It was hydrolyzed to carbanilide, m.p. and mixed 250–251°, with dilute aqueous hydrochloric acid.

A portion of the crude tosylation product was evaporatively distilled at a bath temperature of 120–130° and 0.22 mm. pressure. The distillate contained diphenylcarbodiimide and probably the thionourethan XIV, as shown by infrared absorption at 4.70 μ (N=C=N) and 7.16 μ (probably C=S), but no pure materials could be isolated.

From another reaction of thiourethan VII with tosyl chloride in pyridine the crude product was dissolved in ether and allowed to react with an ethereal picric acid solution. A small amount of picrate (about 5% yield) was isolated, m.p. 110–150°. Its infrared spectrum showed that it was largely anil VIII picrate.

Hydrolysis of the Thiourethan VII–Tosyl Chloride Reaction Product.—The crude product was obtained as above from 10.0 g. (42.3 mmoles) of VII, 12.60 g. (66.1 mmoles) of *p*-toluenesulfonyl chloride and 20 ml. of pyridine. It weighed 12.87 g. and showed no OH absorption at 2.98 μ but contained diphenylcarbodiimide as shown by absorption at 4.68 μ.

A stirred mixture of the crude residue (12.73 g.), 24.0 g. (0.60 mole) of sodium hydroxide and 50 ml. of water was refluxed under nitrogen for 24 hours. The dark reaction mixture gave a positive nitroprusside test for mercaptans. It was diluted with 200 ml. of water and the solution extracted with six 25-ml. portions of methylene chloride. The combined methylene chloride solutions were extracted with five 30-ml. portions of 2 *N* aqueous hydrochloric acid and the acid extracts were chilled and made strongly basic with 6 *N* sodium hydroxide. The resulting solution was extracted with four 25-ml. portions of methylene chloride and the methylene chloride extracts were dried over magnesium sulfate. After filtration, the extracts were evaporated *in vacuo*, leaving 4.48 g. of brown liquid. This was steam distilled and 100 ml. of distillate was collected. The distillate was extracted to obtain 2.33 g. (59%) of crude aniline which gave 1.71 g. of aniline after distillation. The nonsteam-distillable liquid residue, 2.17 g. (31%), was distilled and gave 1.49 g. of *cis*-2-anilinocyclopentanol (XVI), b.p. 88–92° (1–5 μ), $n^{20}D$ 1.5773; λ_{max}^{film} (μ) 2.95 (OH, NH), 6.65 (NH), 7.63 (C–N), 13.35, 14.45 (monosubstituted phenyl).

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.5; H, 8.53. Found: C, 74.1; H, 8.44.

The picrate of XVI was prepared by mixing a solution of 0.20 g. of XVI in 10 ml. of ether with a solution of 0.27 g. of picric acid in 30 ml. of ether. The crude product, 0.31 g., m.p. 147–150°, was recrystallized twice from benzene, m.p. 144–147°; λ_{max}^{KBr} (μ) 3.00 (OH, NH), 6.40, 7.51 (NO_2), 6.69 (NH), 12.66 (trisubstituted phenyl), 13.42, 14.42 (monosubstituted phenyl).

Anal. Calcd. for $C_{17}H_{18}N_4O_8$: C, 50.2; H, 4.46. Found: C, 50.3, 50.5; H, 4.78, 4.66.

When the aqueous portion of the crude hydrolysate (after the methylene chloride extraction) was acidified with 6 *N* hydrochloric acid, hydrogen sulfide was evolved. The acidified solution was extracted with methylene chloride and the extracts were combined with the methylene chloride solution which had been extracted with 2 *N* hydrochloric acid in the separation of XVI and aniline (see above). These combined methylene chloride extracts were evaporated *in vacuo* to leave 3.66 g. of a dark, viscous residue whose infrared spectrum had λ_{max}^{film} (μ) 3.00 (NH, OH), 3.90 (SH), 6.66 (NH), 7.65 (C–N), 13.35, 14.45 (monosubstituted phenyl). No pure materials could be isolated from this mixture.

Hexahydro-3-phenyl-2H-cyclopenta[d]oxazol-2-one (XV).—A solution of 2.0 g. (11.3 mmoles) of crude *cis*-2-anilinocyclopentanol (XVI), 10 ml. of diethyl carbonate and 5 ml. of benzene was distilled until about 2 ml. of benzene was collected. Sodium methoxide (0.05 g.) was added and the reaction mixture was heated at a bath temperature of 130° for 11.5 hours. About 1.0 g. of ethanol was collected as a distillate during this period. Excess diethyl carbonate was removed by evaporation *in vacuo* and the residue was dissolved in 20 ml. of methylene chloride. The solution was washed with three 10-ml. portions of 1 *N* hydrochloric acid and three 15-ml. portions of water and was dried over magnesium sulfate. After filtration, the solution was evaporated to dryness *in vacuo*, leaving 1.88 g. (82%) of solid residue. The material was purified by dissolving 1.0 g. in 60 ml. of hot Skellysolve B and decanting the solution from a small amount of insoluble tar. The crystals which formed on cooling were recrystallized again from Skellysolve B with the aid of Norit, yielding 0.54 g. (44%), m.p. 57–58°. A final recrystallization from Skellysolve B raised the melting point to 58–59°; λ_{max}^{KBr} (μ) 5.77 (urethan C=O), 7.16 (C–N), 13.10, 14.42 (monosubstituted phenyl).

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.9; H, 6.45. Found: C, 70.9; H, 6.50.

Acknowledgments.—The authors are indebted to Dr. Peter Lim for infrared interpretations and to Mr. O. P. Crews, Jr., and his group for the large-scale preparation of intermediates.

MENLO PARK, CALIF.

[CONTRIBUTION FROM THE PHYSIOLOGICAL CHEMISTRY BRANCH, DIRECTORATE OF MEDICAL RESEARCH, U. S. ARMY CHEMICAL WARFARE LABORATORIES]

Stability of Pyridine-2-aldoxime Methiodide. I. Mechanism of Breakdown in Aqueous Alkaline Solution

BY ROBERT I. ELLIN

RECEIVED JULY 22, 1958

The mechanism of the deterioration of pyridine-2-aldoxime methiodide (2-PAM) in aqueous solutions of *p*H values ranging from 7 to 13 have been studied. At the indicated *p*H values, 2-PAM breaks down to N-methyl-α-pyridone. The following mechanism is suggested: (1) 2-PAM is dehydrated to 2-cyanopyridine methiodide, (2) 2-cyanopyridine methiodide is converted to 2-hydroxypyridine methiodide, (3) the latter rearranges to N-methyl-α-pyridone.

Pyridine-2-aldoxime methiodide (I), monoisonitrosoacetone and diacetylmonoxime have been reported to be effective in overcoming the toxic effects occurring in animals poisoned with inhibitors of the enzyme cholinesterase.[1–7] Of the three oximes, pyridine-2-aldoxime methiodide is the fastest known reactivator, *in vitro*, of cholinesterase inhibited by isopropyl methylphosphofluoridate.[2] An effective therapy for poisoning by anticholinesterase agents may be obtained by administering the oxime I in conjunction with the alkaloid atropine.[1,4,5,7] A knowledge of the behavior of dilute solutions of I is therefore desirable. This

(1) B. M. Askew, *Brit. J. Pharmacol.*, **11**, 417 (1956).

(2) D. R. Davies and A. L. Green, *Trans. Faraday Soc.*, **20**, 269 (1955).

(3) B. M. Askew, *Brit. J. Pharmacol.*, **12**, 340 (1957).

(4) H. W. Kewitz, I. B. Wilson and D. Nachmansohn, *Arch. Biochem Biophys.*, **64**, 456 (1956).

(5) J. H. Wills, A. M. Kunkel, R. V. Brown and G. E. Groblewski, *Science*, **125**, 743 (1957).

(6) F. Hobbinger, *Biochem. J.*, **66**, 7 p. (1957).

(7) I. B. Wilson and F. Sondheimer, *Arch Biochem. Biophys.*, **69**, 468 (1957).

paper reports on the stability and breakdown mechanism of I in aqueous alkaline solutions.

The assumption was made that I reacts in basic solution to form the corresponding nitrile, which would be converted to the corresponding carboxylic acid and ammonia.[8] To confirm this mechanism, 2-cyanopyridine methiodide (II) and pyridine-2-carboxylic acid methiodide (III) were synthesized. Ultraviolet spectral curves of I, II and III were determined in aqueous acid and alkaline solution. Molar extinction coefficients at wave lengths of maximum and minimum absorbance, given in Table I, indicate that compound I can be determined quantitatively in the presence of II and III at 292 mμ in acid media or 333 mμ in basic solution.[9]

TABLE I

MOLAR EXTINCTION COEFFICIENTS OF PYRIDINE-2-ALDOXIME METHIODIDE AND ITS HYDROLYTIC PRODUCTS

Compound	Molar extinction coefficients, acid solution (0.1 *N*) HCl) Wave length, mμ	ϵ_{max} × 10³	Molar extinction coefficients, basic solution (0.1 *N*) NaOH) Wave length, mμ	ϵ_{max} × 10³
Pyridine-2-aldoxime methiodide	224(max.)	18.75	225(max.)	17.11
	262(min.)	3.75	253.5(min.)	2.48
	292.5(max.)	12.20	333(max.)	18.27
2-Cyanopyridine methiodide	225(max.)	15.77	226(max.)	19.27
	249.5(min.)	2.02	254(min.)	1.57
	272(max.)	7.01	292(max.)	5.36
	292.5	Negl.	333	Negl.
Pyridine-2-carboxylic acid methiodide	224(max.)	10.60	247(min.)	3.10
	245(min.)	3.73		
	265(max.)	7.02	269(max.)	5.99
	292.5	Negl.	292	Negl.
			333	Negl.
N-Methyl-α-pyridone	226(max.)	5.51	227(max.)	6.54
	245(min.)	0.72	245(min.)	0.27
	292(max.)	5.03	293(max.)	5.75
			333	Negl.

Compound I reacted in a constant temperature bath at 87° at *p*H values ranging from 7 to 13. Ultraviolet spectra were taken to determine the products which formed during the course of reaction. Upon completion of reaction, all samples showed absorbance maxima at 226 and 292 mμ and a minimum absorbance at 245 mμ in both acid and alkaline solution. These results indicated the formation of a compound which was neither the nitrile II nor acid III.

In separate experiments the nitrile and acid were placed in alkaline solution, at *p*H values 7 to 13, at 87°. The unknown compound did not originate from III as no change was observed in the ultraviolet spectrum of the acid. An instantaneous reaction took place in the experiments with nitrile. The ultraviolet spectra of samples withdrawn from the nitrile experiments showed absorption maxima at 226 and 292 mμ and a minimum at 245 mμ in both acid and alkaline solution. As these absorbancies were identical with those obtained after the oxime I was allowed to react in basic solution, the new product must have originated from the nitrile.

When I and II were treated separately at *p*H values ranging from 7 to 13, only one product was isolated, N-methyl-α-pyridone (VI). Pyridine-2-carboxylic acid methiodide (III) was not detected in either reaction. The ultraviolet spectrum of VI, isolated from the alkaline reaction of I and II, was identical with the spectrum of the synthesized ketone. The identity of VI was further confirmed by synthesis of its picrate derivative.[10]

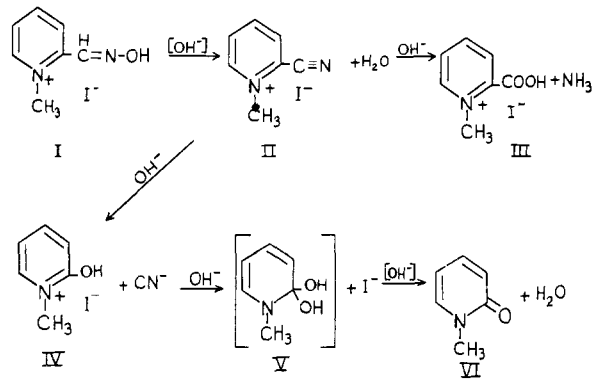

Fig. 1.

OVERALL REACTION

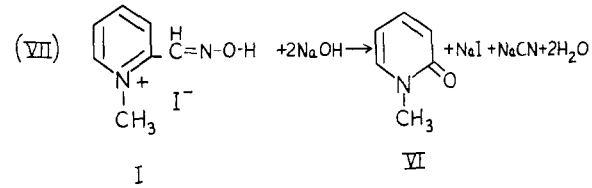

Fig. 2.

The reactivity of 2-cyanopyridine methiodide (II) can be compared to the reactivity of an acyl cyanide, such as benzoyl cyanide. The nitrogen atom of a pyridine ring, having a greater attraction for electrons than a carbon atom, decreases the availability of the latter's unsaturation electrons. Combination with a proton or other electrophilic reagent gives the nitrogen a positive charge which holds the electrons more strongly. The reason for the reactivity of an acyl cyanide and 2-cyanopyridine methiodide (II) could be the same; namely, the carbon to which the nitrile is attached has a lowered electron density, since the adjacent oxygen or nitrogen atom has an even greater electronegativity. The resulting positive carbon atom would be more susceptible to attack by nucleophilic reagents such as ammonia, water or sodium hydroxide. As benzoyl cyanide is known to yield sodium benzoate in alkaline solution,[11] 2-hydroxypyridine methiodide (IV) was postulated as the compound which would form on reaction of II with sodium hydroxide. In basic solution compound IV may exist in its covalent pseudo-form V. A pseudo-basic system of this type would readily lose water. When a quaternary ammonium ion contains an acidic center, in this instance an α-phenolic group, the quaternary ammonium hydroxide will undergo a dehydration in the manner of an internal acid–base neutralization, deprotonating the acidic center and forming what is known as an anhydro-

(8) M. Jordan and C. R. Hauser, THIS JOURNAL, **58**, 1305 (1936).

(9) R. I. Ellin and A. A. Kondritzer, *Anal. Chem.*, in press.

(10) K. Neundlinger and M. J. Chur, *J. prakt. Chem.*, **89**, 466 (1914).

(11) H. v. Kolbe, *Ann.*, **90**, 62 (1854).

base.[12] Compound IV may rearrange, lose water and form N-methyl-α-pyridone (VI) by a similar mechanism. The over-all reaction at *p*H values 7 to 13 is given by equation VII.

The presented mechanism may account for three observations made by this Laboratory: (a) the presence of a green color in commercial preparations of the oxime I; compound VI turns green on exposure to light; (b) the formation of two spots when commercial samples of I were chromatographed on paper; (c) the presence of traces of cyanide ion in I, even after three recrystallizations from ethyl alcohol.

Experimental

2-Cyanopyridine Methiodide (II).—A solution of 5.2 g. of 2-cyanopyridine and 10.5 g. of methyl iodide dissolved in 80 ml. of ethyl alcohol was heated under reflux for 4 hours. A double condenser was used to prevent excessive evaporation of methyl iodide. On cooling, the solid methiodide was filtered and washed with dry ether. Two recrystallizations from absolute ethyl alcohol gave 4.5 g. of yellow crystals, m.p. 183–184°.

Anal. Calcd. for $C_7H_7N_2I$: C, 34.14; H, 2.85. Found: C, 33.9; H, 2.8.

(12) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p. 579.

Pyridine-2-carboxylic Acid Methiodide (III).—A solution of 6.0 g. of pyridine-2-carboxylic acid and 12 g. of methyl iodide dissolved in 75 ml. of ethyl alcohol was heated under reflux for four hours as above. Concentration of the solvent to 30 ml. gave 5.5 g. of yellow crystals. The solid product was recrystallized from propanol, m.p. 164.5–166°.

Anal. Calcd. for $C_7H_8O_2NI$: C, 31.70; H, 3.02. Found: C, 31.6; H, 3.0.

Isolation of N-Methyl-α-pyridone from 2-Cyanopyridine Methiodide.—Add 100 ml. of 0.1*N* NaOH to 0.5 g. of 2-cyanopyridine methiodide dissolved in a minimum of water. The mixture was placed in a water-bath at 87° for 1.5 hours. After cooling, the solution was extracted with two 25-ml. portions of chloroform. On evaporation of the chloroform a colorless oil remained. The oil was identified as N-methyl-α-pyridone by its picrate derivative.

Isolation of N-Methyl-α-pyridone from Pyridine-2-aldoxime Methiodide (I).—Dissolve 0.5 g. of pyridine-2-aldoxime methiodide in a minimum of water, add 100 ml. of 0.1 *N* NaOH and proceed as above. On evaporation of the chloroform, an oil was isolated and identified as N-methyl-α-pyridone by its picrate derivative.

Picrate of N-Methyl-α-pyridone.—Ten ml. of a saturated solution of picric acid was added to 0.5 ml. of synthetic N-methyl-α-pyridone dissolved in 10 ml. of 95% ethanol. The solution was heated to boiling for a few minutes, cooled and the yellow crystals filtered. The picrate was recrystallized from ethyl alcohol, m.p. 145°. The melting point was not depressed on admixture with the picrates prepared above.

ARMY CHEMICAL CENTER, MD.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF NOTRE DAME]

The Mechanism of the Reaction of 2-Picoline N-Oxide with Acetic Anhydride[1]

BY VINCENT J. TRAYNELIS AND ROCCO F. MARTELLO

RECEIVED AUGUST 11, 1958

Both free radical and ionic mechanisms have been proposed for the formation of 2-pyridylmethyl acetate from 2-picoline N-oxide and acetic anhydride. In this work evidence is reported for the presence of free radicals in the reaction mixture; however, these radicals do not appear to be involved in the origin of 2-pyridylmethyl acetate. Thus the alternative ionic path seems most likely with data presented to support an intramolecular rearrangement of the anhydro base II.

In recent years several groups of investigators have described reactions of heterocyclic N-oxides with acid anhydrides. When pyridine N-oxide[2] or 3-picoline N-oxide[3] was employed, the reaction with acetic anhydride resulted in the introduction of an acetoxy group into the 2-position of the pyridine ring; however, with 2- and 4-alkylpyridine N-oxides[3–9] the reaction followed an alternate course which led to 2- and 4-(α-acetoxyalkyl)-pyridines. A specific example of the latter process[3] is the formation of 2-pyridylmethyl acetate from 2-picoline N-oxide and acetic anhydride. Similar reactions have been reported in the quinoline[10–13] and isoquinoline[14] series. The subject of this report deals with reactions of 2-picoline N-oxide and acid anhydrides which may be used to elucidate the mechanism of this process.

Both ionic and free radical mechanisms have been proposed for this reaction; each involves as the initial step the formation of 1-acetoxy-2-methylpyridinium (I) acetate. The ionic path was suggested by Pachter[12] to explain a similar rearrangement with quinaldine N-oxide and extended to the pyridine system by others.[3,5,6] This proceeds through the anhydro base II which results from I by abstraction of an acidic hydrogen from the 2-methyl group by acetate anion. At least two paths are available for the conversion of II to 2-pyridylmethyl acetate (III): (a) by an intramolecular cyclic rearrangement and (b) by a nucleophilic attack of acetate anion on the methylene carbon with elimination of acetate anion.

(1) Presented at the 133rd Meeting of the American Chemical Society at San Francisco, Calif., in April, 1958.

(2) M. Kataka, *J. Pharm. Soc. Japan*, **67**, 51 (1947); *C. A.*, **45**, 9537e (1951).

(3) V. Boekelheide and W. J. Linn, THIS JOURNAL, **76**, 1286 (1954).

(4) G. Kobayashi and S. Furukawa, *Pharm. Bull. Japan*, **1**, 347 (1953); *C. A.*, **49**, 10948e (1955).

(5) O. M. Bullitt, Jr., and J. T. Maynard, THIS JOURNAL, **76**, 1370 (1954).

(6) J. A. Berson and T. Cohen, *ibid.*, **77**, 1281 (1955).

(7) G. Kobayashi, S. Furukawa and Y. Kawada, *J. Pharm. Soc. Japan*, **74**, 790 (1954); *C. A.*, **49**, 1104c (1955).

(8) S. Furukawa, *Pharm. Bull. Japan.*, **3**, 413 (1955); *C. A.*, **50**, 13926a (1956).

(9) F. Cislak, U. S. Patent 2,748,141, May 29, 1956; *C. A.*, **51**, 2878c (1957).

(10) K. Oda, *J. Pharm. Soc. Japan*, **64**, No. 8A, 6 (1944); *C. A.*, **45**, 8523i (1951).

(11) T. Itai, *J. Pharm. Soc. Japan.*, **65**, 70 (1945); *C. A.*, **45**, 8525h (1951).

(12) I. J. Pachter, THIS JOURNAL, **75**, 3026 (1953).

(13) F. Montanari and A. Risaliti, *Gazz. chim. ital.*, **83**, 278 (1953).

(14) M. M. Robison and B. L. Robison, *J. Org. Chem.*, **21**, 1337 (1957); THIS JOURNAL, **80**, 3143 (1958).