Aromatic Substitution via New Rearrangements of Heteroaromatic *N*-Oxides

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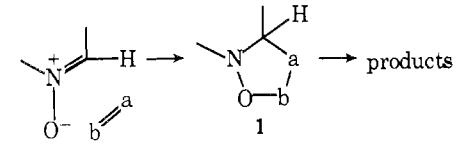
Received August 11, 1975

Six-membered heteroaromatic nitrogen compounds, of which pyridine is the parent, constitute an extremely important branch of chemistry. Its members include vitamins, coenzymes, alkaloids, nucleic acids, and natural pigments (e.g., the pteridines) and find widespread application. Consequently, much effort has been devoted to the convenient synthesis of these substances and their precursors. Just as important, perhaps, is that pyridine is the parent of all the more complex six-membered heteroaromatic nitrogen compounds. Whatever new chemistry is developed with pyridine 1-oxide based on the *N*-oxide function should, in principle, be transferable to the *N*-oxide of these other systems which also have great practical importance.

In contrast to the situation with benzene derivatives and π-excessive heteroaromatic compounds, there were, until recently, relatively few methods available for the ready direct introduction of substituents into π-deficient six-membered heteroaromatic nitrogen compounds. The work initiated by Ochiai on the use of *N*-oxides[1] led to the facile nitration at the position para to the *N*-oxide function,[1] to α acetoxylations,[1] to α alkylations using active methylene compounds and acetic anhydride or enamines and acyl halides,[2] and to α alkylations,[3] α acylations,[4] α halogenations,[5] α chloromercurations,[5] thiolation,[6,7] and aminoalkylations[7] via the 1-oxido-2-pyridyl anions, inter alia. These and other reactions have been reviewed recently.[1,2,8]

A number of novel rearrangements starting with *N*-oxides have led to methods for the introduction of substituents into heteroaromatic nitrogen systems; these are the subject of this Account. Some have already been discussed extensively, e.g., the reactions of 1-acyloxypyridinium (and quinolinium) salts with active methylene compounds, enamines, enol ethers, and indoles,[2] and with carboxylate anions (reactions of *N*-oxides with acid anhydrides),[8-12] and photochemical rearrangements.[8,10,13] These will not be treated further here. We will limit our discussion to those rearrangements which result from the treatment of heteroaromatic *N*-oxides with aryl isocyanates, imidoyl chlorides, nitrilium salts, activated acetylenes, and benzyne, as well as rearrangements involving aryloxypyridinium salts. Most of these reactions involve the addition of an ambident reagent a=b to the equivalent of the nitrone function to give **1** (this could involve a 1,3-dipolar addition or be a



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stepwise process of nucleophilic addition of the oxide oxygen followed by intramolecular nucleophilic cyclization), followed by N–O bond cleavage and rearrangement. In addition to the practical value of making available convenient methods for the introduction of substituents by the net displacement of a nuclear hydrogen, some of these rearrangements appear to proceed by novel mechanisms, the elucidation of which will lead to a better understanding of the chemistry and relative stabilities of some dihydropyridine derivatives.

Aryloxypyridinium Salts (2)

These are prepared by the reaction of pyridine 1-oxides with diazonium tetrafluoroborate salts of aromatic amines bearing electron-withdrawing substituents e.g., NO_2, CN, CF_3.[14,15] Alternatively, the *N*-oxide can be treated with a suitable diaryliodonium tetrafluoroborate to give **2**.[15] Thus, the use of diphenyliodonium tetrafluoroborate in the reaction with 4-methoxypyridine 1-oxide led to the formation of **2** (R = 4-OMe, X = H), the first aryloxypyridinium salt

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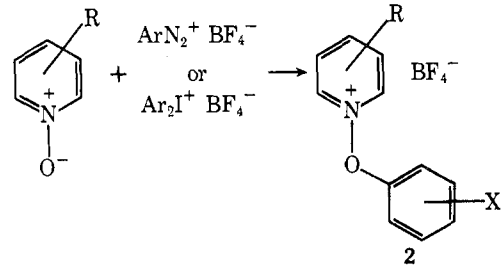
Ichiro Shinkai was born and educated in Japan, was a lecturer at Kyushu University in Fukuoka from 1966 to 1972, and obtained his Ph.D. there in 1971. Since 1972 he has been a Research Associate at the University of Alabama.

(1) E. Ochiai, "Aromatic Amine Oxides", Elsevier, Amsterdam, 1967.
(2) M. Hamana, *J. Heterocycl. Chem.*, **1**, S-51 (1972).
(3) R. A. Abramovitch, M. Saha, E. M. Smith, and R. T. Coutts, *J. Am. Chem. Soc.*, **89**, 1537 (1967); R. A. Abramovitch, E. M. Smith, E. E. Knaus, and M. Saha, *J. Org. Chem.*, **37**, 1690 (1972).
(4) R. A. Abramovitch, E. M. Smith, and R. T. Coutts, *J. Org. Chem.*, **37**, 3584 (1972).
(5) R. A. Abramovitch, J. Campbell, E. E. Knaus, and S. Silhankova, *J. Heterocycl. Chem.*, **9**, 1367 (1972).
(6) R. A. Abramovitch and E. E. Knaus, *J. Heterocycl. Chem.*, **6**, 989 (1969).
(7) R. A. Abramovitch and E. E. Knaus, *J. Heterocycl. Chem.*, **12**, 683 (1975).
(8) R. A. Abramovitch and G. M. Singer, "Pyridine and its Derivatives: A Supplement", Part I, R. A. Abramovitch, Ed., Wiley–Interscience, New York, N.Y., 1974, Chapter 1A, p 1.
(9) V. J. Traynelis in "Mechanisms of Molecular Migrations", Vol. II, B. S. Thyagarajan, Ed., Interscience, New York, N.Y., 1969, p 1.
(10) A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic *N*-Oxides", Academic Press, London, 1971, p 281.
(11) V. J. Traynelis, *J. Am. Chem. Soc.*, **96**, 7289 (1974).
(12) W. E. Parham and P. E. Olson, *J. Org. Chem.*, **39**, 2916 (1974).
(13) H. C. van der Plas, "Ring Transformations of Heterocycles", Vol. 2, Academic Press, New York, N.Y., 1973, p 58; G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, **70**, 231 (1970).
(14) R. A. Abramovitch, S. Kato, and G. M. Singer, *J. Am. Chem. Soc.*, **93**, 3074 (1971).
(15) R. A. Abramovitch and M. Inbasekaran, unpublished results.



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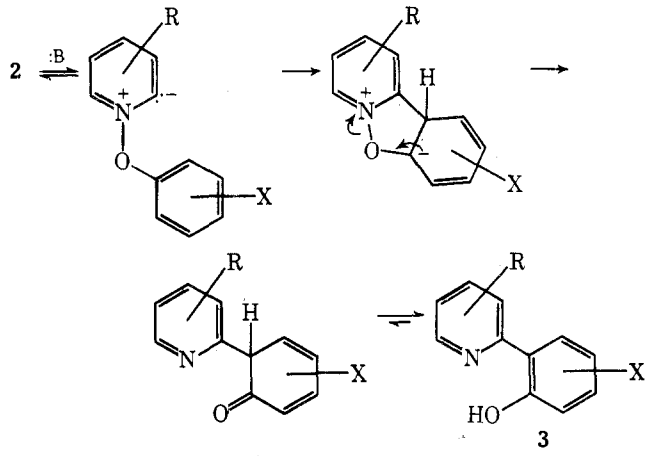
not bearing an electron-withdrawing group in the aryloxy portion of the molecule.[15]

Treatment of the salts **2** with a base such as triethylamine or phenoxide ion induces their rearrangement to 2-*o*-hydroxyarylpyridines (**3**), probably by



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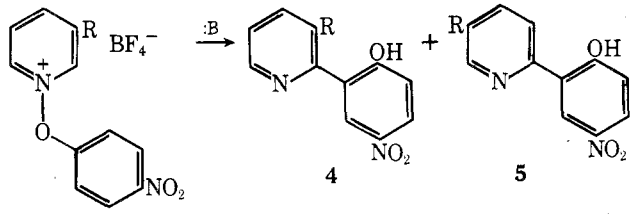
α-hydrogen abstraction followed by intramolecular nucleophilic substitution.[14,15] The rearrangement takes place even when X = H.[15] If R is a 3-substituent, then two possible isomeric products can result. The mechanism proposed above suggests that the isomer will be favored which results from hydrogen abstraction of the more acidic of the two α-protons, combined with steric hindrance to approach of the base,[16] and in the few cases examined so far (R = 3-Br, 3-CH_3, 3-CO_2Me) this does appear to be the case.



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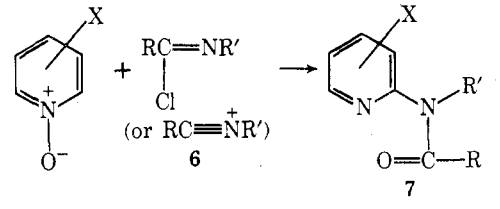
Acylaminations of *N*-Oxides

The reaction of heteroaromatic *N*-oxides (whether five or six membered) with imidoyl halides or with nitrilium salts results in the replacement of the 2-proton by an acylamino group, e.g., **6** → **7**.[17] We shall

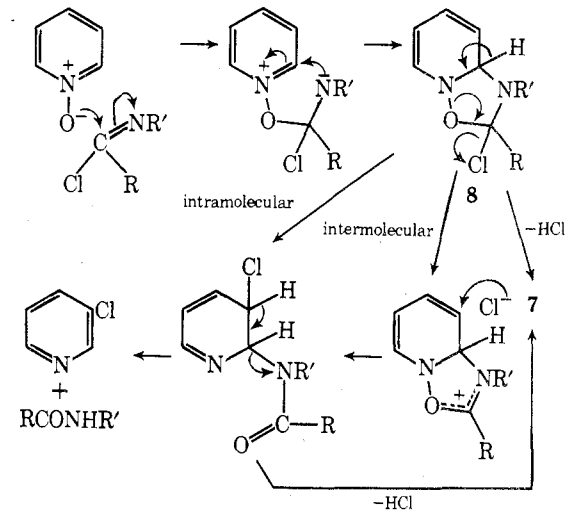


6 7

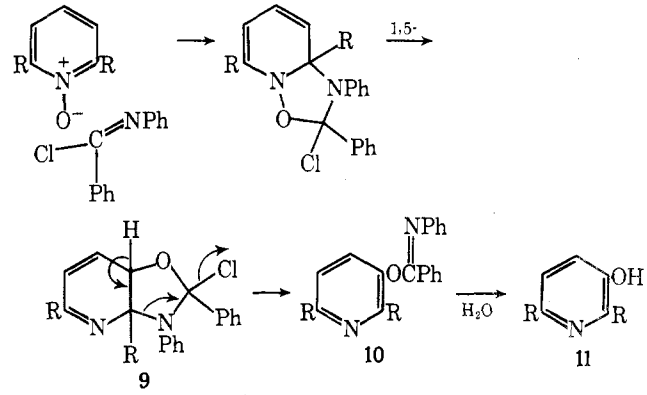
(16) R. A. Abramovitch, G. M. Singer, and A. R. Vinutha, *Chem. Commun.*, 55 (1967).

(17) R. A. Abramovitch and G. M. Singer, *J. Am. Chem. Soc.*, **91**, 5672 (1969); *J. Org. Chem.*, **39**, 1795 (1974).

Scheme I



Scheme II



9 10 11

defer a consideration of the related reaction of *N*-oxides with isocyanates[18] until the last part of this Account.

A nucleophilic attack by the *N*-oxide oxygen at the electrophilic carbon of the reagent followed by intramolecular nucleophilic addition is proposed as the mechanism of formation of the 1,2-dihydropyridine intermediate (**8**) (Scheme I)[8] (a 1,3-dipolar cycloaddition is also possible, but seems less likely in view of some of the by-products formed[19]). An alternative route to **7** will be discussed in the concluding section. If the 2 and the 6 positions of the pyridine ring are blocked, aromatization of the 1,2-dihydro intermediate is no longer possible; it undergoes a 1,5-sigmatropic shift leading to a 2,3-dihydro intermediate (**9**) which can aromatize.[20] This results in the formation of the 3-imidate **10** which, on hydrolysis, gives the 3-hydroxypyridine **11** in which the oxygen atom is that of the original *N*-oxide function (Scheme II). The reaction appears to be quite general, provided the *N*-oxide is basic enough to react with the imidoyl chloride.[21] The same sigmatropic shift occurs with quinoline derivatives, whether[22] or not[20] the 2 position is

(18) H. Seidl, R. Huisgen, and R. Grashey, *Chem. Ber.*, **102**, 926 (1969); E. Hayashi, *J. Pharm. Soc. Jpn.*, **81**, 1030 (1961).

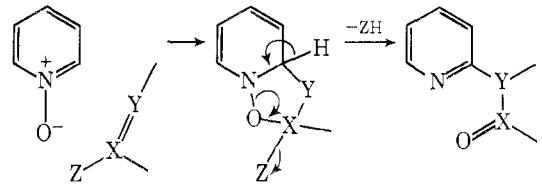
(19) R. A. Abramovitch and P. Tomasik, *J. Heterocycl. Chem.*, **12**, 501 (1975).

(20) R. A. Abramovitch, R. B. Rogers, and G. M. Singer, *J. Org. Chem.*, **40**, 41 (1975); R. A. Abramovitch and R. B. Rogers, *Tetrahedron Lett.*, 1951 (1971).

(21) R. A. Abramovitch and T. D. Bailey, unpublished results, 1974; T. D. Bailey, Ph.D. Dissertation, University of Alabama, 1974.

(22) W. E. Parham and K. B. Sloan, *Tetrahedron Lett.*, 1947 (1971).

Scheme III

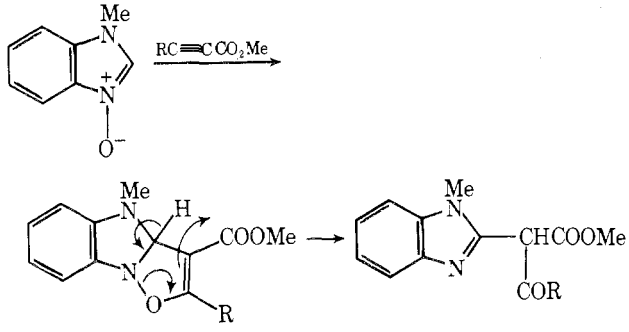


blocked. In the latter case, the normal 2-substituted product accompanies the rearrangement product. The formation of 2,3′-dipyridyl ether as one of the products from the reaction of pyridine 1-oxide with 2-bromopyridines[23] can be rationalized similarly.[8]

Reaction of pyridine 1-oxide with perfluoropropene gave 2-(1,2,2,2-tetrafluoroethyl)pyridine and COF_2.[24] This, together with the above acylaminations, led us to consider the possibility of a general reaction as outlined in Scheme III. In principle, Z could be either a good anionic leaving group, or another π bond to Y. The latter situation was investigated and found to lead to interesting substitution and rearrangement products.

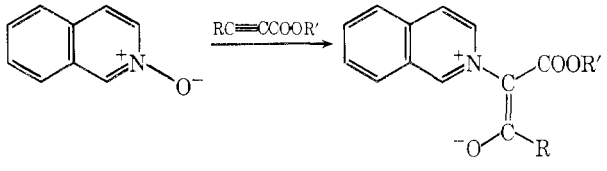
Reactions with Activated Acetylenes

Nitrones undergo 1,3-dipolar cycloaddition with suitable acetylenes[25] and this reaction has been applied successfully to benzimidazole 3-oxides:[26]

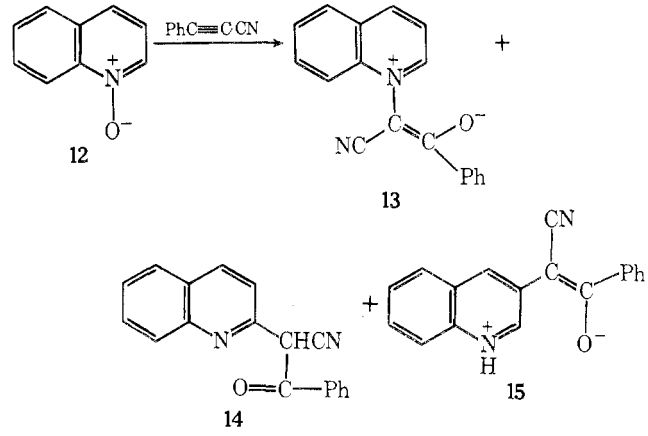


In some cases, interesting ring expansions have been observed,[27] but these are beyond the scope of this Account.

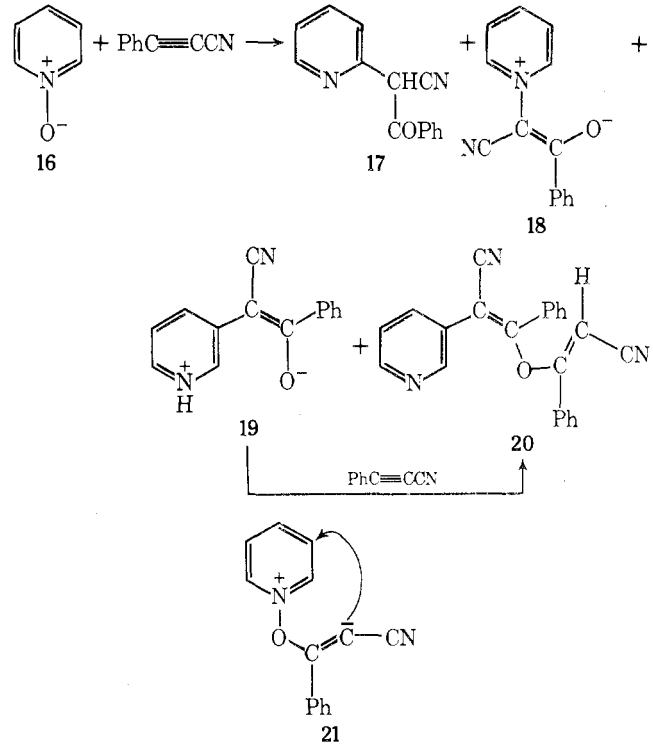
An ylide is formed if a 2-methylbenzimidazole 3-oxide,[28] isoquinoline *N*-oxide,[29] or tricyclic *N*-oxides[30,31] are used.



On the other hand, reaction of phenylpropiolonitrile with quinoline 1-oxide (**12**) gave two 1:1 adducts *in addition* to the ylide **13** (6.5%). The first (10%) was shown to be the expected product (**14**) of cyclization to the 2 position followed by aromatization. The major (18%) fraction, however, was the novel product (**15**) resulting in substitution at the 3 position of the quinoline ring![32]



Pyridine 1-oxide (**16**) behaved similarly, and a small amount of 2-alkylated product (**17**) was formed[32] together with traces of ylide (**18**).[33] The major isomer, however, was again the 3-alkylation product (**19**)[32,33] together with some divinyl ether (**20**) resulting from the addition of **19** to unchanged phenylpropiolonitrile.[34] Other pyridine *N*-oxides behave similarly. 3-Alkylated products are also formed from ethyl propiolate[34] and ethyl phenylpropiolate.[35]



(23) K. Takeda, K. Hamamoto, and H. Tone, *Yakugaku Zasshi*, **72**, 1427 (1952); *Chem. Abstr.*, **47**, 8071*a* (1953); F. Ramirez and P. W. von Ostwalden, *J. Am. Chem. Soc.*, **81**, 156 (1959). See also P. A. de Villiers and H. J. den Hertog, *Recl. Trav. Chim. Pays-Bas*, **76**, 647 (1957), for the similar behavior of 2-hydroxypyridine toluenesulfonate with pyridine 1-oxide.

(24) E. A. Mailey and L. R. Ocone, *J. Org. Chem.*, **33**, 3343 (1968).

(25) R. Crigg, *Chem. Commun.*, 607 (1966).

(26) S. Takahashi and H. Kano, *Tetrahedron Lett.*, 1687 (1963).

(27) W. E. Noland and R. F. Modler, *J. Am. Chem. Soc.*, **86**, 2086 (1964); J. P. Freeman, E. D. Duthie, M. J. O'Hara, and J. F. Hansen, *J. Org. Chem.*, **37**, 2756 (1972).

(28) S. Takahashi and H. Kano, *J. Org. Chem.*, **30**, 1118 (1965).

(29) R. Huisgen, H. Seidl, and J. Wulff, *Chem. Ber.*, **102**, 915 (1969); *Tetrahedron Lett.*, 2023 (1963).

(30) S. R. Challand, C. W. Rees, and R. C. Storr, *J. Chem. Soc., Chem. Commun.*, 837 (1973); S. R. Challand, S. F. Gait, M. J. Rance, and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 26 (1975).

(31) R. M. Acheson, A. S. Bailey, and I. A. Selby, *J. Chem. Soc. C*, 2066 (1967).

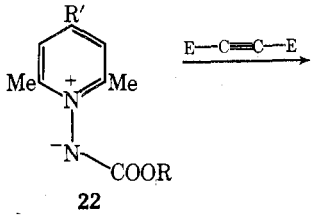
(32) R. A. Abramovitch, G. Grins, R. B. Rogers, J. L. Atwood, M. D. Williams, and S. Crider, *J. Org. Chem.*, **37**, 3383 (1972).

(33) R. A. Abramovitch and I. Shinkai, *J. Chem. Soc., Chem. Commun.*, 569 (1973).

(34) R. A. Abramovitch and I. Shinkai, unpublished results.

(35) R. A. Abramovitch, I. Shinkai, and P. C. Srinivasan, unpublished results.

Formation of the 3-alkylated product by a direct intramolecular attack (**21**) is both sterically and mechanistically unlikely. The reaction of 2-methyl- and 2,6-dimethyl-1-alkoxycarbonyliminopyridinium ylides (**22**) with dimethyl acetylenedicarboxylate gave both the unstable 1,2-dihydropyridine cycloadducts (**23**) and the 3-alkylated products (**24**),[36] e.g.



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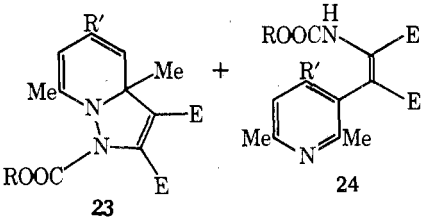


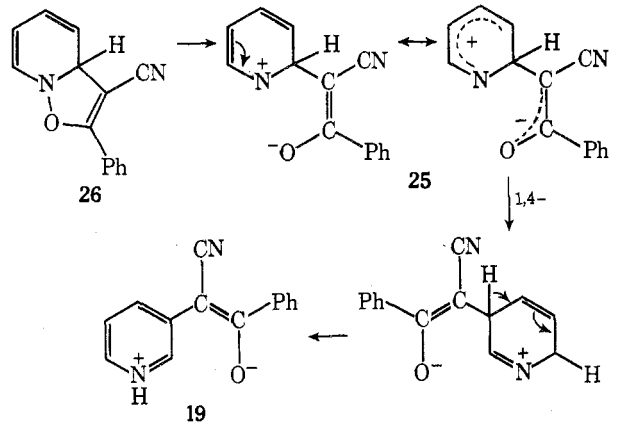
23 **24**

E = COOMe

It was suggested that the initial adduct (**23**) underwent N–N bond fission to give a zwitterion which could undergo either a 1,4 shift of the C-2 vinyl group (presumably $_{\sigma}2_a + _{\pi}2_a + _{\omega}0_a$) or a 1,2 shift to give another 5- or a 3-substituted zwitterion. This would then aromatize to **24** by a 1,4 shift of the β hydrogen.

When this proposed mechanism is applied to pyridine and quinoline 1-oxides (Scheme IV) two objections to it arise: first, the heterolytic N–O bond cleavage leads initially to a nitrenium ion, albeit a resonance-stabilized one. Counterbalancing this energetically unfavorable process somewhat is the fact that the negative charge in the side chain is highly delocalized. Perhaps more important is the fact that zwitterion **25** could itself aromatize by losing a proton to give **17**. This, as noted above, however, is a minor pathway. Instead, the above mechanism would require a 1,2- or 1,4-alkyl shift to occur before aromatization takes place by loss of a β proton, and it is hard to see why loss of a proton from the β position would be more facile than its loss from an α position. A third point is that this mechanism does not account for ylide formation.

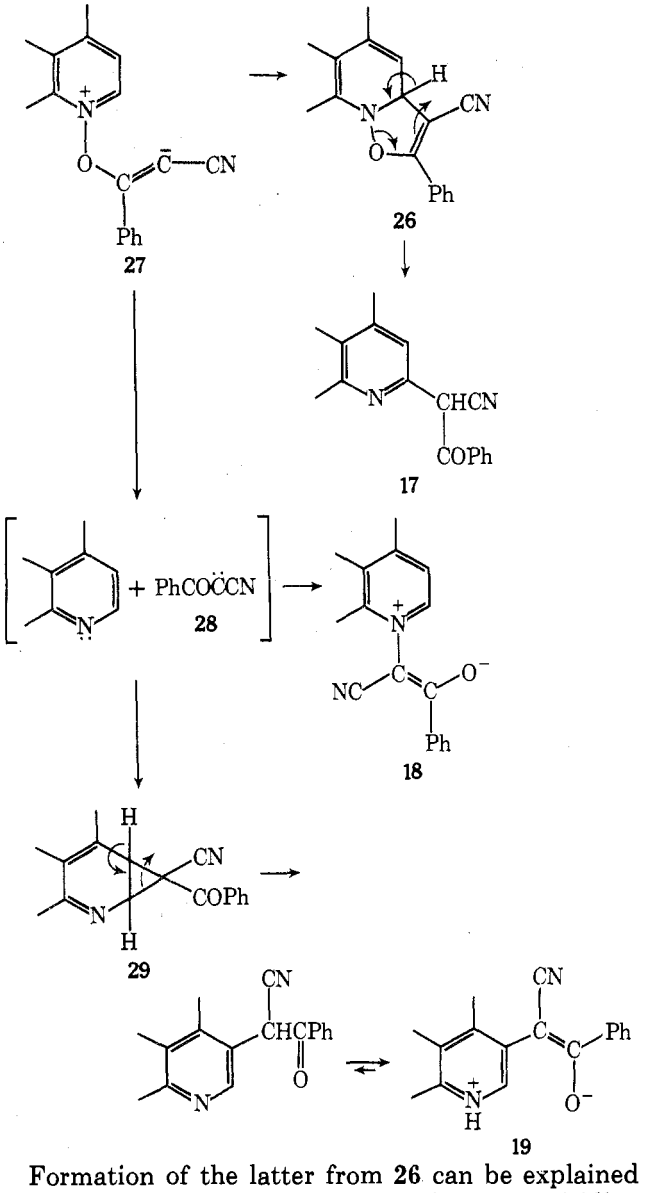
Scheme IV



26 **25** **19**

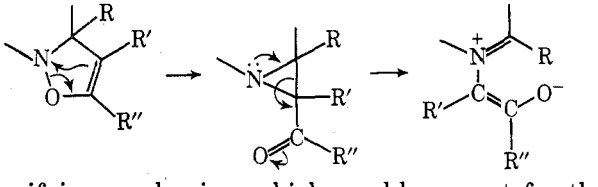
(36) T. Sasaki, K. Kanematsu, and A. Kakehi, *J. Org. Chem.*, **36**, 2978 (1971); T. Sasaki, K. Kanematsu, A. Kakahi, and G. Ito, *Bull. Chem. Soc. Jpn.*, **45**, 2050 (1972).

Scheme V



27 **26** **17** **28** **18** **29** **19**

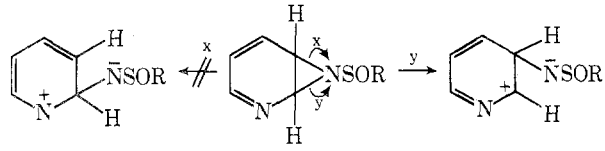
Formation of the latter from **26** can be explained by assuming a ring contraction to form an aziridine derivative followed by ring opening:[2,28-31]



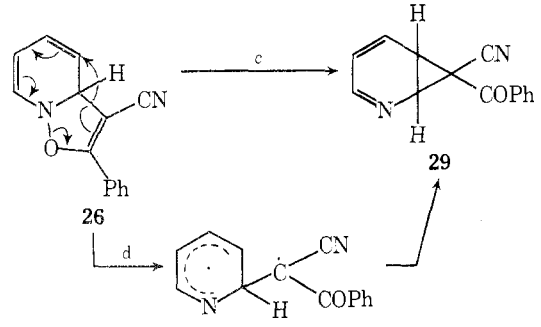
A unifying mechanism which would account for the formation of all the products was tentatively suggested (Scheme V).[33] The 1,2-dihydro derivative **26** was expected to aromatize to give **17**. Alternatively, the initial dipolar intermediate **27** might undergo N–O bond cleavage to give a tight pair (not solvent separated) of neutral pyridine and the highly electrophilic benzoylcyanocarbene (**28**) (the same objection to this process may be lodged as with the formation of a nitrenium ion postulated above). Carbene **28**, being highly electrophilic, might be expected to behave as do the highly electrophilic sulfonyl nitrenes RSO_2N toward pyridines. These have been shown[37] to give only the pyridinium ylides and the 3-sulfonamidopy-

(37) R. A. Abramovitch and T. Takaya, *J. Org. Chem.*, **37**, 2022 (1972).

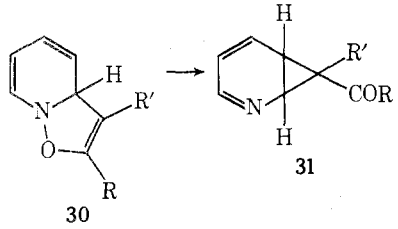
ridines. As expected, none of the 2-sulfonamido derivatives were observed since, to form the latter, an energetically unfavorable ring opening of the intermediate aziridine would have been required.



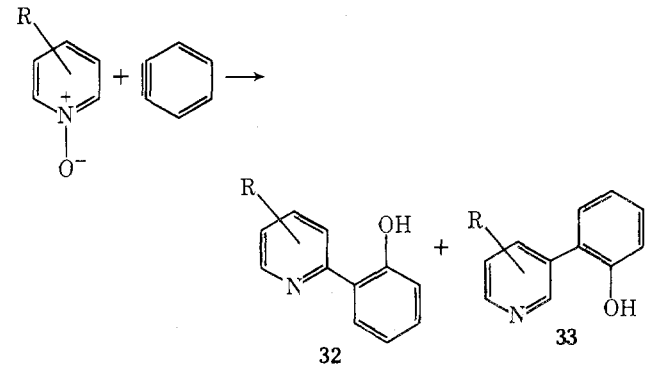
The same considerations would apply to the preferential ring opening of **29.** To test this hypothesis the reaction of authentic **28** with pyridine was examined.[33] Thermolysis of benzoylcyanodiazomethane in pyridine gave a mixture of **18** and **19,** as expected. No **17** was formed. The ratio of **18:19** was 23:3 as compared with a ratio of 61:<1 in the phenylpropiolonitrile reaction. Thus, while the ylide could indeed still be arising from the carbene as in Scheme V in the acetylene reaction, or from **26** via the ring-contraction mechanism, the 3-alkylated product **19** clearly owed its origin to a different mechanism. One possibility is that intermediate **25** (Scheme IV) underwent ring closure to **29,** but the objection to the intervention of **25** would still remain. A much more likely process in our opinion is a concerted rearrangement of **26** to **29** via a symmetry-allowed $[_{\sigma}2_s + {}_{\pi}2_a + {}_{\pi}4_s]$ process (c).[33] A diradical mechanism (d) cannot be ruled out, however.



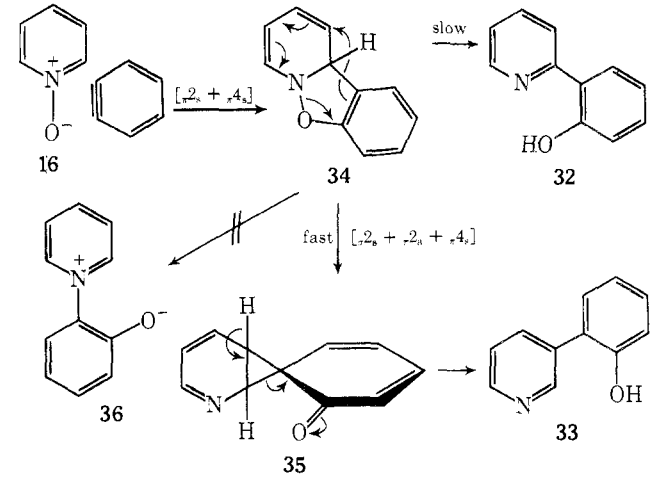
Should mechanism c obtain, then rearrangement (but not the initial addition) should be independent of the nature of the groups on the acetylene, i.e., **30** → **31** should occur irrespective of whether R′ was



electron withdrawing or not. An interesting test case for this would be one in which R and R′ would be –CH=CH–CH=CH– and such an intermediate might result from the 1,3-dipolar cycloaddition of benzyne to pyridine 1-oxides. The reaction of pyridine 1-oxides with benzyne under various conditions was studied,[38] and was found to give mainly the 3-*o*-hydroxyphenylpyridine derivative (**33**) together with minor amounts of **32.** This has been rationalized as in Scheme VI.[38] The driving force leading to the formation of the spirodienone **35** must be appreciable since it leads to the loss of the aromaticity of the benzene ring in **34.** It is interesting to note that no ylides (**36**) were ever detected in these reactions. According to the ring-contraction mechanism for ylide formation (vide supra), one might have expected some to be formed.

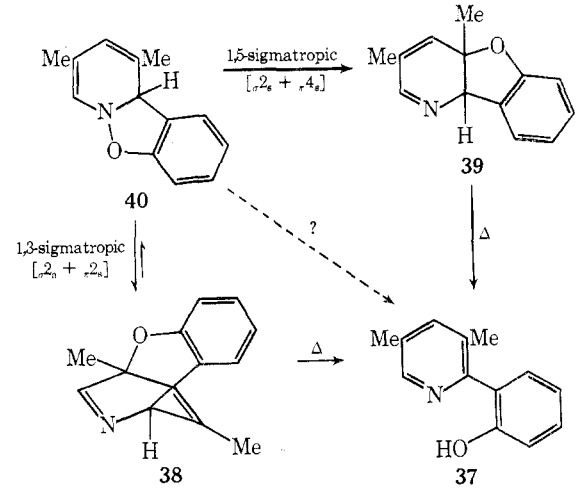


Scheme VI



Also of interest was the fact (predicted) that 3,5-lutidine 1-oxide led to the formation of **37** only. When the addition of benzyne to 3,5-lutidine 1-oxide was carried out under much milder conditions, i.e., conditions of kinetic control, *two* isomeric dihydropyridines were isolated, *neither* of which was **40!** Their structures were established as **38** and **39** and their formation from **40** via 1,3- and 1,5-sigmatropic shifts (the latter is similar to the one observed with

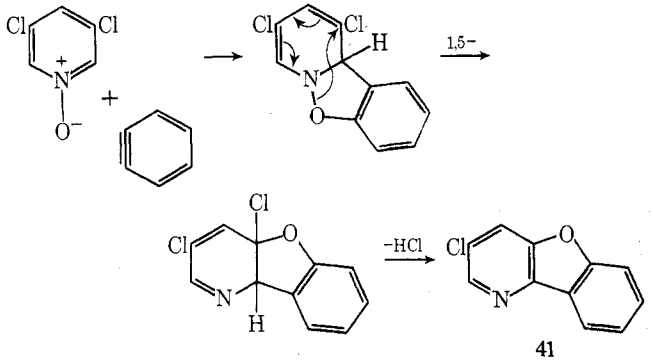
Scheme VII



(38) R. A. Abramovitch and I. Shinkai, *J. Am. Chem. Soc.,* **96,** 5265 (1974).

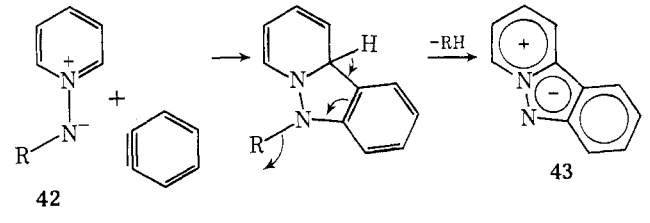
the imidoyl chlorides) is depicted in Scheme VII. Heating either **38** or **39** gives **37.** It is not known whether this involves a reversal to **40** followed by aromatization or whether **38** and **39** go to **37** directly, but we tend to favor the latter hypothesis now (vide infra).

The 1,5-sigmatropic shift in Scheme VII has been confirmed in a one-step synthesis of the benzofuro[3,2-*b*]pyridine ring system by the reaction of 3,5-dichloropyridine 1-oxide with benzyne at 0 °C to give **41.**[38]



41

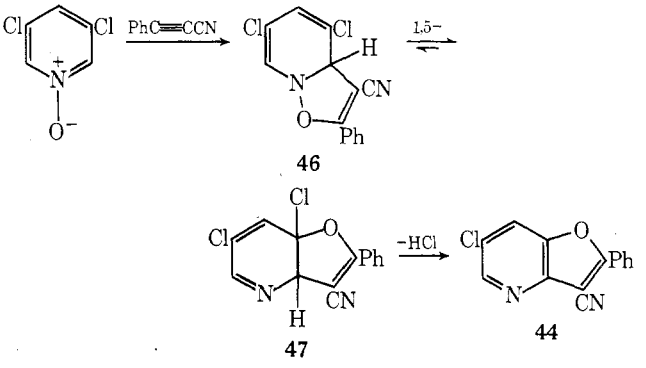
These results emphasize the ease with which 1,2-dihydropyridine 1-oxides rearrange to 2,3-dihydropyridine derivatives. *N*-Iminopyridinium ylides (**42**) do not behave similarly: when **42** (R = $PhSO_2$, CO_2Et) was treated with benzyne the 1,2-dihydro intermediate did not rearrange but lost $PhSO_2H$ or HCO_2Et to give pyrido[1,2-*b*]indazole (**43**) in low yield.[39]



42 **43**

The behavior of 3,5-dichloropyridine 1-oxide with benzyne led us to reexamine the reaction of 3,5-dihalopyridine 1-oxides with activated acetylenes. The reasoning was that, if the 1,5-sigmatropic shift observed with benzyne was a general reaction, it should not depend too much on the nature of R and R′ in **30,** and elimination of H–X from the 2,3-dihydro intermediate (starting with a 3,5-di-X-substituted **30**) would make the rearrangement irreversible. This was indeed found to be the case. In the process, however, a new rearrangement was uncovered.

Reaction of 3,5-dichloropyridine 1-oxide with phenylpropiolonitrile gave 6-chloro-3-cyano-2-phenylfuro[3,2-*b*]pyridine (**44**) and 7-chloro-3-cyano-2-phenylfuro[3,2-*c*]pyridine (**45,** X = Cl). Related products were obtained starting with 3,5-dibromopyridine 1-oxide and suitable acetylenes.[40] Formation of **44** again probably involves a 1,5-sigmatropic shift of the initially formed 1,2-dihydropyridine to a 2,3-dihydro derivative which eliminates HCl. Generation of **45,** however, requires consecutive 3,5 shifts leading eventually to "busing" of the oxygen atom from the

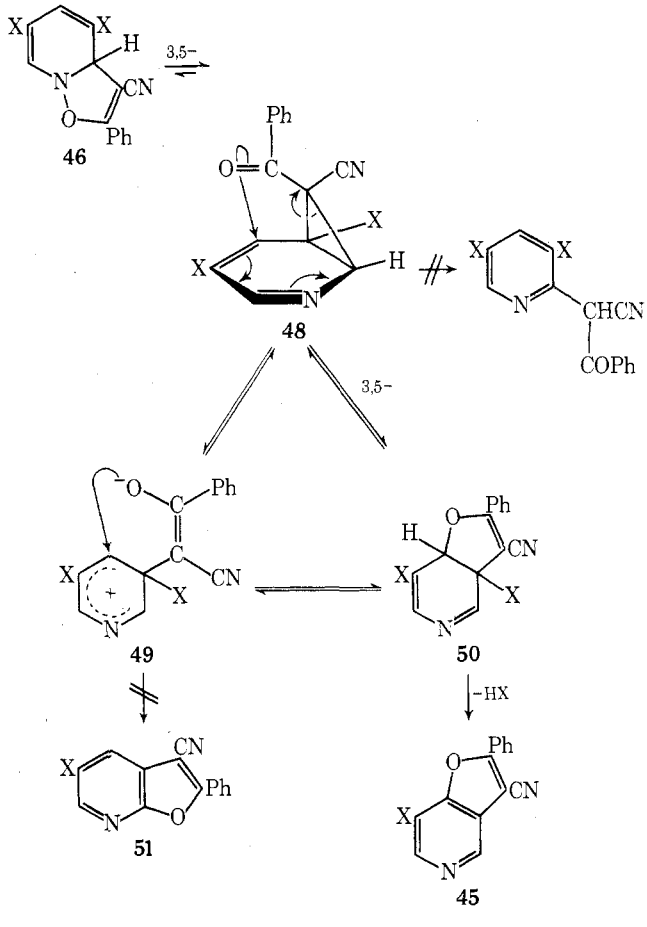


46 **47** **44**

nitrogen atom to C-4. We visualize this involving two competing, probably reversible, rearrangements. The first is the above 1,5 shift of oxygen from nitrogen to the β carbon, **46** → **47,** as has been observed above with 2,6-disubstituted pyridine 1-oxides and imidoyl chlorides and in the formation of **44.** The second involves the same sort of 3,5 rearrangement as has been observed in **26** → **29.** This would lead to a pyridocyclopropane derivative, **48,** which would have a number of options open to it: reversal to **46,** ring opening to **49** (or a diradical), or a second 3,5 shift leading to a 3,4-dihydro intermediate, **50** (also available by ring closure of **49**). Elimination of HX would finally yield **45** (Scheme VIII).

Speaking against the ring opening **48** → **49** (or its radical equivalent) is the fact that **49** might have been expected to close to a certain extent through the pyridine α position as well.[8] No furo[2,3-*b*]pyridine derivative (**51**) could be detected in any of these reac-

Scheme VIII

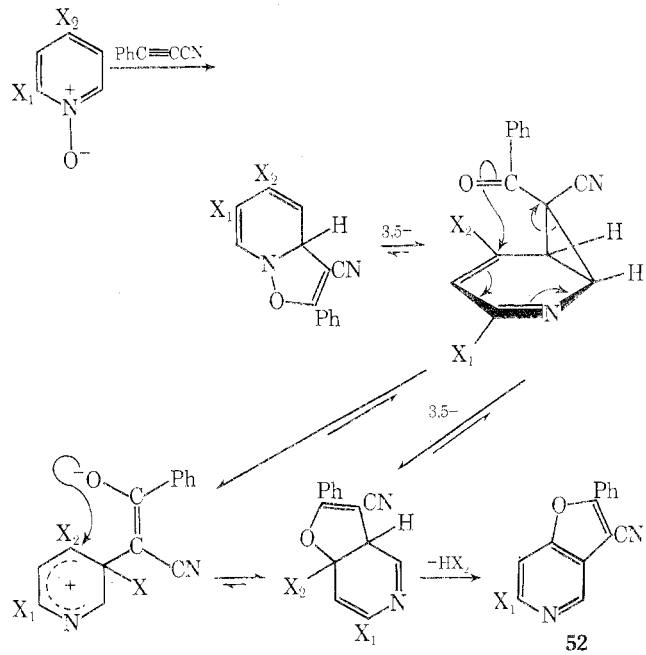


46 **48** **49** **50** **51** **45**

(39) R. A. Abramovitch, J. Laux, and I. Shinkai, unpublished results, 1975; "Abstracts of Papers Presented at the Southeast-Southwest Regional Meeting of the American Chemical Society, Memphis, Tenn., Oct. 1975", paper 451.

(40) R. A. Abramovitch and I. Shinkai, *J. Am. Chem. Soc.*, **97,** 3227 (1975).

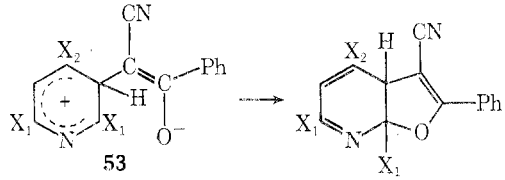
Scheme IX



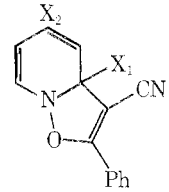
52

tions; **51** clearly could not result from an azanorcaradiene such as **48**.

If the reversibility of the above rearrangement is assumed, as seems necessary, busing of the oxygen to C-4 should be even more facile if a halogen or pseudohalogen were present at that position (since stabilization via a process such as **47** → **44** should no longer be possible). This was indeed found to be the case. Thus, treatment of 4-chloropyridine 1-oxide with phenylpropiolonitrile gave 3-cyano-2-phenylfuro[3,2-*c*]pyridine (**52**, X_1 = H) in excellent yield (also prepared by dehalogenation of **45**). A similar reaction occurred with methyl phenylpropiolate and when the 4-chlorine atom in the pyridine 1-oxide was replaced by a methoxyl or a nitro group.[40] The suggested mechanism is given in Scheme IX. In the hope of testing the concerted 3,5 shift vs. the ring-opening/ring-closure mechanism the reaction of 2,4,6-trichloropyridine 1-oxide or 2,6-dichloropyridine 1-oxide with phenylpropiolonitrile was attempted; unfortunately, the basicity of the *N*-oxide was insufficient to permit any reaction. It had been hoped that, had an intermediate such as **53** (or its diradical counterpart) been formed, some ring closure would have occurred at the α position (**54**). The fact that no such product is obtained when 2,4-dichloro- or 2-chloro-4-nitropyridine 1-oxide is used is inconclusive since it is not known whether or not any cyclization occurs to give



53 54



55

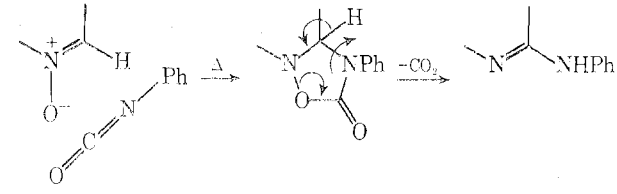
the 1,2-dihydro derivative **55**, a necessary prerequisite for the observation of any furo[2,3-*b*]pyridine derivative via a ring-opened intermediate.

Summarizing the preparative aspects of these reactions of *N*-oxides with activated acetylenes we have shown that: (i) Treatment of a six-membered heteroaromatic *N*-oxide not bearing a 3- or 4-halogen (or pseudohalogen) atom with an activated acetylene leads mainly to β alkylation of the aromatic nucleus. If the β positions are blocked, then α-alkylation occurs. (ii) Reaction of the same compounds with benzyne under conditions of thermodynamic control leads mainly to 3-*o*-hydroxyphenylated pyridine derivatives. If the 3 and 5 positions are blocked, 2-*o*-hydroxyphenylpyridines are formed. In the latter case, the 2,3- and 2,5-dihydropyridine intermediates can be isolated under conditions of kinetic control. (iii) With a 3,5-dihalopyridine derivative the reaction leads mainly to furo[3,2-*b*]pyridines. (iv) With 4-halo- (or pseudohalo-) pyridines good yields of furo[3,2-*c*]pyridines are obtained.

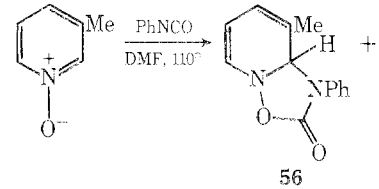
Benzimidazole *N*-oxides react with benzyne unexceptionally to give the 2-*o*-hydroxyphenyl derivative,[41] as do quinoxalone 4-oxides.[42]

Reaction with Phenyl Isocyanate

The 1,3-dipolar cycloaddition of isocyanates and isothiocyanates to heteroaromatic *N*-oxides is a well-known reaction,[26,43-46] a rare example of its failure occurring in the case of 7-azaindole 7-oxide.[46] The reaction has been envisaged as a dipolar addition to the nitrone function followed by aromatization with loss of CO_2, leading to the introduction of an anilino function at the nitrone carbon.



A breakthrough was achieved when it was reported[47] that the 1,2-dihydro intermediates **56** and



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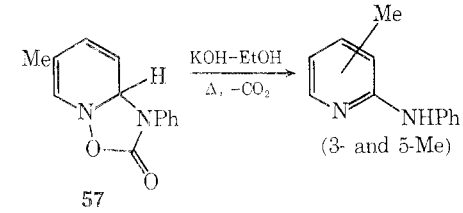


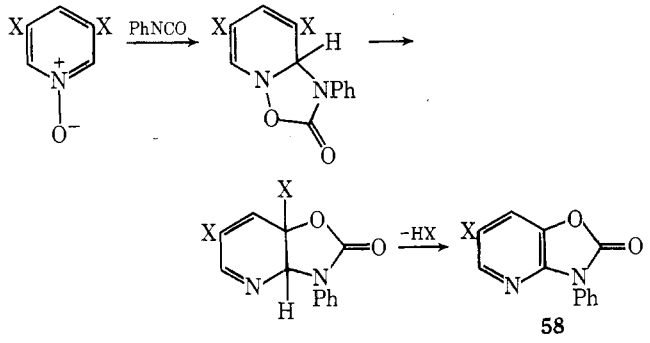
57

(3- and 5-Me)

(41) S. Takahashi and H. Kano, *Chem. Pharm. Bull.*, **12**, 1290 (1964).
(42) J. C. Mason and G. Tennant, *J. Chem. Soc., Chem. Commun.*, 218 (1972).
(43) E. Hayashi, *J. Pharm. Soc. Jpn.*, **81**, 1030 (1961).
(44) E. Hayashi and E. Oishi, *J. Pharm. Soc. Jpn.*, **86**, 576 (1966).
(45) H. Seidl, Dissertation, University of Munich, 1964; H. Seidl, R. Huisgen, and R. Grashey, *Chem. Ber.*, **102**, 926 (1969).
(46) B. A. J. Clark and J. Panick, *J. Chem. Soc., Perkin Trans. 1*, 2270 (1974).
(47) T. Hisano, S. Yoshikawa, and K. Muraoka, *Org. Prep. Proced. Int.*, **5**, 95 (1973); *Chem. Pharm. Bull.*, **22**, 1611 (1974).

57 could be isolated and separated from the reaction of 3-picoline 1-oxide and phenyl isocyanate in dimethylformamide at 110 °C. These were relatively thermally stable, but did aromatize with loss of CO_2 on heating with base (presumably excess *N*-oxide in earlier studies).

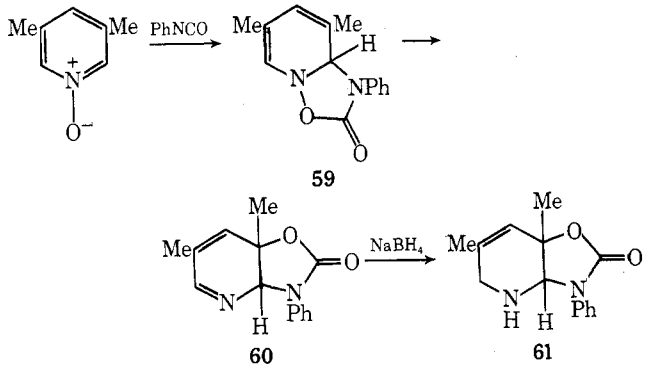
Reaction of 3,5-dibromopyridine 1-oxide with phenyl isocyanate in dimethylformamide gave[48] **58** (it was proposed[48] that the 1,2-dihydro intermediate underwent heterolysis to a stabilized nitrenium ion that cyclized at the 3 position, but this seems unlikely for the reasons adumbrated above in the section on acetylenes). Reaction of 3-bromo- or 3-nitroquinoline 1-



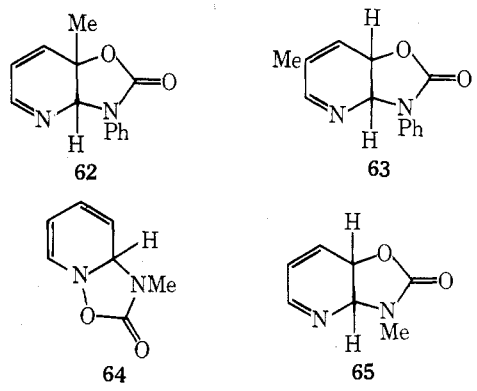
X = Br

oxides with phenyl isocyanate in dimethylformamide at 80° gave similar products,[49] as did 3-bromopyridine 1-oxide.[50] The isolation of the 1,2-dihydro intermediate (**59**) from the reaction of 3,5-lutidine 1-oxide and phenyl isocyanate was reported, and again it was thermally stable, but converted to 2-anilino-3,5-dimethylpyridine in boiling alcoholic potassium hydroxide.[50]

We were particularly struck by the similarity between the published NMR spectrum of **59** and that of the 2,3-dihydro derivative **37.** Most striking are the methyl resonances, one of which is a doublet, the other a singlet. Had structure **59** for the adduct been correct, one might have expected two doublets showing allylic couplings of ca. 1.5 Hz. Reinvestigation of this reaction[34] led to the conclusion that the adduct isolated is, in fact, the 2,3-dihydro derivative **60,** arising from **59** by the now familiar 1,5-sigmatropic shift.

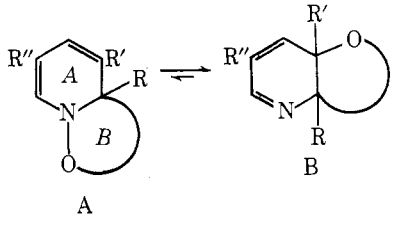


Confirmation of the structure of **60** comes from its reduction with sodium borohydride to give **61** (NH and C=O present, no OH). Reinvestigation of the putative 1,2-dihydro derivatives **56** and **57** showed them to be the corresponding 2,3-dihydro isomers **62** and **63.**[34]



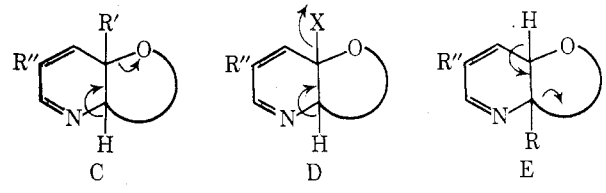
A general picture seems to be emerging from these and the rearrangements reported earlier, namely the great instability of the 1,2-dihydro derivatives of such *N*-oxides relative to the rearranged 2,3-dihydro derivatives. To confirm this, MINDO/2′ calculations were carried out on the relative heats of formation of the 1,2- and 2,3-dihydropyridine derivatives **64** and **65.**[51] The heats of formation (geometry optimized) thus calculated for **64** and **65** were −48.8 and −84.7 kcal/mol, so that $\Delta\Delta H_f = -35.9$ kcal/mol. Even though this difference may be overestimated (MINDO/2′ is known not to be able to take into account satisfactorily such bonds as N–O[52]), it is definitely in the direction predicted and accounts readily for the observed isomerizations.

Indeed, it is tempting to rationalize most of the above results in the last three sections on the basis of a general principle, namely that fused bicyclo-1,2-dihydropyridine 1-oxides (A) are less stable than their 2,3-dihydro counterparts (B) and rearrange



A B

readily to these. Subsequent aromatization occurs mainly (if not invariably) from B if a choice is available. The nature of the product formed would depend on what R and R′ were. Thus, if R = H and R′ ≠ H or halogen, aromatization would occur as in C. If R = H and R′ = halogen or pseudohalogen, elimination of HX as in D leads to a bicyclic system, whereas if R′ = H and R ≠ H, elimination as in E occurs (e.g., 3-imidate formation of 2,6-disubstituted pyridines).



If the *B* ring in A is five-membered and unsaturated (F), another option is available, namely a 3,5-

(48) T. Hisano, T. Matsuoka, and M. Ichikawa, *Heterocycles,* **2,** 163 (1974).

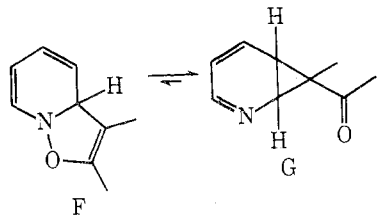
(49) M. Hamana, H. Noda, and M. Aoyama, *Heterocycles,* **2,** 167 (1974).

(50) T. Hisano, T. Matsuoka, and M. Ichikawa, *Org. Prep. Proced. Int.,* **6,** 243 (1974).

(51) R. A. Abramovitch, I. Shinkai, and R. van Dahm, *J. Heterocycl. Chem.,* in press. We thank Dr. W. W. Paudler for "lending" us Mr. van Dahm for this purpose.

(52) M. J. S. Dewar, *Fortschr. Chem. Forsch.,* **23,** 1 (1971).

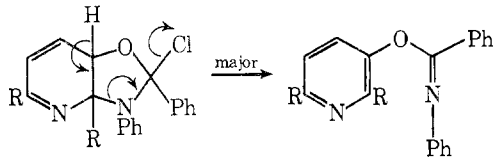
sigmatropic shift leading to an azanorcaradiene (G) which undergoes further transformations. If ring



opening of G occurs *via* a dipolar transition state, then it will take place preferentially so as to give the 3-substituted derivative and thus avoid placing a partial positive charge on the ring nitrogen.

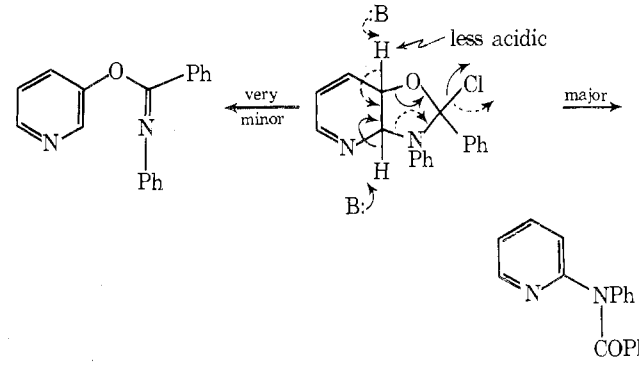
This general scheme would also explain the results obtained on acylamination of six-membered heteroaromatic *N*-oxides. The suggestion here is that, in this case as well, the initially formed 1,2-dihydropyridine rearranges to the 2,3-dihydro isomer and that it is this isomer which aromatizes (Scheme X).

Scheme X



If this is actually the case, reaction of 3,5-dihalopyridine 1-oxide with an imidoyl chloride could lead to elimination of HX from the 2,3-dihydro intermediate and give a bicyclic derivative similar to **58**, though one can anticipate some experimental difficulties, both owing to the weakly basic nature of the required *N*-oxide and to the probable instability of the five-membered ring in the product.

The greated stability of 2,3-dihydro-(B) than 1,2-



(abstraction of more acidic proton; cleavage of weaker bond: C–O rather than C–N)

dihydro derivatives (A) may also help to understand other observations in the literature, including the intramolecular rearrangement of the adduct from pyridine 1-oxide and *p*-toluenesulfonyl chloride at ca. 205° to give 3-tosyloxypyridine,[8,53] and the rearrangement of the oxaziridine formed by the photolysis of 2,4,6-triphenylpyridine 1-oxide to the 2,3-dihydro derivative and subsequent ring opening or ring expansion[54] (the major product arises, however, from the oxaziridine originally formed). 3-Hydroxypyridines have also been obtained by the photolysis of other pyridine 1-oxides, 2-methyl- and 2,6-dimethyl[55] and 2-(1-cyclohexenyl)-4,5-dimethylpyridine 1-oxide,[56] and may well involve the formation of a 2,3-dihydro epoxide.

We thank the National Institutes of Health for the support of this work.

(53) S. Oae, T. Kitao, and Y. Kitaoka, *Tetrahedron*, **19**, 827 (1963); E. Ochiai and T. Yokokawa, *J. Pharm. Soc. Jpn.*, **75**, 213 (1955); *Chem. Abstr.*, **50**, 1819*b* (1956).

(54) P. L. Kumler and O. Buchardt, *Chem. Commun.*, 1321 (1968).

(55) J. Streith, B. Danner, and Ch. Sigwalt, *Chem. Commun.*, 979 (1967).

(56) R. A. Abramovitch and A. Silhankova, unpublished results (1970).