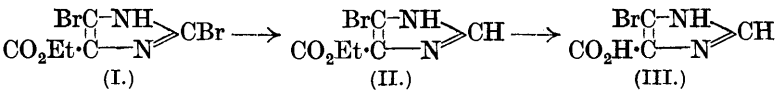
356. *An Investigation into the Formation of* 4(5)-*Aminoglyoxalines. Part II. The Non-reactivity of the Halogen Atom in* 4(5)-*Bromoglyoxaline*-5(4)-*carboxylic Acid.*

By Isidore E. Balaban.

Since 5(4)-bromo-4(5)-nitroglyoxaline (Balaban and Pyman, J., 1924, **125**, 1564) contains the halogen atom in the *o*-position with respect to the nitro-group, and is comparable with *o*-bromonitrobenzene in reactivity, it seemed of special interest to examine 4(5)-bromoglyoxaline-5(4)-carboxylic acid (III), because of the analogy with *o*-bromobenzoic acid, where the halogen atom is in a highly reactive state (Hurtley, J., 1929, 1870; Hamilton and Ludeman, *J. Amer. Chem. Soc.*, 1930, **52**, 3284; Rosenmund, *Ber.*, 1921, **54**, 438).

King and Murch (J., 1923, **123**, 621) anticipated this possible reactivity, for they intended to condense urea with (III). They were, however, prevented from making these experiments owing to the small yields of bromo-acid obtained. This difficulty has now been surmounted and the acid (III) can be readily obtained by the reduction of ethyl 2 : 5-dibromoglyoxaline-4-carboxylate (I) (Balaban and Pyman, J., 1922, **121**, 955) with aqueous sodium sulphite and hydrolysis of the resulting ethyl 4(5)-bromoglyoxaline-5(4)-carboxylate (II) : it is identical with the acid prepared by King and

Murch (*loc. cit.*), for a specimen of which the author desires to thank Dr. King.

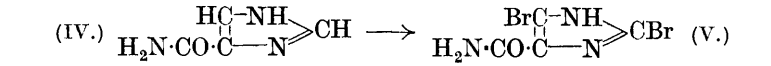


(I.) (II.) (III.)

All the attempted condensations with 4(5)-bromoglyoxaline-5(4)-carboxylic acid have proved fruitless. The acid is recovered unchanged in part or completely destroyed with potassium cyanide, sodium sulphite, sodium arsenite, and ethyl malonate in alcoholic solution. With copper–bronze no satisfactory product has been obtained, and with alcoholic or aqueous ammonia only the *ammonium* salt of the bromo-acid is formed.

It would appear, then, that in the glyoxaline series a nitro-group renders a halogen substituent reactive, whereas carboxyl is without any effect; moreover, the effect of the benzenoid portion of the glyoxaline nucleus is nullified by the rest of the molecule, causing 4(5)-bromoglyoxaline-5(4)-carboxylic acid to behave very differently from *o*-bromobenzoic acid in its reactions.

Glyoxaline-4(5)-*carboxyamide* (IV), which is readily prepared by the interaction of ammonia with ethyl glyoxaline-4(5)-carboxylate,



(IV.) (V.)

could not be converted by the Hofmann reaction into 4(5)-amino-glyoxaline, the initial material being recovered to the extent of about 60% and exhibiting a marked stability towards hypobromite solution. When the amide was brominated with bromine (1 mol.), the main product obtained was 2 : 5-*dibromoglyoxaline*-4-*carboxyamide* (V), which gave 2 : 5-dibromoglyoxaline-4-carboxylic acid on hydrolysis.

Reduction of glyoxaline-4(5)-carboxyamide in acid solution with sodium amalgam gave a very small yield of 4(5)-hydroxymethyl-glyoxaline.

Attempts to introduce an amino-group into the glyoxaline ring (glyoxaline or 5-chloro-1-methylglyoxaline being used) with sodamide in xylene solution proved unsuccessful.

EXPERIMENTAL.

Ethyl 4(5)-*Bromoglyoxaline*-5(4)-*carboxylate* (II).—Ethyl 2 : 5-dibromo-glyoxaline-4-carboxylate (5·2 g.) and anhyd. Na_2SO_3 (5·2 g.; 2 mols.) in H_2O (30 c.c.) were boiled under reflux for 3—3·5 hrs., an oil separating. From the hot filtered solution, 1·7 g., m. p. 170°, were collected. The mother-liquor deposited further crops of material, which after repeated extraction with sat. $NaHCO_3$ aq. was resolved into the monobromo-ester (0·55 g., m. p. 170°) and unchanged dibromo-ester (0·80 g., m. p. 140—143°); yield, 58·9% or, allowing for recovered material, 69·6%.

Hydrolysis of Ethyl 4(5)-*Bromoglyoxaline*-5(4)-*carboxylate.*—The ester (2·0 g.) was heated under reflux with HCl aq. (10 c.c.) and H_2O (20 c.c.) for 1 hr., the free HCl removed, and the solution filtered and made alkaline with sat. Na_2CO_3 aq. The unchanged ester (0·45 g.) was removed; neutralisation of the solution to Congo-paper with HCl aq. gave 1·1 g., m. p. 250° (efferv.), and a second crop (0·1 g., m. p. 250°, efferv.): yield, 69% or, allowing for recovered material, 88·8%. Recrystallised from aq., the acid had m. p. 253° (efferv.) and did not depress the m. p. (265°, efferv.) of King and Murch's 4(5)-bromoglyoxaline-5(4)-carboxylic acid. In various condensations the bromo-acid was recovered having m. p. 255° (efferv.) and after treatment with ethyl sodiomalonate it had m. p. 261° (efferv.). In all cases there was no depression of m. p. in admixture with Dr. King's specimen.

The bromo-acid (0·9 g.) and NH_3 (10 c.c. of aq. solution, *d* 0·880, or 20 c.c. of 3·5% alc. solution), heated for 5 hrs. at 150° in a sealed tube, gave 0·46 g. of the *ammonium* salt; colourless prismatic needles, m. p. 259°, from H_2O (Found: N, 20·2. $C_4H_6O_2N_3Br$ requires N, 20·2%).

Glyoxaline-4(5)-*carboxyamide* (IV).—Ethyl glyoxaline-4(5)-carboxylate (2·0 g.) and NH_3 aq. (*d* 0·880; 20 c.c.) were heated in a sealed tube for 3—4 hrs. at 150°. The pale yellow solution slowly deposited 1·1 g. of the *amide*; almost colourless tablets, m. p. 215°, from hot H_2O (Found in air-dried material: loss at 100°, 14·5; N, 32·4. $C_4H_5ON_3,H_2O$ requires H_2O, 13·9; N, 32·5%). The *picrate* crystallised from H_2O in yellow rectangular plates, m. p. 228° (Found: picric acid, by nitron method, 67·3. $C_4H_5ON_3,C_6H_3O_7N_3$ requires picric acid, 67·3%).

Reduction of Glyoxaline-4(5)-*carboxyamide.*—When the amide was reduced in 15% EtOH with 2·5% Na–Hg, 60% of it was recovered, but in the presence of H_2SO_4, 3·0 g. of the amide gave 1·25 g., m. p. 214° (42% recovery), and 0·58 g. of a picrate, m. p. 208° alone or mixed with 4(5)-hydroxymethylglyoxaline picrate (yield, 26·2% allowing for recovered amide).

Bromination of Glyoxaline-4(5)-*carboxyamide.*—6·4 G. of Br (1 mol.) in $CHCl_3$ (10 c.c.) were added to 4·25 g. of the amide, partly suspended in $CHCl_3$ (30 c.c.). After 10 mins. H_2O (50 c.c.) was added, and the $CHCl_3$ removed in vac.; the remaining liquor slowly deposited 3·13 g., m. p. 253° (decomp.) (yield, 30·3%), and on evaporation to dryness left a residue (5·74 g.), m. p. 216° (efferv.), which was a mixture of hydrobromides. Fractional pptn. with Na_2CO_3 gave (*a*) 1·79 g., m. p. 150° (efferv.); (*b*) 0·06 g., m. p. 212° (unchanged amide). Three recrystns. of (*a*) gave 0·27 g., m. p. 253° alone or mixed with 4(5)-bromoglyoxaline-5(4)-carboxylic acid; the mother-liquors yielded altogether 0·61 g., m. p. 228°, of glyoxaline-4(5)-carboxyamide picrate.

2 : 5-*Dibromoglyoxaline*-4-*carboxyamide* (V) crystallises from H_2O (1 in 40 parts boiling) in colourless needles, m. p. 256° (Found: N, 15·4; Br, 58·8. $C_4H_3ON_3Br_2$ requires N, 15·6; Br, 59·5%). It is sparingly sol. in abs. EtOH and insol. in C_6H_6, $CHCl_3$, and Et_2O. On hydrolysis with HCl–H_2O (1 : 1·5), 2 : 5-dibromoglyoxaline-4-carboxylic acid is obtained, m. p. 225° alone or mixed with a specimen prepared from ethyl 2 : 5-dibromoglyoxaline-4-carboxylate (Balaban and Pyman, *loc. cit.*). When (V) is hydrolysed with conc. HCl, 2 : 5-dibromoglyoxaline (m. p. 193°) is produced.

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