The synthesis of glyoxaline derivaties allied to pilocarpine / by Frank Lee Pyman.

LXI.—*The Synthesis of Glyoxaline Derivatives Allied to Pilocarpine.*

By Frank Lee Pyman.

The idea of preparing glyoxalines containing acidic groups analogous to the homopilopic complex in pilocarpine by condensing a suitable bromoglyoxaline with substances such as ethyl sodiomalonate was put forward by Jowett in 1905 (Trans., **87**, 405). Owing, however, to the difficulty of obtaining at the time suitable bromoglyoxalines in good yield, no condensation experiments were actually carried out. Since then the present author—continuing this line of work at Dr. Jowett's request—has prepared and characterised the bromo- and dibromo-derivatives of 4(or 5)-methylglyoxaline, 1:4-dimethylglyoxaline, and 1:5-dimethylglyoxaline (Trans., 1910, **97**, 1814). A number of bromoglyoxalines being thus available, attempts were made to bring them into reaction in various ways, but in every case unsuccessfully.

In the first place, it was found that these compounds were quite unaffected when heated with ethyl sodiomalonate or ethyl sodioacetoacetate under various conditions, for in each case the bromoglyoxaline was recovered unchanged, and no bromide could be detected in the reaction mixture by means of silver nitrate.

The stability of the bromoglyoxalines indicated by these results is comparable with that of bromobenzene. This compound may be readily brought into reaction by Grignard's method, and attempts were therefore made to convert bromoglyoxalines into magnesium glyoxalyl bromides, which might then be used for the preparation of derivatives in the usual manner.

All attempts, however, to effect the combination of bromoglyoxalines with magnesium, whether by adding traces of iodine or methyl iodide or by using "active" magnesium (Baeyer, *Ber.*, 1905, **38**, 2759), were unsuccessful.

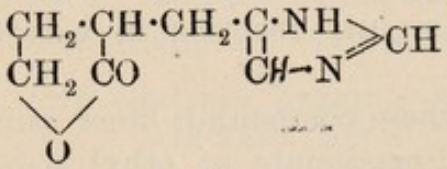
Finally, it was thought that bromoglyoxalines might possibly be brought into reaction by heating them with magnesium alkyl halides at high temperatures, a method employed by Grignard (*Compt. rend.*, 1904, **138**, 1048), and subsequently by Wohl and Berthold (*Ber.*, 1910, **43**, 2177), for the preparation of derivatives of ω-bromophenetole. This method was also unsuccessful, for on heating 2:4-dibromo-1:5-dimethylglyoxaline with magnesium methyl iodide or magnesium phenyl bromide for several hours in boiling xylene, the bromine atoms were to some extent replaced, not by alkyl groups, but by hydrogen, 2(or 4)-bromo-1:5-dimethylglyoxaline and

1 : 5-dimethylglyoxaline being formed. In consequence of these results, attempts to utilise bromoglyoxalines for synthetic purposes were abandoned.

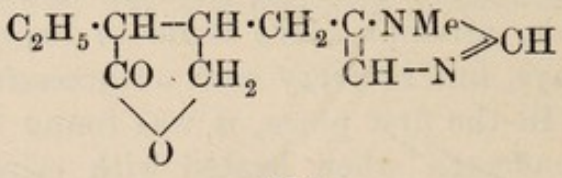
Later, however, the method of preparing glyoxaline derivatives recently employed in the synthesis of 4(or 5)-β-aminoethylglyoxaline (Trans., 1911, **99**, 668) and of histidine (Trans., 1911, **99**, 1386) were applied to the preparation of a number of new compounds, from which a possible physiological action was expected.

The physiological examination of these compounds was carried out by Dr. P. P. Laidlaw, of the Wellcome Physiological Research Laboratories, to whom the author is much indebted, and the results are briefly indicated in the paper.

In the first place, it seemed of interest to prepare the *lactone* of *α(β-hydroxyethyl)β-glyoxaline*-4(or 5)-*propionic acid* (I), for this base has certain constitutional features in common with pilocarpine (II), both compounds containing a glyoxaline ring linked through a methylene group with a butyrolactone residue:

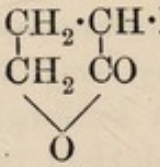


(I.)



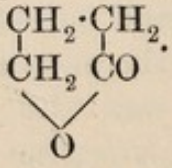
(II.)

This was effected substantially by the method devised by Bentley, Haworth, and Perkin (Trans., 1896, **69**, 169) for the synthesis of lactones of the general formula:



These chemists condensed ω-bromophenetole with ethyl sodiomalonate, hydrolysed the resulting crude ethyl γ-phenoxyethylmalonate, and isolated γ-phenoxyethylmalonic acid; this was converted into γ-phenoxybutyric acid by heating to 200°, and phenol was removed from the latter by means of fuming hydrobromic acid, butyrolactone resulting according to the following scheme:

$$PhO\cdot CH_2\cdot CH_2Br + CNaH(CO_2Et)_2 \longrightarrow PhO\cdot CH_2\cdot CH_2\cdot CH(CO_2Et)_2$$
$$\rightarrow PhO\cdot CH_2\cdot CH_2\cdot CH(CO_2H)_2 \longrightarrow PhO\cdot CH_2\cdot CH_2\cdot CH_2\cdot CO_2H$$



By using the sodium derivatives of ethyl alkylmalonates in the first instance, they obtained the corresponding alkylbutyrolactones.

In the present investigation ethyl γ-phenoxyethylmalonate, which

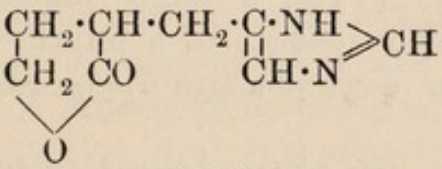
was prepared by the above method, was first isolated and purified. Two molecules of its sodium derivative were then condensed with one molecule of 4(or 5)-chloromethylglyoxaline hydrochloride, *ethyl* 4(or 5)-*glyoxalinemethyl*-γ-*phenoxyethylmalonate* (III) being formed. The salts of this base did not crystallise readily, but a small amount of the *hydrogen oxalate* was obtained in a pure state. Fortunately, it is not necessary to purify the reaction product at this stage, for on heating it with concentrated hydrochloric acid at 150° for two hours, it is converted at once into the *lactone* of α(β-*hydroxyethyl*)β-*glyoxaline*-4(or 5)-*propionic acid* (IV). This is readily isolated and purified in the form of its *picrate*, and is obtained in a yield amounting to 38 per cent. of the theoretical, calculated on the 4(or 5)-chloromethylglyoxaline hydrochloride employed.

The reaction may be represented as follows:

$$PhO\cdot CH_2\cdot CH_2\cdot CNa(CO_2Et)_2 + ClCH_2\cdot \underset{\underset{CH\cdot N}{\|}}{C\cdot NH} \!\!>\!\! CH \longrightarrow$$

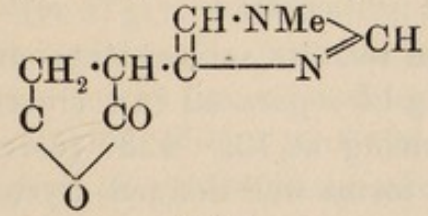
$$PhO\cdot CH_2\cdot CH_2\cdot C(CO_2Et)_2\cdot CH_2\cdot \underset{\underset{CH\cdot N}{\|}}{C\cdot NH} \!\!>\!\! CH \longrightarrow$$

(III.)



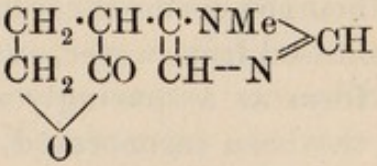
(IV.)

On physiological examination, however, this base was found to possess no pilocarpine-like action. A quantity was then methylated with the view of preparing the two isomeric *N*-methyl derivatives (V*a*) and (V*b*), but only one of the two isomerides was isolated from



(V*a*.)

and



(V*b*.)

the mixture in a pure condition, and this was physiologically inactive; no experiments have been performed to show whether this is the 1:4- or 1:5-derivative.

The next series of experiments carried out resulted in the preparation of compounds containing the skeleton of pilocarpine. By Bone and Sprankling's method (Trans., 1899, **75**, 857) of synthesising alkylsuccinic acids, the esters of substituted α-bromo-fatty acids are condensed with ethyl sodiocyanoacetate, yielding ethyl α-cyano-β-ethylsuccinates; these may be again alkylated on the α-carbon

atom, yielding ethyl α-cyano-αβ-dialkylsuccinates. Both classes of compounds form oils of constant boiling point, which must be mixtures of the two possible racemic forms, *ddll* and *dlld*, on account of the method of synthesis.

On hydrolysis of the ethyl α-cyano-αβ-dialkylsuccinates by means of concentrated hydrochloric acid, the cyano-group is removed, but the asymmetry of both the carbon atoms is preserved, and a mixture of the *ddll* and *dlld* (so-called *cis* and *trans*) αβ-dialkylsuccinic acids results, which can usually be separated by crystallisation:

$$R\cdot CHBr\cdot CO_2Et + CHNa(CN)\cdot CO_2Et \rightarrow R\cdot CH(CO_2Et)\cdot CH(CN)\cdot CO_2Et \xrightarrow{NaOEt+R'I}$$
$$R\cdot CH(CO_2Et)\cdot CR'(CN)\cdot CO_2Et \xrightarrow{\text{conc. HCl}} R\cdot CH(CO_2H)\cdot CHR'\cdot CO_2H$$

Ethyl α-cyano-β-ethylsuccinate formed the starting point of the synthesis mentioned below. This ester was prepared by Jowett (Trans., 1901, **79**, 1348) by the above method as an intermediate product in the synthesis of ethyltricarballylic acid, an oxidation product of the homopilopic acid obtained from pilocarpine.

This ester forms an oil of constant boiling point. When its sodium derivative (VI) is condensed with 4(or 5)-chloromethylglyoxaline hydrochloride (VII), a large quantity of basic ester is formed. This doubtless consists of a mixture of the two isomeric (*ddll* and *dlld*) *ethyl α-cyano-α-4(or 5)-glyoxalinemethyl-β-ethylsuccinates* (VIII):

$$C_2H_5\cdot CH(CO_2Et)\cdot CNa(CN)\cdot CO_2Et + ClCH_2\cdot \underset{\underset{CH\cdot N}{\|}}{C}\cdot NH\rangle CH \rightarrow$$

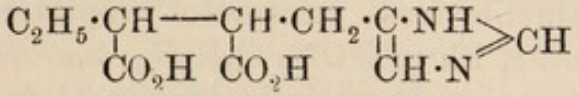
(VI.) (VII.)

$$C_2H_5\cdot \underset{\underset{CO_2Et}{|}}{CH}-\underset{\underset{CO_2Et}{|}}{C(CN)}\cdot CH_2\cdot \underset{\underset{CH\cdot N}{\|}}{C}\cdot NH\rangle CH$$

(VIII.)

When the crude basic ester is converted into its acid oxalate, and crystallised from water, just half of it can be separated in a crystalline form as a sparingly soluble salt melting at 125—128° (corr.), and the base regenerated from this salt forms well defined crystals melting at 105—106° (corr.). This base obviously represents one of the two isomeric (*ddll* or *dlld*) ethyl α-cyano-α-4(or 5)-glyoxalinemethyl-β-ethylsuccinates in a pure state. The half of the crude basic esters remaining after the separation of the oxalate melting at 125—128° was not obtained crystalline, either as salt or base. It doubtless consists of the isomeric ethyl α-cyano-α-4(or 5)-glyoxalinemethyl-β-ethylsuccinate more or less contaminated with the base melting at 105—106°, for it yields on hydrolysis the same products in the same proportion; thus on hydrolysing either the crystalline (m. p. 105—106°) or oily ester with concentrated hydrochloric acid,

apparently the same mixture of the two α-4(or 5)-*glyoxalinemethyl-β-ethylsuccinic acids* (IX) is formed, for in each case the product gradually deposited only a small amount of the same crystalline acid, melting at 236° (corr.), the bulk remaining amorphous. On

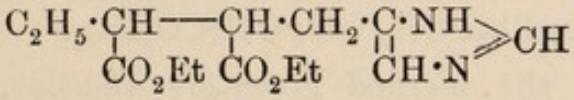


(IX.)

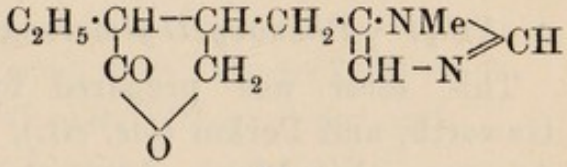
the supposition that an equilibrium mixture of the two acids had been obtained, the amorphous acids were on one occasion again subjected to treatment with concentrated hydrochloric acid, but no more of the crystalline acid could be isolated from the product.

The remaining amorphous acids were then esterified, and an attempt made to separate the resulting ethyl α-4(or 5)-glyoxalinemethyl-β-ethylsuccinates by crystallisation of the hydrogen oxalates, but although crystalline salts were obtained, no satisfactory separation took place.

On esterifying the pure, crystalline α-4(or 5)-glyoxalinemethyl-β-ethylsuccinic acid melting at 236° (corr.) with absolute alcohol and hydrogen chloride, *ethyl* α-4(or 5)-*glyoxalinemethyl-β-ethylsuccinate* (X) was obtained. It was isolated in the form of its beautifully crystalline *hydrogen oxalate*, and in view of the similarity of its structure to that of pilocarpine (XI) was submitted to physiological examination; it proved to be practically inactive:

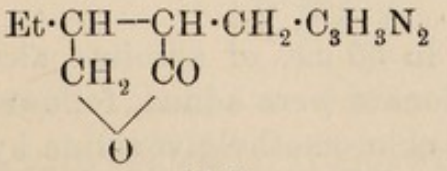


(X.)

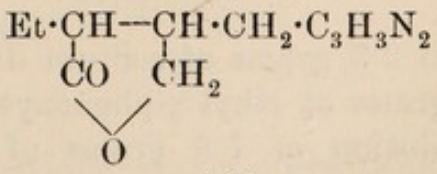


(XI.)

It may perhaps be mentioned at this point that had the isomeric α-4(or 5)-glyoxalinemethyl-β-ethylsuccinic acids been obtainable in good yield, the preparation of their anhydrides, the reduction of these to the corresponding lactones, followed by methylation, and resolution of the products were to have been carried out with the object of synthesising pilocarpine. Owing, however, to the poor yields of the acids, these experiments were discontinued, for each of the (2) corresponding anhydrides might yield two isomeric lactones (A and B) on reduction, and each of the (4) lactones would



(A.)



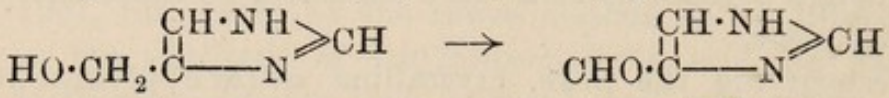
(B.)

yield on methylation two isomeric (1 : 4- and 1 : 5-) *N*-methyl derivatives, thus giving rise in all to eight optically inactive (externally

compensated) isomerides of pilocarpine, which on resolution would yield sixteen optically active forms. In view, therefore, of the poor yield of the crystalline succinic acid, this synthesis was abandoned.

Since it is known that the benzoic acid esters of many amino-alcohols have valuable local anæsthetic properties, 4(or 5)-*benzoyloxymethylglyoxaline*, $Ph{\cdot}CO_2{\cdot}CH_2{\cdot}C_3H_3N_2$, was next prepared, but this compound proved to be entirely unsuitable for its intended use, since the salts reacted strongly acid in aqueous solution. This compound was readily obtained by heating together 4(or 5)-hydroxymethylglyoxaline and benzoyl chloride; 4(or 5)-p-*nitrobenzoyloxymethylglyoxaline* was similarly prepared.

The preparation of 4(or 5)-*glyoxalineformaldehyde* (XII), a compound which may prove of value in synthetic experiments, is also recorded. This substance was prepared by the oxidation of the corresponding alcohol, 4(or 5)-hydroxymethylglyoxaline:



(XII.)

In conclusion, the properties of the free base, 4(or 5)-*β-aminoethylglyoxaline*, which has not previously been isolated, and of some new salts of this compound, are described.

Experimental.

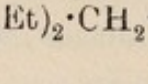
Ethyl γ-Phenoxyethylmalonate, $PhO{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CO_2Et)_2$.

This ester was prepared by the method given by Bentley, Haworth, and Perkin (*loc. cit.*), and fractionated under diminished pressure, when it was obtained as a colourless oil boiling at 226°/40 mm. Although it has previously been purified by Fischer and Blumenthal (*Ber.*, 1907, **40**, 106), and also by Leuchs (*Ber.*, 1911, **44**, 1507), who has recently described an improved method affording an 85 per cent. yield, it does not appear to have been analysed:

0·1304 gave 0·3078 CO_2 and 0·0822 H_2O. C = 64·4; H = 7·1.

$C_{15}H_{20}O_5$ requires C = 64·3; H = 7·2 per cent.

Ethyl 4(or 5)-*Glyoxalinemethyl-γ-phenoxyethylmalonate*,

$PhO{\cdot}CH_2{\cdot}CH_2{\cdot}C(CO_2Et)_2{\cdot}CH_2{\cdot}$  .

To 2·3 grams of sodium dissolved in 50 c.c. of absolute alcohol, 28 grams of ethyl γ-phenoxyethylmalonate were added, followed by a solution of 7·6 grams of 4(or 5)-chloromethylglyoxaline hydrochloride in 40 c.c. of absolute alcohol. The mixture was boiled for one hour under a reflux condenser, filtered from sodium chloride, and the solvent removed by distillation. The resulting oil was

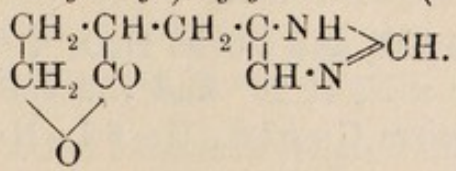
mixed with dilute hydrochloric acid, and extracted with ether to remove the unchanged ethyl γ-phenoxyethylmalonate, then made alkaline with sodium carbonate, and extracted with ether. The basic esters thus obtained amounted to 11 grams, and were mixed with a solution of 4 grams of oxalic acid in 50 c.c. of hot water. This liquor deposited a heavy oil on cooling, and when nearly cold the aqueous layer was poured off from the oil and kept overnight, when it deposited 0·5 gram of *ethyl* 4(or 5)-*glyoxalinemethyl-γ-phenoxyethylmalonate hydrogen oxalate* in clusters of plates melting at 53—55° (corr.). The oil was stirred with water, and kept, when it became mainly crystalline, and the product was collected and dried in the air, when 7 grams of a somewhat viscid, crystalline mass, melting at 45—50°, were obtained. On attempting to recrystallise this from water, a large proportion always separated first as an oil, the liquors then depositing small amounts of the well crystallised salt.

Ethyl 4(or 5)-*glyoxalinemethyl-γ-phenoxyethylmalonate hydrogen oxalate* crystallises from water in clusters of plates melting at 53—55° (corr.). It is sparingly soluble in cold water, and contains a molecule of water of crystallisation:

0·1534 * gave 0·3003 CO_2 and 0·0834 H_2O. C = 53·4; H = 6·1.
0·2068 * „ 10·8 c.c. N_2 at 16° and 761 mm. N = 6·2.
0·1660 * lost 0·0058 in a vacuum over H_2SO_4. H_2O = 3·5.
$C_{19}H_{24}O_5N_2,C_2H_2O_4,H_2O$ requires C = 53·8; H = 6·0; N = 6·0; H_2O = 3·9 per cent.
0·1428 † gave 0·2914 CO_2 and 0·0742 H_2O. C = 55·7; H = 5·8.
$C_{19}H_{24}O_5N_2,C_2H_2O_4$ requires C = 56·0; H = 5·8 per cent.

The base, regenerated from this salt by means of sodium carbonate and ether, was found to yield the lactone of α(β-hydroxyethyl)β-glyoxaline-4(or 5)-propionic acid on treatment with concentrated hydrochloric acid at 150°. For the preparation of the lactone, however, it is unnecessary to isolate the ethyl 4(or 5)-glyoxalinemethyl-γ-phenoxyethylmalonate, the following method giving satisfactory results.

Lactone of α(β-Hydroxyethyl)β-glyoxaline-4(or 5)-propionic Acid,



Twenty-one grams of 4(or 5)-chloromethylglyoxaline hydrochloride were condensed with 75 grams of ethyl γ-phenoxyethylmalonate by

* Air-dried. † Dried in a vacuum.

means of 6·1 grams of sodium, and the resulting crude basic esters were isolated as previously described, except that they were extracted by means of chloroform instead of ether. Without further purification, this oil, which amounted to 30 grams, was made up to a volume of 160 c.c. with concentrated hydrochloric acid, and heated at 150° for three hours in sealed tubes. On cooling, a quantity of phenol separated; this was removed by ether, and amounted to about 6 grams. The liquor was then evaporated to dryness under diminished pressure to remove the excess of hydrochloric acid. The residue was dissolved in 100 c.c. of water, and poured into a hot solution of 30 grams of picric acid in 1·5 litres of water. On cooling, a viscid, orange oil separated rapidly, and by the time the solution had cooled to about 50° this separation was almost complete. On then decanting the warm solution through a moistened filter, a clear filtrate was obtained, which almost immediately deposited crystals of the *picrate* of the *lactone* of *α(β-hydroxyethyl)β-glyoxaline-4(or 5)-propionic acid.* Further quantities of this picrate were obtained by extracting the amorphous picrates with warm water, and after recrystallisation from water 20·5 grams of the pure salt were obtained. This yield amounts to 38 per cent. of the theoretical.

The *lactone* of *α(β-hydroxyethyl)β-glyoxaline-4(or 5)-propionic acid* was isolated by converting its picrate into hydrochloride, rendering the solution alkaline with ammonia, and extracting with chloroform; on the removal of the solvent it occurred as a colourless gum, which soon solidified; it was purified by recrystallisation from acetone. Only a part of the lactone was extracted by chloroform from the ammoniacal solution, part remaining in solution presumably as the ammonium salt of the hydroxy-acid; after boiling the liquor with hydrochloric acid, cooling it, and again adding slight excess of ammonia, further quantities of the lactone could be removed by chloroform.

This base forms colourless, glistening prisms (from acetone), which melt at 110—111° (corr.). It is very readily soluble in water, giving a strongly alkaline solution, very readily so in alcohol or chloroform, fairly easily so in acetone or ethyl acetate, and almost insoluble in ether or benzene:

0·1516 gave 0·3204 CO_2 and 0·0795 H_2O. C = 57·6; H = 5·9.

0·1932 „ 28·2 c.c. N_2 at 20° and 752 mm. N = 16·9.

$C_8H_{10}O_2N_2$ requires C = 57·8; H = 6·1; N = 16·9 per cent.

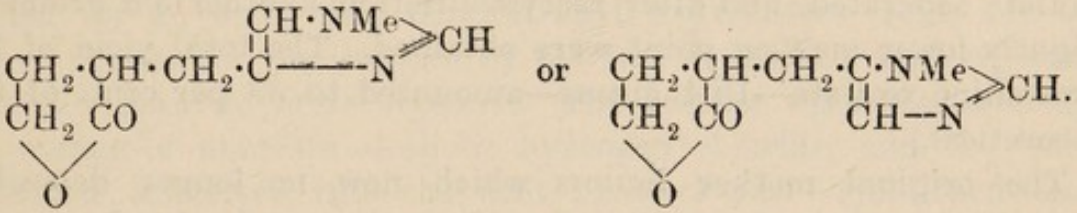
The *hydrochloride* crystallises from absolute alcohol in large, lozenge-shaped prisms, which melt at 136—137° (corr.). It is deliquescent, very readily soluble in water, giving a neutral solution, and easily soluble in absolute alcohol. It is anhydrous:

0·1546 gave 0·2674 CO_2 and 0·0789 H_2O. C = 47·2; H = 5·7.
0·1571 „ 0·1126 AgCl. Cl = 17·7.
$C_8H_{10}O_2N_2$,HCl requires C = 47·4; H = 5·5; Cl = 17·5 per cent.

The *picrate* crystallises from water in flat, glistening, deep yellow needles, which melt at 190—191° (corr.). It is anhydrous, and sparingly soluble in cold water:

0·1528 gave 0·2375 CO_2 and 0·0449 H_2O. C = 42·4; H = 3·3.
0·1024 „ 15·1 c.c. N_2 at 21° and 769 mm. N = 17·4.
$C_8H_{10}O_2N_2$,$C_6H_3O_7N_3$ requires C = 42·5; H = 3·3; N = 17·7 per cent

Lactone of α(β-Hydroxyethyl)β-1-methylglyoxaline-4(or 5)-propionic Acid,

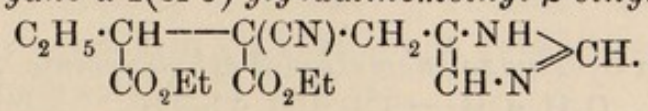


Six grams of the hydrochloride of the lactone of α(β-hydroxyethyl)β-glyoxaline-4(or 5)-propionic acid were dissolved in 50 c.c. of 10 per cent. aqueous sodium hydroxide, and shaken with 6 grams of methyl sulphate. The solution was acidified with hydrochloric acid, and evaporated to low bulk, then made alkaline with ammonia, and extracted with chloroform, this process being twice repeated. The combined chloroform extracts gave 3·0 grams of brown oil. This was converted into the picrate and recrystallised from alcohol, when there were obtained besides considerable quantities of amorphous picrate, and of the picrate of the not methylated lactone, 1·2 grams of the picrate of one of the *N*-methyl derivatives.

The *picrate* of the *lactone* of *α(β-hydroxyethyl)β-1-methylglyoxaline-4(or 5)-propionic acid* crystallises from alcohol in clusters of long, flat needles, which melt at 158° (corr.), after sintering a few degrees earlier. This salt is sparingly soluble in water or alcohol:

0·1476 gave 0·2370 CO_2 and 0·0479 H_2O. C = 43·8; H = 3·6.
$C_9H_{12}O_2N_2$,$C_6H_3O_7N_3$ requires C = 44·0; H = 3·7 per cent.

Ethyl α-Cyano-α-4(or 5)-glyoxalinemethyl-β-ethylsuccinate,



Forty-six grams of ethyl α-cyano-β-ethylsuccinate (Jowett, Trans., 1901, **79**, 1348) were added to a solution of 4·6 grams of sodium in 75 c.c. of absolute alcohol, and the cooled liquid mixed with 15·3 grams of 4(or 5)-chloromethylglyoxaline hydrochloride dissolved in 75 c.c. of absolute alcohol. After boiling for two hours on the

water-bath, the alcohol was distilled off, and the residue mixed with an excess of dilute hydrochloric acid. The neutral esters were then removed by extraction with ether, and the liquid made strongly alkaline with sodium carbonate, when the basic esters were extracted by ether. After the removal of the solvent, about 30 grams of basic oil remained, and this was dissolved in 125 c.c. of 10 per cent. aqueous oxalic acid, treated with animal charcoal, and allowed to crystallise, when *ethyl α-cyano-α-4(or 5)-glyoxalinemethyl-β-ethylsuccinate hydrogen oxalate* separated. This was recrystallised from 30 c.c. of water, when 11·6 grams of the pure salt melting at 125—128° (corr.) were obtained. On concentrating the original mother liquor a further quantity of the crystalline oxalate separated, and after recrystallisation another 3·8 grams of slightly lower melting point were obtained. The total yield of the crystalline oxalate—15·4 grams—amounted to 39 per cent. of the theoretical.

The original mother liquors which now no longer deposited crystalline matter were diluted with water, and the base was regenerated by means of sodium carbonate and ether, when about 15 grams of basic oil (A) were obtained.

The crystalline *ethyl α-cyano-α-4(or 5)-glyoxalinemethyl-β-ethylsuccinate hydrogen oxalate* separates from water in glistening leaflets, which melt at 125—128° (corr.). It is anhydrous, and is sparingly soluble in cold, but readily so in hot, water:

0·2044 gave 0·3816 CO_2 and 0·1084 H_2O. C = 50·9; H = 5·9.

0·1036 „ 9·5 c.c. N_2 at 25° and 763 mm. N = 10·6.

$C_{15}H_{21}O_4N_3,C_2H_2O_4$ requires C = 51·3; H = 5·8; N = 10·6 per cent.

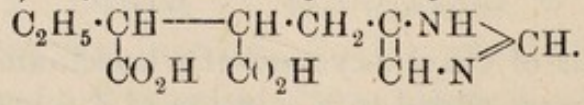
The *base* was regenerated from this salt by means of sodium carbonate and ether. It crystallises from ether in beautiful, large, clear, transparent prisms, which melt sharply at 105—106° (corr.). It is very sparingly soluble in cold water or light petroleum, sparingly so in ether or benzene, and very readily so in the other usual organic solvents:

0·1643 gave 0·3520 CO_2 and 0·1013 H_2O. C = 58·4; H = 6·9.

0·1141 „ 13·6 c.c. N_2 at 25° and 765 mm. N = 13·8.

$C_{15}H_{21}O_4N_3$ requires C = 58·7; H = 6·9; N = 13·7 per cent.

α-4(or 5)-*Glyoxalinemethyl-β-ethylsuccinic Acid*,



The crystalline oxalate obtained in the previous experiment (15·4 grams) was converted into the base, and this boiled for one and a-half hours under a reflux condenser with 100 c.c. of concen-

trated hydrochloric acid. The liquor was then evaporated to dryness under diminished pressure, digested with 20 c.c. of absolute alcohol, and filtered from ammonium chloride (0·8 gram). The alcohol was then removed, and the residue dissolved in 1 litre of boiling water, agitated with the silver carbonate from 10 grams of silver nitrate, filtered from the silver chloride, treated with hydrogen sulphide, and again filtered. The solution was then evaporated to dryness under diminished pressure, when 8·0 grams of a nearly colourless varnish remained. This was dissolved in about 20 c.c. of absolute alcohol, and kept, when 1·6 grams of *α*-4(or 5)-*glyoxalinemethyl-β-ethylsuccinic acid* melting at 220—225° separated. The mother liquor gave no more crystalline matter; it was then again boiled for an hour with concentrated hydrochloric acid, and the above process for the isolation of the free crystalline acid repeated, but still gave no more crystals. The residue was then esterified by means of absolute alcoholic hydrogen chloride, and the esters obtained converted into the acid oxalates and crystallised from water, when a mixture of crystalline oxalates was obtained.

By fractional crystallisation from water a small quantity of a salt was separated, which melted at 133—135° (corr.), gave on analysis figures (C = 51·7; H = 6·7) agreeing for the ester oxalate, and when mixed with the pure ester oxalate [m. p. 137—139° (corr.)] melted at 135—138° (corr.).

The oily ethyl *α*-cyano-*α*-4(or 5)-glyoxalinemethyl-*β*-ethylsuccinate (A, p. 539), amounting to 15 grams, was then hydrolysed, and treated in the same way as the crystalline ester, when a very similar result was obtained. The ammonium chloride separated amounted to 0·9 gram, the crude acids to 10·1 grams, the crystalline acid to 1·55 grams, m. p. 220—225°, and on esterifying the residue a similar mixture resulted.

The crystalline and oily cyano-esters therefore appear to yield on hydrolysis the same mixture of acids in the same proportion.

α-4(or 5)-*Glyoxalinemethyl-β-ethylsuccinic acid*, prepared from either the crystalline or oily cyano-ester and crystallised from water, melts and decomposes at 236° (corr.), and a mixture of the acids from the two sources at the same temperature. It crystallises in crusts formed of clusters of glistening needles. It is anhydrous, and is sparingly soluble in cold, although readily so in hot, water, and very sparingly soluble in alcohol:

0·0921 gave 0·1783 CO_2 and 0·0513 H_2O. C = 52·8; H = 6·2.

$C_{10}H_{14}O_4N_2$ requires C = 53·0; H = 6·3 per cent.

Ethyl α-4(or 5)-*Glyoxalinemethyl*-β-*ethylsuccinate*,
$CO_2Et\cdot CHEt\cdot CH(CO_2Et)\cdot CH_2\cdot C_3H_3N_2$.

Five grams of the acid (m. p. 236°) were boiled with 50 c.c. of absolute alcohol and 50 c.c. of cold saturated absolute alcoholic hydrogen chloride for four hours. The alcohol was then removed, and the residue dissolved in water, made alkaline with sodium carbonate, and extracted with ether.

The crude ester, 6·2 grams, was converted into the acid oxalate, and crystallised from water, when 4·8 grams of the pure salt were readily obtained.

The *hydrogen oxalate* crystallises from water in hard clusters of quadrilateral plates, which melt at 137—139° (corr.). It is readily soluble in hot, sparingly so in cold, water, and is anhydrous:

0·1512 gave 0·2852 CO_2 and 0·0904 H_2O. C=51·4; H=6·7.
$C_{14}H_{22}O_4N_2,C_2H_2O_4$ requires C=51·6; H=6·5 per cent.

4(or 5)-*Glyoxalinemethyl Benzoate*,

$$\begin{array}{l} \qquad\qquad\qquad\qquad CH\cdot NH\!\!> \\ C_6H_5\cdot CO_2\cdot CH_2\cdot C\!\!-\!\!-\!\!-\!\!N\!\!\nearrow \end{array} CH.$$

Ten grams of 4(or 5)-hydroxymethylglyoxaline (Trans., 1911, **99**, 673) and 14·5 grams of benzoyl chloride were stirred together; heat was generated, and the base melted and became a gummy mass. The mixture was digested for half-an-hour in the steam-bath with occasional stirring, and gradually became a chalky, crystalline mass. This was dissolved in water, filtered from a little insoluble matter, extracted with ether to remove impurities, and decolorised by means of animal charcoal. The clear solution was then made alkaline with ammonia, when 4(or 5)-glyoxalinemethyl benzoate separated as an oil, which readily became a sandy, crystalline powder on stirring. This product melted at 140°, and amounted to 13·2 grams, that is, 64 per cent. of the theoretical yield.

4(or 5)-*Glyoxalinemethyl benzoate* crystallises from alcohol in prisms, which melt at 140—141° (corr.). It is insoluble in water, but soluble in dilute acids. It is insoluble in aqueous sodium carbonate or ammonia, but dissolves in cold dilute aqueous sodium hydroxide, decomposing and forming a yellowish-brown solution, from which on acidifying benzoic acid separates. Like all glyoxalines containing an unsubstituted imino-group, it gives an intense red coloration with sodium diazobenzene-*p*-sulphonate; this indicates that the hydroxy- and not the imino-group is the point of attachment of the benzoyl group. It is readily soluble in cold alcohol,

very readily so in hot alcohol, and fairly easily soluble in chloroform or ether:

0·1354 gave 0·3230 CO_2 and 0·0616 H_2O. C = 65·1; H = 5·1.
$C_{11}H_{10}O_2N_2$ requires C = 65·3; H = 5·0 per cent.

The *hydrochloride* crystallises from absolute alcohol in clusters of long, flat needles, which melt at 183—184° (corr.). It is very readily soluble in water, giving an acid solution, readily so in hot absolute alcohol, but sparingly so in cold absolute alcohol:

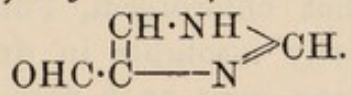
0·1633 gave 0·3290 CO_2 and 0·0692 H_2O. C = 54·9; H = 4·7.
0·1372 „ 0·0810 AgCl. Cl = 14·6.
$C_{11}H_{10}O_2N_2$,HCl requires C = 55·3; H = 4·7; Cl = 14·9 per cent.

4(or 5)-*Glyoxalinemethyl* p-*Nitrobenzoate*,
$NO_2 \cdot C_6H_4 \cdot CO_2 \cdot CH_2 \cdot C_3H_3N_2$,

was prepared by heating together 4(or 5)-hydroxymethylglyoxaline and *p*-nitrobenzoyl chloride for one hour at 130°, and isolated in a manner similar to that employed in the case of 4(or 5)-glyoxalinemethyl benzoate. It crystallises from alcohol in prisms, which melt at 106—107° (corr.). It is insoluble in water, readily soluble in cold alcohol, and very readily so in hot alcohol:

0·1623* gave 0·3168 CO_2 and 0·0528 H_2O. C = 53·2; H = 3·6.
$C_{11}H_9O_4N_3$ requires C = 53·4; H = 3·7 per cent.

4(or 5)-*Glyoxalineformaldehyde*,



Five grams of 4(or 5)-hydroxymethylglyoxaline were dissolved in 100 c.c. of 10 per cent. sulphuric acid, mixed with 3·5 grams of chromium trioxide, and the mixture heated on a steam-bath for an hour; the liquor was mixed with excess of aqueous sodium carbonate, evaporated to dryness in a vacuum, and the residue extracted with alcohol. After removing the solvent at a low temperature, a syrup remained, which became partly crystalline on keeping; the crystals were collected and recrystallised from a little water, when 0·7 gram of the base was obtained.

4(or 5)-*Glyoxalineformaldehyde* crystallises from water in irregular leaflets, which melt at 173—174° (corr.). It is somewhat sparingly soluble in cold, readily so in hot, water:

0·1864 gave 0·3416 CO_2 and 0·0717 H_2O. C = 50·0; H = 4·3.
$C_4H_4ON_2$ requires C = 50·0; H = 4·2 per cent.

The *hydrogen oxalate* separates from water in irregular grains,

* Dried at 100°.

which decompose at 191° (corr.). It is sparingly soluble in cold, easily so in hot, water.

The *picrate* formed striated broken rods (from water), which melt at 195—196° (corr.). It is sparingly soluble in cold, readily so in hot, water:

0·1426 * gave 0·1916 CO_2 and 0·0286 H_2O. C = 36·6; H = 2·2.

$C_4H_4ON_2,C_6H_3O_7N_3$ requires C = 36·9; H = 2·2 per cent.

4(or 5)-β-*Aminoethylglyoxaline.*

Although a considerable number of salts of 4(or 5)-β-aminoethylglyoxaline have previously been described by Windaus and Vogt (*Ber.*, 1907, **40**, 3691) and Ewins and Pyman (Trans., 1911, **99**, 339), the free base has not hitherto been obtained in crystalline form. It may be readily isolated by mixing an aqueous solution of a pure salt (dihydrobromide or di-acid phosphate) with excess of sodium carbonate, evaporating completely dry in a vacuum, and extracting with hot chloroform. The extract is dried with sodium hydroxide, and evaporated to low bulk, when on keeping the base crystallises in clear, colourless, wedge-shaped plates, which melt at 83—84° (corr.), after softening a few degrees earlier.

After drying in a vacuum over sulphuric acid:

0·1878 gave 0·3694 CO_2 and 0·1386 H_2O. C = 53·6; H = 8·3.

$C_5H_9N_3$ requires C = 54·0; H = 8·2 per cent.

This base is very deliquescent, very readily soluble in water or alcohol, readily so in hot chloroform, but sparingly so in cold chloroform, and practically insoluble in dry ether. It distils at 209—210°/18 mm., passing over as a very viscous, colourless oil, which solidifies on seeding, forming a crystalline mass melting at 82—83° (corr.); a small proportion of coloured residue remains in the distillation flask.

The *monohydrobromide* crystallises from absolute alcohol in prismatic rods, which melt at 182—183° (corr.). It is anhydrous, readily soluble in water, giving a strongly alkaline solution, but sparingly soluble in cold absolute alcohol:

0·1290 gave 0·1492 CO_2 and 0·0630 H_2O. C = 31·5; H = 5·5.

$C_5H_9N_3,HBr$ requires C = 31·2; H = 5·3 per cent.

The *di-acid phosphate*, $C_5H_9N_3,2H_3PO_4$, is particularly suitable for the characterisation and purification of 4(or 5)-β-aminoethylglyoxaline on account of its crystalline form and sparing solubility in water. It separates from water in magnificent, clear, colourless, quadrilateral prisms belonging to the monoclinic system; the prisms are almost completely capped by a pair of pyramid faces, but a

* Dried at 100°.

diminutive second pair is nearly always present, and usually a basal plane; orthopinacoid and clinopinacoid faces are sometimes present, and crystals very closely resembling augite in form have been observed. Crystals half-an-inch long and nearly a quarter-of-an-inch broad are deposited from solutions containing only a few grams. This salt melts at 132—133° (corr.) after sintering earlier, and is anhydrous. It is soluble in about four parts of cold water, but readily so in hot water:

0·1836 gave 20·8 c.c. N_2 at 12° and 763 mm. N = 13·7.

0·2028 „ 0·1460 $Mg_2P_2O_7$. PO_4 = 61·4.

$C_5H_9N_3,2H_3PO_4$ requires N = 13·7; PO_4 = 61·9 per cent.

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