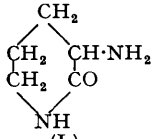
13. *The Anhydrides of Basic Amino-acids.*

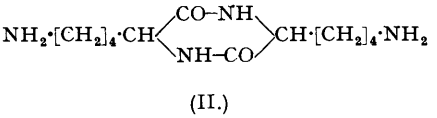
By Donald W. Adamson.

" *dl*-Lysine anhydride " (the product obtained by heating *dl*-lysine methyl ester), which has hitherto been regarded as a substituted diketopiperazine, is now shown to contain at least 40% of dl-3-*aminohomopiperidone*. Similarly, l-3-*aminopyrrolidone* is obtained in good yield by heating the methyl ester of *d*-αγ-diamino-*n*-butyric acid. Some derivatives of these bases are described.

α-Amino-esters are normally converted by heat into the corresponding substituted diketopiperazines, as first observed by Curtius (*Ber.*, 1904, **37**, 1284) for glycine ester. *dl*-Ornithine, however, did not react in this manner, since intramolecular cyclisation to *dl*-3-aminopiperidone (I) occurred even during attempted esterification (Fischer and Zemplen, *Ber.*, 1909, **42**, 4878). The same tendency to cyclisation has been observed with various derivatives of ornithine (Fischer and Bergmann, *Annalen*, 1913, **398**, 115; Thomas, Kapfhammer, and Flaschenträger, *Z. physiol. Chem.*, 1922, **124**, 75).



(I.)



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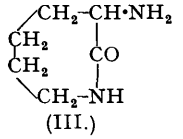
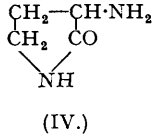


(III.)



(IV.)

On the other hand, " *dl*-lysine anhydride," obtained as a brown, viscous mass by heating *dl*-lysine methyl ester to 100°, was stated to have the diketopiperazine structure (II) (Fischer and Suzuki, *Chem. Zentr.*, 1905, I, 354; *Ber.*, 1905, **38**, 4173). On repeating this preparation, it is now found that the crude anhydride contains 40% of a white crystalline compound (b. p. 167°/12 mm., m. p. 68—71°) which must be identified as the unimolecular anhydride, dl-3-*aminohomopiperidone* (III), by reason of its volatility. The *picrate* and the *hydrochloride* prepared from this compound are similar to those isolated by Fischer and Suzuki (*loc. cit.*), and it is therefore concluded that their crude anhydride consisted of (III) admixed with non-volatile lysyl peptides.

dl-3-Aminohomopiperidone is strongly basic and hygroscopic and is readily hydrolysed to *dl*-lysine hydrochloride by hydrochloric acid. Acetylation with acetic anhydride under mild conditions yields 3-acetamidohomopiperidone, which had been obtained by Wrede (*Z. physiol. Chem.*, 1932, **206**, 146) by hydrolysis of the base $C_{10}H_{14}O_2N_2$, isolated from the acetylation product of certain proteins, or by acetylation of *d*-lysine under vigorous conditions.

The free amino-group of (III), available for coupling, corresponds to the α-amino-group of the parent lysine (the point of linkage in natural products), whereas the ε-amino-group is protected. Accordingly, (III) condensed with *p*-acetamidobenzenesulphonyl chloride to give dl-3-(p-*acetamidobenzenesulphonamido*)*homopiperidone*, which was hydrolysed to ε-*amino*-α-(p-*aminobenzenesulphonamido*)-n-*hexoic acid*. It is also possible that (III) may serve for the synthesis of lysyl peptides (compare Bergmann and Koster, *Z. physiol. Chem.*, 1927, **167**, 91, who report that the lactam group of 3-acetylphenylalanylaminopiperidone may be hydrolysed, leaving the peptide link intact).

As expected, methyl *d*-αγ-diamino-*n*-butyrate (available from glutamic acid; Adamson, J., 1939, 1564) was readily converted into 1-3-*aminopyrrolidone* (IV). The preparation of the *picrate* and the *hydrochloride* of this base and of 3-*acetamido*- and 3-(p-*acetamidobenzenesulphonamido*)-*pyrrolidone* is described.

Experimental.

dl-*Lysine Methyl Ester Dihydrochloride*.—Methyl alcohol (340 c.c.) containing a suspension of *dl*-lysine dihydrochloride (17·0 g.) (Adamson, *loc. cit.*) was saturated with dry hydrogen chloride without cooling. Crystallisation of the hot, clear solution commenced on cooling, and was completed by addition of ether (340 c.c.). After standing overnight, the precipitate was filtered off, washed with methyl alcohol–ether, and dried in a vacuum. Yield, 17·5 g. (98%); m. p. 217—218° (Fischer and Suzuki, *loc. cit.*, give m. p. 218°).

" dl-*Lysine Anhydride*."—Sodium (2 g.) was dissolved in methyl alcohol (100 c.c.) and added to a solution of *dl*-lysine methyl ester dihydrochloride (10 g.) in warm methyl alcohol (100 c.c.). Ether (500 c.c.) was added, and the mixture kept for several hours. Sodium chloride was then removed, and the filtrate evaporated under reduced pressure; the residual gum was heated at 100° for 2 hours. The product (5·3 g.) was a pale brown, viscous mass which partly solidified when kept at 0° for several days (compare Fischer and Suzuki, *loc. cit.*).

dl-3-*Aminohomopiperidone*.—" *dl*-Lysine anhydride " (10 g., prepared as above) was distilled from an oil-bath under reduced pressure. The volatile fraction (3·9 g.), collected at 165—167°/12 mm., solidified on cooling (m. p. 60—63°); redistillation gave long white needles, b. p. 167°/12 mm., m. p. 68—71° (Found : C, 56·4; H, 9·6; N, 21·9. $C_6H_{12}ON_2$ requires C, 56·3; H, 9·4; N, 21·9%). The *base* was soluble in water, sparingly soluble in alcohol. and insoluble in other organic solvents. The distillation residue (*ca.* 6 g.) was a dark brown resin, insoluble in hot water and organic solvents.

Hydrolysis. The base (0·11 g.), dissolved in hydrochloric acid (20%, 3 c.c.), was heated on the water-bath for 1 hour, and the product evaporated to dryness. The residue was dissolved in a little water, and picric acid (0·5 g.) in water (40 c.c.) added; *dl*-lysine dipicrate which separated had m. p. 186—188°, not depressed by admixture with an authentic specimen (Adamson, *loc. cit.*).

Hydrochloride. Dry hydrogen chloride was passed into a solution of the base (0·26 g.) in methyl alcohol (5 c.c.), and the white crystalline *hydrochloride* which separated was filtered off, washed with ether, and dried in a vacuum; m. p. 294—296° (decomp.) (Found : N, 16·5; Cl, 21·2. $C_6H_{13}ON_2Cl$ requires N, 17·0; Cl, 21·6%). Data for the " *dl*-lysine anhydride dihydrochloride " of Fischer and Suzuki (*loc. cit.*) are recorded variously as " m. p. 270° "; " colours at 225°, then sinters and melts at a higher temperature with frothing."

Picrate. Picric acid (0·3 g.) in water (30 c.c.) was added to a solution of the base (0·17 g.) in water (5 c.c.) and set aside for 24 hours. Recrystallisation of the resulting precipitate (0·33 g.) from a little hot water gave long needles of the *picrate*; it darkened at 215°, m. p. 233° (decomp.) (Found: N, 19·8. $C_6H_{12}ON_2,C_6H_3O_7N_3$ requires N, 19·6%). According to Fischer and Suzuki, "*dl*-lysine anhydride dipicrate" darkens at 210°, m. p. 230° (decomp.).

dl-3-*Acetamidohomopiperidone.*—The base (0·5 g.) was dissolved in acetic anhydride (1·2 g.) and heated at 100° for 5 mins., excess of the anhydride then being removed by several evaporations with 5 c.c. portions of ethyl alcohol. The solid residue was obtained as clusters of white needles, m. p. 162°, by recrystallisation from acetone (Found: C, 56·4; H, 8·2; N, 16·3. Calc. for $C_8H_{14}O_2N_2$: C, 56·5; H, 8·2; N, 16·5%) (Wrede, *loc. cit.*, gives m. p. 163°).

3-(p-*Acetamidobenzenesulphonamido*)*homopiperidone.*—The base (1·65 g.) in chloroform (10 c.c.) was added to *p*-acetamidobenzenesulphonyl chloride (3·1 g.) in chloroform (35 c.c.). The crystalline precipitate was washed with boiling water (50 c.c.) and recrystallised from a large volume of alcohol. Yield, 1·85 g., m. p. 286—288° (decomp.) (Found: C, 52·0; H, 5·9; N, 12·8; S, 9·8. $C_{14}H_{19}O_4N_3S$ requires C, 51·7; H, 5·9; N, 12·9; S, 9·8%). A solution of 1·5 g. of this *compound* in hydrochloric acid (12%, 10 c.c.) was refluxed for 2 hours. After neutralisation with ammonia, the solution was cooled to 0° for 2 days, whereupon small prisms of ε-*amino*-α-(p-*aminobenzenesulphonamido*)-n-*hexoic acid* (0·85 g.) separated; recrystallised from a small volume of aqueous alcohol, these had m. p. 286° (decomp.) (Found: N, 13·9; S, 11·1. $C_{12}H_{19}O_4N_3S$ requires N, 14·0; S, 10·6%).

1-3-*Aminopyrrolidone.*—A suspension of *d*-αγ-diamino-*n*-butyric acid dihydrochloride (25 g.) (Adamson, *loc. cit.*) in methyl alcohol (750 c.c.) was saturated with dry hydrogen chloride without cooling. After refluxing for 6 hours, the methyl alcohol and hydrogen chloride were removed by evaporation under reduced pressure at 30°. The residual gum (26·3 g.) was dissolved in hot methyl alcohol (50 c.c.), cooled, and sodium (6·1 g.) dissolved in methyl alcohol (200 c.c.) added. Ether (700 c.c.) was added, sodium chloride filtered off, and the ether and alcohol removed by evaporation at 30°. The solid residue was heated at 100° for 40 mins. and finally distilled, 1-3-*aminopyrrolidone* (8·9 g., 68% yield) being collected at 175°/20 mm.; white needles, m. p. 106—108°, $[\alpha]_D^{18^\circ}$ −31·7° (*c*, 6·69 in water) (Found: C, 48·4; H, 7·8; N, 28·0. $C_4H_8ON_2$ requires C, 48·0; H, 8·0; N, 28·0%). The base quickly absorbs carbon dioxide from the air, is very soluble in water, moderately soluble in alcohol and chloroform, and only sparingly soluble in ether and light petroleum. Hydrolysis with hydrochloric acid gave *d*-αγ-diamino-*n*-butyric acid dihydrochloride, m. p. 193—195°, characterised by conversion into the dipicrate, m. p. 188° (Adamson, *loc. cit.*).

The *hydrochloride* was precipitated as fine white crystals when hydrogen chloride was passed into a solution of the base in alcohol; m. p. 198—200° (Found: N, 20·1; Cl, 25·7. $C_4H_9ON_2Cl$ requires N, 20·5; Cl, 26·0%). The *picrate*, prepared by mixing picric acid and the base in alcoholic solution, was obtained as prisms by recrystallisation from aqueous alcohol; m. p. 185—187° (darkened at 170°) (Found: N, 21·3. $C_4H_8ON_2,C_6H_3O_7N_3$ requires N, 21·3%). Acetylation by means of acetic anhydride gave 3-*acetamidopyrrolidone*; recrystallised from hot acetone, this had m. p. 176° (Found: C, 50·8; H, 6·8; N, 19·8. $C_6H_{10}O_2N_2$ requires C, 50·7; H, 7·0; N, 19·7%).

3-(p-*Acetamidobenzenesulphonamido*)*pyrrolidone.*—The base (1·5 g.) in hot acetone (20 c.c.) was added to *p*-acetamidobenzenesulphonyl chloride (3·4 g.) in hot acetone (20 c.c.). The solid which separated was filtered off and recrystallised several times from hot water; m. p. 222—224° (decomp.) (Found: C, 48·8; H, 5·2; N, 14·4; S, 11·0. $C_{12}H_{15}O_4N_3S$ requires C, 48·5; H, 5·1; N, 14·1; S, 10·8%). A solution of this *compound* (2·5 g.) in hydrochloric acid (12%, 12 c.c.) was boiled under reflux for 2 hours. The cooled solution was neutralised with ammonia, and the precipitate of γ-*amino*-α-(p-*aminobenzenesulphonamido*)-n-*butyric acid* (2·1 g.) recrystallised from much hot water, m. p. 259—260° (decomp.) (Found: N, 15·4; S, 11·8. $C_{10}H_{15}O_4N_3S$ requires N, 15·4; S, 11·7%).

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