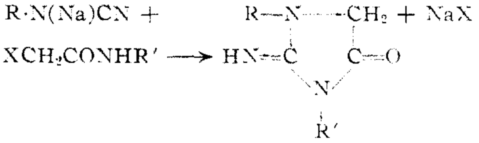
The Preparation of Glycocyamidines from Substituted Cyanamides

By Erick I. Hoegberg and Pierrepont Adams

The chemical synthesis of substituted glycocyamidines by various modifications utilizing glycine derivatives as starting materials has been reported by several investigators.[1-5] A new route to these compounds was discovered during a study of the reactions of sodium arylcyanamides, when it was found that the latter reacted with haloacetamides to yield glycocyamidines in good yields



Several glycocyamidines carrying phenyl or *p*-chlorophenyl substituents in the 1-position were synthesized by means of this reaction, and in addition the *n*-octyl homolog of creatinine was prepared by allowing sodium *n*-octylcyanamide to react with chloroacetamide. When N-substituted α-haloacetamides were used, glycocyamidines substituted in the 3-position were produced.

Experimental

Cyanamides.—Phenylcyanamide,[6] 4-chlorophenylcyanamide,[7] and *n*-octylcyanamide[8] were prepared by methods appearing in the literature. They were converted to their sodium salts by dissolving in one equivalent of aqueous sodium hydroxide or by reaction with one equivalent of methanolic sodium methoxide in an inert organic solvent such as benzene, followed by removal of the organic solvent.

Glycocyamidines.—A solution of equimolecular proportions of an α-haloacetamide and the sodium salt of a monosubstituted cyanamide in a suitable solvent was prepared. The mixture was then either heated to reflux for several hours or allowed to stand at room temperature for several days. When the solvent was water, reaction at room temperature was preferred in order to avoid hydrolysis. If the product precipitated from the reaction mixture, it was isolated by filtration and washed free of sodium halide with water; if the product remained in solution, the solution was evaporated to dryness and the residue washed with water. The glycocyamidines produced were further purified by recrystallization.

The α-haloacetamides used were chloroacetamide, α-chloroacetanilide,[9] α-bromo-N-*n*-octylacetamide,[10] and α-chloro-4-nitroacetanilide.[11] The products prepared and the experimental details are listed in Table I.

The preparation of 1-phenylglycocyamidine was typical of the series: chloroacetamide (9.4 g., 0.1 mole) was dissolved in a solution of sodium phenylcyanamide (14 g., 0.1 mole) in water (100 ml.) and the clear solution was allowed to stand at room temperature. After 48 hours a nearly colorless, crystalline solid had separated from the reaction mixture. This was filtered and dried in a 65° oven, yield 9 g. (51%), m.p. 235–240° (dec.). Recrystallization from 2B ethanol (400 ml.) gave 5 g. of colorless plates, m.p. 239–243° (dec.). Comparable or better yields of 1-phenylglycocyamidine were obtained by refluxing for several hours in an organic solvent as the reaction medium in place of water: acetone (52% yield), ethyl acetate (71%), and acetonitrile (61%).

Table I

Glycocyamidines Prepared

Glycocyamidine	Reaction solvent	Time, hours	Temp., °C.	Yield, %	M.p.,[a] °C.	Analyses, % Calcd.	Found
1-Phenyl	Water[b]	48	25	51	239–243 (dec.)[c,d]	N 24.0	23.8
1,3-Diphenyl	Acetone	48	25	87	164–165[e]	N 16.7	16.8
1-Phenyl-3-*n*-octyl	Ethanol	2	Reflux	28	86–88[f]	N 14.6	14.8
1-Phenyl-3-*p*-nitrophenyl	Ethanol	3	Reflux	78	271–273[g]	N 18.9	18.9
1-*p*-Chlorophenyl	Water	48	25	67	275–278 (dec.)[h]	N 20.0	20.2
1-*n*-Octyl	Acetone	2	Reflux	64	239–244 (dec.)[i]	N 19.9	20.4

[a] Uncorrected. [b] Also prepared using acetone, ethyl acetate, and acetonitrile, respectively, as reaction media. [c] Ellinger and Matsuoka[1] report 235–236° (dec.). [d] Colorless plates from ethanol. [e] Colorless needles from acetone. [f] Colorless crystals, twice recrystallized from methanol. *Anal.* Calcd.: C, 71.1; H, 8.71. Found: C, 71.1; H, 8.87. [g] Yellow crystals from acetone. *Anal.* Calcd.: C, 60.8; H, 4.05. Found: C, 60.8; H, 4.25. [h] Tan crystals from acetone. *Anal.* Calcd.: Cl, 17.6. Found: Cl, 17.6. [i] Colorless crystals from ethanol.

Acknowledgment.—The authors are indebted to the staff of the Analytical and Testing Division for the analyses reported herein and to Dr. J. T. Cassaday for his helpful advice and encouragement.

---

(1) A. Ellinger and Z. Matsuoka, *Z. physiol. Chem.*, **89**, 441 (1914).

(2) T. B. Johnson and B. H. Nicolet, This Journal, **37**, 2416 (1915).

(3) E. Abderhalden and H. Sickel, *Z. physiol. Chem.*, **173**, 51 (1928).

(4) H. King, *J. Chem. Soc.*, 2374 (1930).

(5) J. F. Deck and F. B. Dains, This Journal, **55**, 4986 (1933).

(6) J. L. Osborne and G. Barsky, U. S. Patent 1,611,941, issued December 28, 1926.

(7) H. L. Bami, B. H. Iyer and P. C. Guha, *Science and Culture*, **12**, 448 (1947); *C. A.*, **41**, 4463i (1947).

(8) W. P. Ericks and P. P. McClellan, U. S. Patent 2,331,670, issued October 12, 1943.

(9) W. A. Jacobs and M. Heidelberger, This Journal, **39**, 1439 (1917).

(10) W. E. Weaver and W. M. Whaley, *ibid.*, **69**, 515 (1947).

(11) W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 103 (1915).

American Cyanamid Company
Stamford, Conn.

Received January 29, 1951

Preparation of Propane-1-C^{13}. Electroreduction of Acetone to Propane[1]

By Alvin S. Gordon and Sheldon Heimel

Propane-1-C^{13} has been synthesized using BaC^{13}O$_3$ as the source of C^{13}. Starting with about 45 millimoles of BaC^{13}O$_3$ a 67.5% yield of propane-1-C^{13} based on C^{13}O$_2$ was obtained. The propane is 98–99.3% pure. The following steps were employed[2]

---

(1) This research is part of the work being done at the Bureau of Mines on Contract NA onr 25-47, supported by the Office of Naval Research and the Air Materiel Command.

(2) For complete experimental details order Document 3210 from American Documentation Institute, 1719 N St., N.W., Washington 6, D. C., remitting $1.00 for microfilm (images 1 inch high on standard 35 mm. motion picture film) or $1.00 for photocopies (6 × 8 inches) readable without optical aid.

$$C^{13}O_2 + EtMgI \longrightarrow CH_3CH_2C^{13}OOH \qquad (1)$$

$$CH_3CH_2C^{13}OOH \xrightarrow{LiAlH_4} CH_3CH_2C^{13}H_2OH \qquad (2)$$

$$CH_3CH_2C^{13}H_2OH \xrightarrow{P + I_2} CH_3CH_2C^{13}H_2I \qquad (3)$$

$$CH_3CH_2C^{13}H_2I \xrightarrow[\text{Couple}]{\text{Cu-Zn}} CH_3CH_2C^{13}H_3 \qquad (4)$$

Ordinary propane of almost 100% purity has been prepared from acetone in 70% yield by electrolytic reduction. This reaction may be useful in preparing propane-2-C^{13} since $CH_3C^{13}OCH_3$ has been prepared starting with $BaC^{13}O_3$ in 89% yield by Grosse and Weinhouse.[3]

[3] Grosse and Weinhouse, *Science*, **104**, 402 (1946).

U. S. BUREAU OF MINES
4800 FORBES STREET
PITTSBURGH 13, PENNA.
RECEIVED DECEMBER 4, 1950

Study on the Relation between *p*H of Ion Exchange Resin Phase and the Composition of Solution at Equilibrium

BY MASATAKE HONDA

An essential investigation in ion exchange reactions is a study of the activities of the ions adsorbed by the ion exchange resin. In this work the hydrogen ion activity (*p*H) in the resin phase was determined with appropriate *p*H indicators which were adsorbed as ions.

The experimental data presented in this paper as well as in previous work[1,2] involve the following considerations.

(1) It is assumed that the exchange reaction is purely ionic. The interior of the resin phase is taken as a homogeneous system analogous to a solution. The equilibrium condition for exchange between two ions has been frequently explained by the membrane equilibrium condition,[3] namely, that the chemical potentials of any component in the resin and liquid phases should be equal at equilibrium. Thus for such components as HA, MOH, MA or H_2O where A and M are monovalent anions and cations, respectively, it is true that

$$a_{\mathrm{Hr}}a_{\mathrm{Ar}} = a_{\mathrm{Hs}}a_{\mathrm{As}} \qquad (1a)$$

$$a_{\mathrm{Mr}}a_{\mathrm{OHr}} = a_{\mathrm{Ms}}a_{\mathrm{OHs}} \qquad (1b)$$

$$a_{\mathrm{Mr}}a_{\mathrm{Ar}} = a_{\mathrm{Ms}}a_{\mathrm{As}} \qquad (1c)$$

$$a_{\mathrm{Hr}}a_{\mathrm{OHr}} = a_{\mathrm{Hs}}a_{\mathrm{OHs}} = K_{\mathrm{w}} \qquad (1d)$$

where a_{Hr} is the activity of hydrogen ion in the resin phase and a_{Hs}, the activity in the solution, and so on.

(2) The adsorption of an acid (anion) or alkali (cation) by the resin can be considered as a neutralization reaction which takes place in the resin phase. When any exchange resin has adsorbed a definite amount of an ion at equilibrium, *i.e.*, when the activity of the adsorbed ion is at a definite value, the *p*H in the resin phase should take a fixed value. The presence of a small amount of neutral salt hardly influences the *p*H and the salt concentration in the resin phase is always lower than in solution.[3] This negative adsorption can be attributed to the higher concentration of the common adsorbed ion in the resin phase according to (1c). For an anion exchange resin this leads to

$$a_{\mathrm{Hr}} = f_1(a_{\mathrm{Ar}}) \qquad (2a)$$

or for a cation exchange resin

$$a_{\mathrm{Hr}} = f_2(a_{\mathrm{Mr}}) \qquad (2b)$$

From 1 and 2

$$a_{\mathrm{Ar}} = f_3(a_{\mathrm{Hs}}a_{\mathrm{As}}) \qquad (3a)$$

$$a_{\mathrm{Mr}} = f_4(a_{\mathrm{Ms}}a_{\mathrm{OHs}}) = f_5(a_{\mathrm{Hs}}/a_{\mathrm{Ms}}) \qquad (3b)$$

where a_{Ar} and a_{Mr} are determined by the amount of adsorption.

In a previous study[1] a weak anion exchange resin (*m*-phenylenediamine-HCHO, cyanamid type) was used. In the presence of a salt of the anion it was found that at equilibrium the amount of adsorption (exchange capacity of the anion in m. eq./g.) was determined by the product of the activities of the hydrogen ion and anion in solution, *i.e.*, (3a) is obeyed.

For the adsorption of acetate ion in the presence or absence of 0.002, 0.02 or 0.2 *N* sodium acetate, the relation between *p*H − log a_{acetate} in the solution and the amount of adsorption in the range 0.2 to 3 m. eq./g. obeyed (3a). Here the value of $a_{\mathrm{Hs}}a_{\mathrm{As}}/a_{\mathrm{HAs}}$ is a constant for any weak acid. Because of the addition of sodium acetate, the concentration of HAs (acetic acid) can be regarded as invariable. Hence, the exchange capacity for acetate ion was independent of the concentration of sodium acetate. Relation (3a) was also confirmed for the adsorption of chloride ion in the presence or absence of 0.01 *N* sodium chloride and in dilute zinc chloride solution in the presence of an excess of zinc oxide, on the above resin and later[2] on a *m*-phenylendiamine-HCHO resin or for Amberlite IR-4B (Rohm and Haas Co.).[2] It has been pointed out that the data of Kunin[4] for Amberlite IR-4B satisfy (3a).[1]

In another paper[2] a semi-quantitative study was made of the equilibrium relations between composition of solution, amount of adsorption, and *p*H of the resin. Colorless or faintly colored cation or anion exchange resins, of both weak and strong types, were utilized with appropriate indicators such as sulfonephthaleins or azo dyestuffs.

A more quantitative study is presented here. According to 2 and 3 the amount adsorbed at equilibrium is constant when a_{Hr} is constant and at the same time for anion exchange we have

$$p\mathrm{H_s} + p\mathrm{A_s} = \text{constant} \qquad (4a)$$

and for cation exchange

$$p\mathrm{H_s} - p\mathrm{M_s} = \text{constant} \qquad (4b)$$

The following data validate these relations if it is assumed that a_{Hr} for the resins equilibrated with various solutions are equal when the resins have attained the same color caused by the adsorption of an indicator whose transition point is near a_{Hr}.

Experimental

Each set of experiments was performed simultaneously at room temperature (20 to 25°). $p\mathrm{H_s}$ was measured po-

---

[1] M. Honda, *J. Chem. Soc. Japan*, **71**, 183, 405 (1950); Kagaku no Ryôiki (*J. Japan. Chem.*), Extra Ed. No. **1**, 19 (May, 1949); *cf. C. A.*, **44**, 6753g (1950).

[2] M. Honda, *J. Chem. Soc. Japan*, **71**, 440 (1950).

[3] O. Samuelson, Ph.D. Dissertation, Horsal, Sweden, 1944.

[4] R. Kunin and R. J. Myers, THIS JOURNAL, **69**, 2874 (1947).