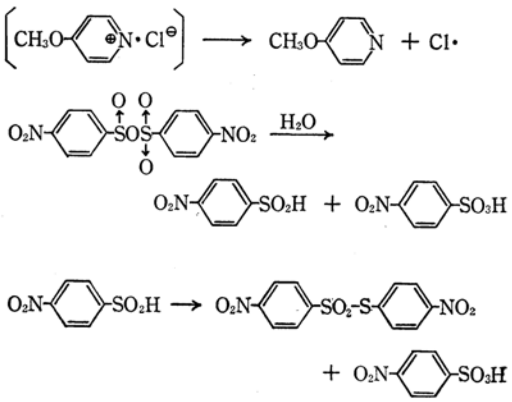
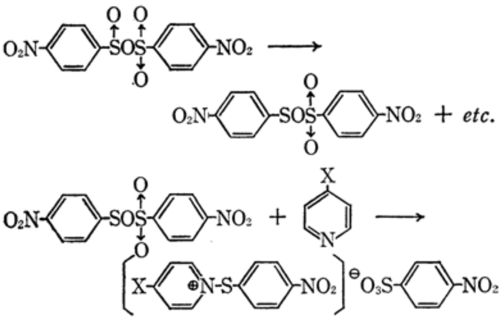
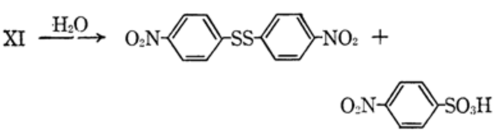




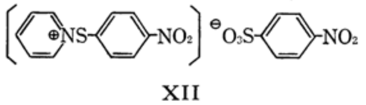
The *p*-nitrophenylsulfinyl *p*-nitrobenzenesulfonate thus formed was actually isolated directly from the chloroform solution of the reaction mixture when it was not washed with water. The sulfinyl sulfonate was identified by comparing its infrared spectra with that of an authentic sample. The fact that *p, p'*-dinitrodiphenyl disulfide was obtainable only when the X salt was heated after the solvent had been removed is intriguing. It would be one of the products in the decomposition of *p*-nitrophenylsulfinyl *p*-nitrobenzenesulfonate, which is presumed to proceed *via* the initial formation of *p*-nitrophenylsulfenyl *p*-nitrobenzenesulfonate. This intermediate immediately reacts with the pyridine base to form the XI salt, which, upon hydrolysis, gives the disulfide and *p*-nitrobenzenesulfonic acid.



XI

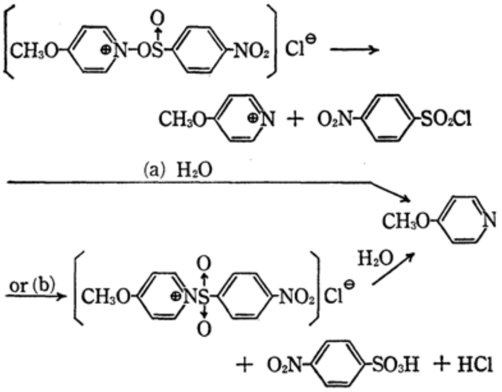


The formation of a similar salt, XII, was actually observed when *p*-nitrophenylsulfinyl *p*-nitrobenzenesulfonate was reacted with pyridine; this salt afforded *p, p'*-dinitrodiphenyl disulfide and *p*-nitrobenzenesulfonic acid in quantitative yields upon hydrolysis.



XII

A similar decomposition of *p*-nitrophenylsulfinyl *p*-nitrobenzenesulfonate was recently found to give *p*-nitrophenylsulfenyl *p*-nitrobenzenesulfonate, which, upon reacting with amine, also was found to give *p*, *p*'-dinitrodiphenyl disulfide and *p*-nitrobenzenesulfonic acid.6) Here, too, the homolytic cleavage of the N–O bond of the X salt is more likely than the heterolytical cleavage, because the following alternative heterolytical cleavage can not explain the formation of the *p*-nitrophenyl *p*-nitrobenzenethiolsulfonate.



(21)

(22)

Among all the compounds hitherto tested, namely, unsubstituted, α-methyl-, 4-nitro-, 4-chloro-, and 4-methoxypyridine *N*-oxides, neither a ring-substituted rearrangement product nor unreacted *N*-oxide was isolated among the products. The reaction products and their distribution seem to indicate that the N–O bond of the incipient salt was homolytically cleaved and that the mode of the N–O bond scission was not affected by the nature of the substituent on the pyridine ring.

Experimental

The Reaction of 4-Nitropyridine *N*-Oxide with *p*-Nitrobenzenesulfenyl Chloride When chloroform solutions of both 4-nitropyridine *N*-oxide (1.5 g) and *p*-nitrobenzenesulfenyl chloride (2.0 g) were mixed at room temperature, a light yellow salt precipitated immediately. This salt was rather unstable and slowly decomposed at room temperature; therefore, the analytical data were found to deviate considerably from the calculated values.

Found: N, 10.12%. Calcd for $C_{11}H_8N_3O_9SCl$: N, 10.67%. However, because of its similarity to similar salts from pyridine and α-picoline *N*-oxide, the salt is considered to have the III structure. Then the solvent was removed *in vacuo* at room temperature; the salt was heated at around 80°C untile the evolution of NO_2 gas had completely ceased and then heated at 180—200°C for an additional five hours. After the reaction, water was added and the mixture was extracted with chloroform. Then an insoluble product was separated by filtration. The insoluble product was the VI salt (2.1 g; mp 223—225°C). The chloroform layer gave *p*, *p*'-dinitrodiphenyl disulfide (0.3 g). The aqueous layer was made neutral with sodium carbonate and extracted with chloroform. After the removal of the solvent, 4-pyridyl-4'-chloropyridinium chloride V (0.4 g) was collected by sublimation at 160°C, while from the residual liquid, after it had cooled and condensed, 0.5 g of sodium *p*-nitrobenzenesulfonate was isolated.

When the VI salt (2.0 g) was hydrolyzed with 40% H_2SO_4 solution in an open atmosphere, *p*, *p*'-dinitrodiphenyl disulfide (0.3 g), 4-(4'-pyridol)pyridine (IV) (0.5 g; mp 177—178°C), and *p*-nitrobenzenesulfonic acid (0.4 g) were obtained.

Found:: C, 69.26; H, 5.12; N, 16.49%. Calcd for IV: C, 69.33; H, 5.25; N, 16.18%.

Found: C, 40.05; H, 4.33; N, 9.59%. Calcd for V: C, 40.09; H, 4.37; N, 9.35%. This compound has two moles of water.

Found: C, 45.29; H, 3.01%. Calcd for salt VI: C, 44.98; H, 2.67%.

The Reaction of 4-Chloropyridine *N*-Oxide with *p*-Nitrobenzenesulfenyl Chloride. Chloroform solutions of both 4-chloropyridine *N*-oxide (1.5 g) and *p*-nitrobenzenesulfenyl chloride (2.0 g) were mixed at room temperature, whereupon the VIII salt precipitated at once with an evolution of heat. After the solvent had been removed, the salt was heated at around 200°C for ten hours. This salt did not melt at around the reaction temperature, but the color gradually changed to a light red. The reaction products were worked up in the same way as in the case of 4-nitropyridine *N*-oxide. The insoluble salt (0.4 g) could not be purified completely, but its infrared spectrum was the same as that of the insoluble product produced by the reaction of the compound V with *p*-nitrophenyl *p*-nitrobenzenethiolsulfonate. This salt was hydrolyzed to give the compound IV, *p*-nitrobenzenesulfonic acid, and *p*, *p*'-dinitrodiphenyl disulfide, suggesting that the salt has the composition shown by IX. The products from the chloroform layer were *p*, *p*'-dinitrodiphenyl disulfide (0.6 g), Compound V (0.02 g), and a mixture of *p*, *p*'-dinitrodiphenyl disulfide and *p*-nitrophenyl *p*-nitrobenzenethiolsulfonate (0.09 g). From the aqueous layer, 4-(4'-pyrydol)pyridine (IV) (0.8 g) and *p*-nitrobenzenesulfonic acid (0.85) g) were obtained.

The Isolation of 1-*p*-Nitrobenzenesulfinyl-4-chloropyridinium Perchlorate. An equimolar amount of perchloric acid (69%) was added to an ethanol solution of the VIII salt. The colorless crystals which were thus precipitated were washed well with ethanol and dried; mp 250—253°C.

Found: N, 7.55%. Calcd for $C_{11}H_8N_2O_7SCl_2$: N, 7.31%.

The Reaction of 4-Methoxypyridine *N*-Oxide with *p*-Nitrobenzenesulfinyl Chloride. The chloroform solutions of both 4-methoxypyridine *N*-oxide (1.5 g) and *p*-nitrobenzenesulfinyl chloride (2.4 g) were mixed at room temperature. The X salt precipitated gradually; mp 183—185°C. The salt was heated in refluxing chloroform for ten hours. After the reaction, the unreacted salt X (1.4 g) was separated by filtration. The chloroform layer, after being washed with water, dried, and evaporated, gave *p*-nitrophenyl *p*-nitrobenzenethiolsulfonate (1.3 g), while the aqueous layer gave 4-methoxypyridine (0.6 g) and *p*-nitrobenzene sulfonic acid (0.8 g.).

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6) Unpublished results from these laboratories.

When the salt X (0.5 g) was heated at around 200°C for five hours without any solvent, *p*, *p'*-dinitrodiphenyl disulfide (0.07 g), 4-methoxypyridine (0.07 g), and *p*-nitrobenzenesulfonic acid (0.18 g) were obtained.

Found: C, 44.04, H, 3.68; N, 8.44%. Calcd for salt X: C, 43,56; H, 3.35; N, 8.47%.

The Reaction of Pyridine with *p*-Nitrophenylsulfinyl *p*-Nitrobenzene Sulfonate. The sulfinyl sulfonate was prepared by mixing *p*-nitrobenzenesulfonic acid and *p*-nitrobenzenesulfinyl chloride in a chloroform solvent at room temperature. The colorless crystals thus obtained were used without any further purification.

The equivalent amounts of this sulfinyl sulfonate and pyridine were refluxed in benzene. When the solvent was then removed, a colorless crystalline salt was obtained. It was once recrystallized with ethanol; mp 151—152°C.

Found: C, 46.67; H, 3.37; N, 9.85%. Calcd for salt XII $C_{11}H_{13}N_3S_2O_7$: C, 46.89; H, 3.02; N, 9.65%.