(which includes the catalyst) was extracted with 25 ml. of water. Evaporation of the extract then gave 0.36 g. of white crystals, m.p. > 360°, which were purified by recrystallization from aqueous acetone.

Anal. Calcd. for $C_{12}H_{26}N_2Cl_2$: C, 53.7; H, 9.7; N, 10.45. Found: C, 53.6; H, 9.6; N, 10.5.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

Amine Oxides. A Comparison of 2-Vinylpyridine *N*-Oxide and the 2,3-Dihydroisoxazolo[2,3-a]pyridinium Ion[1]

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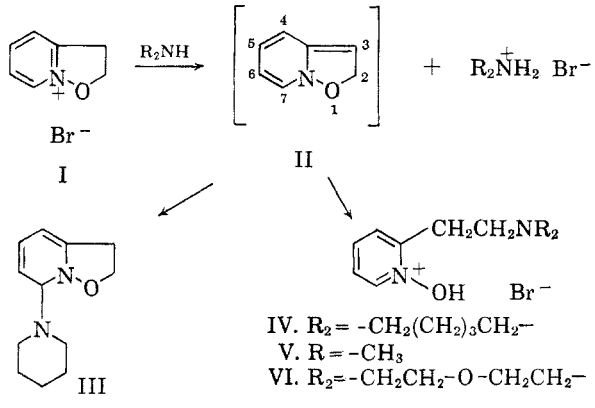
The reaction of 2-vinylpyridine *N*-oxide with nucleophilic reagents occurs readily and follows a course similar to that of 2-vinylpyridine. The adducts obtained with secondary amines are the same as the major products resulting from the reaction of secondary amines with 2,3-dihydroisoxazolo(2,3-a)pyridinium bromide.

Previously,[3] we reported on the preparation of some cyclic quaternary salts derived from pyridine *N*-oxide and their decomposition with base. The reaction of 2,3-dihydroisoxazolo (2,3-a)-pyridinium bromide (I) with aqueous piperidine led to the separation of an unstable crystalline product (III), m.p. 124–126°, of unusual chemical and spectral properties. The composition of this product corresponded to the empirical formula $C_{12}H_{18}N_2O$, which is in accord with that required for an adduct of piperidine and 2-vinylpyridine *N*-oxide. However, the ultraviolet absorption spectrum of the unstable product and its behavior on hydrogenation clearly eliminated this possibility.

Reinvestigation of this reaction has led to the isolation of an additional product (IV), m.p. 167–168.5°, whose composition is in accord with the empirical formula $C_{12}H_{19}N_2OBr$. Although the yields of III and IV varied in individual experiments, IV was predominant in each instance and the sum of III and IV accounted for all the 2,3-dihydrooxazolo (2,3-a) pyridinium bromide employed. As IV had the characteristics of a hydrobromide salt, it was converted to the corresponding free base which was an oil markedly different from III in its spectral properties.

The ultraviolet absorption spectrum of IV showed a single maximum at 263 mμ (ε 11,500), suggesting the possibility that it was a simple pyridine or pyridine *N*-oxide derivative. In the color test devised by Katritzky,[4] IV gave a positive result for the presence of an *N*-oxide function. Treatment of IV, then, with phosphorus trichloride effected removal of the *N*-oxide group and yielded an oil identical in its infrared spectrum and other properties with 2-[β-(*N*-piperidino)ethyl]pyridine. The identity was further established by comparison of the dipicrate derivatives. Thus, IV must be the hydrobromide salt of 2-[β-(*N*-piperidino)ethyl] pyridine *N*-oxide and a possible explanation for its formation is illustrated below.



The reaction of dihydroisoxazolo-[2,3-a]pyridinium bromide (I) with aqueous dimethylamine and with morpholine was also studied and, in each case, gave a single product in high yield. The structure of the dimethylamine product V was established by independent synthesis. The structure VI assigned to the product with morpholine is based on its physical and spectral properties as well as analogy.

Although the structure of I seems clearly established, particularly in view of its spectral properties, a possible explanation for its easy conversion to IV, V and VI on treatment with secondary amines might lie in the existence of an equilibrium between I and the corresponding salt of 2-vinyl pyridine *N*-oxide (VII). To test this possibility a sample of 2-vinylpyridine *N*-oxide was prepared and converted to its picrate. It was readily demonstrated that this picrate was different from, and not easily interconvertible with, the picrate of I.

(1) This investigation was aided by a grant from the National Science Foundation.

(2)(a) To whom inquiries should be addressed. (b) University of Oregon, Eugene, Ore.

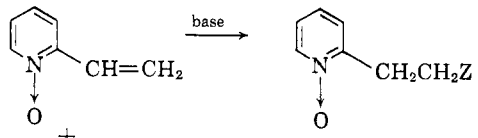
(3) V. Boekelheide and W. Feely, *J. Am. Chem. Soc.*, **80**, 2217 (1958).

(4) N. A. Coats and A. R. Katritzky, *J. Org. Chem.*, **24**, 1836 (1959).

I VII

Thus, under ordinary conditions, there is no evidence for such an equilibrium.

The preparation and polymerization of 2-vinylpyridine *N*-oxide has been reported by Cislak.[5] In our experience 2-vinylpyridine *N*-oxide is prepared most readily and in high yield simply by heating a mixture of 2-(β-hydroxyethyl)pyridine *N*-oxide and potassium bisulfate. Although 2-vinylpyridine *N*-oxide polymerizes on standing, it can be handled satisfactorily if used directly after preparation. We have made a brief examination of its behavior toward various nucleophilic reagents and found, as would be expected from analogy with 2-vinylpyridine, that it readily undergoes the Michael addition in the normal fashion. Thus, with piperidine and dimethylamine, 2-vinylpyridine *N*-oxide gave the expected adducts IV and V in yields of 86 and 78% respectively. This serves as additional evidence for the structures previously assigned to IV and V. The other nucleophiles which have been investigated include diethyl malonate, ethyl acetoacetate, ethanol, and pyrrole. The structures and yields of these adducts are given below. In each case, the structure of the product was proved by deoxygenation to the corresponding adduct of 2-vinylpyridine.



HZ

VIII. Z = $-CH(CO_2C_2H_5)_2$ (42%)
IX. Z = $-CH(CO_2C_2H_5)COCH_3$ (80%)
X. Z = $-OCH_2CH_3$ (41%)
XI. Z = $-N$⟨ ⟩ (73%)

With this knowledge of the properties of 2-vinylpyridine *N*-oxide the question of 2-vinylpyridine *N*-oxide as a likely intermediate in the reaction of dihydroisoxazolo(2,3-*a*)pyridinium bromide (I) with secondary amines can be reexamined. One argument against this probability is the fact that various attempts to convert I to 2-vinylpyridine *N*-oxide by the action of strong base gave no useful products even though subjecting 2-vinylpyridine *N*-oxide to the same reaction conditions led to its recovery in reasonable yield. Furthermore, the reaction of 2-vinylpyridine *N*-oxide with piperidine gave IV as the only product, making it quite unlikely that 2-vinylpyridine *N*-oxide is an intermediate in the formation of III. Attempts to effect a reaction between I and nucleophiles other than secondary amines did not lead to useful products, although these nucleophiles add readily to 2-vinylpyridine *N*-oxide in good yield.

The most plausible reaction scheme appears to be that involving II as a reaction intermediate. The first step, the removal of the proton from C-3, would be analogous to the behavior of 2,3-dihydro-4H-oxazino(2,3-a)-pyridinium bromide on treatment with base.[3] The next step, the reaction of II with a secondary amine, would involve a competition between displacement of oxygen at C-2 and addition to the conjugated system. Based on the observed products with secondary amines, displacement is the favored reaction. In the case of piperidine, where a second product is formed, addition becomes a competitive reaction and structure III would seem a likely formulation for this product. Structure III is in accord with the general instability of the product and accounts reasonably well for its strong maximum in the ultraviolet at 340 mμ (ε 43,000). The irreversible shift of this maximum to a shorter wave length (248 mμ; ε 15,000) by acid and the isolation of piperidine hydrochloride from such solutions is in keeping with this structure. Alternate formulations requiring addition of the piperidine nucleus at C-5 or C-4a seem less feasible. The ultraviolet spectrum would not be in accord with the cross-conjugated system resulting from placing the piperidine nucleus at C-5 and the NMR spectrum, which indicates three vinyl hydrogens, would not be satisfied by having the piperidine nucleus at C-4a. Although structure III can not be considered as established without further evidence, it offers a plausible explanation for the physical and chemical properties of this by-product.

EXPERIMENTAL[6]

Reaction of I *with piperidine.* To 10.0 g. of 2,3-dihydroisoxazolo(2,3-a)pyridinium bromide (I) in 10 ml. of water there was added 5.0 g. of piperidine and the solution was allowed to stand at room temperature for 15 min. It was then gently warmed on the steam bath for 15 min., cooled, and ice water was added until the solution became turbid. When this mixture was allowed to stand, 2.75 g. (27%) of yellow crystals separated and was collected. After recrystallization from ethanol, these crystals (III) melted at 124–126° and their ultraviolet and infrared spectra agreed fully with that of the product previously reported from the reaction of I with piperidine.[3] When the aqueous filtrate remaining after separation of these crystals was concentrated to dryness, there was isolated 10.0 g. of a solid residue. This, on recrystallization from a mixture of acetonitrile and ethyl acetate, gave 8.50 g. (59.0%) of white needles, m.p. 167–168.5°. The ultraviolet absorption spectrum of these crystals (IV) in ethanol showed a single maximum at 263 mμ (ε 11,500).

Anal. Calcd. for $C_{12}H_{19}N_2OBr$: C, 50.22; H, 6.67; N, 9.76. Found: C, 50.84; H, 6.73; N, 9.92.

The *dipicrate* of IV was prepared in ethanol and, after recrystallization from the same solvent, was obtained as yellow needles, m.p. 129–131°.

(5) F. E. Cislak, U.S. Patent **2,749,349** (1956); *Chem. Abstr.*, **51**, 4442 g (1957).

(6) All melting points are corrected. Analyses by Micro-Tech Laboratories, Skokie, Ill., T. Montzka and V. Landeryou, U. of Rochester.

Anal. Calcd. for $C_{24}H_{24}N_8O_{15}$: C, 43.41; H, 3.64; N, 16.85. Found: C, 43.61; H, 3.64; N, 16.40.

Catalytic hydrogenation of IV. A solution of 1.43 g. of IV in 20 ml. of absolute ethanol was added to a suspension of 110 mg. of prereduced Adam's catalyst in 20 ml. of absolute ethanol and the resulting mixture was subjected to hydrogenation at room temperature and atmospheric pressure. When hydrogen absorption was complete (3 days), the reaction was stopped. After removal of the catalyst and solvent, the solid white residue was recrystallized from a mixture of absolute ethanol and ether to give 1.41 g. of white needles, m.p. 288–290°. The identity of these crystals was established by showing that their infrared spectrum agreed in all respects with that of crystals of a dihydrobromide prepared from an authentic sample of *N*-[2-(2′-piperidyl)-ethyl]piperidine.[5]

Anal. Calcd. for $C_{12}H_{26}N_2Br_2$: C, 40.26; H, 7.32; N, 7.83; Br, 44.65. Found: C, 40.62; H, 7.44; N, 7.55; Br, 44.61.

Deoxygenation of IV. To a cold solution of 576 mg. of IV in 15 ml. of chloroform there was added dropwise 1 ml. of phosphorus trichloride. The reaction mixture was heated under reflux on a steam bath for 1 hr. It was then cooled, ice water was added, and the mixture was made basic with an aqueous solution of sodium hydroxide. After separation of the organic layer, it was washed with water, dried, and concentrated. Distillation of the residue gave a pale yellow oil, b.p. 85–100° at 0.1 mm., whose infrared spectrum was in good agreement with that of an authentic sample of 2-[β-(*N*-piperidino)ethyl]pyridine.[7] Further, the dipicrate of this oil was prepared and found to melt at 160–162°, undepressed on admixture of an authentic sample of the dipicrate of 2-[β-(*N*-piperidino)ethyl)pyridine.[7] The infrared spectra in Nujol of the two picrates were in good agreement.

Reaction of I *with dimethylamine.* A solution of 2.0 g. of 2,3-dihydroisoxazolo(2,3-a)pyridinium bromide (I) in 10 ml. of a 25% aqueous solution of dimethylamine was allowed to stand for 15 min. and then was heated under gentle reflux for 30 min. Concentration of the solution under reduced pressure gave a white solid which, after recrystallization from dry acetonitrile, yielded 1.0 g. (72%) of white crystals of the hydrobromide of V, m.p. 130.5–132.5°.

The *dipicrate* of V was prepared in ethanol and, after recrystallization from this solvent, was obtained as yellow needles, m.p. 148–150°.

Anal. Calcd. for $C_{21}H_{20}N_8O_{15}$: C, 40.42; H, 3.23. Found: C, 40.70; H, 3.31.

Reaction of I *with morpholine.* A solution of 5.0 g. of 2,3-dihydroisoxazolo(2,3-a)pyridinium bromide (I) and 2.2 g. of morpholine was allowed to stand at room temperature for 5 min. Then, 25 ml. of water was added and, after an additional 30 min. at room temperature, this solution was concentrated under reduced pressure. The resulting light tan solid was recrystallized from absolute methanol to give 5.70 g. (79%) of VI as white crystals, m.p. 210–212° dec. Its ultraviolet absorption spectrum showed a single maximum at 263 mμ (ε 11,940).

Anal. Calcd. for $C_{11}H_{17}N_2O_2Br$: C, 45.71; H, 5.93; N, 9.69. Found: C, 45.31; H, 6.19; N, 9.69.

The *dipicrate* of VI was prepared in ethanol and, after recrystallization from the same solvent, was obtained as yellow crystals, m.p. 124–126°.

Anal. Calcd. for $C_{23}H_{22}N_8O_{16}$: C, 41.48; H, 3.33. Found: C, 41.73; H, 3.60.

2-Vinylpyridine N-oxide. A finely ground mixture of 7.0 g. of 2-(β-hydroxyethyl)pyridine *N*-oxide, 1.0 g. of freshly-fused potassium bisulfate, and 0.2 g. of methylene blue was heated in a short-path still at 150–200° at 0.1 mm. until nothing further distilled. There was collected 5.4 g. (90%) of a light yellow oil, n_D^{25} 1.6050. Its ultraviolet absorption spectrum showed maxima at 340 (ε 17,646) and 273 mμ (ε 9,330).

The *picrate* of 2-vinylpyridine *N*-oxide was prepared in absolute ethanol and obtained as yellow crystals, m.p. 111–113.[8] A mixture of these crystals and the picrate of I showed a large depression of melting point.

Addition of piperidine to 2-vinylpyridine N-oxide. To a solution of 2.0 g. of piperidine in 5.0 ml. of water 1.2 g. of 2-vinylpyridine *N*-oxide was added and the resulting mixture was allowed to stand at room temperature for 2 hr. Concentration under reduced pressure followed by distillation of the residue gave 1.76 g. (86%) of the free base corresponding to IV as a colorless oil; b.p. 150–160 at 0.05 mm., n_D^{25} 1.5612.

Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80. Found: C, 69.40; H, 8.78.

The *dipicrate* of this oil was prepared and melted at 130–131°, undepressed on admixture of the dipicrate of IV. The infrared spectra of the two samples were superimposable.

Addition of dimethylamine to 2-vinylpyridine N-oxide. A solution of 1.2 g. of 2-vinylpyridine *N*-oxide in 10.0 ml. of a 25% aqueous solution of dimethylamine was allowed to stand at room temperature for 2 hr. It was then concentrated and distilled to give 1.3 g. (78%) of the free base corresponding to V as a yellow oil; b.p. 150–160° at 0.1 mm., n_D^{25} 1.5471. The *picrate* of this oil was prepared in ethanol and melted at 148–150°, undepressed by admixture of the picrate of V. The infrared spectra of the two samples taken in Nujol were superimposable.

Addition of diethyl malonate to 2-vinylpyridine N-oxide. To a solution 0.3 g. of sodium in 32 ml. of diethyl malonate there was added 6.0 g. of 2-vinypyridine *N*-oxide and the resulting mixture was then boiled under reflux for 6 hr. After concentration under reduced pressure, the residue was taken up in hydrochloric acid and extracted with ether. When the aqueous solution had been made basic, it was extracted with three 150-ml. portions of chloroform. The combined chloroform extracts were washed with water, dried and, concentrated. Distillation of the residue gave 5.8 g. (42%) of VIII as a colorless oil; b.p. 140–170° at 0.1 mm., n_D^{25} 1.5040.

Anal. Calcd. for $C_{14}H_{19}NO_5$. C, 59.77; H, 6.81. Found: C, 59.84; H, 6.90.

Deoxygenation of VIII using phosphorus trichloride following the procedure given previously for the deoxygenation of IV gave diethyl 2-(2′-pyridyl)ethyl malonate as a colorless oil in 83% yield. The infrared spectrum and refractive index of this sample were in good agreement with those of an authentic sample.[9]

Addition of ethyl acetoacetate to 2-vinylpyridine N-oxide. This was carried out in a similar fashion to that described above for the addition of diethyl malonate and IX was obtained in 71% yield as a colorless oil; b.p. 180–200° at 1 mm. n_D^{25} 1.5120.

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82. Found: C, 61.72; H, 6.90.

The deoxygenation of IX with phosphorus trichloride was carried out in a similar fashion to that described for the deoxygenation of IV and gave ethyl 2-(2′-pyridyl)ethyl-acetoacetate in 80% yield as a colorless oil. The infrared spectrum and refractive index of this oil were in good agreement with those of an authentic specimen.[9]

Addition of ethanol to 2-vinylpyridine N-oxide. To a solution of 5.0 g. of sodium in 100 ml. of absolute ethanol there was added 5.4 g. of 2-vinylpyridine *N*-oxide and the resulting mixture was boiled under reflux for 8 hr. After concentration, the mixture was taken up in hydrochloric acid and extracted with ether. When the aqueous layer was made basic, it was extracted with chloroform and the chloroform extracts were

(7) W. E. Doering and R. A. N. Weil, *J. Am. Chem. Soc.*, 69, 2461 (1947).

(8) Ref. 5 gives 112–113° as the m.p. for the picrate of 2-vinylpyridine *N*-oxide.

(9) V. Boekelheide and S. Rothchild, *J. Am. Chem. Soc.*, 71, 879 (1949).

washed with water and dried. Concentration of the chloroform solution followed by distillation of the residue gave 3.1 g. of X as a colorless oil; b.p. 160–170° at 0.5 mm., n_D^{25} 1.5490.

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.84. Found: C, 64.55; H, 7.86.

Deoxygenation of X with phosphorus trichloride using the procedure described previously for the deoxygenation of IV gave 2-(β-ethoxyethyl)pyridine in 100% yield as a colorless oil. The infrared spectrum and refractive index of this oil were in good agreement with those of an authentic specimen.[7]

Addition of pyrrole to 2-vinylpyridine N-oxide. A mixture of 0.5 g. of sodium, 13.0 g. of pyrrole, and 5.0 g. of 2-vinyl pyridine *N*-oxide was boiled under reflux for 2 hr. It was then poured into ice water and extracted with three 75-ml. portions of ether. After the ether solution had been dried, it was concentrated and the residue distilled to give an oil (b.p. 160–180° at 0.05 mm.) which crystallized in the receiver as a hygroscopic white solid, m.p. 103–111°. There was obtained 5.6 g. (73%) of XI.

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43. Found: C, 70.08; H, 6.60.

Deoxygenation of XI with phosphorus trichloride was carried out as previously described for the deoxygenation of IV and gave 2[β-(*N*-pyrrolo)ethylpyridine in 52% yield as a colorless oil. The infrared spectrum and refractive index of this oil were in good agreement with those of an authentic specimen.[10]

ROCHESTER, N. Y.

(10) H. E. Reich and R. Levine, *J. Am. Chem. Soc.*, 77, 4913 (1955).

[CONTRIBUTION FROM THE ORGANIC RESEARCH DIVISION, ABBOTT LABORATORIES]

Reductions with Ruthenium. II. Its Use in the Hydrogenation of Pyridines[1]

MORRIS FREIFELDER AND GEORGE R. STONE

Received March 14, 1961

The preparation of a number of piperidines by catalytic hydrogenation of the corresponding pyridines with ruthenium dioxide at 90–100° and 70–100 atmospheres is reported. Its activity in the presence of various substituents is discussed.

The activity of ruthenium catalysts in the hydrogenation of phenylalkylamines[2] led us to conduct a study of it in the reduction of other nitrogen-containing compounds. This report covers the use of ruthenium dioxide in the hydrogenation of pyridine and substituted pyridines.

Low pressure reduction of the pyridine ring requires the presence of acid to prevent poisoning when platinum catalyst is used.[3] This is disadvantageous when it is necessary to isolate the corresponding piperidine base. In addition, there are reports that in some instances hydrogen uptake is slow and further addition of platinum catalyst is necessary.[4] Rhodium has been reported to be effective[5] but in some unpublished work in this laboratory it has been noted that ring reduction appears to be strongly hindered by certain substituents. Raney nickel is the catalyst most widely used for the higher pressure hydrogenation of pyridine compounds. The conditions generally described consist of reaction at 150–300 atmospheres pressure and temperatures above 150° for varying lengths of time.[6] Particularly pyridine itself required more drastic conditions than many of its derivatives.[6]

By contrast, in the presence of ruthenium dioxide pyridine is readily converted to piperidine in quantitative yield under much milder conditions. By raising the reaction temperature to 200° as little as 0.1% of this catalyst is sufficient to carry the reduction to completion in little more than one hour.

The use of alcohols as solvents is often precluded in Raney nickel reductions because of the possibility of *N*-alkylation resulting from the rather rigorous reaction conditions.[7] The hydrogenation of 2,3-dimethylpyridine in ethanol yielding 1-ethyl-2,3-dimethylpiperidine under such conditions is a striking example. The advantage of the use of alcohols is shown in the reduction of 2-β-hydroxyethylpyridine to the corresponding piperidine (XII). In methanol the reaction time was cut from three to four hours without solvent to a matter of a few minutes in its presence. Moreover, in this instance, as well as in other hydrogenations where an alcohol was used, there was no evidence of *N*-alkylation.

Single substituents on the pyridine ring, particularly nonbasic ones, seem to have little effect on the rate of hydrogenation. In the preparation of 2,4,6-trimethylpiperidine (XV), however, steric effects no doubt inhibited ring reduction. The use of alcohol as solvent produced only a moderate increase in the speed of hydrogen uptake.

(1) Presented at the 139th National Meeting of the American Chemical Society, St. Louis, Mo., March 1961.

(2) M. Freifelder and G. R. Stone, *J. Am. Chem. Soc.*, 80, 5270 (1958).

(3) T. S. Hamilton and R. Adams, *J. Am. Chem. Soc.*, 50, 2260 (1928).

(4) J. Overhof and J. P. Wibaut, *Rev. trav. chim.*, 50, 957 (1931), and J. Finkelstein and R. C. Elderfield, *J. Org. Chem.*, 4, 365 (1939).

(5) G. Gilman and G. Cohn, *Advances in Catalysis*, Academic Press, Inc., New York, 1957, Vol. 9, p. 707–715.

(6) H. Adkins, L. F. Kuick, M. Farlow, and B. Wojcik, *J. Am. Chem. Soc.*, 56, 2425 (1934).

(7) J. I. Jones, *J. Chem. Soc.*, 1932 (1950), points out that even some *N*-alkylation occurs when Raney nickel, that has been stored over alcohol, is used.