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LXXVIII.—4-*β*-*Methylaminoethylglyoxaline.*

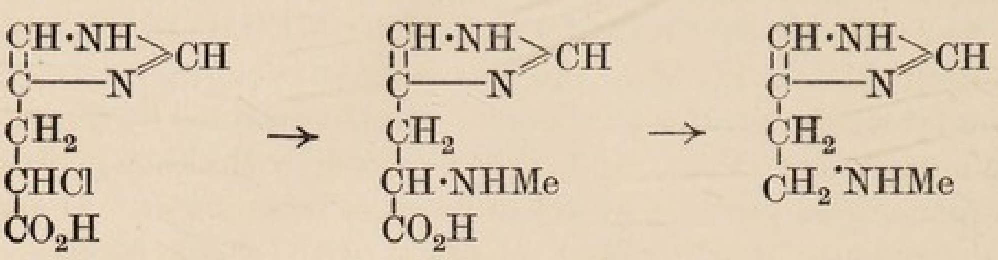
By Robert George Fargher and Frank Lee Pyman.

The isolation of 4-β-aminoethylglyoxaline from ergot, and the recognition of its importance as an intense stimulant of plain muscle, have led in recent years to the synthesis, not only of the substance itself, but also of a number of related compounds, the examination of which has indicated the presence of an optimum side-chain of two carbon atoms between the cyclic system and the amino-group (Ewins, T., 1911, **99**, 2052; Pyman, *ibid.*, 2172; 1916, **109**, 186). As the same optimum condition obtains in the sympathomimetic amines (Barger and Dale, *J. Physiol.*, 1910, **41**, 19), it was deemed of interest, in view of the importance of the *N*-alkyl substituent in that series, to prepare 4-β-*methylaminoethylglyoxaline* and to compare its physiological action with that of the naturally occurring base.

Considerable difficulty has been experienced in devising a practicable mode of preparation. The methods employed by Barger and his collaborators (Walpole, T., 1910, **97**, 941; Barger and Ewins, *ibid.*, 22, 53) for the synthesis of the analogously substituted β-phenylethylmethylamines were inapplicable, methylation of an acyl derivative of 4-β-aminoethylglyoxaline, for example, because of the readiness with which glyoxalines combine with alkyl esters, and syntheses dependent on 4-β-hydroxyethylglyoxaline or glyoxaline-4-acetaldehyde owing to the lack of satisfactory methods for the preparation of these substances.

Eventually, recourse was made to the preparation of dl-α-*methylamino*-β-*glyoxaline*-4-*propionic acid* (II) by the interaction of *dl*-α-chloro-β-glyoxaline-4-propionic acid (I) and 40 per cent.

aqueous methylamine at 110°, and the subsequent decarboxylation of this substance by means similar to those employed by Ewins and Pyman (T., 1911, **99**, 339) in the case of histidine.



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

The yields of 4-β-*methylaminoethylglyoxaline* (III) were even poorer than had been anticipated, and the physiological action was disappointing, since the substance, when compared directly with 4-β-aminoethylglyoxaline, showed only about one-hundredth of the activity.

EXPERIMENTAL.

α-Chloro-β-glyoxaline-4-propionic Acid.

This acid has been prepared from histidine by Windaus and Vogt (*Beitr. Chem. Physiol. Path.*, 1908, **11**, 406) and by Gerngross (*Ber.*, 1909, **42**, 404), both of whom give the melting point as 191° (uncorr.). One of us (T., 1911, **99**, 1394) prepared the racemic variety of the acid synthetically, found that it melted at 201° (corr.), and concluded from the difference between the melting points that the acid prepared from histidine was one of the optically active varieties. Since we were in possession of considerable quantities of histidine, we desired to prepare α-chloro-β-glyoxaline-4-propionic acid from this source for the present investigation, as the synthesis involved a large number of operations. It appeared therefore to be desirable to examine the optical character of the product, a point which had received no attention from the previous investigators. We prepared the acid by the method of Windaus and Vogt, the crude product of the interaction of histidine, fuming hydrochloric acid, and sodium nitrite being esterified, and the ester purified by crystallisation of its hydrogen oxalate from methyl alcohol. Ethyl α-chloro-β-glyoxaline-4-propionate hydrogen oxalate, which was not analysed by the previous investigators, proves to be a *sesquioxalate*.* It melts at 161—163° (corr.), and dissolves

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* The formation of sesquioxalates in the place of the expected acid oxalates has been observed on several occasions amongst the derivatives of glyoxaline (T., 1911, **99**, 678, 1392, 1394). The hydrogen oxalate of ethyl β-glyoxaline-4-propionate is also a sesquioxalate (T., 1919, **115**, 1020) and not a normal acid oxalate containing a molecular proportion of water of crystallisation as stated by Windaus and Vogt (*Ber.*, 1907, **40**, 3693). Ethyl α-hydroxy-β-glyoxaline-4-propionate, however, yields a normal *hydrogen*

readily in water, but sparingly in cold methyl or ethyl alcohol. Late crops, melting as low as 140°, appear to represent the partly racemised salt, as the analytical figures remain unaltered [Found : C = 42·2; H = 4·7; Cl = 13·0. $(C_8H_{11}O_2N_2Cl)_4(C_2H_2O_4)_3$ requires C = 42·2; H = 4·7; Cl = 13·1 per cent.].

From this salt the ester was liberated and hydrolysed by the method of Windaus and Vogt, and the resulting α-chloro-β-glyoxaline-4-propionic acid purified by crystallisation from water. It proved to be optically inactive and identical with the synthetic acid. Either alone or mixed with the synthetic acid, it melted at 201° (corr.), although the melting point may be found as low as 195° when the acid is heated very slowly.

Racemisation of optically active amino-acids on the replacement of the amino-group by the chlorine atom has been observed on other occasions (compare, for instance, McKenzie and Clough, T., 1912, **101**, 391).

dl-α-*Methylamino*-β-*glyoxaline*-4-*propionic Acid* (dl-*Methylhistidine*).

Forty-four grams of α-chloro-β-glyoxaline-4-propionic acid and 176 c.c. of 40 per cent. aqueous methylamine (prepared by saturation in a freezing mixture) were heated in several sealed tubes for five hours at 110°. The resulting liquor was evaporated to dryness and the residue, after removal of methylamine as completely as possible by re-solution and re-evaporation, dissolved in water, and treated with a solution of 115 grams of picric acid in 3300 c.c. of water. On keeping, the liquor deposited first an oil, which was removed by filtration when the liquor was nearly cold, and then 52·3 grams of a well-crystallised picrate. This sintered at about 70° and melted at 132° and proved to be α-*methylamino*-β-*glyoxaline* 4-*propionic acid dipicrate*. By extracting the oil with hot water, some 35 grams of picrates melting indefinitely at about 70° were obtained, whilst the ultimate mother liquors yielded solely methylamine picrate melting at 210°. The picrates melting at 70° yielded after several crystallisations from water about 4 grams of methylhistidine dipicrate and 21 grams of a picrate melting at 189°, which proved to be α-*methylamino*-β-*glyoxaline*-4-*propionic acid sesquipicrate*, the ultimate mother liquors again depositing methylamine picrate. The total yield of methylhistidine is thus 47 per cent. of the theoretical.

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oxalate, which separates from methyl alcohol, in which it is fairly readily soluble, in clusters of prismatic needles which are anhydrous and melt at 143° (corr.), sintering from 135° (Found : C = 43·6; H = 5·3; N = 10·2. $C_8H_{12}O_3N_2,C_2H_2O_4$ requires C = 43·8; H = 5·2; N = 10·2 per cent.).

When less concentrated solutions of methylamine were employed, the yield of methylhistidine was diminished; thus, when a 29 per cent. solution of methylamine was used, the yield of methylhistidine amounted to only 20 per cent. of the theoretical.

α-Methylamino-β-glyoxaline-4-propionic acid dipicrate crystallises from water in well-defined, prismatic needles containing 3 molecules of water of crystallisation, two of which are lost at 60° in a vacuum, and the third slowly at 90° in a vacuum. The air-dried picrate sinters at about 70°, owing to loss of water of crystallisation, and melts definitely at 132° (corr.). It dissolves readily in boiling water but only sparingly in cold (Found: in air-dried material, loss at 60° in a vacuum = 5·4. $C_7H_{11}O_2N_3,2C_6H_3O_7N_3,3H_2O$ requires loss of $2H_2O$, 5·3 per cent. Found: in dried material, C = 35·3; H = 3·3; N = 19·3; further loss at 90° in a vacuum = 2·8. $C_7H_{11}O_2N_3,2C_6H_3O_7N_3,H_2O$ requires C = 35·3; H = 3·0; N = 19·5; H_2O = 2·6 per cent.).

Five grams of air-dried picrate gave 3·32 grams of picric acid, 3·36 grams being required.

α-Methylamino-β-glyoxaline-4-propionic acid sesquipicrate, which closely resembles the dipicrate, crystallises from water in large, glistening, rhombic prisms, which melt at 193° (corr.) and appear to contain 7 molecules of water of crystallisation, of which six are lost at 60° in a vacuum, whilst the last is retained even on further heating at 110° (Found: in air-dried material, loss at 60° in a vacuum = 9·6, 9·4; C = 33·1; H = 3·7.

$$2C_7H_{11}O_2N_3,3C_6H_3O_7N_3,7H_2O$$

requires loss of $6H_2O$ = 9·4; C = 33·35; H = 3·9 per cent.

Found: in dried material, C = 36·8; H = 3·2; N = 20·0.

$$2C_7H_{11}O_2N_3,3C_6H_3O_7N_3,H_2O$$

requires C = 36·8; H = 3·2; N = 20·1 per cent.).

α-Methylamino-β-glyoxaline-4-propionic acid monopicrate was obtained by treating the solution of the base with a molecular proportion of picric acid. It is sparingly soluble in water, from which it separates in minute, flattened prisms, which melt and effervesce at 118° (corr.) and contain 3 molecules of water of crystallisation, which are not lost on heating at 60° in a vacuum (Found: C = 34·7; H = 4·3. $C_7H_{11}O_2N_3,C_6H_3O_7N_3,3H_2O$ requires C = 34·5; H = 4·45 per cent.).

α-Methylamino-β-glyoxaline-4-propionic acid dihydrochloride was prepared from the picrate in the usual manner and crystallised from dilute hydrochloric acid in large, diamond-shaped, colourless plates, which softened at about 127° and melted at 134° (corr.). It dissolves very readily in water, but only sparingly in alcohol. The air-dried salt contains one molecule of water of crystallisation, which is not lost on heating at 60° in a vacuum. The solution in sodium carbonate gives a blood-red colour with sodium diazobenzene-*p*-sulphonate (Found : loss in a vacuum at 60° = 1·2 per cent. In dried material, C = 32·5; H = 5·6; N = 15·9; Cl = 26·9. $C_7H_{11}O_2N_3,2HCl,H_2O$ requires C = 32·3; H = 5·8; N = 16·1; Cl = 27·3 per cent.).

α-Methylamino-β-glyoxaline-4-propionic acid aurichloride separates from water, in which it is only sparingly soluble, in glistening, pale orange, flattened prisms, which are anhydrous and effervesce at 115° (corr.) without melting (Found : Au = 46·7.

$$C_7H_{11}O_2N_3,2HCl,2AuCl_3$$

requires Au = 46·4 per cent.).

α-Methylamino-β-glyoxaline-4-propionic acid is prepared by digesting an aqueous solution of the hydrochloride with slightly more than the quantity of silver carbonate calculated to remove the hydrochloric acid completely. It separates from the resulting solution, after concentration, in needles, which melt and effervesce at 270° (corr.), are anhydrous, and taste sweet with a bitter after-taste (Loss at 110° = 1·3 per cent. Found: in dried material, C = 49·5; H = 6·5; N = 24·5. $C_7H_{11}O_2N_3$ requires C = 49·7; H = 6·6; N = 24·8 per cent.).

The *benzoyl* derivative, obtained by the Schotten-Baumann method, separates from water, in which it is much more readily soluble than the corresponding histidine derivative, in clusters of minute prisms, which give an intense red coloration with sodium diazobenzene-*p*-sulphonate in sodium carbonate solution. The air-dried material retains one-half of a molecular proportion of water of crystallisation, which is lost at 110°. It melts and effervesces at 241° (corr.) [Found : in air-dried material, C = 59·5; H = 5·6; loss at 110° = 2·9. $(C_{14}H_{15}O_3N_3)_2,H_2O$ requires C = 59·5; H = 5·7; H_2O = 3·2 per cent.].

4-β-*Methylaminoethylglyoxaline.*

This base can be prepared in poor yield by the decarboxylation of the preceding benzoyl derivative and hydrolysis of the product or by decarboxylation of methylhistidine by means of 20 per cent. hydrochloric acid at 280°. Unlike the parent base (compare Ewins and Pyman, *loc. cit.*), it cannot be prepared by the action of 20 per cent. sulphuric acid on methylhistidine, the reaction resulting in almost complete decomposition of the methylhistidine and reduction of the sulphuric acid to hydrogen sulphide at temperatures of 270—290°, whilst below 270° little decarboxylation occurs.

(*a*) *Formation of 4-β-Methylaminoethylglyoxaline from Benzoylmethylhistidine.*—1·2 Grams of benzoylmethylhistidine were heated at 240° in a vacuum until all frothing ceased. The dark residue was dissolved in 4 c.c. of 20 per cent. hydrochloric acid, heated for one hour at 180°, and the resulting solution freed from benzoic acid by extraction with ether, basified with sodium carbonate, filtered from insoluble brown matter, acidified to methyl-orange, evaporated to dryness, and extracted with alcohol. The extract, which consisted in part of sodium chloride, was dissolved in a little water and treated with 0·5 gram of picric acid in 12 c.c. of water. After the separation of resinous matter, 0·25 gram of nearly pure 4-β-methylaminoethylglyoxaline dipicrate was obtained. The yield amounts to 10 per cent. of the theoretical.

(*b*) *Formation of* 4-β-*Methylaminoethylglyoxaline from Methylhistidine.*—4·5 Grams of methylhistidine dihydrochloride dissolved in 18 c.c. of 20 per cent. hydrochloric acid were heated in nine sealed tubes for two hours at 280°. The product was basified with sodium carbonate, filtered from insoluble amorphous matter, re-acidified to methyl-orange, evaporated to dryness, and extracted with alcohol. The residue consisted solely of sodium chloride. The extracted material, amounting to 2·5 grams, and consisting in part of sodium chloride, was dissolved in a little water and treated with a hot solution of 3 grams of picric acid in 75 c.c. of water. After the deposition of resinous matter and amorphous picrates, there crystallised 1·0 gram of nearly pure 4-β-methylaminoethylglyoxaline dipicrate, which sintered at 170° and melted and decomposed at about 210°. The mother liquors were used to re-extract the amorphous picrates and yielded altogether a further 0·3 gram of the crystalline dipicrate. The yield thus amounts to 12 per cent. of the theoretical.

4-β-*Methylaminoethylglyoxaline dipicrate* crystallises from water, in which it is sparingly soluble, in well-defined, bright yellow needles, which appear to contain 2 molecules of water of crystallisation, one of which is lost on heating at 60° in a vacuum. The air-dried product shrinks together at about 170°, doubtless owing to loss of water of crystallisation, and melts and decomposes at 220° (corr.) (Found : loss at 60° in a vacuum = 3·6. $C_6H_{11}N_3,2C_6H_3O_7N_3,2H_2O$ requires loss of $1H_2O = 2·9$ per cent.

Found : in material dried at 60° in a vacuum, $C = 36·0$; $H = 3·2$. $C_6H_{11}N_3,2C_6H_3O_7N_3,H_2O$ requires $C = 35·9$; $H = 3·2$ per cent.).

4-β-*Methylaminoethylglyoxaline dihydrobromide*, prepared from the picrate in the normal manner, was obtained on evaporation of the aqueous solution as a somewhat hygroscopic, crystalline powder. It separates from alcohol in fern-shaped clusters of needles, which melt at 275° (corr.) and contain $2H_2O$. It is very readily soluble in water, readily soluble in alcohol, but almost insoluble in ether or ethyl acetate. The solution in sodium carbonate gives a blood-red colour with sodium diazobenzene-*p*-sulphonate (Found: loss at 60° in a vacuum = 2·4 per cent. Found: in dried material, $C = 22{\cdot}4$; $H = 4{\cdot}9$; $N = 12{\cdot}8$. $C_6H_{11}N_3,2HBr,2H_2O$ requires $C = 22{\cdot}3$; $H = 5{\cdot}3$; $N = 13{\cdot}0$ per cent.).

In conclusion, the authors would express their indebtedness to Dr. H. H. Dale, F.R.S., of the staff of the Medical Research Committee, who has carried out the experiments on the physiological action of 4-β-methylaminoethylglyoxaline.

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