[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE ROHM AND HAAS CO.]

Cyanation of Amine Oxide Salts. A New Synthesis of Cyanopyridines

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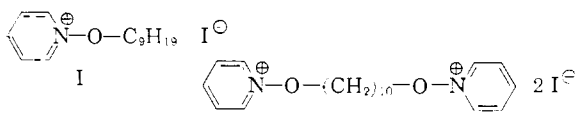
The addition of cyanide ion to N-alkoxy-quaternary salts of pyridines, quinolines and isoquinoline has been found to yield the corresponding cyano-substituted heterocycles under very mild reaction conditions. The reaction offers a new route to cyanopyridines, and supplements the Reissert and Kaufmann reactions in the quinoline and isoquinoline series.

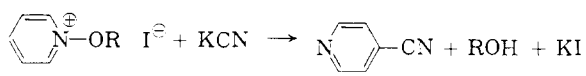
It is known that quaternary salts of amine oxides undergo alkaline decomposition to yield aldehydes and tertiary amines.[1] Ochiai and his colleagues[2] have applied the reaction to salts of pyridine-1-oxides and Katritzky[3] has studied this reaction as a method of deoxygenating pyridine-1-oxides under non-reducing conditions. 1-Benzyloxypyridinium salts have been found to give benzaldehyde and pyridines in good yield upon alkaline decomposition[4] and some work has been done on the cleavage of cyclic amine oxide salts.[5]

During a recent study of the alkaline decomposition reaction, we had occasion to prepare the salts I and II from pyridine-1-oxide and the corresponding alkyl iodides. It was found that upon treatment of these salts in aqueous solution at room temperature with potassium cyanide, the products of the reactions were in both cases 4-cyanopyridine and the corresponding alcohols.

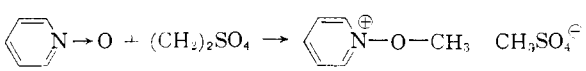


I

II



In studying this reaction more fully, a more convenient method of preparing N-methoxy salts was found which consisted of treating the N-oxides with dimethyl sulfate. This method gave the new N-methoxymethyl sulfate salts. The reaction was mildly exothermic and nearly quantitative.



The resulting salts were generally hygroscopic and difficult to handle although a few were obtained as crystalline substances and characterized. The salts in most cases were dissolved in water without purification and added to an aqueous solution containing an excess of potassium cyanide. The nitriles were isolated in various ways, but in many cases the crystalline products were filtered directly from the reaction mixtures.

Table I shows the products thus far isolated from the cyanation reaction. Tables II and III summarize the picrate and carboxylic acid derivatives from the nitriles.

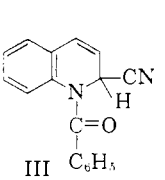
4-Cyanopyridine-1-oxide, when treated with dimethyl sulfate and then potassium cyanide solution, gave 2,4-dicyanopyridine indicating that this reaction sequence may be applied to an N-oxide containing an electron-withdrawing substituent.[6]

This method offers a new route to cyanopyridines, and also an excellent method of preparing cyanoquinolines and isoquinolines. The addition of cyanide ion to the methoxy quaternary salts proceeds readily in aqueous solution, in most cases at temperatures between 0 and 25°. In the pyridine series, product isolation was hampered to some degree by excessive tar formation, although this disadvantage has been overcome to some extent by careful exclusion of air from the reaction vessel.

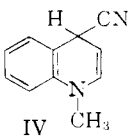
In the quinoline series only 2-substituted derivatives were formed when the 2-position was open; however, when this position was blocked, as in the case of quinaldine, 4-substitution took place with difficulty and in low yield. This is in contrast to the Reissert reaction which fails with quinaldine.[7]

The only other example of the formation of a cyanopyridine by nucleophilic attack of cyanide ion on a pyridinium salt is reported by Ochiai.[8] When 4-chloropyridine-1-oxide was treated under Reissert conditions, 2-cyano-4-chloropyridine was isolated. Although a number of other pyridine-1-oxides were subjected to the same reaction conditions, no other nitriles were isolated.

It is well known that in both the Reissert[9,10] and Kaufmann[11] reactions cyanide ion adds to quinolinium salts to give stable dihydro compounds of the type III and IV, respectively.



III



IV

Although attempts to apply both of these reactions in the pyridine series have been unsuccessful,[10] Karrer[12] recently has isolated VI from V by treatment with cyanide ion.

(1) J. Meisenheimer, *Ann.*, **397**, 273 (1913).

(2) E. Ochiai, M. Katada and T. Naito, *J. Pharm. Soc. Japan*, **64**, 210 (1944); *C. A.*, **45**, 5154 (1951).

(3) A. R. Katritzky, *J. Chem. Soc.*, 2404 (1956).

(4) W. Feely, W. L. Lehn and V. Boekelheide, *J. Org. Chem.*, **22**, 1135 (1957).

(5) V. Boekelheide and W. Feely, THIS JOURNAL, **80**, 2217 (1958).

(6) To test the possibility that cyanide ion might add directly to 4-cyanopyridine-1-oxide, an aqueous solution of potassium cyanide and the N-oxide was heated for a short time. Only isonicotinamide-1-oxide was isolated from the solution.

(7) A. Gassmann and H. Rupe, *Helv. Chim. Acta*, **22**, 1241 (1939).

(8) E. Ochiai and I. Nakayama, *J. Pharm. Soc. Japan*, **65**, 7 (1945).

(9) A. Reissert, *Ber.*, **38**, 1603, 3415 (1905).

(10) The Reissert and related reactions have been reviewed by W. E. McEwen and R. L. Cobb, *Chem. Revs.*, **55**, 511 (1955).

(11) A. Kaufmann, *et al.*, *Ber.*, **42**, 3776 (1906); **44**, 2058 (1911).

(12) M. Marti, M. Viscontini and P. Karrer, *Helv. Chim. Acta*, **39**, 1451 (1956).

TABLE I

CYANOPYRIDINES, QUINOLINES AND ISOQUINOLINE

Abbreviations: E, extraction with $CHCl_3$; D, distillation; F, filtration; R, recrystallization; SD, steam distillation; P, picrate; A, acid; H, hydrochloride.

Products	M.p., °C.	Lit.	Yield, %	Reaction Time, hr.	Reaction Temp., °C.	Isolation	Calcd. C, %	Calcd. H, %	Calcd. N, %	Found C, %	Found H, %	Found N, %	Deriv.[a]
4-Cyanopyridine	80–82	79[a]	32	12	0–10	E, D, R	69.22	3.87	26.91	69.56	4.20	27.01	P, H, A
2-Cyanopyridine	22–25	26[b]	49				—	—	—	—	—	—	—
2-Cyano-6-methylpyridine	71–73	72–74[b]	48	6	10–15	F, R-b.p. 99–106° (30 mm.)	71.17	5.12	23.72	71.11	5.27	23.79	P, A
4-Cyano-2-methylpyridine	46–48	44–46[d]	10		b.p. 125–131°(30 mm.)		—	—	—	—	—	—	—
2-Cyano-4-methylpyridine	89–91	88–89[c]	40	7	10–15	F, R	71.16	5.12	23.72	71.03	5.18	23.71	P
2-Cyano-3-methylpyridine	87–90	87–88[c]	36	6	10–15	F, R	71.16	5.12	23.72	71.15	5.25	23.94	..
2-Cyano-5-methylpyridine	73–75	72–74[c]	6[g]				—	—	—	—	—	—	—
4-Cyano-3-methylpyridine	51–52.5	50–52[c]	6[g]				—	—	—	—	—	—	—
2-Cyano-4,6-dimethylpyridine	55–56	51–52[c]	73	6	20–25	E, D	72.70	6.10	21.20	72.77	6.02	21.23	P
4-Cyano-2,6-dimethylpyridine	77–81	81–82[d]	40	48	25	F, E, D	72.70	6.10	21.20	72.60	6.09	21.43	P, A
2,4-Dicyanopyridine	88–91	....	54	2	0–5	F, R	65.12	2.34	32.55	65.07	2.53	32.21	..
2-Cyanoquinoline	94–96	94[e]	93	4	10–20	F, R	77.91	3.92	18.18	78.22	4.01	17.95	..
2-Cyano-4-methylquinoline	96–98	....	65	6	25	F, R	78.55	4.79	16.66	78.49	4.85	16.90	A
4-Cyano-2-methylquinoline	105–106	....	7.2	12	25–30	SD	78.55	4.79	16.66	78.25	5.04	16.87	A
1-Cyanoisoquinoline	92–93	93[f]	95	4	10–20	F, R	77.91	3.92	18.18	78.02	3.87	18.47	..

[a] Van B. Prijs, A. H. Lutz and H. Erlenmeyer, *Helv. Chim. Acta*, **31**, 571 (1948). [b] G. Mayurnik, A. Moschetto and H. Block, *Ind. Eng. Chem.*, **44**, 1630 (1952). [c] Y. Suzuki, *Pharm. Bull.*, **5**, 13 (1957). [d] E. Ochiai and Y. Suzuki, *ibid.*, **2**, 247 (1954). [e] A. Kaufmann and T. Dandliker, *Ber.*, **46**, 2928 (1913). [f] T. Zincke and F. Krollpfeiffer, *Ann.*, **408**, 338 (1915). [g] These isomers were separated by passing the crude reaction mixture through a 9 ft. 1 in. gas chromatography column packed with 20% *Poly-Tergent* on 30/60 mesh firebrick at 150°. The fractions were collected and recrystallized from ether. H. Meyer, *Monatsh.*, **23**, 437 (1902).

TABLE II

PICRATE DERIVATIVES OF CYANOPYRIDINES

Compound	M.p., °C.	Lit.	Calcd. C, %	Calcd. H, %	Found C, %	Found H, %
4-Cyano-	200–203	230 dec.[a]	43.25	2.12	43.32	2.68
2-Cyano-6-methyl-	105–108	.....	44.96	2.61	45.06	2.80
2-Cyano-4-methyl-	100–102	.....	44.96	2.61	44.69	2.63
2-Cyano-3-methyl-	93– 95	.....	44.96	2.61	44.77	2.68
2-Cyano-4,6-dimethyl-	100–102	.....	46.54	3.07	46.39	3.28
4-Cyano-2,6-dimethyl-	178–181	175.0–177.5[b]	46.54	3.07	46.50	3.30

[a] Van B. Prijs, A. H. Lutz and H. Erlenmeyer, *Helv. Chim. Acta*, **31**, 571 (1948). [b] E. Ochiai and Y. Suzuki, *Pharm. Bull.*, **2**, 247 (1954).

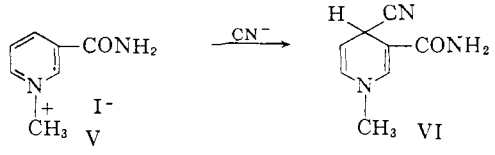
TABLE III

CARBOXYLIC ACIDS DERIVED FROM NITRILES[g]

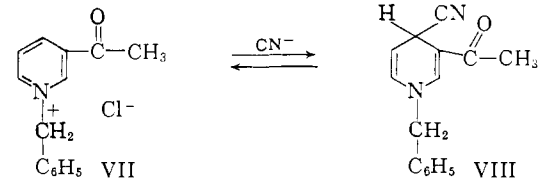
Acid	M.p., °C.	Lit.	Neut. equiv. Calcd.	Neut. equiv. Found
Isonicotinic	307–310	315[a]	123	120
6-Methylpicolinic	129–131	128–129[b]	137	138
2,6-Dimethylisonicotinic	276–280 d.	...[c]	151	153
4-Methylquinaldic	153–155	153–154[d]	187	190
2-Methylcinchoninic	245–249 d.	242[e] 246[f]	187	187

[a] E. Späth and H. Spitzer, *Ber.*, **59**, 1477 (1926). [b] W. Koenigs and G. Happe, *ibid.*, **36**, 2908 (1903). [c] W. Mathes and W. Sauermilch, *ibid.*, **88**, 1276 (1955). [d] W. Koenigs and A. Mengel, *ibid.*, **37**, 1322 (1904). [e] P. Pfitzinger, *J. prakt. Chem.*, **56**, 285 (1897). [f] L. J. Simon, *Ann. chim. phys.*, **9**, 466 (1896). [g] The compositions of the acids were confirmed by analysis.

Anderson[13] has also studied spectral changes in quaternary systems and has obtained VIII from VII.



(13) A. G. Anderson, Jr., and G. Berkelhammer, *J. Org. Chem.*, **23**, 1109 (1958).



Numerous other investigators have proposed cyanodihydropyridine derivatives of pyridinium salts to explain spectral changes that occur when di- and triphosphopyridine nucleotides are treated with cyanide ion.[14–17]

If it is presumed that the first stage of the addition of cyanide ion to the N-alkoxy quaternary salt IX is the formation of the N-alkoxy dihydro compound X, then removal of a proton from X followed by loss of an alkoxide ion would give the nitrile XII. The acidity of hydrogen atoms of this type in Reissert compounds has been demonstrated.[18,19]

(14) O. Meyerhof, P. Ohlmeyer and W. Mahle, *Biochem. Z.*, **279**, 113 (1938).

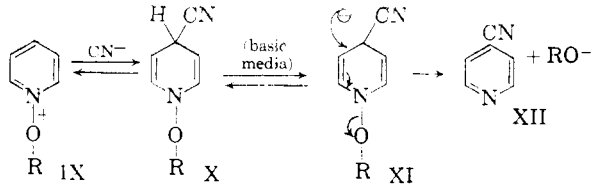
(15) A. San Pietro, *J. Biol. Chem.*, **217**, 579 (1955).

(16) M. R. Lamborg, R. M. Burton and N. O. Kaplan, THIS JOURNAL, **79**, 6173 (1957).

(17) S. P. Colowick, N. O. Kaplan and M. M. Ciotti, *J. Biol. Chem.*, **191**, 447 (1951).

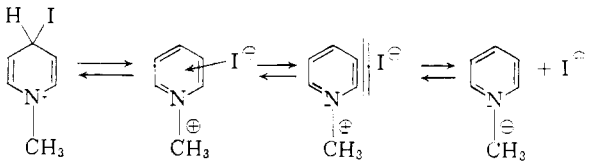
(18) V. Boekelheide and C. Ainsworth, THIS JOURNAL, **72**, 2134 (1950).

(19) V. Boekelheide and C. Liu, *ibid.*, **74**, 4920 (1952).



The driving force of the reaction would be the facile loss of an alkoxide ion with the formation of an aromatic system. No dihydro compounds have as yet been isolated from the reaction mixtures although deep yellow colors have been noted during the early stages of the reactions of the pyridinium salts. Similar colors have previously been associated with dihydro N-alkylpyridine derivatives.[12,13]

Kosower[20] has explained certain spectral changes in solutions of N-methylpyridinium iodide on the basis of a charge transfer complex in equilibrium with both solvent separated ion pairs and dissociated ions.



In order to test the hypothesis that if such a charge transfer complex existed in solutions of N-alkoxypyridinium iodides, a spontaneous reaction might result upon heating which would yield an iodopyridine and an alcohol, *n*-nonyloxypyridinium iodide was heated in aqueous solution. After 3 hours at reflux the salt was recovered unchanged. When the pure iodide was heated at 100°, decomposition to pyridine-1-oxide and *n*-nonyl iodide occurred.

Other aspects and applications of the chemistry of amine oxide salts are being investigated.

Acknowledgment.—The authors are grateful to Drs. W. D. Emmons and B. F. Aycock for their helpful criticisms of the manuscript.

Experimental[21]

Amine Oxides.—The amine oxides were prepared by the method of Ochiai[22] by oxidizing the appropriate heterocyclic base with 30% hydrogen peroxide in glacial acetic acid. When the reaction was complete, the solvent was removed *in vacuo* (10 mm.) upon a steam-bath and the N-oxides were used without further purification.

N-Methoxy Quaternary Methyl Sulfate Salts.—The methoxymethylsulfate salts were prepared directly from the crude N-oxides by treatment with an equimolar quantity of dimethyl sulfate.[23] In all cases the dimethyl sulfate was added slowly to the N-oxide starting at room temperature and, after the initial exothermic reaction, the solutions were heated upon a steam-bath for two hours to ensure complete reaction.

1-Methoxy-2-methylpyridinium Methyl Sulfate.—To 109 g. (1.0 mole) of a powdered 2-picoline-1-oxide slowly was added 126 g. (1.0 mole) of dimethyl sulfate at such a rate that the temperature of the reaction mixture was maintained at 80° throughout the addition. When the addition was complete (about one hour) the solution was heated on a steam-bath for an additional two hours. Upon cooling, the salt crystallized and was recrystallized from anhydrous acetone giving white prisms, melting 57–60°.

Anal. Calcd. for $C_8H_{13}NO_5S$: C, 40.84; H, 5.57; N, 5.96. Found: C, 40.57; H, 5.66; N, 5.63.

1-Methyl-2,6-dimethylpyridinium methyl sulfate was prepared by the same method as 1-methoxy-2-methylpyridinium methyl sulfate using 123 g. (1.0 mole) of 2,6-lutidine-1-oxide and 126 g. (1.0 mole) of dimethyl sulfate. The salt crystallized upon cooling and was recrystallized from anhydrous acetone giving white prisms, melting 95–97°.

Anal. Calcd. for $C_9H_{15}NO_5S$: C, 43.36; H, 6.07; N, 5.62. Found: C, 43.14; H, 6.20; N, 5.49.

1-*n*-Nonyloxypyridinium Iodide (I).—A solution of 24 g. (0.25 mole) of pyridine-1-oxide and 62 g. (0.25 mole) of *n*-nonyl iodide dissolved in 200 ml. of dry acetonitrile was refluxed for 12 hours. Upon cooling the reaction mixture in an ice-bath, crystallization occurred giving 47 g. (55%) of the salt as pale yellow needles, melting 87–90°. This substance was found to be extremely hygroscopic and sensitive to light.

Anal. Calcd. for $C_{14}H_{24}NOI$: N, 4.01. Found: N, 3.87.

Salt II from 1,10-Diiododecane and Pyridine-1-oxide.—A solution of 48 g. (0.50 mole) of pyridine-1-oxide and 78 g. (0.20 mole) of 1,10-diiododecane dissolved in 400 ml. of dry acetonitrile was refluxed for 12 hours. The salt separated from the solution when cool, and upon recrystallization from dry acetonitrile gave orange crystals, melting 118–120° dec.

Anal. Calcd. for $C_{20}H_{30}N_2O_2I_2$: C, 41.11; H, 5.18; N, 4.80. Found: C, 41.28; H, 5.21; N, 4.65.

4-Cyanopyridine. (a) From 1-(*n*-Nonyloxy)-pyridinium Iodide.—To a solution of 19.8 g. (0.30 mole) of potassium cyanide dissolved in 150 ml. of water was added slowly a solution of 35 g. (0.10 mole) of 1-(*n*-nonyloxy)-pyridinium iodide. The yellow color of iodide salt solution was rapidly discharged by this addition and a colorless oil separated from the solution. When the addition was complete (0.5 hour), the mixture was extracted with two 50-ml. portions of ether. The combined ether extract now was washed with two 15-ml. portions of 10% aqueous hydrochloric acid and then with 15 ml. of water. The ether extract next was dried over magnesium sulfate and the ether removed by distillation. The residual oil (13.8 g.) was distilled at atmospheric pressure and the fraction boiling at 210–215° collected, giving 10.5 g. (75%) of *n*-nonyl alcohol, $n^{20}D$ 1.4328.[24]

A portion of the *n*-nonyl alcohol was treated with phenyl isocyanate to give the phenylurethan of *n*-nonyl alcohol, melting 62.5–63.5°.[25]

The combined hydrochloric acid extract was neutralized with sodium carbonate solution and extracted with two 5-ml. portions of ether. The combined ether extract was dried with magnesium sulfate and evaporated, giving 4.4 g. (42%) of crude 4-cyanopyridine. This material was recrystallized three times from water to give a pure sample of 4-cyanopyridine, melting 80–82°. A mixed melting point with an authentic sample[26] of 4-cyanopyridine showed no depression. Furthermore, a comparison of ultraviolet spectra of the two samples showed them to be identical. An infrared comparison of the samples, run as potassium bromide pellets, also showed both samples to be identical.

Picrate.—A small sample of 4-cyanopyridine was dissolved in hot ethanol and treated with excess picric acid. Upon cooling, the picrate separated from the solution as yellow needles, melting 200–203°. A picrate prepared in a similar manner from an authentic sample of 4-cyanopyridine melted at 202–204° and a mixture of the two picrates showed no depression of melting point.

Hydrochloride.—The hydrochloride of 4-cyanopyridine was prepared by dissolving 1 g. of the cyanopyridine in 50 ml. of chloroform. The solution was cooled in an ice-bath and saturated with dry hydrogen chloride. A white, crys-

(20) E. M. Kosower, THIS JOURNAL, **78**, 5700 (1956).

(21) Melting points are uncorrected; analyses by Micro-Tech Laboratories.

(22) E. Ochiai, *J. Org. Chem.*, **18**, 548 (1953); *cf.* V. Boekelheide, *et al.*, THIS JOURNAL, **76**, 1286 (1954); *J. Org. Chem.*, **22**, 589 (1957).

(23) Eastman Organic Chemicals practical grade.

(24) L. M. Ellis, Jr., and E. E. Reid, THIS JOURNAL, **54**, 1678 (1932), report $n^{20}D$ 1.4320.

(25) R. Shriner and R. Fuson, "The Systematic Identification of Organic Compounds," J. Wiley and Sons, Inc., New York, N. Y., 1948, p. 227, report 62°.

(26) Aldrich Chemical Co.

talline hydrochloride separated from the solution. Recrystallization from acetone gave white needles, melting 244–247° with decomposition.[27]

Anal. Calcd. for $C_6H_5N_2Cl$: C, 51.26; H, 3.59. Found: C, 51.52; H, 3.86.

(b) **From the Salt II.**—A solution of 17.4 g. (0.03 mole) of salt II dissolved in 50 ml. of water was added slowly to a solution of 6.6 g. (0.1 mole) of potassium cyanide dissolved in 50 ml. of water at room temperature. The yellow color of the iodide solution was discharged upon addition to the cyanide solution and a white solid separated from the solution. When addition was completed, the solid was separated from the solution by filtration and then recrystallized from a water–ethanol mixture. This yielded 4.3 g. (82%) of 1,10-decanediol, melting 72–74°.[28]

Diacetate.—A solution of the diol in 25 ml. of acetic anhydride was heated on a steam-bath overnight. The solution was evaporated under reduced pressure and the dark residue taken up in a hot water–ethanol mixture. Cooling the solution in an ice-bath gave the diacetate as colorless plates, melting 23–26°.[29]

The aqueous phase was extracted with two 25-ml. portions of ether. The combined extract was dried over magnesium sulfate and evaporated. There remained 2.3 g. (37%) of crude 4-cyanopyridine. A pure sample of the cyanopyridine was obtained by recrystallization from water, melting 79–81°.

(c) **From 1-Methoxypyridinium Methyl Sulfate.**—To a solution of 74 g. (1.5 mole) of sodium cyanide dissolved in 250 ml. of water and cooled to −5° was added slowly a solution of 110 g. (0.5 mole) of 1-methoxypyridinium methylsulfate dissolved in 125 ml. of water over a period of 1 hour. The solution was held between −5 and 0° during the addition and then for 1 hour after the addition was complete. The solution was then allowed to warm slowly to 20° and stirred for 3 hours at which time 250 ml. of chloroform was added. The layers were separated and the aqueous layer was allowed to stand at room temperature overnight and then extracted again with 250 ml. of chloroform. The extracts were dried and the solvent removed giving 37 g. and 10.5 g., respectively, of high boiling residues. The combined residue was distilled at atmospheric pressure and the fraction boiling 200 to 230° collected giving 34 g. (65%) of crude cyanopyridines. A vapor chromatogram showed this mixture contained 20–25% (16% over-all) 4-cyanopyridine and 75–80% (49% over-all) 2-cyanopyridine. Fractional distillation of the mixture gave 10.2 g. of 4-cyanopyridine boiling 208–212° and 19.5 g. of 2-cyanopyridine boiling 220–225°. The first fraction after recrystallization from dilute ethanol gave a sample of 4-cyanopyridine melting 80–82°. A portion of the second fraction was recrystallized from ether and gave a sample of 2-cyanopyridine melting 22–25°.

Cyano-pyridines and -Quinolines.—In general, these nitriles were prepared by the method described above (c) for 4-cyanopyridine. Three examples are described below in detail where there are variations from this procedure. Our initial experiments, described here, were performed in the presence of air (except in the case of 4-cyano-2,6-dimethylpyridine). In all cases, a two- to threefold excess of potassium or sodium cyanide was employed.

4-Cyano-2,6-dimethylpyridine.—To a solution of 23.3 g. (0.1 mole) of 1-methoxy-2,6-dimethylpyridinium methyl sulfate dissolved in 50 ml. of water, and under purified nitrogen, was added a solution of 19.8 g. (0.3 mole) of potassium cyanide dissolved in 75 ml. of water. The solution was allowed to stand at 20° for 2 days at which time the nitrile, which had separated from the solution as long white needles, was removed by filtration, yielding 3.8 g. (29%), melting 80–82°. The filtrate was extracted with two 50-ml. portions of ether which, after drying and evaporating, gave an additional 1.5 g. (11%) of nitrile, melting 77–81°. Sublimation at 50° (760 mm.) gave white needles, melting 83–85°.

4-Cyano-2-methylquinoline.—A solution of 143 g. (0.5 mole) of 1-methoxy-2-methylquinolinium methyl sulfate dissolved in 200 ml. of water was added slowly to a solution of 49 g. (1.0 mole) of sodium cyanide dissolved in 200 ml. of water. The temperature of the reaction mixture was maintained between 25 and 30° throughout the addition. When the addition was complete (1.5 hours), the solution was stirred overnight at room temperature. The dark solid was suspended in 200 ml. of water and steam distilled. A white solid crystallized from the distillate. Recrystallization of the solid gave 6 g. (7.2%) of 4-cyano-2-methylquinoline as white silky needles, melting 105–106°.

2,4-Dicyanopyridine.—To 26 g. (0.25 mole) of 4-cyanopyridine-1-oxide was added slowly 31.5 g. (0.25 mole) of dimethyl sulfate. The solution was heated at 100° for 3 hours and the resulting 1-methoxy-4-cyanopyridinium methyl sulfate was obtained as a thick red oil. This oil was taken up in 100 ml. of water, whereupon 8 g. (0.077 mole) of 4-cyanopyridine-1-oxide separated from the solution. The oxide was removed by filtration and the filtrate, containing 0.173 mole of the methoxy salt, was added slowly to a solution of 33 g. (0.5 mole) of potassium cyanide dissolved in 100 ml. of water. The addition was made at such a rate that the temperature of the reaction mixture varied between 0 and 5°. When the addition was complete, the solution was allowed to stand at room temperature for one hour, and the solid which had separated was filtered and recrystallized from water. There was obtained 11.8 g. (54%) of 2,4-dicyanopyridine, melting 88–91°.

PHILADELPHIA 37, PENNA.

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[CONTRIBUTION FROM THE MERCK, SHARP & DOHME RESEARCH LABORATORIES, DIVISION OF MERCK & CO., INC.]

Coenzyme Q. VII. Isolation and Distribution of Coenzyme Q_{10} in Animal Tissues

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The isolation of coenzyme Q_{10} from beef hearts has been confirmed and extended. Crystalline Q_{10} has been isolated from human hearts and beef striated muscle. Q_{10}, identified by spectra and R_f's, has also been found in the mouse carcass, in the kidney tissue of steers and lambs and in the heart tissue of swine, rats, chicks, turkeys and rabbits.

The isolation of a crystalline substance melting at 48–49° was described first in 1957 by Crane, *et al.*;[1] it was then recognized as a quinone (Q-275)[2] and is now designated coenzyme Q_{10}.[1-4] The original source used by these investigators was mitochondria from beef heart, but later work omitted the preparation of mitochondria.

(1) F. L. Crane, Y. Hatefi, R. L. Lester and C. Widmer, *Biochim. et Biophys. Acta*, **25**, 220 (1957).

(2) F. L. Crane, R. L. Lester, C. Widmer and Y. Hatefi, *ibid.*, **32**, 73 (1959).

(3) R. L. Lester, F. L. Crane and Y. Hatefi, THIS JOURNAL, **80**, 4751 (1958).

(4) Coenzymes Q_6, Q_7, Q_8, Q_9 and Q_{10}, members of the coenzyme Q family, are homologs which differ only in the number of isoprenoid units in the side chain. The number of these units is indicated by the subscript; see ref. 3.