The Synthesis of Oximes. III.[1] Iodine–Dimethyl Sulfoxide Reaction with Methylpyridines

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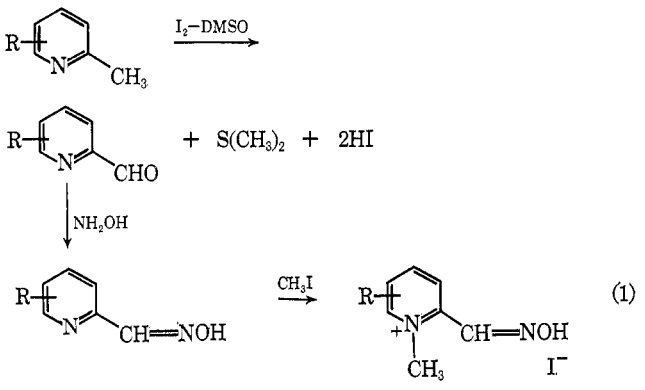
Although 2-pyridinealdoxime methiodide (2-PAM) and certain other heterocyclic aldoxime methiodides are useful antidotes for organophosphorus poisoning,[3] better therapeutic agents are sought. To this end, a search for improved methods of introducing the aldehyde group into heterocyclic nuclei has continued in these laboratories and two new and useful methods have been reported.[1,4] We wish now to report a new and simple one-step procedure for the conversion of methylpyridines into pyridine aldehydes as intermediates for the preparation of pyridine aldoximes and pyridinealdoxime methiodides. This is illustrated by eq 1, as applied to substituted 2-picolines.

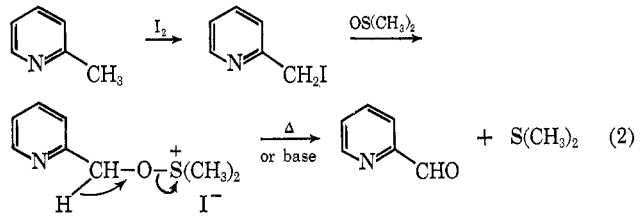


(1)

The 2 picolines were treated with 1 equiv of iodine at room temperature to form a crystalline complex which was dissolved in DMSO. The solution was heated to 140–160°; a vigorous exothermic reaction occurred and dimethyl sulfide was evolved. After neutralization with aqueous alkali, the aldehydes were extracted and purified, or oximated directly. The aldoximes were treated with methyl iodide to form pyridinealdoxime methiodides as candidate enzyme reactivators.

The results (Table I) show that 2-picoline and five substituted 2-picolines were converted in 30–36% yields into the corresponding 2-pyridine aldoximes *via* the 2-pyridine aldehydes. The reaction failed where R was 5-hydroxy, 4-dimethylamino, or 5-dimethylamino. 4-Dimethylamino-2-pyridinealdoxime methiodide was prepared by an alternative procedure and 5-carboxamido-2-pyridine aldoxime was prepared from the 5-carboxymethyl analog. Both 2,4- and 2,6-lutidine were converted into dialdehydes, isolated as the corresponding 2,4-pyridine dialdoxime (32%) and 2,6-pyridine dialdoxime[5] (33%). Quaternization of the aldoximes proceeded readily with the use of methyl iodide in refluxing acetonitrile or methanol. The 2,6-dialdoxime could not be quaternized with methyl iodide; Hackley and coworkers[6] were similarly unsuccessful in the case of 6-methyl-2-pyridine aldoxime. As an example of the iodine–DMSO reaction in the quinoline series, lepidine was converted successively into 4-quinoline aldehyde[7a] (53%), 4-quinoline aldoxime[7b] (90%), and 4-quinolinealdoxime methiodide[7b] (71%).

The conversion of methylpyridines into pyridine aldehydes is visualized as proceeding through the following sequence, using 2-picoline as the example (eq 2).



(2)

The initial picoline–iodine complex, on heating, forms the transient 2-iodomethylpyridine, which reacts with DMSO to form 2-picolyloxydimethyl sulfonium iodide. The latter decomposes on heating (or by treatment with base) to form 2-pyridine aldehyde and dimethyl sulfide. The formation of an oxydimethyl sulfonium halide intermediate which decomposes to liberate dimethyl sulfide has been proposed by Torsell[8] to explain the conversion of alkyl halides and tosylates into aldehydes using DMSO as the nucleophilic oxygen donor.[9]

We were led to the use of iodine as a coreactant by a report by Chinese workers[10] of a closely related reaction. These workers heated equal weights of 2-picoline N-oxide and iodine at 95–100° to form a gum which decomposed at 140–150° to yield 2-pyridine aldehyde (16%, based on iodine, as the bisulfite adduct) together with 2-picoline (37%). Alkaline hydrolysis of the gum gave similar results. These results were verified[11] and extended in these laboratories. It was found that either 2-picoline N-oxide or 2-picoline will form equimolar crystalline complexes with iodine at room temperature. These complexes, either with excess 2-picoline N-oxide or pyridine N-oxide as nucleophilic oxygen sources, may be thermally decomposed at 140–160° or hydrolyzed with base to yield 2-pyridine aldehyde. Similar results were obtained with 5-ethyl-2-picoline N-oxide–iodine or 5-ethyl-2-picoline–iodine complexes using pyridine N-oxide as the nucleophilic oxygen source. The reaction mechanism is undoubtedly similar to that proposed for the iodine–

(1) Part II: B. E. Hackley, Jr., and F. A. Daniher, *J. Org. Chem.*, **32**, 2624 (1967).

(2) (a) Ash Stevens Inc.; (b) Edgewood Arsenal.

(3) D. F. Heath, "Organophosphorus Poisons," Pergamon Press, New York, N. Y., 1961; R. D. O'Brien, "Toxic Phosphorus Esters," Academic Press, New York, N. Y., 1960.

(4) F. A. Daniher, B. E. Hackley, Jr., and A. B. Ash, *J. Org. Chem.*, **31**, 2709 (1966).

(5) See footnote *m*, Table I.

(6) B. E. Hackley, Jr., E. J. Poziomek, G. M. Steinberg, and W. A. Mosher, *J. Org. Chem.*, **27**, 4220 (1962).

(7) (a) C. E. Kwartler and H. G. Lindwall, *J. Amer. Chem. Soc.*, **59**, 524 (1937); (b) see footnote *b*, Table I.

(8) K. Torsell, *Tetrahedron Lett.*, 4445 (1966).

(9) N. Kornblum, W. J. Jones, and G. J. Anderson, *J. Amer. Chem. Soc.*, **81**, 4113 (1959); see also N. Kornblum, *et al.*, *ibid.*, **79**, 6562 (1957).

(10) L. Mao-Chin and C. Sae-Lee, *Acta Chim. Sinica*, **31**, 30 (1965).

(11) The thermal decomposition reaction sometimes occurs violently and due caution should be observed.

TABLE I

IODINE–DMSO REACTION WITH 2-PICOLINES AND LEPIDINE. 2-PYRIDINE ALDOXIMES AND 1-METHIODIDE DERIVATIVES

R	2-Pyridine aldoximes			1-Methiodides		
	Yield, %	Mp, °C	Registry no.	Yield, %	Mp, °C	Registry no.
H	31	112–113[a]		75	224–226[b]	
5-CH_3	33	158–159[a]		84	155–156[c]	22794-99-6
5-C_2H_5	30	147–148[a]		71	138–140[d]	22795-00-2
5-Cl	35	194–195[e]		79	203–204[f]	22795-01-3
5-CO_2CH_3	35	191–192[g]	22794-96-3	72	164–166[h]	22795-02-4
4-CO_2CH_3	36	184–185[i]	22794-97-4	84	119–120[j]	22795-03-5
4-CH=NOH	32	225–227[k]	22866-50-8	79	187–188[l]	22795-04-6
6-CH=NOH	33	207–209[m]		...	...	
4-CH=NOH[n]	48	179–180[b]		71	250–251[b]	22795-05-7
5-$CONH_2$	...	234–236[o]	22794-98-5	82	169–170[p]	22795-06-8
4-$N(CH_3)_2$	...	183–185[q]		56	211–212[r]	

[a] Reference 1. [b] S. G. Ginsburg and I. B. Wilson, *J. Amer. Chem. Soc.*, **79**, 481 (1957). [c] Calcd for $C_8H_{11}N_2OI$: C, 34.55; H, 3.99; N, 10.07; I, 45.64. Found: C, 34.59; H, 4.25; N, 9.69; I, 45.61. [d] Calcd for $C_9H_{13}IN_2O$: C, 37.00; H, 4.49; I, 43.44; N, 9.59. Found: C, 37.26; H, 4.49; I, 43.69; N, 9.63. [e] Reference 4. [f] Calcd for $C_7H_8N_2OICl$: C, 28.15; H, 2.70; N, 9.37; I, 42.57. Found: C, 28.39; H, 2.89; N, 9.14; I, 42.41; pK_a, 7.17 (25°, H_2O). [g] Calcd for $C_8H_8N_2O_3 \cdot {}^1/_2H_2O$: N, 14.81. Found: N, 15.09. [h] Calcd for $C_9H_{11}IN_2O_3$: C, 33.56; H, 3.44; I, 39.40; N, 8.70. Found: C, 33.80; H, 3.72; I, 39.19; N, 8.92. [i] Calcd for $C_8H_8N_2O_3$: C, 53.33; H, 4.47; N, 15.55. Found: C, 53.30; H, 4.54; N, 15.56. [j] Calcd for $C_9H_{11}N_2O_3I$: C, 33.56; H, 3.44; N, 8.69; I, 39.40. Found: C, 33.56; H, 3.41; N, 8.63; I, 39.34. [k] Calcd for $C_7H_7N_3O_2$: N, 25.45. Found: N, 25.63. [l] Calcd for $C_8H_{10}N_3O_2I$: C, 31.29; H, 3.28; I, 41.33. Found: C, 31.26; H, 3.41; I, 41.08; pK_a, 8.28 (25°, H_2O). [m] W. Mathes and W. Sauermilch, *Chem. Ber.*, **88**, 1276 (1955). [n] 4-Quinoline aldoxime and the methiodide. [o] Calcd for $C_7H_7N_3O_2 \cdot {}^1/_2H_2O$: N, 24.12. Found: N, 24.05. [p] Calcd for $C_8H_{10}N_3O_2I \cdot {}^1/_2H_2O$: C, 30.39; H, 3.50; N, 13.22; I, 41.33. Found: C, 30.08; H, 3.39; N, 13.29; I, 40.91; pK_a, 7.20 (25°, H_2O). [q] Prepared by method of ref 1. [r] Calcd for $C_9H_{14}N_3OI$: C, 35.19; H, 4.59; N, 13.68. Found: C, 35.11; H, 5.01; N. 14.07; pK_a. 8.58 (25°, H_2O).

DMSO reaction. An intermediate 2-picolyloxy-2′-picolinium (or pyridinium) iodide is formed, which eliminates pyridine thermally or by basic hydrolysis. Inasmuch as only 2-pyridine aldehyde and 2-picoline were isolated in the Chinese procedure,[10] deoxygenation occurs during the reaction. Deoxygenation by iodine was demonstrated in these laboratories by heating equimolar iodine complexes of 2-picoline N-oxide and pyridine N-oxide at 130 and 160°, respectively; yields of isolated 2-picoline and pyridine were 50% in both cases.

Experimental Section

All melting points are uncorrected. Yield, melting-point, and analytical data are presented in Table I for all compounds synthesized in the course of this work. The pK_a values for four compounds were determined by titrating a 10^{-2} *M* aqueous solution of the aldoxime methiodides with standard base at 25° using a Sargent pH Stat.

The Iodine–DMSO Reaction with 2-Picolines.—Crystalline iodine–picoline complexes were prepared by mixing equimolar amounts of iodine and picoline at room temperature. Each complex, which solidified after cooling and scratching, was dissolved in a small amount of DMSO and dropped into an excess of DMSO preheated to 130°. (The total volume of DMSO was 10 ml per 0.01 mol of iodine.) The mixture was stirred and heated slowly to 140–160°, where a vigorous reaction occurred with the evolution of dimethyl sulfide.[12] The mixture was held at that temperature for 10–15 min, cooled, and neutralized with saturated aqueous sodium bicarbonate. The resulting dark suspension was extracted continuously with ether until the ether extract failed to react with 2,4-dinitrophenylhydrazine. The ether extract was concentrated and treated with an excess of a neutral aqueous solution of hydroxylamine (prepared from the hydrochloride salt and sodium carbonate.) The solution was heated on a steam bath for 30 min, concentrated, and cooled. The oxime usually separated as a crystalline precipitate; otherwise, the oxime was extracted with ether. The crude oxime was recrystallized from methanol, ethanol, or benzene and analyzed, or compared with an authentic sample (Table I).

(12) The formation of dimethyl sulfide was qualitatively confirmed by passage of nitrogen successively through the reaction mixture and a 0.2 *M* aqueous $HgCl_2$ solution. The precipitated complex $[(CH_3)_2S \cdot HgCl_2]$ was collected and identified by its melting point, 180–181°, as reported by H. H. Szamant and O. Cox, *J. Org. Chem.*, **31**, 1595 (1966).

The intermediacy of the aldehyde was shown in one case by isolating 4-quinolinealdehyde in 53% yield through alumina–benzene chromatography.

5-Carboxamido-2-pyridine Aldoxime.—5-Carbomethoxy-2-pyridine aldoxime (0.9 g) was suspended in 25 ml of 28% aqueous ammonium hydroxide and stirred at room temperature for 4 hr. The suspension was refrigerated and crystalline amide (0.6 g) was separated, mp 233–235°. The mother liquor was concentrated under reduced pressure with minimum heating and refrigerated, and additional solid (0.25 g) was separated, mp 232–235°. The combined yield was 90% (or 30% calculated for 5-carbomethoxy-2-picoline). The two crops were recrystallized from methanol–water, mp 234–236°; acceptable nitrogen analysis and a suitable ir spectrum were found.

Pyridine N-Oxides as Nucleophilic Oxygen Sources.—2-Picoline N-oxide (1.09 g) and iodine (2.6 g) were mixed to form a crystalline complex. Pyridine N-oxide (2 g) was added and the mixture was heated with stirring on a steam bath for 8 hr. The dark reaction mixture was distilled under reduced pressure by an aspirator and the fraction (0.7 g) boiling at 30–80° was collected. Tlc showed two spots. The oil was dissolved in ethanol (10 ml), and hydroxylamine (prepared by neutralizing 0.5 g of the hydrochloride salt in 5 ml of water) was added. The solution was refluxed for 2 hr, evaporated to dryness, and extracted with ether. The ether was removed and the product was recrystallized from benzene to yield 2-pyridine aldoxime (355 mg, 30%), mp 110–111°. Alternatively, the dark reaction mixture was neutralized with Na_2CO_3 and extracted with ether. After removal of the ether, the residue was oximated in the same manner to give the same yield (30%) of the aldoxime. 5-Ethyl-2-picoline N-oxide (1.37 g), iodine (2.6 g), and pyridine N-oxide (2 g) were heated on a steam bath for 8 hr. Distillation and oximation yielded 5-ethyl-2-pyridine aldoxime (290 mg, 21%), mp 134–135°.

2-Picoline (0.93 g) and iodine (2.6 g) were mixed to form a crystalline complex. Pyridine N-oxide (2 g) was added and the mixture was heated on a steam bath for 8 hr. Distillation, as described above, gave 2-pyridine aldoxime (256 mg, 24%), mp 113–114°. Similarly, 5-ethyl-2-picoline (1.21 g), iodine (2.6 g), and pyridine N-oxide (2 g) were heated on a steam bath for 8 hr. The product was distilled, diluted with a little water, and treated with SO_2 to yield the 5-ethyl-2-pyridinealdehyde bisulfite adduct (310 mg, 23%), mp 190–192° dec, identical with an authentic sample.

Deoxygenation of Pyridine N-Oxide and 2-Picoline N-Oxide with Iodine.—Pyridine N-oxide (1 equiv) and iodine (1 equiv) were mixed at room temperature to form a crystalline complex. The complex was heated on an oil bath to 160°; a vigorous, exo-

thermic reaction occurred. Pyridine (50%) was distilled from the mixture and characterized as the picrate and hydriodide salts. A 2-picoline N-oxide–iodine complex underwent a similar thermal deoxygenation, but at a lower temperature (130°); 2-picoline (50%) was collected and characterized as the picrate. Although there are several reagents suitable for the deoxygenation of pyridine N-oxides,[13] the thermal degradation of iodine complexes may prove useful in selected cases.

(13) G. J. O'Neill, "Deoxygenation of Pyridine N-Oxides," University Microfilms, Ann Arbor, Mich., 1967. See also F. A. Daniher and B. E. Hackley, Jr., *J. Org. Chem.*, **31**, 4267 (1966).

Intramolecular Condensation Reactions of 1,1,3,3-Tetrakis(2-chloroethyl)urea[1]

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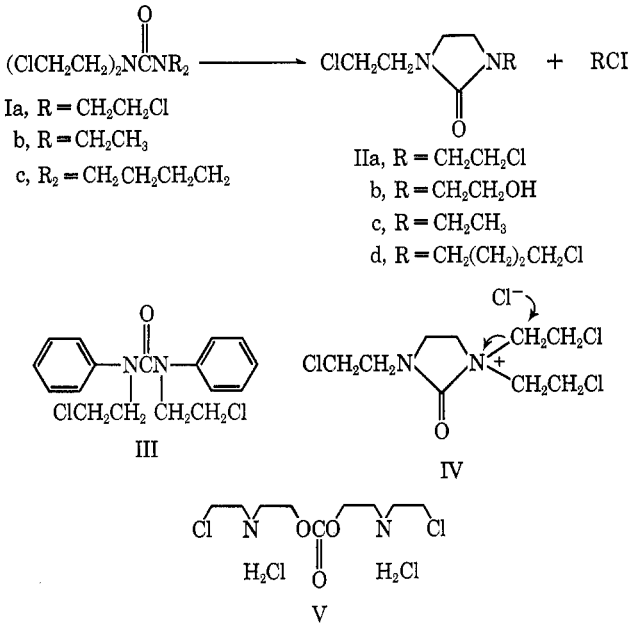
Di- and trisubstituted ureas containing a 2-haloethyl moiety are known to undergo intramolecular alkylation at nitrogen or oxygen, depending on reaction conditions. When the urea is heated in a nonpolar solvent or without solvent, N-alkylation generally occurs and leads to formation of 2-imidazolidinones.[4] By contrast, in aqueous solution, ureas exist in a polarized form,[5] which allows electrophilic attack at oxygen and formation of a 2-amino-2-oxazoline[4b,c,6] or corresponding hydrolysis products.[7] We now report results of a study concerned with subjecting a tetrasubstituted 2-haloethylurea to both intramolecular reaction conditions.

1,1,3,3-Tetrakis(2-chloroethyl)urea (Ia) was prepared in essentially quantitative yield by allowing bis(2-chloroethyl)carbamoyl chloride to react with bis(2-chloroethyl)amine in refluxing benzene. The urea could be purified by column chromatography on Florisil. When an attempt was made to purify Ia by distillation, virtually all of the oily distillate was collected in a single fraction which solidified to colorless prisms, mp 36–37°. Microanalytical data as well as infrared and pmr spectra of the distillate were incompatible with formulation Ia and indicated instead a 1,3-bis(2-chloroethyl)-2-imidazolidinone structure (IIa). This structural assignment was confirmed by the following alternate synthesis.

1,3-Bis(2-hydroxyethyl)-2-imidazolidinone (IIb)[8] was prepared by warming a mixture of 2,2′-(ethylenediimino)diethanol and urea at 190°.[9] Chlorination of IIb utilizing thionyl chloride furnished a crystalline product, mp 35–36°, identical with that isolated from the distillation of urea Ia.



Some aspects of the scope of the cyclization reaction were ascertained by reacting bis(2-chloroethyl)-carbomoyl chloride with diethylamine. The oily product, obtained directly by evaporation of the solvent, was identified as 1-(2-chloroethyl)-3-ethyl-2-imidazolidinone (IIc). Next, bis(2-chloroethyl)carbamoyl chloride was found to react with excess pyrrolidine at room temperature to provide 1-(4-chlorobutyl)-3-(2-chloroethyl)-2-imidazolidinone (IId) in 60% yield.

Finally, N,N′-bis(2-chloroethyl)carbanilide (III), in which the nitrogen atoms are presumably less nucleophilic, was found to be stable at 200°, at which temperature the urea distilled unchanged.

When a Dry Ice trap was placed in the vacuum system during distillation of urea Ia, an 82% yield of 1,2-dichloroethane was collected. Thus imidazolidinone formation may proceed through a quaternary amide which undergoes carbon–nitrogen bond cleavage (IV). There is considerable analogy in the literature for such a proposal.[10] In contrast with the present case, in which intermediate IV arises by alkylation of a secondary amide function, previous examples of N-acylium salts invariably resulted from action of an acylating agent on a tertiary amine.

We next turned attention to transformations of urea Ia in aqueous solution.[11] A mixture of urea Ia and

(1) A preliminary account of this work was presented at the Third Middle Atlantic Regional Meeting of the American Chemical Society, Feb 3, 1968. The present contribution is part XXII of Antineoplastic Agents. For part XXI, see G. R. Pettit and B. J. Danley, *Can. J. Chem.*, **46**, 792 (1968).

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(4) (a) S. Gabriel and R. Stelzner, *Chem. Ber.*, **28**, 2937 (1895); (b) J. P. Picard and A. F. McKay, *Can. J. Chem.*, **31**, 896 (1953); (c) G. R. Pettit, D. S. Blonda, and R. A. Upham, *ibid.*, **43**, 1798 (1965).

(5) N. V. Sidgwick, "The Organic Chemistry of Nitrogen," 3rd ed, Oxford University Press, New York, N. Y., 1966, p 422.

(6) M. E. Kreling and A. F. McKay, *Can. J. Chem.*, **37**, 504 (1959).

(7) E. Khedouri, Y. Kim, and O. M. Friedman, *J. Med. Chem.*, **7**, 653 (1964).

(8) A. B. Steele, U. S. Patent 2,847,418 (Aug 12, 1958).

(9) A. L. Wilson, U. S. Patent 2,517,750 (Aug 8, 1950).

(10) See, *e.g.*, (a) K. C. Murdock, *J. Org. Chem.*, **33**, 1367 (1968); (b) R. F. Meyer and B. L. Cummings, *J. Heterocycl. Chem.*, **1**, 186 (1964); (c) R. C. Clark, A. Mooradian, P. Lucal, and T. J. Slauson, *J. Amer. Chem. Soc.*, **71**, 2821 (1949); (d) J. D. Hobson and J. G. McCluskey, *J. Chem. Soc., C*, 2015 (1967).

(11) Of particular interest here was a recent report concerning changes in biological activity of "aged" bis(2-chloroethyl)carbamates caused by partial conversion into oxazoline derivatives. See R. Wade and F. Bergel, *J. Chem. Soc., C*, 592 (1967).