XLVIII.—*A Study of Some Asymmetric Compounds.*

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ALTHOUGH a great many externally compensated bases and acids of widely different types have been resolved into their components by fractionally crystallising their salts, and although in this way optically active compounds containing asymmetric carbon, nitrogen, sulphur, selenium, tin, and silicon atoms have been obtained, it is still impossible, even in dealing with very closely related or homologous compounds, to form any preconceived opinion as to whether a given optically active base will or will not effect the resolution of a given *dl*-acid, or a given optically active acid that of a given *dl*-base. Thus, although the *dl*-sulphonic acids derived respectively from the homologous compounds, benzylethylpropylsilicyl oxide (Kipping, Trans., 1907, **91**, 209; 1908, **93**, 457) and benzylethyl*iso*butylsilicyl oxide (Luff and Kipping, Trans., 1908, **93**, 2090), may both be resolved with the aid of methylhydrindamine, of the three homologous *dl*-bases, namely, hydrindamine, methylhydrindamine, and pheno-α-amino*cyclo*heptane, only the two latter are resolved by fractionally crystallising their *d*-hydrogen tartrates from water (Kipping and Hunter, Trans., 1902, **81**, 574; Tattersall, Trans., 1904, **85**, 169), in spite of the fact that hydrindamine and pheno-α-amino*cyclo*heptane, which contain only one asymmetric carbon atom respectively, are far more closely related to one another than to methylhydrindamine, the molecule of which contains two different asymmetric carbon atoms. Again, *dl*-hydrindamine may be resolved by crystallising its *d*-bromocamphorsulphonate from a hot mixture of ethyl acetate and alcohol (Kipping, Trans., 1903, **83**, 873), but not by crystallising its *d*-chlorocamphorsulphonate under similar conditions (Trans., 1903, **83**, 902).

Now, if the possibility of the existence in solution of definite partially racemic salts, *d*A*l*B, *d*A*d*B, or *d*A*d*B, *l*A*d*B, be excluded, it would seem that the resolution of any *dl*-compound by the method under discussion is determined entirely by the difference in solubility of the two components, *d*A*l*B and *d*A*d*B, or *d*A*d*B and *l*A*d*B, as the case may be, under the conditions chosen. If, therefore, it is known that a particular *dl*-acid, A, may be resolved by fractionally crystallising its salt with a particular optically active base, B, from a particular solvent, it might be inferred that the resolution of the *dl*-base, B, by fractionally crystallising its salt with the optically active acid, A, from the same solvent, should

also be possible. Both salts contain the component $dAdB$, which is mixed in the first case with $lAdB$, in the second case with an equal quantity of $dAlB$; but $lAdB$ and $dAlB$ are enantiomorphously related, and therefore are equally soluble in any optically inactive solvent; consequently, since $dAdB$ and $lAdB$ are known to be separable owing to their different solubilities, it would seem that $dAdB$ and $dAlB$ should also be separable under the same conditions. Taking a definite example, dl-sulphobenzylethylpropylsilicyl oxide may be resolved with the aid of d-methylhydrindamine; conse-quently it might be concluded that dl-methylhydrindamine should be resolved by fractionally crystallising its salt with one of the active sulphobenzylethylpropylsilicyl oxides under the same con-ditions.

As such a resolution of this dl-base would have afforded a par-ticularly striking demonstration of the asymmetric structure of the silicon compound just named, this case was first examined, and the salt prepared from dl-methylhydrindamine and one of the active silicon acids was submitted to fractional crystallisation under the same conditions as those employed in resolving the dl-silicon com-pound with the active base; the results, however, were negative, inasmuch as all fractions of the salt yielded optically inactive base. This was not due to the racemisation of the active silicon compound; when the latter was recovered from the salt, it still retained its asymmetry, and gave totally different products when treated with d- and with l-methylhydrindamine respectively.

It was thus proved that in this instance the mixture of $dAdB$ and $dAlB$ behaves very differently from the mixture of $dAdB$ and $lAdB$.

Wishing to obtain, if possible, some other example of a similar kind, the case of tartaric acid and methylhydrindamine was examined. dl-Methylhydrindamine may be resolved by fractionally crystallising from water its d-hydrogen tartrate (Tattersall, $loc.\ cit.$), the $dAdB$ salt being less soluble than the $dAlB$ component. Ex-periments showed that the resolution of dl-tartaric acid could be accomplished, possibly even more easily than that of the base, with the aid of d-methylhydrindamine; by fractionally crystallising from water, both the components $lAdB$ and $dAdB$ may be isolated in a state of purity, and a large proportion of the dl-acid may be resolved.

As this result did not afford the desired confirmation of that obtained in the case of methylhydrindamine and the silicon com-pound, experiments were next made with mandelic acid and hydrindamine. It had been shown some years ago (Kipping and Hall, Trans., 1901, **79**, 442) that dl-hydrindamine is not resolved

when its salt with d-mandelic acid is crystallised from alcohol; further, that a mixture of dl-hydrindamine dl-mandelate and dl-hydrindamine d-mandelate is not separated into different fractions when it is crystallised from alcohol; these results seemed to show that the components $dAdB$ and $dAlB$ had the same solubility, and, therefore, that the resolution of dl-mandelic acid could not be accomplished with the aid of one of the active hydrindamines.

Nevertheless, on fractionally crystallising d-hydrindamine dl-mandelate from water, the acid is resolved without the slightest difficulty; a marked difference between the several fractions both in appearance and in melting point is observed after one or two crystallisations, and the pure $lAdB$ salt is obtained in the most sparingly soluble portions. This result was verified by repeating the experiment several times, and was confirmed by resolving the dl-acid with l-hydrindamine in a similar manner, when the pure $dAlB$ salt was obtained as the more sparingly soluble component.

Some time having elapsed since the attempts to resolve dl-hydrindamine with d-mandelic acid were made, and ethyl alcohol (or aqueous alcohol) having then been used as solvent, it was thought advisable to repeat the experiments under conditions as nearly as possible identical with those employed in the resolution of the dl-acid; this was done, and the dl-hydrindamine d-mandelate was repeatedly and systematically crystallised from water, but it remained homogeneous; even when the saturated solution was seeded with the $dAlB$ salt, not the slightest indication of a resolution was observed.

It is thus proved, by the two cases recorded above, that when a $dAdB$ salt is mixed with an equivalent quantity of the corresponding $lAdB$ salt in one case, and of the enantiomorphously related $dAlB$ salt in the other, the mixtures may behave altogether differently towards a given solvent.

From this fact it must be concluded that the presence in the solution of the $dAdB$ salt influences the solubility of the $lAdB$ and $dAlB$ components to a different extent.

Although up to the present there is no experimental evidence on record that the solubilities of two enantiomorphously related compounds are different when they are in presence of some other optically active substance, and attempts to obtain such evidence have failed (Kipping and Pope, this vol., p. 103), the results recorded in this paper may be interpreted in conformity with such a view; a saturated solution of $dAdB + lAdB$ deposits $lAdB$, whereas a saturated solution of $dAdB + dAlB$ deposits the partially racemic salt, even when it is seeded with $dAlB$.

The cause of this different effect of the $dAdB$ salt on the enantio-

morphously related $lAdB$ and $dAlB$ compounds may be independent of any definite combination between the molecules in the solution, or it may be due to the existence of dissolved complexes of a fixed character; that is to say, the solubility of $dAlB$ in presence of $dAdB$ may be greater than that of $lAdB$ for the same reason—whatever that may be—that $dAlB$ is more soluble in alcohol than in petroleum; on the other hand, the $dAdB$ and $dAlB$ components may unite to form in solution definite molecules of the partially racemic salt, possibly because the configurations of the lB and dB molecules better lend themselves to close-packing than the molecules of dA and lA.

The question as to the existence in solution of partially racemic salts has not, to the author's knowledge, been raised, although several workers have tried to find out whether or not racemic compounds exist in a dissolved state. The evidence more recently brought forward (Byk, *Zeitsch. physikal. Chem.*, 1904, **49**, 641; Ranken and Taylor, *Proc. Roy. Soc. Edin.*, 1907, **27**, 172; Stewart, Trans., 1907, **91**, 1537; Dunstan and Thole, Trans., 1908, **93**, 1815) certainly seems to point to the existence of dissolved racemic molecules; the results of this investigation indicate perhaps even more strongly the presence in solution of partially racemic molecules.

EXPERIMENTAL.

Sulphobenzylethylpropylsilicyl Oxide and Methylhydrindamine.

dl-Sulphobenzylethylpropylsilicyl oxide is easily resolved by fractionally crystallising its salt with d-(or with l-)methylhydrindamine from aqueous methyl alcohol (*loc. cit.*); the $dAdB$ salt is ultimately obtained in a pure state in the most sparingly soluble fractions, and melts at 205—207°; the impure $lAdB$ salt, obtained from the mother liquors, melts at about 135°, the pure compound prepared from the l-acid melting at 150—152°.

A sample of the sodium salt of d-sulphobenzylethylpropylsilicyl oxide was treated with dl-methylhydrindamine hydrochloride in aqueous solution; the precipitate remained oily for many hours, even when seeded with crystals of the $dAdB$ salt, but ultimately solidified, and, after having been washed, was fractionally crystallised from aqueous methyl alcohol at the ordinary temperature; after several operations, the most sparingly soluble deposit crystallised rather more readily than the more soluble ones, and it seemed as if a resolution had occurred. After perhaps seven or eight crystallisations, the most sparingly soluble fraction, which then formed only a small proportion of the original preparation, was examined; it melted indefinitely at about 165°, and its melting point was not

raised appreciably after two further crystallisations from anhydrous acetone.   The salt in the more soluble fractions, which often remained oily during several days, was ultimately obtained as a lustrous, crystalline powder, free from oil, and melted fairly sharply at 150—152°.

The extreme fractions of the salt were then separately treated with a slight excess of sodium carbonate, and the methylhydrindamine was distilled in a current of steam; the distillates were neutralised with *d*-bromocamphorsulphonic acid, and the salts thus formed were fractionally crystallised from water.   All the fractions of both preparations consisted of homogeneous deposits of *dl*-methylhydrindamine *d*-bromocamphorsulphonate, and not a trace of the salt of the active base could be detected.   As fractional crystallisation of a mixture of *unequal* quantities of *d*- and *l*-methylhydrindamine *d*-bromocamphorsulphonates easily affords the pure salt of that active base which is present in the larger proportion (Tattersall and Kipping, Trans., 1903, **83**, 929), these results proved that the *dl*-base had not been resolved.

The sodium salt of the acid, which remained after distilling the base in steam, was examined; it gave with *l*-methylhydrindamine hydrochloride an oily precipitate which solidified only very slowly to a gelatinous mass, but with the *d*-base it gave a precipitate which crystallised immediately, and, after recrystallisation once from aqueous methyl alcohol, melted at 200—204°.   Hence the acid consisted mainly, if not entirely, of the optically pure *d*-compound; that it contained a relatively very small quantity of the *l*-acid, however, seems to be probable; otherwise the observed difference in melting points of the various fractions of the *dl*-methylhydrindamine salt can hardly be accounted for.*

The fractional crystallisation of the salt obtained by combining *dl*-methylhydrindamine with a sample of the *l*-silicon derivative confirmed the above observations in every particular.

Tartaric Acid and Methylhydrindamine.

The resolution of *dl*-methylhydrindamine may be accomplished by fractionally crystallising from water its *d*-hydrogen tartrate (Tattersall, *loc. cit.*); from the most sparingly soluble fractions, the pure salt of the *d*-base is obtained, but it is not definitely stated whether or not the salt of the *l*-base can be isolated from the mother liquors.

* The possibility of the occurrence of partial racemisation during the preparation of the active silicon compounds from their methylhydrindamine salts (compare Trans. 1907 **93**, 465) has not yet been further investigated.

A sample of Kahlbaum's racemic acid (1 mol.) * was treated with d-methylhydrindamine (1 mol.), and the salt was fractionally crystallised from water. The first deposit, or that obtained from it after one recrystallisation, consisted almost entirely of the hydrated dAdB salt, which, when dried at 100°, melted at 151—153°, and had the same specific rotation in aqueous solution as the compound obtained in resolving the dl-base with the d-acid:

1·318 grams of anhydrous salt, made up to 25 c.c. in a 2-dcm. tube, gave $a + 3·48°$; whence $[a]_D + 32·4°$.

After further fractionation, the intermediate portions melted indefinitely at temperatures ranging from 168° to 178°, but the most soluble ones had a much higher melting point; the latter, on recrystallisation, gave deposits of the pure anhydrous lAdB salt, identical with the compound (m. p. 197°) prepared by Tattersall by treating the l-base with d-tartaric acid; its specific rotation was determined in aqueous solution:

1·403 grams of dry salt, made up to 25 c.c. in a 2-dcm. tube, gave $a - 0·73°$; whence $[a]_D - 6·5°$.

The pure dAdB and lAdB salts thus obtained were separately converted into the sodium salts, which were strongly dextro- and lævo-rotatory respectively.

The resolution of the dl-acid under the above conditions was so complete that about 4 grams of pure dAdB and about 2 grams of pure lAdB salt were obtained without any difficulty from 10 grams of the original mixture.

Mandelic Acid and Hydrindamine.

dl-Hydrindamine is not resolved when its salt with d-mandelic acid is fractionally crystallised from alcohol, extreme fractions obtained after many operations having the same melting point (138—140°) and the same specific rotation (loc. cit.).

A sample of pure d-mandelic acid was treated with dl-hydrindamine, suspended and dissolved in water, and the solution evaporated, fresh base being added from time to time until a concentrated neutral solution of the salt was obtained; on cooling, the compound separated in prisms, but when cold solutions evaporated spontaneously, hard, compact nodules were deposited. Repeated attempts were made to resolve this salt; it was frac-

* This acid possibly contained a slight excess of d-tartaric acid, but far too small a quantity to be detected polarimetrically (Kipping and Pope, loc. cit.).

tionally crystallised from water at different temperatures, but all
the deposits were similar in character, and had the same melting
point (138—140°).   In some experiments, the warm concentrated
solution was seeded with a specimen of the *dAlB* component (see
below), and, after a small proportion of the salt had crystallised,
this was separated and re-dissolved, but the deposit still consisted
of the partially racemic substance.   It may be concluded, therefore,
that the *dl*-base cannot be resolved with *d*-mandelic acid under
such conditions.

A sample of *dl*-mandelic acid was treated with *d*-hydrindamine
(Trans., 1903, **83**, 876) as described in the case of the *d*-acid and
the *dl*-base.   On cooling the concentrated aqueous solution, lustrous,
transparent needles were first deposited, and then small, opaque,
white masses began to form ; after filtering rapidly and recrystal-
lising this first fraction from water, a salt melting at 160—162°
was obtained.   The mother liquors from this compound gave
opaque deposits, which were systematically crystallised from water,
a little *d*-base being added from time to time as the solutions
became acid during evaporation ; the several fractions thus obtained
were totally different in appearance from the compact nodules of
the homogeneous salt prepared from the *d*-acid and the *dl*-base,
and consisted of very bulky masses, which almost completely hid
the solution ; very often the solutions first set to a translucent mass
of extremely fine filaments, in which a white, opaque growth,
resembling cotton wool in appearance, began to form and gradually
extended.   These observations seemed to point to the presence of
two definite compounds in the deposits, but it was not found possible
to isolate even one; some of these fractions melted from about
125° to 130°, others from 130° to 135°.

d-*Hydrindamine* l-*Mandelate and* l-*Hydrindamine* d-*Mandelate.*

The sparingly soluble salt melting at 160—162°, obtained by
resolving the *dl*-acid with the *d*-base, is the *lAdB* compound; the
enantiomorphously related *dAlB* salt was prepared in a similar
manner by resolving the *dl*-acid with the *l*-base.   These compounds
separate from water in lustrous prisms, and, when pure, melt at
about 164° if quickly heated ; a mixture of the two salts melted
at 138—140°.

Their specific rotations were determined in ethyl-alcoholic (99·8
per cent.) solution :

  lAdB salt : 0·932 gram, made up to 25 c.c. in a 2-dcm. tube, gave
    $a - 4·11°$; whence $[a_D] - 55°$.

dAlB salt: 0·844 gram, made up to 25 c.c. in a 2-dcm. tube, gave
  $a + 3·85°$; whence $[a]_D + 57°$.*

The solutions used in these determinations were separately treated
with sodium carbonate in excess, and the hydrindamine was distilled
in a current of steam; the solutions of the sodium salts were then
concentrated, made up to 25 c.c. with water, and examined polari-
metrically in a 2-dcm. tube.

The solution from the lAdB salt gave $a - 4·25°$, and that from
the dAlB salt gave $a + 4·02°$; calculating the specific rotation of
the mandelic acid contained in the solutions, the values are
$[a]_D - 107°$ and $+ 112°$ respectively.

After evaporating again, the solutions of the sodium salts were
separately treated with excess of dilute hydrochloric acid, and the
precipitates of mandelic acid were recrystallised from a very little
water and dried; they both melted at 130—132°, simultaneously
with a specimen of d-mandelic acid.

These observations prove conclusively that dl-mandelic acid may
be easily resolved with the aid of one of the active hydrindamines,
in spite of the fact that dl-hydrindamine cannot be resolved with
d-mandelic acid under the same conditions.

d-*Hydrindamine* d-*Mandelate.*

This salt, prepared from the d-acid and the d-base, crystallises
from water in lustrous plates or flat prisms; it generally begins to
sinter at about 144°, and melts at 147—148°, but sometimes it
does not liquefy completely until the temperature rises to 157—158°.
This behaviour is due to dimorphism; when the tube containing
the salt is plunged into a bath already heated at 148°, complete
fusion occurs, whereas if the liquefied sample is then allowed to
solidify and again heated, but slowly, it does not melt until
157—158°.

The specific rotation of this salt in ethyl-alcoholic (99·8 per cent.)
solution is practically the same as that of the dAlB compound, as
shown by the following determinations (carried out by Mr. Barrow-
cliff):

  0·997 gram, made up to 100 c.c. in a 2-dcm. tube, gave $a + 1·07°$;
    whence $[a]_D + 53·8°$.
  0·990 gram, made up to 100 c.c. in a 2-dcm. tube, gave $a + 1·06°$;
    whence $[a]_D + 53·6°$.

* A sample of the dAlB salt was prepared some years ago in this laboratory (by
Mr. Barrowcliff) from the d-acid and the l-base, and its specific rotation was deter-
mined in ethyl-alcoholic solution with the following result:

0·995 gram, made up to 100 c.c. in a 2-dcm. tube, gave $a + 1·07°$; whence $[a]_D + 53·6°$.

The Specific Rotation of Mandelic Acid and its Salts.

The value given in the literature for the specific rotation of d-mandelic acid in aqueous solution varies from $[a]_D + 150°$ to $160°$ (compare Kipping and Hall, *loc. cit.*); the d-acid used in the above experiments gave the following result:

0·51 gram, made up to 25 c.c. in a 2-dcm. tube, gave $a + 6·36°$; whence $[a]_D + 156°$.

As the specific rotations of the l- and d-acids, calculated from the results obtained with solutions of their sodium salts, were only $[a]_D - 107°$ and $+ 112°$ respectively, and as these sodium salts were doubtless optically pure, it was obvious that the molecular rotation of the sodium salt must be very much smaller than that of the free optically active acid.

This conclusion was confirmed; the solution of d-mandelic acid which gave $a + 6·36°$, $[a]_D + 156°$, was treated with about 0·6 gram of hydrated sodium carbonate, concentrated a little, and again made up to 25 c.c. and examined in a 2-dcm. tube; the result was $a + 4·82°$; whence the specific rotation calculated for the free *acid* is $[a]_D + 118°$. The difference between this value and those ($-107°$ and $+ 112°$) given above is probably due to a difference in the quantities of sodium carbonate present in the solutions.

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