Cyanoethylation. II. Alkylpyridine Methiodides[1,2]

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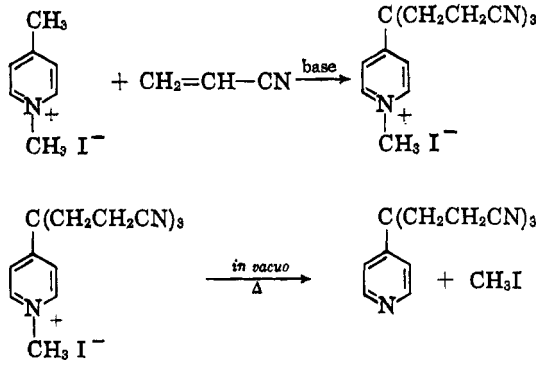
Cyanoethylation of 2- and 4-alkylpyridine methiodides was carried out using triethylamine as catalyst. The number of cyanoethyl groups which could be introduced into some methiodides was limited due to steric factors. Heating the cyanoethylated methiodides *in vacuo* led to the corresponding cyanoethylated alkylpyridines.

It is well-known that the methyl group of 2-picoline methiodide exhibits active hydrogen reactivity, for example in its reaction with aromatic aldehydes.[3] The cyanoethylation (in 34% yield) of 2-picoline methiodide in the presence of sodium methiodide also has been reported.[4] We wished to investigate the cyanoethylation reaction primarily for its potential value as the first step in the synthesis of cyanoethylated alkylpyridines according to the following scheme.



We found that cyanoethylation of 2- and 4-alkylpyridine methiodides proceeded readily in the presence of triethylamine, a catalyst found useful in other cyanoethylations.[2] However, it was observed that, in some cases, the number of cyanoethyl groups introduced was less than the number of active hydrogen atoms in the pyridinium compound.

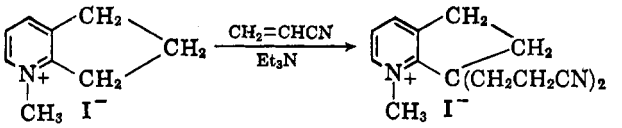
Data on the reactions investigated are given in Table I. The basis for the assignments of structures to the cyanoethylated products will be made clear in the course of the discussion.

The cyanoethylations of 2- and 4-methylpyridine methiodides gave products of unambiguous structure. The results indicated that three cyanoethyl groups can be introduced into a 4-methyl group but only two into a 2-methyl group. In a similar manner, cyanoethylation of the designated methiodides (Table I) led to the formation of III, VII, and X, each containing the anticipated number of cyanoethyl groups.

These results may be explained by a consideration of the structure of the anhydro bases which are undoubtedly intermediates in the cyanoethylation reactions. The anhydro base (XII), derived from dicyanoethylated 2-methylpyridine methiodide, must have a cyanoethyl group *cis* to the N-methyl group. The resulting steric interaction would interfere with the planarity of the structure and, therefore, destabilize the anhydro base, preventing its formation in appreciable amount. There is no such interference in the anhydro base (XIII) derived from dicyanoethylated 4-methylpyridine methiodide. A methyl group would be expected to be nearly as effective as a cyanoethyl group, so it should be possible to introduce only one cyanoethyl group into 2-ethylpyridine methiodide, in agreement with observation.

XII, $R_1 = R_2 = -CH_2CH_2CN$; $R_3 = -H$
XIII, $R_1 = R_2 = -CH_2CH_2CN$; $R_3 = -H$
XIV, $R_1 = -CH_2CH_2CN$ or $-H$; $R_2 = -H$ or $-CH_2CH_2CN$; $R_3 = -CH_3$
XV, $R_1 = R_2 = -CH_2CH_2CN$; $R_3 = -CH_3$

If this explanation is correct, an adjacent C-methyl group should be as effective as an N-methyl group in limiting the entry of cyanoethyl groups. The cyanoethylation of 2,3-dimethylpyridine and 3,4-dimethylpyridine methiodides gives results in agreement with this prediction. Furthermore, in the cyanoethylation of pyrindane methiodide (XVI), where the planar configuration of the anhydro base is necessarily maintained by a cyclic structure, the N-methyl group does not interfere as shown by the fact that two cyanoethyl groups are introduced.



XVI XI

There appears to be a similar, though less well-documented, steric control of the reaction of 2- and 4-alkylpyridine methiodides with aldehydes, as has been discussed by Phillips.[5]

Several of the cyanoethylated methiodides were heated *in vacuo* to obtain the corresponding cyanoethylated alkylpyridines. Data on these reactions are given in Table II. While the yields are not uniformly high, they are acceptable and the reaction seems to be a useful one for the preparation of cyanoethylated alkylpyridines. While the direct cyanoethylation of alkylpyridines has been patented,[6] yields were not given and no characterization of the products was reported.

(1) Support of this work by the Robert A. Welch Foundation is gratefully acknowledged.

(2) Paper I: Joe A. Adamcik and Edward J. Miklasiewicz, *J. Org. Chem.*, **28**, 336 (1963).

(3) C. F. Koelsch, *J. Am. Chem. Soc.*, **66**, 2126 (1944).

(4) E. E. van Tamelen, D. L. Hughes, and C. W. Taylor, *ibid.*, **78**, 4625 (1956).

(5) Arthur P. Phillips, *J. Org. Chem.*, **13**, 622 (1948).

(6) F. E. Cislak, U. S. Patent 2,868,794 (1959).

TABLE I

CYANOETHYLATED METHIODIDES

Pyridine methiodide	Reaction time, hr.	Product	Yield, %	Corrected m.p., °C.	Empirical formula	Analysis, % Calcd. C	Calcd. H	Calcd. N	Calcd. I	Found C	Found H	Found N	Found I
4-Methyl	12	4-[Tris(2-cyanoethyl)methyl]-1-methylpyridinium iodide (I)	92	229.5–230.5	$C_{16}H_{19}N_4I$	48.74	4.86	14.21	32.19	48.83	5.19	13.95	32.08
2-Methyl	2	2-[Bis(2-cyanoethyl)methyl]-1-methylpyridinium iodide (II)	73	141–142[a]	$C_{13}H_{16}N_3I$	45.76	4.73	12.32	37.20	45.91	5.05	12.34	37.36
2,4,6-Trimethyl	22	2,6-Bis[bis-(2-cyanoethyl)-methyl]-4-[tris(2-cyanoethyl)-methyl]-1-methylpyridinium iodide (III)	96	202.5–203.5	$C_{30}H_{36}N_8I$	56.78	5.56	17.66	20.00	56.88	5.70	17.56	20.02
2-Ethyl	24	2-[1-(2-Cyanoethyl)ethyl]-1-methylpyridinium iodide (IV)	45	97	$C_{11}H_{15}N_3I$	43.72	5.00	9.27	42.00	43.98	5.17	9.22	42.31
4-Ethyl	19	4-[1,1-Bis(2-cyanoethyl)ethyl]-1-methylpyridinium iodide (V)	87	126–128	$C_{14}H_{18}N_3I$	47.33	5.11	11.83	35.73	47.35	5.47	11.67	35.48
4-Propyl	24	4-[1,1-Bis(2-cyanoethyl)propyl]-1-methylpyridinium iodide (VI)	99	232.5–235	$C_{15}H_{20}N_3I$	48.79	5.46	11.38	34.37	48.98	5.58	11.15	34.37
2,6-Dimethyl	24	2,6-Bis[bis(2-cyanoethyl)-methyl]-1-methylpyridinium iodide (VII)	75	152–153° dec.	$C_{20}H_{24}N_6I$	52.07	5.24	15.18	27.51	52.30	5.28	15.21	27.50
3,4-Dimethyl	23	4-[Bis(2-cyanoethyl)methyl]-1,3-dimethylpyridinium iodide (VIII)	50	145–146	$C_{14}H_{18}N_3I$	47.23	5.11	11.83	35.73	47.50	5.21	11.95	35.57
2,3-Dimethyl	24	2-(3-Cyanopropyl)-1,3-dimethylpyridinium iodide (IX)	44	192–193	$C_{11}H_{15}N_3I$	43.72	5.00	9.27	42.00	43.50	5.19	9.16	42.22
2,4-Dimethyl	48	2-[Bis(2-cyanoethyl)methyl]-4-[tris(2-cyanoethyl)methyl]-1-methylpyridinium iodide (X)	42[b]	198–200	$C_{23}H_{27}N_6I$	53.70	5.29	16.34	24.67	53.97	5.51	16.16	24.92
Pyrindane methiodide	17	7,7-Bis(2-cyanoethyl)pyrindane methiodide (XI)	71	195.5–196	$C_{15}H_{18}N_3I$	49.06	4.94	11.44	34.56	49.16	4.99	11.39	34.32

[a] Ref. 4, m.p. 139.5–140.5°. [b] Based on impure starting material. See Experimental section.

TABLE II

CYANOETHYLATED ALKYLPYRIDINES

Starting material	Product	Yield, %	B.p. (mm.) or m.p., °C.[a]	Empirical formula	Analysis, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I	4-[Tris(2-cyanoethyl)methyl]-pyridine	43	156	$C_{14}H_{16}N_4$	71.40	6.39	22.21	71.48	6.42	22.30
II	2-[Bis(2-cyanoethyl)methyl]-pyridine	83	182 (1.2)	$C_{12}H_{13}N_3$	72.33	6.58	21.09	71.98	6.81	20.83
III	2,6-Bis[bis(2-cyanoethyl)methyl]-4-[Tris(2-cyanoethyl)methyl]-pyridine	36	131–132.5	$C_{29}H_{32}N_8$	70.70	6.55	22.75	70.83	6.58	22.61
IV	2-[1-(2-Cyanoethyl)ethyl]pyridine	84	170 (45)	$C_{10}H_{12}N_2$	74.96	7.55	17.49	75.05	7.82	16.73
VI	4-[1,1-Bis(2-cyanoethyl)propyl]-pyridine	70	230–235 (1.4) 74.5	$C_{14}H_{17}N_3$	73.97	7.54	18.49	74.10	7.73	18.32
VII	2,6-Bis[bis(2-cyanoethyl)methyl]-pyridine	78	55.5–56	$C_{19}H_{21}N_5$	71.45	6.63	21.93	71.35	6.68	22.10

[a] Melting points are corrected and refer to the analytical sample, boiling points are uncorrected.

Experimental

Methiodides.—The methiodides were prepared by treatment of the appropriate amine with methyl iodide in refluxing benzene. Pyrindane was prepared as described by Prelog and Szpilfogel.[7] Pyrindane methiodide was recrystallized from methanol–ethyl acetate, m.p. 160–162° dec.

Anal. Calcd. for $C_9H_{12}NI$: C, 41.40; H, 4.63; N, 5.36; I, 48.60. Found: C, 41.45; H, 4.79; N, 5.31; I, 48.80.

The gas chromatogram of the commercial sample of 2,4-dimethylpyridine used showed it to be impure, and we were not able to purify either the amine or the methiodide. However, the cyanoethylated product was easily purified. Therefore, the reported yield is based on the impure starting material and the actual yield would be somewhat greater.

Cyanoethylations.—To a mixture of the amine methiodide, enough water to dissolve the salt, two to three times the theoretical quantity of acrylonitrile, and about 0.33 moles of triethylamine per mole of acrylonitrile, sufficient ethanol was added to make a homogeneous solution, and the mixture was refluxed for the time indicated. I, III, and VI crystallized directly from the reaction mixture. Addition of water and ether to the reaction mixture containing VII caused it to separate as an oil which crystallized on cooling in an ice bath. Addition of ether to the reaction mixture containing X caused it to separate in crystalline form. II, IV, V, VIII, IX, and XI were isolated by addition of water, extraction with ether to remove triethylamine and excess acrylonitrile, and evaporation to dryness *in vacuo*. The work-up of the residues varied slightly. Those of II, V, and IX were dissolved in hot ethanol–water containing 5% or less of water; those of IV and VIII were dissolved in hot absolute ethanol; and the residue of XI in hot methanol–ethyl acetate. After treatment with charcoal, crystals formed from these solutions as they cooled; IX was forced from solution by acetone. I, II, VI, IX, and X were recrystallized from ethanol–water; IV from methanol–ethanol; V from acetone–ethanol; VIII from acetone–ethanol–water; XI from ethyl acetate–methanol.

Cyanoethylated Alkylpyridines.—The cyanoethylated pyridinium compound was heated under a pressure of about 1 mm.

(7) V. Prelog and S. Szpilfogel, *Helv. Chim. Acta*, **28**, 1684 (1945).

by a Wood's metal bath. In the decompositions of II, IV, and VI, the bath temperature was slowly raised until the product distilled. In the decompositions of I, III, and VII, the bath temperature was maintained at about 300° for 1.5, 5.5, and 5 hr., respectively, and the product was isolated by dissolving the residue in ethanol–water or ethanol–water–tetrahydrofuran, treating with charcoal, cooling, and filtering. The amines from the decomposition of I, VI, and VII were recrystallized from ethanol–water; the amine from III was recrystallized from ethanol–water–dioxane.

Pyridoxine Chemistry. V. Synthesis of Isopyridoxal, 5-Pyridoxic Acid Lactone, and Their Derivatives[1,2]

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The present paper describes convenient methods of synthesis for isopyridoxal, 5-pyridoxic acid lactone, and certain of their derivatives. The physical and chemical properties and some biological properties of these various compounds have been compared with the corresponding properties of some of their isomeric derivatives in the pyridoxal–pyridoxic acid series. The amide and hydrazide of 5-pyridoxic acid were found to be hydrolyzed with extreme ease, indicating neighboring-group participation of the 4-hydroxymethyl group during hydrolysis. Infrared and proton magnetic resonance spectra of these compounds have been studied. It has been shown that isopyridoxal exists in the hemiacetal form both in the solid state and in aqueous solution.

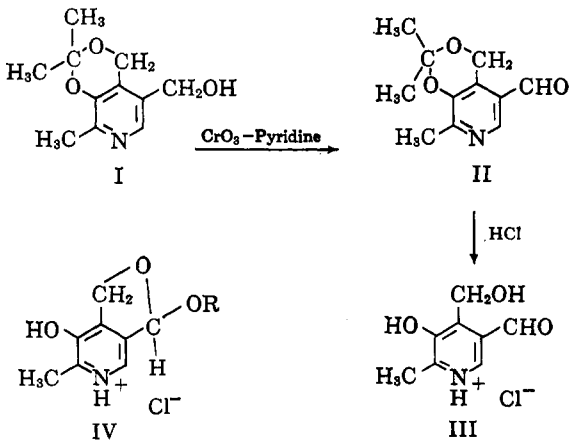
Pyridoxal is metabolized in man and rodents to pyridoxal phosphate and 4-pyridoxic acid or its lactone (β-pyracin). Although pyridoxal is closely related to the cofactor, 4-pyridoxic acid is excreted in the urine, following ingestion of either form of the vitamin. Chemically, both metabolites are formed from pyridoxal with relative ease, since the 4-hydroxymethyl side chain of pyridoxal is preferentially attacked by oxidizing agents.[3]

The ready availability of the starting compounds made it possible to obtain a number of derivatives selectively modified at the 4-position, many of which were found to have a pronounced biological activity. Thus, several hydrazones of pyridoxal were found to inhibit pyridoxal phosphokinase *in vitro*, and pyridoxal methylhydrazone and isonicotinoylhydrazone had weak inhibitory activity on the growth of Sarcoma 180 in mice and also inhibited the growth of some microorganisms.[4] Several thiosemicarbazones show promise as antitubercular drugs,[5] and 4-pyridoxhydrazone was found to inhibit the growth of malignant cells in tissue culture.[6] Derivatives of 4-pyridoxic acid, such as the hydrazone, also have been shown to be active as bacteriostatic agents.[7]

In our studies concerning the synthesis of potential antimetabolites for pyridoxine, it was of interest to determine whether similar modifications in the 5-hydroxymethyl side chain of pyridoxol would yield compounds capable of inhibiting certain enzymes essential in the metabolism of amino acids, and whether such compounds would be of some potential chemotherapeutic value. Isopyridoxal, 5-pyridoxic acid, and the lactone of the latter recently have been found to be metabolites of pyridoxol in certain microorganisms (*Pseudomonas sp.*).[8]

Methods for the synthesis of isopyridoxal[9] and 5-pyridoxic acid lactone (α-pyracin)[10] have been described, but gave poor yields and were impractical. In a preliminary communication,[11] we described a simple and unequivocal method for the synthesis of isopyridoxal, starting from α^4,3-O-isopropylidenepyridoxol (I).[12] (Another name for I is O^3O^4-isopropylidenepyridoxine. The nomenclature of this type of compound presents problems.[13]) Later we developed a convenient method for the preparation of the starting material (I).[14]

Oxidation of I with the chromic anhydride–pyridine complex at room temperature for 2 days gave only a 30% yield of the aldehyde (II). When the reaction mixture was refluxed for 90 min., however, the yield increased to 83%. In the relatively few cases in which the reagent has been used for the synthesis of aldehydes, an increased yield was obtained at moderately elevated temperatures. Very recently, in a systematic study of



(1) For preceding paper in this series: W. Korytnyk and R. P. Singh, *J. Am. Chem. Soc.*, **85**, 2813 (1963).

(2) Presented at the 145th National Meeting of the American Chemical Society, New York, N. Y., September, 1963.

(3)(a) S. A. Harris, D. Heyl, and K. Folkers, *J. Am. Chem. Soc.*, **66**, 2088 (1944); (b) J. W. Huff and W. A. Perlzweig, *J. Biol. Chem.*, **155**, 345 (1944); (c) D. Heyl, *J. Am. Chem. Soc.*, **70**, 3434 (1948).

(4) R. H. Wiley and G. Irick, *J. Med. Pharm. Chem.*, **5**, 49 (1962).

(5) D. D. T. Sah and C. T. Peng, *Arch. Pharm.*, **293**, 501 (1960).

(6) E. Testa, A. Bonati, and G. Pagani, *Chimia* (Aarau), **15**, 314 (1961).

(7) S. Emoto, *J. Sci. Res. Inst.* (Tokyo), **47**, 37 (1953).

(8) V. W. Rodwell, B. E. Volkani, M. Ikawa, and E. E. Snell, *J. Biol. Chem.*, **233**, 1548 (1958).

(9) S. A. Harris, D. Heyl, and K. Folkers, *J. Am. Chem. Soc.*, **66**, 2088 (1944).

(10) S. A. Harris, E. T. Stiller, and K. Folkers, *ibid.*, **61**, 1242 (1939); J. Baddiley and A. P. Mathias, *J. Chem. Soc.*, 2583 (1952).

(11) W. Korytnyk and E. J. Kris, *Chem. Ind.* (London), 1834 (1961).

(12) Dr. H. G. Brooks, Jr., of Iowa State University of Science and Technology, has also obtained II by oxidizing I with manganese dioxide—Dr. D. E. Metzler, private communication.

(13) W. Korytnyk, *J. Org. Chem.*, **27**, 3724 (1962).

(14) W. Korytnyk and W. Wiedeman, *J. Chem. Soc.*, 2531 (1962).