491. 2-*Mercaptoglyoxalines. Part IV.* Bromination with N-Bromosuccinimide. The Reimer–Tiemann Reaction.*

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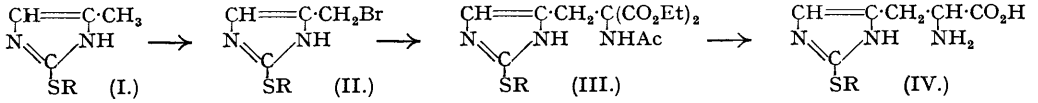
The action of *N*-bromosuccinimide on 2-mercapto-4(5)-methylglyoxaline has been investigated under varying conditions of temperature, solvent, and sulphur protection. From 2-mercapto-4(5)-methylglyoxaline (I; R = H) and its acetylthio-derivative (I; R = Ac), di-[5(4)-bromo-4(5)-methyl-2-glyoxalinyl] disulphide is formed. From the benzylthio-derivative (I; R = CH_2Ph), 2-benzylthio-5(4)-bromo-4(5)-methylglyoxaline results. By the Reimer–Tiemann reaction with 2-mercapto-4(5)-methylglyoxaline (I; R = H), the unstable 5(4)-formyl-2-mercapto-4(5)-methylglyoxaline is formed; this is isolated as the semicarbazone.

The object of the research was to synthesise 4(5)-bromomethyl-2-mercaptoglyoxaline (II; R = H) which could then be condensed with ethyl sodioacetamidomalonate, hydrolysed, and decarboxylated to yield 2-mercaptohistidine (IV; R = H).



Unsuccessful attempts have been made by Jackson and Marvel (*J. Biol. Chem.*, 1933, **103**, 191) to synthesise 4(5)-chloromethyl-2-mercaptoglyoxaline by the action of thionyl chloride or concentrated hydrochloric acid on 4(5)-hydroxymethyl-2-mercaptoglyoxaline. In all cases a polymeric product was obtained.

The reaction between *N*-bromosuccinimide and 2-mercapto-4(5)-methylglyoxaline (I; R = H) was unsuccessful, possibly owing to the insolubility of both reactants in carbon tetrachloride. 2-Benzylthio-4(5)-methylglyoxaline reacted with *N*-bromosuccinimide and benzoyl peroxide at 0° to −5° to yield a compound, $C_{11}H_{11}N_2SBr$, m. p. 154°, which although a monobromo-derivative, was not the required 2-benzylthio-4(5)-bromomethylglyoxaline, as the halogen was very firmly attached to the molecule, not being removed by aqueous or alcoholic potassium hydroxide. With dilute nitric acid, however, bromine was readily removed with the formation of benzyl 4(5)-methyl-5(4)-nitro-2-glyoxalinyl sulphoxide, m. p. 226°.

The bromo-derivative, m. p. 154°, was assigned the structure 2-benzylthio-5(4)-bromo-4(5)-methylglyoxaline. The results of a *C*-methyl determination, together with the stability shown by the substance towards alkali, would eliminate a bromomethyl or bromomethylene structure, and the reactivity with nitric acid was hardly to be expected had the halogenation occurred in the benzene ring. It therefore seems probable that by the action of nitric acid the bromine was removed from the 5(4)-position in the glyoxaline ring and replaced by a nitro-group. Although no halogen-substituted mercaptoglyoxalines have previously been described, Wohl and Markwald (*Ber.*, 1889, **22**, 1353) have shown that by the action of nitric acid on 2-methylthioglyoxaline the 4(5)-nitro-derivative is formed.

The action of two equivalents of *N*-bromosuccinimide on 2-mercapto-4(5)-methylglyoxaline in aqueous solution yielded an amorphous pale yellow insoluble base, $C_8H_8N_4S_2Br_2$, in 91% yield. The failure of this compound to show an absorption maximum in the 2600-A. region and failure to detect a thiol group in the amperometric titration (Kolthoff and Harris, *Ind. Eng. Chem.*, 1945, **18**, 161), together with its basic nature, showed that the thiol group had been modified. The facts that the compound gave the typical sulphur dioxide reaction and could be smoothly reduced by this reagent to 5(4)-bromo-2-mercapto-4(5)-methylglyoxaline, $C_4H_5N_2SBr$, showed conclusively that the *N*-bromosuccinimide besides brominating the nucleus had also oxidised the thiol group to the disulphide. It is difficult to limit the oxidation of 2-mercaptoglyoxalines to the formation of the disulphides (Balaban and King, *J.*, 1927, 1858), since unstable sulphinic acids, which liberate sulphur dioxide to give the corresponding glyoxaline, are usually formed. The preparation of the disulphide from 2-mercapto-4 : 5-diphenylglyoxaline has, however, been

* Part III, preceding paper.

reported by Anschutz and Schwickerath (*Annalen*, 1895, **284**, 99). There is no record in the literature of the isolation of mercaptoglyoxalines by reduction of their disulphides.

5(4)-Bromo-2-mercapto-4(5)-methylglyoxaline, in contrast to the disulphide, could be crystallised from hot water and showed the usual mercaptoglyoxaline behaviour in its ultraviolet absorption spectrum and in amperometric titration. On oxidation with ferric chloride (Pyman, *J.*, 1911, **99**, 668), 4(5)-bromo-5(4)-methylglyoxaline, m. p. 152°, was formed. This had previously been prepared by Pyman and Timmis (*J.*, 1923, **123**, 494) by the bromination of 4(5)-methylglyoxaline. The bromine in this bromoglyoxaline was quite stable to alkaline hydrolysis in contrast to that in the disulphide, from which the corresponding hydroxy-compound was isolated on treatment with 2% sodium hydroxide.

Attempted bromination, by *N*-bromosuccinimide in benzene solution, of 2-acetylthio-4(5)-methylglyoxaline resulted in the cleavage of the somewhat labile acetyl group with formation of di-[5(4)-bromo-4(5)-methyl-2-glyoxalinyl] disulphide. The Reimer–Tiemann reaction has been successfully applied to 2-mercapto-4(5)-methylglyoxaline, 5(4)-formyl-2-mercapto-4(5)-methylglyoxaline being isolated as the semicarbazone, m. p. 294°. The corresponding free aldehyde could not be isolated.

No condensation product could be isolated after reaction (even at −50°) between ω-bromophthalimidoacetone and ethyl sodioacetamidomalonate (cf. Harington and Overhoff, *Biochem. J.*, 1933, **27**, 338).

Experimental.

Analyses are by Drs. Weiler and Strauss.

2-Benzylthio-5(4)-bromo-4(5)-methylglyoxaline.—2-Benzylthio-4(5)-methylglyoxaline (17·1 g.) and benzoyl peroxide (170 mg.) were dissolved in carbon tetrachloride (350 ml.), and the solution cooled in an ice–salt bath to 0° to −5°. Finely powdered *N*-bromosuccinimide (14·9 g.) was slowly added with mechanical stirring during 2 hours and the solution stirred for another hour. The pale yellow powder which was deposited was filtered off and washed with carbon tetrachloride and with cold water. Sodium carbonate solution was added to pH 7 and the insoluble *2-benzylthio-5(4)-bromo-4(5)-methylglyoxaline* (22·8 g., 96%) was collected. Recrystallised from benzene (300 ml.) (charcoal), it formed colourless crystals, m. p. 154° (Found: C, 46·4; H, 3·8; N, 9·5; S, 10·9; Br, 28·0; CMe, 3·4. $C_{11}H_{11}N_2SBr$ requires C, 46·5; H, 3·9; N, 9·9; S, 11·3; Br, 28·2; 1-CMe, 5·3%).

Benzyl 4(5)-Methyl-5(4)-nitro-2-glyoxalinyl Sulphoxide.—2-Benzylthio-5(4)-bromo-4(5)-methylglyoxaline (1·4 g.) was boiled with 3% nitric acid (30 ml.) until dissolution was effected and nitrous fumes were no longer evolved. After filtration of the hot solution, crystals of the *sulphoxide* were deposited on cooling and were recrystallised from water (charcoal). This compound is strongly adsorbed on charcoal and the minimum amount should be used. Recrystallised from ethanol it had m. p. 226° (1·0 g., 77%) (Found: C, 49·4; H, 4·3; N, 15·0. $C_{11}H_{11}O_3N_3S$ requires C, 49·8; H, 4·2; N, 15·8%). The Liebermann nitroso- and the brucine nitrate test were negative.

Di-[5(4)-bromo-4(5)-methyl-2-glyoxalinyl] Disulphide.—*N*-Bromosuccinimide (20·3 g.) in water (700 ml.) was slowly added to 2-mercapto-4(5)-methylglyoxaline (6·5 g.) in water (100 ml.) with mechanical stirring. After 1 hour sodium acetate was added to adjust the solution to pH 7 and the pale yellow precipitate of *di-[5(4)-bromo-4(5)-methyl-2-glyoxalinyl] disulphide* (10·0 g., 91%) was collected. This substance, which does not melt below 300°, was insoluble in all the usual organic solvents and was partly purified by dissolution in dilute hydrochloric acid followed by reprecipitation on adjustment of the pH with sodium acetate (Found: C, 25·6; H, 2·3; N, 14·9; S, 16·9; Br, 40·4. $C_8H_8N_4S_2Br_2$ requires C, 25·0; H, 2·1; N, 14·6; S, 16·7; Br, 41·6%); the chief remaining impurity was di-[4(5)-methyl-2-glyoxalinyl] disulphide, which behaved similarly. The product does not exhibit an absorption maximum between 2100 and 3600 A.

Di-[5(4)-hydroxy-4(5)-methyl-2-glyoxalinyl] Disulphide.—Di-[5(4)-bromo-4(5)-methyl-2-glyoxalinyl] disulphide (2 g.) was refluxed for 30 minutes with 1% aqueous sodium hydroxide (30 ml.), cooled, and filtered. On neutralisation of the filtrate, *di-[5(4)-hydroxy-4(5)-methyl-2-glyoxalinyl] disulphide* (1·2 g., 89%), m. p. 252° (decomp.), was precipitated (Found: C, 37·6; H, 4·3; N, 21·0; S, 12·8. $C_8H_{10}O_2N_4S_2$ requires C, 37·2; H, 3·9; N, 21·7; S, 12·4%). This is insoluble in all the usual organic solvents and does not exhibit an absorption maximum between 2100 and 3600 A. Addition of excess of aqueous picric acid to a solution in dilute hydrochloric acid gave a crystalline picrate which, after recrystallisation from aqueous ethanol, had m. p. 208° (decomp.).

5(4)-Bromo-2-mercapto-4(5)-methylglyoxaline.—Di-[5(4)-bromo-4(5)-methyl-2-glyoxalinyl] disulphide (0·5 g.) was dissolved in 10% hydrochloric acid (15 ml.), and sulphur dioxide was passed through the solution for 1 hour. After storage, orange crystals were collected which readily gave off sulphur dioxide, to leave pale yellow crystals of *4(5)-bromo-2-mercapto-4(5)-methylglyoxaline* (0·21 g., 42%), m. p. 246° (Found: C, 24·9; H, 2·9; N, 15·1; S, 16·7; Br, 40·7. $C_4H_5N_2SBr$ requires C, 24·9; H, 2·6; N, 14·5; S, 16·6; Br, 41·4%). This is sparingly soluble in water and dilute acids, readily so in dilute sodium hydroxide and ethanol, and does not form a picrate. It exhibits an absorption maximum in ethanol at 2700 A., $\varepsilon = 16{,}200$.

Action of N-Bromosuccinimide on 2-Acetylthio-4(5)-methylglyoxaline.—*N*-Bromosuccinimide (2·3 g.) in benzene (200 ml.) was added to 2-acetylthio-4(5)-methylglyoxaline (1·0 g.) and benzoyl peroxide (10 mg.)

in benzene (100 ml.). After storage, the pale yellow precipitate was filtered off and washed with benzene. Dissolving it in water and adjusting the pH to 7 with sodium acetate gave di-[5(4)-bromo-4(5)-methyl-2-glyoxalinyl] disulphide, identical with the material obtained from *N*-bromosuccinimide and 2-mercapto-4(5)-methylglyoxaline.

Reimer–Tiemann Reaction with 2-Mercapto-4(5)-methylglyoxaline.—2-Mercapto-4(5)-methylglyoxaline (5 g.) in 2N-sodium hydroxide (100 ml.) was refluxed for 1 hour with chloroform (5 ml.). The dark red solution was acidified with hydrochloric acid, boiled, and filtered and the green filtrate decolorised with charcoal to give a pale yellow solution, which yielded the oxime [m. p. 234° (decomp.)], the 2 : 4-dinitrophenylhydrazone (m. p. 198°), and the *semicarbazone* [m. p. 294° (decomp.)] of 5(4)-formyl-4(5)-methylglyoxaline, which were all very sparingly soluble. The semicarbazone (0·1 g.) was recrystallised from water (700 ml.) (Found : C, 36·0; H, 4·7; N, 34·7; S, 15·7. $C_6H_9ON_5S$ requires C, 36·2; H, 4·5; N, 35·2; S, 16·1%). An equal volume of saturated aqueous mercuric chloride was added to the remainder of the aldehyde solution, followed by sodium acetate to adjust the pH to 5. The mercury complex was decomposed with hydrogen sulphide. The resulting colourless solution gave positive sulphur dioxide and aldehyde tests but on concentration under reduced pressure the solution became green and finally deposited colourless crystals which almost instantaneously became Prussian-blue-coloured. It was not possible to isolate the analytically pure aldehyde.

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