Preparation of C^{14}-Cyanide from C^{14}-Carbonate[1]

BY J. A. MCCARTER

The importance of cyanide in the synthesis of organic compounds labeled with isotopic carbon requires that it be made available in high yields by simple and inexpensive procedures starting with carbonate. Several methods[2-6] have been described for the conversion of carbonate to cyanide but each is somewhat unsatisfactory when judged by the above standards. The procedure used in this Laboratory is based on the finding by Hood and Salamon[7] that sodium cyanide can be obtained by heating a mixture of sodium carbonate and zinc dust in a stream of ammonia gas. Work in this Laboratory has shown that it is likely that a thermal decomposition product of ammonia rather than ammonia itself is involved in the reaction because it has been found necessary to pass the ammonia over hot iron before passing it over the mixture of alkali carbonate and zinc. An average yield of the order of 90% of theory can be obtained by using potassium carbonate instead of sodium carbonate and by following the procedure described in this communication.

Experimental.—Powdered anhydrous C^{14}-potassium carbonate (0.001 mole) was thoroughly mixed with approximately 1 g. of zinc dust (Reagent grade) and the mixture was transferred to a porcelain combustion boat (Coors Size 2). The boat was then placed in a Vycor combustion tube (750 mm. in length and 19 mm. inside diameter) containing 3–4 g. of iron wire (0.01 inch diameter "for standardizing") in the form of a loose ball occupying the mid-portion of the tube. The boat was pushed into the tube until it touched the iron wire.

The end of the tube nearest the iron wire was connected to an apparatus for the preparation of dry ammonia gas. The other end was attached to a glass tube dipping beneath the surface of water in a test-tube in order to serve as an indicator of the rate of flow of the gas. Ammonia was prepared by warming concd. ammonium hydroxide and dried by passing through two towers of calcium oxide and one of sodium hydroxide pellets. A stream of ammonia was allowed to flow through the tube and when the air in the apparatus had been displaced the central portion of the combustion tube (that part occupied by the boat and iron wire) was heated electrically at 650° for 4 hours. During this time the flow of gas was maintained at a rapid rate but not so rapid as to force water out of the test-tube. The flow of ammonia was continued while the tube was allowed to cool to room temperature.

The boat and its contents were then transferred to an apparatus for the distillation of hydrogen cyanide. The boat was placed in a suitable erlenmeyer flask connected to a water-cooled condenser and 25 ml. of water was added. The tip of the condenser dipped below the surface of an excess (20%) of the theoretical amount of 1 *N* sodium or potassium hydroxide. The contents of the flask was then acidified by the addition of 2 *N* sulfuric acid and was heated gently until 15 to 20 ml. of distillate had been collected. The alkaline cyanide solution was then evaporated to dryness *in vacuo*[5] or used directly.

Analysis by the argentimetric method of the distillate obtained in several experiments showed yields of 88–93% of theory with an average yield of 90%. The specific activity of C^{14}-labeled cyanide prepared by this procedure was unchanged from that of potassium carbonate used as the starting material. C^{14}-Labeled potassium carbonate was readily obtained by passing $C^{14}O_2$ into a slight excess of 4 *N* potassium hydroxide and evaporating the solution to dryness.

The yield of cyanide was decreased by heating the reaction mixture below 630° or over 670°. It was found that the conversion could be accomplished in higher yields in an iron tube but the product thus obtained was less pure than that obtained using the procedure described in this communication.

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(1) The investigation was supported by research grants from the Medical Research Division, National Research Council of Canada.

(2) Cramer and Kistiakowsky, *J. Biol. Chem.*, **137**, 547 (1941).

(3) Adamson, THIS JOURNAL, **69**, 2564 (1947).

(4) Abrams, *ibid.*, **71**, 3835 (1949).

(5) Belleau and Heard, *ibid.*, **72**, 4268 (1950).

(6) Loftfield, *Nucleonics*, 1, 54 (1947).

(7) Hood and Salamon, *Chem. Zentr.*, **66**, I, 670 (1895).

N,N-Disubstituted Amidines. IV. Heterocyclic Amidines and Cinnamamidines[1]

BY EMIL LORZ, LEWIS P. ALBRO[2] AND RICHARD BALTZLY

The compounds reported in this note were prepared in the prosecution of leads developed in our earlier work on amidines.[3] Compound LXVII[4] was synthesized in the expectation that it would have antihistaminic properties—an expectation that was not fulfilled. The other substances fall into three classes.

(a) **Cinchoninamidines.**—Compounds LXI–LXIII are variations of a type (Compounds XIV–XX) previously reported.[3a] As compared to N,N-di-*n*-hexylcinchoninamidine (XVIII) the chlorine substitution has little effect on potency; the 2-butoxy group increases toxicity and probably potency, without certain advantage.[5]

(b) **Nicotinamidines.**—Since N,N-di-*n*-butylnicotinamidine (LXIV) showed fair activity as an injection anesthetic (about eight times that of Procaine) though impotent when applied topically, Compounds LXV and LXVI were prepared in the hope of finding increased potency combined with the rather low toxicity of the parent substance. Toxicities remained low but the potencies did not increase.

(c) **Cinnamamidines.**—The unsubstituted cinnamamidine (VIII) first reported[3a] had considerable local anesthetic activity (14 times that of cocaine topically, 13 times that of Procaine by injection). Compounds LXVIII–LXX were synthesized to ascertain the effect of alkoxyl substitution. The results with the three substances were fairly consistent. All were more potent than the parent amidine topically and less active by injection. Compounds VIII and LXIX are about equally toxic (LD_{50}, 24 and 30 mg./kg. in mice) while LXVIII and LXX were considerably less so (LD_{50}, 68 and 124 mg./kg.). Work on this series was discontinued in part because all the methoxy cinnamamidines showed a considerable lag in the onset of anesthesia and in part because the necessary intermediates were relatively expensive to prepare.

(1) The work here reported is part of a joint research carried out in collaboration with a pharmacological group in these laboratories.

(2) Biochemical Research Foundation, Academy St., Newark, Delaware.

(3) Lorz and Baltzly, THIS JOURNAL, (a) **70**, 1904 (1948); (b) **71**, 3992 (1949); (c) **73**, 93 (1951).

(4) The Roman numerals refer to the compounds listed in Table I, numbering being consecutive with that of our earlier papers.

(5) Potencies of several of these substances are indicated in an approximate fashion in Table II. The expressions of potency are the same as those employed in our third paper (ref. 3c) and the remarks made there as to the significance that can be attached to local anesthetic tests on laboratory animals apply also to the compounds of the present paper.

TABLE I

HETEROCYCLIC AND CINNAMAMIDINE HYDROCHLORIDES, R—C(=NH)—NR'R''·HCl

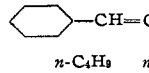
Compd. no.	R	—NR'R''	Method of isolation	Yield, %[a]	M. p., °C.[b]	Empirical formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
LXI	2-$C_4H_9(n)OC_9H_5N$[c]	$-N(C_4H_9)_2(n)$	B	79	197	$C_{22}H_{33}N_3O\cdot HCl$	67.41	67.50	8.74	8.88
LXII	6-Cl-C_9H_5N[c]	$-N(C_6H_{13})_2(n)$	C	81	216[d]	$C_{22}H_{32}ClN_3\cdot 2HCl$	59.12	59.35	7.67	7.37
LXIII	6-Cl-C_9H_5N[c]	n-$C_4H_9NC_6H_4OCH_3$-2	B'	74[e]	240[f] (dec.)	$C_{21}H_{22}ClN_3O\cdot HCl$	62.38	62.62	5.73	6.01
LXIV	3-C_5H_4N[g]	$-N(C_4H_9)_2(n)$	A	84[h]	139	$C_{14}H_{23}N_3\cdot HCl$	62.32	62.45	8.97	9.02
LXV	3-C_5H_4N[g]	$C_2H_5NCH_2C_6H_5$	A'	70[i]	153	$C_{15}H_{17}N_3\cdot HCl$	65.34	65.23	6.53	6.37
LXVI	3-C_5H_4N[g]	$CH_3NC_{10}H_7(\alpha)$	C	80[j]	242 (dec.)	$C_{17}H_{15}N_3\cdot HCl$	68.57	68.36	5.38	5.52
LXVII	9-$C_{13}H_8N$[k]	$CH_3N(CH_2CH_2)_2N$	B'	75[j]	250 (dec.)	$C_{19}H_{20}N_4\cdot 2HCl\cdot 2H_2O$[l]	55.18	54.75	6.34	6.48
LXVIII	4-$CH_3OC_6H_4CH{=}CH$	$-N(C_4H_9)_2(n)$	C	81[j]	215	$C_{18}H_{28}N_2O\cdot HCl$	66.56	66.20	8.94	8.88
LXIX	2,5-$(CH_3O)_2C_6H_3CH{=}CH$	$-N(C_4H_9)_2(n)$	C	80	192	$C_{19}H_{30}N_2O_2\cdot HCl$	64.32	64.34	8.74	8.65
LXX	3,4-$(CH_3O)_2C_6H_3CH{=}CH$	$-N(C_4H_9)_2(n)$	C	60	186	$C_{19}H_{30}N_2O_2\cdot HCl$	64.32	64.28	8.74	8.76

[a] Yields are calculated on the basis of the quantities of nitrile used and, unless otherwise stated, of crude hydrochloride isolated. [b] Melting points below 220° are corrected. [c] 4-Quinolyl radical. [d] A presumably pure but unanalyzed monohydrochloride melted at 187°. [e] The yield of pure hydrochloride was 57%. [f] The dihydrochloride melts at 227°. *Anal.* Calcd. for $C_{21}H_{22}ClN_3O\cdot 2HCl$: C, 57.22; H, 5.49. Found: C, 56.95; H, 5.41. [g] Pyridyl radical. [h] Yield of base b. p., 148° (1 mm). The yield of purified hydrochloride was 74%. [i] Yield based on purified hydrochloride. [j] Yield reckoned on quantity of crude base. [k] Acridyl radical. [l] The anhydrous salt is extremely hygroscopic. The hydrate lost weight equivalent to the calculated water content when dried at 75° and 0.0005 mm. pressure.

For several of the cinchoninamidines and cinnamamidines titration curves were determined in 50% methanol.[3b] The values for pK_a so obtained are shown in Table II together with those for some related amidines prepared earlier. The cinnamamidines are stronger bases than analogous benzamidines and their basicity is relatively unaffected by ring substitution.

TABLE II

LOCAL ANESTHETIC POTENCIES AND ACID DISSOCIATION CONSTANTS OF CINCHONINAMIDINE AND CINNAMAMIDINE HYDROCHLORIDES

Substitutions	R'	R''	pKa in 50% methanol	Compd. no.	Potency as local anesthetic
 —C(=NH)—NR'R''·HCl Cinchoninamidine hydrochlorides					
None	C_2H_5	C_2H_5	10.14	XIV	—[a]
None	n-C_3H_7	n-C_3H_7	9.81	XV	—[a]
None	n-C_4H_9	n-C_4H_9	9.85	XVI	+
None	n-C_6H_{13}	n-C_6H_{13}	9.65	XVIII	+++
2-n-C_4H_9O	n-C_4H_9	n-C_4H_9	11.13	LXI	+++
6-Cl	n-C_6H_{13}	n-C_6H_{13}	9.21	LXII	+++
6-Cl	n-C_4H_9	o-$CH_3OC_6H_4$	8.60	LXIII	++
 —CH=CH—C(=NH)—NR'R''·HCl, Cinnamamidine hydrochlorides					
None	n-C_4H_9	n-C_4H_9	11.69	VIII	++
4-CH_3O	n-C_4H_9	n-C_4H_9	11.60	LXVIII	+++
3,4-$(CH_3O)_2$	n-C_4H_9	n-C_4H_9	11.60	LXX	+++

[a] Potency less than 0.1 that of cocaine.

The cinchoninamidines are considerably weaker bases than α-naphthamidines,[3c] an effect that could be expected from the known influence of the cyclic nitrogen. This effect seems to be largely abolished in the 2-butoxycinchoninamidine (LXI). This is formally a cyclic imido-ether and it would appear that the imido-ether resonance overcomes the electron-withdrawing tendencies of the ring nitrogen. The drift toward weaker basicity with increase in size of the N-alkyl groups (XIV–XVIII) has been checked carefully and appears to be real. We have no parallel figures for other series with which to compare these results.

Experimental

The additions of bromomagnesium secondary amides to the appropriate nitriles were carried out by the methods described previously.[3a] The yields and properties of the resultant amidines are shown in Table I, the methods of isolation (A, A', B, etc.) referring to the procedures of our earlier papers.[3a,3b] The amidine hydrochlorides were crystallized from absolute ethanol or from ethanol–ether mixtures.

Nitriles.—Acridine-9-nitrile was prepared by the method of Lehmstedt and Dostal,[6] 2-butoxy-4-cyanoquinoline by that of Wojhan.[7]

The 6-chlorocinchoninonitrile[8] required for Compounds LXII and LXIII was obtained through a sequence of reactions analogous to that of the familiar 4-cyanoquinoline synthesis.[9]

Two of the intermediates appear to be new.

6-Chloro-1-methylquinolinium Methylsulfate.—This was formed in 93% yield by the methylation of 6-chloroquinoline with methyl sulfate in benzene. It forms rather deliquescent crystals melting at 161°.

Anal. Calcd. for $C_{11}H_{12}ClNO_4S$: C, 45.60; H, 4.18. Found: C, 46.04; H, 4.42.

6-Chloro-4-cyanoquinoline Methiodide.—The 6-chloro-1-methylquinolinium methylsulfate was converted in 95% yield to 6-chloro-4-cyano-N-methylquinoline by the action of potassium cyanide in water. The rather unstable dihydro compound was oxidized by alcoholic iodine solution in the presence of pyridine to the stable 6-chloro-4-cyanoquinoline methiodide. Recrystallized from water this forms garnet-colored plates, m.p. 199.5°. The yield of purified salt from this step was 54%.

Anal. Calcd. for $C_{11}H_6ClIN_2$: C, 39.96; H, 2.44. Found: C, 40.00; H, 2.59.

Conversion to 6-chloro-4-cyanoquinoline was accomplished in 80% yield by heating the methiodide at 220–240° *in vacuo* in a flask sealed to a long vertical condenser leading into a filtering flask containing 3 *N* hydrochloric acid. The sublimed product was dissolved out of the condenser with dilute hydrochloric acid and the liberated base was crystallized from ethanol.

Cinnamonitriles.—The methods of preparation used were rather unsatisfactory. The greatest loss appeared to be in the distillation of the nitriles which was at 1 mm. pressure. It is probable that better results could be obtained by using high vacuum for this step. The yield of 4-methoxycinnamonitrile by the dehydration of the amide with thionyl chloride in benzene was 58% (after distillation and recrystallization from alcohol). That of 3,4-dimethoxycinnamonitrile was only 22%.

3,4-Dimethoxycinnamide, m.p. 166.5°. *Anal.* Calcd. for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32. Found: C, 64.20; H, 6.20.

(6) Lehmstedt and Dostal, *Ber.*, **72**, 806 (1939).

(7) Wojhan, *Arch. Pharm.*, **274**, 100 (1936).

(8) Work, *J. Chem. Soc.*, 426 (1942).

(9) Kaufmann and Widmer, *Ber.*, **44**, 2062 (1911); Ainley and King, *Proc. Roy. Soc.* (*London*), **B125**, 70 (1938).

3,4-Dimethoxycinnamonitrile, m.p. 98°. *Anal.* Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.82. Found: C, 69.99; H, 5.72.

2,5-Dimethoxycinnamonitrile.—The sodium salt of 2,5-dimethoxybenzylidenepyruvic acid was obtained by condensing 2,5-dimethoxybenzaldehyde with sodium pyruvate in aqueous methanol in the presence of alkali (50% more sodium hydroxide than required to neutralize the pyruvic acid).[10] The crude sodium salt was converted to the oxime which was dehydrated by heating with acetic anhydride. After distillation the yield was about 20%. The nitrile crystallizes in needles from methanol and melts at 75°. *Anal.* Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.82. Found: C, 69.84; H, 5.72.

The authors wish to express their gratitude to Mr. Samuel Blackman for the micro-analyses here reported.

(10) *Cf.* Erlenmeyer, *Ber.*, **37**, 1318 (1904).

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Solubility of Nitroguanidine in Water

BY WILLIAM MCBRIDE, RONALD A. HENRY, JOSEPH COHEN AND SOL SKOLNIK

The approximate solubility of nitroguanidine, $NH_2C(NH)NHNO_2$, in distilled water at 25 and 100° has been given by Davis,[1] and at 19.3 and 100° by Thiele.[2] More exact determinations at 19.5, 50 and 100° have been reported by Desvergnes.[3] These determinations are not in good agreement, however, since they show a variation of almost 25% at 100° (see Fig. 1). Because of this divergence and because of the lack of data at the intermediate temperatures, the solubility of this compound in water has been carefully remeasured.

The results are plotted in Fig. 1. In the range 30 to 70°, the solubility can be expressed with an accuracy of 0.3% by the equation

$$\log(\text{solubility in g./100 g. of water}) = -1963.2/T + 6.1255$$

calculated from the data by the method of least squares. The *p*H of the solutions after equilibrium was attained varied between 6.7 and 7.0, measured at 25°. Above 70° the solubility can be expressed with an accuracy of 1.3% by the equation

$$\log(\text{solubility in g./100 g. of water}) = -2167.0/T + 6.7215$$

In this higher temperature range, because of the autocatalytic hydrolysis of nitroguanidine, the solutions become alkaline and the *p*H (25°) varied from 7.0 to 7.3, except for two determinations at 89 and 95° in which the *p*H increased to 8.3. It was noted that the *p*H of a saturated solution of nitroguanidine increased from 6.6 to 8.3 after one hour at 94.7°, or to 8.8 after 5.5 hours at 88.8°. Since nitroguanidine is amphoteric,[2,4] its solubility will increase as the solution becomes more alkaline. The variations in the solubility, as reported for 100°, could be explained if no control had been maintained over the *p*H of the solutions, or if long periods of time had been allowed for solution equilibrium to be reached. Extrapolation of the present data to 100° gives a solubility of 8.22 g./100 g. of water, lower than the previously reported values.

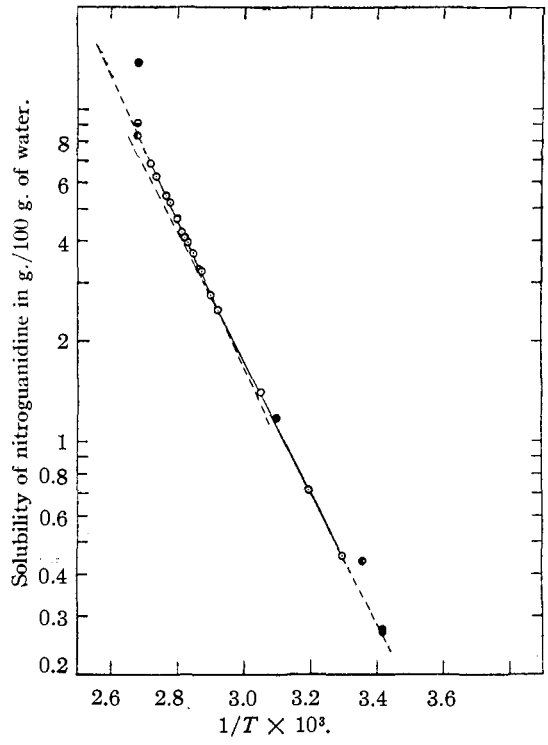

Fig. 1.—The solubility of nitroguanidine in water as a function of temperature: ⊙, present determination; ◐, Davis; ◒, Thiele; ●, Desvergnes.

From a statistical analysis of the data it can be concluded that the change in slope of the solubility curve is probably continuous throughout the range 30 to 100°, and that there is no justification for assuming a sharp inflection and a phase change at the temperature corresponding to the intersection of the two linear equations. The absence of a change of phase in this temperature range has also been confirmed experimentally by means of thermal differential analysis, dilatometric studies and X-ray studies.

Experimental

The nitroguanidine was a sample of commercial material that had been recrystallized twice from water (50 g./liter). Since the melting point of nitroguanidine is not a good criterion of purity, several attempts were made to determine its purity by the method of phase analysis.[5] Although the results were not completely satisfactory, they indicated a purity of better than 99.5%.

For the solubility determination, 2 to 10 g. of nitroguanidine was suspended in 125 ml. of distilled water, and the solution brought to equilibrium with stirring. Below 70°, 2 to 17 hours, depending on the particular temperature, were allowed for equilibrium to be reached; above 70°, one-half to one hour was allowed. Below 85°, equilibrium was approached from both the hot and cold sides; above 85°, from the hot side only. Fifteen- to 25-g. samples of the solution were removed by pressure filtration through a fine pored, sintered Pyrex glass disk into a receiver which was an integral part of apparatus immersed in the bath. Adequate precautions were taken to prevent evaporation losses during the sampling. The samples were sealed, cooled, weighed and evaporated to dryness in a vacuum desiccator at room temperature so as to avoid hydrolysis. Final drying to constant weight of solute was accomplished by heating at 100° for one to two hours. The average deviation for duplicate determinations below 85° was 2.2 parts per 1000;

(1) Davis, "Chemistry of Powder and Explosives," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 381; also see Davis, THIS JOURNAL, **47**, 1063 (1925).

(2) Thiele, *Ann.*, **270**, 18 (1892); also see Pritchard and Wright, *Can. J. Research*, **25F**, 257 (1947).

(3) Desvergnes, *Rev. chim. ind.*, **38**, 265 (1929).

(4) Hahn, Pribyl, Lieber, Caldwell and Smith, THIS JOURNAL, **66**, 1223 (1944).

(5) Webb, *Ind. Eng. Chem., Anal. Ed.*, **20**, 100 (1948).