IV.—*Characterisation of Racemic Compounds.*

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WE have previously shown (Trans., 1897, **71**, 989) that the results of the study of a number of externally compensated substances indicate that only one method is at present of really practical use for characterising solid racemic compounds, that, namely, which is based on the determination of the crystalline forms of the optically active and externally compensated materials; and, in accordance with this conclusion, we defined crystalline racemic and pseudoracemic compounds from a purely crystallographic standpoint (*loc. cit.*, 993).   But the crystallographic constants of an organic substance are not always determinable with ease and completeness; hence the establishment of other criteria of racemism is a matter of considerable importance.

Now, Liebisch has shown (*Annalen*, 1895, **286**, 140) that a comparison of the densities of the optically active and externally compensated compounds affords a very simple method for the determination of racemism (compare Walden, *Ber.*, 1896, **29**, 1692); unfortunately, however, the results of the experimental determination of a difference between two density constants, especially when this difference is very small, as it frequently may be, can hardly be considered so conclusive as those derived from the much more complex series of constants constituting the crystallographic properties.

This difficulty of ascertaining, except by crystallographic· determinations, whether certain substances are really racemic on the one hand, or merely pseudoracemic or externally compensated mixtures on

the other, has led to attempts being made to devise simpler methods for the determination of racemism. Thus, Ladenburg (*Ber.*, 1894, **27**, 3065) formulates " eine allgemeine Methode, um Gemenge enantiomorpher Körper von racemischen Verbindungen zu unterscheiden. Sobald es gelingt, die in Frage stehende Substanz, die wenigstens einen kleinen Ueberschuss der einen drehenden Modification enthalten muss, durch Behandlung mit inactiven Körpern in Fractionen von verändertem Drehungsvermögen zu verwandeln, liegt stets eine Verbindung vor."

Now this method, if really applicable, should prove of great value, but inasmuch as Ladenburg adduces no experimental evidence supporting its validity as a means of discrimination, but uses it without further inquiry in order to decide as to the racemic nature of externally compensated coniine, the conclusions based on its use cannot be regarded as in any way decisive.

Moreover, the method is arrived at by means of a curiously fallacious piece of reasoning, for, just before the above quotation, Ladenburg writes : " es ist, wie ich glaube, eine bisher ausnahmlos bestätigte Thatsache, dass enantiomorphe Körper stets die gleiche Löslichkeit besitzen und daher auch in Verbindung mit inactiven Stoffen nicht durch Krystallisation oder partielle Fällung getrennt werden können."

Now there seems not the least justification, experimental or theoretical, for the deduction which Ladenburg draws from the fact of the equal solubility of the two enantiomorphously related substances, namely, that a mixture of unequal quantities could not be separated by crystallisation or partial precipitation. There is, in fact, no evidence that an inactive non-racemic mixture has the same solubility as either of its active components and if its solubility be greater, then, on concentrating a solution containing such a non-racemic mixture together with excess of one enantiomorph, at constant temperature, that excess would crystallise first, leaving material of lower specific rotation in solution ; a continuation of this process would ultimately afford a mother liquor containing an inactive non-racemic mixture. The solution would then go on depositing dextro- and lævo-material in equal proportion as evaporation proceeded, casual disturbances of equilibrium such as always occur in a crystallising solution being, of course, disregarded. Obviously, therefore, any arguments based upon our present knowledge of the laws governing solubility should have led Ladenburg to a conclusion diametrically opposed to that at which he actually arrived.

The question of the racemic nature of externally compensated coniine has lately been again considered, and Küster (*Ber.*, 1898, **31**, 1847), arguing from the solubility products of the various isomerides, con-

cludes that a large part of the inactive substance exists in solution in a racemic condition. Although this conclusion may be true, yet, inasmuch as no case has been investigated in which the solubility values indicate that no racemism occurs in the solution, or in the solid state, as the case may be, Küster's method cannot be accepted. A hypothesis founded upon one set of phenomena often gives valuable indications as to the direction in which work should be done in connection with the examination of a second set of phenomena, but these are merely indications, and require experimental verification before the hypothesis can be extended so as to cover the new ground. The cases dealt with by Küster are instances in which the ordinary solubility laws applying to two mutually inactive solutes are not followed ; when a case is found amongst externally compensated substances in which the solubility determinations indicate the non-existence of a racemic compound in solution, Küster's method will become of practical value. Until then, however, it must be classed with Ladenburg's method as an untried one.

In order to ascertain the accuracy or otherwise of Ladenburg's argument, we have examined three cases experimentally ; those, namely, of sodium ammonium tartrate, sodium potassium tartrate, and potassium hydrogen tartrate.

Sodium Ammonium Dextro- and Lævo-tartrates.

An externally compensated mixture of dextro- and lævo-sodium ammonium tartrates is known to be non-racemic at ordinary temperatures, but becomes racemic at and above 27° (van't Hoff and Deventer, *Ber.*, 1886, **19**, 2148); below this temperature, the salt separates from solution as a mere mixture of the two tartrates.

Now, if Ladenburg's rule be applicable, on crystallising the sodium ammonium salt of racemic acid with an excess of sodium ammonium dextrotartrate below 27°, the successive fractions should have the same specific rotation ; but, as a matter of fact, the behaviour of the mixture on crystallisation is that which would be expected from our interpretation of the laws governing the equilibrium of such solutions.

In a preliminary experiment, an intimate mixture of 25 grams of sodium ammonium dextrotartrate with 5 grams of the corresponding lævotartrate was made ; it was found to have the specific rotation $[a]_D = +15\cdot60°$ in a 5 per cent. solution, instead of the calculated value $[a] = +15\cdot76°$. The mixture was dissolved in cold water and set aside to evaporate; after several days, a fraction (1) separated and was collected, washed with cold water, and dried in the air. The mother liquor and washings were mixed and set aside to crystallise,

when a further separation (2) was obtained; this was removed as before, the mother liquors evaporated to dryness, and the residue collected. During the experiment, the laboratory temperature never rose above 15°; the weights and rotations of these fractions were as follows.

	Weight.	$[a]_D$
Total material	30 g.	$+15 \cdot 60°$
First fraction, (1)	8 g.	$+23 \cdot 51$
Second ,, (2)	13 g.	$+20 \cdot 27$
Third ,, (3)	8 g.	0

Instead of all the .three separations having the same specific rotation as the original mixture, as required by Ladenburg's rule, the first two fractions consisted almost entirely of dextrotartrate, whilst a 5 per cent. aqueous solution of the residue in the mother liquor had no observable rotation in a 200 mm. tube.

In order to trace this process of separation more carefully, and thus obtain further data, the following experiments were made. A mixture of 26·1 grams of sodium ammonium dextrotartrate, with an equal weight of the salt obtained from racemic acid, was made; this mixture, having a specific rotation of $[a]_D = +11 \cdot 82°$, was dissolved in water and allowed to crystallise spontaneously at the ordinary laboratory temperature, which never rose above 18°, namely, 9° below the temperature at which a racemic compound begins to separate. As the various deposits were obtained, they were separated by means of the filter pump (but not washed free from mother liquor) and examined, the fractionation proceeding in accordance with the following scheme (next page).

The weights, w, and the specific rotations a, of the various fractions are given in columns 2 and 3 respectively of Table I (p. 41), columns 5 and 6 give respectively the excess of dextro- over inactive salt in 100 parts of the various fractions, and the actual weights in grams of the excess of dextro-salt in these fractions.

The weight of salt recovered from the 52·2 grams dissolved was $\Sigma w = 51 \cdot 25$ grams; the weighted mean specific rotation of all the fractions is $\Sigma wa/\Sigma w = +12 \cdot 20°$, and if the weight of salt taken, namely, 52·2 grams be substituted for Σw, the mean specific rotation $\Sigma wa/52 \cdot 2 = +11 \cdot 98°$ is obtained.

The mixture of salts actually had the specific rotation $[a]_D = +11 \cdot 82°$ so that within the limits of the experimental errors unavoidably incurred in so long a series of fractionations, the whole of the salt used is accounted for.

The specific rotation of sodium ammonium dextrotartrate,
$$\mathrm{Na(NH_4)C_4H_4O_6 + 4H_2O},$$
is $[a]_D = +23 \cdot 64°$, and the first large deposit of 32·1 grams contained

26·1 grams. d-Na(NH$_4$)C$_4$H$_4$O$_6$,4H$_2$O.
26·1 grams. i-Na(NH$_4$)C$_4$H$_4$O$_6$,4H$_2$O.

Dissolved.

Mother liquor.

Crystals.

32·1 g.   M. L.

Crystals.   Mother liquor.

9·8 g.   12·3 g.   M. L.   19·25 g.   15·1 g.   M. L. m_3 11·6 g.

C.   C.   C.   C.   M. L.

h_1 4·85 g. l_1 2·5 g. m_1 4·15 g. m_2 3·5 g.

4·95 g.   M. L.   9·8 g.   M. L.

C.   C. l_3 3·7 g.

h_2 3·25 g. l_2 6·1 g.

h_3 1·7 g.   8·5 g.   M. L.

10 g.   M. L.   C. k_3 3·9 g.

C. k_2 4·6 g.

k_1 1·5 g.
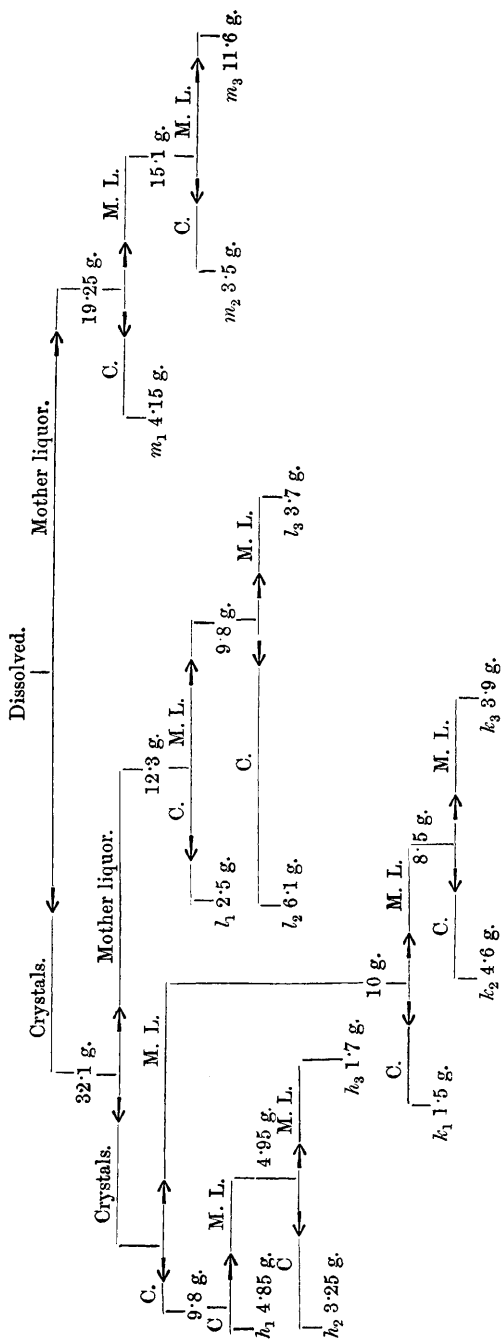
TABLE I.

1.	2.	3.	4.	5.	6.
Fraction.	w. grams.	a.	wa.	Percentage excess of d-salt.	Weight of excess of d-salt. D.
h_1	4·85	$+23·23$	$+112·67$	$+98·26$	$+4·766$
h_2	3·25	$+23·23$	$+75·50$	$+98·26$	$+3·194$
h_3	1·70	$+21·55$	$+36·64$	$+90·36$	$+1·550$
k_1	1·50	$+23·47$	$+35·20$	$+99·28$	$+1·488$
k_2	4·60	$+23·12$	$+106·35$	$+97·80$	$+4·499$
k_3	3·9	$+23·02$	$+89·78$	$+97·38$	$+3·798$
l_1	2·5	$+22·51$	$+56·27$	$+95·22$	$+2·381$
l_2	6·1	$+10·51$	$+64·11$	$+46·46$	$+2·712$
l_3	3·7	0	0	0	0
m_1	4·15	$+15·52$	$+64·41$	$+65·65$	$+2·724$
m_2	3·5	$-22·40$	$-78·40$	$-94·75$	$-3·316$
m_3	11·6	$+5·41$	$+62·76$	$+22·88$	$+2·655$

$$\Sigma w = 51·25. \qquad \Sigma wa = +625·29. \qquad \Sigma D = +26·451.$$

$$\frac{\Sigma wa}{\Sigma w} = +12·20°. \qquad \frac{\Sigma wa}{52·2} = +11·98°$$

28·25 grams of sodium ammonium dextrotartrate and 3·85 grams of the isomeric lævo-salt; this corresponds with 24·4 grams of the sodium ammonium dextrotartrate with 7·7 grams of the inactive mixture, so that nearly the whole of the 26·1 grams of the dextro-salt originally taken was deposited in the first crop of crystals. After the next separation, m_1, from the mother liquor, 27·1 grams of the dextrotartrate had separated in addition to inactive material; consequently, the mother liquor was strongly lævorotatory, and the next separation, m_2, was a lævorotatory one. Practically, all the excess of the dextrorotatory salt was contained in the first fractions, h_1, h_2, h_3, k_1, k_2, k_3, and l_1, which consisted almost entirely of this salt, but still contained small quantities of the inactive material, partly because the crystals were not washed, and partly, no doubt, because of occluded mother liquor, which is often present in noticeable quantity. The further changes during crystallisation will be understood from the tabulated results.

In a recent paper (Trans., 1897, **71**, 999), we have shown that externally compensated camphorsulphonic chloride (Trans., 1893, **63**, 560) and camphorsulphonic bromide (Trans., 1895, **67**, 359) are probably pseudoracemic; consequently, they behave, on crystallisation, like non-

racemic compounds and the ethylic acetate solutions of a strongly dextrorotatory mixture of the sulphonic chlorides deposits, on evaporation, part, or the whole, of the excess of the dextro-compound ; after the solution has thus become nearly or quite inactive, further crystallisation affords deposits which sometimes contain an excess of one or other isomeride, a behaviour which is obviously very similar to that of the sodium ammonium tartrates.

Sodium Potassium Dextrotartrate and Racemate.

Having shown by the foregoing experiments that Ladenburg's method does not hold in the case of non-racemic sodium ammonium dextro- and lævo-tartrates, namely, in the only test case on which the method has yet been worked out, we thought it advisable to apply the same method to a case in which a crystalline racemic compound undoubtedly exists, in order to ascertain whether the fractional separation occurs in a manner essentially different from that observed in the case of a non-racemic mixture.

Sodium potassium dextrotartrate is isomorphous with the corresponding sodium ammonium salt and, at temperatures between $-6°$ and $+41°$, forms a racemic compound with the isomeric lævotartrate (van't Hoff and Deventer, *Zeit. physik. Chem.*, 1895, **17**, 505); it therefore forms a racemic compound at ordinary temperatures. The optically active substances have the composition $NaKC_4H_4O_6 + 4H_2O$, whilst the composition of the racemate is $NaKC_4H_4O_6 + 3H_2O$.

A mixture of 47·4 grams of sodium potassium dextrotartrate with 44·4 grams of the racemate (molecular proportions) was dissolved in water and fractionally crystallised as before ; the scheme given on the next page shows how the various fractions were collected. Table II (p. 44) gives the weights, w, and the specific rotations, a, for the D-line ; columns 5 and 6 give the values corresponding with those in Table I.

The specific rotation of the anhydrous dextrotartrate, $KNaC_4H_4O_6$, is $[a]_D = +29·67°$ (Landolt) ; that of the mixture of 47·4 grams of hydrated dextrotartrate with 44·4 grams of the racemic salt is, therefore, $[a]_D = +11·41°$. The weighted mean specific rotation of all the separated fractions is

$$[a]_D = \frac{\Sigma wa}{\Sigma w} = +11·34°,$$

whilst

$$\frac{\Sigma wa}{91·8} = +11·28°.$$

$$\left\{ \begin{array}{ll} 47 \cdot 4 \text{ grams.} & d\text{-NaKC}_4\text{H}_4\text{O}_6,4\text{H}_2\text{O} \\ 44 \cdot 4 \text{ grams.} & i\text{-NaKC}_4\text{H}_4\text{O}_6,3\text{H}_2\text{O} \end{array} \right\}$$

dissolved

Mother liquor

Crystals — 40·15 g.

Crystals — 27 g. M. L.

C. — h_1 9·15 g.

17·85 g. M. L.

C. — h_2 10·40 g.

h_3 7·45 g.

Mother liquor — 13·15 g. M. L.

C. — k_1 4·45 g.

k_2 8·70 g.

Mother liquor — 51·1 g. M. L.

Crystals — 20 g.

C. — M. L.

l_1 7·8 g.

l_2 12·2 g.

31·1 g. M. L.

C. — m_1 3·3 g.

27·8 g. M. L.

C. — m_2 3·4 g.

24·4 — C. — M. L.

m_3 6·7 g.

m_4 8·7 g.

17·7 g. M. L.

C. — m_5 9·0 g.

TABLE II.

1	2.	3.	4.	5.	6.
Fraction.	w. grams.	a.	wa.	Percentage excess of d-salt.	Weight of excess of d-salt. D.
h_1	9·15	$+22\cdot08°$	$+202\cdot0$	$+99\cdot73$	$+9\cdot125$
h_2	10·40	$+21\cdot77$	$+226\cdot6$	$+98\cdot33$	$+10\cdot230$
h_3	7·45	$+21\cdot56$	$+160\cdot6$	$+97\cdot38$	$+7\cdot255$
k_1	4·45	$+21\cdot25$	$+94\cdot6$	$+95\cdot98$	$+4\cdot271$
k_2	8·70	$+17\cdot50$	$+152\cdot2$	$+79\cdot22$	$+6\cdot891$
l_1	7·8	$+21\cdot35$	$+166\cdot5$	$+96\cdot43$	$+7\cdot523$
l_2	12·2	$+4\cdot58$	$+55\cdot9$	$+31\cdot90$	$+3\cdot364$
m_1	3·3	$-20\cdot00$	$-66\cdot0$	$-90\cdot34$	$-2\cdot981$
m_2	3·4	$+10\cdot00$	$+34\cdot0$	$+45\cdot17$	$+1\cdot536$
m_3	6·7	$+1\cdot35$	$+9\cdot0$	$+6\cdot10$	$+1\cdot408$
m_4	8·7	0	0	0	0
m_5	9·0	0	0	0	0

$\Sigma w = 91\cdot25.$ $\Sigma wa = +1035\cdot4.$ $\Sigma D = +47\cdot622$ $\Sigma D = 53\cdot584.$

$$\frac{\Sigma wa}{\Sigma w} = +11\cdot34°.\qquad \frac{\Sigma wa}{91\cdot8} = +11\cdot28°.$$

The agreement between the quantities and specific rotations of the material taken, and the quantities and specific rotations of the fractions recovered, is hence highly satisfactory.

From an inspection of Table II, it is seen that the successive fractions separating from the solution decrease in specific rotation, that is to say, they contain decreasing quantities of the dextrotartrate in excess of the racemate, and ultimately the mother liquors contain nothing but pure racemate. The table also shows the following curious facts: the fractions h, k, and l contain 48·66 grams of the dextrotartrate as such, whilst material corresponding with only 47·4 grams was used; the difference of 1·26 grams, therefore, must be ascribed either to experimental error or to the fact that part of the racemate used was resolved, and the dextrorotatory component deposited here. That the latter alternative is the true one is shown by the mother liquor becoming lævorotatory. Consequently, on crystallising the latter, the first deposit, m_1, is strongly lævorotatory, containing 90·34 grams of lævotartrate to each 9·66 grams of racemate; 2·98 grams of lævotartrate crystallised as such in m_1, whilst the solution only contained 1·26 grams excess of this salt. In the end, therefore, 50·38 (47·4 + 2·98) grams of dextrotartrate had separated

from solution as such, or about 3 grams more than had been used ; it follows, therefore, that a partial resolution of the racemate had occurred, about 6 grams being so resolved. The good agreement of the sums of the weights of salt separated from the solution and the mean rotation of the fractions, on the one hand, with the weight of salt and the mean specific rotation which should have been obtained, on the other hand, is proof that we are not here being misled by experimental error.

The interesting work of Purdie on the resolution of lactic acid into its optically active components (Trans., 1893, **63**, 1143) affords a case, similar to the above, of the resolution of a racemic compound. Racemic zinc ammonium lactate crystallises with $3H_2O$, and when its supersaturated solution is sown with a crystal of either of the optically active isomerides, that particular isomeride separates in crystals containing $2H_2O$; this resolution is similar to that which has occurred in fractions l_2 and m_1 of our mixture.

We are thus led to the following conclusion : a racemic compound may, under certain conditions, be resolved into its optically active components by simple crystallisation, at temperatures at which the racemic compound is more stable than the mixture of the two optically active salts.

A comparison of Tables I and II shows that the fractional crystallisation has followed much the same course in the case of the racemic compound as in that of the non-racemic mixture ; the separation of the racemic compound from the dextrorotatory one is, however, not quite so sharp as in the separation of the non-racemic mixture.

Potassium Hydrogen Dextrotartrate and Racemate, $KHC_4H_4O_6$.

In the foregoing cases, the inactive mixture or compound is more soluble than either of the active components ; it seemed desirable, therefore, to investigate a case in which the contrary is true. Such a case was found on examining the behaviour of the potassium hydrogen tartrates. On crystallising a mixture of equal quantities of the dextrotartrate and of the racemate, by allowing the hot solution to cool, it was found that the mother liquor contained a salt of much higher specific rotation than that of the mixture deposited ; by repeatedly recrystallising the deposit, the specific rotation of the material in the successive mother liquors remained nearly constant, and of very much higher value than that of the crystalline separations. Owing to the sparing solubility of these two salts, they had to be dissolved in dilute ammonia for the rotation determinations. The results need not be quoted in full, because they were in so many respects similar to the preceding cases, and the experimental error was greater.

The examination of these three cases shows that Ladenburg's method does not constitute a means of discriminating between cases in which a solid racemic compound is formed, and those in which a mere inactive mixture is obtained ; a scrutiny of Tables I and II will show that this method gives practically the same results with a well-defined racemic compound as with a non-racemic mixture.

It may possibly be objected that, although inactive sodium ammonium tartrate does not exist as a solid racemic compound at ordinary temperatures, it may exist as a racemic compound in solution ; to make this assumption unsupported by experimental evidence is, however, unjustifiable, and can only be regarded as an expression of opinion.

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