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SOME REACTIONS OF AMINOOXY ACIDS

SYNTHESIS OF DL-O-UREIDOHOMOSERINE

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Abstract—DL-O-ureidohomoserine (α-amino-γ-ureido-oxybutyric acid), ureido-oxyacetic acid and their derivatives were synthesized by reaction of the corresponding amino-oxy acids with potassium cyanate. The reactions of amino-oxyacetic acid with arylisocyanates and phosgene were studied. The copper complex and cyclohexylamonium salt of amino-oxyacetic acid were isolated.

AMINO-OXY acids have been reported to have antibacterial activity;[1] furthermore amino-oxyacetic acid has been reported to have pronounced inhibition activity on "γ-aminobutyric acid α-ketoglutaric acid transaminase".[2] N-Oxyureas have been found to possess antitumor activity.[3]

L-O-Ureidohomoserine (α-amino-γ-ureido-oxybutyric acid) was isolated[4] as the enzymatic degradation product of canavanine. Kihara and Snell synthesized DL-O-ureidohomoserine; the product has been proved only chromatographically without its isolation.[4] They used the cupric ion method[5] for masking the α-amino group of canaline, which was obtained in low yield from homoserine by Kitagawa's procedure.[6]

The synthesis of DL-O-ureidohomoserine described here, offers the first practical preparation of this compound. This synthesis was based on canaline which was obtained from γ-butyrolactone by methods which were improved in this laboratory; either through α-benzamido-γ-halogenobutyrate[7,8] or by a direct alkylic opening of α-benzamido-γ-butyrolactone by means of oxime salts.[9]

Because of the great difference between the dissociation constants of the α-amino group and the γ-amino-oxy group in canaline, only the α-amino group in the free base takes part in the formation of the inner salt, while the terminal amino-oxy group

[1] D. McHale, J. Green and P. Mamalis, *J. Chem. Soc.* 225 (1960); S. A. Price, P. Mamalis, D. McHale and J. Green, *British J. Pharmac. Chemotherapy* **15**, 243 (1960); B. E. Volcani and E. E. Snell, *J. Biol. Chem.* **174**, 893 (1948); N. H. Horowitz and A. M. Srb, *Ibid.* 371; T. Suzuki and S. Muraoka, *J. Pharm. Soc. Japan* **212**, 207 (1955); E. Testa, B. J. R. Nicolaus, L. Mariani and G. Pagani, *Helv. Chem. Acta* **46**, 766 (1963).

[2] E. L. Schumann, L. A. Paquette, R. V. Heinzelman, D. P. Wallach, J. P. Da Vanzo and M. E. Greig, *J. Med. Pharm. Chem.* **5**, 464 (1962).

[3] B. Stearns, K. A. Losee and J. Bernstein, *J. Med. Chem.* **6**, 210 (1963); E. Boyland and R. Nery, *Nature, Lond.* **203**, 1379 (1964).

[4] H. Kihara and E. E. Snell, *J. Biol. Chem.* **226**, 485 (1957).

[5] A. C. Kurtz, *J. Biol. Chem.* **122**, 477 (1937–8); M. Wada, *Biochem. Z.* **224**, 420 (1930); S. W. Fox, M. S. Dunn and M. P. Stoddard, *J. Org. Chem.* **6**, 410 (1941).

[6] M. Kitagawa, *J. Biochem. Japan* **24**, 107 (1936).

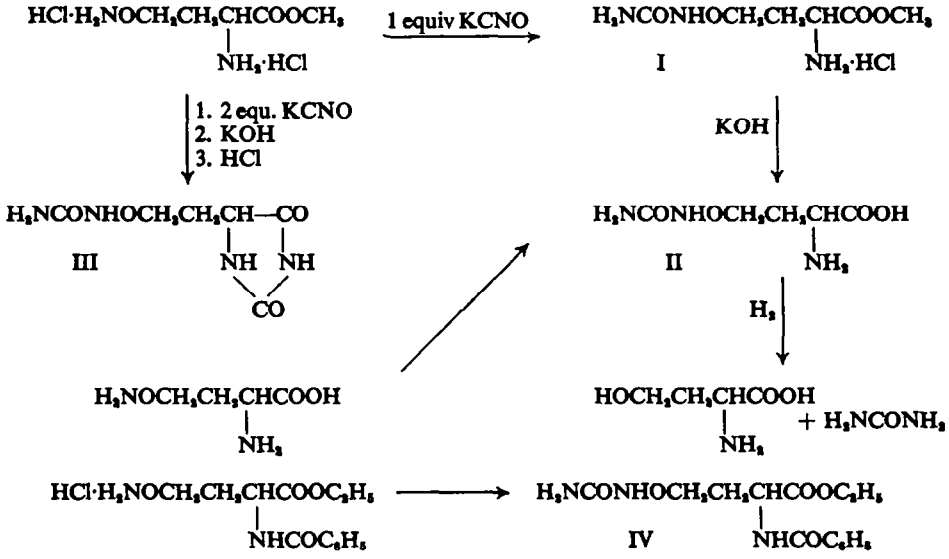
[7] Y. Knobler and M. Frankel, *J. Chem. Soc.* 1632 (1958).

[8] M. Frankel, Y. Knobler and G. Zvilichovsky, *Ibid.* 3127 (1963).

[9] Y. Knobler, C. Gilon and M. Frankel, *Israel Chem. J.* **1**, 242 (1963).

remains almost quantitatively un-ionized. Thus it was possible to synthesize O-ureidohomoserine without masking the α-amino group. Both methyl canalinate dihydrochloride[10] and free canaline[7] gave with one equivalent of potassium cyanate products of carbamylation of the terminal group, yielding methyl DL-O-ureidohomoserinate hydrochloride (I) and free DL-O-ureidohomoserine (II). In the case of methyl canalinate dihydrochloride, the less basic amino-oxy group was liberated from its hydrochloride by one equivalent of potassium cyanate, whereas the α-amino group remained almost quantitatively protonized. Methyl canalinate dihydrochloride gave with 2 equivalents of cyanate ethyl α-ureido-γ-ureidoxybutyrate which was transformed to the hydantoin derivative (III) of O-ureidohomoserine.

Ethyl N^{α}-benzoyl-DL-O-ureidohomoserinate (IV) was obtained by reaction of potassium cyanate with ethyl α-benzamido-γ-amino-oxybutyrate hydrochloride, an intermediate in the synthesis of canavanine.[8] The N^{α}-benzoyl group could not be removed from ethyl N^{α}-benzoyl-O-ureidohomoserinate (IV) without decomposition of the ureido-oxy group. The ester (I) could be hydrolyzed to the free amino acid which was identical with O-ureidohomoserine (II), which was obtained from free canaline.



DL-O-Ureidohomoserine gave positive ninhydrin test and negative Jaffe's test (orange–red colour with alkaline picrate solution). When shaken with palladium black in hydrogen under pressure, cleavage to homoserine and urea occurred. This hydrogenolysis confirms the structure of DL-O-ureidohomoserine which was synthesized here.

The acidity of the ureido-oxy group in DL-O-ureidohomoserine and its derivatives (I–IV) could not be measured by potentiometric titration because it has a pK_a value above 11. The carboxyl group was found to have $pK_a = 2{\cdot}5$, the α-amino group in DL-O-ureidohomoserine (II) has $pK_a = 8{\cdot}9$ (30°) and the α-amino group in its ester

[10] M. Frankel, S. Bittner and Y. Knobler, *J. Chem. Soc.* 3941 (1964).

(I) $pK_a = 6{\cdot}95$ (30°). When the hydantoin derivative (III) was titrated potentiometrically, it was found to posses an acidic hydrogen with $pK_a = 8{\cdot}6$ (30°), which is due to the acidity of the hydantoin moiety.

Amino-oxyacetic acid hemihydrochloride[11] gave with potassium cyanate ureido-oxyacetic acid (78%) and the same reaction with ethyl animo-oxyacetate[12] yielded ethyl ureido-oxyacetate (92%). Amino-oxyacetic acid and its ethyl ester also reacted with phenyl and naphthylisocyanate yielding the appropriate derivative of ureido-oxyacetic acid and of ethyl ureido-oxyacetate.

$$RNCO + H_2NOCH_2COOR' \longrightarrow RNHCONHOCH_2COOR'$$

$$R = H, C_6H_5, C_{10}H_7$$

$$R' = H, C_2H_5$$

On heating the aryl derivatives of ureido-oxyacetic acid and of its ester in an inert solvent (xylene), symmetrical diaryl ureas were isolated. The aryl derivatives gave with 15% nitric acid a specific yellow colour reaction, sometimes accompanied by a yellow precipitate.

Jones and Neuffer have studied the reaction of O-alkylhydroxylamines with phosgene and obtained unidentified products.[13]

The reaction of amino-oxyacetic acid hemihydrochloride with phosgene yielded the N-carboxychloride of amino-oxyacetic acid (V), which was characterized by the reaction with aniline to give ε-phenylureido-oxyacetic acid.

$$COCl_2 + H_2NOCH_2COOH \longrightarrow ClCONHOCH_2COOH \longrightarrow C_6H_5NHCONHOCH_2COOH$$

V

By reaction of amino-oxyacetic acid N-carboxychloride with triethylamine an oligomeric product was obtained, which is insoluble in cold water and very soluble when heated (10 g per 1 ml of water at 40°). This compound crystallizes from water as a hydrate; on heating the hydrate to 60–65° it loses its water and dissolves in it. By recrystallization from absolute ethanol an anhydrous product is obtained, which is converted again to the hydrate by moisture. This product is acidic, dissolves in cold bicarbonate solution and precipitates from alkaline solution on acidification and cooling. There is no evidence for a terminal amino-oxy group, as this oligomer does not give Jaffe's test. According to analytical results a heptamer is presumed, which by withdrawal of a molecule of HCl between a terminal N-carboxy-chloride group and a preceding NH group of the chain forms a terminal six membered ring.

VI

By potentiometric titration of the oligomer (VI) we found the mol. wt. of its pentahydrate to be 642 (calculated according to formula VI, M.W. = 645). The first dissociation constant, which is due to the terminal carboxyl group was found to be $pK_a = 3{\cdot}5$. In the titration curve we found evidence for additional acidic hydrogens,

[11] Purchased from Eastman Organic Chemicals, N.Y., U.S.A.

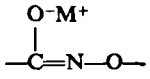
[12] M. Frankel, G. Zvilichovsky and Y. Knobler, *J. Chem. Soc.* 3931 (1964).

[13] L. W. Jones and L. F. Neuffer, *J. Amer. Chem. Soc.* **39**, 652 (1917).

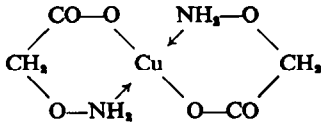
neutralization of which consumed an additional 5 equivs of sodium hydroxide. The oligomer (VI) yielded on alcoholysis, with ethanolic hydrogen chloride, the calculated amount of ethyl amino-oxyacetate.[12] The amount of CO_2, obtained by hydrolysis of the terminal ring, was estimated by titration of the gas with potassium methoxide. Aminolysis in pure aniline or cyclohexylamine afforded symmetrical diphenyl or dicyclohexyl-ureas, confirming the above mentioned ureidic termination of the oligomer (VI).

On treatment with a solution of barium hydroxide the oligomer (VI) yielded an insoluble barium salt in which all the acidic hydrogens, including those of the carboxyl group, amidooxy linkages and the terminal ring, are replaced by barium ions. The oligomer (VI) gave an insoluble cupric salt on treatment with copper acetate. In the cupric salt only six out of the seven acidic hydrogens are replaced by the metal ions, because of the lower acidity of the terminal ureido-oxy group and insufficient basicity of copper acetate.

IR spectrum of the oligomer (VI) shows strong C=O stretching bands at 6·1 microns; after conversion into its metal salt (Ba or Cu salts), this band disappears and a new strong band appears at 6·25–6·4 microns; due to appearance of C=N bonds in the enolic ions of the successive amido-oxy linkages:



Contrary to some findings,[14] a deep blue copper complex of amino-oxyacetic acid could be isolated, with analytical results in agreement with formula VII.



VII

Amino-oxyacetic acid gave with cyclohexylamine a crystalline salt which was readily isolated, and had a sharp m.p.

EXPERIMENTAL

Methyl DL-O-*ureidohomoserinate hydrochloride* (I). Methyl DL-canalinate dihydrochloride[10] (2·2 g) was dissolved in water (10 ml) and KCNO (0·8 g) in water (10 ml) was added; the pH of the solution was then 5. The reaction mixture was filtered and the solution kept overnight at 4°. It was then acidified to congo-red with conc HCl, EtOH was added and the inorganic salt which separated filtered off and the solution evaporated *in vacuo* to dryness. The residue was dissolved in abs EtOH and excess of dry ether added. The precipitate was dissolved again in abs EtOH (10 ml) and kept at 4° for several days, after which crystals of methyl DL-O-ureidohomoserinate hydrochloride precipitated (1·2 g, 52% yield) m.p. 158–160°. The product gave a positive ninhydrin test and a negative Jaffe's test. (Found: C, 31·9; H, 6·35; N, 18·7; Cl, 15·6. $C_6H_{14}N_3O_4Cl$ requires: C, 31·7; H, 6·2; N, 18·5; Cl, 15·6%.)

This ester (0·22 g) was hydrolyzed by 2N KOH (2 ml) at room temp (24 hr) and after neutralization to pH = 5 with conc HCl and keeping overnight at 4°, DL-O-ureidohomoserine precipitated (0·06 g) m.p. 208° and was identical with DL-O-ureidohomoserine, synthesis of which is described below (by mixed m.p. and IR spectrum).

DL-O-*Ureidohomesrine* (II). DL-canaline[7-9] (1·34 g) was dissolved in water (10 ml), conc HCl

[14] E. Testa, B. J. R. Nicolaus, L. Mariani and G. Pagani, *Helv. Chem. Acta* **46**, 766 (1963).

(0·86 ml) and KCNO (0·81 g) in water (3 ml) were added. The reaction mixture was filtered from some impurities. The solution (pH = 5) was kept overnight at room temp and then for 2 days at 4°, while crystals separated (1·0 g), m.p. 204°. After keeping the solution for several days at 4° an additional amount precipitated (0·2 g), overall yield 67%. On recrystallization from a small amount of water, DL-O-ureidohomoserine melted at 208°. The product gave a positive ninhydrin test and a negative Jaffe's test. Potentiometric titration showed M.W. = 180 (calc. for O-ureidohomoserine, 177); pK_a values (30°): pK_a (COOH) = 2·5; $pK_a(NH_3^+)$ = 8·9. (Found: C, 33·2; H, 6·4; N, 23·7, $C_5H_{11}N_3O_4$ requires: C, 33·9; H, 6·3; N, 23·7%.)

5-(2-Ureidooxyethyl)hydantoin (III). Methyl DL-canalinate dihydrochloride (2·2 g) was dissolved in water (10 ml) and KCNO (1·62 g) in water (10 ml) was added. The pH was 7·5. The reaction mixture was kept overnight at room temp, and then evaporated to dryness *in vacuo*. The residue was dissolved in 2N KOH (12 ml), kept at room temp overnight and filtered. The solution was acidified to pH = 1 with conc HCl and cooled for 2 days at 4°, while crystals of the hydantoin precipitated (0·9 g). After concentration of the solution into half of its volume and cooling overnight, an additional crop precipitated (0·3 g), overall yield 60%. 5-(2-Ureidooxyethyl)hydantoin melts at 220° and gives negative ninhydrin and Jaffe's tests. The product is soluble in NaOHaq; potentiometric titration showed pK_a = 8·6 (due to the hydantoin ring) and M.W. = 200 (Calc 202). It has a sharp band at 5·65 microns and a strong band at 5·8 microns (the spectrum was taken in nujol), confirming its hydantoin structure. (Found: C, 35·65; H, 4·95; N, 27·7. $C_6H_{10}N_4O_4$ requires: C, 35·65; H, 5·0, N, 27·7%.)

Ethyl DL-N^{α}-*benzoyl-O-ureidohomoserinate* (IV). Ethyl α-benzamido-γ-amino-oxybutyrate[8] (1 g) was dissolved in water (4 ml) and KCNO (0·3 g) in water (0·5 ml) was added. After the exothermic reaction stopped a white precipitate separated. The ethyl N^{α}-benzoyl-O-ureidohomoserinate which was crystallized from water (0·87 g, 87% yield) melted at 161° and gave a negative Jaffe' stest. (Found: C, 54·7; H, 6·4; N, 14·1; OEt, 14·6. $C_{14}H_{19}N_3O_5$ requires: C, 54·4; H, 6.2; N, 13·6; OEt, 14·6%.)

Hydrogenolysis of DL-*O-ureidohomoserine.* DL-O-Ureidohomoserine (II, 0·02 g) was shaken with H_2 (3 atm.) in presence of Pd–C for 4 hr. The catalyst was removed by filtration and the presence of DL-homoserine was proved chromatografically with an authentic sample of DL-homoserine (TLC, with ninhydrin). The solution was acidified with one drop of conc HCl, boiled for 1 min and kept overnight at room temp; homoserine lactone which formed was proved chromatographically, comparison with an authentic sample of DL-homoserine lactone hydrochloride. This hydrogenolysis confirms the constitution of DL-O-ureidohomoserine which was sysnthesized.

Procedure for potentiometric titrations. A "Radiometer Copenhagen" titrator with glass and calomel electrodes was used. To 0·05 mmole of the compound in water (5 ml), 2M NaCl (0·5 ml) and water (4·5 ml) were added. Titrations were carried out at 30° with either 0·2N NaOH or 0·2N HCl, using "Agla" micrometer syringe. The pK_a values were taken from the mid-points of the pH neutralization curves.

Ureido-oxyacetic acid. Amino-oxyacetic acid hemihydrochloride[11] (1·64 g) was dissolved in water (3 ml) and KCNO (1·8 g) in water (2 ml) was added to the solution. After the exothermic reaction ceased, it was kept overnight at room temp and filtered. The solution was acidified with conc HCl to pH = 1; 20 sec after acidification white needles separated. After keeping overnight at 4° the ureido-oxyacetic acid (1·65 g, 78% yield) was collected, m.p. 165°. The product could be recrystallized from a small amount of water (m.p. 165°). The product gave acidic aqueous solutions, and could be titrated either with phenolphthaleine or potentiometrically (pK_a = 2·6 at 30°). (Found: C, 26·85; H, 4·5; N, 21·2. $C_3H_6N_2O_4$ requires: C, 26·85; H, 4·5; N, 20·9%.)

Ethyl ureido-oxyacetate. Ethyl amino-oxyacetate hydrochloride[12] (3·1 g) was dissolved in water (7 ml), KCNO (1·64 g) in water (4 ml) was added portionwise during 20 min. After the exothermic reaction ceased, white needles separated at room temp. The crystals were collected and the solution kept overnight at 4°, while an additional amount of product precipitated (overall wt 3·0 g, 92%). The ethyl ureido-oxyacetate melted at 123–124°. (Found: C, 37·3; H, 6·3; N, 17·0; OEt, 25·5. $C_5H_{10}N_2O_4$ requires: C, 37·0; H, 6·2; N, 17·3; OEt, 27·8%.)

ε-Phenylureido-oxyacetic acid. Amino-oxyacetic acid hemihydrochloride (1·99 g) was dissolved in 1N NaOH (5 ml). Phenylisocyanate (1·1 ml) and 1N NaOH (9 ml) were added portionwise during 1 hr, while shaking the reaction mixture. The pH was kept during the addition at 6–7. Then more 1N NaOH (5 ml) was added and the solution was filtered to remove some impurities. After the solution was acidified with HCl to pH = 2 and cooled, ε-phenylureido-oxyacetic acid precipitated

(1·75 g, 83% yield). After recrystallization from water the product melted at 190°. This acid gives a specific colour reaction when heated in 15% HNO_3. (Found: C, 51·4; H, 4·75; N, 13·3. $C_9H_{10}N_2O_4$ requires: C, 51·4; H, 4·8; N, 13·3%.)

ε-Naphthylureido-oxyacetic acid. Amino-oxyacetic acid hemihydrochloride (1·09 g) was dissolved in 1N NaOH (5 ml) and napthylisocyanate (2·0 ml) and 1N NaOH (9 ml) were added portionwise with shaking during 2 hr. The reaction mixture was shaken an additional 2 hr, 1N NaOH (5 ml) was added and the solution filtered from some impurities. On acidification with hydrochloric acid ε-naphthylureido-oxyacetic acid separated (2·15 g, 83% yield). After recrystallization from water the product melted at 164°. This acid gives a specific yellow colour reaction when heated in 15% HNO_3, accompanied by separation of a yellow precipitate. (Found: C, 59·3; H, 4·6; N, 10·6. $C_{13}H_{12}N_2O_4$ requires: C, 60·0, H, 4·6; N, 10·75%.)

Ethyl ε-phenylureido-oxyacetate. Ethyl amino-oxyacetate hydrochloride (3·1 g) was dissolved in water (5 ml), 1N NaOH (19 ml) was added while cooling on ice. The pH was 7. Phenylisocyanate (3 ml) was introduced portionwise while cooling and shaking during 30 min. After keeping for 15 min at room temp EtOH (15 ml) was added; the reaction mixture was heated to 65° and filtered from some diphenylurea (0·25 g). White needles separated on cooling the solution at 0° for 3 hr (1·6 g). Upon addition of water a further amount precipitated (1·5 g). The first crop melted at 86° and the second at 65–75°; after recrystallization from EtOH–water (1:1) it melted at 86°, overall yield 65%. This ester gave the specific yellow colour test with 15% HNO_3. (Found: C, 55·5; H, 6·1; N, 11·5; OEt, 18·8. $C_{11}H_{14}N_2O_4$ requires: C, 55·5; H, 5·9; N, 11·8; OEt, 18·9%.)

Ethyl ε-naphthlyureido-oxyacetate. This ester was prepared from ethyl amino-oxyacetate hydrochloride (3·1 g) and naphthylisocyanate (4 ml) by the same procedure as above. The ethyl ε-naphthylureido-oxyacetate (3·5 g, 60% yield) melts at 94–96° and gives with warm 15% HNO_3 the specific colour reaction, followed by separation of a yellow precipitate. (Found: C, 63·2; H, 5·8; N, 9·4; OEt, 16·1. $C_{15}H_{16}N_2O_4$ requires: N, 62·5; H, 5·6; N, 9·7; OEt, 15·6%.)

Heating ethyl arylureido-oxyacetate in xylene. Ethyl ε-naphthylureido-oxyacetate (0·5 g) was heated under boiling xylene (8 ml) for 24 hr. The solution was filtered and kept at −10° for several days. White crystals precipitated (0·1 g), they melted at 260° and were identical by mixed m.p. and IR spectra with those of symmetrical dinaphthylurea. The same result was obtained with ethyl ε-phenylureido-oxyacetate, yielding diphenylurea.

Reaction of amino-oxyacetic acid with phosgene. Amino-oxyacetic acid hemihydrochloride (1·09 g) was stirred in dry AcOEt (50 ml), phosgene was bubbled for 20 min at room temp and then for 30 min at 58°. After all the solid dissolved, N_2 was bubbled for 3 hr to withdraw excess of phosgene. The solution was evaporated to dryness *in vacuo* and the residue was dissolved in dry dioxan (10 ml), aniline (5 ml) was added and the mixture allowed to stand for 30 min at room temp. Aniline hydrochloride was filtered off and 1N NaOH (10 ml) and ether (10 ml) were added. The aqueous layer was cooled and acidified with HCl. A white solid separated (1 g) which melted at 190° and was identical with ε-phenylureido-oxyacetic acid, by m.m.p. and IR spectrum. (Found: N, 13·4; $C_9H_{10}N_2O_4$ requires: N, 13·3%.)

Oligomer of amino-oxyacetic acid (VI). Amino-oxyacetic acid hemihydrochloride (8·56 g) and dry AcOEt (120 ml) were stirred, phosgene was bubbled at room temp for 30 min and then at 58° until the solid dissolved. N_2 was bubbled until all phosgene was withdrawn (3 hr). The solution was filtered and cooled, triethylamine (20 ml) was added portionwise with shaking and cooling during 30 min. The solvent was evaporated *in vacuo* at room temp and the residue dissolved in hot water (20 ml). The aqueous solution was acidified with conc HCl to pH = 2, warmed to 30–40°, filtered and then kept for 1 hr at room temp and then 1 hr at 4°. The white precipitate was collected (6·0 g, 80% yield). This oligomer crystallizes from water with 5 mols of solvent. Mol. wt. by potentiometric titration was found 642 (Calc, for the penta hydrate: mol. wt. = 645). $pK_{a_1} = 3·5$; $pK_{a_2} = 5·85$; $pK_{a_3} = 7·05$; $pK_{a_4} = 8·25$; $pK_{a_5} = 9·35$; $pK_{a_6} = 10·2$. The product is also soluble in bicarbonate solution, gives negative Jaffe's test and loses its water at 60°. At this temp the product melts and solidifies again, and then melts at 130°. (Found: C, 28·0; H, 5·4; N, 15·2. $C_{15}H_{21}N_7O_{16}.5H_2O$ requires: C, 27·9; H, 4·8; N, 15·2%.)

After drying the hydrate in 100° or after recrystallization from absolute EtOH it melted at 130°. (Found: C, 32·35: H, 4·4; N, 17·2. $C_{15}H_{21}N_7O_{16}$ requires: C, 32·4; H, 3·8; N, 17·6%.)

Barium salt of oligomer (VI). The oligomer (VI; 0·13 g) was dissolved in hot water (1 ml), saturated $Ba(OH)_2$aq (25 ml) was added, and the solution heated to 90°. After cooling to room temp, the

Ba salt (0·2 g, quantitative yield) was collected. (Found: C, 15·4; H, 2·8; N, 7·8; Ba, 41·5. $(C_{12}H_{14}N_7O_{16})_2$ $Ba_7.14H_2O$ requires; C, 15·6; H, 2·4; N, 8·5; Ba, 41·6%.)

Copper salt of oligomer (VI). The oligomer (VI; 0·13 g) was dissolved in water (1 ml) by heating to 40°, copper acetate monohydrate (0·15 g) in water (9 ml) was added and the reaction mixture was shaken for some min. A green salt precipitated and was collected as the dodecahydrate (0·142 g, 75% yield). The solution was blue but no additional crop precipitated on cooling. (Found: C, 19·3; H, 4·1; N, 10·2. $C_{16}H_{16}N_7O_{16}Cu_2.12H_2O$ requires: C, 18·8; H, 4·0; N, 10·2%.)

After drying *in vacuo* at 100° the complex gave analytical results for a trihydrate. (Found: C, 22·8; H, 3·4; N, 12·2; $C_{16}H_{16}N_7O_{16}Cu_2,3H_2O$ requires: C, 22·7; H, 2·7; N, 12·3%.)

Determination of CO_2 formed on hydrolysis of the oligomer (VI). The oligomer (VI; 0·05 g) was boiled with 4N H_2SO_4 (5 ml). Pure N_2 was bubbled during the reaction, directing the CO_2 which was formed to a solution of benzylamine and dioxan in EtOH (1:3:3). The amount of CO_2 was estimated by titration with 0·1N benzenic potassium methoxide, with thymol blue as indicator.

Aminolysis of the oligomer (VI). The oligomer (VI; 0·65 g) was refluxed in aniline (3 ml) for 3 hr. The precipitate which was formed at first, dissolved during the reflux. By adding excess dichloromethane a white product precipitated (m.p. 190–210°), which after recrystallization from dichloromethane (0·2 g) melted at 230° and was identical with sym-diphenylurea, by IR spectra and m.p. (Found: N, 13·2. Calc. for $C_{13}H_{12}N_2O$: N, 13·2%.)

Under similar conditions oligomer (VI) gave with cyclohexylamine, N,N'-dicyclohexylurea (0·25 g). (Found: N, 12·4. Calc. for $C_{13}H_{24}N_2O$: N, 12·5%.)

Alcoholysis of the oligomer (VI). The oligomer (VI; 0·13 g) was refluxed in 10% ethanolic HCl (5 ml) for 4 hr, the solution cooled and dry ether was added until turbidity, and kept overnight at −10°. Crystals which were identical with ethyl amino-oxyacetate hydrochloride[15] (by m. m.p. and IR spectrum), separated (0·2 g, 90%). (Found: N, 9·0. Calc. for $C_4H_{10}NO_3Cl$: N, 9·0%.)

Copper complex of amino-ocyacetic acid (VII). Amino-oxyacetic acid hemihydrochloride (1·09 g) was dissolved in water (3 ml) and then $CuCO_3$ was added portionwise until no more CO_2 was formed. In order to avoid excess $CuCO_3$, few crystals of the hemihydrochloride were added (no more effervescence of CO_2). The mixture was kept for 3 hr at room temp and the blue complex collected by filtration (0·9 g, 85% yield). The complex has no m.p. but explodes above 200°. (Found: C, 19·9; H, 3·3; N, 11·8. $C_4H_6N_2O_6Cu$ requires: C, 19·7; H, 3·3; N, 11·5%.)

Cyclohexylammonium salt of amino-oxyacetic acid. Amino-oxyacetic acid hemihydrochloride (1·09 g) was dissolved in hot cyclohexylamine (3 ml). On cooling, a white solid precipitated, which was recrystallized once from cyclohexylamine and then from dichloromethane (1·7 g, 90% yield). m.p. 145°. (Found: C, 50·5; H, 9·5; N, 15·1. $C_8H_{18}N_2O_3$ requires: C, 50·5; H, 9.5; N, 14·7%.)

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