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Contributors

Jowett, Hooper Albert Dickinson, 1870-1936.
Royal College of Surgeons of England

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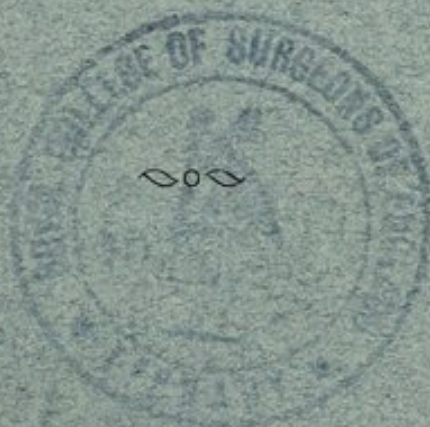
THE CONSTITUTION OF PILOCARPINE

(PART IV.)

BY

H. A. D. JOWETT, D.Sc.

[From the Transactions of the Chemical Society, 1903]

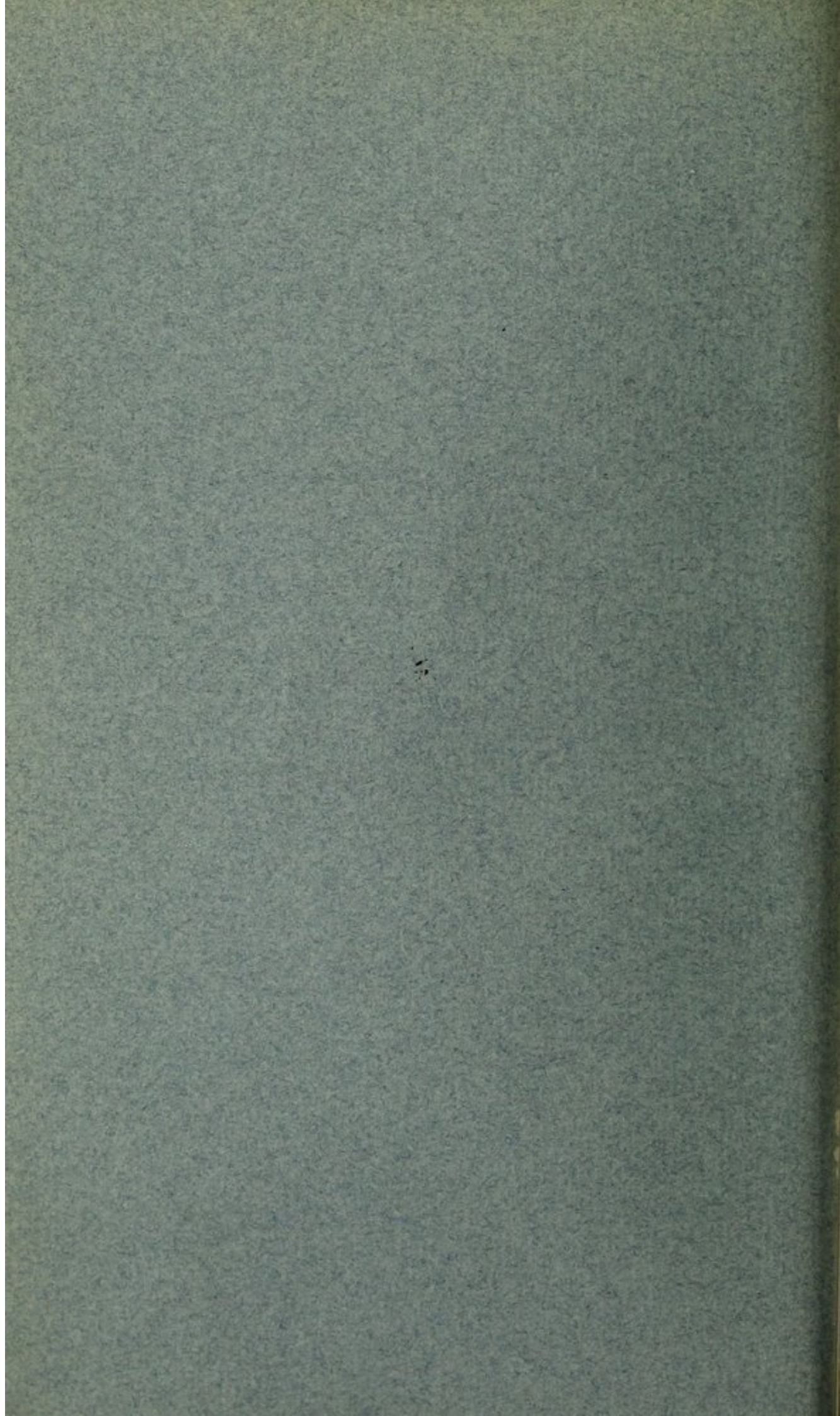


THE WELLCOME CHEMICAL RESEARCH LABORATORIES

FREDERICK B. POWER, Ph.D., *Director*

6, King Street, Snow Hill

LONDON, E.C.



leaving the question of the isomerism between pilocarpine and isopilocarpine an open one.

Although the experimental results recorded in this paper show that the above formula is possibly correct, yet the evidence from which Pinner and Schwarz deduced their formula is open to criticism.

Whilst these authors have confirmed my statements regarding the formation of homopilopic acid by the oxidation of isopilocarpine, they have not proved that this acid is produced when pilocarpine is oxidised. The diamide of the acid obtained by them from pilocarpine by oxidation melted at 182° , whilst the diamide of homopilopic acid melts at 208° . Therefore either the acid produced by the oxidation of pilocarpine is isomeric and not identical with homopilopic acid, or the diamide obtained by Pinner and Schwarz was impure. The experiments recorded in this paper show that the latter is the correct explanation, and that when pilocarpine is oxidised, homopilopic acid, identical in all respects with that previously described, is produced. Pinner and Schwarz have also stated that certain conclusions made by me with regard to the existence of the :NH group in isopilocarpine are incorrect,* and offer another explanation of the facts. I have proved that their explanation is correct by preparing directly from isopilocarpine methiodide the picrate previously supposed to be methyl isopilocarpine picrate. The compound thus previously described should therefore be named isopilocarpine methyl picrate.

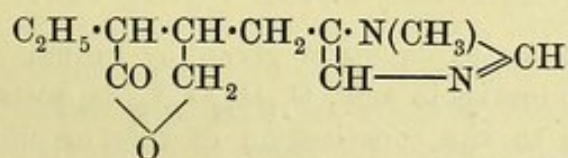
In former papers I showed that isopilocarpine and pilocarpine contain no ordinary double bond, and further experiments recorded in this paper demonstrate the extraordinary stability of isopilocarpine towards reducing agents, and also prove its mono-acidic character, which had previously been shown to be due to the nitrogen atom other than the methylamine residue.

Pinner and Schwarz seem to have overlooked these facts, as they describe (*Ber.*, 1902, 35, 204, 2443) similar experiments to prove that bromine forms substitution and not additive compounds, and make no mention of my results. Moreover, I gave the most conclusive proof of the composition of the dibromo-compounds by reducing them to the original alkaloids (*Trans.*, 1901, 79, 601). It is unfortunate that Pinner and Schwarz were not able to adduce more conclusive proof of the formation of methylurea by the oxidation of pilocarpine. If, however, a small amount of this base were formed it would not necessitate the existence of a glyoxaline ring in the pilocarpine molecule, as it might be equally well produced from the betaine formula mentioned in the latter part of the paper. It is true that Pinner and Schwarz have shown that there is an analogy between certain reactions

* I had arrived at this opinion before the publication of Pinner and Schwarz's paper, but was reserving the correction until the results could be fully discussed.

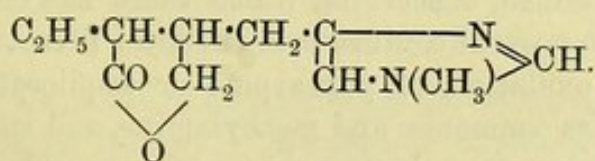
of pilocarpine and its derivatives and those of glyoxaline, yet, as is shown in the latter part of this paper, there are several other formulae equally probable, including the isomerides dependent on the point of attachment of the non-nitrogenous group to the nitrogen ring. In consideration of all these points, and in view of the experimental results recorded in this and the following paper (p. 464), I am able to confirm with a certain reservation the formula for pilocarpine suggested by Pinner and Schwarz.

The constitution of homopilopic acid having been determined, the problem of the nature of the remainder of the molecule has been attacked from two points. Firstly, by preparing substances containing possibly the same group as *isopilocarpine*, and studying their behaviour with certain reagents in order to determine if there was any analogy between them and this alkaloid. The substances thus studied were 1:4(or 1:5)-dimethylglyoxaline and 1:3-dimethylpyrazole, and the results are recorded in the following paper. Secondly, by endeavouring to obtain from *isopilocarpine* substances containing the nitrogen ring intact, which has been accomplished by distillation with soda lime. From the crude product thus obtained 1-methylglyoxaline, 1:4(or 1:5)-dimethylglyoxaline, 1:4(or 1:5)-methylamylglyoxaline, and probably 1:4(or 1:5)-methylamyleneglyoxaline have been isolated and identified. The identification of the first three substances has been rendered conclusive by the preparation and analysis of crystalline derivatives and by their products of oxidation. It may be mentioned that the aurichloride of the substance described in an early paper (Trans., 1900, 17, 853) as methylpyridine was undoubtedly dimethylglyoxaline. The analytical figures agree equally well for the latter substance, and a small amount of impurity would account for the low melting point. The bearing of these and previous results on the constitution of *isopilocarpine* is fully discussed, and the following formula proposed for *isopilocarpine*. It will be seen that I is identical with that suggested by Pinner and Schwarz,



I.

or



II.

varying with the conditions of experiment. These substances occur in the oxidation liquors as the potassium salts of the corresponding hydroxy-acids. These acids may be considered to be the lactonic acids of α -hydroxymethyl- β -ethylsuccinic and β -hydroxymethyl- α -ethylglutaric acids, though complete proof of this can only be obtained by synthesis. The acid obtained by Pinner and Kohlhammer by the oxidation of pilocarpine, which was first named by them *piluvic* acid, $C_8H_{12}O_5$, and subsequently *homopilomalic* acid, $C_8H_{14}O_5$, was undoubtedly homopilopic acid, though the salts examined by them were those of the corresponding hydroxydibasic acid. As this hydroxy-acid is unstable, immediately losing water with formation of the lactonic acid, and as Pinner and Schwarz in their last paper definitely accept my conclusions regarding this acid, the names *piluvic* and *homopilomalic* acid may be abandoned. The acid, $C_7H_{12}O_5$, obtained by Pinner and Kohlhammer by the oxidation of pilocarpoic acid, which was first named *isohydrochelidonic* acid and subsequently *pilomalic* acid, appears to be a distinct acid, and not the hydroxy-acid of pilopic acid; it should therefore be considered as an acid of unknown constitution.

With regard to Pinner and Schwarz's suggestion to alter the name of the acid, first described by me, from *dibromoisopilocarpinic* to *dibromoisocarpoic* acid on account of its possible confusion with *dibromoisopilocarpic* acid, I see no reason for such a change, and would prefer to retain the original name for this acid. The confusion has arisen by an incorrect translation of these names into German, the acid obtained from *dibromoisopilocarpine* and corresponding to the acid of which *isopilocarpine* is the lactone is *dibromoisopilocarpic* acid or "*dibromoisopilocarpinsäure*," whereas *dibromoisopilocarpinic* acid would be "*dibromoisopilocarpininsäure*," and not "*dibromoisopilocarpinsäure*" as rendered by Pinner and Schwarz (compare also *Chem. Centr.*, 1901, i, 1059). The difference in terminology would thus be the same in German as in English, and no new name is required.

Finally, in view of the researches which have resulted in establishing the constitution of pilocarpine (compare Feist, *Arch. Pharm.*, 1902, 240, 3), it would seem important that the widely quoted statements of Hardy and Calmels regarding this alkaloid, including its alleged synthesis by them, should now cease to receive scientific recognition.

EXPERIMENTAL.

Distillation of isopilocarpine with Soda-lime.

After several preliminary experiments, the best method of procedure was found to be as follows. One part of *isopilocarpine* nitrate was mixed with eight times its weight of a mixture of equal parts of soda-lime and slaked lime and the mixture then placed in an iron tube,

which fitted into an ordinary combustion furnace, replacing the bed on which the glass combustion tube usually rests. The tube was closed at each end by caps, which could be unscrewed, and contained iron delivery tubes at each end. It was filled so that a clear space was left above the powder, the air displaced with hydrogen, the tube then gradually heated, and the gases, &c., evolved passed into aqueous hydrochloric acid. When the whole length of tube had been heated and no more gas was evolved, hydrogen was passed through. The acid solution was then boiled with a little animal charcoal, filtered, and extracted with ether; the acid liquid was then made decidedly alkaline with excess of caustic alkali, extracted several times with ether, the ethereal solution washed with water, dried over potassium carbonate and distilled.

The residue, which was a dark-coloured, strongly smelling liquid, was next distilled under diminished pressure, and the portion distilling between 100° and 200° under 10 mm. pressure collected. The yield of distillate was about 17 per cent. of the base taken. It was then distilled several times under 10 mm. pressure and the following fractions collected:

(1) B. p. $100-120^{\circ}$, 1 part. (2) B. p. $120-150^{\circ}$, 1 part. (3) B. p. $150-160^{\circ}$, 5 parts.

These fractions were then further examined.

Fraction b. p. $100-120^{\circ}$ under 10 mm. Pressure.

This was a colourless liquid with the characteristic odour of a glyoxaline, rapidly becoming brown, and immiscible with water. An attempt to distil it under the ordinary pressure was not very successful, and though the chief portion boiled at $210-215^{\circ}$, decomposition occurred, and a large proportion of the whole was left behind in the flask as a thick, red oil.

The distillate was analysed:

0.1406 gave 0.3418 CO_2 and 0.108 H_2O . C = 66.3; H = 8.5.

$\text{C}_5\text{H}_8\text{N}_2$ requires C = 62.5; H = 8.3 per cent.

The analytical figures and its behaviour towards various reagents (*vide infra*) showed that this fraction, despite its fairly constant boiling point, was far from pure.

Fraction b. p. $120-150^{\circ}$ under 10 mm. Pressure.

This fraction, which was very small for such a wide range of temperature, was so evidently a mixture that it was not further examined. It

became oxidised and discoloured much more rapidly than either of the other fractions.

Fraction b. p. 150—160° under 10 mm. Pressure.

This was by far the largest fraction, and was a thick, yellow liquid which slowly became discoloured, but was much more stable than either of the other fractions. A portion, which boiled at 158—160° under 10 mm. pressure, was analysed with the following result :

0.213 gave 0.5610 CO₂ and 0.176 H₂O. C = 71.8 ; H = 9.2.

0.1956 „ 0.5148 CO₂ „ 0.160 H₂O. C = 71.8 ; H = 9.1.

0.075 „ 12.8 c.c. nitrogen at 17° and 745 mm. N = 19.0.

C₉H₁₄N₂ requires C = 72.0 ; H = 9.3 ; N = 18.7 per cent.

C₉H₁₆N₂ „ C = 71.1 ; H = 10.5 ; N = 18.4 „

Although the analytical figures agree remarkably well for those required for the formula C₉H₁₄N₂, an amount of impurity might be present, as in the first fraction, to cause the slight variation from the numbers required for the formula C₉H₁₆N₂. Other experiments, shortly to be described, show that the fraction contained substances corresponding to both of the above formulæ.

Identification of 1-Methylglyoxaline.

In view of the fact that the lowest members of the glyoxaline series are not readily extracted from their aqueous solution by ether, the alkaline liquid after extraction with ether (p. 465) was neutralised, evaporated to a low bulk, and treated by the method described for the isolation of methylglyoxaline. The ethereal solution left, after removal of the ether by distillation, a liquid which distilled completely at 200—205°. This colourless liquid had the peculiar odour characteristic of the glyoxalines, was miscible with water, alcohol, or ether, and was quite stable :

0.1882 gave 0.4146 CO₂ and 0.134 H₂O. C = 60.1 ; H = 7.9.

C₄H₆N₂ requires C = 58.5 ; H = 7.3 per cent.

C₅H₈N₂ „ C = 62.5 ; H = 8.3 „

The analytical figures indicating a mixture of methyl- and dimethylglyoxalines, the picrate and platinichloride were prepared and examined.

Platinichlorides.—These were prepared by fractional precipitation with platinic chloride.

The first fraction melted at 239° and on analysis :

0.1028 gave 0.0334 Pt. Pt = 32.5.

(C₅H₈N₂)₂.H₂PtCl₆ requires Pt = 32.4 per cent.

The fifth fraction melted at 195° and on analysis:

0.0678 gave 0.0228 Pt. $Pt = 33.6$.

$(C_4H_6N_2)_2, H_2PtCl_6$ requires $Pt = 33.9$ per cent.

The intermediate fractions melted between 195° and 239° .

The *picrates* were prepared by precipitating a solution of the hydrochloride with picric acid. The crystalline precipitate melted at 157° , but after frequent recrystallisation two fractions were obtained melting at 158° and 167° respectively, and further crystallisation did not affect these melting points; 1-methylglyoxaline boils at $197-199^{\circ}$, its platinichloride melts at $190-191^{\circ}$, and its picrate at 158° (*Ber.*, 1889, 22, 1359).

The constants of dimethylglyoxaline and its salts agree with these recorded in the next section of the paper.

The fraction b. p. $200-205^{\circ}$ contained, therefore, 1-methylglyoxaline and dimethylglyoxaline.

Identification of 1:4(or 1:5)-Dimethylglyoxaline.

The hydrochloride of the fraction boiling at $100-120^{\circ}$ under 10 mm. pressure, does not crystallise, and the platinichloride and aurichloride, when prepared in the usual way, undergo reduction, but the former double salt was obtained as follows. The oil was shaken up with three times its volume of water and the aqueous layer separated and converted into the hydrochloride. On adding platinic chloride a yellow crystalline precipitate was obtained which was separated and examined. When prepared in this way the platinichloride had no tendency to undergo reduction.

Dimethylglyoxaline platinichloride, when crystallised from hot water, separated in orange-coloured, cubical crystals, which melted at $238-239^{\circ}$ with decomposition. The melting point was not affected by further recrystallisation. When mixed with an equal weight of 1:4(or 1:5)-dimethylglyoxaline platinichloride (see following paper) the mixture melted at $238-239^{\circ}$:

0.0678 gave 0.0222 Pt. $Pt = 32.7$.

0.104 „ 0.0336 Pt. $Pt = 32.3$.

0.1174 „ 0.0380 Pt, 0.087 CO_2 , and 0.039 H_2O . $Pt = 32.4$;
 $C = 20.2$; $H = 3.7$.

0.112 gave 8.8 c.c. nitrogen at 17° and 745 mm. $N = 8.9$.

$(C_5H_8N_2)_2, H_2PtCl_6$ requires $Pt = 32.4$; $C = 20.0$; $H = 3.0$; $N = 9.3$ per cent.

Dimethylglyoxaline aurichloride was prepared from the hydrochloride obtained by decomposing the platinichloride with hydrogen sulphide. On adding auric chloride to the aqueous solution of the hydrochloride,

yellow acicular crystals separated, which, when collected and dried, first on a porous tile, and then in a desiccator over sulphuric acid, melted at 214—215°:

0.1096 gave 0.0492 Au, 0.0566 CO₂, and 0.0252 H₂O. Au = 44.9 ;
C = 14.1 ; H = 2.5.

C₅H₈N₂HAuCl₄ requires Au = 45.1 ; C = 13.8 ; H = 2.1 per cent.

The pure hydrochloride in 2 per cent. aqueous solution was optically inactive.

Dimethylglyoxaline picrate, prepared from the pure hydrochloride by precipitation with picric acid, formed yellow acicular crystals which melted at 167°. The melting point was not affected by further recrystallisation from water or alcohol. When mixed with an equal weight of 1:4 (or 1:5)-dimethylglyoxaline picrate (m. p. 167°), the mixture melted at 140—145°. This experiment was repeated several times with different specimens with confirmatory results.

Oxidation of the fraction boiling at 100—120° with potassium permanganate.—In order to obtain further proof of the presence of dimethylglyoxaline in this fraction, the whole liquid containing the portions both soluble and insoluble in water was oxidised with permanganate and the products of oxidation isolated and examined.

Three grams of oil required 15 grams of permanganate in 1 per cent. aqueous solution to produce a permanent colour, and the resulting liquid after removing the manganese peroxide by filtration was worked up in the usual manner.

The bases obtained were identified as ammonia and methylamine. The platinum salt of the latter base was analysed.

0.1758 gave 0.0732 Pt. Found Pt = 41.6. Calculated Pt = 41.3 per cent.

The acids obtained were acetic and butyric acids (the latter derived from the portion of the oil insoluble in water).

The silver salts were fractionally precipitated and analysed.

1st fraction. 0.061 gave 0.034 Ag. Ag = 55.7.

C₄H₇O₂Ag requires Ag = 55.4 per cent.

The last fraction. 0.0582 gave 0.0374 Ag. Ag = 64.3.

C₂H₃O₂Ag requires Ag = 64.7 per cent.

The analyses of the platinichloride and aurichloride prove the existence in the first fraction of a substance of the formula C₅H₈N₂, whilst its general properties and its oxidation to ammonia, methylamine, and acetic acid, prove that it is a dimethylglyoxaline with one methyl group attached to nitrogen.

It therefore remains to be decided to which of the three carbon atoms the other methyl group is attached. Of the three isomerides possible, two are known and have been characterised (compare p. 464).

The constitution of 1:2-dimethylglyoxaline is definitely established, but that of the other synthetical dimethylglyoxaline is still uncertain; the dimethylglyoxaline derived from *isopilocarpine* is, however, *not* identical with it.

The following table shows the close similarity existing between the derivatives of these isomerides:

| | | 1:2. | 1:4 (or 1:5). | From <i>isopilocarpine</i> . |
|-----------------|-------|----------|---------------|---------------------------------|
| Base..... | b. p. | 205—206° | 203° | 210—215° |
| Aurichloride | m. p. | 215° | 215° | 214—215° |
| Platinichloride | m. p. | 230° | 238—239° | 238—239° |
| Picrate | m. p. | 179° | 167° | 167° |

The only difference between the 1:4(or 1:5)-isomeride and that from *isopilocarpine* is that the mixture of equal weights of their picrates, each melting at 167°, melts at 140—145°.

The glyoxalines are, therefore, isomeric and not identical. The constituent of the fraction, b. p. 100—120° under 10 mm. pressure, and soluble in water, is therefore 1:4(or 1:5)-*dimethylglyoxaline*.

Identification of 1:4(or 1:5)-Methylamylglyoxaline.

The attempted preparation of a crystalline hydrochloride from the fraction b. p. 150—160° under 10 mm. pressure being unsuccessful, the platinichloride was prepared as follows. The base was dissolved in alcohol, made faintly acid with aqueous hydrochloric acid, and platinic chloride in aqueous solution added. A yellow, crystalline precipitate separated, which was allowed to remain in contact with the solution until the latter began to darken, the crystals were then rapidly collected, washed, and dried.

Methylamylglyoxaline platinichloride forms light brownish-coloured, tabular crystals which melt at 198°. The melting point was not altered by further crystallisation. On analysis:

0.172 gave 0.0466 Pt. Pt = 27.1.

0.1092 „ 0.0298 Pt, 0.1254 CO₂, and 0.0468 H₂O. Pt = 27.3
C = 31.3; H = 4.8.

0.124 gave 0.034 Pt, 0.1418 CO₂, and 0.054 H₂O. Pt = 27.4;
C = 31.2; H = 4.8.

(C₉H₁₆N₂)₂.H₂PtCl₆ requires Pt = 27.3; C = 30.3; H = 4.7 per cent.

The hydrochloride, obtained from the pure platinichloride by treatment with hydrogen sulphide, yielded a crystalline *picrate* melting at 134°, but an amorphous *aurichloride*. In 5 per cent. aqueous solution the hydrochloride was optically inactive.

The *methylamylglyoxaline*, obtained from the pure hydrochloride by

adding excess of potassium carbonate and extracting with ether, was a colourless, viscid oil with a feebly basic odour, insoluble in water:

0.1026 gave 0.2672 CO_2 and 0.0954 H_2O . $\text{C} = 71.0$; $\text{H} = 10.3$.

0.1092 „ 0.2844 CO_2 „ 0.0982 H_2O . $\text{C} = 71.0$; $\text{H} = 10.0$.

$\text{C}_9\text{H}_{16}\text{N}_2$ requires $\text{C} = 71.1$; $\text{H} = 10.5$ per cent.

Oxidation of the Fraction, b. p. 145—160° under 10 mm., with Permanganate.

This fraction, containing, besides methylamylglyoxaline, the substance boiling between it and dimethylglyoxaline and yielding butyric acid on oxidation, was oxidised with excess of permanganate, and the bases and acids isolated by the usual method.

The bases formed were identified as ammonia and methylamine; the platinichloride of the latter on analysis gave: $\text{Pt} = 41.2$ (calculated $\text{Pt} = 41.3$ per cent).

The acids formed were identified as *n*-hexoic and *n*-butyric acids.

The crude acids were purified by distillation, when three fractions were obtained: (1) a small fraction below 125°, chiefly ether, &c.; (2) 125—160°; (3) 160—190°. Only a slight residue was left in the distilling flask.

Fraction (2) smelt very strongly of butyric acid, whilst fraction (3) had a pleasanter smell and was more viscid.

Fraction (2), b. p. 125—160°.

The acid was converted into the barium salt and precipitated in two fractions with silver nitrate. The silver salts were analysed, with the following result:

1. 0.1176 gave 0.0656 Ag. $\text{Ag} = 55.7$.

2. 0.24 „ 0.1334 Ag. $\text{Ag} = 55.6$.

$\text{C}_4\text{H}_7\text{O}_2\text{Ag}$ requires $\text{Ag} = 55.4$ per cent.

The anilide, prepared in the usual way and recrystallised from ligroin, melted at 82°. *iso*Butyranilide melts at 102.5°, and butyranilide at 90°. The low melting point is due to the presence of the higher anilide which is sparingly soluble in ligroin, and is not easily separated. The corresponding acid was undoubtedly *n*-butyric acid.

Fraction (3), b. p. 160—190°.

The acid was converted into the silver salts by fractional precipitation in the usual manner, and on analysis:

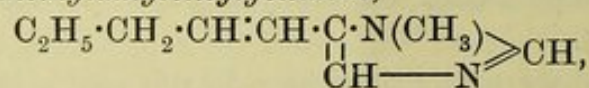
1. 0.114 gave 0.0546 Ag. Ag = 47.9.

2. 0.0364 „ 0.0178 Ag. Ag = 48.8.

$C_6H_{11}O_2Ag$ requires Ag = 48.4 per cent.

The anilide, prepared in the usual way and purified by recrystallisation from ligroin until of constant melting point, melted at 94—95°; *n*-hexoanilide melts at 95°. The acid was therefore *n*-hexoic acid.

The analyses of the pure base and platinichloride, and the products of oxidation, prove that one constituent of this fraction is methylamylglyoxaline, and from the fact that it is formed with 1:4(or 1:5)-dimethylglyoxaline, it may be inferred that the substituent groups occupy the same position in each case. With regard to the more volatile constituent of the fraction yielding butyric acid on oxidation, the analysis of the fraction boiling at 145—160° under 10 mm. pressure would indicate that it has the formula $C_9H_{14}N_2$. In this case it might be regarded as *methylamyleneglyoxaline*,



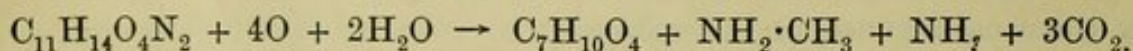
which, with permanganate, would oxidise at the double bond as well as the glyoxaline ring, giving *n*-butyric acid. The unsaturated nature of the compound would also account for its readiness to oxidise. This fraction (b. p. 145—160° under 10 mm. pressure) contains, therefore, 1:4(or 1:5)-*methylamylglyoxaline*, and probably 1:4(or 1:5)-*methylamyleneglyoxaline*.

*iso*Pilocarpine, when distilled with soda-lime, yields ammonia, methylamine, 1-methylglyoxaline, 1:4(or 1:5)-dimethylglyoxaline, 1:4(or 1:5)-methylamylglyoxaline, and probably 1:4(or 1:5)-methylamyleneglyoxaline.

Oxidation of isoPilocarpinolactone.

In order to determine the constitution of dibromo*isopilocarpinic* acid and of *isopilocarpinolactone*, the latter was oxidised with permanganate, and the resulting product treated in the same manner as in the case of *isopilocarpine*, in order to isolate the bases and acids formed.

Five grams of *isopilocarpinolactone* (m. p. 83°) dissolved in water were oxidised with a slight excess (9 grams) of permanganate in 1 per cent. aqueous solution. At 12°, the colour of the permanganate was immediately discharged until the above quantity had been added, when the slight excess remained unchanged. In this respect the lactone differs from *isopilocarpine*, where the colour is not discharged so readily. The amount of oxidising agent used agreed well with the following equation. Calculated 8.3 grams; required 9 grams.



The bases obtained were identified as ammonia and methylamine. The platinichloride of the latter was analysed.

0.109 gave 0.045 Pt. Found Pt = 41.3. Calculated Pt = 41.3 per cent.

The acid was isolated as the ethyl ester, which distilled completely at 160—170° under 20 mm. pressure; titration of this derivative showed that the acid was monobasic and lactonic.

After hydrolysis, 0.3886 ester required for neutralisation 2.2 c.c. *N*-alkali solution cold and 4.0 c.c. hot. Calculated for an acid $C_7H_{10}O_4$ the requisite quantities are 2.1 c.c. and 4.2 c.c. respectively.

On hydrolysis, the acid was obtained as a colourless oil which quickly became solid. The crystals, after crystallisation from hot benzene, melted at 104°, and on analysis:

0.1052 gave 0.2044 CO_2 and 0.0616 H_2O . C = 53.0; H = 6.5.

$C_7H_{10}O_4$ requires C = 53.2; H = 6.3 per cent.

The aqueous solution of the acid was dextrorotatory, and with barium carbonate yielded a barium salt which was analysed with the following result.

0.128 gave 0.066 $BaSO_4$. Ba = 30.3.

$(C_7H_9O_4)_2Ba$ requires Ba = 30.4 per cent.

The acid was therefore pilopic acid.

The oxidation products of *isopilocarpinolactone* with permanganate solution are therefore ammonia, methylamine, and pilopic acid.

Oxidation of Pilocarpine with Potassium Permanganate.

Twenty grams of pure pilocarpine were oxidised with 63 grams of permanganate at the ordinary temperature, and the products of oxidation isolated as described under the oxidation of *isopilocarpine*.

The ethyl ester obtained was distilled under 10 mm. pressure, and the following fractions separated:

1. 165—175° 2. 175—180° 3. Above 180°.

The first fraction was analysed with the following result:

0.128 gave 0.277 CO_2 and 0.0918 H_2O . C = 59.0; H = 8.0.

$C_{10}H_{16}O_4$ requires C = 60.0; H = 8.0 per cent.

These figures are almost identical with those previously obtained by Pinner and Kohlhammer (*Ber.*, 1900, 33, 1424).

When the ester was treated with excess of strong aqueous ammonia, the crystalline diamide of homopilopic acid (m.p. 208°) was obtained.

The second fraction was hydrolysed and the acid obtained titrated; in the cold, 0.42 required 24.4 c.c. normal alkali solution for neutralisation, and, when boiled with excess of alkali and titrated back with acid,

47.6 c.c. : calculated for an acid, $C_8H_{12}O_4$, the requisite quantities are 24.4 c.c. and 48.8 c.c. respectively.

The specific rotation in aqueous solution was determined with the following result :

$\alpha_D = +2.1^\circ$; $l = 1$ dcm. ; $c = 4.78$; $[\alpha]_D = +43.9^\circ$; homopilopie acid has $[\alpha]_D +45.4^\circ$.

The barium salt was prepared in the usual way by neutralisation with barium carbonate :

0.393 gave 0.1914 $BaSO_4$. $Ba = 28.6$.

$(C_8H_{11}O_4)_2Ba$ requires $Ba = 28.6$ per cent.

When treated with ammonia, the third fraction yielded the diamide m. p. 208° , which furnished the following data :

0.0976 gave 0.1834 CO_2 and 0.0764 H_2O . $C = 51.2$; $H = 8.7$.

$C_8H_{16}O_3N_2$ requires $C = 51.1$; $H = 8.5$ per cent.

A determination of its specific rotation gave the following result :

$\alpha_D = +0.2^\circ$; $l = 1$ dcm. : $c = 0.934$; $[\alpha]_D = +21.4^\circ$.

Pinner and Schwarz found for the amide (m. p. 206°) $[\alpha]_D = +20.8^\circ$. The above results prove conclusively that the oxidation product of pilocarpine with permanganate at the ordinary temperature consists almost entirely of homopilopie acid.

Miscellaneous Experiments with isoPilocarpine.

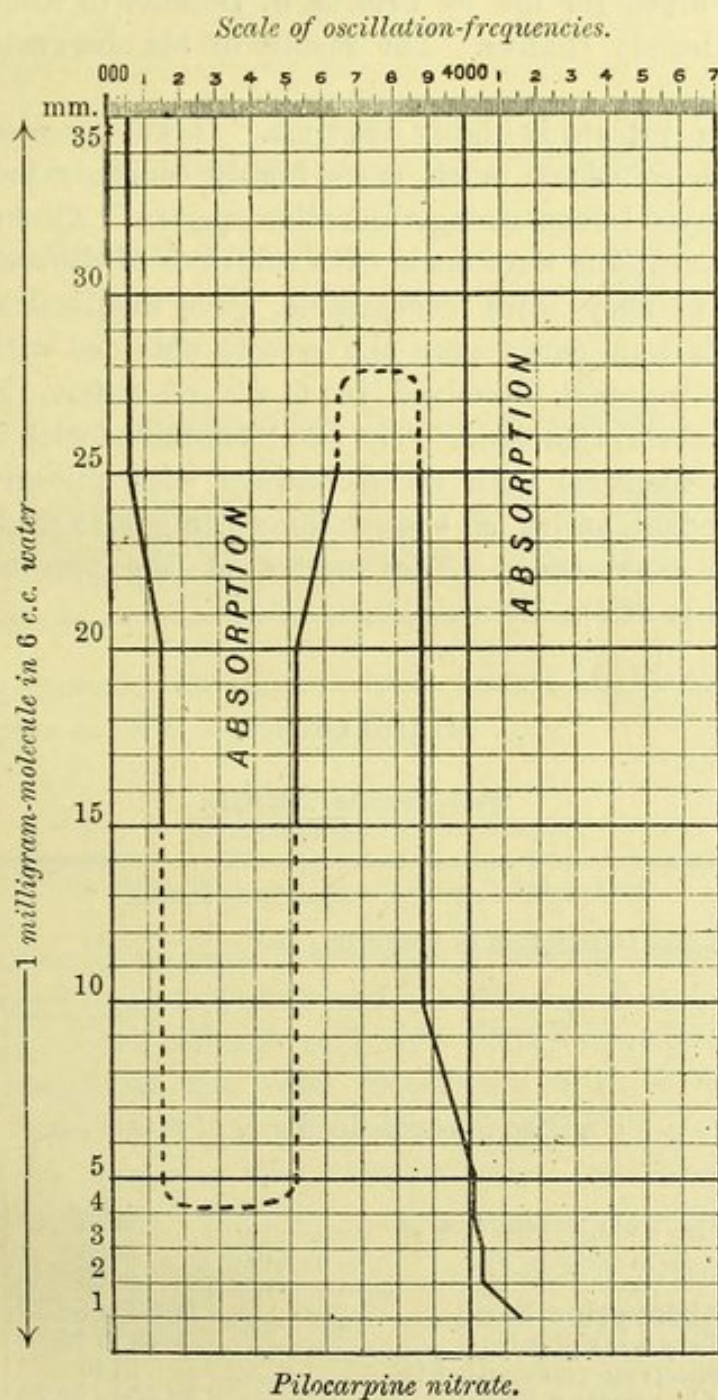
The extraordinary stability of *isopilocarpine* towards reducing agents has already been noticed, even sodium in boiling amyl-alcoholic solution failing to attack it. An attempt was therefore made to reduce it electrolytically by Tafel's method (*Ber.*, 1900, 33, 2209), but this was also unsuccessful.

Attempts were also made to form diacidic salts of *isopilocarpine*, first, by heating with excess of methyl iodide in a sealed tube for 2 hours at 100° , and, secondly, by heating with concentrated hydrochloric acid at 180° , but in both cases only the normal mono-acidic products were obtained.

In view of the suggestion by Pinner and Schwarz that the compounds previously described as methyl*isopilocarpine* derivatives were not such, but *isopilocarpine* methyl compounds, picric acid was added directly to an aqueous solution of *isopilocarpine* methiodide when a crystalline picrate was obtained (m. p. 136°), identical with that previously described as methyl*isopilocarpine* picrate. As no change other than simple replacement of the iodine by the picric acid radical can be assumed, it follows that the substance described as methyl*isopilocarpine*

picrate is really *isopilocarpine methyl picrate* and that *isopilocarpine* contains the :N and not the :NH residue.

A previous attempt to titrate *isopilocarpine* not having given perfectly satisfactory results, the experiment was repeated:



0.1316 when boiled with excess of caustic alkali and titrated back with acid required, 6.8 c.c. decinormal soda for neutralisation, with phenolphthalein as indicator, the calculated amount being 6.3 c.c. *isoPilocarpine* behaved therefore as a normal lactone.

The Absorption Spectra of Pilocarpine Nitrate and isopilocarpine Nitrate.

The absorption spectra of pilocarpine and isopilocarpine have been kindly determined for me by Prof. J. J. Dobbie, to whom I wish to express my hearty thanks. The results of his observations were as follows.

Pilocarpine nitrate is highly diactinic. It was necessary therefore to work with solutions much more highly concentrated than those usually employed in examining absorption spectra. Three independent series of observations were made with solutions of different strengths, and, so far as they were comparable, gave identical results. The measurements and curve give the results obtained with a solution containing 1 mg. mol. dissolved in 6 c.c. of water. There is one well-marked absorption band. The results obtained with isopilocarpine nitrate were identical with those obtained with pilocarpine nitrate; three independent series of observations being also made in the case of the former substance. The spectra of the two nitrates were identical (see p. 452).

MEASUREMENTS.

Pilocarpine Nitrate.

| Thickness of layer of liquid in millimetres. | Description of spectrum. | $1/\lambda$. | λ . |
|--|---|---------------------|---------------------|
| 1 milligram-mol. in 6 c.c. of water. | | | |
| 35 | Spectrum transmitted to | 3053 | 3275 |
| 30 | " " | 3053 | 3275 |
| 25 | " " | 3053 | 3275 |
| | Absorption band | 3053 to 3633 | 3275 to 2752 |
| | Very weak spectrum..... | 3633 to 3880 | 2752 to 2577 |
| 20 and 15 | Spectrum transmitted to | 3140 | 3185 |
| | Absorption band | 3140 to 3520 | 3185 to 2841 |
| | Spectrum | 3520 to 3880 | 2841 to 2577 |
| 10 | Spectrum transmitted to | 3880 | 2577 |
| | Very weak in position of absorption band. | | |
| 5 and 4 | Spectrum transmitted to | 4008 | 2495 |
| | Weak in position of absorption band. | | |
| 3 and 2 | Spectrum transmitted to | 4040 | 2475 |
| 1 | " " | 4133 | 2419 |

Pilocarpine Nitrate (continued).

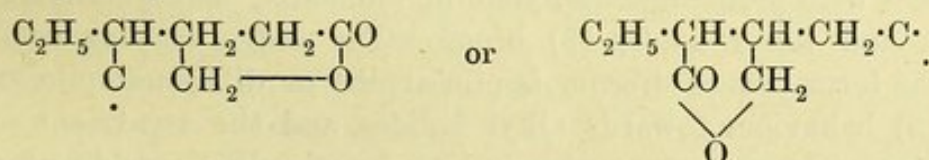
| Thickness of layer of liquid in millimetres. | Description of spectrum. | $1/\lambda$. | λ . |
|---|-------------------------------|---------------|-------------|
| 1 milligram-mol. in 30 c.c. of water. | | | |
| 4 and 3 | Spectrum transmitted to | 4133 | 2419 |
| 2 | " " | 4183 | 2391 |
| 1 | " " | 4250 | 2353 |
| 1 milligram-mol. in 150 c.c. of water. | | | |
| 5, 4 and 3 | Spectrum transmitted to | 4250 | 2353 |
| 2 | " " | 4340 | 2304 |
| 1 | " " | 4370 | 2288 |

The measurements for *isopilocarpine* nitrate are identical with those for *pilocarpine* nitrate.

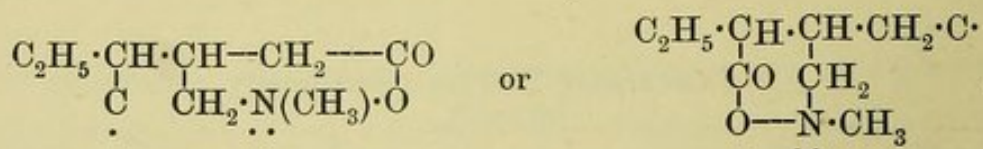
DISCUSSION OF RESULTS.

The Constitution of isoPilocarpine.

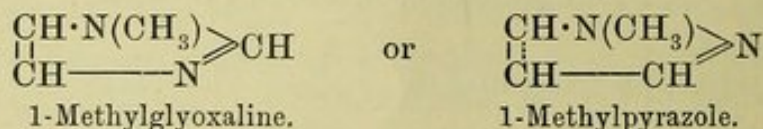
Since *isopilocarpine* on oxidation with potassium permanganate yields the potassium salt of a hydroxy-acid, $C_8H_{14}O_5$, of which homopilocarpic acid, $C_8H_{12}O_4$, is the lactonic acid, and as the constitutional formula of the hydroxy-acid has been determined with a high degree of probability to be $C_2H_5 \cdot CH(CO_2H) \cdot CH(CO_2H) \cdot CH_2 \cdot CO_2H$, it is permissible to assume that *isopilocarpine* contains one of the following complexes:



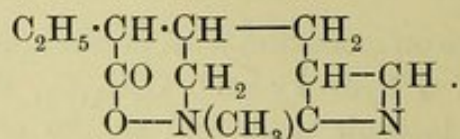
Since a formula containing either of these complexes would yield nomopilocarpic acid on oxidation, it follows that either formula would be equally valid. There is also a third possibility to consider in connection with a formula for *isopilocarpine*, that is the existence of a betaine grouping in the molecule. If this were the case the following type of formula would account for the products of oxidation:



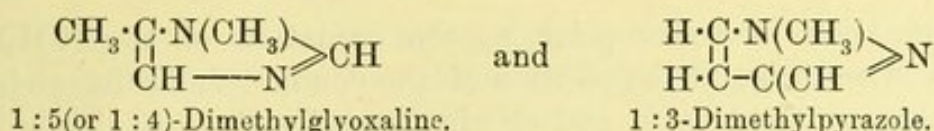
On oxidation the nitrogen atom is split off as methylamine and is replaced by hydroxyl, yielding homopilopic acid. In addition to the existence of one of the above complexes in the molecule the occurrence of the nitrogen atoms as $\text{N}:$ and $:\text{N} \cdot \text{CH}_3$ has been proved, and subtracting these groups from the empirical formula of *isopilocarpine*, $\text{C}_{11}\text{H}_{16}\text{O}_2\text{N}_2$, the condition of two carbon and two hydrogen atoms remains to be explained. Assuming first that the two nitrogen atoms are present in the same complex, I have been able to construct only two possible formulæ for the group to be attached to the homopilopic residue, one being a glyoxaline and the other a pyrazole residue.



The homopilopic residue might be attached to any of the three carbon atoms in the ring by replacement of hydrogen, and the alkaloid would thus be a substituted glyoxaline or pyrazole. If, however, one of the nitrogen atoms, for example, that in the methylamine residue, is quinquevalent, the homopilopic complex must be attached to a ring containing one nitrogen atom, and, on these grounds, the following formula for the alkaloid might be suggested:



Besides these three possibilities there are also many others depending on the point of attachment of the two groups. The reactions of *isopilocarpine* which have been most thoroughly studied are (1) oxidation with permanganate, yielding ammonia, methylamine, homopilopic and lower acids, (2) bromination under varying condition with the formation of dibromo*isopilocarpine* or dibromo*isopilocarpinic acid*, (3) behaviour towards alkyl iodides and the treatment of the quaternary ammonium compounds with caustic alkali, yielding methylamine and the respective alkylamine. These reactions would not enable us to decide between the three types of formulæ previously mentioned. In order to trace the analogy which might exist between *isopilocarpine* and glyoxaline or pyrazole derivatives, the following dimethyl-compounds of the latter have been prepared and their reactions studied (see pp. 465, 467):



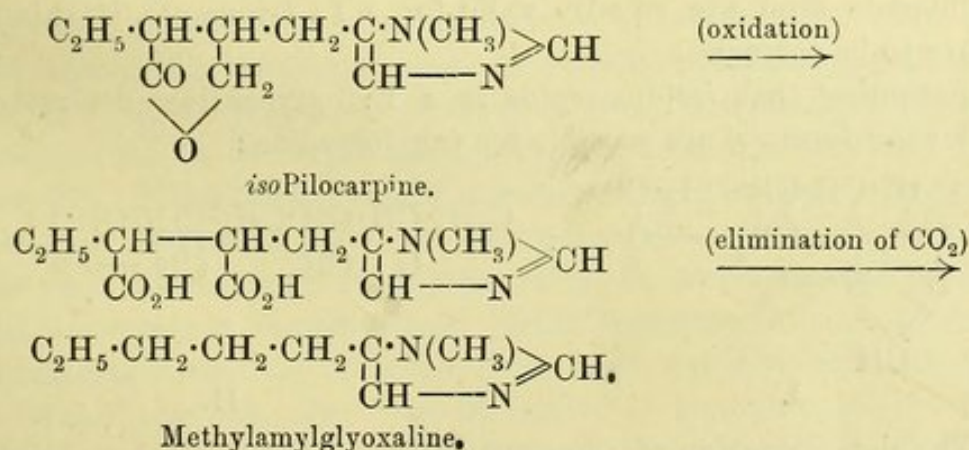
The results of the examination showed a remarkable analogy between the behaviour of *isopilocarpine* and that of dimethylglyoxaline, and a striking dissimilarity between that of *isopilocarpine* and dimethylpyrazole.

The results are shown in the following table:

| Reaction. | Pyrazole. | Glyoxaline. | isoPilocarpine. |
|--|-----------------------------------|--|--|
| Oxidation with permanganate | { Pyrazole carb- oxylic acid } | { Ammonia, methylamine and acetic acid } | { Ammonia, methyl- amine and homo- pilocarpic acid } |
| Bromination | Dibromo-compound | Dibromo-compound | Dibromo-compound |
| { Bromination at 100° } | { Dibromo-compound } | { Acid containing N and Br } | { Dibromo <i>isopilo</i> - carpinic acid } |
| Methiodide with caustic potash at 180° | { Very slight reaction } | { Methylamine and acetic acid } | { Methylamine and homopilocarpic acid } |

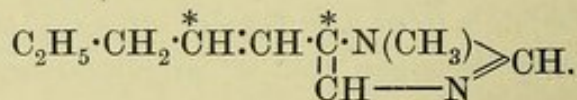
These results amplify and confirm the analogy existing between pilocarpine and glyoxaline derivatives, first pointed out by Pinner and Schwarz (*loc. cit.*), and exclude any formula for pilocarpine or *isopilocarpine* containing a pyrazole ring. The glyoxaline formula for *isopilocarpine* suggested by the above-mentioned analogy receives conclusive proof from the formation of various glyoxaline derivatives by distillation of the alkaloid with soda-lime. The crude product thus formed has been proved to contain 1-methylglyoxaline, 1:4(or 1:5)-dimethylglyoxaline, 1:4(or 1:5)-methylamylglyoxaline and probably 1:4(or 1:5)-methylamyleneglyoxaline together with ammonia and methylamine. Their formation is most readily explained by supposing that the (CH₂OH) group is oxidised to carboxyl with subsequent elimination of carbon dioxide yielding methylamylglyoxaline.

Assuming the following formula for *isopilocarpine*, the change might be thus represented.



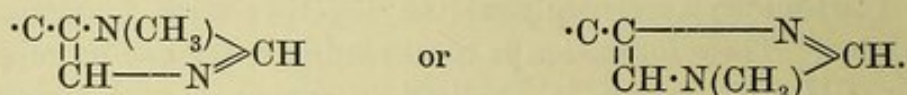
The unsaturated methylamyleneglyoxaline is probably produced by

the elimination of water prior to the oxidation of the (CH_2OH) group, and a change in the position of the double bond thus produced with subsequent oxidation and elimination of carbon dioxide, giving rise to the following glyoxaline.



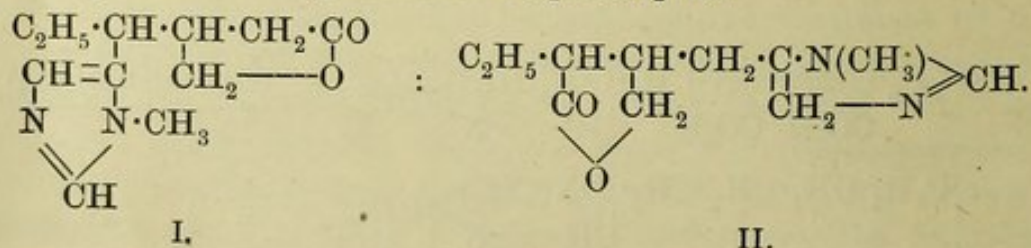
This compound oxidises at both the points marked with an asterisk, yielding butyric and carbonic acids, ammonia, and methylamine. The other glyoxalines, as well as ammonia and methylamine, are produced by further disruption of the molecule and the final fission of the glyoxaline ring itself. It has previously been shown that glyoxaline derivatives are very stable under similar conditions, for example, 2-methylglyoxaline was prepared by passing 1-methylglyoxaline through a red-hot tube (Wallach, *Ber*, 1883, 16, 542). These facts, taken in conjunction with the analogies shown to exist between *isopilocarpine* and glyoxaline derivatives, seem to afford conclusive evidence that *isopilocarpine* is a glyoxaline derivative, and accordingly the betaine formula suggested for *isopilocarpine* must be abandoned. The glyoxaline formula having been adopted, two problems remain for solution: (1) the determination of the point of attachment of the glyoxaline and homopilopic complexes, (2) choice of the appropriate formula for the homopilopic residue.

The identification of the dimethylglyoxaline formed with the 1:4- (or 1:5)-isomeride proves that one of the following complexes must exist in *isopilocarpine*.



Inasmuch as it is impossible at the present time to decide between these formulæ, during the remainder of the discussion it will be assumed that *isopilocarpine* is a 1:5-glyoxaline derivative. The arguments used are equally valid for a 1:4-formula, if this should prove to be correct.

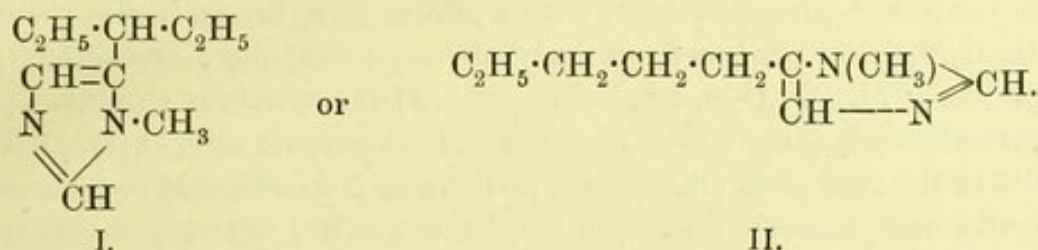
Assuming that *isopilocarpine* is a 1:5-glyoxaline derivative the following formulæ are possible for *isopilocarpine*:



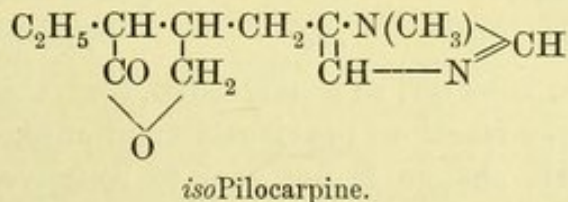
The determination of the constitution of the methylamylglyoxaline formed renders it possible to decide between these two formulæ.

The formation of the methylamylglyoxaline can best be explained, as already indicated, by the oxidation of the (CH₂OH) group to carbonyl and subsequent elimination of carbon dioxide.

The methylamylglyoxaline thus derived from formula I or II will have the following constitution:



These compounds would yield on oxidation either (I) diethylacetic acid or (II) *n*-hexoic acid, besides ammonia and methylamine. The identification of the acidic product as *n*-hexoic acid justifies the adoption of formula II. From the experimental results recorded in this and previous papers and the deductions made therefrom, it is possible to propose the following constitutional formula for *isopilocarpine* with a considerable degree of certainty, although complete proof can be furnished by synthesis alone. The formula given subject to the reservation previously mentioned.



The Constitution of Pilocarpine.

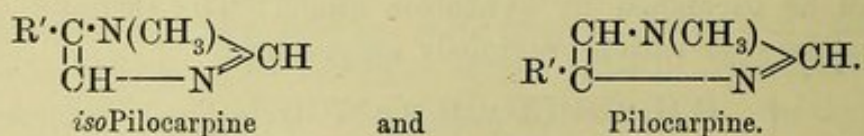
In former papers it was explained that, after having arrived at the constitution of *isopilocarpine*, the more stable of the two alkaloids, it might be possible from a consideration of its formula and a comparison of the two alkaloids to pass to the formula of *pilocarpine*. This procedure seemed also necessary, since in certain reactions, for example, fusion with caustic potash or distillation with soda-lime, the products obtained would be those produced from *isopilocarpine* and not from *pilocarpine*. Since *isopilocarpine* is formed from *pilocarpine* by simple means, such as heating alone or with water, the relationship must be a close one. Furthermore, since *pilocarpine*, by oxidation with permanganate, at ordinary temperatures, yields homopilopic acid, identical in all respects with that obtained from *isopilocarpine*, both alkaloids must contain this complex. The formation of homopilopic acid from *pilocarpine* might be thought to exclude the possibility of stereoisomerism, for the only asymmetric carbon atoms present are those in

the homopilopic complex and the glyoxalines obtained were optically inactive.

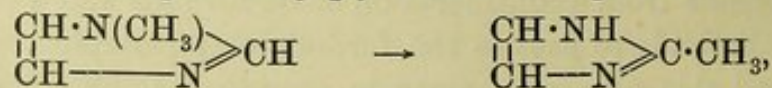
There are also two reactions in which the alkaloids apparently differ, which, as Pinner and Schwarz have pointed out, would favour the view of structural isomerism. These reactions are (1) the action of bromine under pressure, when, with pilocarpine, bromocarpinic acid, $C_{10}H_{15}O_4N_2Br$, is produced, whilst with *isopilocarpine*, dibromo*isopilo*-carpinic acid, $C_{11}H_{14}O_4N_2Br_2$, is formed; (2) the action of chromic acid on pilocarpine leading to the formation of pilocarpoic acid, $C_{11}H_{16}O_5N_2$, whilst in the case of *isopilocarpine*, no definite product could be isolated, and the action seemed to result in the general disruption of the molecule.

If the alkaloids are structural isomerides, the difference must lie in the point of attachment of the homopilopic complex to the glyoxaline ring, since both alkaloids must contain the homopilopic residue, and from the very close relationship of the alkaloids and their method of conversion it is almost certain that both contain a glyoxaline ring.

The relationship would be shown thus, where R' = homopilopic complex:



These formulæ are, however, so nearly alike that they fail to explain the differences in the reactions previously mentioned. The mechanism of such an isomeric change is not easy to conceive, for, as it takes place by heat alone, it is most likely to occur by a migration either of the homopilopic residue to the contiguous carbon atom, or of the methyl group from one nitrogen atom to the other with rearrangement of the double linkings. A migration of the methyl group from the nitrogen to the contiguous carbon atom takes place in the formation of 2-methylglyoxaline by passing 1-methylglyoxaline through a red-hot tube,



but this cannot take place in the conversion of pilocarpine into *isopilocarpine*, since both alkaloids contain the $\text{:N} \cdot \text{CH}_3$ group. The theory of structural isomerism therefore appears improbable.

If the alkaloids are stereoisomerides, this must be due to the asymmetric carbon atoms which occur only in the homopilopic residue. The formation of homopilopic acid from pilocarpine by oxidation can be readily explained when it is considered that the homopilopic acid is produced in the presence of free alkali and purified by the distillation of its ester, both of which factors would conduce to the formation of the stable modification.

With regard to the other two apparent differences, a satisfactory explanation can be offered of at least one of the reactions.

When bromine acts on pilocarpine or *isopilocarpine* under pressure, the crystalline compound isolated in each case is different, but it by no means follows that the reaction does not proceed similarly in both cases. It may be that more than one substance is formed, and that they differ in their ability to crystallise, just as pilocarpine methiodide is amorphous whilst *isopilocarpine* methiodide is crystalline. Further, I have previously shown (Trans., 1901, 79, 598) that there is experimental evidence that the reactions are similar, and that dibromopilocarpinic acid might be present in the mother liquors from which bromocarpinic acid has crystallised, just as bromo*isocarpinic* acid might be present in the filtrates from which dibromo*isopilocarpinic* acid has been obtained. The yield of crystalline acid obtained is in harmony with this suggestion. The reaction of the alkaloids with chromic acid has not been sufficiently studied to permit of any deductions being made in support of either theory.

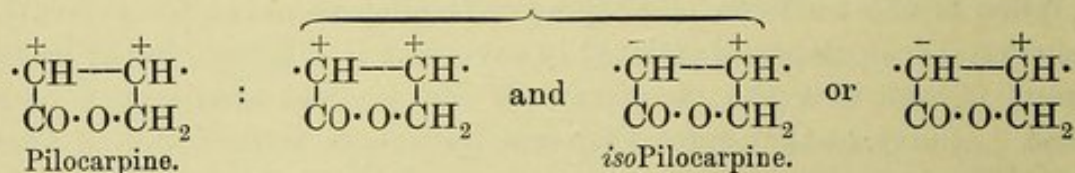
A consideration of the specific rotation of pilocarpine and its derivatives affords support both for the theory of the stereoisomerism of the alkaloids and also for the constitutional formula proposed. In the cases of pilocarpine, *isopilocarpine*, homopilopie acid, and pilopie acids it has been noted that the specific rotation of the substances in alkaline solution is much less than in aqueous solution. This is in harmony with the general rule of the specific rotation of lactones in alkaline and aqueous solution, and the gradual change in the specific rotation of an aqueous solution of pilocarpine, from $+100^\circ$ to $+77^\circ$ is undoubtedly due to the opening of the lactone ring.

Three possible explanations as to the nature of the stereoisomerism may be briefly mentioned.

1. The fact that the conversion of pilocarpine into *isopilocarpine* is accompanied by a change in the specific rotation from $+100.5^\circ$ to $+42.8^\circ$ suggests that partial racemisation may be the cause of the isomeric change. Of the two asymmetric carbon atoms in *isopilocarpine*, one is attached to a carboxyl residue, whilst the other is attached to a methylene group. In accordance with general views on this subject, it may be assumed that the first of these asymmetric carbon atoms undergoes inversion, and that the optical activity of *isopilocarpine*, homopilopie and pilopie acids is due to the carbon atom attached to the $-\text{CH}_2-$ group. Many examples of this type of change could be quoted, but it will be sufficient to refer to the example given by Pasteur of the change of quinine into quinicine.

2. That pilocarpine contains two non-equivalent asymmetric carbon atoms, and that in the formation of *isopilocarpine* complete inversion of the asymmetric carbon atom attached to the carboxyl residue takes

place. The relation between pilocarpine and *isopilocarpine* might then be represented as follows :



In the latter case, the specific rotation of *isopilocarpine* would be the difference between the rotatory powers of the two asymmetric carbon atoms, and *isopilocarpine* would be incapable of resolution.

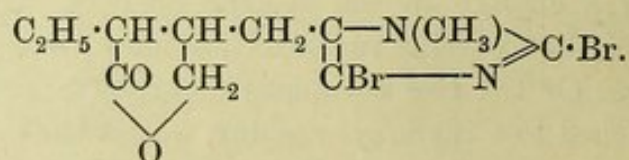
3. That, in addition to either of the above causes of isomerism, the bases may be also geometrical isomerides, corresponding to *cis*- and *trans*-modifications. The difference in the melting points of the salts and in the stability of pilocarpic and *isopilocarpic* acids (Pinner and Schwarz, *Ber.*, 1902, 35, 201) tends to support this view.

These conclusions are also supported by the fact that the alkaloids, pilocarpine and *isopilocarpine*, give absolutely identical absorption spectra, and it has been shown (Hartley, *Phil. Trans.*, 1885, ii, 471) that stereoisomeric alkaloids give identical spectra, whilst any considerable difference in structure is accompanied by a corresponding difference in the absorption spectra.

In view of all these facts, it seems most probable that pilocarpine and *isopilocarpine* are stereoisomerides, and must therefore be represented by the same structural formula.

Formulae of various Derivatives of Pilocarpine and isoPilocarpine.

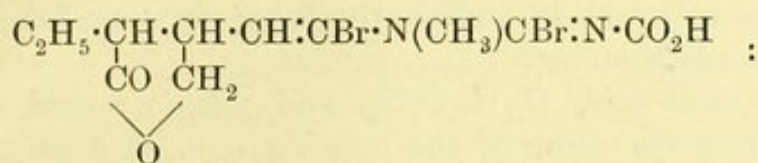
Dibromo-pilocarpine and isoPilocarpine.—From the analogy with the glyoxalines examined there can be no doubt that substitution takes place in the glyoxaline ring, and the constitutional formulae of each of these substances may be written :



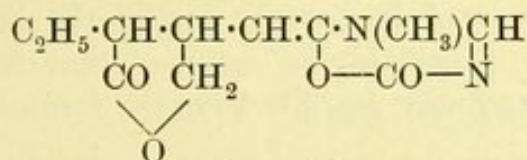
Dibromoisopilocarpinic Acid and isoPilocarpinolactone.—The constitution of these two substances can be proposed with a great degree of certainty from the formation of ammonia, methylamine, and pilopic acid by the oxidation of *isopilocarpinolactone* and from the formation of pilopic acid by the action of sodium and alcohol on *dibromoisopilocarpinic acid* (*Trans.*, 1901, 79, 592).

The formation of pilopic acid proves the existence of the pilopic complex in these substances, and the oxidation must therefore have taken place in the glyoxaline ring.

The following formulæ are proposed :

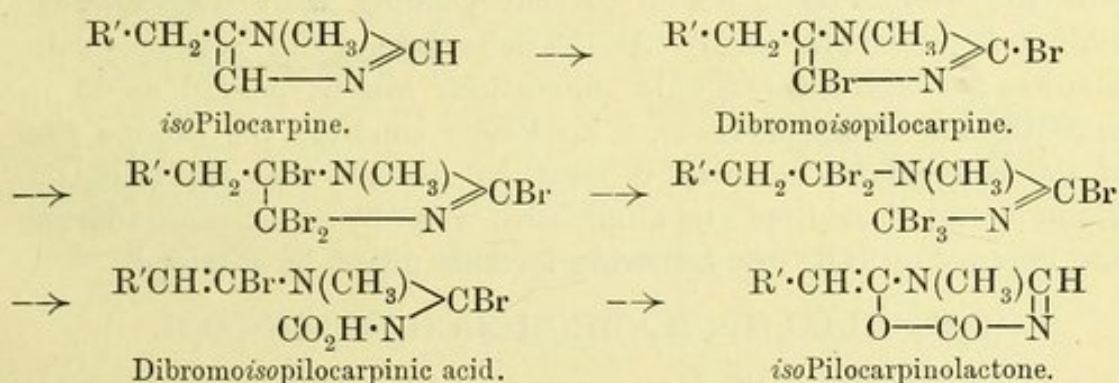


Dibromoisopilocarpinic acid.

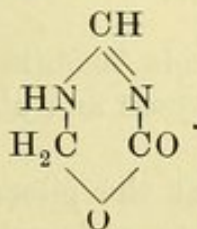


*iso*Pilocarpinolactone.

The mode of formation of these substances may be explained by assuming that bromination first takes place with formation of dibromoisopilocarpine, which unites with excess of bromine with disruption of the double bond and formation of a tribromo-acid, this product then losing HBr, yielding dibromoisopilocarpinic acid. The stages in the reaction may be expressed in the following manner, where R' = the pilopic residue.



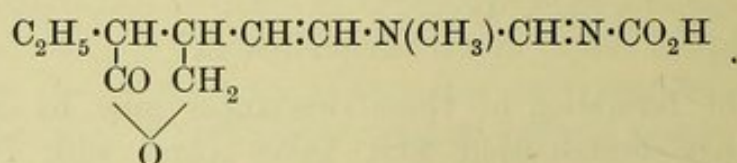
These formulæ explain perfectly the formation of pilopic instead of homopilopic acid on oxidation and the greater readiness to oxidise with permanganate, as well as the formation of ammonia and methylamine and the other characters of these compounds. If these formulæ are correct, and they are strongly supported by experimental evidence, then *isopilocarpinolactone* must be regarded as the first member of a new type of ring compounds of which the parent substance would be



Preliminary experiments on the action of bromine under pressure on dimethylglyoxaline (p. 467) indicate that a similar reaction occurs with other derivatives of glyoxaline, and this change will be further

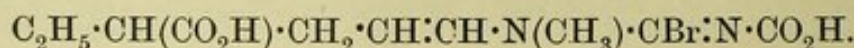
studied with these substances, as *isopilocarpinolactone* cannot be conveniently obtained in sufficiently large amount for a complete study of the reaction.

isoPilocarpinic acid, $C_{11}H_{16}O_4N_2$, and *pilopinic acid*, $C_8H_{11}O_4N$, obtained during the course of the investigation, were only isolated in very small amounts, and the first not even characterised. Having regard to its method of formation, during the bromination of *isopilocarpine*, it may reasonably be assumed that it is related to *isopilocarpinolactone* and may possibly have the formula



I can offer no suggestion as to the constitution of *pilopinic acid*, and the very small yield obtained precludes its further examination.

Bromocarpinic acid, $C_{10}H_{15}O_4N_2Br$, was obtained by Pinner and Kohlhammer by the action of bromine under pressure on *pilocarpine*, the reaction being similar to that yielding with *isopilocarpine*, *dibromoisopilocarpinic acid*. As the behaviour of this acid on oxidation has not been studied, only suggestions can be offered as to its constitution. Since, however, it no longer contains the lactone ring of the homopilopie complex, it must be assumed that the (CH_2OH) group has been oxidised and eliminated, when by an alternate addition and removal of HBr the following formula might be obtained.

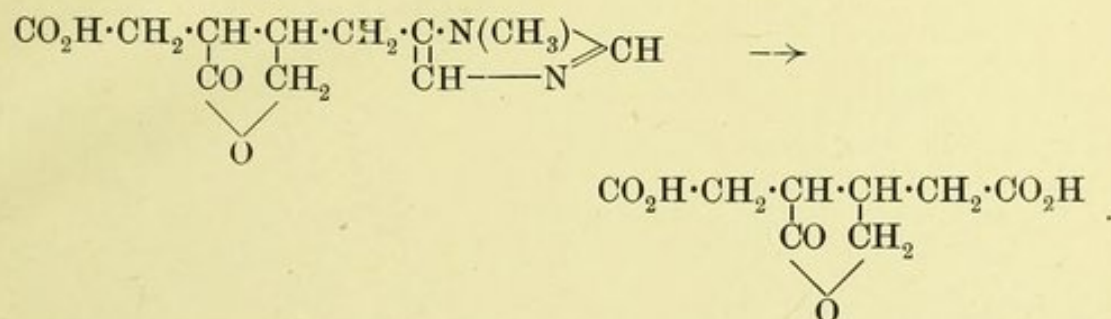


Pilocarpoic acid, $C_{11}H_{16}O_5N_2$, and *pilomalic acid*, $C_7H_{12}O_5$, were obtained by Pinner and Kohlhammer, the former by the oxidation of *pilocarpine* with chromic acid, and the latter by oxidation of the *pilocarpoic acid* with permanganate. The only information available about the first of these acids is that it is dibasic towards baryta, but neither the acid nor its barium salt were obtained crystalline. The second acid is crystalline, dibasic, laevorotatory, and apparently non-lactonic, although the simple experiment of titration does not appear to have been made.

The formation of these acids is quite inexplicable if the formula proposed for *pilocarpine* by myself and also by Pinner and Schwarz is correct.

These authors suggest that the *pilocarpoic acid* is formed by the oxidation of a methyl group to carboxyl, but a consideration of the formula for *pilocarpine* shows that this explanation is quite untenable. There are only two methyl groups in *pilocarpine*: (1) the methyl of the homopilopie residue; (2) the methyl of the methyl-

amine residue. If the former were oxidised, pilocarpoic acid on oxidation with permanganate should yield a dibasic and lactonic acid having the formula $C_8H_{10}O_6$, the glyoxaline ring undergoing oxidation in the usual way:



This, however, is not the case, as pilomalic acid, $C_7H_{12}O_5$, is dibasic. If the methyl of the methylamine residue were oxidised, then pilocarpoic acid on oxidation with permanganate should yield homopilopic acid, which again does not occur. Furthermore, both of these reactions are, *a priori*, extremely unlikely.

The explanation of Pinner and Schwarz is therefore quite untenable, and in the absence of any information as to the reactions of these acids no suggestions as to their constitution can be offered.

In conclusion, it may be pointed out that pilocarpine and *isopilo-*carpine are the first and only known members of a new class of alkaloids, containing a glyoxaline ring.

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