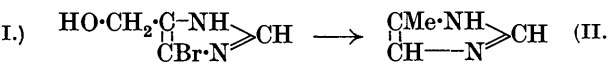
CCCCXI.—*The Condensation of Glyoxalines with Formaldehyde.*

By Robert Grindley and Frank Lee Pyman.

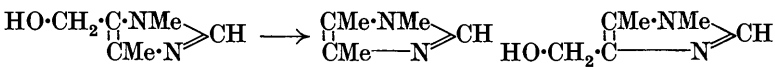
Few examples of the condensation of glyoxalines with aldehydes have been studied hitherto. Windaus (*Ber.*, 1909, **42**, 758) has shown that the condensation product of 4(5)-methylglyoxaline and formaldehyde is 4(5)-methyl-5(4)-hydroxymethylglyoxaline, since it gave 4 : 5-dimethylglyoxaline on reduction, and Ewins (J., 1911, **99**, 2052) isolated the condensation product in a yield of 43%. Chloral also substitutes 4(5)-methylglyoxaline in the 5(4)-position (Gerngross, *Ber.*, 1912, **45**, 509), whilst both histidine (Wellisch, *Biochem. Z.*, 1913, **49**, 173) and histamine (Fränkel and Zeimer, *ibid.*, 1920, **110**, 234) yield dicyclic compounds on condensation with methylal and hydrochloric acid, the glyoxaline ring being here also substituted in the 5(4)-position. On the other hand, 5-chloro-1-methylglyoxaline condenses with formaldehyde to give 5-chloro-1-methyl-2-hydroxymethylglyoxaline in good yield (Sarasin, *Helv. Chim. Acta*, 1923, **6**, 377; 1924, **7**, 713; Sonn, Hotes, and Sieg, *Ber.*, 1924, **57**, 953, 2134) and 5-bromo-1-methylglyoxaline similarly yields a 2-hydroxymethyl derivative (Balaban and Pyman, J., 1924, **125**, 1564). Sonn, Hotes, and Sieg (*loc. cit.*) have also stated, without giving experimental details, that 1-methylglyoxaline condenses with formaldehyde mainly in the 2-position, and that 4 : 5-dibromo-1-methylglyoxaline does not condense with formaldehyde. It would thus appear from previous work that glyoxalines with a free imino-group give 4(5)-hydroxymethyl deriv-

atives, and *N*-methylated glyoxalines give 2-hydroxymethyl derivatives, whilst the accumulation of acidic groups in the molecule, as in 4 : 5-dibromo-1-methylglyoxaline, prevents condensation. The present investigation was carried out with the object of amplifying the experimental material, and the results are in harmony with the conclusions summarised above, except that it has been shown that an *N*-methylated glyoxaline may yield a 5-hydroxymethyl derivative. The ready condensation of 5-chloro-1-methylglyoxaline with formaldehyde reported by previous investigators (*supra*) was confirmed, and in our hands the yield of 5-chloro-1-methyl-2-hydroxymethylglyoxaline was 89%, but attempts to condense the isomeric 4-chloro-1-methylglyoxaline with formaldehyde under similar conditions were unsuccessful, 4-chloro-1-methylglyoxaline being recovered unchanged to the extent of 60%. As an example of an unmethylated 4(5)-halogen-substituted glyoxaline, 4(5)-bromoglyoxaline was available and this was found to give a poor yield of 4(5)-*bromo*-5(4)-*hydroxymethylglyoxaline* (I) together with some unchanged base and much amorphous material. The constitution of the product (I) was established through its reduction by hydriodic acid and phosphorus to 4(5)-methylglyoxaline (II).



(I.) (II.)

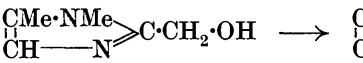
Next, the effect of the more strongly polar nitro-group was examined, and the condensation of 4(5)-nitroglyoxaline and its two isomeric *N*-methyl derivatives with formaldehyde was attempted; 4(5)-nitroglyoxaline and 4-nitro-1-methylglyoxaline were then recovered unchanged to the extent of more than 90%. 5-Nitro-1-methylglyoxaline was recovered unchanged to the extent of 68% only, this indicating that some condensation had taken place, although the presumed condensation product could not be isolated in a pure state. The condensation of the two *N*-methyl derivatives of 4(5)-methylglyoxaline was then studied. 1 : 4-Dimethylglyoxaline condensed with formaldehyde, giving a 44% yield of 1 : 4-*dimethyl*-5-*hydroxymethylglyoxaline* (III), the constitution of this product being proved through its reduction by hydriodic acid and phosphorus to the 1 : 4 : 5-trimethylglyoxaline (IV) previously made by Jowett (J., 1905, **87**, 405) by the methylation of 4 : 5-dimethylglyoxaline.



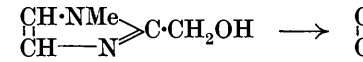
(III.) (IV.) (V.)

In earlier attempts to orient the base (III), 4(5)-methyl-5(4)-hydroxymethylglyoxaline was methylated, a mixture of (III)

with the isomeric 1 : 5-dimethyl-4-hydroxymethylglyoxaline (V) being expected. The only methylation product isolated in a pure state was not identical, but isomeric, with (III) and is consequently 1 : 5-*dimethyl*-4-*hydroxymethylglyoxaline* (V). The condensation of 1 : 5-dimethylglyoxaline with formaldehyde, however, did not give rise to this product but to an isomeride, which must consequently be 1 : 5-*dimethyl*-2-*hydroxymethylglyoxaline* (VI). Its constitution was confirmed by reduction, a trimethylglyoxaline being thus obtained which was not identical with 1 : 4 : 5-trimethylglyoxaline, and must consequently be 1 : 2 : 5-*trimethylglyoxaline* (VII).

(VI.)  (VII.)

The condensation of 1-methylglyoxaline with formaldehyde gave 1-*methyl*-2-*hydroxymethylglyoxaline* (VIII) as stated by Sonn, Hotes, and Sieg (*loc. cit.*), the yield being more than 60%. The constitution of this base was established through its reduction to 1 : 2-dimethylglyoxaline (IX).

(VIII.)  (IX.)

Finally, the condensation of glyoxaline with formaldehyde was studied, but no crystalline products could be isolated.

EXPERIMENTAL.

Condensation of Glyoxalines with Formaldehyde.—The general method of procedure was as follows: The glyoxaline base and 40% aqueous formaldehyde (abbreviated below to formaldehyde) were enclosed in a sealed tube or pressure bottle and heated in an oil-bath. Except in the cases of 4(5)-nitroglyoxaline and 4-nitro-1-methylglyoxaline, the products were worked up by adding picric acid (1 mol.) in hot aqueous solution; as a rule, resinous picrates then separated first, followed by the crystalline picrates of the hydroxymethyl compound and of the unchanged glyoxaline in this order. The identity of the material recovered unchanged was established in each case by the mixed m. p. method.

4(5)-*Nitroglyoxaline and Formaldehyde.*—(*a*) 4(5)-Nitroglyoxaline (7·0 g.) and formaldehyde (10 c.c.; 2·3 mols.) were heated for 3 hours at 125°. The base was then mainly undissolved, and after washing with water and crystallisation from glacial acetic acid, 6·83 g. of unchanged 4(5)-nitroglyoxaline, m. p. 311—312° (corr.), were recovered; yield, 97·6%.

(*b*) 4(5)-Nitroglyoxaline (2·0 g.) and formaldehyde (2·8 c.c.; 2·2 mols.), heated for 6 hours at 150°, gave 1·92 g. of recovered 4(5)-nitroglyoxaline, m. p. 310—312° (corr.); yield, 96·0%.

4-*Nitro*-1-*methylglyoxaline and Formaldehyde.*—4-Nitro-1-methylglyoxaline (1·08 g.) and formaldehyde (1·9 c.c.; 3 mols.) were heated for 5 hours at 135°. The base was then mainly undissolved, and after crystallisation from water 0·98 g. of unchanged 4-nitro-1-methylglyoxaline, m. p. 134° (corr.), was recovered; yield, 90·8%.

5-*Nitro*-1-*methylglyoxaline and Formaldehyde.*—(*a*) 5-Nitro-1-methylglyoxaline (0·65 g.) and formaldehyde (1·6 c.c.; 4 mols.) were heated for 5 hours at 125°. The product gave with hot aqueous picric acid, first resinous picrates, then crude 5-nitro-1-methylglyoxaline picrate. This was recrystallised from water, 0·64 g., m. p. 151—152°, and 0·60 g., m. p. 149—151°, being obtained; yield, 68·1%.

(*b*) A similar result was obtained on heating the reactants for 6 hours at 130°, 5-nitro-1-methylglyoxaline picrate being recovered in 52% yield together with a resinous picrate. In both cases, the base and hydrochloride prepared from the resinous picrate failed to crystallise.

4(5)-*Bromoglyoxaline and Formaldehyde.*—This condensation was carried out under various conditions as shown below, and the products were worked up as picrates. The fourth column gives the yield (*a*) of 4(5)-bromo-5(4)-hydroxymethylglyoxaline isolated as pure picrate, and the fifth the yield (*b*) of 4(5)-bromoglyoxaline recovered as pure picrate. Considerable quantities of resinous picrates were also obtained.

Mols. CH_2O used.	Duration of heating (hrs.).	Temp.	*a*, %.	*b*, %.
2·5	2	110°	Nil	98·1
3	1	150	,,	53·7
1·5	2	150	,,	42·7
3	3	150	8·8	30·0
3	4	150	9·3	35·2
3	5	150	10·4	10·6
3	8	150	0·3	Nil
3	3½	160	1·5	3·8

4(5)-*Bromo*-5(4)-*hydroxymethylglyoxaline* (I) crystallises from alcohol in colourless plates, m. p. 116—117° (corr.), which contain $\frac{1}{2}H_2O$ (Found, in air-dried base: loss at 80°, 5·3. $C_4H_5ON_2Br,\frac{1}{2}H_2O$ requires H_2O, 4·8%. Found in dried base: C, 26·9; H, 3·0. $C_4H_5ON_2Br$ requires C, 27·1; H, 2·8%). It is sparingly soluble in cold water, readily soluble in alcohol, acetone, or chloroform, but insoluble in ether or benzene. The *hydrochloride* crystallises from alcohol in colourless prisms, m. p. 157° (corr.; eff.) [Found in salt dried at 100° (loss 0·8%): C, 22·5; H, 2·8. $C_4H_5ON_2Br,HCl$ requires C, 22·5; H, 2·8%]. It is very easily soluble in water, and easily soluble in hot alcohol or concentrated hydrochloric acid.

The *picrate* crystallises from water in yellow, lustrous, serrated

needles, containing $1H_2O$, which is lost at 95° but not in a vacuum over sulphuric acid at the ordinary temperature. The dried salt has m. p. 180° (corr.). It is sparingly soluble in cold water, but readily soluble in hot water, alcohol, or acetone (Found in air-dried salt: loss at 95°, 4·5. $C_4H_5ON_2Br,C_6H_3O_7N_3,H_2O$ requires H_2O, 4·3%. Found in dried salt: C, 29·3; H, 2·2. $C_4H_5ON_2Br,C_6H_3O_7N_3$ requires C, 29·6; H, 2·0%).

Reduction. 4(5)-Bromo-5(4)-hydroxymethylglyoxaline hydrochloride (0·45 g.), hydriodic acid (1·9 c.c.; *d* 1·7), and red phosphorus (0·13 g.) were heated in a sealed tube for 5½ hours at 160°. The product was diluted with water, filtered, and extracted with chloroform whilst acid to remove impurities. The aqueous solution was then concentrated, saturated with potassium carbonate, and extracted first with chloroform, then with ether. The extracts were converted into picrates, and gave 0·55 g. of 4(5)-methylglyoxaline picrate, m. p. 159—160° (corr.), alone or mixed with a known specimen; yield, 83·9%.

4-*Chloro*-1-*methylglyoxaline and Formaldehyde.*—4-Chloro-1-methylglyoxaline (1·77 g.) and formaldehyde (5·5 c.c.; 4·8 mols.) were heated for 4 hours at 130°, and the product was converted into picrates; 3·16 g. of 4-chloro-1-methylglyoxaline picrate, m. p. 166°, were obtained (yield, 60·2%) together with a resinous picrate. The base and hydrochloride from the latter failed to crystallise.

5-*Chloro*-1-*methylglyoxaline and Formaldehyde.*—5-Chloro-1-methylglyoxaline (1·08 g.) and formaldehyde (2·4 c.c.; 3·5 mols.), heated for 8 hours at 135—140°, gave 5-chloro-1-methyl-2-hydroxymethylglyoxaline, isolated as picrate, m. p. 151° (corr.), in 89% yield. Sarasin (*loc. cit.*) and Sonn, Hotes, and Sieg (*loc. cit.*) record yields of 95 and 80% respectively.

1 : 4-*Dimethylglyoxaline and Formaldehyde.*—1 : 4-Dimethylglyoxaline (10·6 g.) and formaldehyde (22·3 c.c.; 3 mols.) were heated for 6 hours at 125°, and the product was converted into picrates and crystallised fractionally from water and methyl alcohol; 17·5 g. of pure 1 : 4-dimethyl-5-hydroxymethylglyoxaline picrate (yield, 44·6%) were obtained together with 1·43 g. of pure 1 : 4-dimethylglyoxaline picrate (yield, 4·0%).

1 : 4-*Dimethyl-5-hydroxymethylglyoxaline* (III) crystallises from absolute alcohol in small, colourless prisms, m. p. 126—127° (corr.) (Found: C, 57·0; H, 8·0; N, 22·0. $C_6H_{10}ON_2$ requires C, 57·1; H, 7·9; N, 22·2%). It is very readily soluble in water or alcohol, readily soluble in chloroform, but very sparingly soluble in ether.

The *hydrochloride* crystallises from concentrated hydrochloric acid in colourless plates, m. p. 145° (corr.), which are very hygroscopic.

The *hydrogen oxalate* crystallises from absolute alcohol in colourless prisms, m. p. 106—107° (corr.) (Found: C, 44·6; H, 5·6. $C_6H_{10}ON_2,C_2H_2O_4$ requires C, 44·4; H, 5·6%). It is very readily soluble in water, less soluble in cold alcohol.

The *picrate* crystallises from water in yellow prisms, m. p. 167—168° (corr.), which suffer no loss at 110°. It is sparingly soluble in cold water, alcohol, or acetone, but readily soluble in the hot solvents. Attempts to estimate carbon and hydrogen in this salt were frustrated by explosions.

Reduction. 1 : 4-Dimethyl-5-hydroxymethylglyoxaline (0·63 g.), hydriodic acid (1·5 c.c.; *d* 1·7), and red phosphorus (0·082 g.) were heated in a sealed tube for 6 hours at 160°. The product was diluted with water, filtered, made strongly alkaline with sodium hydroxide, and extracted with chloroform and ether. The extracts were converted into picrates and gave 1 : 4 : 5-trimethylglyoxaline picrate in 79% yield (1·26 g., m. p. 218—219°, + 0·08 g., m. p. 215—216°). This salt was identified by the mixed m. p. method, with the help of a specimen of 1 : 4 : 5-trimethylglyoxaline picrate, m. p. 218°, prepared by Jowett (J., 1905, **87**, 405) for which we are indebted to the Wellcome Chemical Research Laboratories. The salt was also analysed (Found: C, 42·7; H, 3·9. Calc.: C, 42·9; H, 3·8%), and from it the base was prepared. This was not completely purified (it had m. p. 39—40°; Jowett gives 46°), but was converted into the chloroaurate. This had m. p. 201° (corr.) (Jowett gives 202°) (Found: Au, 43·6. Calc.: Au, 43·8%).

1 : 5-*Dimethylglyoxaline and Formaldehyde.*—1 : 5-Dimethylglyoxaline (1·4 g.) and formaldehyde (4·9 c.c.; 4·5 mols.) were heated for 6 hours at 130° and the product was converted into picrates, 1·75 g. of pure 1 : 5-dimethyl-2-hydroxymethylglyoxaline picrate (yield, 33·8%) and 2·06 g. of 1 : 5-dimethylglyoxaline picrate, m. p. 163—164° (yield, 43·5%), being isolated. Under milder conditions (4 hours at 115—120°) no condensation product was isolated, but 1 : 5-dimethylglyoxaline was recovered as picrate in 83% yield.

1 : 5-*Dimethyl-2-hydroxymethylglyoxaline* (VI) crystallises from absolute methyl alcohol in colourless, hexagonal plates, m. p. 126—127° (corr.) (Found in air-dried base: loss at 110°, 4·1. $C_6H_{10}ON_2,\frac{1}{2}H_2O$ requires H_2O, 6·7%. Found in dried base: C, 57·4; H, 7·9. $C_6H_{10}ON_2$ requires C, 57·1; H, 7·9%). It is very readily soluble in water, readily soluble in methyl or ethyl alcohol or chloroform, but very sparingly soluble in ether. A mixture of approximately equal parts of this base and 1 : 4-dimethyl-5-hydroxymethylglyoxaline, which also melts at 126—127°, had m. p. 76—80°.

The *picrate* crystallises from water in small, yellow, anhydrous prisms, m. p. 174° (corr.) (Found: C, 40·7; H, 3·9; N, 19·6. $C_6H_{10}ON_2,C_6H_3O_7N_3$ requires C, 40·6; H, 3·7; N, 19·7%). It is sparingly soluble in cold water or alcohol.

Reduction. 1 : 5-Dimethyl-2-hydroxymethylglyoxaline (0·39 g.), hydriodic acid (0·9 c.c.; *d* 1·7), and red phosphorus (0·051 g.) were heated in a sealed tube for 6 hours at 160°. After dilution, filtration, and extraction with chloroform to remove impurities, the liquor was saturated with potassium carbonate and extracted with chloroform, which took up a brown mobile oil (0·37 g.) having a faint pyridine-like odour. This was converted into picrate; 1 : 2 : 5-trimethylglyoxaline picrate (0·97 g.; m. p. 204°; yield 92·2%) was then obtained.

1 : 2 : 5-*Trimethylglyoxaline picrate* (VII) crystallises from water in long, pale yellow, lustrous, anhydrous needles, m. p. 208—209° (corr.) (Found: C, 42·6; H, 4·0; N, 20·7. $C_6H_{10}N_2,C_6H_3O_7N_3$ requires C, 42·5; H, 3·8; N, 20·6%). It is sparingly soluble in cold water or alcohol. A mixture of approximately equal parts of this salt with 1 : 4 : 5-trimethylglyoxaline picrate (m. p. 218°) had m. p. 194—195°. The base prepared from the pure picrate did not crystallise, and was converted into the *chloroaurate*, which crystallised from dilute hydrochloric acid in orange-yellow, anhydrous plates, m. p. 186—187° (corr.) (Found: Au, 43·6. $C_6H_{10}N_2,HAuCl_4$ requires Au, 43·8%).

Methylation of 4(5)-*Methyl*-5(4)-*hydroxymethylglyoxaline.*—Attempts to methylate this base by heating with either methyl iodide or methyl sulphate failed, for no crystalline substance other than a small proportion of the unchanged material could be isolated (as picrate) from the reaction product, but methylation with methyl sulphate and aqueous sodium hydroxide was more successful.

4(5)-Methyl-5(4)-hydroxymethylglyoxaline (2·35 g.) was methylated by the gradual addition with shaking of 10% aqueous sodium hydroxide (23·6 c.c.) and methyl sulphate (2·4 c.c.). After the mixture had been kept for 2 hours, chloroform extracted a yellowish-brown, crystalline mass (0·8 g.), which was converted into picrate and this crystallised from water, 0·5 g. of pure 1 : 5-dimethyl-4-hydroxymethylglyoxaline picrate being obtained: yield, 6·7%.

1 : 5-*Dimethyl*-4-*hydroxymethylglyoxaline* (V) crystallises from absolute methyl alcohol in colourless, hexagonal plates, m. p. 164—165° (corr.) (Found: C, 57·2; H, 8·0. $C_6H_{10}ON_2$ requires C, 57·1; H, 7·9%). It is very readily soluble in water, and readily soluble in methyl or ethyl alcohol, acetone, or chloroform. The *picrate* crystallises from water in small, pale yellow, anhydrous prisms, m. p. 178—179° (corr.) (Found: C, 40·7; H, 3·7; N, 19·5.

$C_6H_{10}ON_2,C_6H_3O_7N_3$ requires C, 40·6; H, 3·7; N, 19·7%). It is sparingly soluble in cold water or alcohol.

1-*Methylglyoxaline and Formaldehyde.*—(*a*) 1-Methylglyoxaline (2·8 g.) and formaldehyde (4·6 c.c.; 3·5 mols.) were heated for 5 hours at 140°. The product was converted into picrates, and these crystallised fractionally from water. First, a molecular compound of 1-methyl-2-hydroxymethylglyoxaline picrate and 1-methylglyoxaline picrate (5·48 g.; m. p. 144—145°) separated, then 1-methyl-2-hydroxymethylglyoxaline picrate (4·42 g.; m. p. 137°). The yield of 1-methyl-2-hydroxymethylglyoxaline is thus 62·6%, whilst 24·6% of 1-methylglyoxaline was recovered unchanged. (*b*) 1-Methylglyoxaline (3·1 g.) and formaldehyde (4·4 c.c.; 3·0 mols.), heated for 4 hours at 130°, gave 11·35 g. of the picrate, m. p. 144—145°, and some 1-methylglyoxaline picrate (0·11 g.; m. p. 158°). The yield of 1-methyl-2-hydroxymethylglyoxaline is here 46·1%, whilst 47·0% of 1-methylglyoxaline was recovered unchanged.

1-*Methyl-2-hydroxymethylglyoxaline* (VIII) crystallises from chloroform in colourless prisms, m. p. 116° (corr.) [Found in base dried at 80° (loss 1·3%): C, 53·4; H, 7·0. $C_5H_8ON_2$ requires C, 53·6; H, 7·1%]. It is readily soluble in water or alcohol, soluble in hot acetone or chloroform, but insoluble in ether or benzene. It is not volatile in steam. The picrate crystallises from water in small, yellow, lustrous prisms, m. p. 138° (corr.) [Sonn, Hotes, and Sieg (*loc. cit.*) give m. p. 136—137° (uncorr.)] (Found: loss at 100°, 3·3. $C_5H_8ON_2,C_6H_3O_7N_3,\frac{1}{2}H_2O$ requires H_2O, 2·6%. Found in dried salt: C, 38·8; H, 3·2. $C_5H_8ON_2,C_6H_3O_7N_3$ requires C, 38·7; H, 3·2%). It is very sparingly soluble in cold water.

Reduction. 1-Methyl-2-hydroxymethylglyoxaline (0·7 g.), hydriodic acid (1·4 c.c.; *d* 1·7), and red phosphorus (0·06 g.) were heated at 155—160° for 5 hours, and the product was worked up in the usual way; 1:2-dimethylglyoxaline picrate (0·6 g.; yield 29·5%; m. p. 178—179°, alone or mixed with an authentic specimen for which we are indebted to the Wellcome Chemical Research Laboratories) was then obtained together with 1-methyl-2-hydroxymethylglyoxaline picrate (0·49 g.; yield 23·0%; m. p. 136—137°).

The *molecular compound* of 1-methyl-2-hydroxymethylglyoxaline picrate and 1-methylglyoxaline picrate crystallises from water in pale yellow needles, m. p. 145—146° (corr.) [Found in air-dried salt: loss at 100°, 1·1. $C_4H_6N_2,C_5H_8ON_2,(C_6H_3O_7N_3)_2,\frac{1}{2}H_2O$ requires H_2O, 1·4%. Found in dried salt: C, 38·8; H, 3·2; N, 21·7. $C_4H_6N_2,C_5H_8ON_2,(C_6H_3O_7N_3)_2$ requires C, 38·7; H, 3·1; N, 21·5%]. It is almost insoluble in cold water, but readily soluble in hot water. A mixture of this picrate with 1-methyl-2-hydroxy-

methylglyoxaline picrate (m. p. 138°) melted at 129—130°, whilst a mixture with 1-methylglyoxaline picrate (m. p. 159°) melted at 139—140°. On converting the picrate, m. p. 145—146°, into the corresponding bases and distilling with steam, 1-methylglyoxaline was carried over and 1-methyl-2-hydroxymethylglyoxaline remained unvolatilised. The separated bases were then converted into picrates and identified in the usual way. The constitution of the picrate, m. p. 145—146°, as an equimolecular compound of the picrates of 1-methyl-2-hydroxymethylglyoxaline and 1-methylglyoxaline was confirmed by preparing it from the two salts.

MUNICIPAL COLLEGE OF TECHNOLOGY,
UNIVERSITY OF MANCHESTER. [*Received, November 9th*, 1927.]