115. 2-*Mercaptoglyoxalines. Part XI.* The Preparation of Mixed* 1 : 5-*Disubstituted* 2-*Mercaptoglyoxalines and the Corresponding Thiazolo*(3′ : 2′-1 : 2)*glyoxalines.*

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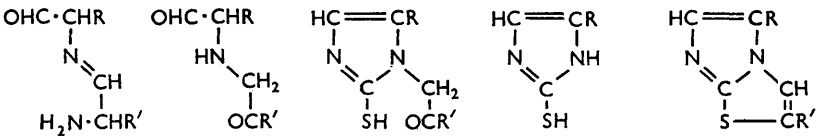
In confirmation of the reaction mechanism suggested in Part IX [1] to account for the formation of 1 : 5-disubstituted 2-mercaptoglyoxalines (III; R = R′) obtained when α-amino-aldehydes are condensed with thiocyanate at pH 4, mixtures of alanine and α-phenylglycine were esterified, reduced, and condensed with thiocyanate, giving the 2-mercaptoglyoxalines (III; R ≠ R′). These have been cyclised to the thiazologlyoxalines (V).

In Part IX [1] we reported the production of 1 : 5-disubstituted 2-mercaptoglyoxalines (III; R = R′) by the action of thiocyanate at pH 4 on amino-aldehydes obtained by the Akabori reduction of certain amino-acids. To account for the production of the amino-aldehydes (II; R = R′) we postulated the intermediate formation of Schiff's bases (I; R = R′) followed by deamination.

Confirmation that the intermediate was not dependent on the Akabori reduction procedure was provided by the finding that α-aminopropionaldehyde diethyl acetal, when hydrolysed to the aldehyde and condensed with thiocyanate at pH 4, gave 1-acetonyl-2-mercapto-5-methylglyoxaline [1] as the only isolable product.



(I) (II) (III) (IV) (V)

If this mechanism is correct it might be possible by treating with thiocyanate a mixture of different amino-aldehydes to obtain mercaptoglyoxalines (III) in which the groups R ≠ R′. This has been found for mixtures of alanine with α-phenylglycine or α-*p*-methoxy- or α-3 : 4-dimethoxy-phenylglycine. α-Phenylglycine was chosen because its phenyl substituent would offer a suitable contrast to the alkyl substituent of alanine and provide amino-ketones of potential pharmacological interest.

The simple mercaptoglyoxalines (IV) from α-phenylglycine, α-*p*-methoxyphenylglycine, and α-3 : 4-dimethoxyphenylglycine were first prepared by the usual reaction with thiocyanate at pH 2 with the aldehydes obtained by reduction of the ethyl esters, then the corresponding 1 : 5-disubstituted mercaptoglyoxalines (III; R = R′) were obtained by reaction with the thiocyanate at pH 4. Finally mixtures of equimolecular amounts of alanine with one of the α-phenylglycines were esterified, reduced, and condensed, the corresponding disubstituted mercaptoglyoxalines [III; R = Ph or C_6H_4·OMe or $C_6H_3(OMe)_2$, R′ = Me) being isolated by fractional crystallisation.

Attempts to form mixed 1 : 5-disubstituted 2-mercaptoglyoxalines from mixed esters of glycine and alanine failed.

In the case of α-phenylglycine, owing to the precipitation which occurred at pH 4, the

* Part X, *J.*, 1956, 1103.

[1] Lawson and Morley, *J.*, 1955, 1695.

cyclisation with thiocyanate was effected at pH *ca.* 2·8 which resulted in a mixture of the glyoxalines (IV; R = Ph) and (III; R = R′ = Ph). The latter on benzylation gave 2-benzylthio-1-phenacyl-5-phenylglyoxaline, m. p. 117°, which was not the same substance as Dodson [2] obtained (m. p. 142°) by the action of phenacyl bromide on 2-benzylthio-4(5)-phenylglyoxaline (or by heating *S*-benzyl*iso*thiuronium chloride with phenacyl bromide). Dodson's provisional assignment of the 2-benzylthio-1-phenacyl-4-phenylglyoxaline structure to his compound, on the basis of the analogy with Forsyth and Pyman's [3] work on the methylation of 4(5)-phenylglyoxaline, is therefore correct.

With the α-phenylglycine derivatives steam-distillation of the solutions after the condensation with thiocyanate gave small quantities of phenacyl alcohols (reduced Fehling's solution, but gave no Schiff's reaction; product from α-phenylglycine ester gave a 2 : 4-dinitrophenylhydrazone with an absorption maximum [4] at 3780 Å). It was isolated from the steam-distillate and its formation may be by the sequence :

$$^{+}NH_3\cdot CHPh\cdot CHO \longrightarrow {}^{+}NH_3\cdot CPh{:}CH\cdot OH \longrightarrow Ph\cdot CO\cdot CH_2\cdot OH + NH_4^{+}$$

initiated by the relatively high activity of the α-hydrogen atom.

Whilst the reaction of thiocyanate with a mixture of the amino-aldehydes from α-phenylglycine and alanine might be expected to give either isomer (III; R = Ph, R′ = Me or *vice versa*), or a mixture of both, only one product was isolated. This substance was assigned the first of the two possible structures since its dinitrophenylhydrazone failed to show any high-intensity absorption in the 3800 Å region. By analogy, the disubstituted glyoxalines obtained from the other α-phenylglycines were assigned the corresponding structures. The failure to isolate the isomeric phenacyl ketones suggests that the α-amino-phenylacetaldehyde was the component which exclusively provided the amino-group for the Schiff's base condensation. This would be consistent with the effect of the phenyl substituent in weakening the basicity of the amino-group and therefore offering a smaller proportion of ammonium ion at pH *ca.* 4 than that provided by the alanine component.

In a manner similar to that already described, hydrochloric acid cyclised the mercapto-glyoxalines (III) to the thiazologlyoxalines (V).

Experimental

1-Acetonyl-2-mercapto-5-methylglyoxaline.—α-Aminopropionaldehyde diethyl acetal (2·0 g.) was hydrolysed by warm 3N-hydrochloric acid for 15 min. The pH of the solution was adjusted to 4 and ring closure effected in the usual way by heating with potassium thiocyanate (1·0 g.). After treatment with charcoal, 1-acetonyl-2-mercapto-5-methylglyoxaline crystallised (35%), having m. p. 181—183°.

Preparation of α-Methoxyphenylglycines.—The substituted α-phenylglycines were prepared from the corresponding aldehydes by the method of Marvel and Noyes.[5] α-*p*-Methoxyphenyl-glycine (33% yield) had m. p. 235° (sublimes) (Found : C, 59·6; H, 6·0. Calc. for $C_9H_{11}O_3N$: C, 59·6; H, 6·1%). α-(3 : 4-*Dimethoxyphenyl)glycine hydrochloride* (yield 20%) had m. p. 229° (decomp.) (Found : C, 45·5; H, 5·7. $C_{10}H_{13}O_4N,HCl,H_2O$ requires C, 45·2; H, 6·0%).

Preparation of 2-Mercaptoglyoxalines from α-Phenylglycine.—α-Phenylglycine (20 g.) was esterified and reduced with sodium amalgam (2·5%, 400 g.) as previously described.[1] The resulting solution, freed from mercury, was adjusted to pH 2·8, treated with potassium thio-cyanate (18 g.), and boiled for 30 min. The solution was distilled at atmospheric pressure until solid began to appear and, on storage, a mixture of fine needles and dense prisms crystallised. These were separated by hand. The prisms (6·0 g.), 2-mercapto-4(5)-phenylglyoxaline, crystal-lised from aqueous ethanol, had m. p. 265—266°. The needles consisting of 2-*mercapto*-1-*phenacyl*-5-*phenylglyoxaline* (2 g.), recrystallised from ethanol, had m. p. 216—218° (decomp.) (Found : C, 69·3; H, 4·5; N, 9·6. $C_{17}H_{14}ON_2S$ requires C, 69·4; H, 4·8; N, 9·5%). Light absorption : $\lambda_{max.}$ 2240, 2670, and 2940 Å (ε 12,400, 13,400, and 15,700 in EtOH). Heating equimolecular amounts of 2-mercapto-1-phenacyl-5-phenylglyoxaline and benzyl chloride in

[2] Dodson, *J. Amer. Chem. Soc.*, 1948, **70**, 2753.
[3] Forsyth and Pyman, *J.*, 1925, **573**.
[4] Cf. Braude and Jones, *J.*, 1945, **498**.
[5] Cf. Steiger, *Org. Synth.*, 1955, **3**, 84.

ethanol on the steam-bath followed by evaporation and neutralisation with sodium carbonate gave 2-*benzylthio*-1-*phenacyl*-5-*phenylglyoxaline*, m. p. 117° (needles from aqueous ethanol) (Found: C, 74·6; H, 5·2. $C_{24}H_{20}ON_2S$ requires C, 75·0; H, 5·2%). The distillate (above) was extracted with ether, and the residue after removal of the ether gave phenacyl alcohol (0·1 g.), plates [from light petroleum (b. p. 60—80°)], m. p. 84—86°. *Phenacyl alcohol* 2 : 4-*dinitrophenylhydrazone* (red needles from benzene) had m. p. 220—222° (Found: C, 53·0; H, 3·8; N, 17·6. $C_{14}H_{12}O_2N_4$ requires C, 53·2; H, 3·8; N, 17·7%). Light absorption: $\lambda_{max.}$ 3780 Å (ε 25,800 in EtOH).

A mixture of alanine (7·5 g.) and α-phenylglycine (12·7 g.), esterified and reduced in the usual manner, was condensed with thiocyanate at pH 4·5. The crystals, which separated after filtration, concentration, and cooling of the resulting solution, were extracted with boiling benzene, which on evaporation left 1-*acetonyl*-2-*mercapto*-5-*phenylglyoxaline*; recrystallised from ethanol, this had m. p. 201° (pale yellow felted needles; 1·5 g.) (Found: C, 61·8; H, 5·3; N, 12·4. $C_{12}H_{12}ON_2S$ requires C, 62·1; H, 5·2; N, 12·1%). The *oxime*, prisms (from ethanol), had m. p. 235° (decomp.) (Found: C, 57·9; H, 5·1. $C_{12}H_{13}ON_3S$ requires C, 58·2; H, 5·2%). The 2 : 4-*dinitrophenylhydrazone* had m. p. 252° (decomp.) (prisms from toluene) (Found: C, 51·8; H, 3·9. $C_{18}H_{18}O_4N_6S$ requires C, 52·2; H, 3·9%). Light absorption: $\lambda_{max.}$ 3580 Å (ε 21,300 in EtOH).

Preparation of 2-*Mercaptoglyoxalines from* α-p-*Methoxyphenylglycine*.—α-*p*-Methoxyphenylglycine (5 g.), when esterified, reduced and condensed at pH 2·0 with thiocyanate as above, gave 2-*mercapto*-4(5)-p-*methoxyphenylglyoxaline* (3·0 g.), prisms (from ethanol), m. p. 240° (Found: C, 58·3; H, 5·0. $C_{10}H_{10}ON_2S$ requires C, 58·3; H, 4·9%). *p*-Methoxyphenacyl alcohol, m. p. 103—104°, was isolated from the mother-liquors by ether-extraction. Condensation with thiocyanate at pH 4·0 gave 2-*mercapto*-1-p-*methoxyphenacyl*-5-p-*methoxyphenylglyoxaline*, m. p. 190° (from ethanol) (Found: C, 63·7; H, 4·9. $C_{19}H_{18}O_3N_2S$ requires C, 64·4; H, 5·1%). When a mixture of α-*p*-methoxyphenylglycine (15 g.) and alanine (7·5 g.) was used and the thiocyanate condensation effected at pH 4·0, 1-*acetonyl*-2-*mercapto*-5-p-*methoxyphenylglyoxaline* (2·5 g.), m. p. 248° (decomp.), prisms from ethanol, was obtained (Found: C, 59·2; H, 5·4; N, 10·4. $C_{13}H_{14}O_2N_2S$ requires C, 59·5; H, 5·3; N, 10·7%).

Preparation of 2-*Mercaptoglyoxalines from* α-3 : 4-*Dimethoxyphenylglycine*.—α-3 : 4-Dimethoxyphenylglycine, treated as above and condensed with thiocyanate at pH 2, gave 2-*mercapto*-4(5)-(3 : 4-*dimethoxyphenyl*)*glyoxaline* (2·5 g.), m. p. >300°, prisms from ethanol (Found: C, 55·9; H, 5·2; N, 11·5. $C_{11}H_{12}O_2N_2S$ requires C, 56·0; H, 5·1; N, 11·9%). Condensation with the thiocyanate at pH 4 gave 1-(3 : 4-*dimethoxyphenacyl*)-5-(3 : 4-*dimethoxyphenyl*)-2-*mercaptoglyoxaline*, plates (from ethanol), m. p. 206° (Found: C, 60·6; H, 5·1; N, 6·9. $C_{21}H_{22}O_5N_2S$ requires C, 60·8; H, 5·3; N, 6·8%). A mixture of 3 : 4-dimethoxyphenylglycine (5·0 g.) and alanine (2·5 g.) gave 1-*acetonyl*-2-*mercapto*-5-(3 : 4-*dimethoxyphenyl*)*glyoxaline* (1·5 g.) (from aqueous ethanol), m. p. 224° (Found: C, 57·2; H, 5·7. $C_{14}H_{16}O_3N_2S$ requires C, 57·5; H, 5·5%).

Ring Closure of the 1 : 5-*Disubstituted* 2-*Mercaptoglyoxalines*.—Ring closure was effected by boiling the above 1 : 5-disubstituted 2-mercaptoglyoxalines for 1 hr. in concentrated hydrochloric acid. The compounds (see Table) obtained on addition of water were crystallised as the hydrochlorides from aqueous ethanol or converted into the free *bases* and crystallised as such from benzene–light petroleum (b. p. 60—80°). Yields were >90%.

Thiazolo(3′ : 2′-1 : 2)*glyoxalines* (V).

R	R′	Form & m. p.	Formula	Found (%) C	Found (%) H	Required (%) C	Required (%) H
Ph	Ph	Needles, 124°	$C_{17}H_{12}N_2S$	73·6	4·2	73·9	4·3
Ph	Me	Blades, 181	$C_{12}H_{10}N_2S$	67·1	4·8	67·3	4·7
C_6H_4·OMe	Me	Needles, 217	$C_{13}H_{12}O_2N_2S,HCl,H_2O$ *	52·4	5·2	52·2	5·0
$C_6H_3(OMe)_2$	$C_6H_3(OMe)_2$	Needles, 233	$C_{21}H_{20}O_4N_2S,HCl$	58·5	5·1	58·3	4·9
$C_6H_3(OMe)_2$	Me	Needles, 230	$C_{14}H_{14}O_2N_2S,HCl,H_2O$	51·4	5·2	51·1	4·9
$C_6H_3(OMe)_2$	Me	Prisms, 169—170	$C_{14}H_{14}O_2N_2S$	61·6	5·1	61·3	5·1

* The *picrate*, plates from ethanol–toluene, had m. p. 223° (decomp.) (Found: C, 48·5; H, 3·2. $C_{19}H_{15}O_8N_5S$ requires C, 48·3; H, 3·2%).

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