63. *The Reaction of Cyanamide with α-Amino-acetals and α-Amino-aldehydes.*

By Alexander Lawson.

2-Aminoglyoxalines (II) are obtained in good yield by the action of cyanamide on α-amino-acetals followed by hydrolysis and ring closure. A number of α-amino-esters have been reduced by the Akabori method and condensed with cyanamide to give, after ring closure, the glyoxalino-glyoxalines (IV).

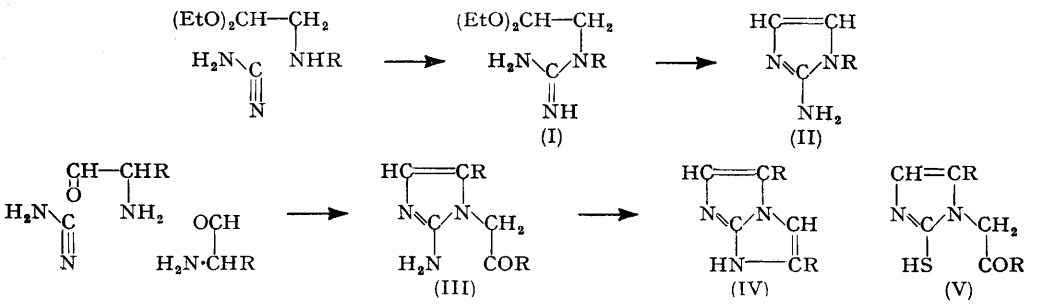
The preparation of 2-aminoglyoxaline and its derivatives has been described by Pyman and his co-workers [1] and by De Cat and van Dormael.[2] They introduced the amino-group into a preformed glyoxaline ring by the reduction of a *para*-substituted 2-phenylazoglyoxaline obtained by condensing the diazonium compound with the glyoxaline. Theoretically, an obvious route to 2-aminoglyoxalines is the condensation of cyanamide with α-aminocarbonyl compounds, but Norris and McKee [3] reported that condensations of *p*-chlorophenacylamine hydrochloride with cyanamide, dicyandiamide, and sodium dicyandiamide were unsatisfactory though they obtained moderate yields of 2-guanidinoglyoxalines from *p*-chlorophenacylamine hydrochloride and various cyanoguanidines. Leonard, Curtin, and Beck [4] describe the preparation of 2-aminobenziminazole derivatives by condensing *o*-phenylenediamines with cyanogen bromide, a method originally used by Ziegelbauer.[5]

No crystalline material could be isolated on reaction of aminoacetaldehyde with cyanamide at various pH, presumably because the conditions favourable for the condensation led to decomposition of the amino-aldehyde. However the amino-acetal reacted smoothly in acetic acid, giving the acetate of the diethoxyethylguanidine (I; R = H) which on treatment with hydrochloric acid cyclised to the hydrochloride of the strongly basic 2-aminoglyoxaline [1a] (II; R = H). In addition to the derivatives described by Pyman *et al.* 2-acetamidoglyoxaline hydrochloride was prepared, which crystallised as the monohydrate and gave 2-acetamidoglyoxaline, prepared by Pyman *et al.*, on treatment with sodium carbonate. Although 2-aminoglyoxaline is only a monoacidic base, like guanidine itself, the acetyl derivative still apparently retains considerable basicity.

In a similar way *N*-methylamino-acetal on reaction with cyanamide followed by ring closure gave 2-amino-1-methylglyoxaline (II; R = Me).

[1] Pyman and co-workers, *J.*, (*a*) 1919, 217; (*b*) 1920, 1426; (*c*) 1925, 2012.
[2] De Cat and van Dormael, *Bull. Soc. chim. belges*, 1950, **59**, 273.
[3] Norris and McKee, *J. Amer. Chem. Soc.*, 1955, **77**, 1056.
[4] Leonard, Curtin, and Beck, *ibid.*, 1947, **69**, 2459.
[5] Ziegelbauer, *Monatsh.*, 1896, **17**, 653.

In order to account for the formation of glyoxalinothiazoles by reaction between thiocyanate and amino-aldehydes at pH 4, it was postulated [6] that the latter substances underwent a Schiff's base condensation with subsequent deamination. Something about the behaviour of amino-aldehydes under conditions at which condensation with cyanamide might be expected to take place being therefore known, it seemed worth while to attempt such condensations using the solution resulting from the Akabori reduction [7] of amino-esters. In the case of alanine ester, reaction between the α-aminopropionaldehyde in solution at pH 4 and cyanamide gave the glyoxalinoglyoxaline (IV; R = Me) in about 30% yield.



With the esters of leucine, norleucine, α-amino-octanoic acid, and phenylalanine, boiling the solutions containing the amino-aldehydes with cyanamide gave varying yields of sparingly soluble hydrochlorides of bases which on the evidence of the analytical results, the absence of typical aldehyde properties, and their ability to give oximes, have been assigned the structure of 5-alkyl-2-amino-1-oxoalkylglyoxalines (III) [analogous glyoxalinyl ketones (V) were obtained from the corresponding reaction between the amino-aldehydes and thiocyanate [6]]. The hydrochlorides of these bases (III) on treatment with acetic anhydride gave acetyl derivatives similar to those described for the simpler 2-aminoglyoxalines above. From the compounds (III) the glyoxalinoglyoxalines (IV) were obtained either by the action of hydrochloric acid or, as in the case of the phenylalanine derivative, by spontaneous ring closure of the corresponding free base.

The filtrates from the hydrochlorides of the bases (III), when made alkaline and extracted with ether, gave, together with some unchanged amino-ester, considerable quantities of non-crystalline basic material. This, together with the products obtained similarly from other amino-esters which did not give sparingly soluble hydrochlorides, are being further examined. Guanidine derivatives appear to be present since crystalline picrates obtained gave the Jaffé reaction.

Experimental

N-(2 : 2-*Diethoxyethyl*)*guanidine* (I; R = H).—Aminoacetaldehyde diethyl acetal (4 g.) was heated for 1 hr. on a water-bath with cyanamide (2·5 g.) dissolved in water containing a few drops of acetic acid.[8] After concentration under reduced pressure, the residual syrup was triturated with anhydrous ether, and the gummy residue treated with acetone (30 ml.) to give the colourless crystalline *guanidine acetate* (1·8 g.). Recrystallisation from ethanol–ether gave prisms, m. p. 139—140° (Found: C, 45·8; H, 8·7; N, 17·7. $C_7H_{17}O_2N_3,CH_3{\cdot}CO_2H$ requires C, 45·9; H, 8·9; N, 17·8%).

2-*Aminoglyoxaline* (II; R = H).—The above acetate (1 g.) was warmed in concentrated hydrochloric acid (3 ml.) for a few min. on the water-bath. Water was added and evaporation of the solution to dryness under reduced pressure, and again after addition of water, left the crystalline 2-aminoglyoxaline hydrochloride (quantitative yield) which on recrystallisation from ethanol–ether (somewhat hygroscopic plates) had m. p. 155° (Fargher and Pyman [1a] found 152°) (Found: C, 29·7; H, 5·1; N, 34·9. Calc. for $C_3H_5N_3,HCl$: C, 30·1; H, 5·1; N, 35·1%). This gave a picrate, felted needles (from ethanol), m. p. 231°, and the acetyl derivative had m. p. 285° (decomp.). 2-*Acetamidoglyoxaline hydrochloride*, prepared by warming the hydrochloride

[6] Lawson and Morley, *J.*, 1955, 1695.
[7] Akabori, *Ber.*, 1933, **67**, 151.
[8] Kurzer and Lawson, *Org. Synth.*, 1954, **34**, 67.

with acetic anhydride for a few min. and recrystallising the product from ethanol, gave needles, m. p. 143° (Found: C, 33·5; H, 5·5; N, 23·4. $C_5H_7ON_3,HCl,H_2O$ requires C, 33·4; H, 5·6; N, 23·4%).

N-2 : 2-*Diethoxyethyl*-N-*methylguanidine* (I; R = Me).—The *acetate* (5·0 g.) obtained as above from methylaminoacetaldehyde diethyl acetal (5·5 g.) and a solution of cyanamide (5 g.) in aqueous acetic acid, and recrystallised from alcohol–ethyl acetate, had m. p. 202° (needles) (Found: C, 48·2; H, 9·3; N, 16·6. $C_8H_{19}O_2N_3,CH_3{\cdot}CO_2H$ requires C, 48·2; H, 9·2; N, 16·8%). The *picrate* (needles from water) had m. p. 117° (Found: C, 40·3; H, 5·5; N, 20·0. $C_{14}H_{22}O_9N_6$ requires C, 40·3; H, 5·3; N, 20·1%).

2-*Amino*-1-*methylglyoxaline* (II; R = Me).—The *hydrochloride*, obtained from the acetal by the above method in quantitative yield, had m. p. 84° (prismatic needles from ethanol–ethyl acetate) (Found: C, 31·5; H, 6·7; N, 27·6. $C_4H_7N_3,HCl,H_2O$ requires C, 31·7; H, 6·6; N, 27·7%). The *picrate* (prisms from aqueous ethanol) had m. p. 212° (Found: C, 36·9; H, 3·1. $C_{10}H_{10}O_7N_6$ requires C, 36·8; H, 3·1%). The free base obtained by extraction of an alkaline solution of the hydrochloride with chloroform and purified by distillation at 12 mm. was too hygroscopic for analysis. It was sparingly soluble in ether and benzene. The hydrochloride, warmed with acetic anhydride, give an *acetyl derivative* (needles from aqueous ethanol), m. p. 141° (Found: C, 37·1; H, 6·1; N, 21·6. $C_6H_9ON_3,HCl,H_2O$ requires C, 37·1; H, 6·2; N, 21·7%).

2 : 3-*Dihydro*-4 : 5′-*dimethylglyoxalino*(1′ : 2′-1 : 2)*glyoxaline* (IV; R = Me).—DL-α-Alanine (10 g.) was esterified with ethanol and reduced with sodium amalgam as previously described.[6] To the solution of the resulting amino-aldehyde, cyanamide (10 g.) in 10% aqueous acetic acid (60 ml.) was added and the mixture brought to pH 4·0—5·0 and boiled for 30 min. The cooled and filtered solution was then made alkaline with solid sodium hydrogen carbonate and extracted with ether to remove unused cyanamide and dicyandiamide. Sodium hydroxide was next added and the solution again extracted with ether. The ether solution after drying (Na_2SO_4) was evaporated and anhydrous hydrogen chloride passed into the residue dissolved in a little anhydrous ether. The dark precipitated *hydrochloride* (3·2 g.) recrystallised from ethanol as colourless prisms, m. p. 272° (decomp.) (Found: C, 49·1; H, 6·1; N, 24·3. $C_7H_9N_3,HCl$ requires C, 49·0; H, 5·8; N, 24·5%). The free *base*, prisms (from ethanol), m. p. 125°, was extracted from an alkaline solution of the hydrochloride with chloroform (Found: C, 61·8; H, 6·7; N, 31·0. $C_7H_9N_3$ requires C, 62·1; H, 6·7; N, 31·1%). The *picrate*, needles (from ethanol), had m. p. 226° (Found: C, 43·0; H, 3·4; N, 23·0. $C_{13}H_{12}O_7N_6$ requires C, 42·8; H, 3·3; N, 23·0%).

2-*Amino*-5-iso*butyl*-1-(4-*methyl*-2-*oxopentyl*)*glyoxaline* (III; R = Bu^i).—L-Leucine (10 g.), esterified and reduced as above, was condensed with cyanamide at pH 5·0. The resulting solution was filtered and cooled to give a precipitate of the *hydrochloride* (3 g.) which crystallised from water as flat needles, m. p. 179° (Found: C, 55·4; H, 8·8; N, 14·5. $C_{13}H_{23}ON_3,HCl$ requires C, 56·8; H, 8·8; N, 15·3%). The free *base*, needles from benzene–light petroleum, had m. p. 118° (Found: C, 66·0; H, 9·7; N, 17·6. $C_{13}H_{23}ON_3$ requires C, 65·9; H, 9·7; N, 17·7%). The *picrate*, felted needles from ethanol, had m. p. 214° (Found: C, 49·1; H, 5·6. $C_{19}H_{26}O_8N_6$ requires C, 49·2; H, 5·6%). By the action of acetic anhydride at 100° on the above hydrochloride there was obtained an *acetyl derivative*, needles (from aqueous ethanol), m. p. 151° (Found: C, 54·1; H, 8·2. $C_{15}H_{25}O_2N_3,HCl,H_2O$ requires C, 54·0; H, 8·4%).

4 : 5′-*Di*iso*butyl*-2 : 3-*dihydroglyoxalino* (1′ : 2′-1 : 2)*glyoxaline* (IV; R = Bu^i).—The above hydrochloride (0·5 g.) was warmed on the boiling-water bath with concentrated hydrochloric acid (10 ml.) for 4 hr. Water was added and after removal of a little unchanged starting material by filtration the solution was evaporated under reduced pressure and again after the addition of ethanol. The oily residue (0·3 g.) was crystallised from ethyl acetate–ethanol to give the somewhat hygroscopic *hydrochloride* as flat prisms, m. p. 113° (Found: C, 59·5; H, 8·7; N, 15·9. $C_{13}H_{21}N_3,HCl$ requires C, 61·0; H, 8·6; N, 16·4%). The *picrate*, prepared from the hydrochloride, recrystallised from ethanol as needles, m. p. 128° (Found: C, 50·9; H, 5·5. $C_{19}H_{24}O_7N_6$ requires C, 50·9; H, 5·4%).

2-*Amino*-5-n-*butyl*-1-2′-*oxohexylglyoxaline* (III; R = Bu^n).—DL-Norleucine (10 g.), esterified, reduced, and condensed with cyanamide as in the case of leucine (above), gave the *hydrochloride* (2·7 g.) as plates, m. p. 160° (from aqueous ethanol) (Found: C, 55·8; H, 8·8; N, 15·5. $C_{13}H_{23}ON_3,HCl$ requires C, 56·9; H, 8·8; N, 15·3%). The free *base*, felted needles from benzene–light petroleum, had m. p. 94° (Found: C, 65·4; H, 9·7; N, 17·8. $C_{13}H_{23}ON_3$ requires C, 65·7; H, 9·7; N, 17·7%). The *picrate*, felted needles from ethanol, had m. p. 190° (Found: C, 49·0; H, 5·4. $C_{19}H_{26}O_8N_6$ requires C, 49·1; H, 5·6%). The *oxalate*, needles from water, had m. p. 177° (Found: C, 54·6; H, 7·2; N, 12·3. $C_{13}H_{23}ON_3,H_2C_2O_4$ requires C, 55·0;

H, 7·6; N, 12·8%). An *acetyl derivative* prepared as in the case of the leucine isomer (above) crystallised from ethanol as felted needles, m. p. 149° (Found : C, 54·6; H, 8·3. $C_{15}H_{25}O_2N_3$,HCl,H_2O requires C, 54·0; H, 8·4%). The *oxime hydrochloride*, plates from water, had m. p. 150° (Found : C, 54·2; H, 8·8. $C_{13}H_{24}ON_4$,HCl requires C, 54·1; H, 8·7%).

4 : 5′-*Dibutyl*-2 : 3-*dihydroglyoxalino*(1′ : 2′-1 : 2)*glyoxaline* (IV; R = Bu^n).—Ring closure of the above hydrochloride as in the previous case gave the hygroscopic *hydrochloride*, prisms (from ethyl acetate–ethanol), m. p. 111° (Found : C, 61·2; H, 8·6; N, 15·8. $C_{13}H_{21}N_3$,HCl requires C, 61·0; H, 8·6; N, 16·4%). The *picrate*, needles from ethanol, had m. p. 131° (Found : C, 51·0; H, 5·3. $C_{19}H_{24}O_7N_6$ requires C, 50·9; H, 5·4%).

2-*Amino*-5-*hexyl*-1-2′-*oxo-octylglyoxaline* (III; R = C_6H_{11}).—The *hydrochloride* was prepared as above from DL-α-amino-octanoic acid and recrystallised from ethanol as felted needles, m. p. 167° (yield 10%) (Found : C, 61·0; H, 9·8; N, 12·5. $C_{17}H_{31}ON_3$,HCl requires C, 61·8; H, 9·7; N, 12·7%). The free *base*, felted needles from benzene–light petroleum, had m. p. 98° (Found : C, 68·9; H, 10·6; N, 14·3. $C_{17}H_{31}ON_3$ requires C, 69·6; H, 10·6; N, 14·3%). The *picrate*, needles from ethanol, had m. p. 185° (Found : C, 52·5; H, 6·6. $C_{23}H_{34}O_8N_6$ requires C, 52·8; H, 6·5%).

2-*Amino*-5-*benzyl*-1-(2-*oxo*-3-*phenylpropyl*)*glyoxaline* (III; R = CH_2Ph).—The *hydrochloride* prepared as above from phenylalanine crystallised from aqueous ethanol as felted needles, m. p. 193° (decomp.) (yield 32%) (Found : C, 66·8; H, 5·9; N, 11·8. $C_{19}H_{19}ON_3$,HCl requires C, 66·9; H, 5·9; N, 12·3%). The *picrate*, prepared from the hydrochloride and recrystallised from ethanol, had m. p. 219° (Found : C, 56·1; H, 4·3. $C_{25}H_{22}O_8N_6$ requires C, 56·1; H, 4·1%). The *oxime hydrochloride*, needles from water, had m. p. 171° (Found : C, 60·9; H, 6·0; N, 15·1. $C_{19}H_{20}ON_4$,HCl,H_2O requires C, 60·9; H, 6·1; N, 14·9%).

4 : 5′-*Dibenzyl*-2 : 3-*dihydroglyoxalino*(1′ : 2′-1 : 2)*glyoxaline* (IV; R = CH_2Ph).—The *base* was obtained from the above hydrochloride by addition of alkali to an aqueous solution and extraction with ether. It crystallised from aqueous ethanol in prismatic needles, m. p. 164° (Found : C, 79·4; H, 6·1; N, 15·1. $C_{19}H_{17}N_3$ requires C, 79·5; H, 5·9; N, 14·6%). The *picrate*, needles from ethanol, had m. p. 182° (Found : C, 57·9; H, 3·7. $C_{25}H_{20}O_7N_6$ requires C, 58·1; H, 3·9%).

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