CXIII.—*Some Salts of* d- *and* l-*a-Phenylethylamines.*

By Albert Edward Hunter and Frederic Stanley Kipping.

During the investigation of the salts of hydrindamine and of methylhydrindamine (this vol., p. 873 *et seq.*), we were led to examine those of several other optically active and *dl*-bases, and amongst these some salts of *dl*-*a*-phenylethylamine.

This base is easily prepared by the reduction of acetophenone oxime and has been resolved into its *d*- and *l*-components by Loven (*Ber.*, 1896, **29**, 2313); * as the method which he employed was not a very satisfactory one, we tried fractionally crystallising the *d*-bromocamphorsulphonate of the *dl*-base, and in the first place isolated a salt melting at about 206—207°.

Although in dilute aqueous solution the molecular rotation of this salt is $[M]_D + 271°$ (which is identical with that of the acid), the salt is not partially racemic, but is that of the *l*-base, the basic ion having no appreciable activity; the free base, however, in aqueous alcoholic solution is lævorotatory, its specific rotation being $[a]_D - 25°$; this behaviour recalls that of the *d*- and *l*-hydrindamines (compare Kipping, this vol., p. 873). The *d*-bromocamphorsulphonate of the *d*-base, which remains in the mother liquors from the preceding compound, was only obtained in an impure condition.

When pure *l*-phenylethylamine *d*-bromocamphorsulphonate was decomposed with barium hydroxide and regenerated from its component acid and base, the original salt was recovered apparently unchanged, showing that the base does not racemise under these conditions; when, further, this regenerated salt was repeatedly and systematically crystallised from water, it was not resolved into fractions having appreciably different specific rotations, a result which seems to show that the optically active *a*-phenylethylamine does not give rise to separable isomeric salts such as are obtained from hydrindamine.

Similar experiments were made with the *d*-chlorocamphorsulphonate of the *l*-base, but here also systematic crystallisation of the regenerated salt failed to reveal the existence of isomerides, the first and last fractions having practically the same specific rotation.

The salts obtained by combining the *dl*-base and the *l*-base respectively with Reychler's *d*-camphorsulphonic acid were also prepared, and it is interesting to note that the two substances differ very little

---

* Having gathered from a recent communication (Thomé, *Ber.*, 1903, **36**, 582) that Loven was continuing his work on this compound, and had already published further results in journals which were not accessible to us, we communicated with him, and found that we were working on different lines.

in melting point and have practically the same specific rotation, the data being as follows :

	m. p.	$[\alpha]_D$.	$[M]_D$.
dl-Phenylethylamine *d*-bromocamphorsulphonate	141—144°	+14·6°	+51·5°
l-Phenylethylamine *d*-bromocamphorsulphonate	149—150	14	50

Obviously, in this case, it would be barely possible to distinguish between the two salts by optical examination alone.

The benzoyl derivative prepared from the *l*-base is optically inactive, probably owing to racemisation having occurred.

Resolution of dl-*α-Phenylethylamine.*

α-Phenylethylamine, prepared by reducing acetophenoneoxime with sodium amalgam and acetic acid in dilute alcohol, is neutralised with an aqueous solution of *d*-bromocamphorsulphonic acid and the solution concentrated; the first and several subsequent deposits consist of compact prismatic crystals, but when about 40 per cent. of the total salt has been separated, the solution yields long, feathery needles, very different in character from the crystals previously obtained. The first deposits, when crystallised several times from water, give long, well-defined, anhydrous prisms, which are only sparingly soluble in water, and which melt sharply at 206—207°; the feathery needles, when fractionally crystallised, yield further quantities of the sparingly soluble salt, which it is extremely difficult, if not impossible, to separate entirely. A sample of the readily soluble salt, which had been fractionally crystallised some 20 or 30 times, melted indefinitely at about 80° when dried on porous earthenware, and appeared to contain water of crystallisation; when dried at 60° for several hours, it melted at about 160°.

Samples of the two salts, dried at 100°, were examined optically in a 200 mm. tube with the following results :

			α_D.	$[\alpha]_D$.	$[M]_D$.
Salt, m. p. 206°	0·5 gram	20 c.c. of water	+3·14°	+62·8°	+271°
,, 160°	0·5 ,,	25 ,,	2·45	61·2	264

The molecular rotation of *d*-bromocamphorsulphonic acid being +270°, it seemed probable that both these salts were partially racemic, and this view was apparently confirmed by the fact that the benzoyl derivatives of the bases from each of the salts, prepared by the Schotten-Baumann method, were identical in melting point and outward properties with the derivative obtained from the original *dl*-base; mixtures of the three compounds also melted at the same temperature as the single substance, namely, at 120°.

When, however, a small quantity of the pure, sparingly soluble salt was decomposed with barium hydroxide, the liberated base distilled in steam, and combined again with the acid recovered from the barium salt, the product was found to consist entirely of the salt melting at 206—207°; the readily soluble salt, when regenerated in a similar manner, was also unchanged.

Now, if these salts represented isomeric, partially racemic compounds, such as are obtained from hydrindamine, each should have given a mixture of the two isomerides; as this was not the case, we concluded that, in spite of their apparently anomalous molecular rotations, they were really the salts of the two enantiomorphously related bases.

This view was confirmed by decomposing with barium hydroxide a sample of the pure sparingly soluble salt (m. p. 206—207°) having a specific rotation $[\alpha]_D$ +63·2°; the liberated base was distilled in steam and the distillate neutralised with hydrochloric acid; the hydrochloride which was ultimately obtained from the solution was recrystallised from water and from ethyl acetate and dried at 100°.

One gram of this salt, when dissolved in water and the solution diluted to 25 c.c., was examined in a 200 mm. tube and gave α_D −0·3°, whence $[\alpha]_D$ − 3·7°.

As the base appeared to have only a very small specific rotation in solutions of its salts, 1 gram of the hydrochloride was decomposed with caustic potash and the liberated base distilled in steam; the first 25 c.c. of the distillate, when clarified by the addition of alcohol and examined in a 200 mm. tube, gave α_D −1·33°, so that the specific rotation $[\alpha]_D$ of the free base is at least − 22°.

Other determinations in which the quantity of base in the solution was subsequently estimated by titration gave $[\alpha]_D$ − 25°; there is therefore no doubt that fractional crystallisation of the *d*-bromocamphorsulphonate of *dl*-α-phenylethylamine effects a resolution into the salts of the *d*- and *l*-bases.

The salt of the *l*-base is readily soluble in hot water, alcohol, and chloroform, sparingly so in cold water, acetone, and carbon tetrachloride, and practically insoluble in ethyl acetate; the salt of the *d*-base is very soluble in cold water and many organic solvents, but only sparingly so in ethyl acetate.

Regeneration of l-α-*Phenylethylamine* d-*Bromocamphorsulphonate.*

It has already been stated that the regenerated *l*-α-phenylethylamine *d*-bromocamphorsulphonate is free from the salt of the *d*-base, and is apparently identical with the original substance. In order to try to isolate isomeric salts such as are obtained from hydrindamine and from methylhydrindamine (*loc. cit.*), a considerable quantity of the pure salt melting at 206—207° was decomposed and regenerated from the same acid and the same base.

Although the salt thus obtained was subjected to a prolonged process of fractional crystallisation, the most readily soluble portion, which at first melted at about 202°, when crystallised twice from water melted at 206°, and appeared to be identical with the most sparingly soluble fraction.

As hydrolytic dissociation might possibly account for the failure to isolate isomeric compounds, a second experiment was made, the regenerated salt being fractionally crystallised from a mixture of absolute alcohol and ethyl acetate; the result, however, was the same as before, the first and last fractions differed in melting point by barely 1°, and they had the same specific rotation, namely, $[\alpha]_D + 50°$ in a 3 per cent. chloroform solution.

l-α-*Phenylethylamine* d-*Chlorocamphorsulphonate.*

A solution of the *l*-base prepared from pure *l*-α-phenylethylamine *d*-bromocamphorsulphonate was neutralised with *d*-chlorocamphorsulphonic acid and evaporated; the first deposit, which consisted of long, slender needles, was then recrystallised several times from hot water, in which it was readily soluble; the most sparingly soluble fraction, which then melted at about 198°, was dried at 100° and examined optically.

0·5 gram dissolved in water, the solution diluted to 20 c.c., and examined in a 200 mm. tube, gave $\alpha_D + 2·4°$, whence $[\alpha]_D + 48°$, and $[M]_D + 186°$.

The molecular rotation for *d*-chlorocamphorsulphonic acid being $[M]_D + 188°$, this result agrees with those obtained in the determinations made with the *d*-bromocamphorsulphonate in showing that the basic ion is practically devoid of optical activity. The whole of the *d*-chlorocamphorsulphonate was next submitted to fractional crystallisation, and after some 20—30 operations a small quantity of salt was obtained from the last mother liquors; this melted a few degrees lower than the first fraction, but when examined optically it gave the following result, which is practically the same as that obtained with the sparingly soluble fraction referred to above:

0·143 gram dissolved in water, the solution diluted to 20 c.c., and examined in a 200 mm. tube, gave $\alpha_D + 0·68°$, whence $[\alpha]_D + 47·5°$, and $[M]_D + 184°$.

Further fractional crystallisation failed to afford any indication of the presence of isomeric salts, the values finally obtained for the first and last fractions being $[\alpha]_D + 185·5°$ and 188° respectively in aqueous solution.

Salts with Reychler's d-*Camphorsulphonic Acid.*

As the *d*-bromocamphorsulphonate of the *d*-base could not be completely separated from the salt of the *l*-base on account of its greater solubility in water, we attempted to prepare the pure *d*-base with the aid of Reychler's *d*-camphorsulphonic acid. Pope and Harvey (Trans., 1899, **75**, 1110) describe the salt of the inactive base as crystallising from acetone in plates melting at 141—143°, and classify it as a partially racemic compound; on repeating the work, our results appeared to agree with theirs, but the melting point of the salt of the *dl*-base was found to be raised several degrees by prolonged crystallisation.

The impure *d*-base obtained from the crude *d*-bromocamphorsulphonate was combined with Reychler's acid and the salt fractionally crystallised both from acetone and from ethyl acetate; the melting point rose slowly on repeated crystallisation from about 140° to 146°, and the specific rotation of a sample of the salt was then determined.

One gram dissolved in water and the solution diluted to 20 c.c. gave, in a 200 mm. tube, $\alpha_D + 1{\cdot}46^\circ$, whence $[\alpha]_D + 14{\cdot}6^\circ$ and $[M]_D + 51{\cdot}5^\circ$.

The molecular rotation for salts of Reychler's acid with inactive bases being $[M]_D + 51^\circ$, this result seemed to indicate the presence of *dl*-base, but bearing in mind the behaviour of *l*-α-phenylethylamine *d*-bromocamphorsulphonate, it was quite possible that the salt was that of the *d*-base; as a matter of fact, the base obtained from this salt was found to have a specific rotation of about $[\alpha]_D + 8^\circ$, showing that the preparation consisted of very unequal quantities of the salts of the *d*- and *l*-bases. The salt was therefore crystallised again several times, but although the melting point eventually reached 149° the specific rotation of the base contained in it remained practically the same as before; the base liberated from the most readily soluble fraction had also approximately the same specific rotation as that obtained from the most sparingly soluble portion.

In order to compare the physical properties of the salt of the *l*-base with that of the *dl*-compound, the Reychler salt was prepared from the pure *l*-base; when crystallised from ethyl acetate several times, it was obtained in plates which were, as far as could be ascertained, identical in appearance with the crystals of the corresponding salt of the *dl*-base and melted at 149—150°.

Optical examination gave the following result: 0·22 gram dissolved in water and the solution diluted to 20 c.c., gave, in a 200 mm. tube, $\alpha_D + 0{\cdot}31^\circ$, whence $[\alpha]_D + 14^\circ$ and $[M]_D + 50^\circ$.

These experiments show that the salts of the two enantiomorphously related bases differ but little from each other and from the salt of the *dl*-base both in solubility and in melting point, so that Reychler's acid is useless for the resolution of the *dl*-base. Whether the salt of the *dl*-base is partially racemic or a mere mixture, there is insufficient evidence to decide.

Benzoyl Derivative from the l-*Base.*

As the benzoyl derivatives prepared from the *d*- and from the *dl*-base respectively melted, as already mentioned, at the same temperature, it seemed desirable to ascertain if the base had undergone racemisation during benzoylation. For this purpose, a small quantity of the pure *d*-chlorocamphorsulphonate was shaken up with strong caustic soda solution and benzoyl chloride in the usual way, and the resulting product crystallised from dilute alcohol.

A solution of about 1 gram in sufficient alcohol to fill a 200 mm. tube was found, on examination in the polarimeter, to possess no optical activity whatever; and, on subsequent hydrolysis with strong hydrochloric acid, the base recovered was found to have undergone complete racemisation. The base itself seems to be stable, and apparently does not undergo racemisation when heated; a sample of the crude *d*-base, which had been distilled under reduced pressure and subsequently under atmospheric pressure, was still optically active.

It seems, therefore, that the base undergoes racemisation during the preparation of the benzoyl derivative.

The authors beg to acknowledge their indebtedness to the Government Grant Committee of the Royal Society for financial assistance in carrying out this work.

UNIVERSITY COLLEGE,
NOTTINGHAM.