2-Mercaptoglyoxalines. Part IX. The Preparation of 1 : 5-Disubstituted 2-Mercaptoglyoxalines from α-Amino-acids.*

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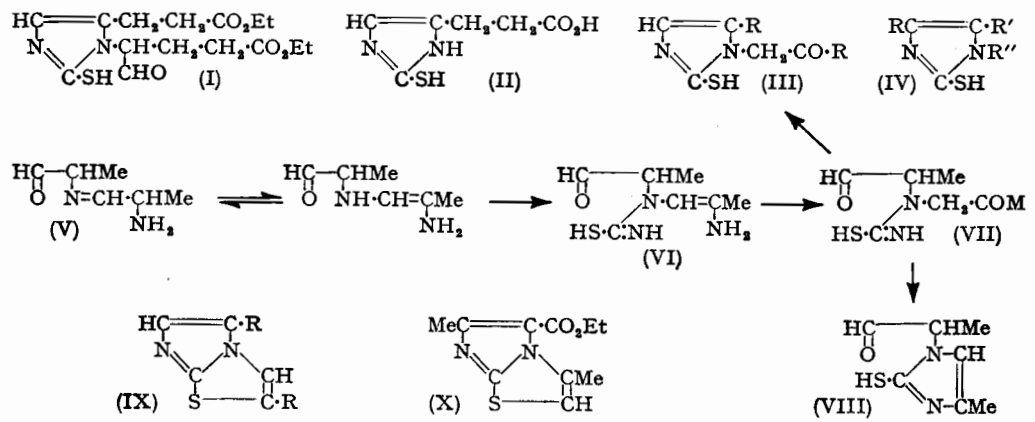
The reduction of α-amino-acid esters by the Akabori procedure and condensation of the resulting carbonyl compounds with thiocyanate at pH 4 gives 1 : 5-disubstituted 2-mercaptoglyoxalines (III). The constitution of these compounds is proved by synthesis of the derivative (IV; R = H, R′ = Me, R″ = Pr^n) obtained by Wolff–Kishner reduction of (III; R = Me). These ketones (III) have been converted into thiazolo(3′ : 2′-1 : 2)glyoxalines (IX) by ring closure.

IN Part VIII * it was reported that reduction of ethyl glutamate by sodium amalgam under less acid conditions than were used in the Akabori procedure (*Ber.*, 1933, **67**, 151), followed by ring closure with thiocyanate, gave a substance believed to be the glyoxaline (I), or the 1 : 4-disubstituted isomer, in addition to the expected mercaptoglyoxalinylpropionic acid (II). The essential condition for the formation of these disubstituted mercaptoglyoxalines is that the condensation with thiocyanate should be carried out at pH 4 and they are then formed almost exclusively. At higher pH values, excessive decomposition with blackening takes place, and under more acid conditions (pH 2) only the mercaptoglyoxaline having no *N*-substituent is isolated.

To determine the structure of these disubstituted mercaptoglyoxalines the product obtained from alanine was more closely studied, as being the most readily accessible. This product gave the iodoform reaction, showing it to be, not the aldehyde, but the ketone (III; R = Me) or the 1 : 4-disubstituted isomer. It could not, however, be converted into



the sulphur-free glyoxaline by treatment with Raney nickel in boiling ethanol (Cook, Downer, and Heilbron, *J.*, 1948, 1262), and attempts at reductive fission of the *N*-acetonyl group by sodium in liquid ammonia (Heath, Lawson, and Rimington, *J.*, 1951, 2218) gave only unchanged starting material. The reduction failed also with 2-mercapto-1-methylglyoxaline. The product from alanine was, however, reduced by the Wolff–Kishner procedure used by Huang-Minlon (*J. Amer. Chem. Soc.*, 1946, **68**, 2487) to a product identical with 2-mercapto-5-methyl-1-*n*-propylglyoxaline (IV; R = H, R′ = Me, R″ = Pr^n) synthesised from α-*n*-propylaminopropionaldehyde diethyl acetal and ammonium thiocyanate.

2-Mercapto-4-methyl-1-*iso*propylglyoxaline (IV; R = Me, R′ = H, R″ = Pr^i) has been synthesised from α-*iso*thiocyanatopropionaldehyde diethyl acetal and *iso*propylamine,

* Part VIII, *J.*, 1954, 3283.

and also the corresponding 1 : 5-disubstituted glyoxaline (IV; R = H, R′ = Me, R″ = Pr^{i}) from α-*iso*propylaminopropionaldehyde diethyl acetal.

In view of the above identification it appears that the product obtained from alanine ethyl ester is 1-acetonyl-2-mercapto-5-methylglyoxaline (III; R = Me). This substance probably arises as a result of the intermediate formation from two molecules of the amino-aldehyde of the Schiff's base (V) which would isomerise, not as suggested in Part VIII (*loc. cit.*), but by an imino-enamine rearrangement which would be made irreversible by the reaction with the thiocyanate. The 1 : 2-unsaturated amine (VI) so formed would then be spontaneously deaminated, in accordance with the known instability of such compounds, to give the ketone (VII). Deamination of aminoacetaldehyde in warm slightly acid solution was observed by Fischer (*Ber.*, 1893, **26**, 194). The keto-aldehyde (VII) could cyclise to give either the 1-1′-formylethylglyoxaline (VIII) or the acetonyl derivative (III; R = Me). No aldehyde was isolated from the reaction and indeed it might be expected that the intermediate thiourea would cyclise more readily by reaction with the aldehyde than with the ketone group. The considerable darkening of the reaction mixture and the tar formation may indicate that an alternative ring closure also takes place to some extent.

Disubstituted mercaptoglyoxalines analogous to that prepared from alanine were obtained from α-aminobutyric acid (III; R = Et), leucine (III; R = Bu^{i}), norleucine (III; R = Bu^{n}), phenylalanine (III; R = CH_2Ph), and glutamic acid (III; R = $CH_2{\cdot}CH_2{\cdot}CO_2Et$) (cf. Part VIII, *loc. cit.*). It has not been possible to isolate the corresponding derivative from glycine.

When 1-acetonyl-2-mercapto-5-methylglyoxaline (III; R = Me) was refluxed with concentrated hydrochloric acid, there was formed by loss of water a low-melting, water-insoluble, base, having no free thiol group. The formation of this substance is best accounted for on the basis of loss of water of the enol form of the ketone with the mercapto-hydrogen atom to give the diheterocyclic derivative 5 : 5′-dimethylthiazolo-(3′ : 2′-1 : 2)glyoxaline (IX; R = Me). Corresponding derivatives from the ketones derived from α-aminobutyric acid, leucine, and norleucine were likewise prepared. The reaction is similar to that described by Ajello and Miraglia (*Gazzetta*, 1948, **78**, 921) in which 1-allyl-4-methyl-2-thiouracil in hot hydrochloric acid gave 1 : 6-dihydro-4 : 5′-dimethyl-6-oxothiazolidino-(3′ : 2′-1 : 2)pyrimidine. A compound (X) having a fused thiazole–glyoxaline ring skeleton of the type here described was obtained by Ochiai (*Ber.*, 1936, **69**, 1650) by refluxing ethyl 2-acetonylthio-4-methylglyoxaline-5-carboxylate with phosphorus oxychloride.

Experimental

1-*Acetonyl*-2-*mercapto*-5-*methylglyoxaline* (III; R = Me).—DL-α-Alanine ester hydrochloride prepared from alanine (50 g., 0·56 mole) was reduced at pH 2·0—4·5 with finely divided sodium amalgam (2·5%; 2 kg.) as previously described (Bullerwell *et al.*, *J.*, 1952, 1350), the mixture being stirred for 0·5 hr. after all the amalgam had been added. The solution was decanted from the mercury and filtered, and the pH of the filtrate adjusted (if necessary) to pH 4 with sodium hydrogen carbonate. On refluxing with potassium thiocyanate (70 g., 0·72 mole) the solution became dark brown, and after 0·75 hr. it was concentrated, at atmospheric pressure, until crystals began to appear. The dark brown product was filtered off and crystallised from water (charcoal), to give 1-*acetonyl*-2-*mercapto*-5-*methylglyoxaline*, white blades, m. p. 182—183° (16·5 g., 35%) (Found: C, 49·4; H, 6·0; N, 16·6; S, 18·6. $C_7H_{10}ON_2S$ requires C, 49·4; H, 5·9; N, 16·5; S, 18·7%). The absorption maximum was at 2580 Å (ε = 16,600) in H_2O and at 2740 Å (ε 15,900) in $CHCl_3$. The compound was soluble in chloroform or ethyl acetate, sparingly so in water or ethanol, and insoluble in ether. It gave the iodoform reaction. The *semicarbazone* had m. p. 250—251° (decomp.) (Found: C, 42·5; H, 5·9. $C_8H_{13}ON_5S$ requires C, 42·3; H, 5·7%). The *oxime* had m. p. 210—211° (decomp.) (Found: C, 45·5; H, 6·1; N, 22·9. $C_7H_{11}ON_3S$ requires C, 45·4; H, 6·0; N, 22·7%). $\lambda_{max.}$ = 2660 Å (ε = 15,500) in EtOH.

Adding the thiocyanate to the amino-aldehyde solution at pH *ca.* 3·0 gave a mixture of 2-mercapto-4(5)-methylglyoxaline (28·4 g., 44·5%), m. p. 246° (decomp.), and 1-acetonyl-2-mercapto-5-methylglyoxaline (7·2 g., 15%), from which the ketone was extracted with chloroform.

5-*Ethyl*-2-*mercapto*-1-2′-*oxobutylglyoxaline* (III; R = Et).—DL-α-Aminobutyric acid (10 g.) was esterified and the ester hydrochloride reduced as above with sodium amalgam (2·5%; 400 g.). The resulting solution was condensed at pH 3·8 with ammonium thiocyanate (12 g.). Refluxing for 0·75 hr. and evaporation of the solution to a small volume gave 5-*ethyl*-2-*mercapto*-1-2′-*oxobutylglyoxaline* (colourless needles) mixed with tar. After repeated recrystallisation from benzene–light petroleum (b. p. 60—80°) the substance had m. p. 118—120° (1·4 g., 14·6%) (Found: C, 55·0; H, 6·9. $C_9H_{14}ON_2S$ requires C, 54·5; H, 7·1%).

5-n-*Butyl*-2-*mercapto*-1-2′-*oxohexylglyoxaline* (III; R = Bu^n).—DL-α-Norleucine (10 g.) was esterified and reduced as for alanine, the ammonium thiocyanate (9·0) being added at pH 3·5. The solution on refluxing for 0·5 hr. deposited a red oil which solidified on cooling and was filtered off (5·7 g.). It was possible to separate the mixture by fractional crystallisation from ether or, better, by extraction with hot light petroleum (b. p. 60—80°). The petroleum deposited 5-n-*butyl*-2-*mercapto*-1-2′-*oxohexylglyoxaline*, needles (1·8 g., 18·6%), m. p. 98—100° (Found: C, 61·0; H, 8·5; N, 11·0; S, 12·4. $C_{13}H_{22}ON_2S$ requires C, 61·4; H, 8·65; N, 11·0; S, 12·6%). The insoluble residue, crystallised from water, gave 4(5)-butyl-2-mercaptoglyoxaline (4·2 g., 35%), m. p. 125—127°.

5-iso*Butyl*-2-*mercapto*-1-(4-*methyl*-2-*oxopentyl*)*glyoxaline* (III; R = Bu^i).—L-Leucine (10 g.) was treated as above, the ammonium thiocyanate (9·0 g.) being added at pH 4. The solution, which darkened when heated, deposited on cooling 5-iso*butyl*-2-*mercapto*-1-(4-*methyl*-2-*oxopentyl*)*glyoxaline* (3·5 g.). Crystallisation from aqueous ethanol and then from ethanol gave colourless needles, m. p. 153—154° (1·1 g., 11·3%) (Found: C, 60·4; H, 8·6; N, 11·1. $C_{13}H_{22}ON_2S$ requires C, 61·4; H, 8·65; N, 11·0%).

5-*Benzyl*-2-*mercapto*-1-(2-*oxo*-3-*phenylpropyl*)*glyoxaline* (III; R = CH_2Ph).—DL-β-Phenylalanine (10 g.) was esterified and reduced as above. Precipitation commenced as soon as the ammonium thiocyanate (9·0 g.) was added, but heating was continued for 0·5 hr. The product partially dissolved in boiling water from which 4(5)-benzyl-2-mercaptoglyoxaline (3·6 g., 31%), m. p. 220—223° (decomp.), crystallised. The insoluble residue crystallised from ethyl acetate to give the *ketone*, felted needles (0·8 g., 7·7%), m. p. 162—163° (Found: C, 70·7; H, 5·6; N, 8·4; S, 9·8. $C_{19}H_{18}ON_2S$ needles C, 70·8; H, 5·6; N, 8·7; S, 9·9%).

α-iso*Propylaminopropionic Acid*.—To *iso*propylamine (35·4 g., 0·6 mole) in water (20 ml.), α-bromopropionic acid (30·6 g., 0·2 mole) was added slowly, with ice-cooling and stirring. The mixture was then kept at room temperature for 68 hr. and the excess of *iso*propylamine removed by distillation at reduced pressure. After several hours at 0°, the precipitate was filtered off and washed with ethanol, and the α-iso*propylaminopropionic* acid crystallised from ethanol, to give needles (13·6 g., 52%) which sublimed at 295—300° (Found: C, 55·0; H, 10·0. $C_6H_{13}O_2N$ requires C, 55·0; H, 9·9%). Attempts to reduce the ester hydrochloride with sodium amalgam failed to give any amino-aldehyde.

α-iso*Propylaminopropionaldehyde Diethyl Acetal*.—α-Bromopropionaldehyde diethyl acetal (31·8 g.), *iso*propylamine (63 g.), and ethanol (20 ml.) were heated together in a pressure-bottle for 10 hr. at 100°. The excess of *iso*propylamine and ethanol was removed under slightly reduced pressure and the residue was taken up in a little water, saturated with solid potassium carbonate, and extracted with chloroform. The chloroform layer was dried (K_2CO_3) and on removal of the solvent the residue was fractionated, to give 14·2 g. (50%) of the *acetal*, b. p. 86—88°/26 mm. (Found: N, 7·2. $C_{10}H_{23}O_2N$ requires N, 7·4%).

2-*Mercapto*-5-*methyl*-1-iso*propylglyoxaline*.—α-*iso*Propylaminopropionaldehyde diethyl acetal (2·4 g.), potassium thiocyanate (2·4 g.), 2N-hydrochloric acid (10 ml.), and ethanol (10 ml.) were heated under reflux for 10 hr. The solution was evaporated to dryness under reduced pressure, and extracted with acetone. Evaporation of the acetone left a dark-brown oil which was taken up in 3N-sodium hydroxide and decolorised with charcoal. Acidification, extraction with chloroform, and removal of the solvent gave a light yellow solid *glyoxaline* which, crystallised from ether or light petroleum (b. p. 60—80°), had m. p. 198—199° (0·25 g., 8%) (Found: C, 54·2; H, 7·7; N, 17·7. $C_7H_{12}N_2S$ requires C, 53·9; H, 7·7; N, 18·0%).

α-iso*Thiocyanatopropionaldehyde Diethyl Acetal*.—A mixture of the α-amino-acetal (10 g.), carbon disulphide (6·7 g.), 5N-sodium hydroxide (15 ml.), and water (34 ml.) was warmed gently and shaken until dissolution was effected. The solution was cooled to 0° and treated with an ice-cold solution of basic lead acetate (40 ml.; 25% w/v) with stirring and then an ice-cold solution of normal lead acetate (20 g.) in water (50 ml.) was gradually added. The mixture was kept cold for 0·5 hr., then gradually warmed on the steam-bath with stirring. The coloured precipitate gradually blackened, and the product was isolated by steam-distillation and extraction of the distillate with ether. The ethereal layer was dried (K_2CO_3), the solvent

removed, and the light yellow pungent oil fractionated, to give 9·4 g. (73·5%) of the colourless iso*thiocyanato-acetal*, b. p. 125°/27 mm. (Found: C, 49·3; H, 7·9; N, 7·3. $C_8H_{15}O_2NS$ requires C, 50·8; H, 7·9; N, 7·4%).

2-*Mercapto-4-methyl*-1-iso*propylglyoxaline*.—The foregoing product (3·8 g.), *iso*propylamine (2 g.), and ethanol (5 ml.) were heated on the water-bath for 30 min. (heat was evolved on initial mixing). The solvent was removed and the remaining oil refluxed with 30% sulphuric acid (10 c.c.) for 10 hr. The cooled solution was extracted with chloroform, and the dried chloroform layer was evaporated to give a brown oil, which was extracted with ether. Removal of the solvent and crystallisation from light petroleum (b. p. 60—80°) gave 2-*mercapto-4-methyl*-1-iso*propylglyoxaline* (white needles; 0·3 g., 9·5%), m. p. 156—158° (Found: C, 54·3; H, 7·7; N, 17·7. $C_7H_{12}N_2S$ requires C, 53·9; H, 7·7; N, 18·0%).

α-n-*Propylaminopropionaldehyde Diethyl Acetal*.—The α-bromo-acetal (31·8 g.), *n*-propylamine (63 g.), and ethanol (20 ml.) were heated together in a pressure-bottle for 12 hr. at 100°. The mixture was worked up as for the *iso*propyl derivative. The *product* was a colourless oil (12·9 g., 45%), b. p. 98°/30 mm. (Found: C, 63·4; H, 12·0; N, 7·4. $C_{10}H_{23}O_2N$ requires C, 63·5; H, 12·1; N, 7·4%).

2-*Mercapto-5-methyl*-1-n-*propylglyoxaline*.—*Method* I. α-*n*-Propylaminopropionaldehyde diethyl acetal (3·8 g.), ammonium thiocyanate (2·4 g.), 2N-hydrochloric acid (20 ml.), and ethanol (5 ml.) were refluxed for 3 hr. Next morning the crystals which had separated were collected and washed with water. Crystallisation from benzene–light petroleum (b. p. 60—80°) gave 2-*mercapto-5-methyl*-1-n-*propylglyoxaline*, broad needles (2·6 g., 84%), m. p. 166—167° (Found: C, 54·5; H, 7·6. $C_7H_{12}N_2S$ requires C, 53·9; H, 7·7%). This was identical (mixed m. p.) with the product obtained from 1-acetonyl-2-mercapto-5-methylglyoxaline by Wolff–Kishner reduction.

Method II. 1-Acetonyl-2-mercapto-5-methylglyoxaline (0·75 g.), hydrazine hydrate (1 ml., 90% w/w), potassium hydroxide (1·4 g.), and ethylene glycol (50 ml.) were refluxed for 1·5 hr. The water was then distilled off until the temperature reached 190° and the solution was refluxed for a further 5 hr. The cooled solution was acidified (some hydrogen sulphide was given off) and extracted with chloroform (2 × 50 ml.). On removal of the chloroform, the gummy residue was crystallised first from ether and then from benzene–light petroleum (b. p. 60—80°), to give the *glyoxaline* (0·23 g., 30%), m. p. 165—167° (Found: C, 53·7; H, 7·8; N, 18·1; S, 20·4. $C_7H_{12}N_2S$ requires C, 53·9; H, 7·7; N, 18·0; S, 20·5%).

5 : 5′-*Dimethylthiazolo*(3′ : 2′-1 : 2)*glyoxaline* (IX; R = Me).—1-Acetonyl-2-mercapto-5-methylglyoxaline (0·5 g., 0·003 mole) was refluxed with concentrated hydrochloric acid (5 ml.) for 0·5 hr., cooled, and made alkaline (pH 10). The oily product solidified at 0° and crystallised from light petroleum (b. p. 60—80°) to give the *thiazologlyoxaline* as white diamond-shaped plates, m. p. 88—89° (yield quantitative) (Found: C, 55·3; H, 5·5; N, 17·9; S, 20·4. $C_7H_8N_2S$ requires C, 55·3; H, 5·3; N, 18·4; S, 21·0%), which was very soluble in organic solvents, but insoluble in water. Light absorption: max. at 2480 Å (ε 5400) in EtOH.

5 : 5′-*Di*iso*butylthiazolo*(3′ : 2′-1 : 2)*glyoxaline* (IX; R = Bu^i).—5-*iso*Butyl-2-mercapto-1-(4-methyl-2-oxopentyl)glyoxaline (0·35 g., 0·0014 mole) on similar treatment gave a white solid which crystallised from light petroleum (b. p. 60—80°) to give the 5 : 5′-*di*iso*butyl* compound, m. p. 96—98°, in quantitative yield (Found: C, 65·7; H, 8·4; N, 11·8. $C_{13}H_{20}N_2S$ requires C, 66·1; H, 8·5; N, 11·9%).

5 : 5′-*Di*-n-*butylthiazolo*(3′ : 2′-1 : 2)*glyoxaline* (IX; R = Bu^n).—5-*n*-Butyl-2-mercapto-1-2′-oxohexylglyoxaline (0·15 g., 0·0006 mole) on similar treatment gave an oil which did not solidify at 0° and from which 5 : 5′-*di*-n-*butylthiazolo*(3′ : 2′-1 : 2)*glyoxaline picrate* was obtained as yellow needles (0·23 g., 84%), m. p. 185—186° (from ethanol) (Found: C, 48·7; H, 5·0; N, 15·3. $C_{19}H_{23}O_7N_5S$ requires C, 49·0; H, 5·0; N, 15·1%).

5 : 5′-*Diethylthiazolo*(3′ : 2′-1 : 2)*glyoxaline* (IX; R = Et).—5-Ethyl-2-mercapto-1-2′-oxobutylglyoxaline (0·6 g., 0·003 mole) on similar treatment gave an oil (quantitative yield) which did not crystallise. It readily afforded 5 : 5′-*diethylthiazolo*(3′ : 2′-1 : 2)*glyoxaline picrate*, yellow needles (from ethanol), m. p. 238—240° (decomp.) (Found: C, 44·0; H, 3·8. $C_{15}H_{15}O_7N_5S$ requires C, 44·0; H, 3·7%).

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