aliphatic or aromatic amines, carbon monoxide, and sulfur.[3-5]

$$2RNH_2 + CO + S \longrightarrow RNHCONHR + H_2S$$

In the course of those investigations, it was observed that in the preparation of ureas, a loss in yield occurred when methanol was used as a solvent, and the corresponding urethane could be isolated as a portion of the product. Therefore, the possibility was considered of establishing a preparative method for urethanes from mixtures of amines, alcohols, carbon monoxide, and sulfur by suitable modifications of the urea procedure.

Such a preparation is feasible, for example in the case of methyl N-phenylurethane, provided conditions exist that allow the equilibrium, $PhNHCONHPh + MeOH \rightleftharpoons PhNHCO_2Me + PhNH_2$, to favor urethane formation under experimental conditions. The preparation of methyl-N-phenylurethane in this manner was demonstrated when mixture of 0.1 mole of diphenylurea and 150 ml. of methanol were heated in an autoclave for five hours. The results are summarized in Table I.

TABLE I

REACTION OF METHANOL AND DIPHENYLUREA

	Product composition		
Temp., °C.	Aniline (% yield)	Methyl-N-phenylurethane (% yield crude)	Diphenylurea (% recovered)
120	37.4	34.4[a]	45.8
160	79.8	70.8	None

[a] After recrystallization from petroleum ether (b.p. 60–90°), yield 26.2%, m.p. 45°.

Subsequently, however, it was found that the reaction of aniline, carbon monoxide, and sulfur in the presence of a large excess of methanol gave a yield no larger than 13.5%, even under the most favorable experimental conditions. The low yield in these experiments was somewhat surprising in view of the conversions of diphenylurea to methyl-N-phenylurethane shown in Table I and the high yields of diphenylurea that are possible from carbon monoxide, sulfur, and aniline.

It then seemed that if the conditions of the experiment could first be adjusted to produce diphenylurea, and subsequently readjusted to induce methanolysis of the urea, the yield of urethane could be increased. In an additional experiment, 0.2 mole of aniline, 0.4 mole of sulfur, 0.4 mole of carbon monoxide, 2 g. of triethylamine, and 150 ml. of methanol were heated in an autoclave under conditions known to be favorable to the formation of diphenylurea (4 hr. at 120°). At the conclusion of the initial heating period, the autoclave was immediately heated to 160° and maintained at that temperature for eight hours. Under these conditions, the yield of crude urethane was increased to 24.3%, a higher value than had been obtained for any other combination of experimental conditions.

It appears that temperatures favoring methyl-N-phenylurethane formation from diphenylurea are unfavorable for the formation of diphenylurea or diphenylurea precursors, which may form methyl-N-phenylurethane by interaction with methanol. The preferred synthesis route would then involve the preparation and isolation of diphenylurea in the manner described earlier.[5] The diphenylurea may then be converted to the urethane in good yield by methanolysis at higher temperatures.

Experimental

All experiments were carried out in a 2.1 Magnedash autoclave. The following is typical of a series of experiments in which methyl-N-phenylurethane was prepared directly from aniline, carbon monoxide, sulfur, and methanol.

The autoclave was charged with 18.6 g. (0.2 mole) of aniline, 6.7 g. (0.2 mole) of sulfur, 10.1 g. of triethylamine, 120 ml. of methanol, and carbon monoxide at 300 p.s.i.g. After a warm-up period of 1 hr., the autoclave was heated at 160° for 5 hr., cooled to 80°, and vented. The products were washed from the bomb, diluted with methanol to about 250 ml., and filtered. The methanol solution was evaporated to dryness, and the residue was treated with 100 ml. benzene to yield 0.37 g. benzene-insoluble diphenylurea, m.p. 230–232° (yield 1.8%). The benzene-soluble portion was extracted with three 25-ml. portions of 2.5 *N* hydrochloric acid, evaporated, and the residue was extracted with several portions of petroleum ether (b.p. 60–90°). Evaporation of the solvent extracts gave a residue which was recrystallized from petroleum ether to yield 4.07 g. (13.5% yield) of methyl-N-phenylurethane, melting 47–50°.

In variations of this procedure, the following conditions were employed: (a) Either an aniline–sulfur mole ratio of 1:1.05 or 1:1.5; (b) triethylamine or sodium methoxide as a catalyst; (c) either an aniline–catalyst mole ratio of 1:0.1 or 1:0.5; (d) 80 or 120 ml. of methanol; (e) an initial carbon monoxide pressure of 150 or 300 p.s.i.g.; (f) a temperature of 160 or 200°; and (g) a heating time of 3 or 5 hr.

(1) Monsanto Chemical Co.

(2) Midwest Research Institute.

(3) R. A. Franz and F. Applegath, *J. Org. Chem.*, **26**, 3304 (1961).

(4) R. A. Franz, F. Applegath, F. V. Morriss, and F. Baiocchi, *ibid.*, **26**, 3306 (1961).

(5) R. A. Franz, F. Applegath, F. V. Morriss, F. Baiocchi, and C. Bolze *ibid.* **26**, 3309 (1961).

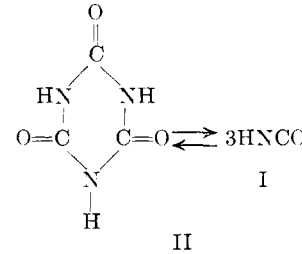
Reactions of Isocyanic Acid with Acid Chlorides. Preparation of Acyl Isocyanates, Isocyanatosilanes, and Phosphor(diisocyanatidites)

PAUL R. STEYERMARK

Contribution No. 45 from Washington Research Center, W. R. Grace & Company (Research Division), Clarksville, Maryland

Received August 3, 1962

Isocyanic acid (I), which can be obtained readily by thermal decomposition of cyanuric acid (II), has been studied in this laboratory for the past three years. It has been found that isocyanic acid undergoes some interesting reactions, which may be of practical value.



$$\rightleftharpoons 3HNCO \quad (1)$$

I

II

In this paper we report the preparation of acyl isocyanates, isocyanatosilanes, and phosphor(isocyanatidites) from isocyanic acid and the corresponding acid chlorides.

Acyl isocyanates, RCONCO (R = CH_3 and C_6H_5), were first made by Billeter[1] by reaction of the corresponding acyl chlorides with silver cyanate. This reaction was used later by seveal workers[2-4] to prepare acyl isocyanates. Waltmann and Wolf[5] claim preparation of acyl isocyanates by phosgenation of carboxylic acid amides. This reaction apparently gives the corresponding carbamoyl chlorides from which the free isocyanates are obtained by treatment with lime.

Forbes and Anderson[6] reported the preparation of silicon isocyanates, $Si(NCO)_4$, by a reaction of silicon chloride with silver cyanate. The same general technique has been used for the preparation of several isocyanatosilanes from chlorosilanes and silver cyanate.[7-11]

Goubeau and Paulin[12] used three different techniques to prepare isocyanatosilanes: heating chlorosilanes with urea for several hours at 240–300°; allowing chlorosilanes to react with lead cyanate; and adding glacial acetic acid to slurries of chlorosilanes and potassium cyanate in ether. The highest yields were obtained with a 100% excess of potassium cyanate and 34% excess of acetic acid. Since the free isocyanic acid did not react with chlorosilanes in the presence of various acidic catalysts, the authors explained the specific catalytic activity of acetic acid by the formation of an intermediate from acetic acid and potassium cyanate.

Phosphorus isocyanate, $P(NCO)_3$, and phosphoryl isocyanate, $PO(NCO)_3$, were first made by Forbes and Anderson[6] by a reaction of silver cyanate with phosphorus trichloride and with phosphoryl chloride, respectively. The first organophosphorus isocyanates were reported by Haven,[13] who allowed silver cyanate to react with organophosphorus chlorides. Phosphonic chlorides reacted more slowly and gave lower yields of isocyanates than the corresponding phosphonous chlorides.

Kirsanov[14] prepared in high yields phosphoryl dichloride isocyanate (III) which was converted in three steps to phosphor(isocyanatidates) (IV) as shown in reaction 2.[15]

$$PCl_5 + C_2H_5OCONH_2 \longrightarrow \underset{\text{III}}{Cl_2P(O)NCO} \xrightarrow{CH_3OH} Cl_2P(O)NHCOOCH_3 \xrightarrow{2RONa} (RO)_2P(O)NHCOOCH_3 \xrightarrow{\text{heat}} \underset{\text{IV}}{(RO)_2P(O)NCO} \quad (2)$$

R = CH_3, C_6H_5, p-BrC_6H_4

A Belgian patent[16] claims preparation of organophosphorus isocyanates from the corresponding organophosphorus chlorides and alkali metal cyanates in polar solvents. Use of lithium cyanate in inert solvents had been claimed earlier by Jenkins[17].

We have found that acyl isocyanates, isocyanatosilanes, and organophosphorus isocyanates can be prepared by reactions of the corresponding chlorides with isocyanic acid in the presence of tertiary amines.

$$RCOCl + HNCO + B \longrightarrow RCONCO + BH^+Cl^- \quad (3)$$

$$R_nSiCl_{4-n} + (4-n)HNCO + (4-n)B \longrightarrow R_nSi(NCO)_{4-n} + (4-n)BH^+Cl^- \quad (4)$$

$$R_nPCl_{3-n} + (3-n)HNCO + (3-n)B \longrightarrow R_nP(NCO)_{3-n} + (3-n)BH^+Cl^- \quad (5)$$

These reactions gave high conversions and good yields of the isocyanates. Any inert solvent in which the resulting tertiary ammonium chloride is insoluble may be used. Unlike the previous reactions of acid chlorides with metal cyanates, the reactions with isocyanic acid are carried out in homogenous solutions. They are fast and exothermic; usually cooling is necessary.

Since isocyanic acid is a potentially cheap starting material, this technique may be quite attractive.

On the other hand, the use of a base during the preparation of isocyanates may cause side reactions, such as polymerization of isocyanates, trimerization of isocyanic acid, or formation of quaternary ammonium adducts with the acid chlorides.

No problems were encountered in the preparation of isocyanatosilanes. They were easy to isolate, did not polymerize or undergo side reactions during their distillation, and were stable on storage at room temperature.

Isolation of only two acyl isocyanates was attempted. Because of their high reactivity, acyl isocyanates readily undergo polymerization in the presence of bases. Bases stronger than pyridine caused considerable polymerization.

This reaction was particularly well suited for the preparation of phosphor(isocyanatidites) $ROP(NCO)_2$ (V). Alkyl and arylphosphonous isocyanates and phosphorus isocyanate polymerized readily during the distillation and thus could not be isolated pure or were isolated in low yields only.

The reaction could not be used to prepare isocyanates from phosphonic chlorides either because of lack of reactivity or because of side reactions. Thus, phosphoryl chloride and ethyl phosphorochloridate gave mainly polymeric products, while butyl phosphorochloridate and methyl phosphorochloridothioate did not react at all.

Experimental[18]

Materials.—Acyl chlorides either were Eastman White Label chemicals or they were made in this laboratory. Some, but not all of them, were distilled immediately before use. Silicon tetrachloride from Linde Co., Division, Union Carbide Corp.,

(1) O. Billeter, *Ber.*, **36**, 3213 (1903).
(2) A. J. Hill and W. M. Degnan, *J. Am. Chem. Soc.*, **62**, 1595 (1940).
(3) T. Lieser and K. Macura, *Ann.*, **548**, 226 (1941).
(4) C. L. Arcus and B. S. Prydal, *J. Chem. Soc.*, 4018 (1954), and 1091 (1957).
(5) E. Waltmann and E. Wolf, U. S. Patent 2,346,202 (April 11, 1944).
(6) G. S. Forbes and H. H. Anderson, *J. Am. Chem. Soc.*, **62**, 761 (1940).
(7) G. S. Forbes and H. H. Anderson, *ibid.*, **69**, 3048 (1947).
(8) G. S. Forbes and H. H. Anderson, *ibid.*, **70**, 1043 (1948).
(9) G. S. Forbes and H. H. Anderson, *ibid.*, **70**, 1222 (1948).
(10) D. X. Klein, U. S. Patent 2,532,559 (December 5, 1950).
(11) H. Gilman, B. Hofferth, and M. W. Melvin, *J. Am. Chem. Soc.*, **72**, 3045 (1950).
(12) J. Goubeau and D. Paulin, *Chem. Ber.*, **93**, 1111 (1960).
(13) A. C. Haven, Jr., *J. Am. Chem. Soc.*, **78**, 842 (1956).
(14) A. V. Kirsanov, *Zh. Obshch. Khim.*, **24**, 1033 (1954) [*Chem. Abstr.*, **49**, 8787b (1955)].
(15) A. V. Kirsanov and I. N. Zhmurova, *Zh. Obshch. Khim.*, **26**, 2642, (1956) [*Chem. Abstr.*, **51**, 1820g (1957)]; *Zh. Obshch. Khim.*, **27**, 1002 (1957) [*Chem. Abstr.*, **52**, 3715h (1958)].
(16) Belgian Patent 591,707 (to Imperial Chemical Industries) (November 30, 1960).
(17) L. H. Jenkins, U. S. Patent 2,873,171 (February 10, 1959).
(18) Both the melting points and the boiling points were uncorrected. Microanalyses were by Clark Microanalytical Laboratory, Urbana, Ill., and Huffman Microanalytical Laboratories, Wheatridge, Colo. We are grateful to Mr. L. Peters for the infrared spectra.

was distilled through a 50-plate Oldershaw column at reflux ratio 10:1.[19] Trimethylchlorosilane and dimethylchlorosilane, graciously offered by General Electric Co., Silicon Products Dept., Waterford, N. Y., were distilled in a conventional glass equipment before use. Baker "Analyzed Reagent" phosphorus trichloride was used as received.

Anhydrous tetrahydrofuran and ethyl ether were distilled from sodium. In later experiments Baker "Analyzed Reagent" ether was used as received. Fisher "Certified Reagent" pyridine was dried over barium oxide. Eastman White Label anhydrous trimethylamine was used as received.

Isocyanic acid was obtained by cracking isocyanuric acid at about 600° and collecting the monomeric isocyanic acid in the solvent.[20] Concentration of isocyanic acid was determined either by precipitation of silver cyanate and titration of silver or by titration of solutions of isocyanic acid in dimethylformamide with sodium methoxide in benzene in the presence of thymol blue indicator.[21]

Although toluene is a good solvent for isocyanic acid, tetrahydrofuran and ether were preferred for the reactions with acid chlorides. Aliphatic hydrocarbons are very poor solvents for isocyanic acid.

Preparation of Phosphorodichloridites.—Methyl, ethyl, and phenyl phosphorodichlorides were prepared by adding ether solutions of the corresponding anhydrous alcohols to equivalent amounts of phosphorus trichloride below 0°. The solutions were left several hours at room temperature, then fractionated on glass columns packed with Raschig rings. The pure phosphorodichloridites were obtained in 42–75% yields. Their physical constants are reported in Table I.

TABLE I

PHYSICAL CONSTANTS OF PHOSPHORODICHLORIDITES

Compound	B.p., °C. (mm.)	n_D (°C.)
CH_3OPCl_2	92–95[a]	1.4735[a] (19.5)
$C_2H_5OPCl_2$	116–118[b]	1.4628 (19.5)
$C_6H_5OPCl_2$	100–110 (12)	1.5779 (22)

[a] Reported,[22] b.p. 91–92°, $n^{20}D$ 1.4750. [b] Reported,[23] b.p. 117–118°.

Acetyl Isocyanate.—To a solution of 18.1 g. (0.23 mole) of acetyl chloride and 9.9 g. (0.23 mole) of isocyanic acid in anhydrous ethyl ether there was added dropwise at −10° 18.1 g. (0.23 mole) of pyridine with efficient stirring. The mixture was kept for several hours at 0°; then the precipitate of pyridine hydrochloride was filtered. Conversion, based on chloride titration from the pyridine hydrochloride, was 83%.[24] Ether was distilled from the filtrate through a 30-cm. Vigreux column. The residue (9.8 g.) was distilled through a 30-cm. column packed with glass rings. The fraction boiling at 79–80° (758 mm.) was collected. The material weighed 2.9 g. (15% yield) and had the following physical constants: d^{25}_{25} 1.0826 and $n^{25}D$ 1.4029.

On treatment with a benzene solution of aniline the isocyanate gave the known N-acetyl-N'-phenylurea, m.p. 186–88.

Anal. Calcd. for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 61.13; H, 5.40; N, 16.06.

Benzoyl Isocyanate.—Reaction of 38.5 g. (0.27 mole) of benzoyl chloride with equivalent amounts of isocyanic acid in tetrahydrofuran and pyridine at −10° gave 48.4 g. of tetrahydrofuran-insoluble material. It was found to contain 24 g. of pyridine, hydrochloride (76% conversion) and a water-insoluble material, m.p. 150–160°, which was not further identified. Distillation of the tetrahydrofuran solution gave 12.7 g. of a liquid, b.p. 81–87° (10 mm.). Its infrared spectrum had both isocyanate absorption at 2250 cm.$^{-1}$ and carbonyl absorption at 1775 cm.$^{-1}$. Chloride titration showed that the material consisted of a mixture of 7.1 g. of unchanged benzoyl chloride, the remaining 5.6 g. probably being benzoyl isocyanate (14% yield). On standing for 1 hr. at room temperature in a glass-stoppered flask, a solid material separated. Recrystallized from acetone–petroleum ether, it melted at 188–191°. The material was identified as N,N'-dibenzoylurea, formed by slow hydrolysis of benzoyl isocyanate.

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.15; H, 4.51; N, 10.44. Found: C, 67.21; H, 4.50; N, 10.51.

Other Acyl Isocyanates.—In subsequent experiments isolation of pure acyl isocyanates was not attempted. Chloride from pyridine hydrochloride precipitates was determined by Volhard titrations. The crude solutions of isocyanates were concentrated at a reduced pressure to remove unchanged isocyanic acid, and the isocyanates were titrated with dibutylamine and hydrochloric acid in toluene to the bromophenol blue end point. Methanol or isopropyl alcohol were added to maintain a homogeneous solution.[25] Any unchanged acyl chlorides in the solutions were determined by hydrolysis of aliquots and titration of chloride.[26] The isocyanate titration was corrected for the acyl chloride content.

Yields were calculated on the basis of quantitative conversions. In most cases the differences between the yields of the isocyanates and the conversions were due to the formation of polymeric materials.

The results are summarized in Table II.

TABLE II

PREPARATION OF ACYL ISOCYANATES

Isocyanate	% Conversion[a]	% Yield[b]
Stearoyl	90	87
Palmitoyl	76	57
Myristoyl	68	..
Methacryloyl	78	72
o-Methoxybenzoyl	..	87
2,4-Dichlorobenzoyl	67	48
Sebacoyl	97	90
Azelaoyl	91	92
Glutaroyl	79	40
Pimeloyl	72	49
Adipoyl	80	None[c]
Terephthaloyl	74	None[c]
Oxalyl	91	None[c]
Malonyl	..[d]	..

[a] By titration of chloride from pyridine hydrochloride. [b] By titration of the NCO groups. [c] Only polymeric material isolated. [d] Quaternary pyridinium adduct formed.

Preparation of Isocyanatosilanes.—The following general preparative procedure was used: An approximately 1 *N* solution of trimethylamine in ether was slowly added with stirring at −10 to 10° to a solution of an equivalent amount of chlorosilane and a 10–15% excess of isocyanic acid in ether. The mixture was allowed to warm to room temperature, and the precipitate of trimethylammonium chloride was filtered. Ether was distilled from the filtrate on a steam bath using a Vigreux column. The liquid residue was fractionated through a spinning band column.[27] The products were identified by their boiling points, refraction indices, and infrared spectra. All isocyanatosilanes were found by gas chromatography on 5% silicone grease on Haloport F (F & M Corp., Avondale, Pa.) to be 97–100% pure. Table III summarizes the experimental details.

In earlier experiments pyridine was used as the proton acceptor and tetrahydrofuran as solvent. Very similar results were obtained at that time. However, trimethylamine was found to be more convenient because of its low boiling point, which allows easy removal of any excess amine left. For the same reason ether was the preferred solvent. Trimethylamine hydrochloride in less hygroscopic and, therefore, easier to filter than pyridine hydrochloride.

(19) We are grateful to Dr. M. C. Vanik for a sample of the distilled silicon tetrachloride.

(20) Dr. R. E. Gilman, formerly of this laboratory, designed an isocyanic acid generator and studied the conditions of the pyrolysis.

(21) Mr. J. D. Sheehan developed this titration technique.

(22) A. Ya. Yakubovitch and V. A. Ginsburg, *Zh. Obshch. Khim.*, **22**, 1534 (1952) [*Chem. Abstr.*, **47**, 9254i (1953)].

(23) M. G. Cook, J. D. Ileff, B. C. Saunders, G. J. Stacey, H. G. Watson, I. G. E. Wilding, and S. J. Woodcock, *J. Chem. Soc.*, 2921 (1949).

(24) We have found in subsequent preparations of acetyl isocyanate and other acyl isocyanates that the reaction mixture could be filtered a few minutes after the addition of pyridine without decrease in conversion.

(25) "Spielberger's method" reported by W. Siefken, *Ann.*, **562**, 99 (1949).

(26) Pyridinium chloride was found by chloride titration to be insoluble in ether at room temperature. In tetrahydrofuran pyridinium chloride was soluble to the extent of 42 mg. per 100 ml.

(27) Nester & Faust, Newark, Del.

TABLE III

PREPARATION OF ISOCYANATOSILANES FROM CHLOROSILANES AND ISOCYANIC ACID

Starting chlorosilane	Molar fraction	Conversion, %[a]	Isocyanatosilane	Yield, %[b]	B.p., mm.	$n^{20.5}D$
$SiCl_4$	0.071	96	$Si(NCO)_4$	60	73/2[c]	1.4595[c]
$(CH_3)_3SiCl$	.51	83	$(CH_3)_3SiNCO$	57	89/754[d]	1.3940[d]
$(CH_3)_2SiCl_2$	.083	97	$(CH_3)_2Si(NCO)_2$	58	130–132[e]	1.4195[e]

[a] By titration of chloride from trimethylammonium chloride formed in the reaction. [b] Based on a quantitative conversion. [c] Reported,[7] b.p. 185.6°/760 mm. and n^{20} 1.4610. [d] Reported,[8] b.p. 91° and n^{20} 1.3960. [e] Reported,[8] b.p. 131.2° and n^{20} 1.4221.

TABLE IV

PREPARATION OF PHOSPHOR(DIISOCYANATIDITES) FROM PHOSPHORODICHLORIDITES AND ISOCYANIC ACID

R	Conversion, %	Yield, %[a]	B.p., °C./mm.[b]	n_D/t	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found	P Calcd.	P Found
CH_3[c]	94	64.3	56/18	1.4815/22	$C_3H_3N_2O_3P$	24.67	24.72	2.07	2.18	19.19	19.02	21.21	20.7
C_2H_5	90	51.5	70/27	1.4720/22	$C_4H_5N_2O_3P$	30.01	29.93	3.15	3.70	17.50	17.04	19.35	19.3
C_6H_5	88	61	76–78/0.20–0.25	1.5505/21	$C_8H_5N_2O_3P$	46.17	46.06	2.42	2.78	13.46	13.19	14.88	14.6

[a] By titration of chloride from either pyridine hydrochloride or trimethylammonium chloride formed in the reaction. [b] Based on a quantitative conversion. [c] Bisbenzylamine derivative, m.p. 122–123° (from ethanol). *Anal.* Calcd. for $C_{17}H_{21}N_4O_3P$: C, 56.66; H, 5.88; N, 15.55; P, 8.60. Found: C, 56.76; H, 6.03; N, 15.34; P, 8.4.

Phosphor(diisocyanatidites)(V).—These compounds were prepared by reactions of the corresponding phosphorodichloridites with isocyanic acid in ether in the presence of either pyridine or trimethylamine. The reaction products were purified by distillation through a spinning band column. The experimental details are given in Table IV.

Diphenyl Phosphorochloridite, $(C_6H_5O)_2PCl$.—This material, b.p. 170–173° (4 mm.), always was obtained during the preparation of phenyl phosphorodichloridite.

Diphenyl Phosphor(isocyanatidite), $(C_6H_5O)_2PNCO$.—Reaction of diphenyl phosphorochloridite with a 25% excess of isocyanic acid in ether in the presence of trimethylamine gave a 70% yield of diphenyl phosphor(isocyanatidite), b.p. 149–150° (1.2 mm.), $n^{21}D$ 1.5716. Conversion was found by chloride titration to be 88%.

Anal. Calcd. for $C_{13}H_{10}NO_3P$: C, 60.24; H, 3.89; N, 5.40 P, 11.95. Found: C, 60.34; H, 4.02, N, 5.62; P, 12.4.

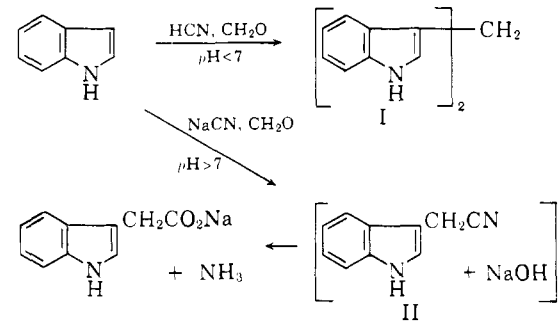
The Cyanomethylation of Indole

J. N. COKER, O. B. MATHRE, AND W. H. TODD

Research Division, Electrochemicals Department, E. I. du Pont de Nemours and Company, Inc., Wilmington, Delaware

Received August 30, 1962

The utility of 3-indolacetonitrile as a precursor of tryptophan[1] has prompted a study of the cyanomethylation of indole. The preparation of the nitrile directly from indole, formaldehyde, and an alkali cyanide is reported in the patent literature.[2–4] Our efforts to confirm these reports have met with only limited success, due to two competing reactions under the conditions employed. In neutral or acidic solution, the reaction was found to be predominantly between indole and formaldehyde, yielding 3,3′-diindolylmethane. Under alkaline conditions, on the other hand, cyanomethylation of the indole to 3-indoleacetonitrile (II) did occur. However, alkali hydroxide was also formed, and under the conditions required to accomplish the cyanomethylation reaction, the nitrile product was hydrolyzed almost as rapidly as it was produced to 3-indoleacetic acid.



A variety of conditions have been investigated in an attempt to arrest the reaction of indole, formaldehyde, and an alkali cyanide at the nitrile stage. Use of a dipotassium phsophate buffer was found to repress the hydrolysis of the nitrile somewhat, but the yield of nitrile based on indole was still low (*i.e.*, approximately 15%).[5] On the other hand, alumina was found to be completely inoperable as a buffer, a salt of 3-indoleacetic acid being obtained as the main product. No cyanomethylation products resulted in experiments in which either magnesium acetate or dimethylamine acetate was used as the buffer. Likewise no reaction was observed when zinc cyanide or cuprous cyanide was used in place of the alkali cyanide. It should be noted that the reaction of 1-acetyl-3-acetoxymethylindole, obtained by heating gramine with acetic anhydride and fused sodium acetate,[6] with potassium cyanide gave a 38% yield of the nitrile.

Experimental[7]

3-Indoleacetonitrile from Indole, Formaldehyde, and Potassium Cyanide.—Indole (39 g., 0.33 mole), potassium cyanide (22 g., 0.34 mole), dipotassium phosphate trihydrate (85 g., 0.37 mole), and aqueous formaldehyde (30 ml. 36.2% solution equivalent to 10.9 g. or 0.36 mole) were mixed with ethanol (100 ml.) and water (70 ml.). The mixture was sealed in a Hastelloy B-lined shaker tube under nitrogen and heated for 4 hr. at 150°. After cooling to 0–5°, the mixture was discharged and filtered.

(1) J. N. Coker, W. L. Kohlhase, M. Fields, A. O. Rogers, and M. A. Stevens, *J. Org. Chem.*, **27**, 850 (1962).
(2) W. Salzer and H. Andersag, German Patent 722,809.
(3) K. Bauer and H. Andersag, U. S. Patents 2,222,344 and 2,315,661.
(4) Japanese Patent 16,544.
(5) O. B. Mathre, U. S. Patent 2,927,117.
(6) E. Leete and L. Marion, *Can. J. Chem.*, **31**, 775 (1953).
(7) All melting points are uncorrected.