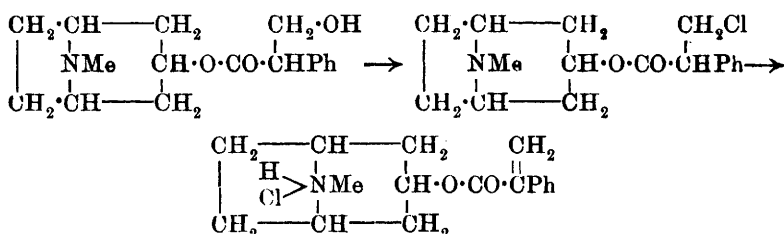# LXXXII.—*The Stereochemistry of Hyoscine.*
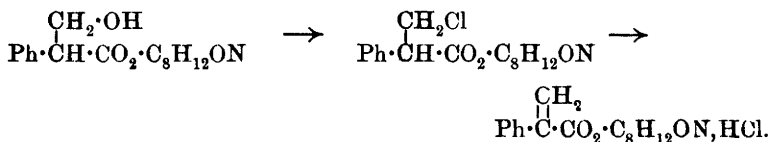
By HAROLD KING.

IN a former communication (this vol., p. 476), it was shown that by resolution of a weakly active hyoscine by means of *d-α*-bromo-*π*-camphorsulphonic acid, *d*-hyoscine bromocamphorsulphonate was obtained as the more sparingly soluble salt. The base proved to be the enantiomorph of the therapeutically valuable *l*-hyoscine of commerce. The unexpected discovery was made, however, that *d*- and *l*-hyoscines gave *dl*-oscine on hydrolysis with acid or alkali, whereas benzoyl-*d*-oscine under similar conditions gave optically pure *d*-oscine. Furthermore, the *d*- and *l*-oscine bases prepared by resolution of *dl*-oscine were not racemised by acid or alkali. On these grounds, *d*- and *l*-hyoscines were regarded as partially racemic esters, the optical activity being solely conditioned by the activity of the tropyl radicle.

In the present communication, further confirmatory evidence is adduced. In 1908, Wolffenstein and Mamlock (*Ber.*, **41**, 730) showed that atropine (tropyltropine) can be converted into

β-chlorohydratropyltropine, and that, on evaporation of the ethereal solution of this base, an intramolecular change takes place, hydrogen chloride being transferred from carbon to nitrogen, with the formation of *apo*atropine hydrochloride.

$$
\begin{array}{l}
\text{CH}_2\cdot\text{CH}\!\!-\!\!-\!\!\text{CH}_2 \qquad \text{CH}_2\cdot\text{OH} \qquad \text{CH}_2\cdot\text{CH}\!\!-\!\!-\!\!\text{CH}_2 \qquad \text{CH}_2\text{Cl} \\
\quad|\quad\ \ \text{NMe}\quad \text{CH}\cdot\text{O}\cdot\text{CO}\cdot\text{CHPh} \;\rightarrow\; |\quad\ \ \text{NMe}\quad \text{CH}\cdot\text{O}\cdot\text{CO}\cdot\text{CHPh}\!\rightarrow \\
\text{CH}_2\cdot\text{CH}\!\!-\!\!-\!\!\text{CH}_2 \qquad\qquad\qquad\quad \text{CH}_2\cdot\text{CH}\!\!-\!\!-\!\!\text{CH}_2
\end{array}
$$

$$
\begin{array}{l}
\text{CH}_2\!\!-\!\!-\!\!\text{CH}\!\!-\!\!-\!\!\text{CH}_2 \qquad \text{CH}_2 \\
\quad|\quad\ \overset{\text{H}}{\underset{\text{Cl}}{>}}\!\text{NMe} \quad \text{CH}\cdot\text{O}\cdot\text{CO}\cdot\overset{||}{\text{C}}\text{Ph} \\
\text{CH}_2\!\!-\!\!-\!\!\text{CH}\!\!-\!\!-\!\!\text{CH}_2
\end{array}
$$

Willstätter and Hug (*Zeitsch. physiol. Chem.*, 1912, **79**, ·146) showed that, in a precisely similar manner, *l*-hyoscine on treatment with thionyl chloride gave β-chlorohydratropyloscine hydrochloride, and the ethereal solution of the base, on evaporation, gave *apo*hyoscine (*apo*scopolamine) hydrochloride.

$$
\begin{array}{l}
\text{CH}_2\cdot\text{OH} \qquad\qquad\quad\ \rightarrow \qquad \text{CH}_2\text{Cl} \qquad\qquad\qquad \rightarrow \\
\text{Ph}\cdot\text{CH}\cdot\text{CO}_2\cdot\text{C}_8\text{H}_{12}\text{ON} \qquad\qquad \text{Ph}\cdot\text{CH}\cdot\text{CO}_2\cdot\text{C}_8\text{H}_{12}\text{ON} \\
\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \text{CH}_2 \\
\qquad\qquad\qquad\qquad\qquad\qquad\qquad\ \text{Ph}\cdot\overset{||}{\text{C}}\cdot\text{CO}_2\cdot\text{C}_8\text{H}_{12}\text{ON},\text{HCl}.
\end{array}
$$

This reaction destroys the asymmetry of the tropyl group, and could it be carried out under mild conditions, so as to preclude hydrolysis and racemisation, it should indicate whether the oscine portion of the molecule is active or inactive in *l*-hyoscine. Willstätter and Hug, apparently unaware of the significance of this reaction, did not record the polarimetric examination of *apo*-hyoscine. Moreover, they used potassium carbonate for liberating the bases from their salts, this alkali being known to racemise *l*-hyoscine partly if contact is at all prolonged (Schmidt, *Arch. Pharm.*, 1898, **47**, 236), and their yield of *apo*hyoscine was only 50 per cent., the loss being attributed to hydrolysis. It has now been found that, on replacing potassium carbonate by the much weaker alkali sodium hydrogen carbonate, the reaction proceeds quantitatively throughout, and the resulting *apo*hyoscine is optically inactive.

To complete the proof of the partial racemic ester nature of *l*-hyoscine, the resolution of *apo*hyoscine has been attempted.

apoHyoscine camphorsulphonate (m. p. 157—158°) is a very readily soluble salt which can be recrystallised from a mixture of alcohol and ether, but shows no signs of resolution. The bromocamphorsulphonate was not obtained crystalline, but the

d-*hydrogen tartrate* crystallises well from water. It contains two molecules of water of crystallisation, melts at 95—97°, and has $[\alpha]_D + 8\cdot6°$ in water. Repeated crystallisation failed to change its melting point or its specific rotation.

The results so far obtained are best explained on the assumption already made that *d*- and *l*-hyoscines are partially racemic esters, *d*-hyoscine being composed of *d*-tropyl-*d*-oscine and *d*-tropyl-*l*-oscine, whilst *l*-hyoscine contains the enantiomorphs. Although *d*-hyoscine is not further resolved by *d*-α-bromo-π-camphorsulphonic acid, it does not follow that *l*-hyoscine is not resolvable by the same acid or that either base is not resolvable by other optically active acids. The behaviour of pure *d*- and *l*-hyoscines towards the optically active acids, *d*-camphor-β-sulphonic, *d*-α-bromo-π-camphorsulphonic, and *d*-tartaric has now been investigated, but in no case was there any indication of resolution. The *d*-hydrogen tartrate of *d*-hyoscine could only be obtained as an uncrystallisable syrup.

The properties of the various crystalline camphorsulphonates are shown in the following table:

	d-Camphor-β-sulphonate.			*d*-α-Bromo-π-camphorsulphonate		
	M. p.	$[M]_D$ salt.	$[M]_D$ basic ion (calc.).	M. p.	$[M]_D$ salt.	$[M]_D$ basic ion (calc.).
d-Hyoscine	175—177°	$+156\cdot7°$	$+106\cdot3°$	158—160°	$+370\cdot5°$	$+91\cdot8°$
l-Hyoscine	186—187°	$-40\cdot8°$	$-91\cdot2°$	169—170°	$+172\cdot4°$	$-106\cdot3°$

The value obtained by direct observation on *d*- or *l*-hyoscine hydrobromides was $[\alpha]_D \pm 33°$ or $[M]_D \pm 100°$ (this vol., pp. 503, 504).

A peculiar numerical relationship is observable in the calculated molecular rotatory powers of the basic ions, the significance of which is not clear. It suggests a further resolution of *d*- and *l*-hyoscines, but, apart from these values, there is no evidence to support it, the picrate, for instance, prepared from *d*-hyoscine camphorsulphonate, being identical with that prepared from *d*-hyoscine bromocamphorsulphonate.

In addition to the above salts, *l*-hyoscine was found on one occasion to form a labile salt with *d*-α-bromo-π-camphorsulphonic acid. This salt melted at about 150° and had $[\alpha]_D + 25\cdot5°$, $[M]_D + 157°$, but it was not obtained quite pure, as after two crystallisations it became transformed into the ordinary form of higher melting point (169—170°), and subsequent attempts to reproduce it were unsuccessful. Whether the tautomerism is centred in the bromocamphorsulphonic acid portion of the molecule, as has only rarely been observed (Kipping and Tattersall, T., 1903, **83**, 918), or in the hyoscine portion of the molecule, must

for the present remain undecided. In this connexion, however, it is possibly significant that Wentzel (*Dissertation*, cited by Hesse, *J. pr. Chem.*, 1901, [ii], **64**, 274), by crystallising *l*-hyoscine hydrobromide from alcohol, obtained a lævo-hyoscine hydrobromide of much higher rotatory power, namely, $[a]_D - 32\cdot9°$, which fell, on keeping, to $-25\cdot8°$, the usually observed value. Hesse (*ibid.*, 353) ·claims to have partly substantiated this observation. This enhanced value for the anhydrous *l*-hyoscine hydrobromide gives a calculated value $[a]_D + 24\cdot8°$ for the *d*-*a*-bromo-π-camphorsulphonate, a value of the same order as that observed, $[a]_D + 25\cdot5°$, for the labile bromocamphorsulphonate described above.

The present author has obtained another *l*-hyoscine bromocamphorsulphonate, $[a]_D + 17\cdot9°$, m. p. 200°, during the resolution of a weakly active hyoscine by means of *a*-bromo-π-camphorsulphonic acid. The amount of material was, however, only sufficient to prove the identity of the *l*-hyoscine. It is not improbable that the acid contained in this salt is an isomeric acid which was present as an impurity in the original ammonium *a*-bromo-π-camphorsulphonate used.

EXPERIMENTAL.

Preparation of dl-apo*Hyoscine from* l-*Hyoscine.*

The method employed for preparing this base is a modification of that given by Willstätter and Hug (*loc. cit.*).

l-Hyoscine hydrobromide (3·87 grams) was converted into the base by the use of sodium hydrogen carbonate and chloroform. The chloroform-free base was warmed gently with 10 c.c. of thionyl chloride. The reaction proceeded smoothly, and, after keeping the product overnight, the thionyl chloride was distilled off under diminished pressure, and the last traces were removed by repeated extraction and evaporation with ether. The β-chlorohydratropyloscine hydrochloride was dissolved in a little water, the solution rendered alkaline with sodium hydrogen carbonate, and the base thoroughly extracted with ether. Unlike *l*-hyoscine, this chlorosubstituted base could be readily extracted. The ethereal solution was evaporated to dryness, leaving a pale yellow oil, which immediately became opalescent, and, on digesting on the water-bath with fresh ether, no longer dissolved, but commenced to crystallise at the edges. On keeping for two days, it had crystallised completely in rosettes of stout needles consisting of *apo*hyoscine hydrochloride.

A 2·5 per cent. aqueous solution was neutral to litmus, and when examined in a 2-dcm. tube proved to have no action on the plane of polarised light.

The salt (2·7 grams) was dissolved in water (15 c.c.), the solution rendered alkaline with sodium hydrogen carbonate, and the base completely extracted with ether. On removal of the solvent, the base crystallised readily in rhomboidal plates. It melted at 75—78°, and amounted to 2·4 grams. Theory requires 2·5 grams. It was recrystallised from light petroleum (b. p. 40—60°), and separated in magnificent rhomboidal plates. The yield was 2·2 grams, and the base now melted at 79—80° (79—80° corr.).

The base was examined in 2·5 per cent. solution in absolute alcohol in a 2-dcm. tube, but was quite inactive.

Willstätter and Hug record the melting point 97° for *apo*hyoscine base, but this appears to be a misprint for 79°, as the nitrate, picrate, and aurichloride were found to melt at 157° (decomp.), 217—218°, and 188° respectively, in substantial agreement with Willstätter and Hug's recorded values, 157°, 217°, and 183—184° respectively. The appearance and solubilities of the base and these salts were also in agreement. (Aurichloride.— Found: $Au = 31·5$. $C_{17}H_{19}O_3N, AuCl_3, HCl$ requires $Au = 31·5$ per cent.).

dl-apo*Hyoscine Camphor-β-sulphonate.*

*apo*Hyoscine base was converted into its salt with camphor-β-sulphonic acid. It crystallised from a mixture of absolute alcohol and ether in irregular-shaped leaflets. It was recrystallised twice, yielding, finally, 0·65 gram melting at 157—158° (160·5—161·5° corr.).

The specific rotation was determined in water.

$c = 2·069$; $l = 2$-dcm.; $\alpha + 0·404°$; $[\alpha]_D + 9·76°$; $[M]_D + 50·5°$.

The value of $[M]_D$ is in excellent agreement with that recorded by Graham (T., 1912, **101**, 747), namely, $[M]_D + 50·4°$ for the camphorsulphonic acid ion. That there was no resolution was confirmed by extracting the base from the solution, which had been used for determining the rotatory power, after rendering alkaline with sodium hydrogen carbonate and examining the solution of the base in absolute alcohol. It had no effect on the plane of polarised light.

The salt with d-α-bromo-π-camphorsulphonic acid was not obtained crystalline.

dl-apo*Hyoscine d-Hydrogen Tartrate.*

One gram of *apo*hyoscine nitrate was regenerated to base, using sodium hydrogen carbonate and ether. The d-hydrogen tartrate

of the base was prepared in aqueous solution by combination with one equivalent proportion (0·45 gram) of *d*-tartaric acid. On concentrating the solution to about 10 c.c., *apo*hyoscine *d*-hydrogen tartrate crystallised in clusters of radiating, white needles. The product was collected and washed with water. When dried in the air, it amounted to 1·15 grams. It was recrystallised four times from water, the properties of the successive fractions being as follows:

I. 1·15	grams,	m. p.	97°,	$[\alpha]_D + 8\cdot74°.$
II. 1·0	gram,	,,	95—97°,	$[\alpha]_D + 8\cdot35°.$
III. 0·75	,,	,,	95—97°,	$[\alpha]_D + 7\cdot78°.$
IV. 0·45	,,	,,	95—97°,	$[\alpha]_D + 8\cdot59°.$

Employing Landolt's value, $[M]_D + 42\cdot84°$, for ammonium hydrogen tartrate, the calculated value for *dl-apo*hyoscine *d*-hydrogen tartrate is $[\alpha]_D + 9\cdot1°$, in approximate agreement with the values recorded above. The base when recovered from the fourth fraction was examined in absolute alcohol, but the solution was devoid of optical activity.

dl-apo*Hyoscine* d-*hydrogen tartrate* is sparingly soluble in cold, but dissolves freely in hot water. It crystallises with two molecular proportions of water in clusters of long needles. In a capillary tube it melts at 95—97° (95—97° corr.), and effervesces at 115°, but it melts below 90° when exposed on a watch-glass to a temperature of 90—95°. The water of crystallisation is not lost when the salt is dried in a vacuum over sulphuric acid:

0·1037, air-dried, gave 0·2031 CO_2 and 0·0579 H_2O. C = 53·4; H = 6·2.

$C_{17}H_{19}O_3N,C_4H_6O_6,2H_2O$ requires C = 53·5; H = 6·2 per cent.

The specific rotation was determined in dilute aqueous solution, using the air-dried salt.

$c = 2\cdot008$; $l = 2$-dcm.; $\alpha + 0\cdot345°$; $[\alpha]_D + 8\cdot6°$; $[M]_D + 40\cdot5°$.

d-*Hyoscine Camphor-β-sulphonate.*

Almost pure *d*-hyoscine base (1·5 grams) was neutralised with camphor-β-sulphonic acid (1·15 grams). The syrupy salt was obtained crystalline by boiling with anhydrous ethyl acetate. It amounted to 2·3 grams and had $[\alpha]_D + 27\cdot6°$. It was recrystallised thrice more from anhydrous ethyl acetate, the specific rotation of the three fractions being successively $[\alpha]_D + 29\cdot5°$, $+ 29\cdot4°$, $+ 29\cdot3°$. The final fraction amounted to 1·5 grams.

d-*Hyoscine camphor-β-sulphonate* crystallises well from anhydrous

ethyl acetate, in which it is sparingly soluble, in elongated, hexagonal-shaped leaflets or in acicular needles. Each fraction examined appeared to contain one molecule of water, which was lost at 95°. The anhydrous salt melted at 175—177° (179—181° corr.).

For the first crops of successive crystallisations, the percentage losses at 95° were 2·95, 3·33, 1·9, 2·95.

$C_{17}H_{21}O_4N,C_{10}H_{16}O_4S,H_2O$ requires $H_2O = 3·25$ per cent.

0·1055, dried at 95°, gave 0·2339 CO_2 and 0·0663 H_2O. $C = 60·5$; $H = 7·0$.

$C_{17}H_{21}O_4N,C_{10}H_{16}O_4S$ requires $C = 60·5$; $H = 7·0$ per cent.

The specific rotatory power of the anhydrous salt was determined in water.

$c = 1·994$; $l = 2$-dcm.; $\alpha + 1°10'$; $[\alpha]_D + 29·25°$; $[M]_D + 156·7°$.

Employing the value $[M]_D + 50·4°$ for the camphor-β-sulphonic acid ion, the calculated molecular rotation of the d-hyoscinium ion is $[M]_D + 106·3°$, whence $[\alpha]_D + 34·9°$. The value found by direct observation of d-hyoscine hydrobromide was $[\alpha]_D + 33·2°$ (this vol., p. 503).

The picrate prepared from the four times recrystallised camphor-β-sulphonate by double decomposition was identical with d-hyoscine picrate obtained from d-hyoscine α-bromo-π-camphorsulphonate.

d-Hyoscine d-hydrogen tartrate was prepared, but all attempts to crystallise it failed.

l-*Hyoscine Camphor-β-sulphonate.*

Pure l-hyoscine base (1·4 grams) was neutralised in aqueous solution with Reychler's camphorsulphonic acid (1·0 gram). The dehydrated, syrupy salt was dissolved in anhydrous ethyl acetate, and, on keeping, crystallised homogeneously in clusters of large plates. The salt, when collected, amounted to 1·7 grams, melted at 187—188°, and had $[\alpha]_D - 7·2°$. It was recrystallised twice more, the melting point remaining the same and the rotation being virtually unaltered with $[\alpha]_D - 8·1°$ and $[\alpha]_D - 7·6°$ successively.

l-*Hyoscine camphor-β-sulphonate* crystallises from anhydrous ethyl acetate in transparent, rectangular plates. It melts at 186—187° (190—191° corr.):

0·2181, dried at 95°, lost nil.

0·0951 gave 0·2117 CO_2 and 0·0588 H_2O. $C = 60·7$; $H = 6·9$.

$C_{17}H_{21}O_4N,C_{10}H_{16}O_4S$ requires $C = 60·5$; $H = 7·0$ per cent.

The specific rotation was determined in water.

$c = 2·006$; $l = 2$-dcm.; $\alpha - 18·33'$; $[\alpha]_D - 7·6°$; $[M]_D - 40·8°$.

whence is calculated $[M]_D$ for l-hyoscinium ion $-91\cdot2°$ and $[\alpha]_D -30\cdot0°$.

l-*Hyoscine* d-*α-Bromo-π-camphorsulphonate*.

This salt crystallises from anhydrous ethyl acetate in minute needles. The rotation is unchanged after repeated crystallisation, 5·3 grams having $[\alpha]_D +28\cdot28°$ yielding, finally, 1·8 grams having $[\alpha]_D +28\cdot05°$. It melts, when dried at 110°, at 169—170° (172·5—173·5° corr.). It is deliquescent in a damp atmosphere, and then crystallises in microscopic, rectangular leaflets, probably a hydrated form. The anhydrous salt was analysed, with the following result:

0·2168, dried at 95°, lost 0·0003. Loss = 0·1 per cent.

0·0997, ,, 95°, gave 0·1934 CO_2 and 0·0538 H_2O. C = 52·9; H = 6·0.

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

The specific rotation was determined in water.

$c = 2\cdot026$; $l = 2$-dcm.; $\alpha +1°8\cdot2'$; $[\alpha]_D +28\cdot05°$; $[M]_D +172\cdot4°$.

This gives a value $[M]_D -106\cdot3°$ for the molecular rotation of the l-hyoscinium ion and $[\alpha]_D -34\cdot9°$.

Labile Salt.—On one occasion, a labile form of l-hyoscine bromocamphorsulphonate was isolated, the exact conditions being as follows. 7·5 Grams of freshly prepared, syrupy l-hyoscine bromocamphorsulphonate were repeatedly evaporated to dryness under diminished pressure with absolute alcohol in order to remove all adhering water. The residue, freed as completely as possible from absolute alcohol, was then dissolved in anhydrous ethyl acetate, and, on keeping for two days, a mixture of two salts separated in what appeared to be approximately equal proportions. One salt had the characteristic crystalline appearance of l-hyoscine d-$α$-bromo-$π$-camphorsulphonate described above, but the other formed tufts of much larger needles with a more glistening appearance. A trace of each was removed, when the former melted at 169—170°, and was thus ordinary l-hyoscine bromocamphorsulphonate, whilst the second melted, either air-dried or dried at 100°, at 150°. The whole of the deposit was collected and recrystallised from ethyl acetate. It separated overnight in tufts of silky needles, which melted at 150°, but was contaminated by a much smaller proportion, this time, of ordinary l-hyoscine bromocamphorsulphonate, easily discernible as smaller, white tufts of needles. The product amounted to 3·6 grams.

$c = 2\cdot068$; $l = 2$-dcm.; $\alpha +1°3\cdot4'$; $[\alpha]_D +25\cdot5°$.

O O*

This value is distinctly less than $[\alpha]_D + 28 \cdot 0°$ observed for ordinary *l*-hyoscine bromocamphorsulphonate. The product was again recrystallised, but gave the ordinary form of *l*-hyoscine bromocamphorsulphonate melting at 169—170°. All attempts again to isolate this labile salt from this particular batch of material were unsuccessful.

l-*Hyoscine Bromocamphorsulphonate*, m. p. 200°.

By resolution of a weakly active hyoscine by *d*-α-bromo-π-camphorsulphonic acid (this vol., p. 502), it was shown that the more sparingly soluble salt was *d*-hyoscine α-bromo-π-camphorsulphonate, and that from the mother liquors a deliquescent salt having a specific rotation approximating to that of a *l*-hyoscine *d*-α-bromo-π-camphorsulphonate could be isolated.

The final mother liquor, on prolonged keeping at a low temperature, deposited 1·65 grams (1·6 per cent. yield) of a salt crystallising in rosettes of rectangular leaflets. It was not deliquescent and melted at 199—200° (203—204° corr.).

The specific rotation was determined on material dried at 95°.

$$c = 1 \cdot 943 ; \quad l = 2\text{-dcm.} ; \quad \alpha + 41 \cdot 7' ; \quad [\alpha]_D + 17 \cdot 9°.$$

0·1028 gram, dried at 95°, gave 0·1994 CO_2 and 0·0553 H_2O.
$C = 52 \cdot 9 ; \; H = 6 \cdot 0.$

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

0·1 Gram of this salt was converted into the picrate, which amounted to 0·09 gram and melted at 183—186°. On recrystallisation, it gave 0·08 gram melting at 185—186°, and when mixed with *l*-hyoscine picrate, no depression in the melting point was observed.

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LONDON, E.C.   [*Received, June 27th*, 1919.]