Preparation and properties of 1:4:5-trimethylglyoxaline / by Hooper Albert Dickinson Jowett.

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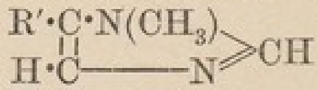
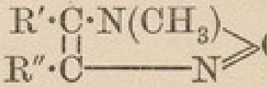
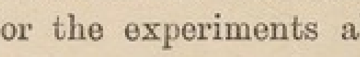
L.—*Preparation and Properties of* 1 : 4 : 5-*Trimethylglyoxaline.*

By Hooper Albert Dickinson Jowett.

In previous papers on the constitution of pilocarpine (Trans., 1903, 83, 438), it was shown that this alkaloid must be regarded as a glyoxaline derivative, and, furthermore, that the lower members of the series, for example, 1 : 4- (or 1 : 5-) and 1 : 2-dimethylglyoxalines, did not possess the physiological action of pilocarpine. It was therefore thought desirable to attempt the preparation of glyoxalines containing acidic groups analogous to the homopilopic complex in pilocarpine by condensing a suitable bromoglyoxaline with substances such as ethyl sodiomalonate. The only bromo-derivative of glyoxalines of the type  $\begin{array}{l}R'\cdot C\cdot N(CH_3)\\ \quad \| \\ H\cdot C\text{———}N\end{array}\!\!>CH$ which has been prepared is a dibromodimethylglyoxaline (Jowett and Potter, Trans., 1903, **83**, 466), monobromo-derivatives not having been obtained. It may be noted that only the dibromo-derivatives of pilocarpine and *iso*pilocarpine have been prepared. The only monobromoglyoxalines available would thus appear to be of the type  $\begin{array}{l}R'\cdot C\cdot N(CH_3)\\ \quad \| \\ R''\cdot C\text{———}N\end{array}\!\!>CBr$, which, if condensed with aliphatic sodium derivatives, would yield bases differing, however, from pilocarpine in the point of attachment of the acidic complex. It was decided to attempt the preparation of 2-bromo-1 : 4 : 5-trimethylglyoxaline as the most suitable substance for the purpose of condensation.

1 : 4 : 5-*Trimethylglyoxaline* was prepared from 4 : 5-dimethylglyoxaline, which had previously been obtained by Künne (*Ber.*, 1895, **28**, 2039). It is a crystalline base, yielding a series of crystalline salts, which were prepared and characterised. On bromination, the desired *monobromotrimethylglyoxaline* was obtained. It is a crystalline base forming crystalline salts which have been prepared and characterised. In this respect, it differs from dibromopilocarpine and dibromo*iso*pilocarpine, which possess only feeble basic properties (Trans., 1901, **79**, 586). Although the required bromoglyoxaline has been obtained, the yield, unfortunately, was so small that it was not considered practicable to prepare sufficient material for the experiments above mentioned. The amount of bromotrimethylglyoxaline obtained from one kilogram of methyl ethyl ketone under the best conditions was only two to three grams. All attempts to improve this yield having failed, it is intended to attack the problem from another standpoint.

EXPERIMENTAL.

1 : 4 : 5-*Trimethylglyoxaline*,  $\begin{array}{l}CH_3\cdot C\cdot N(CH_3)\\ \qquad \| \\ CH_3\cdot C\text{———}N\end{array}\!\!>CH.$

4 : 5-Dimethylglyoxaline was prepared from the corresponding mercaptan by treatment with nitric acid, the mercaptan being obtained from methyl ethyl ketone according to the method described by Künne (*loc. cit.*). Despite numerous experiments, the maximum yield of

pure base was only 4 per cent. of the ketone taken. The base distilled at 165° under 10 mm. pressure and melted at 117°, this being the temperature given by Künne. The nitrate, after recrystallisation until the melting point was constant, formed colourless, acicular crystals which fused at 180° with effervescence. Künne gave the melting point as 164°.

Dimethylglyoxaline picrate crystallises in brilliant yellow needles, which, after purification by recrystallisation from hot water and drying at 110°, melt at 196—197°. The picrates of the glyoxalines afford one of the easiest methods of identification of these bases, as they are readily formed, crystallise with facility, and have well defined melting points.

Trimethylglyoxaline is best prepared by the action of sodium methylsulphate on the sodium derivative of dimethylglyoxaline, according to Titherley's general method (Trans., 1901, **79**, 401). In conducting this operation, it was found necessary, in order to obtain the best yield, to work with not more than 5 grams of glyoxaline at a time, and to expose as large a surface as possible of the mixed sodium salts to the action of heat. Even under the best conditions, the yield of trimethylglyoxaline was only 32 per cent. of the dimethylglyoxaline taken. The crude product, obtained by extracting the sodium salts with ether and removing the ether by distillation, was fractionated under 20 mm. pressure, when the greater portion distilled at 115—120°, a little unchanged dimethylglyoxaline being recovered from the higher fractions. On redistillation, the greater portion boiled at 117° under 20 mm. pressure and solidified in the receiver to a mass of long, acicular crystals. These were drained on porous earthenware and then dried in a vacuum over sulphuric acid. The crystals melt at 46° and are soluble in all proportions in water, alcohol, or ether. On exposure to the air for only a few seconds they absorb moisture and liquefy.

0·1386 gave 0·3340 CO_2 and 0·1132 H_2O. $C=65·7$; $H=9·1$.
0·0972 ,, 21·6 c.c. nitrogen at 18° and 761 mm. $N=25·2$.
$C_6H_{10}N_2$ requires $C=65·5$; $H=9·1$; $N=25·4$ per cent.

The base has the characteristic odour of the glyoxalines previously described.

Attempts to prepare the base by the action of dimethyl sulphate on dimethylglyoxaline were unsuccessful.

Trimethylglyoxaline nitrate, $C_6H_{10}N_2,HNO_3,H_2O$, separates from its aqueous solution in long, acicular crystals which, after purification by recrystallisation, melt at 46°. It is readily soluble in water or alcohol, but insoluble in ether. When crystallised from alcoholic solution by the addition of ether, the crystals melt indefinitely at from 50° to 70°, owing to partial dehydration. Owing to the low melting point of the hydrate, the water of crystallisation could not be determined by the ordinary methods. On analysis, the salt (m. p. 46°) gave the following result:

0·149 gave 0·210 CO_2 and 0·0962 H_2O. C = 38·4; H = 7·2.
$C_6H_{10}N_2,HNO_3,H_2O$ requires C = 37·7; H = 6·8 per cent.

Trimethylglyoxaline hydrochloride, $C_6H_{10}N_2,HCl,H_2O$, separates from its aqueous solution in long, acicular crystals which, when dried in the air, melt indefinitely at about 80°, but after drying either in a desiccator over sulphuric acid or at 110°, the crystals melt sharply at 199°. The crystals are freely soluble in water or alcohol, but insoluble in ether.

0·225 air dried salt lost 0·025 at 110°. H_2O = 11·1.
0·20 anhydrous salt gave 0·1954 AgCl. Cl = 24·2.
$C_6H_{10}N_2,HCl,H_2O$ requires H_2O = 10·9.
$C_6H_{10}N_2,HCl$ requires Cl = 24·2 per cent.

The *aurichloride* formed yellow, acicular crystals which, after drying at 110°, melted at 202°.

0·122 gave 0·0536 Au. Au = 43·9.
$C_6H_{10}N_2,HAuCl_4$ requires Au = 43·8 per cent.

The *platinichloride* slowly separated from its aqueous solution as yellow crystals which, after drying at 110°, melted at 224—225°.

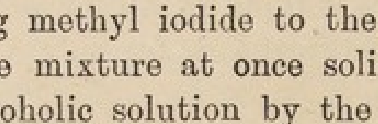
0·0926 gave 0·0288 Pt. Pt = 31·1.
$(C_6H_{10}N_2)_2,H_2PtCl_6$ requires Pt = 31·0 per cent.

The *picrate* formed yellow, acicular crystals which, after recrystallisation from hot water and drying at 110°, melted at 218°.

The *methiodide* was prepared by adding methyl iodide to the base, when a violent reaction occurred and the mixture at once solidified. The crystals were recrystallised from alcoholic solution by the addition of ether, and separated in long needles readily soluble in water or alcohol, insoluble in ether, and, after drying at 110°, melted at 158°.

0·189 gave 0·176 AgI. I = 50·3.
$C_6H_{10}N_2,CH_3I$ requires I = 50·4 per cent.

2-*Bromo*-1 : 4 : 5-*trimethylglyoxaline*,



$$\begin{array}{l} CH_3\cdot C\cdot N(CH_3) \\ \quad\;\; \| \\ CH_3\cdot C\text{———}N \end{array} \!\!> CBr.$$

Preliminary experiments proved that this substance could not be prepared by methods analogous to those employed in the case of 1 : 4- (or 1 : 5-) dimethylglyoxaline and pilocarpine. It was ultimately obtained by the following method.

Trimethylglyoxaline (2·8 grams) was dissolved in about 10 c.c. of carbon disulphide, and to the solution 4·1 grams of bromine in 10 c.c. of carbon disulphide were gradually added. Considerable heat was evolved and the mixture was kept cool. After a certain quantity of bromine had been added, a crystalline solid, presumably the hydrobromide of the base, began to separate, and this was dissolved by the addition of a little alcohol to the mixture. The solvent was then removed by distillation, the residue dissolved in water, excess of potassium carbonate added, and the alkaline liquid extracted several times with ether. The ethereal solution was then washed and dried, and, after distillation, left a residue which was crystallised from hot water. The best yield of crystalline product obtained was 22 per cent. of the base taken.

Bromotrimethylglyoxaline, $C_6H_9N_2Br,2H_2O$, crystallises from hot water in long, silky needles, which, when dried in the air, melt at 49°, but after drying in a desiccator over sulphuric acid fuse at 83°. It is readily soluble in hot water, alcohol, or ether, but sparingly so in cold water. Its aqueous solution is feebly alkaline, but the base dissolves readily in acids forming salts. It has a characteristic powerful narcotic odour.

0·2880 air-dried lost 0·0480 in a vacuum over H_2SO_4. $H_2O = 16·6$.
$C_6H_9N_2Br,2H_2O$ requires $H_2O = 16·0$ per cent.

The dried base (m. p. 83°) was analysed with the following result:

0·0844 gave 0·0841 AgBr. Br = 42·4.
$C_6H_9N_2Br$ requires Br = 42·3 per cent.

The *hydrobromide* crystallises in hard cubes which are soluble in water or alcohol, but insoluble in ether. When dried at 110°, the crystals melt at 208°.

0·1139 gave 0·1565 AgBr. Br = 58·5.
$C_6H_9N_2Br,HBr$ requires Br = 59·2 per cent.

The *aurichloride* formed yellow, acicular crystals which were sparingly soluble in cold water, but more freely in the hot solvent. After drying at 110°, the crystals melted at 191°.

0·1874 gave 0·0698 Au. Au = 37·2.
$C_6H_9N_2Br,HAuCl_4$ requires Au = 37·2 per cent.

The *picrate* formed yellow, acicular crystals, which, after recrystallisation from hot water and drying at 110°, melted at 173°.

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