The resolution of hyoscine and its components, tropic acid and oscine / by Harold King.

Contributors

King, Harold.
Wellcome Chemical Research Laboratories.

Publication/Creation

London : Wellcome Chemical Research Laboratories, 1919.]

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XXXVII.—*The Resolution of Hyoscine and its Components, Tropic Acid and Oscine.*

By Harold King.

Hyoscine or scopolamine, the tropyl ester of oscine, and one of the group of Solanaceous alkaloids, receives varied and extensive use in medicine, and has on that account attracted the attention of many workers both from the chemical aspect and from the medicinal.

During the last few years, the subject has acquired an additional interest and importance as a result of the recognition that oscine (or scopoline), the basic hydrolytic product, is capable of resolution into its constituents *d*- and *l*-oscine. This follows from the resolution of benzoyloscine by Tutin in 1910 (T., **97**, 1793) and from the partial elucidation of the structural formula of oscine by Schmidt and Hess and their co-workers, whereby it seems certain that oscine, unlike tropine, is not internally compensated. Apart from these two separate results, and in spite of the vast amount of work that has been carried out on oscine and hyoscine, there was nothing known which definitely pointed to this conclusion. Since tropic acid is also capable of resolution, and Gadamer (*Arch. Pharm.*, 1901, **239**, 294) has shown that *l*-tropic acid may be obtained by hydrolysis of *l*-hyoscine, it follows that tropyloscine (hyoscine) might exist in ten, or possibly eleven, stereoisomeric forms consisting of four optically active, four partially racemic, two fully racemic, and one double racemic compound. The problem is in some ways analogous to that presented by the ten tetrahydroquinaldinomethylenecamphors obtained by Pope and Read (T., 1913, **103**, 1515), but with this difference, that in the case of the hyoscines an approach is at present (apart from the rarity of the materials) not possible from the synthetic side, as hyoscine has as yet not been obtained by the esterification of oscine by tropic acid. The elucidation of the chemistry of the isomeric hyoscines and the correct allocation of the medicinal properties to be attributed to each is of considerable moment for both sciences.

Our knowledge of the hyoscines as revealed by previous workers, so far as it appertains to the present subject, may be very briefly summarised.

Naturally occurring *laevo*-hyoscine has been obtained in a state of purity by several workers, and in the form of its well-crystallised hydrobromide is a commercial product. In the plant, it is apparently accompanied to some extent by *dl*-hyoscine, from which

it can be separated by fractional crystallisation of the hydrobromides. Racemic hyoscine base, which can also be obtained from *l*-hyoscine by the action of alkalis, forms two hydrates, one crystallising with two molecules of water, and known as atroscine (Hesse), the other with one molecule of water. Two attempts to resolve racemic hyoscine are recorded, the first by Schmidt (*Arch. Pharm.*, 1898, **236**, 56), who found that the salt with thiocyanic acid did not separate into two mechanically separable crystalline enantiomorphs, as was the case with racemic lupanine (Schmidt and Davis, *Arch. Pharm.*, 1897, **235**, 196), the second by Gadamer (*Arch. Pharm.*, 1901, **239**, 294), who states that the quinic acid and *d*-mandelic acid salts of *dl*-hyoscine are very readily soluble and possess little crystallising power, and are therefore not suitable for the resolution of hyoscine.

The primary mode of attack adopted in the present investigation is based on some unpublished preliminary experiments by Tutin, who showed that *l*-hyoscine of commerce forms a soluble, deliquescent salt with *d*-bromocamphorsulphonic acid which can be recrystallised from dry ethyl acetate containing alcohol, and also that when *l*-hyoscine is racemised by alkali, the product as a salt with the same acid can likewise be recrystallised, and the successive fractions of salt so obtained show a progressive variation in rotatory power. The author here gratefully acknowledges his indebtedness to Mr. Tutin for placing these results at his disposal.

A quantity of crystalline hydrobromides of feeble lævorotatory power, obtained as a by-product in the manufacture of the therapeutically valuable *l*-hyoscine, was fractionally crystallised as a salt with *d*-α-bromo-π-camphorsulphonic acid, when the first salt to be isolated was *meteloidine bromocamphorsulphonate* (m. p. 224—227°). This salt crystallises exceedingly well, and contains *i*-meteloidine (compare Pyman and Reynolds, T., 1908, **93**, 2077). On continuing the fractionation, d-*hyoscine bromocamphorsulphonate* was obtained in a state of purity. It melted at 159—160°, and crystallised in glistening, acicular needles.

d-*Hyoscine hydrobromide* was prepared from it, and found to crystallise with three molecules of water and to possess a specific rotatory power $[\alpha]_D + 23{\cdot}1°$, which corresponds with a value $[\alpha]_D + 33{\cdot}4°$ for the *d*-hyoscinium ion. For comparison, some of the maximum values recorded by previous observers for the *laevo*-salt are tabulated below.

l-*Hyoscine Hydrobromide.*

	$[\alpha]_D$ anhydrous salt.	$[\alpha]_D$ ionic value.
Schmidt[1]	−25·7°	−32·5°
Hesse[2]	−25·9	−32·7
Thoms and Wentzel[3]	−25·76	−32·5
Carr and Reynolds[4]	−26·0	−32·8
Willstätter and Hug[5]	−26·0	−32·8
King[6]	−25·9	−32·7

d-*Hyoscine Hydrobromide.*

King[7]	+26·3°	+33·2°

[1] *Arch. Pharm.*, 1892, **230**, 207. [2] *J. pr. Chem.*, 1901, [ii], **64**, 353.
[3] *Ber.*, 1901, **34**, 1023. [4] T., 1910, **97**, 1330.
[5] *Zeitsch. physiol. Chem.*, 1912, **79**, 146. [6] P. 504. [7] P. 503.

These values show that the purified *l*-hyoscine hydrobromide of previous workers and the *d*-hyoscine hydrobromide now isolated for the first time represent one pair out of the eleven possible stereoisomeric hyoscines.

On mixing equal weights of pure *d*- and *l*-hyoscine hydrobromides and recrystallising the mixture from water, *dl*-hyoscine hydrobromide, also crystallising with three molecules of water and in a form indistinguishable from the active components, was obtained. It differs from the active components in that it very readily effloresces and in that the base obtained from it is crystalline and contains two molecules of water. For the further characterisation of these three related compounds, their *aurichlorides*, *auribromides*, and *picrates* were prepared. The results are shown in the following table:

	l-Hyoscine.	*d*-Hyoscine.	*dl*-Hyoscine.
Base—			
Appearance	Syrup.	Syrup.	Prisms.
H_2O	—	—	$2H_2O$
M. p.	—		38—40°
Hydrobromide—			
Appearance	Large rhombic tablets.	Large rhombic tablets.	Large rhombic tablets.
H_2O	$3H_2O$	$3H_2O$	$3H_2O$
M. p. (anhydrous)	193—194°	193—194°	181—182°
$[\alpha]_D$ (anhydrous)	−25·9°	+26·3°	—
Picrate—			
Appearance	Slender matted needles.	Slender matted needles.	Needles.
M. p.	187—188°	187—188°	173·5—174·5°

	l-Hyoscine.	*d*-Hyoscine.	*dl*-Hyoscine.
Aurichloride—			
Appearance	Needles, both edges serrated.	Needles, both edges serrated.	Needles, one edge serrated.
M. p.	204—205°	204—205°	214—215°
Auribromide—			
Appearance	Chocolate-red leaflets.	—	Chocolate-red leaflets.
M. p.	187—188°	—	209—210°

Some of these call for further remark in view of the results of previous observers. The racemic base crystallising with $2H_2O$ is probably a purer form of Hesse's atroscine (*Ber.*, 1896, **29**, 1776), which melted at 36—37°, and was obtained by fractionally crystallising commercial samples of hyoscine hydrobromide. It was obtained on one other occasion by Gadamer (*Arch. Pharm.*, 1898, **236**, 382), who gives the melting point 37—38°. The *dl*-hyoscine hydrobromide agrees in its properties with those recorded by Hesse (*Annalen*, 1899, **309**, 75; *J. pr. Chem.*, 1901, [ii], **64**, 353).

The picrates have been recommended for identifying the mydriatic alkaloids by Carr and Reynolds (T., 1912, **101**, 949), who describe *l*-hyoscine and *dl*-hyoscine picrates as slender, matted needles melting respectively at 180—181° and 193°. Neither of these melting points is in agreement with the results here recorded, which, however, do find support in the only two other recorded melting points of the picrates: Schmidt (*Arch. Pharm.*, 1894, **232**, 409) describes *l*-hyoscine picrate as melting at 187—188°, and Finnemore and Braithwaite (*Pharm. J.*, 1912, **89**, 136), from an examination of commercial samples of hyoscine hydrobromide of varying rotatory power, give figures which show that *l*-hyoscine picrate melts at 187—188° and *dl*-hyoscine picrate at 174—175°.

The aurichlorides have been described by almost all previous workers on the hyoscines, but there is complete disagreement between the recorded melting points. This is all the more surprising, as several workers have had in hand pure *l*-hyoscine hydrobromide. To quote only two of these, Schmidt (*Arch. Pharm.*, 1910, **248**, 641) states that *l*-hyoscine aurichloride of various origins has previously been shown to melt when quite pure at 210—214°, whereas Hesse (*J. pr. Chem.*, 1901, [ii], **64**, 274) states that after many crystallisations he never found any salt to melt above 198°. The melting points now recorded for the *d*- and *l*-hyoscine aurichlorides are for salts prepared in two different ways and recrystallised to constant melting point. In substantial agreement with these values, Thoms and Wentzel (*Ber.*, 1901, **34**, 1023) give 204°, and Finnemore and Braithwaite (*loc. cit.*) record

several almost pure commercial *l*-hyoscine hydrobromides as furnishing aurichlorides melting at 200—204°.

Tropic Acid. The Acid Constituent of Hyoscine.

As has already been stated, Gadamer showed that *l*-hyoscine on hydrolysis with the base tropine gave *l*-tropic acid. This crude acid, on purification by recrystallisation from water, gave *l*-tropic acid melting at 125—126°, and having a specific rotatory power in water $[\alpha]_D$ −71·8°. Gadamer regarded this as optically pure, since Ladenburg and Hundt (*Ber.*, 1889, **22**, 2591) record the value $[\alpha]_D$ +71·4° for pure *d*-tropic acid melting at 127—128°.

Instead of employing a base for the hydrolysis, *l*-hyoscine has now been hydrolysed by boiling with dilute hydrochloric acid, when a crude *l*-tropic acid (m. p. 125—127°, $[\alpha]_D$ −70·5°) was obtained, which on recrystallisation gave *l*-tropic acid melting at 127—128° and having $[\alpha]_D$ −76° in water. As this rotation was numerically considerably greater than the value recorded by the aforementioned workers, it was necessary to repeat the resolution of tropic acid.

A comparison of the results obtained with those of previous investigators is shown in the following table:

	Ladenburg and Hundt.	Amenomiya.[1]	King.
Quinine d-*tropate*—			
M. p.	186—187°	189—190°	191·5—192·5°
$[\alpha]_D$ 95 per cent. alcohol	—	—	−114°
Quinine l-*tropate*—			
M. p.	178°	184—185°	185—186°
$[\alpha]_D$ 95 per cent. alcohol	—	—	−141°
d-*Tropic acid*—			
M. p.	127—128°	126—127°	128—129°
$[\alpha]_D$ water	—	—	+81·6°
$[\alpha]_D$ alcohol	+71·4°	+71·3°	+71·8°
l-*Tropic acid*—			
M. p.	123°	126°	128—129°
$[\alpha]_D$ water	—	−72·7°	−81·2°
$[\alpha]_D$ alcohol ...	−65·1°	—	—

[1] *Arch. Pharm.*, 1902, **240**, 501.

It is at once seen that Ladenburg and Hundt's value $[\alpha]_D$ +71·4° is the value in alcoholic solution, Gadamer having regarded it as the value in water, as the aforementioned investigators were not

very explicit, merely stating that the specific rotatory power was +71·4° in solutions of various concentration.

As previous workers appeared to have experienced some difficulty in obtaining pure quinine *l*-tropate from the mother liquors, a variant was made by converting the recovered partly resolved *l*-tropic acid into the quinidine salt. Further, by use of the two stereoisomeric alkaloids quinine and quinidine, but commencing the resolution with quinidine, 55 per cent. of pure quinidine *l*-tropate was first isolated, then an 80 per cent. yield of pure quinine *d*-tropate, and simultaneously a 14 per cent. yield of pure quinine *l*-tropate. On reverting to quinidine, a further 19 per cent. yield of quinidine *l*-tropate was obtained. In this way, approximately 84 per cent. of the tropic acid was resolved into its constituents. It would, however, be probably an advantage, other factors being equal, to start the resolution with quinine and follow with quinidine, since experiment showed that, starting with quinine, 66 per cent. of quinine *d*-tropate was obtained pure, and, as stated above, starting with quinidine only, 55 per cent. of quinidine *l*-tropate could be separated.

It is interesting to note that previous attempts to use quinine and quinidine for the resolution of externally compensated acids, in the above sense, have not always been successful. Whereas Fischer, Scheibler, and Groh (*Ber.*, 1910, **43**, 2022) found that in the resolution of formyl-β-alanine, quinine separated the lævo-component and quinidine the dextro-, Scheibler and Wheeler (*Ber.*, 1911, **44**, 2686) found that in the resolution of *dl*-leucine the same two alkaloids always gave the lævo-acid first. This was also the experience of McKenzie (T., 1899, **75**, 969) in the resolution of mandelic acid.

Oscine. The Basic Hydrolytic Product of Hyoscine.

There are numerous instances recorded in the literature of the hydrolysis of *l*-hyoscine by alkalis, but the basic hydrolytic product, oscine, $C_8H_{13}O_2N$, was invariably found to be devoid of optical activity, even in the presence of borates or strong acids (Gadamer, *Arch. Pharm.*, 1901, **289**, 322). The only occasion on which *l*-hyoscine has been hydrolysed by acids is recorded by Hesse (*Annalen*, 1892, **271**, 100), who carried out the hydrolysis with concentrated hydrochloric acid in a sealed tube at 80—100°. This furnished the base, oscine, but there is no record of its polarimetric examination.

To decide this matter, pure *l*-hyoscine has now been hydrolysed by boiling with excess of 10 per cent. hydrobromic acid, the change

of rotation being followed polarimetrically. When hydrolysis was complete, the *l*-tropic acid was removed by extraction with ether, and the residual solution of oscine hydrobromide was found to be devoid of optical activity. As Tutin had shown that benzoyl-*d*-oscine on hydrolysis with hydrochloric acid gave *d*-oscine, the hydrolysis of *l*-hyoscine was repeated, using hydrochloric acid. Again the oscine hydrochloride solution was inactive. As it was conceivable that the benzoylation of oscine might have effected some fundamental change in the configuration of oscine, whereby the benzoylated product became externally compensated, and therefore capable of resolution, it was necessary to prove that oscine itself could be resolved into its constituents, *d*- and *l*-oscine.

Several salts of oscine with optically active acids were prepared and examined. The salt with Reychler's camphorsulphonic acid was not obtained crystalline, but with *d*-α-bromo-π-camphorsulphonic acid a markedly crystalline salt was obtained, which melted at 232—233°. This salt, however, proved to be a partial racemate. With *d*-α-bromo-β-camphorsulphonic acid, a very readily soluble, crystalline salt was isolated, but beyond recording a single rotation, it was not followed further, as *d*-tartaric acid was found to be eminently suitable for the resolution of oscine.

The separation of *dl*-oscine into its two pure enantiomorphs can be effected by use of *d*-tartaric acid alone, the acid salts being used for this purpose in aqueous solution. The more sparingly soluble salt, which separated almost pure after two crystallisations, is l-*oscine* d-*hydrogen tartrate monohydrate* (m. p. 173—174°, anhydrous), which crystallises magnificently in clear tablets or octahedra. Employing 14 grams of oscine in combination with a like quantity of *d*-tartaric acid, between 70 and 80 per cent. of this component was separated with no great difficulty. The d-*oscine* d-*hydrogen tartrate* contained in the mother liquors can be obtained pure either by isolation as the *monohydrate*, a very readily soluble, metastable salt melting below 100°, or, preferably, as the stable anhydrous salt (m. p. 167—168°). The proportion of this salt obtained in a state of purity is largely a function of time, as it crystallises very slowly, but uncommonly well, in hexagonal-shaped tablets from the cold, syrupy mother liquors.

l-*Oscine picrate*, *hydrochloride*, and *base* were obtained without bringing into contact with alkali at any stage, but this was found afterwards to be an unnecessary precaution, as *l*-oscine is not racemised by boiling with 10 per cent. acid or alkali, and only partly by saturated baryta at 150°.

d-*Oscine picrate*, *hydrochloride*, and *base* were prepared in the usual manner by liberating the base from the hydrogen tartrate

by a strong alkali. The properties of these salts as compared with the *dl*-oscine salts are shown in the following table:

	d-Oscine.	*l*-Oscine.	*dl*-Oscine.
Base—			
Appearance	Needles.	Needles.	Needles or tablets.
M. p.	109—110°	109—110°	109—110°
$[\alpha]_D$ water	+54·8°	−52·4°	—
Picrate—			
Appearance	Dimorphous rhombs and needles.	Dimorphous rhombs and needles.	Flattened rhombs.
M. p.	237—238°	237—238°	237—238°
Hydrochloride—			
Appearance	Warts composed of prisms. Very deliquescent.	Warts composed of prisms. Very deliquescent.	Warts composed of prisms (anhydrous). Tablets (hydrated).
M. p.	273—274°	273—274°	273—274°
$[\alpha]_D$ in water of basic ion	+24·0°	−24·2°	—

It is noteworthy that the active and *dl*-isomerides have the same melting points, and mixtures of the active with the *dl* show no depression of the melting point. In the case of the bases, the melting-point curve is thus of the same type as is found for the camphoroximes.

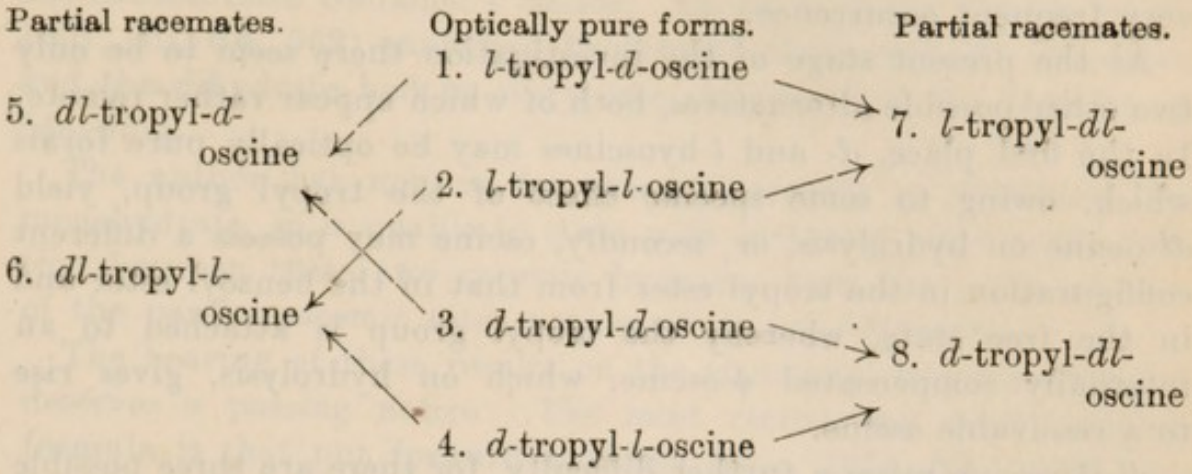
By hydrolysis of benzoyl-*d*-oscine, Tutin (*loc. cit.*) obtained a value for the *d*-oscinium ion of $[\alpha]_D$ +129°,* which he regarded as only approximate. As this was very different from the value recorded above, it was necessary to repeat the resolution of benzoyl-oscine. Pure benzoyl-*d*-oscine hydrochloride was obtained having a value $[\alpha]_D$ +13·4° for the benzoyl-*d*-oscinium ion, in agreement with the value +12·9° calculated from the rotation of the bromo-camphorsulphonate. This hydrochloride was submitted to hydrolysis by acids and alkalis. In both cases the result was the same, a solution being obtained which, on removal of benzoic acid, gave values $[\alpha]_D$ +26·0° and $[\alpha]_D$ +25·8°, by acid and alkali hydrolysis respectively, for the *d*-oscinium ion. Moreover, the hydrochloride and picrate were isolated from the product of acid hydrolysis, and the properties were in agreement with the *d*-oscine salts obtained by the tartaric acid resolution of oscine.

Interpretation of Results.

The question now arises, which of the eight possible optically active stereoisomeric hyoscines do *d*- and *l*-hyoscine represent?

* Tutin gives the value +77·7°, having overlooked the loss of the benzoyl group.

The various possibilities are shown in the following table, the centre column representing optically pure forms, which, combined, as shown by the arrows, yield partially racemic forms:



Of these, 1 to 6 are at once excluded, since *l*-hyoscine on hydrolysis with acid or alkali gives *l*-tropic acid and *dl*-oscine, whereas benzoyl *d*-oscine under similar conditions yields optically pure *d*-oscine. On these grounds, *l*- and *d*-hyoscine, represented by 7 and 8, are therefore partially racemic esters, *l*-hyoscine being a molecular combination of *l*-tropyl-*d*-oscine and *l*-tropyl-*l*-oscine, whilst *d*-hyoscine is a similar combination of *d*-tropyl-*d*-oscine and *d*-tropyl-*l*-oscine.

The known inactivation of *l*-hyoscine by alkalis would, on this basis, simply consist in the change of configuration of the tropyl portion of the molecule, probably through the intermediary of the

$$\mathrm{Ph{\cdot}\overset{\displaystyle CH_2{\cdot}OH}{\overset{|}{C}}{\cdot}\overset{\displaystyle H}{\overset{|}{C}}O_2R} \rightleftharpoons \mathrm{Ph{\cdot}\overset{\displaystyle CH_2{\cdot}OH}{\overset{|}{C}}{:}C\begin{matrix}OH\\OR\end{matrix}} \rightleftharpoons \mathrm{Ph{\cdot}\overset{\displaystyle CH_2{\cdot}OH}{\overset{|}{C}}{\cdot}\overset{\displaystyle CO_2R}{\overset{|}{C}}H}$$

enolic form, and each constituent ester of the partial racemate should give rise to a new ester.

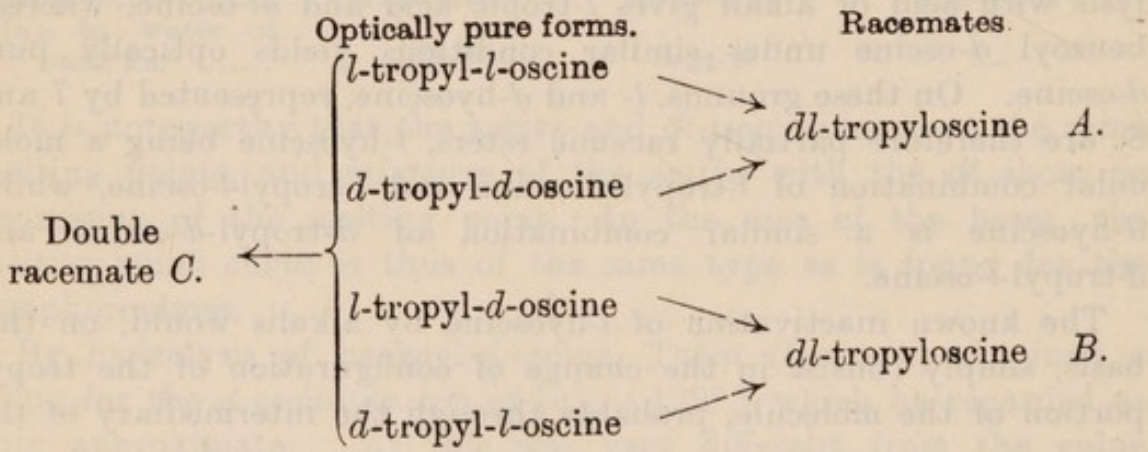
In support of this, some work, which is reserved for future publication, on the re-resolution of racemised *d*-hyoscine has resulted in the isolation of two esters only, *d*- and *l*-hyoscine, which is not surprising, as these, being partial racemates, would contain the four expected optically pure forms.

As opposed to the partial racemic ester nature of *d*- and *l*-hyoscines may be cited the rarity of the occurrence of partial racemates in nature, and the novel behaviour of the hyoscines towards *d*-bromocamphorsulphonic acid, which, so far as *d*-hyoscine is concerned, only resolves *dl* or weakly active hyoscine as far as the partially racemic ester stage. Although this behaviour is, as far as it has been possible to ascertain, unique, it is only necessary to

recall that in the early days of the application of Pasteur's methods of resolution the formation of partially racemic salts was only rarely observed, whereas at the present time it is recognised as of very frequent occurrence.

At the present stage of the investigation there seem to be only two other possible alternatives, both of which appear rather remote. In the first place, *d*- and *l*-hyoscines may be optically pure forms which, owing to some specific effect of the tropyl group, yield *dl*-oscine on hydrolysis, or, secondly, oscine may possess a different configuration in the tropyl ester from that in the benzoyl ester and in the free state, whereby the tropyl group is attached to an internally compensated ψ-oscine, which on hydrolysis, gives rise to a resolvable oscine.

dl-Hyoscine raises a further difficulty, for there are three possible *dl*-hyoscines, as is shown by the following arrangement:



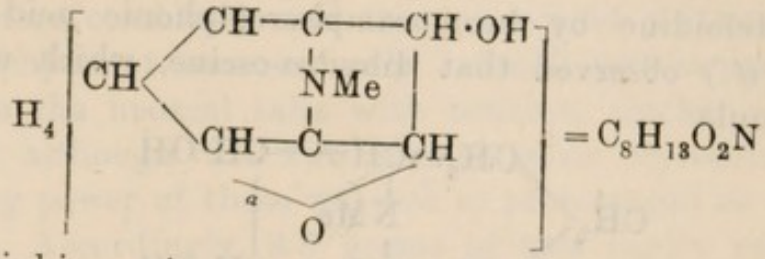
The optically pure forms may be combined in pairs, as indicated, to form two different simple racemates, *A* and *B*, or all four forms may be combined to form a double racemate, *C*. On the acceptation of the partial racemic ester nature of *d*- and *l*-hyoscines, *dl*-hyoscine hydrobromide crystallising with three molecules of water, and obtained by crystallising together equal weights of *d*- and *l*-hyoscine hydrobromides, constitutes a double racemic salt, the absence of any indication of the presence of another salt and the identical crystalline appearance of *d*- or *l*-hyoscine hydrobromide and this salt supporting this view. Moreover, the base crystallising with $2H_2O$ is the base contained in this *dl*-salt, as both give the same picrate.

As has already been indicated in the opening paragraph, there is another hydrate of racemic hyoscine base, containing $1H_2O$ and melting at 56—57°. It was first obtained by Schmidt (*Arch. Pharm.*, 1894, **232**, 409), was re-examined by Luboldt (*ibid.*, 1898, **236**, 11), and more fully investigated by Gadamer (*ibid.*, 382). The last-named investigator showed that the dihydrate can readily

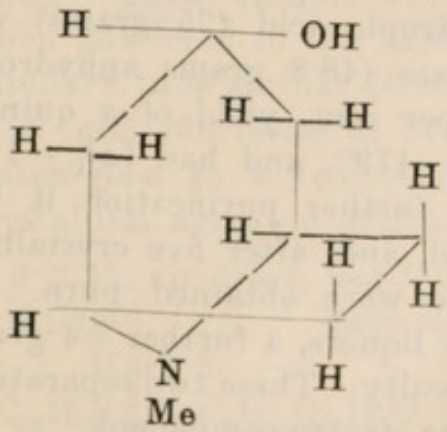
be converted into the monohydrate, but the reverse change was only effected with difficulty. Both hydrates were afterwards described by Hesse (*J. pr. Chem.*, 1901, [ii], **64**, 353), who could not substantiate Gadamer's claims. In reply, Kunz-Krause (*ibid.*, 1901, [ii], **64**, 569) examined Gadamer's three-year-old specimens, and the dihydrate had in every case changed into the base (m. p. 54—55°).

The author has not, so far, been successful in obtaining this monohydrate, so is unable to state with certainty what is the relation between these two racemic hydrates from the point of view of the partial racemic ester nature of *d*- and *l*-hyoscine.

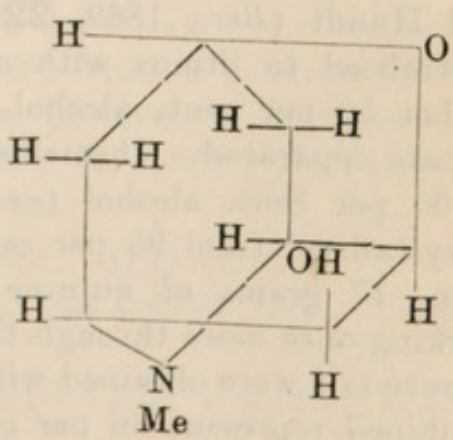
The bearing of these results on the structural formula of oscine deserves a passing notice. The most recent and most complete formula is that put forward by Hess (*Ber.*, 1918, **51**, 1007), who ascribes to oscine the structure



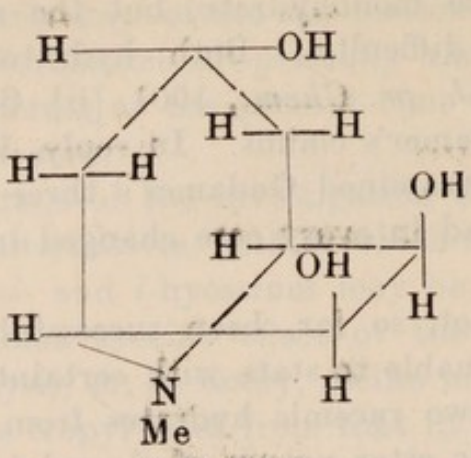
where the linking *a* is regarded as being probably attached to one of the carbon atoms of the piperidine nucleus. The experiments on the stability of the active oscines towards racemising agents certainly support this linking. Pyman and Reynolds (T., 1908, **98**, 2077) have pointed out the close relationship which exists between tropine, oscine, and teloidine, all of which contain eight carbon atoms and a hydroxyl group in the molecule. Moreover, their acyl derivatives are found together in *Datura meteloides*. The author is tempted to make the suggestion that, like tropine, the oxygen atom in question in oscine is attached to the γ-position in the piperidine ring. Oscine would therefore be the internal anhydride of a trihydroxytropine, and this trihydroxytropine may be teloidine. The formulæ suggested are:



Tropine.

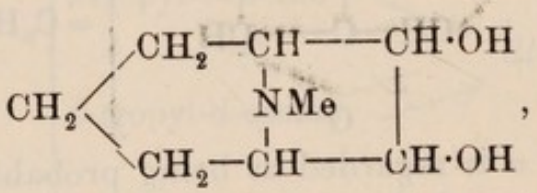


d- or *l*-Oscine ?



Teloidine ?

Teloidine would thus be internally compensated, and in support of this view may be cited the occurrence of meteloidine (tiglyl-teloidine), in nature devoid of optical activity, and the non-resolution of meteloidine by bromocamphorsulphonic acid. Further, Hess (*loc. cit.*) observed that dihydro-oscine, which undoubtedly has the formula



readily produces a silver mirror when treated with ammoniacal silver nitrate solution. The author finds that teloidine and meteloidine, unlike oscine, also readily reproduce this characteristic of dihydro-oscine, the reducing property being probably associated with the adjacent hydroxyl groups, as is found in tartaric acid.

Experimental.

Resolution of Tropic Acid.

With Quinine.—Following the method described by Ladenburg and Hundt (*Ber.*, 1889, **22**, 2591), tropic acid (25 grams) was neutralised to litmus with quinine base (48·8 grams anhydrous) in hot 50 per cent. alcohol. A 49 per cent. yield of a quinine tropate separated. It melted at 176—179°, and had $[\alpha]_D$ −126° in 95 per cent. alcohol ($c=1$). For further purification it was recrystallised from 95 per cent. alcohol, and, after five crystallisations, 17 grams of quinine *d*-tropate were obtained pure. By working once more through the mother liquors, a further 7·4 grams of pure salt were obtained without difficulty. These two separations combined represent 66 per cent. of the dextro-component.

Quinine *d*-tropate crystallises from 8 parts of boiling alcohol in

groups of radiating needles. In water it is very sparing soluble. It melts at 191·5—192·5° (195·5—196·5° corr.):

0·1035, dried at 100°, gave 0·2706 CO_2 and 0·0633 H_2O. C = 71·3; H = 6·8.

$C_{20}H_{24}O_2N_2,C_9H_{10}O_3$ requires C = 71·0; H = 7·0 per cent.

The specific rotation was determined in 95 per cent. alcohol.

$c = 1·01$; $l = 2$-dcm.; α_D −2°18′; $[\alpha]_D$ −113·8°.

In absolute alcohol the rotation is smaller.

$c = 1·013$; $l = 2$-dcm.; α_D −2°6·4′; $[\alpha]_D$ −104·0°.
$c = 1·002$; $l = 2$-dcm.; α_D −2°5·4′; $[\alpha]_D$ −104·3°.

As previous observers appeared to have experienced some difficulty in obtaining quinine *l*-tropate in a state of purity, no attempt was made at this stage to isolate this salt. The mother liquors were therefore combined, and the tropic acid containing excess of the lævo-component was recovered. Small test samples were converted into the neutral salts with brucine, cinchonine, and quinidine, but although the two former gave crystalline salts, the crystallising power of these was not so pronounced as the salt with quinidine. Accordingly, 3·5 grams of this partly resolved tropic acid were crystallised as quinidine salt, when 4·2 grams of quinidine *l*-tropate were obtained of constant specific rotatory power.

Resolution with Quinidine and Quinine.—*dl*-Tropic acid (15 grams) was neutralised with quinidine dissolved in 50 c.c. of 95 per cent. alcohol. On keeping, 22 grams of crystalline material separated. It was obviously a mixture, and had $[\alpha]_D$ +151° in 95 per cent. alcohol ($c = 2$). After four crystallisations, the specific rotation was constant at $[\alpha]_D$ +145°, and the collected quinidine *l*-tropate amounted to 5·5 grams.

Quinidine l-*tropate* crystallises from 95 per cent. alcohol, in which it is soluble in its own weight at 80°, in clusters of well-formed, stout, transparent prisms containing one molecule of water. These exhibit a pronounced heliotrope triboluminescence when powdered in the dark. The air-dried salt when heated in a capillary tube shrinks from about 110°, liquefies between 118° and 120°, and effervesces at 124°. When, however, it is exposed on a watch-glass to a temperature of 90°, it melts completely, and crystallises again on addition of alcohol:

0·2038, air-dried, lost 0·0069 at 100°. $H_2O = 3·4$.
0·1029 ,, gave 0·2590 CO_2 and 0·0672 H_2O. C = 68·7; H = 7·3.

$C_{20}H_{24}O_2N_2,C_9H_{10}O_3,H_2O$ requires $H_2O = 3·5$; C = 68·5; H = 7·1 per cent.

Its specific rotation was determined in 95 per cent. alcohol, and is dependent on the concentration.

$c=0{\cdot}979$; $l=2$-dcm.; $\alpha_D+2°55{\cdot}2'$; $[\alpha]_D+149{\cdot}1°$.
$c=1{\cdot}995$; $l=2$-dcm.; $\alpha_D+5°46{\cdot}5'$; $[\alpha]_D+144{\cdot}7°$.

The mother liquors were worked up further, and gave an additional 7·2 grams, $[\alpha]_D+146°$. This is approximately a 55 per cent. yield of quinidine *l*-tropate. As the liquors now showed no tendency to crystallise at all readily, they were combined, and the tropic acid was recovered by use of ether and hydrochloric acid (10 per cent.). On now crystallising as the quinine salt, after three crystallisations, 14·8 grams of quinine *d*-tropate were obtained pure, $[\alpha]_D-114°$ ($c=1$), and a further 2·8 grams with $[\alpha]_D-115°$. The first mother liquors on concentration deposited quinine *l*-tropate as a homogeneous crop (4·8 grams) of glistening, triangular plates having $[\alpha]_D-139°$, and melting at 184—185°. It was recrystallised twice from 95 per cent. alcohol, the specific rotation remaining constant at $[\alpha]_D-140{\cdot}7°$ and the melting point at 185—186°, but the form of the crystals changed to needles very similar in appearance to quinine *d*-tropate.

Quinine *l*-tropate melts at 185—186° (189—190° corr.). It is very much more readily soluble in hot alcohol than is quinine *d*-tropate. The diverse crystalline forms described above do not constitute a case of dimorphism, but merely represent extreme crystalline forms. By suitably modifying the conditions of crystallisation, a series of intermediate forms may be obtained consisting of more or less elongated trapezoidal plates. Unlike quinine *d*-tropate, this salt exhibits a very faint triboluminescence, the intensity of which is not visibly affected by the form of the crystals:

0·1083, dried at 100°, gave 0·2817 CO_2 and 0·0668 H_2O. C = 71·0; H = 6·9.
$C_{20}H_{24}O_2N_2,C_9H_{10}O_3$ requires C = 71·0; H = 7·0 per cent.

The tropic acid contained in the residual liquors was reconverted into the quinidine salt, when 4·3 grams of quinidine *l*-tropate were obtained, having $[\alpha]_D+145°$. The residual solution was not further examined.

By the use of the two bases quinidine and quinine, there were thus isolated in an approximate state of purity 88 per cent. of quinine and quinidine *l*-tropates and 80 per cent. of quinine *d*-tropate. The proportion of tropic acid resolved is 84 per cent.

Quinidine *d*-tropate was not isolated, but, on keeping in the ice-chest, a small crop of white, woolly needles separated from the

mother liquors (together with quinidine *l*-tropate), which was probably this salt in an impure condition.

d-*Tropic Acid.*

Pure quinine *d*-tropate (16 grams) was acidified with 50 c.c. of 5 per cent. hydrochloric acid and completely extracted with purified ether. The crude acid so obtained (5·1 grams) melted at 127—128°, and had $[\alpha]_D$ +77·2° in water ($c=1$). On recrystallisation from water, the melting point rose to 128—129°, and the rotation to $[\alpha]_D$ +79°. After two more crystallisations, the melting point remained unchanged, but the rotation rose to $[\alpha]_D$ +81·6°. The yield was 3·1 grams.

d-Tropic acid crystallises from water in delicate, lustrous scales, which become transformed on keeping in contact with the solution into elongated prisms of hexagonal cross-section. Both forms melt at 128—129° (129—130° corr.) and are anhydrous:

0·2014 was equivalent to 11·9 c.c. *N*/10-baryta.

M.W. = 169. $C_9H_{10}O_3$ requires M.W. = 166.

The specific rotation was determined in alcohol and in water.

In water:

$c=1·027$; $l=2$-dcm.; α_D +1°40·6′; $[\alpha]_D$ +81·6°.

In absolute alcohol:

$c=0·997$; $l=2$-dcm.; α_D +1°24·2′; $[\alpha]_D$ +70·3°.

$c=2·472$; $l=2$-dcm.; α_D +3°33·1′; $[\alpha]_D$ +71·8°.

The specific rotation of the ion was determined by dissolving 0·200 gram of *d*-tropic acid and 0·0638 gram of anhydrous sodium carbonate in water and making up to 20 c.c. The dissolved carbon dioxide was not removed:

$l=2$-dcm.; α +1°22·9′; $[\alpha]_D$ for ion +69·4°; $[M]_D$ for ion +114·7°.

Gadamer (*Arch. Pharm.*, 1901, **239**, 294) has previously noted a fall of rotation of *l*-tropic acid on converting into a salt, but has not followed it quantitatively.

l-*Tropic Acid.*

From Quinidine l-*Tropate.*—Four grams of pure quinidine *l*-tropate, on treatment with hydrochloric acid (10 per cent.) and extraction with ether, gave 1·35 grams of *l*-tropic acid, which, after three crystallisations from water, gave 0·5 gram melting at 128—129° (129—130° corr.). The specific rotatory power was determined in water, and was slightly less than that of the purest *d*-tropic acid:

$c=0·995$; $l=2$-dcm.; α_D −1°37′; $[\alpha]_D$ −81·2°.

From Quinine l-*Tropate.*—5·8 Grams of this salt gave 2·0 grams of *l*-tropic acid, which was recrystallised four times from water, giving 1·35 grams melting at 128—129°, and with a specific rotation −81·2°:

$c=1·002$; $l=2$-dcm.; α_D −1°37·6′; $[\alpha]_D$ −81·2°.

l-Tropic acid prepared in this way had the same general properties as the dextro-acid. It is very sparingly soluble in cold benzene, but freely so in cold methyl ethyl ketone or ethyl acetate. From the latter solvent, it crystallises exceedingly well in clear tablets:

0·1975 was equivalent to 11·72 c.c. *N*/10-baryta .

M.W. = 168. $C_9H_{10}O_3$ requires M.W. = 166.

The Resolution of Oscine.

Partial Racemate with d-α-*Bromo-π-camphorsulphonic Acid.*—Two and a-half grams of oscine were converted into this salt, which was very conveniently recrystallised from absolute alcohol. The first crop of crystals weighed 4·9 grams, melted at 232°, and gave $[\alpha]_D$ +58·8° in water ($c=2$). It was recrystallised twice more from absolute alcohol, yielding, finally, 3·6 grams melting at 232—233°. The specific rotation determined in water was practically unchanged:

$c=2·001$; $l=2$-dcm.; α_D +2°22·4′; $[\alpha]_D$ +59·3°; $[M]_D$ +276·7°.

The value for the molecular rotation 276·7° is in good agreement with the molecular ionic value 278·7 for bromocamphorsulphonic acid (Pope and Read, T., 1910, **97**, 2200).

dl-*Oscine* d-α-*bromo-π-camphorsulphonate* crystallises exceedingly well from absolute alcohol in clear, diamond-shaped plates. Ten parts by volume of boiling absolute alcohol are required to dissolve one part by weight of the salt. It melts at 232—233° (237—238° corr.):

0·0995, dried at 100°, gave 0·1703 CO_2 and 0·0526 H_2O. C = 46·69; H = 5·91.

$C_8H_{13}O_2N,C_{10}H_{15}O_4BrS$ requires C = 46·34; H = 6·05 per cent.

Behaviour with d-α-*Bromo-β-camphorsulphonic Acid.*—Six and a-half grams of oscine were combined with an equivalent of *d*-α-bromo-β-camphorsulphonic acid. The salt could not be obtained crystalline either from water or from a mixture of ethyl acetate and absolute alcohol. A very concentrated solution of the salt in absolute alcohol, however, crystallised as a cake of needles on keeping for a prolonged time in the ice-chest. It was too readily soluble for systematic fractionation from absolute alcohol, and the addition of dry ethyl acetate unexpectedly prevented crystallisa-

tion. The first crop of crystals from absolute alcohol was collected, and weighed 8·7 grams. It melted at 150—155°, and its specific rotation was determined in water:

$c=2·00$; $l=2$-dcm.; α_D +2°27·4′; $[\alpha]_D$ +61·4°; $[M]_D$ +286·3°.

This product was recrystallised from absolute alcohol, but in the meantime tartaric acid had effected the resolution of oscine quite simply, so the investigation of the above salt was discontinued.

With Camphor-β-sulphonic Acid.—Attempts to crystallise this salt were ineffective.

Resolution by d-*Tartaric Acid.*—*dl*-Oscine (13·9 grams) was converted into its *d*-hydrogen tartrate by addition of 13·5 grams of *d*-tartaric acid in aqueous solution. The solution was concentrated to a low bulk, and gave 13·8 grams of a salt crystallising in hexagonal plates and with a specific rotation $[\alpha]_D$ +3·5° in water. After one more crystallisation, it gave 10·2 grams and had $[\alpha]_D$ +1·1°. This value was not appreciably altered by subsequent repeated crystallisation, and represents the optical constant of the salt *l*-oscine *d*-hydrogen tartrate.

l-*Oscine* d-*hydrogen tartrate* crystallises with one molecule of water of crystallisation in large and clear octahedra. Very often these have a flattened appearance, and, more rarely, one-half the faces may be almost entirely suppressed, with the formation of tetrahedra. Unbroken crystals melt at 134° with effervescence, but when powdered partly melt at about 130° and gradually liquefy up to 160°. The anhydrous material melts at 173—174° (176·5—177·5° corr.). It is readily soluble in cold water, but the crystals can be washed with 50 per cent. alcohol with little loss. From dilute alcoholic solutions, this salt tends to separate as an oil:

0·3126, dried at 105°, lost 0·0181. $H_2O=5·8$.

$C_8H_{13}O_2N,C_4H_6O_6,H_2O$ requires $H_2O=5·6$ per cent.

0·1159, dried at 100°, gave 0·1996 CO_2 and 0·0690 H_2O. C=47·0; H=6·7.

$C_8H_{13}O_2N,C_4H_6O_6$ requires C=47·2; H=6·3 per cent.

The specific rotation was determined in water:

$c=2·007$; $l=2$-dcm.; α_D +2·56′; $[\alpha]_D$ +1·06°.

The average value, for nine different samples of the pure salt, of $[\alpha]_D$ was +1·29°, the extremes being +0·93° and +1·56°. Taking this average value for $[\alpha]_D$, the molecular rotation $[M]_D$ is calculated as +4·18°, and employing Landolt's value (*Ber.*, 1873, **6**, 1075) for the molecular rotation of ammonium hydrogen tartrate,

$+42{\cdot}84°$, the value for the *l*-oscinium ion is $[M]_D -38{\cdot}66°$, whence $[\alpha]_D -24{\cdot}7°$.

On continuing the fractionation of the mother liquors, 71 per cent. of the *l*-oscine *d*-hydrogen tartrate present was isolated in a state of purity. The separation was materially accelerated by inoculation of the less mobile solutions, followed by addition of alcohol in insufficient amount to precipitate an oil. The residual solutions, now relatively rich in *d*-oscine *d*-hydrogen tartrate, were concentrated to a syrup, and, on allowing to remain in a desiccator exposed to a dehydrating agent, crystallised as a striated mass of crystals. These were collected, freed from the adhering syrupy mother liquor, first by suction and then by very limited use of 50 per cent. alcohol as a washing agent. The salt was a monohydrate, and gave $[\alpha]_D +23{\cdot}7°$. It was recrystallised from water, and separated under similar conditions as a felted mass of needles. These now gave $[\alpha]_D +27{\cdot}3°$ (anhydrous).

d-*Oscine* d-*hydrogen tartrate monohydrate* melts from 55° to 65°, forming a meniscus at the latter temperature. It readily effloresces when exposed to the atmosphere, and when dehydrated in a vacuum over sulphuric acid loses its water of crystallisation. The anhydrous material still melts at 55—65°. This is probably the melting point of an amorphous form, as, on keeping, it acquires the melting point of the crystalline anhydrous salt, namely, 163—165° (see below).

Three different samples of the salt were analysed for their water content. The first, representing a freshly collected salt, gave the following result:

0·4502, dried over H_2SO_4, lost 0·0320. $H_2O = 7{\cdot}1$;

and a salt which showed some signs of efflorescence gave the following:

0·2023 lost 0·0091. $H_2O = 4{\cdot}5$.

$C_8H_{13}O_2N,C_4H_6O_6,H_2O$ requires $H_2O = 5{\cdot}6$ per cent.

On keeping for some time, this salt had completely effloresced:

0·1180, dried at 100°, lost nil.

0·1180, dried at 100°, gave 0·2055 CO_2 and 0·0649 H_2O.

C = 47·5; H = 6·15.

$C_8H_{13}O_2N,C_4H_6O_6$ requires C = 47·2; H = 6·3 per cent.

The specific rotation of the dehydrated salt was determined in water:

$c = 0{\cdot}949$; $l = 2$-dcm.; $\alpha_D +31{\cdot}1'$; $[\alpha]_D +27{\cdot}3°$.

When the hydrated salt is washed with absolute alcohol, it is transformed into a white, crystalline powder, which is the

anhydrous salt and the stable form at the ordinary temperature. When crystallised from water, the anhydrous salt separates from a syrupy solution very slowly in large, hexagonal-shaped tablets, which, unlike the hydrated salt, can be washed freely with 50 per cent. alcohol. If a syrupy solution is inoculated with a trace of both forms, hydrated and anhydrous, the hydrated form crystallises first, filling the liquid space, and, on keeping, disappears entirely, being replaced by the stable, anhydrous form. For the isolation of pure *d*-oscine *d*-hydrogen tartrate, the latter form is the more convenient. The process is, however, very slow, owing to the solubility of *d*-oscine *d*-hydrogen tartrate and the slow velocity of crystallisation from viscous solutions.

d-*Oscine* d-*hydrogen tartrate* melts at 167—168° (170—171° corr.).

The specific rotation was determined in water and for a salt which had been crystallised to constant rotation:

$c = 1{\cdot}016$; $l = 2$-dcm.; $\alpha + 34'$; $[\alpha]_D + 27{\cdot}87°$; $[M]_D + 85{\cdot}17°$.

This gives a value $+42{\cdot}3°$ for the molecular rotation of the *d*-oscinium ion and $[\alpha] + 27{\cdot}10°$. This is somewhat greater numerically than the value $[\alpha]_D - 24{\cdot}7$ obtained by a similar calculation for the *l*-oscinium ion. As this is beyond the limits of experimental error, it is probably another example of the phenomenon first drawn attention to by Pope and Read (T., 1912, **101**, 760), who show conclusively that the molecular rotatory power in aqueous solution of certain salts of the type *l*-base *d*-acid is in agreement with the value calculated from the separate ions, but that the combination *d*-base *d*-acid gives an abnormal value.

l-*Oscine Picrate*.—Six grams of pure *l*-oscine *d*-hydrogen tartrate were added to a boiling saturated solution of 4·25 grams of picric acid in 80 c.c. of water. As the solution cooled, the major portion of the salt crystallised in long needles, but when only luke-warm a denser form appeared in the shape of small, modified rhombs. The yield was 6·35 grams and the melting point 237° (decomp.). The combined product was recrystallised from 35 c.c. of hot water, and, on removing the source of heat, separated at once in long, glistening needles. These were collected while the solution was still warm, the filtrate continuing to deposit solely needles for some time, and then rhombs. The filtrate was heated to dissolve all the crystals, and when cold only deposited the rhomb-like form of crystal, which closely resembles *dl*-oscine picrate. The yield of needles was 4·95 grams, melting at 237—238° (decomp.) (242·5—243·5° corr.), whilst the rhombs amounted to 0·95 gram, and also melted at 237—238° (decomp.). Both forms are

anhydrous, and either form when mixed with *dl*-oscine picrate, which itself also melts at 237—238°, shows no depression of the melting point. At the ordinary temperature, the needle form of picrate is certainly the unstable one, as is readily shown by adding a drop of saturated picric acid solution to a few small crystals of *l*-oscine *d*-hydrogen tartrate and rubbing with a glass rod. The crystals dissolve instantly, and a homogeneous crop of needles first makes its appearance, followed quickly by minute rhombs, and in a short time the needles will have entirely disappeared, their disintegration and solution being readily followed with the aid of a microscope. This behaviour is useful as a test as to whether one is dealing with active or *dl*-oscine salts, since *dl*-oscine picrate has always been observed to separate in small, flattened rhombs.

l-*Oscine Hydrochloride*.—Four grams of *l*-oscine picrate (needle form) were decomposed by shaking with three molecular proportions of 5 per cent. hydrochloric acid, and the picric acid was removed by ether. The solution of the *l*-oscine hydrochloride was completely dehydrated by repeated evaporation to dryness with absolute alcohol, leaving, finally, a white, crystalline powder, which was dissolved in 10 c.c. of boiling absolute alcohol. On keeping, *l*-oscine hydrochloride separated in aggregates of small prisms in the form of warts; a few isolated prisms were also present. The product was collected, and amounted to 1·4 grams. It melted and decomposed at 273—274° (281—282° corr.). A mixture with *dl*-oscine hydrochloride (m. p. 273—274°) also melted at the same temperature. Unlike *dl*-oscine hydrochloride, the *laevo*-salt is very highly deliquescent. A direct comparison of the two was made by exposing a few crystals of each on watch-glasses to the atmosphere. In a few minutes, the *laevo*-salt had completely liquefied, whilst the *dl*-salt was apparently unaffected. On keeping for an hour, however, the latter showed signs of deliquescence, and the deliquesced salt recrystallised in well-formed tablets melting partly at about 100°, and probably representing the monohydrated *dl*-oscine hydrochloride described by Luboldt (*Arch. Pharm.*, 1898, **236**, 18).

The specific rotation of *l*-oscine hydrochloride was determined in water, employing a salt which had been dried at 100°:

$c = 0{\cdot}997$; $l = 2$-dcm.; $\alpha = -23{\cdot}6'$; $[\alpha]_D$ $-19{\cdot}71°$; $[M]_D$ $-37{\cdot}76°$;

whence $[\alpha]_D$ for the *l*-oscinium ion is $-24{\cdot}2°$, whereas the value calculated from the molecular rotation of *l*-oscine *d*-hydrogen tartrate was $-24{\cdot}7°$.

l-*Oscine Hydrochloride from* l-*Oscine Picrate* (*Rhombs*).—As has been indicated above, *dl*-oscine picrate and *l*-oscine picrate melt at the same temperature, and the stable modification of

l-oscine picrate crystallises very similarly to *dl*-oscine picrate. It was therefore necessary to prove that this stable form of *l*-oscine picrate did actually contain the active base. Accordingly, 0·5 gram of *l*-oscine picrate (rhombs) was converted as quantitatively as possible by means of ether and three molecular proportions of *N*/10-hydrochloric acid into *l*-oscine hydrochloride. The solution was concentrated somewhat and made up to 20 c.c. In a 2-dcm. tube the observed rotation was $\alpha_D -25·3'$, from which it is calculated that the *l*-oscinium ion has $[\alpha]_D -21°$, a value in good agreement with that observed directly for *l*-oscinium hydrochloride. The solution was then dried, and the hydrochloride recrystallised from alcohol. It gave 0·11 gram of highly deliquescent *l*-oscine hydrochloride melting at 271—272°, and when tested with saturated picric acid solution gave the unstable needle form of *l*-oscine picrate, changing into rhombs.

l-*Oscine Base*.—To avoid the action of alkalis, which it was thought might cause partial racemisation, *l*-oscine base was prepared as follows. *l*-Oscine picrate (4·75 grams) was treated with three equivalents of dilute sulphuric acid solution, and the picric acid removed by purified ether. After treating with charcoal to remove the last traces of picric acid, the solution was concentrated under diminished pressure to about 20 c.c., and excess of pure barium carbonate added. On allowing to remain overnight, the solution was free from sulphanion, and only contained *l*-oscine partly present as carbonate. The major portion of the *l*-oscine was readily removed by extraction with freshly purified chloroform, the remainder being retained by the dissolved carbon dioxide. When the latter solution was evaporated to dryness in a vacuum over sulphuric acid and redissolved in a little water, the rest of the oscine was readily extracted by chloroform. In this way, the *l*-oscine was recovered quantitatively as base. The first chloroform extract on complete removal of the solvent crystallised at once. The product was white and amounted to 1·45 grams. It had a specific rotatory power of $[\alpha]_D -52·8°$ in water. It melted at 109—110°, the same as *dl*-oscine, whilst a mixture of the two showed no depression of the melting point. When recrystallised from light petroleum, it separated in long needles. The melting point was unchanged at 109·5—110·5° (corr.).

The specific rotatory power was determined in water:

$$c=1·010;\ l=2\text{-dcm.};\ \alpha -1°3·6';\ [\alpha]_D -52·4°.$$

With Mayer's reagent (potassium mercuric iodide), *l*-oscine base gives no precipitate, but in the form of a salt it gives a crystal-

line precipitate. The presence of a slight excess of acid prevents the separation of crystals. *dl*-Oscine behaves similarly.

Action of Acids and Alkalis on l-*Oscine.*—A solution of 0·2 gram of *l*-oscine in water having an observed rotation of α_D −1°1·7′ in a 2-dcm. tube was treated with one drop (0·04 c.c.) of 50 per cent. potassium hydroxide solution. After nineteen hours, the observed rotation was unchanged, α_D −1°1·5′.

The same solution was heated on the boiling-water bath for an hour. At the end of this period, the rotation was still −1°1·7′. Five c.c. of 50 per cent. potassium hydroxide were now added, and the solution was boiled for an hour. Making a correction for the change in volume, the observed rotation was unchanged, α_D −1°1·2′. This means that 0·2 gram of *l*-oscine was not racemised by boiling for an hour with excess of 10 per cent. potassium hydroxide solution.

There was, however, partial racemisation when 0·2 gram of *l*-oscine was heated with 15 c.c. of saturated baryta solution for four hours at 150°, the value of $[\alpha]_D$ having fallen to about one-half its original value.

The action of boiling 10 per cent. hydrobromic acid also failed to racemise *l*-oscine, for 1 gram of *l*-oscine *d*-hydrogen tartrate in 30 c.c. of 10 per cent. hydrobromic acid had an observed rotation, α_D −21·1′, in a 2-dcm. tube, and after three hours' boiling the rotation was practically unaltered, α_D −22·6′.

d-*Oscine Base.*—One gram of pure *d*-oscine *d*-hydrogen tartrate was dissolved in 10 c.c. of 5 per cent. sodium hydroxide solution, and the base extracted with purified chloroform. The combined extracts were clarified by shaking with anhydrous potassium carbonate, filtered, and the solvent removed by distillation. The residual base crystallised instantaneously throughout on touching one spot with a glass rod. A similar very high velocity of crystallisation had previously been noticed with the chloroform-free *laevo*-oscine base. It was crystallised from light petroleum, and separated in long, radiating needles, often forming fasciated growths. It melted at 109—110° (109·5—110·5° corr.), and a mixture with pure *dl*-oscine also at the same temperature.

Its specific rotation was determined in water:

$$c = 1{\cdot}029\,;\ l = 2\text{-dcm.}\,;\ \alpha_D + 1°7{\cdot}6'\,;\ [\alpha]_D + 54{\cdot}8°.$$

d-*Oscine Picrate.*—The solution of the base which had been used for determining the rotatory power was treated with an equivalent of picric acid (0·3 gram) and rapidly concentrated to about 10 c.c. On allowing to cool, long, radiating, glistening needles of *d*-oscine

picrate (0·3 gram) separated. These melted at 237—238° (242·5—243·5° corr.). The mother liquors were concentrated, and, when quite cold, the stable dimorph separated in small, flattened rhombs exactly as observed in the case of *l*-oscine picrate. This form also melted at 237—238°. A mixture with *d*-oscine picrate, obtained by acid hydrolysis of benzoyl-*d*-oscine, also melted at the same temperature.

d-*Oscine Hydrochloride.*—To complete the analogy with the *laevo*-series, this salt was prepared and its specific rotation determined. For this purpose, 0·2078 gram of *l*-oscine base was neutralised with the calculated quantity, 13·4 c.c., of *N*/10-hydrochloric acid, and the volume made up to 20 c.c. In a 2-dcm. tube was found α_D 30·1′, whence $[\alpha]_D$ for the *d*-oscinium ion is +24·0°, a value in agreement with $[\alpha]_D$ −24·2° observed for the *l*-oscinium ion.

The solution just employed was evaporated to dryness and the residue crystallised from absolute alcohol, when *d*-oscine hydrochloride separated in warts with a few isolated prisms. The melting point was 273—274°, and the salt was very deliquescent.

Resolution of Benzoyloscine.

This was effected substantially as described by Tutin (T., 1910, **97**, 1793).

Five grams of *dl*-oscine hydrobromide were converted into the base, which was heated to 160° with 10 c.c. of benzoyl chloride, when a brisk reaction ensued with simultaneous crystallisation of the benzoyloscine hydrochloride. The solid was collected, washed with ether, and dried at 100°. The crude product melted at 240° and amounted to 5·45 grams, that is, an 83 per cent. yield. It was dissolved in water, and the solution, after decolorisation with a little charcoal, was rendered alkaline with sodium hydrogen carbonate, and completely extracted with chloroform. The benzoyloscine left on removing the chloroform was neutralised to litmus with *d*-α-bromo-π-camphorsulphonic acid, and the salt fractionated from absolute alcohol. The *d*-benzoyloscine bromocamphorsulphonate was obtained pure after three crystallisations, and melted at 247—248° (Tutin gives 246—246·5°). The specific rotation was determined in water:

c=1·998; l=2-dcm.; α_D +2°11·3′; $[\alpha]_D$ +54·74°; $[M]_D$ +312·3°.

The calculated value of the molecular rotatory power of the *d*-benzoyloscinium ion is therefore 312·3—278·7=33·6°, whence $[\alpha]_D$ for the *d*-benzoyloscinium ion is +12·9°.

Benzoyl-d-*oscine Hydrochloride.*

Pure benzoyl-*d*-oscine bromocamphorsulphonate (2·8 grams) was triturated with 30 c.c. of water and three molecular proportions of sodium hydrogen carbonate. Benzoyl-*d*-oscine base appeared to separate in needles, which were immediately dissolved by chloroform. The free base, on removal of the solvent, was exactly neutralised with *N*/10-hydrochloric acid, and, after filtering from a little greasy matter, was concentrated rapidly under diminished pressure to a very small volume. On keeping for a short time, the whole of the liquid became filled with perfectly formed rectangular leaflets, which in a few hours were completely transformed into fine needles. These were collected and washed with absolute alcohol. They amounted to 1·1 grams, and melted and decomposed at 280° (287° corr.) (Tutin gives 283—284°). The product was anhydrous. Its specific rotation was determined in dilute aqueous solution:

$c=2{\cdot}005$; $l=2$-dcm.; α_D $+28{\cdot}35'$; $[\alpha]_D$ $+11{\cdot}79°$; $[M]_D$ $+34{\cdot}83°$.

From this is calculated $[\alpha]_D$ $+13{\cdot}4°$ for the benzoyl-*d*-oscinium ion, a value which compares favourably with the value $+12{\cdot}9°$ calculated above from the bromocamphorsulphonate. This value is somewhat higher than Tutin's value, $[\alpha]_D$ $+10{\cdot}0°$, which is obtained by calculation from the value $[M]_D$ $+297{\cdot}0°$ for benzoyl-*d*-oscine bromocamphorsulphonate.

Hydrolysis of Benzoyl-d-*oscine.*

With Hydrochloric Acid.—The solution just employed (20 c.c.), containing 0·4001 gram of benzoyl-*d*-oscine hydrochloride, was treated with 9·7 c.c. of 31 per cent. hydrochloric acid, thus bringing the volume approximately to 30 c.c. and the strength of the acid to 10 per cent. The rotation was observed, and the solution was then boiled gently to hydrolyse the benzoyl-*d*-oscine, the rotation being observed at intervals, just as is described under the hydrolysis of *l*-hyoscine (p. 507).

Initial reading. $+20'$; $l=2$-dcm.
After 1 hour's boiling, $+20{\cdot}5'$.
After 3 hours' boiling, $+22{\cdot}0'$.

Hydrolysis was now complete, as there was a copious separation of benzoic acid, and the solution gave no turbidity with Mayer's reagent. The observed rotation is therefore due to the *d*-oscinium ion, and the final value, $+22'$, corresponds with a specific rotation of the *d*-oscinium ion of $+26°$, which is of the same order as that

obtained by calculation from the rotation of *d*-oscine *d*-hydrogen tartrate, namely, $[\alpha]_D$ 27·1°, and that directly observed, $[\alpha]_D$ 24·0°, for *d*-oscinium hydrochloride prepared from the tartrate.

The free benzoic acid was removed by extraction with purified ether, and the aqueous liquor concentrated to a syrup under diminished pressure on the water-bath. On dehydration of the syrup by evaporation with absolute alcohol, the residue crystallised. It was dissolved in a little hot absolute alcohol, and, on keeping, 0·07 gram of crystals resembling ammonium chloride were collected. They melted and decomposed in the neighbourhood of 243° (pure *d*-oscine hydrochloride melts at 273°), and were highly deliquescent.

Twenty milligrams of this salt, when treated with an equal weight of picric acid in hot aqueous solution, gave a picrate crystallising in long, fine needles, and later a few rhombs separated, a behaviour which is exactly reproduced by the addition of picric acid solution to the pure *d*- or *l*-oscine *d*-hydrogen tartrates (p. 495). This picrate, when collected and dried, melted and decomposed at 237—238°. A mixture with *d*-oscine picrate melted in the same bath at 237—238°. The alcoholic mother liquors of the above 0·07 gram of *d*-oscine hydrochloride were combined with picric acid (both in aqueous solution). The addition of the picric acid first precipitated amorphous matter, which was separated, and later a well-crystallised picrate. This salt crystallised in small rhombs, melted and decomposed at 235°, and was in all probability the stable form of *d*-oscine picrate.

With Alkali.—Pure benzoyl-*d*-oscine hydrochloride (0·4009 gram) was dissolved in water, and 5 c.c. of 10 per cent. sodium hydroxide were added. The oily base, which separated rapidly, disappeared on boiling. After an hour, the solution was cooled and neutralised to Congo paper with hydrochloric acid. The precipitated benzoic acid was completely removed by ether extraction, and the extracted aqueous liquor was also free from non-hydrolysed benzoyloscine, as was indicated by the absence of a turbidity on treatment with Mayer's reagent in acid solution. In neutral or very faintly acid solution it gave the well-crystallised precipitate observed with oscine salts. The solution was rapidly concentrated and made up to 20 c.c. In a 2-dcm. tube it gave α_D +32·8′, whence the *d*-oscinium ion has $[\alpha]_D$ +25·8°, a value in good agreement with that observed by acid hydrolysis, $[\alpha]_D$ +26·0°, and that observed for pure *d*-oscine hydrochloride, $[\alpha]_D$ +24·0°.

d-*Hyoscine*.

The starting material for the isolation of *d*-hyoscine consisted of 75 grams of well-crystallised hydrobromides obtained as a by-product in the manufacture of *l*-hyoscine. It was slightly lævorotatory, having $[\alpha]_D$ −4·1° (c=2·3, anhydrous), and contained 9 per cent. of water of crystallisation, which was lost over sulphuric acid. It was regenerated to base, using sodium hydrogen carbonate and chloroform for the purpose, the weight of base being about 55 grams. This was converted into its salt with *d*-α-bromo-π-camphorsulphonic acid, and crystallised from a mixture of dry ethyl acetate and absolute alcohol. In a few days there was a copious, crystalline separation, which was collected, and amounted to 38·5 grams. It was deliquescent and had $[\alpha]_D$ +46·4° (c=2), and on two more crystallisations gave 8·8 grams of pure meteloidine bromocamphorsulphonate.

Meteloidine d-α-*bromo*-π-*camphorsulphonate* crystallises exceedingly well from absolute alcohol, in which it is soluble to the extent of about 1 part in 10 (boiling), or from a mixture with dry ethyl acetate in clusters of prisms. It also crystallises well from water. It melts at 224—227° (228·5—231·5° corr.), and is anhydrous:

0·1410 gave 0·2547 CO_2 and 0·0808 H_2O. C=49·3; H=6·4.
$C_{13}H_{21}O_4N,C_{10}H_{15}O_4BrS$ requires C=48·75; H=6·4 per cent.

Its specific rotatory power was determined in water:

c=2·039; l=2-dcm.; α_D +1°56′; $[\alpha]_D$ +47·42°; $[M]_D$ +268·7°.

This value for the molecular rotation is somewhat smaller than that given by Pope and Read for the bromocamphorsulphonic acid ion (T., 1910, **97**, 2200). That the meteloidine was inactive was confirmed in two ways:

(1) A small quantity of the above salt was converted into base, avoiding conditions which might favour racemisation by using sodium hydrogen carbonate and chloroform. The base crystallised readily, and was identical in appearance and other properties with a sample of meteloidine kindly supplied by Dr. Pyman, and which was known to be inactive (Pyman and Reynolds, T., 1908, **93**, 2077).

(2) One-half a gram of *i*-meteloidine base was converted into its bromocamphorsulphonate, and the solution evaporated to dryness with absolute alcohol. The crystalline residue was triturated with a little dry ethyl acetate, in which the crystals are practically insoluble, and collected. The rotation of this salt, representing

practically the whole of the meteloidine, was found to be the same as the previously described salt:

$c=1{\cdot}969$; $l=2$-dcm.; $\alpha+1°51'$; $[\alpha]_D+47{\cdot}0°$; $[M]_D+266{\cdot}3°$.

It melted at 224—225°, and a mixture of the two salts showed no depression of the melting point.

Isolation of d-*Hyoscine Bromocamphorsulphonate.*—On continuing the fractionation, the original mother liquors gave a second crop of crystals, 24·5 grams, $[\alpha]_D+44{\cdot}5°$, which, after ten recrystallisations, gave 11·6 grams of pure *d*-hyoscine bromocamphorsulphonate melting at 159—160° and having $[\alpha]_D+60{\cdot}1°$. This was twice more recrystallised, and gave 8·3 grams with $[\alpha]_D+60{\cdot}3°$.

d-*Hyoscine* d-*α-bromo-π-camphorsulphonate* crystallises from a mixture of absolute alcohol and excess of dry ethyl acetate in clusters of glistening, acicular needles. After being dried at 110° it melts at 158—160° (161·5—163·5° corr.). Its specific rotation was determined in water at 16°.

$c=2{\cdot}005$; $l=2$-dcm.; $\alpha+2°25'$; $[\alpha]_D+60{\cdot}3°$; $[M]_D+370{\cdot}5°$.

From this it is calculated that the molecular rotatory power of the *d*-hyoscinium ion is 91·8° and the specific rotatory power $[\alpha]_D$ is +30·2° (see *d*-hyoscine hydrobromide). The salt is not deliquescent:

0·2730 lost 0·0022 at 100°. Loss = 0·8.

0·1238, dried at 100°, gave 0·2394 CO_2 and 0·0675 H_2O. C = 52·8; H = 6·1.

$C_{17}H_{21}O_4N,C_{10}H_{15}O_4BrS$ requires C = 52·7; H = 5·9 per cent.

The fractionation of the various liquors was continued, when further small quantities, 4·5 grams in all, of meteloidine bromocamphorsulphonate, and an additional 12·5 grams of pure *d*-hyoscine bromocamphorsulphonate, $[\alpha]_D+60{\cdot}5°$, were obtained. The original mother liquors now gave 10 grams of a deliquescent salt, $[\alpha]_D+30{\cdot}8°$, and 2·7 grams, $[\alpha]_D+27{\cdot}3°$, both of which had the properties of a slightly impure *l*-hyoscine bromocamphorsulphonate, which requires a calculated value of $[\alpha]_D+29°$. On recrystallisation, these gave salts of higher specific rotation. It was not found possible to isolate pure *l*-hyoscine bromocamphorsulphonate from the mother liquors.

d-*Hyoscine Hydrobromide.*—Six grams of pure *d*-hyoscine bromocamphorsulphonate were converted into base, using chloroform and sodium hydrogen carbonate for the regeneration. The base was neutralised with hydrobromic acid and the solution concentrated under diminished pressure. *d*-Hyoscine hydrobromide separated on keeping in large tablets (2 × 1 cm.).

d-*Hyoscine hydrobromide* crystallises exceedingly well from water in rectangular-shaped tablets with bevelled edges. It crystallises with three molecules of water, the hydrate melting in a capillary tube at 54·5—55° (54·5—55° corr.). It is rendered anhydrous by drying over sulphuric acid in a vacuum. The behaviour of the anhydrous salt on heating is very varied. It sometimes melts sharply at 168°, resolidifies, and melts at 193—194° (197—198° corr.). Occasionally, the intermediate melting point is not observed at all, or is only indicated by a slight shrinking. If the anhydrous salt is dried for half an hour at 120°, only the higher melting point, 193—194°, is observed. The probable explanation is that the product, which melts at 168°, is either an amorphous form or a metastable, crystalline form of the anhydrous salt, and the transformation of one form into the other is accelerated by rise of temperature. *l*-Hyoscine hydrobromide behaves similarly:

0·1842, dried over H_2SO_4, lost 0·0228. $H_2O = 12·38$.
0·1813, dried at 100°, lost 0·0226. $H_2O = 12·47$.
0·1587, „ 100° gave 0·0778 AgBr. Br = 20·85.

$C_{17}H_{21}O_4N,HBr,3H_2O$ requires $H_2O = 12·33$ per cent.
$C_{17}H_{21}O_4N,HBr$ requires Br = 20·80 per cent.

The specific rotatory power of the hydrated salt was determined in water:

$c = 2·842$; $l = 2$-dcm.; $\alpha + 1°18·5'$; $[\alpha]_D + 23·02°$.
$c = 2·525$; $l = 2$-dcm.; $\alpha + 1°10'$; $[\alpha]_D + 23·10°$.

The mean of these values gives for the anhydrous salt $[\alpha]_D + 26·3°$ and for the *d*-hyoscinium ion $[\alpha]_D + 33·2°$. The latter value is in approximate agreement with that calculated from the molecular rotation of the bromocamphorsulphonate (p. 502), namely, +30·2°.

d-*Hyoscine Aurichloride.*—*d*-Hyoscine bromocamphorsulphonate (0·3 gram) was dissolved in 5 c.c. of warm water, and 5 c.c. of 10 per cent. hydrochloric acid were added, followed by 7 c.c. of gold chloride solution (1 in 30). The aurichloride separated, partly in isolated, minute, rectangular plates, but for the most part in fern-like growths or spangles. It melted at 202—203° and weighed 0·32 gram. It was twice recrystallised from 2·5 per cent. hydrochloric acid, the melting point each time remaining at 204—205° (208—209° corr.) (decomp.). The recrystallised solid separated in long, flattened, orange-yellow needles with both edges serrated:

0·1266, air-dried, gave 0·0387 Au. Au = 30·6.

$C_{17}H_{21}O_4N,AuCl_3,HCl$ requires Au = 30·7 per cent.

d-*Hyoscine Picrate.*—Prepared from *d*-hyoscine bromocamphorsulphonate by double decomposition in aqueous solution, this salt separated as a netted mass of needles melting and decomposing at 187—188° (see *l*-hyoscine picrate).

l-*Hyoscine.*

l-*Hyoscine Hydrobromide.*—The properties of this salt are the same as those of *d*-hyoscine hydrobromide. The rotation of the purest hydrobromide crystallised from water was a fraction less than *d*-hyoscine hydrobromide. For various samples, the following values were obtained:

$c=2{\cdot}454$; $l=2$-dcm.; $\alpha=-1°7'$: $[\alpha]_D$ $-22{\cdot}75°$.
$c=2{\cdot}543$; $l=2$-dcm.; $\alpha=-1°9{\cdot}3'$; $[\alpha]_D$ $-22{\cdot}71°$.
$c=2{\cdot}045$; $l=2$-dcm.; $\alpha=-55{\cdot}43'$; $[\alpha]_D$ $-22{\cdot}58°$.

The mean of the first two values gives $[\alpha]_D$ $-25{\cdot}93°$ for the anhydrous salt, and for the *l*-hyoscinium ion $[\alpha]_D$ $-32{\cdot}73°$, whereas for the purest *d*-hyoscine hydrobromide the values were 26·3° and 33·2° respectively. The use of *l*-α-bromo-π-camphorsulphonic acid for purifying the *l*-hyoscine would no doubt lead to complete accord between the rotatory powers of the two enantiomorphs.

l-*Hyoscine Aurichloride.*—*l*-Hyoscine hydrobromide (0·2 gram) was converted into base, using sodium hydrogen carbonate and chloroform. A solution of the hydrochloride was mixed with gold chloride solution, and the *l*-hyoscine aurichloride collected. It weighed 0·28 gram, and melted and decomposed at 204—205°. It was recrystallised from one hundred times its weight of 2·5 per cent. hydrochloric acid, and separated in complex, needle-shaped growths serrated on both edges, exactly as observed for the dextro-enantiomorph. The melting and decomposing point was unchanged (208—209° corr.):

0·1075, air-dried, gave 0·0331 Au. Au = 30·8.

$C_{17}H_{21}O_4N,AuCl_3,HCl$ requires Au = 30·7 per cent.

l-*Hyoscine Auribromide.*—This was prepared by Jowett's method (T., 1897, **71**, 680), by dissolving 0·2 gram of *l*-hyoscine hydrobromide in excess of hydrobromic acid and adding gold chloride solution. The yield was 0·4 gram (m. p. 187—188°). It was recrystallised from boiling 2·5 per cent. hydrobromic acid (40 c.c.), and gave 0·35 gram of long, rectangular, chocolate-red leaflets still melting and decomposing at 187—188° (191—192° corr.):

0·1075, air-dried, gave 0·0258 Au. Au = 24·0.

$C_{17}H_{21}O_4N,AuBr_3,HBr$ requires Au = 24·0 per cent.

l-*Hyoscine Picrate.*—0·20 Gram of *l*-hyoscine hydrobromide by

double decomposition with a hot saturated picric acid solution gave 0·25 gram of *l*-hyoscine picrate crystallising in slender, primrose-yellow needles (m. p. 187—188°). It required a hundred times its weight of boiling water to dissolve it, and then separated in flat, irregular, six-sided scales covered with striations. Occasionally, these scales were united in the form of long, flat, serrated needles. It now melted and decomposed at 187·5—188·5° (191—192° corr.), and amounted to 0·2 gram.

dl-*Hyoscine.*

dl-*Hyoscine Hydrobromide.*—Two and a-half grams each of the purest *d*-hyoscine and *l*-hyoscine hydrobromides were combined and recrystallised from water. The product crystallised exceedingly well with three molecules of water of crystallisation, and was indistinguishable from the active *d*- or *l*-hyoscine hydrobromides. The crystals were collected, and amounted to 3·3 grams. In a capillary tube, the uncrushed crystals melted at 55—58°, but powdered crystals only partly melted up to 60°, owing to rapid loss of water. The anhydrous salt melts at 181—182° (185—186° corr.). The hydrated salt effloresces on exposure to the air, in this respect differing from the active components. A 2·5 per cent. solution in water was optically inactive:

0·2217 uneffloresced salt lost 0·0274 in a vacuum. $H_2O = 12·36$.
0·1943, dried in a vacuum, gave 0·0949 AgBr. Br = 20·8.
$C_{17}H_{21}O_4N,HBr,3H_2O$ requires $H_2O = 12·33$ per cent.
$C_{17}H_{21}O_4N,HBr$ requires Br = 20·8 per cent.

dl-*Hyoscine Base.*—One gram of *dl*-hyoscine hydrobromide was converted into base, using chloroform and sodium hydrogen carbonate. The chloroform-free base was moistened with water, and when kept for some hours in a freezing mixture crystallised in minute needles. The product was collected, washed with water, and, when dried in the air, amounted to 0·55 gram. It melted at 38—40°:

0·1034, in a vacuum over H_2SO_4, lost 0·0104. $H_2O = 10·1$.
$C_{17}H_{21}O_4N,2H_2O$ requires $H_2O = 10·6$ per cent.

It was recrystallised by dissolving in a little warm alcohol and adding water until a turbidity developed. On inoculation, it crystallised slowly in well-formed, transparent, chisel-shaped prisms. The melting point was unchanged at 38—40° (38—40° corr.). When dried in a vacuum over sulphuric acid, it lost two molecules of water:

0·0770 lost 0·0082. $H_2O = 10·6$.

$C_{17}H_{21}O_4N,2H_2O$ requires $H_2O = 10·6$ per cent.

The anhydrous material consisted of a clear varnish, and had no definite melting point.

The melting point of the dihydrate was unchanged after keeping in a Jena-glass tube for ten months.

dl-*Hyoscine Picrate*.—This salt was prepared in aqueous solution by adding a saturated solution of picric acid to a solution of *dl*-hyoscine hydrobromide. An oil separated at first, but was displaced, on warming, by short needles, which melted and decomposed at 173—174°. These were recrystallised from one hundred parts of boiling water, and separated in rosettes of long needles, melting and decomposing at 173·5—174·5° (177·5—178·5° corr.).

The same salt is obtained from the *dl*-base.

dl-*Hyoscine Aurichloride*.—This salt crystallises in long, flat needles with one edge serrated on mixing aqueous solutions of the two components. It melted and decomposed at 214—215°. On recrystallisation from 2·5 per cent. hydrochloric acid, it separated in stout, boat-shaped crystals melting and decomposing at 218—219° (corr.):

0·1175 gave 0·0358 Au. Au = 30·5.

$C_{17}H_{21}O_4N,AuCl_3,HCl$ requires Au = 30·7 per cent.

dl-*Hyoscine Auribromide*.—On mixing *dl*-hyoscine hydrobromide dissolved in excess of hydrobromic acid with gold chloride solution, this salt crystallises in chocolate-coloured leaflets of indefinite shape melting and decomposing at 209—210°. On recrystallisation from 50 parts of dilute hydrobromic acid solution, it separated in chocolate-red leaflets very similar in appearance to the *laevo*-salt. The melting and decomposing point was unchanged at 213—214° (corr.):

0·1123 gave Au = 0·0268. Au = 23·9.

$C_{17}H_{21}O_4N,AuBr_3,HBr$ requires Au = 24·0 per cent.

Jowett (*loc. cit.*) has described a hyoscine auribromide melting at 210°, which probably indicates that his starting material, hyoscine hydrobromide, was optically inactive, or practically so.

Hydrolysis of l-*Hyoscine*.

With Hydrobromic Acid.—Pure hydrated *l*-hyoscine hydrobromide (1·4447 grams), $[\alpha]_D - 22·7°$ ($c = 2·5$), was dissolved in 30 c.c. of 10 per cent. hydrobromic acid, and the rotation determined. The solution was then boiled gently under reflux, the

rotation being observed at definite intervals by cooling the solution and removing the requisite volume for the observation. On completion of the latter, the solutions were recombined and the boiling started afresh. The following data were obtained, using a 2-dcm. tube:

Initial reading	−141′	After 4 hours' boiling	−159′
After 1 hour's boiling ...	−149′	„ 6 „ „	−161′
„ 2 hours' „ ...	−153′	„ 9 „ „	−157′

The solution was now thoroughly extracted with purified ether to remove the *l*-tropic acid. The residual aqueous solution still showed a rotation of −10′, and contained non-hydrolysed hyoscine, as it gave a reaction with Mayer's reagent (oscine gives no reaction in acid solution of this strength). The hydrolysis was continued for a further five hours, when the rotation rose to −11′, and the reaction for hyoscine was negative. On removal of the *l*-tropic acid by ether, the residual solution was inactive.

The ethereal extracts gave 0·65 gram of crude *l*-tropic acid melting at 125—127° and having $[\alpha]_D$ −70·5° in water ($c=1$). On recrystallisation from water, it melted at 127—128° and gave $[\alpha]_D$ −76° ($c=2$).

The *dl*-oscine hydrobromide solution was concentrated rapidly under diminished pressure to a syrup, when it acquired a purple colour, which disappeared on dilution with water, but in absolute alcohol became brown. The syrupy residue crystallised on inoculating with *dl*-oscine hydrobromide. The crude product melted at 270° and weighed 0·75 gram (theory, 0·78). It was triturated with a little absolute alcohol, and the crystals were collected. The product consisted of granular crystals with a violet colour (probably containing traces of a perbromide (compare Schmidt, *Arch. Pharm.*, 1905, **243**, 567), weighed 0·53 gram, and melted at 280°. A mixture with pure *dl*-oscine hydrobromide (m. p. 282°) also melted at 280°. The filtrate was now evaporated to dryness under diminished pressure, dissolved in 10 per cent. sodium hydroxide solution, and completely extracted with chloroform. On removal of the chloroform, 0·15 gram of base was obtained, which only crystallised on inoculation with the *dl*-oscine base of commerce. It melted at 98—100°, and a mixture with pure oscine melted at 103°.

The products of the hydrolysis are therefore *l*-tropic acid and *dl*-oscine.

With Hydrochloric Acid.—Pure *l*-hyoscine base prepared from 0·5014 gram of *l*-hyoscine hydrobromide, $[\alpha]_D$ −22·75° ($c=2·5$), using sodium hydrogen carbonate and chloroform, was dissolved in

30 c.c. of 10 per cent. hydrochloric acid. The rotation was followed as in the case of the hydrobromide.

Initial reading	$-52'$
After 2 hours' boiling	$-55'$; $l = 2$-dcm.
„ 4 „ „	$-56'$
„ 8 „ „	$-54{\cdot}5'$

On removal of the *l*-tropic acid (0·15 gram; m. p. 124—125°) by ether, the acid aqueous solution was optically inactive, and when evaporated to dryness with absolute alcohol gave 0·13 gram of *dl*-oscine hydrochloride crystallising in minute, rectangular plates, or associated together in fern-like growths. It was converted into the picrate, which crystallised in small, flattened rhombs or tablets melting and decomposing at 231°. A mixture with pure *dl*-oscine picrate, which crystallises similarly and melts and decomposes at 237—238°, melted intermediately at 232°.

In conclusion, the author desires to express his warmest thanks to Dr. Pyman for his advice and criticism throughout the course of the work.

The Wellcome Chemical Research Laboratories,
London, E.C. [*Received, March 26th*, 1919.]

PRINTED IN GREAT BRITAIN BY R. CLAY AND SONS, LTD.,
BRUNSWICK STREET, STAMFORD STREET, S.E. 1, AND BUNGAY, SUFFOLK.