489. 2-*Mercaptoglyoxalines. Part II.* Application of the Mannich Reaction. Protection of the Thiol Group.*

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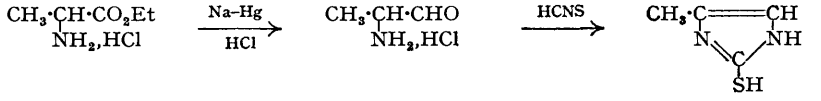
Methods of preparing 2-mercapto-glyoxaline and -4(5)-methylglyoxaline, in larger quantities than have previously been reported, are given. The thiol group can be protected by benzylation in liquid ammonia. The Mannich reaction has been applied unsuccessfully to 2-mercaptoglyoxaline, but successfully to 2-mercapto-4(5)-methylglyoxaline to give 5(4)-dimethylamino-methyl-2-mercapto-4(5)-methylglyoxaline.

Akabori (*Ber.*, 1933, **66**, 151) prepared 2-mercapto-glyoxaline and -4(5)-methylglyoxaline from glycine and alanine respectively, by the reduction of their ethyl esters with sodium amalgam to yield the corresponding amino-aldehydes, followed by ring closure of the latter with sodium thiocyanate. By a modification of his technique a fairly large-scale preparative method for 2-mercapto-4(5)-methylglyoxaline was obtained. This compound has also been prepared from hydroxyiminoacetone by reduction with hydrogen and palladium–charcoal to aminoacetone hydrochloride and then ring closure with potassium thiocyanate, but this method is not so convenient for large quantities.



Du Vigneaud and Behrens (*J. Biol. Chem.*, 1937, **117**, 27) showed that when histidine was treated in liquid ammonia with sodium and benzyl chloride it yielded a monobenzyl derivative in which the benzyl group was attached to the glyoxaline-nitrogen atom and that the histidine could be regenerated by reductive fission with sodium in liquid ammonia. This reaction has been applied to the 2-mercaptoglyoxalines. One equivalent of sodium was rapidly absorbed by the thiol group; a second equivalent can be introduced to replace the imino-hydrogen atom,

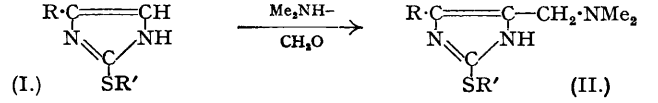
* Part I, preceding paper.

though this reaction is considerably slower. It was therefore possible to limit the reactions to the first stage. By the action of benzyl chloride on the monosodium derivatives, 2-benzylthioglyoxaline and -4(5)-methylglyoxaline were obtained in good yield.

The evidence that the compounds are *S*-benzyl and not *N*-benzyl derivatives is given by the ultra-violet absorption spectra which no longer exhibit the maxima at *ca.* 2600 A. characteristic of the free thiol group in this series, by the failure of the compounds to give the typical yellow colour with sulphur dioxide (Balaban and King, *J.*, 1927, 1858), and by their basic nature. As will be reported in a later paper the protecting groups in such alkylthioglyoxalines may be readily removed by fission with sodium in liquid ammonia. The dibenzyl derivatives of the mercaptoglyoxalines could not be obtained crystalline.

A monoacetyl-2-mercapto-4(5)-methylglyoxaline has been prepared. This substance is readily decomposed by water or alcohol with regeneration of the mercaptoglyoxaline and the change can be followed spectroscopically. In chloroform solution it is stable and unlike the 2-mercaptoglyoxalines with free thiol groups does not show an absorption maximum in the 2600-A. region. On the basis of this evidence together with its solubility in non-polar solvents, it has been assigned an acetylthio-structure. Cook, Downer, and Heilbron (*J.*, 1948, 1262) prepared two monoacetyl derivatives of 5-benzamido-2-mercaptoglyoxaline which were both stable to water and to which they tentatively assigned *N*-acetyl and *S*-acetyl structures respectively. A diacetyl product having one labile acetyl group was given the structure of a *NS*-diacetyl derivative.

The Mannich reaction has been applied to 2-mercaptoglyoxaline (I; R = R′ = H) 2-mercapto-4(5)-methylglyoxaline (I; R = Me, R′ = H), and their respective benzylthio-derivatives. Only in the case of 2-mercapto-4(5)-methylglyoxaline did the reaction proceed smoothly, yielding the expected Mannich base (II; R = Me, R′ = H). This base yields an acetate, m. p. 145°, and a picrate, m. p. 194°. It still exhibits the typical mercaptoglyoxaline properties, *e.g.*, the absorption maximum at 2600 A. and the yellow colour with sulphur dioxide. The benzylthio-derivatives yielded resins; the isolation of the picrate of 2-benzylthio-5(4)-dimethylaminomethyl-4(5)-methylglyoxaline (II; R = Me R′ = CH_2Ph) indicated that, although the reaction was complex, some of the desired product was formed.



(I.) (II.)

When the reaction was applied to 2-mercaptoglyoxaline a neutral product resulted. Addition to this of sodium carbonate caused evolution of formaldehyde, but there was no liberation of dimethylamine. The compound had typical mercaptoglyoxaline properties. The formula, $C_4H_6ON_2S$, indicated a monoformaldehyde addition compound. This was confirmed by the fact that the same substance resulted from the action of formaldehyde and hydrochloric acid alone on 2-mercaptoglyoxaline. From this evidence the structure 1-hydroxymethyl-2-mercaptoglyoxaline was assigned to this material.

Experimental.

Analyses are by Drs. Weiler and Strauss.

2-Mercapto-4(5)-methylglyoxaline.—DL-α-Alanine (50 g.) in ethanol (450 ml.) was esterified by saturation with hydrogen chloride without cooling and then refluxed for 0·5 hour; benzene (75 ml.) was added and most of the solvent removed under reduced pressure. The alanine ethyl ester was dissolved in water (700 ml.) and cooled to 0° to −5° by the addition of solid carbon dioxide. Sodium amalgam (2·5%; 2050 g.) was added in small portions with stirring, the solution being kept acid by the addition from time to time of 15% hydrochloric acid (420 ml.). The temperature was kept at 0° to −5° throughout, and stirring continued for 0·5 hour after the addition of the amalgam. The solution was filtered, boiled for 1 hour with ammonium thiocyanate (100 g.), and distilled at atmospheric pressure till crystals appeared. After storage at 4° the cream-coloured crystals of 2-mercapto-4(5)-methylglyoxaline, m. p. 246°, were separated (38 g., 59%). The absorption maximum in water was at 2580 A., ε = 14,600, and in chloroform at 2730 A., ε = 14,600. This substance when pure is colourless, not pale yellow as described in the literature.

The above substance was also prepared from hydroxyiminoacetone (10 g.) which was hydrogenated for 10 hours over palladium–charcoal (5 g. of 10%) in ethanolic 1·5N-hydrogen chloride. After removal of the solvent, water (10 ml.) and sodium thiocyanate (12 g.) were added and the solution heated on a boiling water-bath for 1 hour. On cooling the product separated. Recrystallised from water (charcoal), the crystals of 2-mercapto-4(5)-methylglyoxaline melted at 246° (4·5 g., 51%).

2-Mercaptoglyoxaline.—Glycine ethyl ester hydrochloride (100 g.) was reduced with sodium amalgam and cyclised as described above. The same quantities of amalgam, acid, and ammonium thiocyanate

were used. The resulting solution was then distilled until 500 ml. of distillate had been collected, and mercuric chloride (100 g.), dissolved in boiling water (300 ml.), was added. The mercury complex was decomposed with hydrogen sulphide to yield colourless crystals of 2-mercaptoglyoxaline, m. p. 226° (25 g., 19%). The absorption maximum in water was at 2580 A., $\varepsilon = 14,600$.

2-*Acetylthio*-4(5)-*methylglyoxaline*.—2-Mercapto-4(5)-methylglyoxaline (10 g.), pyridine (50 ml.), and acetic anhydride (15 ml.) were heated under reflux on a boiling water-bath for 1 hour. The solution was concentrated under reduced pressure, benzene (20 ml.) was added, and the crude acetyl compound which separated was collected and washed with benzene. The 2-*acetylthio*-4(5)-*methylglyoxaline* recrystallised from benzene as white needles, m. p. 200°. On concentration, the mother-liquor and washings yielded a second crop, the total yield being 11·1 g. (81%). The material was soluble in ether and ethanol (Found : C, 46·3; H, 5·4; N, 17·5; S, 19·7. $C_6H_8ON_2S$ requires C, 46·2; H, 5·1; N, 18·0; S, 20·5%). The absorption maximum in chloroform was at 3250 A., $\varepsilon = 11,700$.

2-*Benzylthio*-4(5)-*methylgloxaline*.—2-Mercapto-4(5)-methylglyoxaline (22·8 g.) was dissolved in liquid ammonia (300 ml., approx.), and sodium (4·7 g.) was slowly added to the well-stirred mixture until the whole solution remained blue for about 20 seconds. Benzyl chloride (26 ml.) was then added dropwise and stirring continued for a further 0·5 hour. The ammonia was allowed to evaporate spontaneously. The solid residue was dissolved in 4% (w/v) hydrochloric acid (350 ml.), and the excess of benzyl chloride extracted with ether. The extracts were bulked and washed with 1% (w/v) hydrochloric acid. The solution was then made alkaline with sodium hydroxide and extracted with chloroform. The oil remaining after removal of the chloroform under reduced pressure was dissolved in ethyl acetate (40 ml.), seeded, and left overnight at −10°. The white crystals of 2-*benzylthio*-4(5)-*methylglyoxaline*, m. p. 102° (30·6 g.), were collected. On concentration of the mother-liquor a further 4 g. were obtained (total, 85·6%). The compound is soluble in methanol, ethanol, acetic acid, pyridine, acetone, benzene, chloroform, or carbon tetrachloride, sparingly so in ether and ethyl acetate, insoluble in water and light petroleum (Found : C, 64·3; H, 6·4; N, 13·7; S, 14·8. $C_{11}H_{12}N_2S$ requires C, 64·7; H, 5·9; N, 13·7; S, 15·7%).

2-*Benzylthioglyoxaline*.—2-Mercaptoglyoxaline (20 g.) was converted into 2-*benzylthioglyoxaline* by the procedure described for 2-benzylthio-4(5)-methylglyoxaline. The white solid residue left on evaporation of the ammonia was dissolved in 4% (w/v) hydrochloric acid (350 ml.) and extracted with ether. The aqueous layer was made alkaline with sodium hydroxide and after storage at 4° the 2-benzylthioglyoxaline was filtered off and washed with water. The dried material recrystallised from boiling benzene (1 l.) (charcoal) as very light fine white needles, m. p. 153° (34 g., 90%), soluble in ethanol, sparingly so in benzene, chloroform, or ether (Found: C, 63·5; H, 5·7; N, 14·2; S, 16·6. $C_{10}H_{10}N_2S$ requires C, 63·1; H, 5·3; N, 14·7; S, 16·8%).

5(4)-*Dimethylaminomethyl*-2-*mercapto*-4(5)-*methylglyoxaline Acetate*.—33% (w/v) Aqueous dimethylamine (15 ml.) was cooled to 0° and acetic acid (15 ml.) was added so that the temperature did not rise above 5°, followed by 40% aqueous formaldehyde, the temperature still being kept below 5°. To this solution, 2-mercapto-4(5)-methylglyoxaline (11·4 g.) was added with mechanical shaking at room temperature until dissolution was effected. After being kept the solution was distilled under reduced pressure to a thick syrup. The 5(4)-*dimethylaminomethyl*-2-*mercapto*-4(5)-*methylglyoxaline acetate* crystallised from ethanol (120 ml.). On cooling to −10° the short white needles, m. p. 148° (15 g.), were filtered off, washed with ethanol, and dried. On concentration of the mother-liquor and washings, a second crop of crystals was obtained (total, 18·9 g., 81·8%). The substance was very soluble in water and sparingly so in ethanol (Found : C, 46·9; H, 7·5; N, 17·8; S, 13·7. $C_9H_{17}O_2N_3S$ requires C, 46·7; H, 7·4; N, 18·2; S, 13·8%).

5(4)-*Dimethylaminomethyl*-2-*mercapto*-4(5)-*methylglyoxaline*.—The free *base* was precipitated by treating a strong aqueous solution of the acetate with an equivalent amount of sodium carbonate solution. It is not necessary to isolate the acetate, as the thick syrup obtained in the previous preparation readily crystallised when made faintly alkaline with ammonia solution. After storage at 4° the crystals were filtered off, washed with water, and dried. The substance did not melt but decomposed at 280° (Found : C, 49·4; H, 7·7; N, 24·7; S, 18·2. $C_7H_{13}N_3S$ requires C, 49·1; H, 7·7; N, 24·5; S, 18·7%). The mother-liquors were made faintly acid with acetic acid, concentrated to dryness under reduced pressure, and dissolved in the minimum amount of water. On neutralisation with aqueous ammonia and storage at 4° a further crop of crystals (3·4 g.) was obtained. The total yield was 14·5 g. (84·7%). The base is soluble in hot ethanol, sparingly soluble in water or cold ethanol, and its absorption maximum in ethanol is at 2660 A., $\varepsilon = 15,000$.

1-*Hydroxymethyl*-2-*mercaptoglyoxaline*.—(Method I) A solution of dimethylamine, acetic acid, and formaldehyde prepared as above was added dropwise, with mechanical stirring, to 2-mercaptoglyoxaline (10 g.) in water (50 ml.). After storage at 4°, crystallisation commenced. The 1-*hydroxymethyl*-2-*mercaptoglyoxaline*, m. p. 161° (9·2 g., 71%), was recrystallised from ethanol (Found : C, 37·3; H, 4·7; N, 20·8; S, 24·1. $C_4H_6ON_2S$ requires C, 36·9; H, 4·6; N, 21·5; S, 24·6%).

(Method II) 2-Mercaptoglyoxaline (5 g.) was dissolved in concentrated hydrochloric acid (30 ml.), and 40% formaldehyde solution (3·8 ml.) was slowly added. The clear solution, after storage, was distilled to dryness under reduced pressure. The solid residue was dissolved in water (5 ml.) and neutralised with sodium carbonate. Crystallisation of the 1-hydroxymethyl-2-mercaptoglyoxaline, m. p. 161° (3·9 g., 60%), rapidly occurred. The absorption maximum in water was at 2550 A., $\varepsilon = 15,000$.

Mannich Reaction with 2-*Benzylthio*-4(5)-*methylglyoxaline*.—A solution of dimethylamine, acetic acid, and formaldehyde was prepared as in the preparation of 5(4)-dimethylaminomethyl-2-mercapto-4(5)-methylglyoxaline acetate. This was added to 2-benzylthio-4(5)-methylglyoxaline (20·4 g.), dissolution being effected by shaking. After storage at room temperature, water (40 ml.) was added and the solution neutralised with sodium hydroxide. The precipitated gum was extracted with ether, and the extracts

were washed with water and dried (Na_2SO_4). Removal of the ether under reduced pressure left a clear, pale yellow, viscous residue which was soluble in ethanol, acetone, chloroform, ethyl acetate, benzene, or ether, and could not be obtained crystalline. Treatment with excess of ethanolic picric acid gave crystals of 2-*benzylthio*-5(4)-*dimethylaminomethyl*-4(5)-*methylglyoxaline dipicrate*; recrystallised (charcoal) from boiling water (3 l.), this had m. p. 204° (Found: C, 43·4; H, 3·5. $C_{26}H_{25}O_{14}N_9S$ requires C, 43·4; H, 3·5%). The twice recrystallised picrate (3·6 g.) was shaken with N-sodium hydroxide (50 ml.) and extracted with ether. The colourless, glassy residue left on evaporation of the ether was dissolved in light petroleum (b. p. 40—60°) (75 ml.) and cooled to −10°. After 4 weeks, white crystals of 2-*benzylthio*-5(4)-*dimethylaminomethyl*-4(5)-*methylglyoxaline*, m. p. 91° (0·8 g.), separated (Found: C, 64·2; H, 7·0; N, 16·2; S, 12·3. $C_{14}H_{19}N_3S$ requires C, 64·3; H, 7·3; N, 16·1; S, 12·3%).

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