Registry No.—I, 23265-28-3; II, 23265-29-4; VI, 23265-30-7; VII, 23265-31-8; triphenylphosphine, 603-35-0; triethyl phosphite, 122-52-1.

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Base-Catalyzed Deuterium Exchange in Pyridine N-Oxides[1]

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In connection with another study, we observed that 4-benzylpyridine N-oxide (I), recovered after a reflux period of 24 hr in equimolar triethylamine and excess deuterium oxide, exchanged hydrogen for deuterium in excess of the calculated amount for the two benzylic hydrogens.[2] The nuclear magnetic resonance spectrum of the deuterated compound compared well with that of the reference compound, differing only in that a small peak appeared at τ 6.06 replacing the sharp singlet for the benzylic hydrogens. Integration of the peak areas, however, indicated that the doublet at τ 1.89 for the two α hydrogens of the pyridine ring and the multiplet with a sharp peak at τ 2.76 for the two β hydrogens and five phenyl hydrogens were not in a 2:7 ratio. By assuming nonexchange of the β and the phenyl hydrogens, we calculated 95% exchange of the benzylic hydrogens and 17% exchange of the α hydrogens from the integration of the respective peak areas (this is consistent with the elemental analysis of an exchange of 21.00 atom % excess deuterium).[3]

Considerable attention of late has been given to H–D exchange in heterocyclic N-oxide systems. Substituted pyridine N-oxides and similar compounds exchange rapidly in the α position of the ring under basic conditions; for a review of the literature see ref 5. Under acidic conditions similar systems exhibited exchange at the β position when the species reacting was in the conjugate acid form.[6]

In this note we wish to report H–D exchange in the aromatic ring and the side chain of alkylpyridine N-oxides[7] and, qualitatively, the dependence of the exchange on base strength; this is readily seen from the data in Table I for the benzylpyridine N-oxides. Our investigation of the isomeric picoline N-oxides revealed ring-proton exchange as well as side-chain exchange. Prior studies of Zatsepina[8] reported exchange of the protons of the side chains of 2- and 4-picoline N-oxides (III and IV) but not ring-proton exchange. For 2-picoline N-oxide (III), α-proton exchange accompanied methyl-proton exchange in the presence of sodium carbonate and sodium deuteroxide. The relative amount of ring- and side-chain exchange varied with reaction time and base. Typical results follow: for sodium carbonate, 0.5-hr reaction time, α-proton exchange, 12%, 2-methyl proton, 66%; 5-hr reaction time, α-proton exchange, 45%, 2-methyl proton, 97%; for sodium deuteroxide, 0.5 hr, 86% for both ring and methyl protons. The 4 isomer, 4-picoline N-oxide (IV), presented an interesting contrast insofar as the amount of ring exchange exceeded side-chain proton exchange in the presence of triethylamine and sodium carbonate. Typical results follow: for triethylamine, 72 hr, α-proton exchange, 40%, 4-methyl proton exchange, 20%; for sodium carbonate, 0.5 hr, 80 and 50%, respectively, for α-proton and 4-methyl proton exchange; for sodium deuteroxide the amount of side chain and ring exchange was equivalent. As reported previously,[8] 3-picoline N-oxide (V) exhibited both ring- and methyl-proton exchange. Since ring exchange for 2- and 4-picoline N-oxides (III and IV) was not taken into account in the prior publications,[8] the velocity constants given for III and IV are in error in those references; exchange, however, was noted for V and appropriate corrections were made in the velocity constant.

The conditions used for the exchange reactions were mild and yields were good (87%, average). Since deoxygenation of the N-oxides under specific conditions is reported to be facile,[9] deuterated pyridine derivatives may be conveniently prepared by this procedure.

TABLE I

DATA FOR BASE-CATALYZED EXCHANGE OF BENZYLPYRIDINE N-OXIDES IN HEAVY WATER[a]

N-Oxide	Expt	Base	Time, hr	Exchange,[b] % α protons	Exchange,[b] % Side-chain protons
4-Benzylpyridine N-oxide (I)	1	Et_3N[c]	20	17	95
	2	Na_2CO_3[d]	0.5	18	94
	3[e]	Na_2CO_3	5	100	100
2-Benzylpyridine N-oxide (II)	4	Et_3N	21	3	100
	5	Na_2CO_3	0.5	3	78
	6	Na_2CO_3	5	30	100

[a] All nmr spectra were determined in deuteriochloroform solutions. [b] Calculated on the basis of the assumption that only the α protons of the hetero ring readily exchange. Electronic integration of peak intensities was used for the calculations. [c] Reflux temperature, 76°. [d] Reflux temperature, 100°. [e] Good correlation of 2–5 intensity ratio was obtained in the case of 4-benzylpyridine N-oxide (I); the singlet at τ 2.98 and the singlet at τ 2.76, representing the β and the phenyl protons, respectively, were the only signals in the nmr spectrum.

(1) A preliminary report of this work was presented: Abstracts, Second Middle Atlantic Regional Meeting, of the American Chemical Society, New York, N. Y., Feb 1967, p 65.

(2) V. J. Traynelis and S. A. I. Gallagher, unpublished results. *Anal.* Calcd for $C_{12}H_9D_2NO$: D, 18.18 atom % excess deuterium. Found: D, 21.00 atom % excess deuterium. This analysis was performed by Josef Nemeth, Urbana, Ill.

(3) We were prompted to make this assumption on the evidence of results obtained in expt 3, Table I, footnote *e*. Also, extremely slow or no exchange in the β position has been reported for 3-bromopyridine N-oxide in the presence of sodium deuteroxide at 150° [4] and deuterated 3-chloropyridine N-oxide in the presence of sodium methoxide–methanol.[5]

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

(5) J. A. Zoltewicz and G. M. Kauffman, *J. Org. Chem.*, **34**, 1405 (1969).

(6) P. Bellingham, C. D. Johnson, and A. R. Katritzky, *J. Chem. Soc., B*, 1226 (1967), and references cited therein.

(7) A referee called to our attention the kinetic studies of Zatsepina, *et al.*,[8] on the H–D exchange of methyl derivatives of pyridine N-oxide. Qualitatively, our findings are in agreement with the reported data except where noted below.

(8) (a) N. N. Zatsepina, I. F. Tupitsyn, and L. S. Efros, *J. Gen. Chem. USSR*, **33** (8), 2636 (1963); (b) *ibid.*, **34** (12), 4124 (1964).

(9) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., New York, N. Y., 1967, p 184.

Experimental Section

The liquid N-oxides were purified by vacuum distillation prior to use, and the melting points of the picrates matched those reported in the literature. The melting points of the solid N-oxides and their picrates were in agreement with literature values except in the following cases: 4-benzylpyridine N-oxide (I), mp 105–107° (lit.[10] mp 151°); the picrate of 4-picoline N-oxide (IV), mp 154° (lit.[11] mp 159–160°).

General Procedure for Exchange Reactions.—An equimolar mixture of the N-oxide (*ca.* 5 g) and base in deuterium oxide (15 ml) was refluxed for the appropriate amount of time. After the reflux period, the mixture was extracted with chloroform (200–300 ml) and the extract was dried over anhydrous sodium sulfate. After removal of the drying agent, the chloroform and organic base when present were removed by flash evaporation. The N-oxides so recovered were placed in a vacuum desiccator for drying, since most of the N-oxides are hygroscopic. Most of the deuterated N-oxides were of sufficient purity to be directly submitted for nmr analysis.[12] All recovered N-oxides had melting points which matched the literature values for the undeuterated analogs (or were slightly higher). The ir spectra exhibited a weak C–D stretch at 4.3–4.4 μ with variation of the O–H out-of-plane region at 11–15 μ. Yields of the recovered deuterated pyridine N-oxides averaged 87%.

Registry No.—I, 7259-53-2; II, 20531-86-6.

(10) A. R. Hands and A. R. Katritzky, *J. Chem. Soc.*, 1754 (1958). We were never able to duplicate the reported melting point for this compound. *Anal.* Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99. Found: C, 77.51; H, 5.99. Analysis was performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points are uncorrected.

(11) V. Boekelheide and W. J. Linn, *J. Amer. Chem. Soc.*, **76**, 1286 (1954).

(12) All nmr spectra were obtained through the courtesy of Dr. Vincent J. Traynelis, West Virginia University, Morgantown, W. Va., to whom we wish to express our gratitude.

Preparation and Ring Opening of 1,2,3,4-Tetrahydro-2-oxopyrimido-[2,1-*b*]benzothiazol-5-ium Chloride[1]

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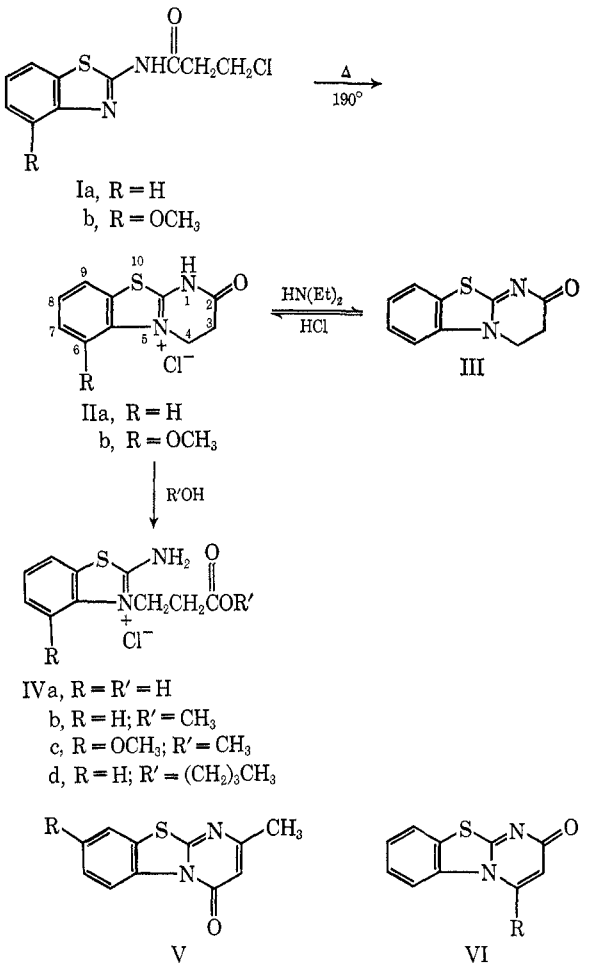
The synthesis of 1,2,3,4-tetrahydro-2-oxopyrimido-[2,1-*b*]benzothiazol-5-ium chloride (IIa) by fusion of 2-(3-chloropropionylamino)benzothiazole (Ia) has been recently reported.[3] These studies were carried out in the course of our investigations with 3-aminoisoquinoline and the 1,3-diazatricyclic ring system, such as VII, which could be similarly prepared by fusion of 3-chloro-N-(isoquinolin-3-yl)propionamide. We now wish to report the details of the synthesis and spectral characteristics of the benzothiazolium salts (II) and the observed facile ring-opening reaction which occurs when II is treated with water or alcohol to form the novel amino acids IV.

Compounds of structure V have been prepared by Antaki and Petrov[4] by heating 2-aminobenzothiazoles with β-aminocrotonic ester. Schrader[5] indicated that



acylacetamidobenzothiazoles could be dehydrated to VI, but no details were given and the structure remains uncertain.

We have found that 1,2,3,4-tetrahydro-2-oxopyrimido[2,1-*b*]benzothiazol-5-ium chloride (IIa) can be readily prepared by fusion of 2-(3-chloropropionylamino)benzothiazole (Ia) at 190°. Treatment of the quaternary halide IIa with anhydrous diethylamine resulted in the isolation of a halogen-free compound, which was assigned structure III. Tsatsas and Costakis[6] isolated III as a side product by treatment of equimolar quantities of 2-aminobenzothiazole and β-chloropropionyl chloride in alkaline medium. We could readily convert III into II with chloroform saturated with hydrogen chloride. The spectra (nmr and uv) and the elemental analyses of II and III confirm the proposed structures and agree with the structure for III as previously suggested.[6] These authors[6] claimed that the insolubility of their compound III kept them from obtaining an nmr spectrum. We had no difficulty in obtaining an nmr spectrum of this compound in deuteriochloroform.

In attempting to obtain nmr spectra of IIa in deuterium oxide solution, however, we found that a mixture of IIa and the ring-opened amino acid IVa was obtained. Spectral evidence indicated that, after the solution had stood at room temperature for 12 hr, the hydrolysis had gone to completion and pure IVa

(1) Presented in part at the First Northeast Regional Meeting of the American Chemical Society, Boston, Mass., Oct 1968.

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(3) J. L. Neumeyer and K. K. Weinhardt, *Chem. Commun.*, 1423 (1968).

(4) H. Antaki and V. Petrov, *J. Chem. Soc.*, 551 (1951).

(5) G. Schrader, German Patent 603,623 (1937); Friedländer's Fortschritte der Teerfarbenfabrikation und verwandter Industriezweige, Vol. 21, Julius Springer, Berlin, 1937, p 317.

(6) G. Tsatsas and E. Costakis, *Chem. Commun.*, 991 (1967).