

DIPHENYLCYANAMIDE DERIVATIVES¹BY J. R. ROBINSON² AND W. H. BROWN

Abstract

Diphenylcyanamide is conveniently prepared by the action of cyanogen chloride on diphenylamine. When it is hydrolyzed in the presence of hydroxylated solvents, of the type ROH, stable isoureas are formed. These are readily hydrolyzed in aqueous alkaline medium to the corresponding urea derivative. Chlorination of diphenylcyanamide occurs in the *para* positions yielding a nitrogen analogue of DDT. This chlorinated derivative is only 1/80th as toxic as DDT to *Sitophilus granarius* (L).

Diphenylcyanamide (I) has been reported by von Braun (2), Werner (26), and Kurzer (10). Since only a few direct derivatives have been recorded (3, 4, 5, 9, 26), an investigation of this compound is of interest. For example, *p*, *p'*-dichlorodiphenylcyanamide (II) is a nitrogen analogue of 1,1-bis-(*p*-chlorophenyl)-2,2,2-trichlorethane (DDT) and might show insecticidal activity.

It has been found that diphenylcyanamide (I) is formed in excellent yield by treating diphenylamine (IX) with cyanogen chloride at 60°C. and 5 atm. pressure. When it is hydrolyzed in aqueous alkaline medium, N, N-diphenylurea (III) results. Michler (16) and Kurzer (11) have reported other methods for preparing this latter compound. When a solution of diphenylcyanamide (I) in methanolic potassium hydroxide is refluxed for 72 hr., diphenylamine (IX) is produced. If, however, the reaction is interrupted after two hours, N, N-diphenylmethylisourea (IV) is the major product. The isourea is readily converted to N, N-diphenylurea (III) by boiling with aqueous potassium hydroxide for 2.5 hr.

When ethanol is used as solvent instead of methanol, the corresponding ethylisourea (V) is readily obtained.

Pyrolysis of N, N-diphenylmethylisourea (IV) leads to the formation of N, N-diphenylurea (III) in poor yield.

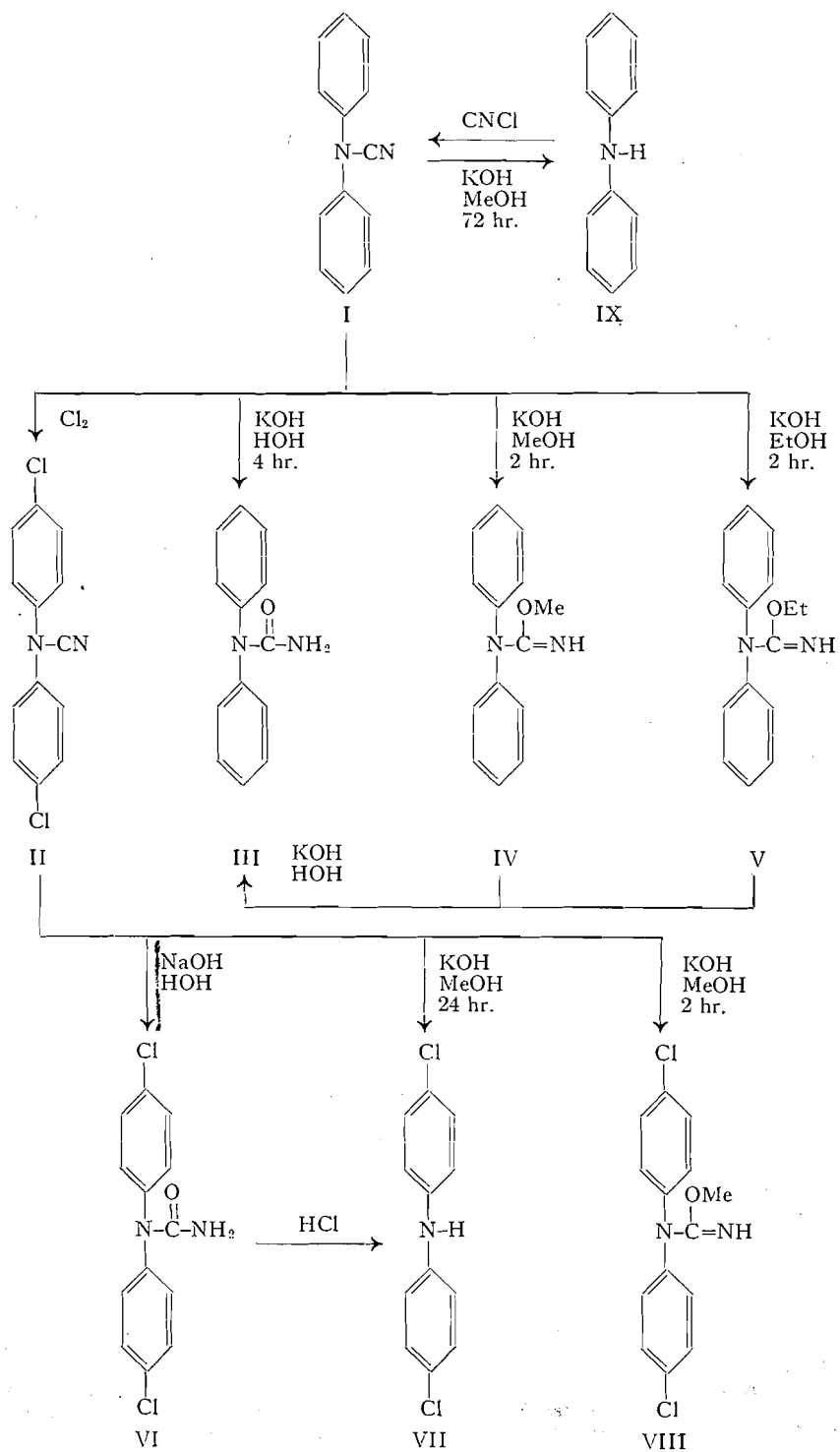
Treatment of a chloroform solution of diphenylcyanamide (I) with chlorine gives *p*, *p'*-dichlorodiphenylcyanamide (II). This latter compound when refluxed in a solution of potassium hydroxide in methanol for two hours forms N, N-di-*p*-chlorophenylmethylisourea (VIII). If the reaction is allowed to proceed for 24 hr., *p*, *p'*-dichlorodiphenylamine (VII) results. An authentic sample of *p*, *p'*-dichlorodiphenylamine was prepared by the methods of Claus and Shaare (8) and Chapman (7).

Aqueous alkaline hydrolysis of *p*, *p'*-dichlorodiphenylcyanamide (II) gives N, N-di-*p*-chlorophenylurea (VI), which hydrolyzes with difficulty in dilute hydrochloric acid solution to *p*, *p'*-dichlorodiphenylamine (VII).

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Discussion

Pinner (18) was among the first to report the synthesis of iminoethers.* Many investigators (1, 12, 13, 14, 15, 17, 19, 20, 21, 22, 23, 24, 25) have extended the field, but none of the N, N-diphenyl type is reported. McKee (13) predicted that disubstituted cyanamides would most readily add alcohols when catalyzed by the corresponding alkoxide ion, rather than by protons. The authors' findings with respect to diphenylcyanamide bear this out. Methanol adds to diphenylcyanamide in two hours in the presence of methoxide ion in 88% yield, whereas the reaction requires 80 days in the presence of hydrogen chloride to give a yield of 3.5%.

Toxicology

Tests† show that *p, p'*-dichlorodiphenylcyanamide (II) possesses an estimated median lethal concentration of about eighty times that of DDT to *Sitophilus granarius* (L). The other derivatives of diphenylcyanamide were also screened for activity, but did not indicate toxicity great enough to warrant quantitative investigation.

Browning *et al.* (6) have tested a number of N-substituted *p, p'*-dichlorodiphenylamines for biological activity. Their results show that groups such as methyl, trichloromethyl, and trichloroacetyl do not increase the toxicity of the parent compound. The cyanide group does have an enhancing effect according to the present authors' findings.

Experimental‡

Diphenylcyanamide

After treating 34 gm. (0.2 mole) of diphenylamine with 12.3 gm. (0.2 mole) of cyanogen chloride at 60°C. for one and one-half hours in a capped ginger ale bottle, the reaction mixture was allowed to stand at room temperature for 24 hr. As a safety precaution, the bottle was kept immersed in a steel-jacketed water bath throughout the course of the reaction.

The ether-soluble portion of the resulting solid was crystallized three times from absolute ethanol, giving 17.5 gm. (90%) of a white granular solid, which melted at 73°C.

p, p'-Dichlorodiphenylcyanamide

Chlorine was bubbled into a solution of 7.76 gm. (0.04 mole) of diphenylcyanamide in 30 ml. of chloroform at 5-6°C. for one hour. The solution was

* These compounds are recorded in the literature under various names; imino- or imidoethers imino- or imidoesters and esters of imidic acids. Those of the type $R_2N-C(OR')=NH$ are called isocarbamides, carbimidoethers (esters), pseudoureas, or isoureas.

† Material tested by the Entomology Section, Defence Research Board Experimental Station, Suffield, Alta.

‡ All melting points have been corrected against reliable standards. Combustion analyses are by A. E. Ledingham, Dominion Rubber Research Laboratories, Guelph, Ont.; R. G. Pyke, Department of Chemistry, University of Toronto, and J. F. Eagen, National Research Council, Ottawa.

treated with 10% aqueous sodium carbonate, washed with water, and finally dried over anhydrous sodium sulphate. When the chloroform was distilled off, there remained 12.1 gm. of golden yellow oil which crystallized spontaneously. Crystallization from ethanol yielded 6.1 gm. (58%) of long colorless needles melting at 114-115°C. Calc. for $C_{13}H_8Cl_2N_2$: C, 59.31; H, 3.06; Cl, 26.94; N, 10.65%. Found: C, 59.06; H, 3.06; Cl, 26.90; N, 10.64%.

N, N-Diphenylurea

To a solution of 1.12 gm. (0.02 mole) of potassium hydroxide in 100 ml. of water was added 3.88 gm. (0.02 mole) of diphenylcyanamide, and the mixture refluxed for four hours. The resulting solid weighed 4.2 gm. (100%) and melted at 192-193°C. A mixed melting point with an authentic sample of *N, N*-diphenylurea (EK 4979) was not depressed.

N, N-Diphenylmethylisourea (alkoxide catalysis)

To a solution of 0.28 gm. (0.005 mole) of potassium hydroxide in 20 ml. of methanol was added 0.97 gm. (0.005 mole) of diphenylcyanamide. The resulting solution was refluxed for two hours. After cooling, the solution was diluted with 100 ml. of water. An oil separated and crystallized after vigorous stirring. The product was found to be extremely soluble in all the common organic solvents as well as in 10% hydrochloric acid solution. Purification was achieved by dissolving it in excess acetone, then adding water dropwise while stirring at high speed. By this means 1.0 gm. (88%) of long fine needles was obtained melting at 77-78°C. Calc. for $C_{14}H_{14}ON_2$: C, 74.30; H, 6.24; $-OCH_3$, 13.71; N, 12.40%. Found: C, 74.55; H, 6.20; $-OCH_3$, 13.97; N, 12.57%.

The same product was obtained (82%) when 0.23 gm. (0.01 gm-atom) of sodium metal was used in place of potassium hydroxide.

N, N-Diphenylmethylisourea (proton catalysis)

A solution of 1.94 gm. (0.01 mole) of diphenylcyanamide in 60 ml. of methanol was saturated with dry hydrogen chloride at 6°C. After standing 80 days at 10°C., 0.08 gm. (3.5%) of *N, N*-diphenylmethylisourea was isolated from the solution.

N, N-Diphenylethylisourea (alkoxide catalysis)

To a solution of 2.8 gm. (0.05 mole) of potassium hydroxide in 50 ml. of absolute ethanol was added 9.7 gm. (0.05 mole) of diphenylcyanamide and the resulting solution refluxed for two hours. The reaction mixture was cooled, diluted with 150 ml. of water, and extracted with four 25 ml. portions of ether. The ether extract was treated with an excess of concentrated hydrochloric acid and the resulting precipitate taken up in 75 ml. of water. This aqueous solution was made alkaline with 20% potassium hydroxide solution. The resulting precipitate was purified by crystallization from acetone-water as described above, yielding 9.0 gm. (75%) of white crystals melting at 55-56°C. Calc. for $C_{15}H_{16}ON_2$: C, 74.96; H, 6.72; $-OC_2H_5$, 18.76%. Found: C, 74.92; H, 6.70; $-OC_2H_5$, 18.69%.

N, N-Di-p-chlorophenylurea

A suspension of 1.05 gm. (0.004 mole) of dichlorodiphenylcyanamide in 15 ml. of 6 *N* aqueous sodium hydroxide solution was refluxed for 17 hr. Bumping became so severe that the refluxing had to be stopped. The suspension was left standing at room temperature for an additional 10 days. A white crystalline solid, which melted at 220-222°C., weight 1.1 gm. (98%), was filtered off. Crystallization from ethanol and acetone-water did not raise the melting point. Calc. for $C_{13}H_{10}ON_2Cl_2$: C, 55.52; H, 3.58; N, 9.97%. Found: C, 57.20; H, 3.42; N, 10.28%.

p, p'-Dichlorodiphenylamine

A solution of 1.32 gm. (0.005 mole) of *p, p'*-dichlorodiphenylcyanamide in 50 ml. of 20% methanolic potassium hydroxide was refluxed for 24 hr. After cooling and diluting with 100 ml. of water a white precipitate was obtained which was crystallized from petroleum ether (65-110°C.). In this manner 1.03 gm. (87%) of purified material was obtained, melting at 77-78°C. A mixed melting point with an authentic sample of *p, p'*-dichlorodiphenylamine was not depressed.

N, N-Di-p-chlorophenylmethylisourea

A solution of 2.1 gm. (0.008 mole) of *p, p'*-dichlorodiphenylcyanamide in 15 ml. of methanol containing 0.56 gm. (0.01 mole) of potassium hydroxide was refluxed for two hours. The solution was cooled and diluted with 50 ml. of water. The crystalline precipitate was filtered off and crystallized four times from ethanol, yielding 1.7 gm. (72%) of purified product melting at 109-110°C. Calc. for $C_{14}H_{12}ON_2Cl_2$: C, 56.95; H, 4.08; N, 9.50; Cl, 24.04; $-OCH_3$, 10.52%. Found: C, 57.05; H, 4.28; N, 9.41; Cl, 24.14; $-OCH_3$, 10.49%.

Pyrolysis of N, N-Diphenylmethylisourea

After heating 0.9 gm. (0.004 mole) of *N, N*-diphenylmethylisourea in a pyrex test tube at 140-160°C. for four hours, the reaction mass was treated with 5 ml. of ether. Immediate crystallization resulted. The crystals weighed 0.1 gm. (12%) and melted at 192-193°C. after crystallization from methanol. A mixed melting point with *N, N*-diphenylurea showed no depression.

N, N-Diphenyl-N'-methylurea

This compound was prepared for comparison with *N, N*-diphenylmethylisourea in the early stages of the investigation.

A solution of 0.46 gm. (0.002 mole) of diphenylcarbonyl chloride (E.K. 801) in 25 ml. anhydrous ether was treated with excess methylamine which was distilled from a 33% aqueous solution. After one hour the reaction was stopped, the solid material filtered off, and the ether evaporated to give 0.6 gm. of crude product, which melted at 167-168°C. The crude material was purified by crystallization from methanol-water and ethanol-water giving 0.35 gm. (78%) of product melting at 173°C. Calc. for $C_{14}H_{14}ON_2$: C, 74.30; H, 6.24; N, 12.40%. Found: C, 74.40; H, 6.20; N, 12.61%.

Acknowledgments

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