671. *2-Mercaptoglyoxalines. Part V.* The Preparation of 4(5)-Substituted 2-Mercaptoglyoxalines from Amino-acids.*

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Improved methods are described for the reduction of α-amino-esters to amino-aldehydes, from which the correspondingly 2-mercaptoglyoxalines are obtained by the action of thiocyanate. The method is not entirely a general one; it has been successful with all amino-acids used except cysteine, threonine, tryptophan, and valine.

The effectiveness of 2-mercaptoglyoxaline and its substitution products in inhibiting thyroxine synthesis by the thyroid gland (Stanley and Astwood, *Endocrinol.*, 1949, **44**, 588; Searle, Lawson, and Morley, *Biochem. J.*, 1951, **49**, 125) has evoked considerable interest in their synthesis (Jones, Kornfeld, McLaughlin, and Anderson, *J. Amer. Chem. Soc.*, 1949, **71**, 4000). One of the simplest methods of wide application for the preparation of 4(5)-substituted derivatives is the action of thiocyanic acid on α-amino-aldehydes which, as Neuberg (*Ber.*, 1908, **41**, 959) showed, could be obtained by the reduction of esters of α-amino-acids by sodium amalgam. This reaction was employed later by Akabori (*Ber.*, 1933, **67**, 151, 159) who described the reduction of ethyl esters of a limited number of amino-acids and the subsequent production of the corresponding 2-mercaptoglyoxalines.

To improve the somewhat variable, low yields (particularly in the case of glycine) obtained by the Akabori procedure and so facilitate the use of these compounds as starting material for further synthetic work, a study has been made of this reduction, with an extended range of amino-acids. The method cannot be considered an entirely general one since a uniform procedure is not applicable in all cases, and furthermore with cysteine, threonine, tryptophan, and valine no yield of the corresponding mercaptoglyoxaline has so far been isolated.

The use of solid carbon dioxide as an internal cooling agent during the reduction of the amino-acid esters has been described in Part II (*J.*, 1951, in the press). By this means the

* Part IV, *J.*, 1951, 2223.

optimum temperature of reduction (0°) can be steadily maintained and the time of addition of the amalgam and hence the risk of hydrolysis of the ester reduced.

The α-amino-aldehydes obtained by reduction are not stable in alkaline solution and as the pH optimum for the reduction is between 2 and 3 a fairly strict control of the pH during the reduction is necessary.

These pH and temperature conditions, whilst proving advantageous in the case of alanine were, however, not in themselves satisfactory with glycine, serine, and histidine, in particular. With glycine, the isolation of the 2-mercaptoglyoxaline still required the laborious separation as the mercuric chloride complex and its subsequent decomposition with hydrogen sulphide. With serine and histidine no yield of the corresponding mercaptoglyoxalines was obtained. These difficulties were to a large extent overcome by carrying out the reduction in the presence of thiocyanate. It is possible that as soon as the labile amino-aldehyde is formed it undergoes the first stage of its reaction with thiocyanic acid to give the substituted thiourea which then cyclises when the solution is boiled.

It has been shown by Dixon and Taylor (*J.*, 1916, **109**, 1244) that thiourea in cold aqueous solution reacts with acetaldehyde to give a type of Schiff's base, from which the aldehyde can be regenerated by boiling it with acids. The use of thiourea to protect the amino-aldehyde was therefore examined in the case of glycine ester. The result was successful, although the hope that the thiourea would, on subsequent treatment, decompose to liberate enough thiocyanic acid to bring about ring closure was not realised, and the yield of mercaptoglyoxaline (22%) obtained after the addition of thiocyanate was restricted by the difficulty of separation from the thiourea.

Coppin and Titherly (*J.*, 1914, **105**, 32) have described the reversible formation of 2 : 2 : 2-trichloro-1-hydroxyethylurea from chloral and urea. The use of the latter compound as a temporary stabilising agent for the amino-aldehydes has proved most advantageous, and in the case of glycine ester 35—40% yields were obtained without the use of mercuric chloride.

It has been found difficult to crystallise the more soluble mercaptoglyoxalines from solutions containing appreciable excess of thiocyanates. In the preparation of 2-mercaptoglyoxaline and 4-hydroxymethyl-2-mercaptoglyoxaline from glycine and serine, respectively, it was therefore found desirable to use only a little more than the theoretical amount of thiocyanate.

Experimental.

2-Mercaptoglyoxaline.—Glycine ester hydrochloride (10 g.) was dissolved in ice-cold water (50 ml.). The solution was efficiently stirred and kept at 0° by the addition of small pieces of solid carbon dioxide; potassium thiocyanate (7 g.) was then added, followed by freshly prepared sodium amalgam (2·3%, 300 g.) in small portions during 45 minutes.

Throughout the reaction, the pH of the solution was kept at approximately 2·3 by addition of 5N-hydrochloric acid (60 ml.) from a dropping funnel. When all the hydrochloric acid had been used, the solution was decanted from the mercury, filtered, and boiled under reflux for 40 minutes. It was then evaporated to dryness under reduced pressure and the residue was extracted with ethanol. After removal of the alcohol, the product was crystallised from boiling water; it had m. p. 225—227° (yield 2·8 g., 33%). By carrying out the reduction in the presence of urea (5 g.) and postponing the addition of the thiocyanate till all the sodium amalgam had been used, a purer product was isolated in 40% yield.

2-Mercapto-4-methylglyoxaline.—DL-Alanine (18 g.) was suspended in absolute ethanol (300 ml.), which had been previously saturated with dry hydrogen chloride, and the mixture heated on the water-bath until all had passed into solution. Benzene (100 ml.) was then added and the solvents were removed by distillation under reduced pressure. The semi-solid residue, together with potassium thiocyanate (40 g.) was dissolved in ice-cold water (100 ml.), the pH being adjusted to 2·3 and the temperature kept at 0° by means of solid carbon dioxide. Sodium amalgam (2·3%, 600 g.) was used under the conditions described for the reduction of glycine ester. The resulting solution was boiled under reflux for 30 minutes and concentrated until the product began to crystallise. Evaporation of the mother liquor to dryness followed by extraction with ethanol gave more material. The product had m. p. 246° (total yield 12·8 g., 55%).

2-Mercapto-4-propylglyoxaline.—When the same method as that described for alanine was used, DL-norvaline (5 g.) gave 2-mercapto-4-propylglyoxaline (3·9 g., 64%). After recrystallisation from water the needles had m. p. 183—184°.

4-n-Butyl-2-mercaptoglyoxaline.—DL-Norleucine (5 g.) treated as above gave *4-butyl-2-mercaptoglyoxaline* (2·0 g., 34%). Recrystallisation from water gave needles, m. p. 127·5°, sparingly soluble in cold water but soluble in ethanol (Found : C, 53·2; H, 7·7. $C_7H_{12}N_2S$ requires C, 53·8; H, 7·7%).

Di-(2-mercapto-4-glyoxalinyl)methane.—αγ-Diaminoglutaric acid (5 g.), obtained by the method described by Carter *et al.* (*J. Biol. Chem.*, 1949, **178**, 331) and treated as above, gave *di-(2-mercapto-4-*

glyoxalinyl)methane (2·1 g., 32%). The compound did not melt below 300°. It was soluble in ethanol and concentrated hydrochloric acid, and recrystallised from the latter solvent in pale yellow needles (Found: C, 38·8; H, 3·8. $C_7H_8N_4S_2$ requires C, 39·6; H, 3·8%).

2-Mercapto-4-glyoxalinylacetic Acid.—DL-Aspartic acid (5 g.), treated as above, yielded *2-mercapto-4-glyoxalinylacetic acid* (3·25 g., 71%), which crystallised from water as pale yellow needles, m. p. 245°, which were slightly soluble in cold water, more so in ethanol (Found: C, 37·9; H, 4·1. $C_5H_6O_2N_2S$ requires C, 38·0; H, 3·8%). When heated at 210°, slight darkening occurred and carbon dioxide was evolved, giving 4-methyl-2-mercaptoglyoxaline, mixed m. p. 245°.

4-p-Hydroxybenzyl-2-mercaptoglyoxaline.—L-Tyrosine (5 g.) reacted in the manner described above to give *4-p-hydroxybenzyl-2-mercaptoglyoxaline* (2·5 g., 44%). Recrystallised from ethanol, the compound had m. p. 248° (Found: C, 58·1; H, 5·0; N, 12·8; S, 14·5. $C_{10}H_{10}ON_2S$ requires: C, 58·3; H, 4·9; N, 13·6; S, 15·5%). It was sparingly soluble in water and ethanol.

4-4′-Aminobutyl-2-mercaptoglyoxaline.—DL-Lysine monohydrochloride (5 g.) was esterfied and reduced as in the case of alanine except that a smaller quantity of potassium thiocyanate (3 g.) was used. The resulting solution was heated on the water-bath for 1 hour and was then adjusted to pH 6 by the addition of dilute ammonia solution. Evaporation to dryness was carried out under reduced pressure, and the product was isolated after an extraction with ethanol. Recrystallisation from water gave *4-4′-aminobutyl-2-mercaptoglyoxaline hydrochloride* (1·7 g., 30%), m. p. 214° (Found: C, 40·1; H, 6·8; N, 19·7. $C_7H_{13}N_3S,HCl$ requires C, 40·5; H, 6·7; N, 20·2%). The hydrochloride (1·2 g.) was dissolved in a little water and N-sodium hydroxide (5·8 ml.) was added. The free *base* separated, and after being recrystallised from water had m. p. 123° (Found: C, 49·1; H, 7·5. $C_7H_{13}N_3S$ requires C, 49·1; H, 7·6%).

4-4′-Glyoxalinylmethyl-2-mercaptoglyoxaline.—The methyl ester hydrochloride obtained from L-histidine (5 g.) was treated in the same way as glycine ester hydrochloride with two modifications: the solution of the amino-aldehyde and thiocyanate was heated on the water-bath for 1 hour instead of being boiled under reflux, and the pH was brought to 6·0 before evaporation to dryness. *4-4′-Glyoxalinylmethyl-2-mercaptoglyoxaline thiocyanate* (2·6 g., 42%) was obtained and was recrystallised from water forming brown needles, m. p. 207° (Found: C, 40·2; H, 3·9. $C_7H_8N_4S,CHNS$ requires C, 40·2; H, 3·8%). The free *base* separated when the thiocyanate (0·5 g.) was dissolved in a little hot water and N-sodium hydroxide (2·1 ml.) was added; recrystallised from water it formed pale brown needles, m. p. 251° (Found: C, 47·6; H, 4·0; N, 30·7; S, 17·6. $C_7H_8N_4S$ requires C, 46·7; H, 4·4; N, 31·1; S, 17·8%).

4-3′-Guanidinopropyl-2-mercaptoglyoxaline.—L-Arginine monohydrochloride (10 g.) was esterified by use of ethanol (300 ml.) saturated with hydrogen chloride. The reduction was carried out with sodium amalgam (300 g.) in the presence of potassium thiocyanate (5 g.). The solution so obtained was heated on the water-bath for 1 hour, adjusted to pH 8 with ammonia solution, and evaporated to dryness under reduced pressure. The product was then extracted with ethanol and isolated as the hydrochloride; recrystallised from water, *4-3′-guanidinopropyl-2-mercaptoglyoxaline monohydrochloride* (4·0 g., 29·5%), m. p. 245°, was obtained (Found: C, 36·0; H, 5·8; N, 31·6; S, 13·0. $C_7H_{13}N_5S,HCl$ requires C, 35·7; H, 5·9; N, 29·7; S, 13·6%). The free *base monohydrate*, m. p. 158°, was obtained by treating an aqueous solution of the hydrochloride with an equivalent amount of N-sodium hydroxide (Found: C, 38·5; H, 6·9. $C_7H_{13}N_5S,H_2O$ requires C, 38·7; H, 6·9%).

4-Hydroxymethyl-2-mercaptoglyoxaline.—DL-Serine (5 g.) was converted into its methyl ester hydrochloride by Fischer's method (*Ber.*, 1905, **38**, 4193). The crude product was reduced in the presence of potassium thiocyanate (5 g.) with sodium amalgam (2·3%, 300 g.). The resulting solution was concentrated under reduced pressure to 40 ml., filtered, and then heated for 30 minutes on the steam-bath. Solid sodium hydrogen carbonate was added to bring the pH to 7·5, and then after being acidified with dilute acetic acid, the solution was boiled with charcoal and filtered. The product was then worked up in the same way as described for 2-mercaptoglyoxaline; it had m. p. 206° (1·1 g., 18%) (Found: C, 37·3; H, 4·7. $C_4H_6ON_2S$ requires C, 36·9; H, 4·6%).

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