Some derivatives of 4(or 5)-methyl-glyoxaline / by Arthur James Ewins.

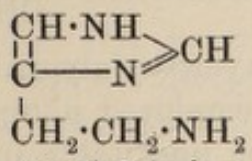
CCXXXII.—*Some Derivatives of 4(or 5)-Methylglyoxaline.*

By Arthur James Ewins.

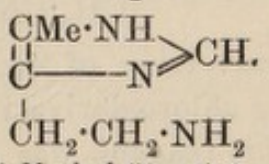
The recent discovery of the high degree of physiological activity attaching to the base 4(or 5)-β-aminoethylglyoxaline (Dale and Laidlaw, *J. Physiol.*, 1910, **41**, 318) and its possible therapeutical importance, has served to stimulate research in the direction of glyoxaline derivatives generally. The most interesting result so far has been the synthesis and resolution of the biochemically important amino-acid histidine (α-amino-β-glyoxaline-4(or 5)-propionic acid) by Pyman (this vol., p. 1386), who has also devised a new synthetic method of preparing the base 4(or 5)-β-aminoethylglyoxaline (this vol., p. 668) in place of the tedious and expensive method employed by Windaus and Vogt (*Ber.*, 1907, **40**, 3691). Of the numerous derivatives obtained in the course of this work, however, none was found to be possessed of physiological activity in any marked degree.

Quite recently Windaus and Opitz (*Ber.*, 1911, **44**, 1721) have obtained the alcohol 4(or 5)-β-hydroxyethylglyoxaline corresponding with the active base already mentioned, and, moreover, have synthesised 4(or 5)-β-aminomethylglyoxaline, the lower homologue of this base. From experiments carried out in these laboratories, this new base has been found, however, to be almost devoid of physiological action.

The present communication deals in the main with the synthesis of a methyl homologue of 4(or 5)-β-aminoethylglyoxaline, namely, 4(or 5)-methyl-5(or 4)-β-aminoethylglyoxaline, which it was expected might prove physiologically interesting. The structural relationship of the two bases is best seen from the following formulæ:



4(or 5)-β-Aminoethylglyoxaline.

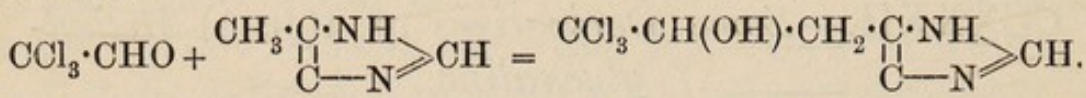


4(or 5)-Methyl-5(or 4)-β-aminoethylglyoxaline.

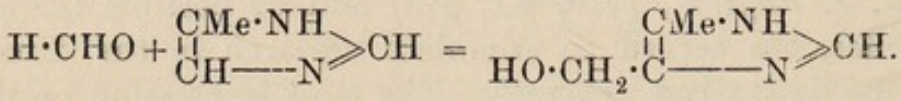
these bases in each case being tautomeric (compare Pyman, Trans., 1910, **97**, 1814).

The synthesis of this methyl homologue of 4(or 5)-β-aminoethylglyoxaline was suggested by an observation made by Windaus (*Ber.*, 1909, **42**, 758). It had been recorded by O. Gerngross (*Ber.*, 1909, **42**, 398) that 4(or 5)-methylglyoxaline on treatment with chloral formed an additive product, which he considered to be

4-γγγ-trichloro-β-hydroxypropylglyoxaline, the reaction being formulated thus:

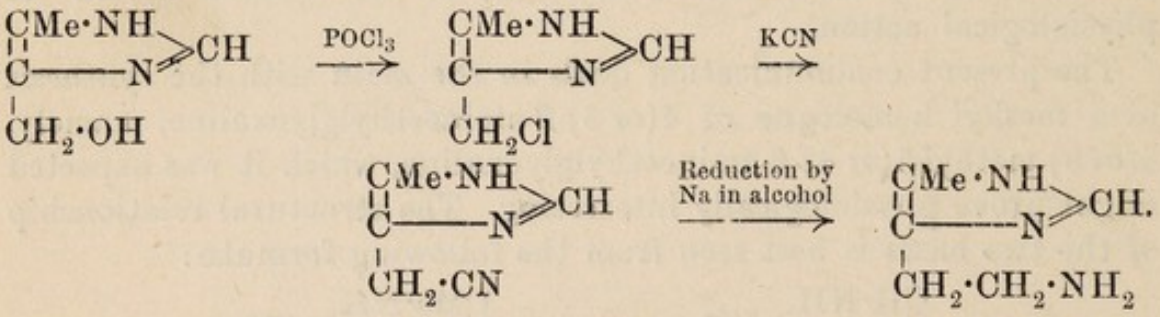


Windaus (*loc. cit.*), however, found that 4(or 5)-methylglyoxaline on treatment with formaldehyde yielded a product which on reduction gave 4:5-dimethylglyoxaline. The additive product must therefore be produced according to the equation:



The methylhydroxymethylglyoxaline so produced was not obtained by Windaus in a pure condition; but as the required 4(or 5)-methyl-5(or 4)-aminoethylglyoxaline should be readily obtainable from this hydroxy-derivative by a series of reactions analogous to those employed by Pyman in the conversion of 4(or 5)-hydroxymethylglyoxaline into 4(or 5)-β-aminoethylglyoxaline, the work of Windaus was repeated with a view to the isolation of 4(or 5)-methyl-5(or 4)-hydroxymethylglyoxaline in the pure state. This was readily accomplished after slightly modifying the conditions of Windaus's experiment, and a good yield (50 per cent. of the theory) of the base was isolated by means of its pure, crystalline picrate.

The conversion of 4(or 5)-methyl-5(or 4)-hydroxymethylglyoxaline into the required base was carried out on the lines of Pyman's synthesis, the reactions being represented thus:



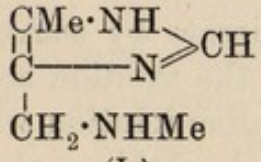
For the conversion of 4(or 5)-hydroxymethylglyoxaline into the corresponding chloro-derivative Pyman employed phosphorus pentachloride. This reagent was found to be unsuitable in the case of the methyl homologue. With the hydrochloride of the chloro-derivative no reaction occurred in the cold (compare Pyman), and with the free base, or on heating with the hydrochloride, a considerable amount of charring occurred. By employing phosphoryl chloride, however, the reaction proceeded quite smoothly, and a quantitative yield of the chloro-derivative was obtained.

Like 4(or 5)-chloromethylglyoxaline, the methyl homologue is extremely reactive; thus on treating a freshly prepared ice-cold

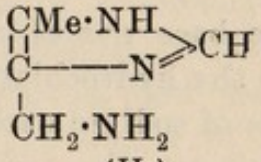
aqueous solution of the base with a similarly cold solution of picric acid, a crystalline picrate was obtained, which was found to consist of nearly pure 4(or 5) - methyl - 5(or 4)-hydroxymethylglyoxaline picrate, the chlorine atom of the base having been replaced by hydroxyl by the action of the water even at 0°.

The conversion of 4(or 5)-methyl-5(or 4)-chloromethylglyoxaline into the corresponding cyano-compound and the reduction of the latter to the ethylamine base followed exactly on the lines of Pyman's synthesis.

By the action of cold aqueous methylamine and of cold concentrated aqueous ammonia on 4(or 5)-methyl-5(or 4)-chloromethylglyoxaline, two other bases, namely, 4(or 5)-*methyl*-5(or 4)-*methylaminomethylglyoxaline* (I) and 4(or 5)-*methyl*-5(or 4)-*aminomethylglyoxaline* (II), were obtained, although the yields obtained were comparatively small (10—20 per cent.).



(I.)



(II.)

With the exception of 4(or 5)-methyl-5(or 4)-cyanomethylglyoxaline and of 4(or 5)-methyl-5(or 4)-β-aminoethylglyoxaline, all the glyoxaline derivatives obtained during the course of this investigation give an intense red colour with *p*-diazobenzenesulphonic acid in alkaline solution (Pauly's histidine reagent, *Zeitsch. physiol. Chem.*, 1904, **42**, 508). It may be also mentioned that it appears to be a general property of glyoxaline derivatives that they form phosphotungstates, which are soluble in hot water or cold acetone, and may usually be crystallised from dilute acetone, a property which is often of considerable advantage as a means of separation and purification.

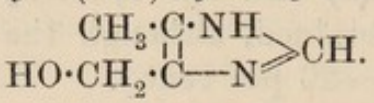
The physiological action of the various bases obtained during the course of this work was investigated by Dr. P. P. Laidlaw, of these laboratories, to whom the author wishes to express his thanks. It was found that the bases 4(or 5)-methyl-5(or 4)-aminomethylglyoxaline and 4(or 5) - methyl - 5(or 4)-methylaminomethylglyoxaline were physiologically almost inactive. 4(or 5)-Methyl-5(or 4)-β-aminoethylglyoxaline was, however, found to be physiologically active, chiefly in producing a decided fall in blood pressure (vasodilator effect) when injected intravenously, similar to, although somewhat less powerful than, that produced by 4(or 5)-β-aminoethylglyoxaline. It has also a motor effect on plain muscle, but its activity in this direction is far less (only about 1/200th or less) than that produced by the last-mentioned base.

EXPERIMENTAL.

Interaction of 4(or 5)-*Methylglyoxaline and Formaldehyde.*

Five grams of 4(or 5)-methylglyoxaline were heated in a sealed tube for two hours at 120° with 10 c.c. of a 40 per cent. solution of formaldehyde. There was no pressure on opening the tube, and to the clear, light yellow contents was added a hot saturated aqueous solution of 6·5 grams of picric acid. On cooling, a yellow, crystalline solid separated, which after recrystallisation from dilute (50 per cent.) alcohol was obtained quite pure. Yield, 9 grams.

4(or 5)-*Methyl*-5(or 4)-*hydroxymethylglyoxaline*,



The free base was obtained from the picrate by converting the latter into the hydrochloride, and treating the solution so obtained with excess of sodium carbonate. The alkaline solution was evaporated to dryness, the residue extracted with absolute alcohol, and the solution concentrated. On keeping, the crystalline base slowly separated in stout, hexagonal prisms, melting at 138°:

0·1568 gave 0·3074 CO_2 and 0·1002 H_2O. C = 53·5; H = 7·1.
0·3084 „ 68·2 c.c. N_2 (moist) at 23° and 758 mm. N = 25·2.
$C_5H_8ON_2$ requires C = 53·6; H = 7·1; N = 25·0 per cent.

The base is very readily soluble in water or alcohol, but sparingly so in most other organic solvents. Solutions of the base or of its salts give an intense cherry-red coloration with *p*-diazobenzenesulphonic acid. In neutral or alkaline solution it gives a precipitate with mercuric chloride, which is soluble in dilute acid. With phosphotungstic acid solution it gives a precipitate, which is readily soluble in hot water or cold acetone, and may readily be crystallised from dilute acetone, forming fan-shaped clusters of short, broad prisms.

The *hydrochloride*, obtained from the picrate in the usual manner, crystallises from absolute alcohol, the yield being increased by addition of a little dry ether. It forms stout, hexagonal plates, melting at 240—242°. The salt is deliquescent, and readily soluble in water or alcohol:

0·1658 gave 0·2440 CO_2 and 0·0892 H_2O. C = 40·1; H = 5·9.
0·1340 „ 22·4 c.c. N_2 (moist) at 23° and 758 mm. N = 19·0.
0·1580 „ 0·1524 AgCl. Cl = 23·8.
$C_5H_8ON_2$,HCl requires C = 40·3; H = 6·0; N = 18·8;
Cl = 24·0 per cent.

The *picrate* obtained as described above crystallises from hot 50 per cent. alcohol in long, thin prisms, melting to a red liquid at 180—181°:

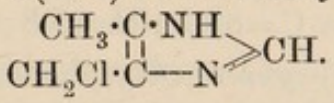
0·1374 gave 0·1938 CO_2 and 0·0410 H_2O. C = 38·5; H = 3·3.

0·2596 „ 47·2 c.c. N_2 (moist) at 25° and 766 mm. N = 20·8.

$C_5H_8ON_2,C_6H_3O_7N_3$ requires C = 38·7; H = 3·2; N = 20·6 per cent.

This salt is very sparingly soluble in cold water or alcohol, but fairly readily so in these solvents when hot.

4(or 5)-*Methyl*-5(or 4)-*chloromethylglyoxaline*,



The *hydrochloride* of this base was readily obtained as follows: Five grams of 4(or 5)-methyl-5(or 4)-hydroxymethylglyoxaline hydrochloride were suspended in about 20 c.c. of phosphoryl chloride, and the mixture gently warmed on a sand-bath under a reflux condenser. Hydrogen chloride was evolved, and solution was complete in about fifteen minutes. The excess of phosphoryl chloride was removed by distillation in a vacuum, and the residual syrupy liquid dissolved in a small quantity of hot saturated alcoholic solution of hydrogen chloride. On cooling, the crystalline hydrochloride of 4(or 5)-methyl-5(or 4)-chloromethylglyoxaline rapidly separated. Precipitation was completed by the addition of a little dry ether. For analysis the salt was recrystallised from absolute alcohol. It forms thin, rectangular plates, melting at 222°. The yield is quantitative:

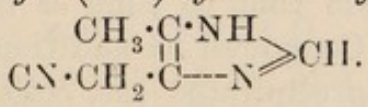
0·0776 gave 0·1014 CO_2 and 0·0328 H_2O. C = 35·6; H = 4·7.

0·0996 „ 0·1718 AgCl. Cl = 42·7.

$C_5H_7N_2Cl,HCl$ requires C = 35·9; H = 4·8; Cl = 42·5 per cent.

This salt is very readily soluble in cold methyl alcohol.

4(or 5)-*Methyl*-5(or 4)-*cyanomethylglyoxaline*,



This substance was prepared from the corresponding chloro-derivative by the method which was found by Pyman (*loc. cit.*) to yield the best results with 4(or 5)-chloromethylglyoxaline. Fifteen grams of 4(or 5)-methyl-5(or 4)-chloromethylglyoxaline hydrochloride were dissolved in 180 c.c. of absolute alcohol, and the solution slowly added drop by drop to a solution of 50 grams of potassium cyanide in about 60 c.c. of water. The mixture was kept well stirred and at a temperature of 0°. The precipitated salts were collected, washed with alcohol, and the filtrate and washings treated with

90 c.c. of saturated sodium carbonate solution. The mixture was evaporated to dryness under diminished pressure, the residue extracted with warm ethyl acetate, and the solvent evaporated. From the residual brown, syrupy liquid the 4(or 5)-methyl-5(or 4)-cyanomethylglyoxaline crystallised out on keeping. Yield, 2·7 grams (24 per cent. of the theoretical).

For analysis the base was recrystallised from water, when it was obtained in large, rectangular prisms, melting at 163—164°:

0·2274 gave 0·4954 CO_2 and 0·1264 H_2O. C = 59·4; H = 5·7.

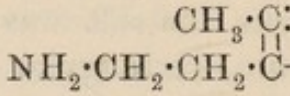
0·1194 „ 34·0 c.c. N_2 (moist) at 15° and 772 mm. N = 34·7.

$C_6H_7N_3$ requires C = 59·5; H = 5·8; N = 34·7 per cent.

4(or 5)-*Methyl*-5(or 4)-*cyanomethylglyoxaline* is moderately soluble in cold, and very readily so in hot, water. Solutions of the base give with mercuric chloride a white precipitate, soluble in dilute acids. The *phosphotungstate* of the base is almost insoluble in cold water, but readily soluble in hot water or cold acetone. It crystallises from dilute acetone in long needles. With *p*-diazobenzenesulphonic acid in alkaline solution (sodium carbonate) an intense deep reddish-brown coloration is produced, the colour being strikingly different from that usually given by simple glyoxaline derivatives.

The *picrate* crystallises from hot water in prisms melting at 172°.

4(or 5)-*Methyl*-5(or 4)-*β-aminoethylglyoxaline*,



The reduction of 4(or 5)-methyl-5(or 4)-cyanomethylglyoxaline to the required base was carried out by means of sodium in concentrated alcoholic solution.

2·5 Grams of 4(or 5)-methyl-5(or 4)-cyanomethylglyoxaline were dissolved in a minimum quantity of absolute alcohol, and 6·5 grams of sodium was added in small portions to the gently boiling solution. Alcohol was added from time to time as necessary. The solution was then made acid to Congo-red by addition of concentrated hydrochloric acid, and the precipitated salt collected. The filtrate was rendered alkaline with sodium carbonate, evaporated to dryness, and dissolved in a little absolute alcohol. On keeping, nothing separated out, and the solution was then treated with a hot saturated solution of picric acid. The crystalline *picrate* of 4(or 5)-methyl-5(or 4)-β-aminoethylglyoxaline rapidly separated. Yield, 2·7 grams (22 per cent. of the theoretical):

0·1594 gave 0·2158 CO_2 and 0·0402 H_2O. C = 36·9; H = 2·8.

0·1100 „ 20·2 c.c. N_2 (moist) at 19° and 761 mm. N = 21·2.

$C_6H_{11}N_3,(C_6H_3O_7N_3)_2$ requires C = 37·0; H = 2·9; N = 21·6 per cent.

The *dihydrochloride* crystallises from absolute alcohol in colourless, prismatic needles, melting at 231—232°:

0·1295 gave 0·1732 CO_2 and 0·0801 H_2O. C = 36·5; H = 6·8.

$C_6H_{11}N_3,2HCl$ requires C = 36·7; H = 6·6 per cent.

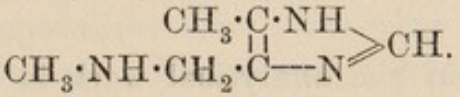
This salt is anhydrous, very sparingly soluble in hot absolute alcohol, very readily so in cold water, and fairly readily so in cold methyl alcohol. With *p*-diazobenzenesulphonic acid in alkaline solution a reddish-yellow colour is produced. The aqueous solution of the salt is precipitated by mercuric chloride, the precipitate being soluble in dilute acids. The phosphotungstate of the base is readily soluble in hot water or in cold acetone.

The *dihydrobromide* crystallises from absolute alcohol, on addition of dry ether, in stout, hexagonal prisms, melting at 212°:

0·1028 gave 0·1348 AgBr. Br = 55·8.

$C_6H_{11}N_3,2HBr$ requires Br = 55·8 per cent.

4(or 5)-*Methyl*-5(or 4)-*methylaminomethylglyoxaline*,



This base was obtained by the action of methylamine on 4(or 5)-methyl-5(or 4)-chloromethylglyoxaline.

0·5 Gram of 4(or 5)-methyl-5(or 4)-chloromethylglyoxaline was dissolved in a few c.c. of methyl alcohol, and the solution added drop by drop to 2·5 c.c. of an aqueous solution of methylamine, which was kept at a temperature of about 0°. The solution was then evaporated to dryness, the residue dissolved in a little water, and treated with a hot saturated aqueous solution of picric acid. The heavy, yellow oil which separated from the hot solution was collected, and from the filtrate on cooling the crystalline 4(or 5)-*methyl*-5(or 4)-*methylaminomethylglyoxaline dipicrate* separated. It crystallises from water in prisms melting at 222°. Yield, 20 per cent. of theory:

0·1218 gave 0·1654 CO_2 and 0·0352 H_2O. C = 37·0; H = 3·2.

0·0944 „ 17·4 c.c. N_2 (moist) at 16° and 764 mm. N = 21·6.

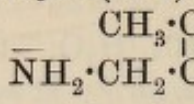
$C_6H_{11}N_3,(C_6H_3O_7N_3)_2$ requires C = 37·0; H = 2·9; N = 21·6 per cent.

The *dihydrochloride* crystallises from absolute alcohol in stout prisms, melting at 246—247°:

0·1014 gave 0·1480 AgCl. Cl = 36·1.

$C_6H_{11}N_3,2HCl$ requires Cl = 36·2 per cent.

4(or 5)-*Methyl*-5(or 4)-*aminomethylglyoxaline*,



This base was obtained from 4(or 5)-methyl-5(or 4)-chloromethylglyoxaline by the method employed for the preparation of the foregoing base, using concentrated aqueous ammonia (0·88) in place of methylamine. The yield of base was very poor, amounting to only 10 per cent. of the theory.

The *picrate* crystallises from hot water in clusters of well-formed prisms, melting at 216—217°:

0·0934 gave 0·1224 CO_2 and 0·0240 H_2O. C = 35·7; H = 2·8.

$C_5H_9N_3,(C_6H_3O_7N_3)_2$ requires C = 35·8; H = 2·6.

The *hydrochloride* crystallises from absolute alcohol in stout, rectangular prisms, melting at 233—234°.

Solutions both of this and of the foregoing base give with *p*-diazobenzenesulphonic acid an intense cherry-red colour.

The greater part of the analytical work in connexion with this investigation has been carried out by Mr. C. J. Gobell, to whom the author wishes to express his thanks.

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