494. *The Preparation of α-N-Alkylamino-nitriles, -amides, and -acids.*

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Various α-*N*-alkylamino-nitriles have been prepared from appropriate aldehydes and amines; they are conveniently hydrolysed to the corresponding α-*N*-alkylamino-amides and -acids by concentrated sulphuric acid. In this way, the amino-acids have been obtained in overall yields of 75—80%.

α-*N*-Alkylamino-acids were required in synthetical studies related to a series of antibiotics (Cook, Cox, and Farmer, this vol., p. 1022; see also Plattner and Nager, *Helv. Chim. Acta*, 1948, **31**, 2192, 2203). Several α-*N*-alkylamino-amides and -nitriles were also required in a similar connection (Azole Series, Part XXI, succeeding paper) and it was convenient to use the same starting materials in all three cases.

N-Alkylamino-nitriles have been prepared from aldehydes and ketones by the treatment of cyanohydrins with amines (see, *inter al.*, Jacobson, *J. Amer. Chem. Soc.*, 1945, **67**, 1996) and by the reaction of Schiff's bases with hydrogen cyanide (see, *inter al.*, Trollais, *Bull. Soc. chim.*, 1947, 959) but in most cases it is convenient to avoid the isolation of the intermediate stages. One of the most satisfactory procedures is that of Knoevenagel and Mercklin (*Ber.*, 1884, **17**, 678) in which the carbonyl compound is treated with sodium hydrogen sulphite, followed by the amine and potassium cyanide. This method was used in the present work to prepare α-methylamino-*n*-valeronitrile, α-*methylamino*iso*valeronitrile*, α-iso*propylamino*-n-*valeronitrile*, and α-*iso*propyalmino*iso*valeronitrile and the first case was studied in some detail in order to ascertain the most satisfactory conditions. By use of equimolecular proportions of each reactant, the desired product was obtained in 65% yield, together with a high-boiling compound which was found to be *methyliminobis*-n-*valeronitrile*. The use of two molecular proportions of methylamine eliminated this product and gave 85% of α-methylamino-*n*-valeronitrile whilst 1·5 molecular proportions gave an 80% yield of the desired nitrile; the last proportion was used in subsequent similar preparations.

This method was not satisfactory with lower homologues of the series because the high solubility of the nitriles in water made isolation difficult. Blitz and Slotte (*J. pr. Chem.*, 1926, [ii], **113**, 252) described a preparation of methylaminoacetonitrile in which potassium cyanide was added to a mixture of formaldehyde and methylamine hydrochloride; the product, after extraction with ether, was purified by conversion into its hydrochloride. Repetition of this work, however, gave a crude oil which on distillation was found to contain a large amount of a high-boiling *compound* which appeared analytically to be derived by the elimination of water from methylaminoacetonitrile and two molecular parts of formaldehyde. On treatment with sulphuric acid in ethanol, it formed a sulphate, m. p. 160°, which proved to be the sulphate of methylaminoacetonitrile as it was also obtained from the low-boiling product, although it did not correspond with that described by Délépine (*Bull. Soc. chim.*, 1903, **29**, 1198) as "not melting below 210°." This property of aldehyde derivatives of amino-nitriles of forming salts of the parent compounds on treatment with acid is likely to be general, so that no amino-nitrile preparation in which the product is not isolated by distillation can be regarded with complete confidence.

Methylaminoacetonitrile was obtained in practically quantitative yield by the treatment of hydroxyacetonitrile with alcoholic methylamine; iso*propylaminoacetonitrile* was obtained in a similar way, and in both cases the products were isolated by fractionation of the reaction mixture. An attempt to prepare aminoacetonitrile under the same conditions gave an anomalous result. Menge (*J. Amer. Chem. Soc.*, 1934, **56**, 2197) claimed a quantitative conversion using liquid ammonia but, when the hydroxyacetonitrile was kept at 0° for 24 hours in a large excess of methanolic ammonia and the solvent removed below 50°, a yellow oil was obtained which, although it contained some aminoacetonitrile, consisted mainly of a high-boiling *compound* which polymerised when set aside for several days, even at 0°. This product was found to have the composition required of 1 mol. of amino- + 1 mol. of hydroxy-acetonitrile, and on treatment with sulphuric acid in ethanol yielded aminoacetonitrile sulphate.

This reaction appears to be peculiar to hydroxyacetonitrile since, when α-hydroxy-*n*-valeronitrile was treated with ammonia under the same conditions, α-*amino*-n-*valeronitrile* was obtained in good yield (66%) and the high-boiling by-product was the expected *iminobis*-n-*valeronitrile*. Although the amino-nitrile boiled over a narrow temperature range, it could not be obtained completely free from the imino-nitrile. This is due to the ease with which it loses ammonia, a tendency which has been noted, with similar compounds, by other workers.

The usual method for the preparation of amides of amino-acids consists in treating the corresponding esters with ammonia, but a number of by-products are formed and yields are often poor. Lipp (*Annalen*, 1880, **205**, 14) and Gulewitsch and Wasmus (*Ber.*, 1906, **39**, 1189) treated amino-nitriles with fuming hydrochloric acid and isolated the hydrochlorides of the corresponding amides from the reaction mixture, but the yields were not reported. Attempts to use this technique with methylaminoacetonitrile gave largely sarcosine and ammonium chloride, and it seemed that more closely controlled conditions were required. Tiemann and Stephan (*Ber.*, 1882, **15**, 2035) converted several arylamino-nitriles into the corresponding amides by treatment with concentrated sulphuric acid, isolating the product by pouring the reaction mixture on ice and neutralising it with ammonia; when this was done with methylaminoacetonitrile, no product could be isolated from the aqueous solution, but, if instead the sulphuric acid solution was poured into well-cooled and stirred 95% ethanol, N-*methylglycine amide hydrogen sulphate* crystallised in quantitative yield. When this salt was suspended in methanol and neutralised with sodium methoxide, removal of the sodium sulphate and evaporation gave N-*methylglycine amide* in 90% yield. Aminoacetonitrile sulphate was converted into glycine amide in the same way in 90% yield, and a similar technique was used to prepare N-iso*propylglycine amide* and N-*methylnorvaline amide*.

In view of the absence of by-products in the above reactions it seemed that this technique might usefully be employed in the hydrolysis of amino-nitriles to amino-acids. Cocker and Lapworth (*J.*, 1931, 1391) pointed out that alkaline conditions should be avoided because of the simultaneous dissociation which takes place, and recommended the use of 40% sulphuric acid. α-Methylamino-*n*-valeronitrile was hydrolysed under these conditions, and *N*-methylnorvaline was isolated in 65% yield; a non-basic oil was formed at the same time. When the nitrile was first heated with the same amount of concentrated sulphuric acid for 1 hour, the solution diluted with water to 40% sulphuric acid and boiled under reflux for 5 hours, the amino-acid was obtained in 95% yield. The hydrolysis mixture could be worked up according to the method recommended by Cocker and Lapworth (*loc. cit.*) using barium carbonate etc., but it was more convenient to add the calculated amount of sodium hydroxide and, after evaporation to dryness, to extract the amino-acid with methanol.

This hydrolysisprocedure proved to be equally satisfactory in the hydrolysis of α-*iso*propylamino-*n*-, α-methylamino*iso*-, and α-*iso*propylamino*iso*-valeronitrile. In the last two cases, the N-*methylvaline amide* and N-iso*propylvaline amide* formed during the first stage of the reaction were surprisingly resistant to hydrolysis and could be isolated on working up the product; after the mixture had been heated under reflux for 5 hours, hydrolysis was only 30% complete, and even after 16 hours 30% of the amide remained unchanged.

By the use of the methods outlined above, *N*-methylvaline, *N*-methylnorvaline, N-iso*propylvaline*, and N-iso*propylnorvaline* were obtained from the corresponding aldehydes in yields of 75—80%.

Experimental.

Preparation of α-Methylamino-n-valeronitrile.—*n*-Butyraldehyde (50 g.) was added with cooling and stirring to a solution of sodium pyrosulphite (55 g.) in water (150 c.c.). After 30 minutes, 33% aqueous methylamine (67 c.c., 1 equiv.) was run in rapidly, and after a further 30 minutes finely powdered potassium cyanide (45 g.) was added. Stirring was continued for 1 hour, whereafter the oily layer was separated and the solution extracted with ether (2 × 150 c.c.). After being dried, the solvent was removed and the product distilled *in vacuo*. The first fraction, b. p. 85°/25 mm., was α-methylamino-*n*-valeronitrile (50 g., 65%). The second fraction, b. p. 100°/10^{-5} mm., was *methyliminobis-n-valeronitrile* (13 g., 20%) (Found: C, 68·3; H, 9·7. $C_{11}H_{19}N_3$ requires C, 68·4; H, 9·8%). This experiment was repeated using 1·5 and 2 equivalents of methylamine; the yields of α-methylamino-*n*-valeronitrile were 80% and 85%, respectively, whilst the formation of the iminobisnitrile was correspondingly reduced.

*Preparation of α-Methylamino*iso-, α-iso*Propylamino*-n-, *and* α-iso*Propylamino*iso-*valeronitrile.*—The technique described above was used to prepare the three nitriles, with in each case 1·5 molecular equivalents of the necessary amine. α-*Methylamino*iso*valeronitrile*, b. p. 70°/20 mm., was obtained in 80% yield (Found: N, 25·0. $C_6H_{12}N_2$ requires N, 25·0%). α-iso*Propylamino*-n-*valeronitrile*, b. p. 86°/20 mm., was obtained in 80% yield (Found: C, 68·9; H, 11·5; N, 20·0. $C_8H_{16}N_2$ requires C, 68·6; H, 11·4; N, 20·0%). α-*iso*Propylamino*iso*valeronitrile, b. p. 86°/25 mm., was obtained in 85% yield. In each case, the product was a colourless liquid, with a pungent odour, which could be stored for several months without deterioration.

Preparation of Methylaminoacetonitrile.—Methylamine hydrochloride (100 g.) was dissolved in 40% formaldehyde solution (200 g.) and cooled to 0°; potassium cyanide (100 g.) in water (100 c.c.) was added during 3 hours with stirring. The oily layer was removed and, after being kept overnight, the solution was extracted with ether (3 × 300 c.c.). The combined product was dried and distilled, the first fraction, b. p. 65°/20 mm., being methylaminoacetonitrile (50 g., 47%). This formed a *sulphate*, m. p. 160°, which crystallised from ethanol as white needles (Found: N, 23·8.

$C_3H_6N_2,\frac{1}{2}H_2SO_4$ requires N, 23·6%). The second *fraction*, b. p. 90°/0·1 mm., amounted to 65 g. (Found: C, 53·9; H, 7·4; N, 24·9. $C_5H_8ON_2$ requires C, 53·6; H, 7·1; N, 25·0%). On treatment with ethanolic sulphuric acid, this formed the sulphate, m. p. 160°, described above.

Hydroxyacetonitrile (100 g.) was added to a solution of methylamine (80 g., 1·5 equivs.) in methanol (250 c.c.) cooled in ice. The mixture was set aside overnight and distilled. The fraction, b. p. 65—8°/20 mm., was methylaminoacetonitrile (114 g., 93%).

Preparation of iso*Propylaminoacetonitrile*.—This was obtained by treating hydroxyacetonitrile (100 g.) with *iso*propylamine (103 g., 1·5 equivs.) in methanol (250 c.c.) and setting the mixture aside for 16 hours. The *product*, b. p. 83—85°/20 mm., amounted to 155 g. (90%) (Found: C, 61·0; H, 10·3; N, 28·8. $C_5H_{10}N_2$ requires C, 61·2; H, 10·2; N, 28·6%). It was a colourless liquid with a strong basic odour.

Action of Alcoholic Ammonia on Hydroxyacetonitrile.—Hydroxyacetonitrile (30 g.) in methanol (100 c.c.) was added cautiously to liquid ammonia (100 c.c.), and the mixture was set aside for 24 hours at 0°. The excess of ammonia and methanol was then removed *in vacuo* below 50°, and the yellow oil which remained was distilled. The main *fraction*, b. p. 70—72°/1 mm., amounted to 20 g. (Found: C, 42·3; H, 6·4; N, 37·1. $C_4H_7ON_3$ requires C, 42·5; H, 6·2; N, 37·1%) whilst a thick dark residue remained in the flask. A portion of the main fraction was dissolved in ethanol and a solution of ethanolic sulphuric acid was added until the mixture was just acid to Congo-red. The white solid was purified by dissolution in the minimum amount of water, followed by addition to ethanol. It melted at 173° (decomp.) and did not depress the m. p. of an authentic specimen of aminoacetonitrile sulphate.

*Action of Alcoholic Ammonia on α-Hydroxy-*n*-valeronitrile*.—Hydroxy-*n*-valeronitrile (30 g.) in methanol (100 c.c.) was added cautiously to liquid ammonia (100 c.c.) and set aside at 0° for 24 hours. The ammonia and methanol were removed *in vacuo* below 50°, and the product distilled. The main fraction, b. p. 86°/20 mm., was *α-amino-*n*-valeronitrile* (Found: C, 62·9; H, 10·5; N, 27·3. $C_5H_{10}N_2$ requires C, 61·2; H, 10·2; N, 28·6%). It was a colourless liquid which smelled strongly of ammonia after several days at 0° and amounted to 20 g. (66%). A second fraction, b. p. 100°/10^{-5} mm., was *iminobis-*n*-valeronitrile* and weighed 7 g. (Found: C, 66·9; H, 9·7; N, 23·3. $C_{10}H_{17}N_3$ requires C, 67·0; H, 9·5; N, 23·5%).

Preparation of N*-Methylglycine Amide*.—Methylaminoacetonitrile sulphate (30 g.) was added with shaking to concentrated sulphuric acid (60 c.c.) and heated at 100° for 1 hour. It was then cooled and run into 95% ethanol (400 c.c.) with efficient stirring and cooling in ice. The *N-methylglycine amide hydrogen sulphate* which crystallised was filtered off, washed with a little ice-cold ethanol, and dried *in vacuo* (yield, 46 g., 98%). It could be recrystallised from methanol as colourless hygroscopic cubes, m. p. 102° (Found: N, 15·0. $C_3H_8ON_2,H_2SO_4$ requires N, 15·1%). The hydrogen sulphate (30 g.) was suspended in methanol (100 c.c.) and cooled in ice, and sodium methoxide in methanol was run in with stirring until the mixture was just alkaline to phenolphthalein. It was filtered to remove the sodium sulphate which was washed with more methanol, and the combined filtrates were evaporated *in vacuo*. The N*-methylglycine amide* which remained amounted to 13 g. (90%) and sublimed rapidly *in vacuo* leaving very little residue. The product was obtained as white hygroscopic prisms, m. p. 70—72° (Found: C, 40·7; H, 9·1; N, 31·6. $C_3H_8ON_2$ requires C, 40·9; H, 9·1; N, 31·8%).

Preparation of Glycine Amide, N-iso*Propylglycine Amide, and* N*-Methylnorvaline Amide*.—Glycine amide was prepared by the procedure outlined above, in 90% overall yield, from aminoacetonitrile sulphate. The product, m. p. 65—66°, did not depress the m. p. of authentic glycine amide. In the preparation of the other two amides, a clear solution was obtained on adding the sulphuric acid reaction mixture to ethanol and it was necessary to neutralise the whole of the acid. N-iso*Propylglycine amide* (91%) was obtained as white prisms, m. p. 68°, which sublimed *in vacuo* and liquefied on exposure to moist air (Found: N, 24·0. $C_5H_{12}ON_2$ requires N, 24·1%). N*-Methylnorvaline amide* (87%) also sublimed as white prisms, m. p. 102—103° (Found: C, 55·6; H, 10·9; N, 21·5. $C_6H_{14}ON_2$ requires C, 55·4; H, 10·8; N, 21·5%).

Preparation of N*-Methylnorvaline and* N-iso*Propylnorvaline*.—α-Methylamino-*n*-valeronitrile (50 g.) was added with cooling and stirring to concentrated sulphuric acid (90 g.), and the mixture was heated at 100° for 1 hour. Ice (70 g.) was added and the stirrer was removed after careful washing with water (50 c.c.) so that none of the acid was lost. The mixture was then heated under reflux for 5 hours, and a solution of sodium hydroxide (72·5 g., 1 equiv.) in water (150 c.c.) was added cautiously. The water was removed *in vacuo*, and the product extracted with hot methanol (4 × 300 c.c.). Evaporation of the methanol left a white solid which, after being washed with acetone (200 c.c.), was nearly pure *N*-methylnorvaline. It sublimed without melting, as white prisms (56 g., 96%). In the same way, N-iso*propylnorvaline* was obtained from *α-iso*propylamino-*n*-valeronitrile in 94% yield, as a white powder which also sublimed without melting (Found: C, 60·3; H, 10·7; N, 9·0. $C_8H_{17}O_2N$ requires C, 60·5; H, 10·7; N, 8·8%).

Preparation of N*-Methylvaline Amide and* N*-Methylvaline*.—α-Methylamino*iso*valeronitrile (50 g.) was hydrolysed with concentrated sulphuric acid (90 g.) according to the procedure outlined above. The extraction with methanol, however, yielded a crude product which separated into two components on being washed with acetone. The insoluble material was *N*-methylvaline (19 g., 32%) which sublimed, without melting, as white prisms. From the acetone solution, there was obtained on evaporation a thick yellow oil (37 g., 63%) which slowly crystallised and which sublimed *in vacuo* as colourless prisms, m. p. 85°. This proved to be N*-methylvaline amide* (Found: C, 55·2; H, 10·9; N, 21·2. $C_6H_{14}ON_2$ requires C, 55·4; H, 10·8; N, 21·5%). When the period of hydrolysis was extended to 18 hours, the product contained 70% of *N*-methylvaline and 25% of *N*-methylvaline amide and it was only after 40 hours that the amount of amide became unimportant.

Preparation of N-iso*Propylvaline Amide and* N-iso*Propylvaline*.—The hydrolysis of *α-iso*propylamino*iso*valeronitrile was carried out using the procedure described above. After a period of reflux of 5 hours, the products obtained were N-iso*propylvaline* (26%), which sublimed, without melting, as white prisms (Found: C, 60·7; H, 10·9; N, 8·7. $C_8H_{17}O_2N$ requires C, 60·5; H, 10·7; N, 8·8%), and N-iso*propylvaline amide* (68%), m. p. 61°, which sublimed in a high vacuum as white prisms (Found:

C, 60·9; H, 11·5; N, 17·6. $C_8H_{18}ON_2$ requires C, 60·8; H, 11·4; N, 17·7%). After a period of reflux of 16 hours, the yield of the amino-acid was 68% and that of the amide was 30%.

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