108. 4(5)-β-*Alkylaminoethylglyoxalines.*

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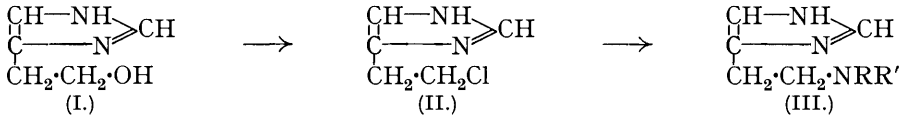
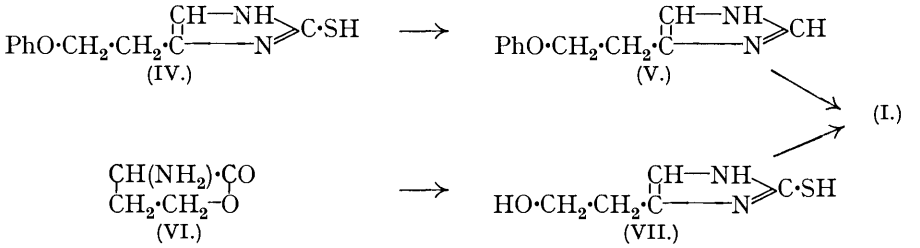
THE preparation of a series of β-*N*-alkylated histamines (III) for comparison of their physiological properties has been impracticable hitherto owing to the difficulty of access to 4(5)-β-hydroxyethylglyoxaline (I), from which they could be readily prepared by way of 4(5)-β-chloroethylglyoxaline (II).



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

4(5)-β-Hydroxyethylglyoxaline was obtained by the action of barium nitrite upon histamine hydrochloride in 19% yield (Windaus and Opitz, *Ber.*, 1911, **44**, 1721), and subsequently the yield was increased to 64% by Wrede and Holtz (*Pflüger's Archiv*, 1934, **234**, 432), the product being purified as the chloroplatinate in each case. After various alternative syntheses had been attempted without success, an application of Akabori's method (*Ber.*, 1933, **66**, 153; Akabori and Nurmano, *ibid.*, p. 159) of synthesising 4(5)-alkylglyoxalines was tried. *Ethyl α-amino-γ-phenoxybutyrate* was reduced to the crude aminoaldehyde, which, on condensation (as hydrochloride) with ammonium thiocyanate, gave 4(5)-β-*phenoxyethyl-2-thiolglyoxaline* (IV). This readily gave 4(5)-β-*phenoxyethylglyoxaline* (V) on oxidation, but dephenoxylation did not proceed satisfactorily and gave only very poor yields of 4(5)-β-hydroxyethylglyoxaline. When, however, α-aminobutyrolactone hydrobromide (VI) was reduced under the conditions employed by Akabori for the reduction of α-amino-esters, and the product condensed (as salt) with ammonium thiocyanate, 4(5)-β-*hydroxyethyl-2-thiolglyoxaline* (VII) was readily obtained, and gave on oxidation 4(5)-β-*hydroxyethylglyoxaline*, which was now obtained for the first time in crystalline form.



(IV.) (V.) (I.) (VI.) (VII.)

4(5)-β-Hydroxyethylglyoxaline was converted smoothly by means of thionyl chloride into 4(5)-β-*chloroethylglyoxaline hydrochloride* (II), which on heating under pressure with the appropriate amines in alcoholic solution gave histamine, 4(5)-β-*methylaminoethylglyoxaline*, 4(5)-β-*dimethylaminoethylglyoxaline*, 4(5)-β-*trimethylaminoethylglyoxaline chloride hydrochloride*, and 4(5)-β-*ethylaminoethylglyoxaline*. 4(5)-β-Methylaminoethylglyoxaline was also prepared by the action of 4(5)-chloroethylglyoxaline hydrochloride on *p*-toluenesulphonmethylamide, followed by hydrolysis of the product. In both cases the dipicrate had m. p. 188° and the dihydrobromide m. p. 167°.

It follows that Fargher and Pyman (J., 1921, **119**, 734) were mistaken in believing that they had obtained 4(5)-β-methylaminoethylglyoxaline by the decarboxylation of *dl*-methylhistidine, for their product formed a dipicrate, m. p. 220°, and a dihydrobromide, m. p. 275°. Moreover, Fargher and Pyman's product had only about one-hundredth of the oxytocic activity of histamine, whereas the true 4(5)-β-methylaminoethylglyoxaline is approximately equal to histamine in its oxytocic action. The physiological actions of the 4(5)-β-alkylaminoethylglyoxalines have been studied by Dr. A. Vartiainen at the National Institute for Medical Research and will be described elsewhere later. Attempts to oxidise 4(5)-β-hydroxyethylglyoxaline to glyoxaline-4(5)-acetaldehyde were unsuccessful (cf. Wrede and Holtz, *loc. cit.*).

Experimental.

α-Amino-γ-phenoxybutyric acid and α-aminobutyrolactone hydrobromide were prepared essentially by the method of Fischer and Blumenthal (*Ber.*, 1907, **40**, 106) from γ-phenoxyethylmalonic acid. This was prepared by the method of Bentley, Haworth, and Perkin (J., 1896, **69**, 161), who give m. p. about 142°, and found to have m. p. 144—145° (corr.; efferv.); Peacock and Tha (J., 1928, 2303), who prepared the acid in a different manner, give m. p. 134—136°.

Bromination of γ-phenoxyethylmalonic acid in dry ether by Fischer and Blumenthal's method is liable to lead to products brominated in the nucleus, and the following method of preparing α-bromo-γ-phenoxyethylmalonic acid was found to be more suitable for work on a larger scale. Phenoxyethylmalonic acid (100 g.) in alcohol-free ether (1200 c.c.) was boiled over a 100-watt lamp in a flask fitted with a good reflux condenser, and bromine (26 c.c.) was slowly added. The bromine was absorbed quickly after approximately 50% had reacted. At the end the ethereal solution was washed with dilute sodium bisulphite solution, then water, the ether removed by distillation, and dry benzene added to the residue and distilled until all the water was removed. On cooling, α-bromo-γ-phenoxyethylmalonic acid crystallised; it was washed with light petroleum. This gave, on decarboxylation, crude α-bromo-γ-phenoxybutyric acid, which gave α-amino-γ-phenoxybutyric acid when heated with aqueous ammonia (*d* 0·91) at 100° in an autoclave. *Ethyl α-amino-γ-phenoxybutyrate hydrochloride*, prepared from the acid, hydrogen chloride and alcohol, crystallised from alcohol in needles, m. p. 210° (corr.) (Found: Cl, 13·7. $C_{12}H_{17}O_3N$,HCl requires Cl, 13·6%).

4(5)-β-*Hydroxyethyl-2-thiolglyoxaline*.—α-Aminobutyrolactone hydrobromide (9·0 g.) was dissolved in alcohol (30 c.c.) and water (30 c.c.) and cooled with stirring to below − 15°. Sodium amalgam (3%, 170 g., 4—10 mesh) was added at such a rate as to keep the temperature below − 10°. 5*N*-Hydrochloric acid was added to keep the mixture faintly acid to Congo-paper throughout the experiment. Stirring was continued for 10 minutes after the last addition of amalgam, then the upper layer was poured off, and the mercury washed with water. To the combined aqueous liquors ammonium thiocyanate (8 g.) was added, followed after 30 minutes by 5*N*-hydrochloric acid (5 c.c.), and the whole was evaporated to dryness in a vacuum. The residue was extracted three times with alcohol and the united extracts were made acid to Congo-paper with 5*N*-hydrochloric acid. Water (20—25 c.c.) was added, and the whole concentrated to very low bulk in a vacuum and allowed to cool. On standing or more especially after seeding, 4(5)-β-*hydroxyethyl-2-thiolglyoxaline* separated in very variable yield (max., about 55%). Recrystallised from water or alcohol, it formed small colourless plates, m. p. 193° (corr.) (Found: C, 41·9; H, 5·75; N, 19·2; S, 22·5. $C_5H_8ON_2S$ requires C, 41·7; H, 5·6; N, 19·4; S, 22·2%).

It is readily soluble in alcohol or hot water, but very sparingly soluble in ether.

4(5)-β-*Hydroxyethylglyoxaline*.—4(5)-β-Hydroxyethyl-2-thiolglyoxaline (5 g.) was slowly added to boiling 10% nitric acid (130 c.c.), the reaction, once started, proceeding smoothly with the evolution of brown fumes. The resulting solution was poured on ice, and an excess of phosphotungstic acid (10% w/v in 5% sulphuric acid) added. The whitish precipitate was filtered off and washed, then stirred into boiling water (500 c.c.). Barium hydroxide was added to the solution until it reacted red to brilliant-yellow; the mixture was then filtered hot, treated with carbon dioxide, and a little charcoal added. When the mixture was acid to brilliant-yellow it was filtered hot; the filtrate was evaporated to dryness in vacuum. The colourless gum remaining was dissolved in methyl alcohol, filtered, and again taken to dryness. The first batch solidified only after several months in a desiccator; subsequent batches crystallised readily on seeding (yield, 3·1 g.; 80%). 4(5)-β-Hydroxyethylglyoxaline crystallises from dry chloroform in colourless hexagonal plates, m. p. 92° (corr.) (Found: C, 53·5; H, 7·2; N, 24·95. Calc. for $C_5H_8ON_2$: C, 53·6; H, 7·1; N, 25·0%). It is very readily soluble in water, alcohol or acetone, very sparingly soluble in ether, but insoluble in benzene. The *picrate* separates from concentrated aqueous solution in yellow needles, m. p. 144° (corr.) (Found: N, 20·7. $C_5H_8ON_2,C_6H_3O_7N_3$ requires N, 20·5%). It is soluble in cold water to the extent of about 1·5%. The chloroplatinate and the picrolonate had the m. p.'s recorded by Windaus and Opitz (*loc. cit.*).

4(5)-β-*Phenoxyethyl-2-thiolglyoxaline*.—α-Amino-γ-phenoxybutyric acid (5 g.) was refluxed for 1 hour with alcohol (75 g.) and hydrogen chloride (5 g.), the alcohol was distilled off, with the addition of dry benzene (50 c.c.), to low bulk, the residue was cooled to − 10° with stirring, and 3% sodium amalgam (80 g.) was gradually added, the solution being kept acid to Congo-paper with dilute hydrochloric acid. At the end the aqueous layer was decanted, the mercury

washed with water, and to the united aqueous liquor ammonium thiocyanate (4 g.) was added. After 1 hour the mixture was evaporated to low bulk; an oil then separated, which was removed and on keeping partly solidified. The addition of a little acetone gave almost pure 4(5)-β-*phenoxyethyl-2-thiolglyoxaline* (2·5 g., 45%). Recrystallised from alcohol, it formed almost colourless needles, m. p. 172° (corr.) (Found: C, 59·9; H, 5·1; N, 12·5; S, 14·2. $C_{11}H_{12}ON_2S$ requires C, 60·0; H, 5·4; N, 12·7; S, 14·5%). Equally good results were obtained by using preformed ethyl α-amino-γ-phenoxybutyrate hydrochloride.

4(5)-β-*Phenoxyethylglyoxaline*.—4(5)-β-Phenoxyethyl-2-thiolglyoxaline (2·5 g.) was slowly added to boiling 10% nitric acid (50 c.c.). When the evolution of brown fumes ceased, the mixture was cooled (an oily nitrate then separated), made alkaline with sodium hydroxide, and extracted with ether. The base was converted into the *hydrochloride* (yield, 1·9 g.; 75%), which crystallised from alcohol–acetone in colourless prismatic needles, m. p. 136—137° (corr.) (Found: N, 12·5; Cl, 15·6. $C_{11}H_{12}ON_2$,HCl requires N, 12·5; Cl, 15·8%). It is very readily soluble in water and alcohol. The oxalate had m. p. 191° (corr.), and the picrate m. p. 122° (corr.). The base regenerated from a pure salt was obtained as a colourless gum which slowly crystallised and then melted at about 70°.

Dephenoxylation.—4(5)-β-Phenoxyethylglyoxaline hydrochloride (1·25 g.) and 85% hydrobromic acid (6 c.c.) were boiled under reflux for 4 hours. The mixture was diluted and distilled in a vacuum to remove phenol. The residue was made alkaline and extracted with ether to remove unchanged phenoxyethylglyoxaline, and the liquor acidified with sulphuric acid and precipitated with phosphotungstic acid. The base, regenerated in the usual way, was converted into the chloroplatinate, which had m. p. 173°, alone or mixed with authentic 4(5)-β-hydroxyethylglyoxaline chloroplatinate. The yield was very small.

4(5)-β-*Chloroethylglyoxaline Hydrochloride*.—4(5)-β-Hydroxyethylglyoxaline (1·2 g.) was treated with thionyl chloride (10 c.c.). The reaction was completed on the steam-bath; the residue after removal of the excess of thionyl chloride rapidly crystallised, in almost theoretical yield. Recrystallised from anhydrous alcohol and ether, 4(5)-*chloroethylglyoxaline hydrochloride* formed colourless hygroscopic needles, m. p. 126° (corr.) (Found: N, 16·5; Cl′, 21·5. $C_5H_7N_2Cl$,HCl requires N, 16·7; Cl′, 21·3%).

β-*Amino- and* β-*Alkylamino-derivatives of* 4(5)-*Ethylglyoxaline*.—4(5)-β-Hydroxyethylglyoxaline (2·24 g.) was freshly converted into 4(5)-β-chloroethylglyoxaline hydrochloride, which was heated for about 12 hours with 10—15 c.c. of a 30% solution of the appropriate amine in absolute alcohol in a sealed tube at 100°. The product was washed out, treated with a slight excess of sodium carbonate, and taken to dryness in a vacuum. The residue was dissolved in a slight excess of dilute hydrochloric acid and poured into a boiling saturated solution of picric acid (approximately theoretical amount). The dipicrate separated on cooling and was recrystallised from water (charcoal), in which it was sparingly soluble. The picrates, when treated with hydrochloric acid and ether, gave solutions of the dihydrochlorides, which were taken to dryness; the residues were crystallised from absolute alcohol or alcohol–acetone.

4(5)-β-*Methylaminoethylglyoxaline dipicrate* (yield, 60%) crystallises from water in pale yellow, flat needles which lose water at 100° to give opaque orange needles, m.p. 188° (corr.) (Found: loss at 100°, 3·0. $C_6H_{11}N_3,2C_6H_3O_7N_3,H_2O$ requires loss, 3·0%. Found in dried salt: C, 36·8; H, 3·2; N, 21·8. $C_6H_{11}N_3,2C_6H_3O_7N_3$ requires C, 37·0; H, 2·9; N, 21·6%). The *dihydrochloride* is very soluble in water and crystallises from absolute alcohol in colourless needles, m. p. 176—177° (corr.) (Found: C, 36·7; H, 6·4; N, 20·9; Cl, 35·65. $C_6H_{11}N_3,2HCl$ requires C, 36·4; H, 6·6; N, 21·2; Cl, 35·8%). The *dihydrobromide* crystallises from alcohol in colourless needles, m. p. 167° (corr.) (Found: N, 14·7; Br, 55·7. $C_6H_{11}N_3,2HBr$ requires N, 14·7; Br, 55·8%).

4(5)-β-*Dimethylaminoethylglyoxaline dipicrate* (yield, 65%) forms anhydrous orange-yellow plates from water, m. p. 233° (corr.) (Found: N, 21·0. $C_7H_{13}N_3,2C_6H_3O_7N_3$ requires N, 21·1%). The *dihydrochloride* crystallises in deliquescent needles from absolute alcohol, m. p. 188° (corr.) [Found: (micro.) C, 39·6; H, 7·05; N, 19·7. $C_7H_{13}N_3,2HCl$ requires C, 39·6; H, 7·1; N, 19·8%].

4(5)-β-*Trimethylaminoethylglyoxaline dipicrate* (yield, 70%) crystallises from water in small orange-yellow needles, m. p. 212° (corr.) [Found: C, 39·5; H, 2·8; N, 20·4. $C_8H_{16}N_3(C_6H_2O_7N_3),C_6H_3O_7N_3$ requires C, 39·3; H, 3·4; N, 20·6%].

4(5)-β-*Trimethylaminoethylglyoxaline chloride hydrochloride* forms extremely deliquescent, colourless needles from absolute alcohol, m. p. 229° (corr.) [Found (micro.): C, 42·2; H, 7·6; N, 18·3. $C_8H_{16}N_3Cl$,HCl requires C, 42·5; H, 7·5; N, 18·6%].

4(5)-β-*Ethylaminoethylglyoxaline dipicrate* (yield, 55%) crystallises from water in yellow

needles which lose water at 100° to give opaque orange needles, m. p. 186° (corr.) (Found: loss, 5·6. $C_7H_{13}N_3,2C_6H_3O_7N_3,2H_2O$ requires loss, 5·7%. Found in dried salt: N, 21·2. $C_7H_{13}N_3,2C_6H_3O_7N_3$ requires N, 21·1%). The *dihydrochloride* crystallises in colourless plates, m. p. 169° (corr.), from methyl alcohol–acetone [Found (micro.): C, 39·7, 39·5; H, 7·0, 7·1; N, 19·7; Cl, 33·0. $C_7H_{13}N_3,2HCl$ requires C, 39·6; H, 7·1; N, 19·8; Cl, 33·5%].

4(5)-β-Aminoethylglyoxaline (histamine) was formed when alcoholic ammonia was used in the reaction. It was isolated and identified as the dipicrate, which melted at 238° (corr.), alone or mixed with a reference specimen.

4(5)-β-Methylaminoethylglyoxaline was also prepared by the following method. 4(5)-β-Chloroethylglyoxaline hydrochloride (1·7 g.) was refluxed for 18 hours with alcohol (35 g.), potassium hydroxide (3 g.), and *p*-toluenesulphonmethylamide (5·5 g.). The alcohol was removed by distillation, and the residue made alkaline with sodium hydroxide and extracted with ether. The ether on evaporation left a gummy mass, which was dissolved in alcohol (charcoal) and filtered, and the alcohol removed by evaporation. The residue was hydrolysed by heating with sulphuric acid (14 pts.) and water (6 pts.) at 175° for 15 minutes. After cooling and dilution with water, the solution was decolorised with charcoal, rendered alkaline with sodium hydroxide, re-acidified with hydrochloric acid, and taken to dryness in a vacuum. An alcoholic extract of the residue gave with aqueous picric acid 4(5)-β-methylaminoethylglyoxaline dipicrate, which melted at 188° (corr.) alone or mixed with a specimen prepared from 4(5)-β-chloroethylglyoxaline hydrochloride and alcoholic methylamine. Identification was confirmed by the m. p. alone or mixed of the dihydrobromide, 167° (corr.).

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