254. *Synthesis of ω-Aminoalkyl Cyanides.*

By Alan A. Goldberg and William Kelly.

A number of ω-aminoalkyl cyanides have been prepared by interaction of ω-bromoalkyl cyanides with potassium phthalimide followed by deacylation of the resulting ω-cyanoalkylphthalimides with hydrazine. The synthetic method would appear to be general for the production of any ω-aminoalkyl cyanide.

The literature relating to aminoalkyl cyanides is not extensive. Aminomethyl cyanide (Klages, *J. pr. Chem.*, 1902, **65**, 188; Anslow and King, *J.*, 1929, 2463; Menge, *J. Amer. Chem. Soc.*, 1934, **56**, 2197), 1-aminoethyl cyanide (Dubsky, *Ber.*, 1916, **49**, 1048), 2-aminoethyl cyanide (Whitmore *et al.*, *J. Amer. Chem. Soc.*, 1944, **66**, 725), and 2-aminopropyl cyanide (Bruylants, *Bull. Soc. chim. Belg.*, 1923, **32**, 256) have been prepared by special methods not of general application. In addition, ω-aminoamyl cyanide has been prepared by the high pressure semihydrogenation of adiponitrile (U.S.PP. 2,208,598, 2,234,566).

ω-Aminoalkyl cyanides were required for the synthesis of a group of new aminoalkyl substituted heterocycles, and a convenient and general method was sought for their preparation. It has been found that ω-cyanoalkylphthalimides, readily available from potassium phthalimide and ω-bromoalkyl cyanides or from ω-bromoalkylphthalimides and potassium cyanide, can be deacylated with hydrazine by the Ing and Manske reaction (*J.*, 1926, 2348) with production of the aminoalkyl cyanide in substantial yield. It is of interest that the intermediate formed by the interaction of hydrazine and the phthalimidoalkyl cyanide yields phthalyl hydrazide and the aminoalkyl cyanide on acidification with hydrochloric acid without prolonged hydrolysis; this accords with the recent observations of Mosher (*J. Amer. Chem. Soc.*, 1946, **68**, 1565) on the decomposition of similar compounds. Deacylation with constant-boiling hydrochloric acid or by the modified method of Gabriel (cf. *Ber.*, 1911, **44**, 3632) with 5N-hydrochloric acid *via* the phthalamic acid is not possible owing to simultaneous hydrolysis of the cyano-group. Since various αω-alkylenediols are now available which are readily converted through the alkylene dibromides into the corresponding ω-bromoalkyl cyanides, and an αω-alkylene dibromide, $Br\cdot[CH_2]_n\cdot Br$, can be transformed into the ω-bromoalkyl cyanide, $Br\cdot[CH_2]_{n+1}\cdot CN$ (cf. Willstätter and Ettlinger, *Annalen*, 1903, **326**, 99; Leuchs, *Ber.*, 1911, **44**, 1510; Cheney and Piening, *J. Amer. Chem. Soc.*, 1945, **67**, 731; Breslow and Hansen, *ibid.*, p. 686), the method appears to be general for the synthesis of ω-aminoalkyl cyanides.

In this manner 3-amino-*n*-propyl cyanide, 5-amino-*n*-amyl cyanide, and 10-amino-*n*-decyl cyanide have been obtained. Contrary to the impression given by the literature the aminoalkyl cyanides are stable provided they are kept under anhydrous conditions. Protection of the amino-group by acylation allows the terminal cyano-group to undergo its functional reactions—*e.g.*, thioamide, imino-ether, and amidine transformation—and, often, subsequent formation of the 2-(acylamidoalkyl) heterocycle. The synthesis of a series of 2-(ω-aminoalkyl)-thiazoles and -pyrimidines from these acylamidoalkyl cyanides is described in the following paper; the synthesis of a number of 2-(ω-aminoalkyl)-iminazoles and -iminazolines will be reported shortly.

EXPERIMENTAL.

3-*Phthalimido*-n-*propyl Cyanide*.—A solution of potassium cyanide (75 g.) in water (150 c.c.) was added dropwise during 1½ hours to a stirred refluxing solution of trimethylene dibromide (202 g.) in alcohol (300 c.c.). Stirring at the reflux was continued for a further 1 hour, water (750 c.c.) added, and the solution extracted with chloroform (3 × 150 c.c.). The combined extracts after drying and distillation yielded recovered trimethylene dibromide (41 g.), b. p. 55°/14 mm., 3-bromopropyl cyanide (45 g.), b. p. 90—92°/13 mm., and tetramethylene dicyanide (17 g.), b. p. 138—140°/13 mm. (cf. Gabriel, *Ber.*, 1889, **22**, 3336).

Potassium phthalimide (60 g.) was refluxed with a solution of 3-bromopropyl cyanide (44 g.) in absolute alcohol (200 c.c.) for 10 hours, alcohol (*ca.* 100 c.c.) distilled off, and the residual solution poured into water (1 l.). The oil which separated rapidly solidified (56 g.; m. p. 60°); it was collected and recrystallised from dilute methyl alcohol, 3-*phthalimidopropyl cyanide* being obtained in white plates, m. p. 65—66° (Found: N, 13·2. $C_{12}H_{10}O_2N_2$ requires N, 13·1%).

3-*Amino*-n-*propyl Cyanide.*—Hydrazine hydrate (50% w/w solution; 25·5 g.) was added to a solution of the foregoing phthalimido-cyanide (40 g.) in alcohol (150 c.c.) at 50° and the resulting solution allowed to cool and kept at room temperature for 1 hour. Water (50 c.c.) was added, and the solution rendered just acid to Congo-red by concentrated hydrochloric acid, warmed to 60°, and kept for 2 hours. The insoluble phthalyl hydrazide was removed and the filtrate evaporated at reduced pressure at <40° to small volume. The residue was chilled, basified with 10N-sodium hydroxide (150 c.c.), extracted with ether (5 × 100 c.c.), the ethereal solution dried, and anhydrous alcoholic hydrogen chloride (10% w/w) added in order to precipitate the hydrochloride (10·5 g.; m. p. 134—136°); recrystallisation from anhydrous alcohol gave 3-*amino*-n-*propyl cyanide hydrochloride* in white plates, m. p. 138—140° (Found: N, 23·0; Cl, 29·8. $C_4H_8N_2$,HCl requires N, 23·2; Cl, 29·5%). The hydrochloride (20 g.) was added to 10N-sodium hydroxide (50 c.c.) and the whole thoroughly extracted with ether; after drying over potassium carbonate the ethereal solution was distilled, 3-*amino*-n-*propyl cyanide* being obtained as a colourless water soluble oil, b. p. 95—97°/20 mm. (Found: N, 33·8. $C_4H_8N_2$ requires N, 33·4%).

3-*Benzamidopropyl Cyanide.*—Benzoyl chloride (21 c.c.) was added dropwise during ½ hour to a rapidly stirred solution of sodium carbonate (25 g.) and 3-aminopropyl cyanide hydrochloride (20 g.) in water (200 c.c.) at 15°. Stirring at room temperature was continued for 2 hours, and the white insoluble 3-*benzamidopropyl cyanide* collected, washed with water and dried in a vacuum; yield 25 g., m. p. 74—76°. For analysis a sample was recrystallised from aqueous methyl alcohol and obtained in colourless nacreous plates, m. p. 78—80° (Found: C, 70·0; H, 6·5; N, 15·1. $C_{11}H_{12}ON_2$ requires C, 70·3; H, 6·4; N, 14·9%).

5-*Phthalimido*-n-*amyl Cyanide.*—5-Bromopentanecarboxylic acid was obtained by the action of hydrobromic–sulphuric acids on the lactone mixture obtained by the potassium persulphate oxidation of *cyclo*hexanone (Brown and Partridge, *J. Amer. Chem. Soc.*, 1944, **66**, 839; Robinson and Smith, *J.*, 1937, 371). This was converted in 86% yield into the amide and the latter into 5-bromoamyl cyanide in 80% yield by the method of Breslow and Hansen (*J. Amer. Chem. Soc.*, 1945, **67**, 686).

Potassium phthalimide (50 g.) was refluxed with a solution of 5-bromoamyl cyanide (45 g.) in anhydrous alcohol (150 c.c.) for 24 hours. Alcohol (*ca.* 125 c.c.) was distilled off, water (125 c.c.) added, and the solution extracted with ether. Removal of the ether from the dried solution yielded 5-phthalimidoamyl cyanide (52 g.) as an oil which could not be induced to crystallise (cf. Albert, *Ber.*, 1909, **42**, 557).

5-*Amino*-n-*amyl Cyanide.*—Hydrazine hydrate (50% w/w aqueous solution; 72 g.) was refluxed with a solution of 5-phthalimidoamyl cyanide (152 g.) in alcohol (300 c.c.) for 1 hour and the solution left overnight. The solid mass was dissolved in water (1000 c.c.), the solution rendered just acid to Congo-red by the addition of 10N-hydrochloric acid (*ca.* 120 c.c.), and the precipitate of phthalyl hydrazide removed. The filtrate and washings were evaporated to small volume under reduced pressure at <40°, and the chilled residue was basified with 10N-sodium hydroxide and extracted with chloroform (3 × 100 c.c.). The extract was dried (K_2CO_3) and distilled, 5-*aminoamyl cyanide* (52 g.) being obtained as a colourless oil, b. p. 116—118°/14 mm. (Found: N, 24·8. $C_6H_{12}N_2$ requires N, 25·0%).

A solution of the foregoing base (11·1 g.) and sodium carbonate (7·5 g.) in water (100 c.c.) was stirred at 15° and benzoyl chloride (11·3 c.c.) added slowly. Stirring was continued for a further 2 hours, and the precipitated 5-benzamidoamyl cyanide collected, washed with cold water, and dried in a vacuum; yield 18·6 g., m. p. 94—96°. A sample crystallised from benzene–ligroin in colourless acicular prisms, m. p. 98° (Found: C, 72·1; H, 7·4; N, 13·3. Calc. for $C_{13}H_{16}ON_2$: C, 72·2; H, 7·5; N, 13·0%). Von Braun and Steindorff (*Ber.*, 1904, **37**, 2915) prepared this compound from *N*-benzoylpiperidine and record m. p. 95° (cf. Ainley and King, *Proc. Roy. Soc.*, 1938, **125**, *B*, 60). A solution of 5-aminoamyl cyanide (2·0 g.) and sodium carbonate (3·5 g.) in 50% acetone (50 c.c.) was stirred at 20° with *p*-acetamidobenzenesulphonyl chloride (4·2 g.) for 1 hour. The 5-(p-*acetamidobenzenesulphonamido*)*amyl cyanide* (5·1 g.; m. p. 112°) was filtered off and washed with water; it separated from dilute methyl alcohol in colourless plates, m. p. 114° (Found: N, 13·8; S, 10·5. $C_{14}H_{19}O_3N_3S$ requires N, 13·6; S, 10·4%).

10-*Bromodecyl Cyanide.*—A mixture of 10-bromodecanecarboxylic acid (102 g.; Ashton and Smith, *J.*, 1934, 438) and thionyl chloride (150 c.c.) was kept at room temperature for 1½ hours and then refluxed for a further ½ hour. The excess of thionyl chloride was distilled off at reduced pressure and the residual oil added slowly to rapidly stirred aqueous ammonia (*d* 0·88; 1000 c.c.) at 10°. Stirring was continued for a further 2 hours and the pale brown precipitate of 10-bromodecanecarboxylamide (98 g.; m. p. 84—86°) collected, washed with water, and dried in a vacuum. A sample crystallised from benzene in cream plates, m. p. 90° (Found: N, 5·6; Br, 29·8. Calc. for $C_{11}H_{22}ONBr$: N, 5·3; Br, 30·3%). In one preparation the crude acid chloride was distilled and obtained as a colourless oil, b. p. 176—178°/1 mm., but distillation was normally found to be unnecessary.

The foregoing amide (98 g.) was refluxed with thionyl chloride (100 c.c.) for 75 minutes. After removal of the excess thionyl chloride the residue was distilled and yielded 10-*bromodecyl cyanide* (86 g.) as a pale golden oil, b. p. 158—164°/4 mm. (cf. Trunel, *Compt. rend.*, 1933, **197**, 453) (Found in redistilled sample: N, 5·5; Br, 31·9. $C_{11}H_{20}NBr$ requires N, 5·7; Br, 32·4%).

10-*Phthalimidodecyl Cyanide.*—10-Bromodecyl cyanide (84 g.) and potassium phthalimide (66 g.) were refluxed with alcohol (200 c.c.) for 24 hours. Alcohol (160 c.c.) was distilled off, and the residue, after the addition of water (500 c.c.), extracted with chloroform (2 × 150 c.c.). The extract was dried (K_2CO_3) and the chloroform removed to leave 10-phthalimidodecyl cyanide (97 g.) as a brown oil which failed to crystallise.

10-*Amino*-n-*decyl Cyanide*.—A solution of the foregoing phthalimidocyanide (76 g.) in methyl alcohol (200 c.c.) was refluxed for 1 hour with 50% w/w hydrazine hydrate (30 g.) and then kept at 20° overnight. Water (1000 c.c.) was added followed by 10N-hydrochloric acid until an acid reaction to Congo-red was obtained, the precipitate removed, and the filtrate evaporated to small volume at reduced pressure at <40°, the residue strongly basified with cold 10N-sodium hydroxide and extracted with chloroform. After drying over potassium carbonate, the chloroform solution yielded 10-*aminodecyl cyanide* as an amber water-soluble oil (29 g.), b. p. 138—142°/2 mm.; on redistillation it was obtained as a colourless oil, b. p. 136—138°/2 mm. (Found: N, 15·0. $C_{11}H_{22}N_2$ requires N, 15·4%).

Benzoyl chloride (7·8 g.) was added dropwise to a stirred mixture of the foregoing amino-cyanide (10·0 g.), sodium carbonate (10 g.), and water (100 c.c.) at 15°. Stirring was continued for 1 hour, and the precipitated 10-*benzamidodecyl cyanide* collected, washed with water and dried in a vacuum (15·4 g.; m. p. 54°); it crystallised from benzene–ligroin in colourless needles, m. p. 64° (Found: C, 75·4; H, 9·1; N, 10·0. $C_{18}H_{26}ON_2$ requires C, 75·5; H, 9·1; N, 9·8%).

Interaction of the aminocyanide with *p*-acetamidobenzenesulphonyl chloride in the presence of sodium carbonate in aqueous acetone in the same manner as described above yielded 10-(p-*acetamidobenzenesulphonamido*)*decyl cyanide*, which separated from aqueous methyl alcohol in colourless needles, m. p. 94° (Found: N, 11·3; S, 8·2. $C_{19}H_{29}O_3N_3S$ requires N, 11·1; S, 8·4%).

Aminomethyl Cyanide Hydrochloride.—Calcium carbonate (50 g.) was added portionwise to a rapidly stirred solution of aminomethyl cyanide sulphate (50 g.; *Org. Synth.*, Coll. Vol. I, 298) in water (200 c.c.). The excess of calcium carbonate and calcium sulphate were filtered off, and the solution acidified to Congo-red with hydrochloric acid and evaporated to dryness at reduced pressure at <40°. The residue was washed with a small amount of cold alcohol and recrystallised from methyl alcohol–diethyl ether, aminomethyl cyanide hydrochloride being obtained in colourless plates, m. p. 144—146°, which slowly turned purple in contact with the air (Found: N, 30·5; Cl, 37·9. Calc. for $C_2H_4N_2,HCl$: N, 30·3; Cl, 38·4%) (Menge, *loc. cit.*, gives m. p. 165° darkening at 135°).

Benzamidomethyl Cyanide.—Benzoyl chloride (50 g.) was added dropwise to a rapidly stirred solution of aminomethyl cyanide sulphate (50 g.) and sodium carbonate (70 g.) in water (150 c.c.), the temperature not being allowed to exceed 15°. Stirring was continued at room temperature for 8 hours, and the white insoluble *benzamidomethyl cyanide* collected, washed with water, and dried; yield 44 g., m. p. 136—138°. A sample crystallised from methyl alcohol in colourless rectangular plates, m. p. 142—144° (Found: N, 17·7. $C_9H_8ON_2$ requires N, 17·5%).

p-*Acetamidobenzenesulphonamidomethyl Cyanide* (cf. Cocker, *J.*, 1940, 1574).—Sodium carbonate (20 g.) was added to a cold rapidly stirred solution of aminomethyl cyanide sulphate (16·4 g.) in water (50 c.c.); acetone (80 c.c.) was added followed by finely divided *p*-acetamidobenzenesulphonyl chloride (20 g.), and the mixture stirred at room temperature for 3 hours. After the addition of water (50 c.c.) the insoluble *p*-acetamidobenzenesulphonamidomethyl cyanide (17 g.; m. p. 190—192°) was collected, washed with water, and dried; a sample separated from ethyl alcohol in colourless leaves, m. p. 192° (Found: N, 16·8; S, 12·8. Calc. for $C_{10}H_{11}O_3N_3S$: N, 16·6; S, 12·7%).

1-*Aminoethyl Cyanide* (cf. Dubsky, *loc. cit.*).—A solution of potassium cyanide (80 g.) in water (200 c.c.) was added slowly to a stirred mixture of ammonium chloride (72 g.), ether (600 c.c.), and acetaldehyde (32 g.) at 10°. Stirring was continued for 12 hours at 15°, the ether layer separated, and the aqueous layer extracted with ether (2 × 100 c.c.). The combined ether solutions were *completely* dried over ignited potassium carbonate, the ether removed, and the residual oil distilled, 1-aminoethyl cyanide (25 g.) being obtained as a colourless oil, b. p. 53—55°/14 mm. A sample which had been kept for 6 months at 20° under anhydrous conditions redistilled at the same b. p. leaving no residue; a sample kept in the presence of moisture became full of crystalline solid after several weeks. The hydrochloride was obtained in colourless needles, m. p. 144—146°, by the addition of absolute ethereal hydrogen chloride to a solution of the base in absolute alcohol (Found: N, 26·7; Cl, 33·3. $C_3H_6N_2,HCl$ requires N, 26·3; Cl, 33·3%).

1-*Benzamidoethyl Cyanide*.—Benzoyl chloride (19 g.) was added dropwise to a stirred solution of 1-aminoethyl cyanide (8·6 g.) and sodium carbonate (10 g.) in water (20 c.c.) maintained at 15° by external cooling. Stirring was continued for 10 hours, and the precipitate of 1-*benzamidoethyl cyanide* (15·0 g.; m. p. 102—104°) collected, washed with cold water and dried in a vacuum; a sample separated from benzene in colourless needles, m. p. 108° (Found: C, 68·9; H, 5·8; N, 16·4. $C_{10}H_{10}ON_2$ requires C, 69·0; H, 5·8; N, 16·1%).

2-*Benzamidoethyl Cyanide*.—2-Aminoethyl cyanide was obtained by the method of Whitmore *et al.* (*loc. cit.*). The best yields were obtained by standing the mixture of vinyl cyanide and ammonia at *ca.* 30° for 48 hours in a glass pressure bottle; 120 g. of freshly distilled vinyl cyanide yielded 40 g. of 2-aminoethyl cyanide, b. p. 80—85°/17 mm., and 80 g. of bis-compound, b. p. 200—220°/12 mm. It was found essential to use a 10-inch Vigreux column for removal of the aqueous ammonia since the aminocyanide is slightly volatile in water vapour.

Benzoyl chloride (80 c.c.) and 5N-sodium hydroxide (180 c.c.) were added simultaneously to a rapidly stirred solution of the foregoing amino-cyanide (40 g.) in water (120 c.c.) in such a manner that the mixture was maintained throughout at 10—12° and at pH 8·5—10·0. After the addition (45 minutes) the mixture was stirred at room temperature for a further 2 hours, and the 2-benzamidoethyl cyanide filtered off, washed with dilute sodium carbonate and water, and dried in a vacuum at 20—30°. Yield, 92 g. of a white powder, m. p. 94—96°, which was pure enough for further use; a sample crystallised from 10% alcohol in colourless needles, m. p. 96—98° (Found: N, 16·3. Calc. for $C_{10}H_{10}ON_2$: N, 16·1%).

The authors thank Mr. N. Virgo for some of the analyses.

RESEARCH LABORATORIES, MESSRS. WARD, BLENKINSOP & CO. LTD.,
BRADFORD-ON-AVON.
[*Received, October 21st*, 1946.]