161. *Melting-point Curves of Optical Isomerides.*

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THE melting-point curves of optical isomerides of certain substances in the camphor series have already been discussed (Ross and Somerville, J., 1926, 129, 2770), the conclusion being reached that acids and some esters were more likely to form racemic compounds than other substances. In the present instance attention was first directed to $\gamma\gamma\gamma$-trichloro-β-hydroxybutyric acid and its methyl ester, both of which could be obtained in a suitable form for the investigation of m.-p. curves, a condition which is common enough with esters, but not with acids. In extending the investigation to mandelic acid, it was hoped to be able to determine the form of the m.-p. curves of isomerides of the acid and of its methyl and ethyl esters. When mandelic acid was carefully melted in a m.-p. tube of the type already described (Ross and Somerville, *loc. cit.*), it did not give a definite m. p., but turned brown when molten, the smell of benzaldehyde being recognisable. Repeated melting gave increasing low m. p.'s. There was distinct evidence of decomposition, even when all possible precautions were taken to prevent the temperature rising much above the m. p., and so the attempt to determine the m.-p. curve of (—)- and (+)-mandelic acids was temporarily abandoned. Subsequent experiments showed that by a modification of the apparatus it may be possible to determine more accurately the m. p.'s of mixtures of the acids. In previous investigations it was shown that the best criterion of purity of the isomerides was that they should have identical m. p.'s.

A further difficulty in determining the m.-p. curve of isomerides of mandelic acid is that the two forms of the acid are usually prepared by entirely different methods, as is the case here (see below), and are purified only by recrystallisation. This leads to the possibility that any impurity which may still be present in one isomeride will be a different impurity from that in the other. Differences in the physical properties of optical isomerides have been suggested in the case of mandelic acid, etc. (cf. Campbell and Garrow, *Trans. Faraday Soc.*, 1930, **26**, 560), but it seems likely that these results might be explained by the presence of traces of impurities in the isomerides. With mandelic acid, the decomposition at the m. p. and the difference in method of preparation of the two isomerides seriously affect the reliability of the results obtained.

EXPERIMENTAL.

Preparation of Optical Isomerides.—*r*-$\gamma\gamma\gamma$-Trichloro-β-hydroxybutyric acid was prepared by the interaction of chloral hydrate and malonic acid (von Auwers and Wissenbach, *Ber.*, 1923, **56**, 755), and resolved by means of quinine (McKenzie and Plenderleith, J., 1923, **123**, 1093), the yield of (—)-acid being much greater than that of the (+)-acid. The (—)-acid obtained had s. p. 99·9°, α — 0·64°, $[\alpha]_{\mathrm{D}}^{17^\circ}$ — 32·0° ($l = 2$, $c = 1$ in ethyl alcohol), and the (+)-acid s. p. 100·1°, $[\alpha]_{\mathrm{D}}^{17^\circ}$ + 32·0°; for the (—)-acid McKenzie and Plenderleith gave m. p. 104—105°, $[\alpha]_{\mathrm{D}}^{17^\circ}$ — 29·6°. The difference in the m. p.'s is accounted for by the different methods employed in the two cases, setting points being determined in the present instance, and the m. p. of the (—)-acid, when taken in the usual way, was 103°.

The methyl ester was prepared as follows. A solution of the acid (15 g.) in methyl alcohol (12 c.c.) was saturated with hydrogen chloride. After most of the alcohol had been removed under diminished pressure, the solution was again saturated with hydrogen chloride, the product poured into water, and extracted with ether. The ethereal solution was washed with potassium bicarbonate solution, the ether removed, and the product crystallised from light petroleum. In this way a (—)-ester of m. p. 58° and a (+)-ester of m. p. 60° were obtained. Further recrystallisation of both samples yielded substances melting at only slightly higher temperatures, and very little difference was observed in the specific rotations of the two forms of the ester. The difference in the setting points of the two isomerides pointed to the presence of impurities, and it was decided to try the effect of distillation under a high vacuum. By this treatment a (—)- and a (+)-ester, both of which had the same setting point, were obtained. The difficulty of getting pure samples of two optical isomerides is well illustrated in the present case, and the best test of purity seems to be the finding of identical setting points for the two forms of the isomeride.

Methyl (—)-$\gamma\gamma\gamma$-*trichloro*-β-*hydroxybutyrate* had m. p. 62·6°, α 0·75°, $[\alpha]_{\mathrm{D}}^{17^\circ}$ —37·5° ($l = 2$, $c = 1$ in ethyl alcohol), and the (+)-*methyl* ester had m. p. 62·6°, $[\alpha]_{\mathrm{D}}^{17^\circ}$ + 37·0° (Found : C, 27·1; H, 3·6; Cl, 48·0. $C_5H_7O_3Cl_3$ requires C, 27·1; H, 3·2; Cl, 48·0%).

Measurements of the conductivities of solutions of the racemic acid at 25° were made, in order to get values for comparison with the strength of known acids.

Concn.	$N/8$	$N/16$	$N/32$	$N/64$	$N/128$	$N/256$	$N/512$	$N/1024$
μ_v	9·95	14·50	21·51	28·92	40·44	55·49	75·34	105·2
m	0·0266	0·0388	0·0548	0·0773	0·1081	0·1484	0·2014	0·2811
$K \times 10^5$ ...	9·08	9·76	9·95	10·12	10·23	10·09	9·92	10·74

This gives a value for the dissociation of the acid, $K = 10 \times 10^{-5}$, which is about twice that for benzoic acid.

(—)-Mandelic acid was prepared from amygdalin by treatment with hydrochloric acid, and the (+)-acid by resolving the inactive acid with cinchonine. After the acids had been so prepared, they were purified by repeated recrystallisation from benzene to which a small quantity of acetone had been added. The esters were prepared from the purest acid isomerides, obtained as above, by the Fischer–Speier method with sulphuric acid. After a number of recrystallisations from light petroleum, to which a drop or two of benzene had been added, the (—)- and the (+)-acid still had different m. p.'s. It was eventually found that the best method of purification was to distil the ester under a high vacuum, thereby removing traces of impurities. Finally, esters with the following properties were found : (—)-methyl mandelate had m. p.

54·4°, α − 2·44°, $[\alpha]_D^{16°}$ − 122° (l = 2, c = 1 in acetone), and the (+)-isomeride had m. p. 54·4°, $[\alpha]_D^{16°}$ + 124°; (−)-ethyl mandelate had m. p. 29·8°, α − 1·93°, $[\alpha]_D^{16°}$ − 96·5° (l = 2, c = 1 in acetone), and the (+)-ester had m. p. 29·8°, $[\alpha]_D^{16°}$ + 96·0°.

Determination of Setting Points.—The apparatus employed and the manner of determining the setting points were as already described (Ross and Somerville, *loc. cit.*). The temperatures were measured by means of a copper–constantan thermocouple, and in each case stirring was carried out by an electro-magnetic arrangement. Temperatures were checked with a standard thermometer, due allowance being made for the length of emergent stem.

γγγ-Trichloro-β-hydroxybutyric Acid and its Methyl Ester.

	Substances used for calibration.	Table and fig.	Remarks.
Acid	*m*-Dinitrobenzene (89·3°) Benzoic acid (121·9°)	I, 1	Setting point; acid seeded in each case; glycerol-bath for heating.
Ester	Urethane (45·7°) *p*-Bromophenol (62·6°)	II, 2	Setting point; ester seeded in each case; water-bath for heating.

TABLE I.

(+)-Acid, %.	S. p.	(+)-Acid, %.	S. p.
0·0	99·9°	50·0	118·3°
4·6	97·9	53·9	116·1
8·9	96·6	54·4	116·8
9·1	96·6	67·2	109·3
12·3	96·8	72·8	107·2
14·2	98·8	80·2	99·2
16·7	99·4	83·3	99·6
25·6	103·5	91·0	97·2
33·9	108·9	95·3	98·5
38·8	112·2	100·0	100·1
42·2	115·1		

TABLE II.

(+)-Ester, %.	S. p.	(+)-Ester, %.	S. p.	(+)-Ester, %.	S. p.
0·0	62·6°	41·6	58·0°	73·4	50·9°
5·6	59·2	41·8	57·7	76·0	49·8
10·4	56·9	50·0	58·8	78·7	48·0
16·3	51·7	53·1	58·5	78·9	48·4
22·1	48·6	57·3	58·3	82·0	50·4
22·2	48·3	62·3	57·2	85·6	52·5
25·2	49·6	65·6	55·6	89·7	56·2
27·8	51·9	65·8	55·8	94·5	58·8
28·0	52·3	68·1	55·1	100·0	62·6
35·8	56·1				

In the two foregoing cases the type of curve (Figs. 1 and 2) shows that a racemic compound has been formed.

FIG. 1.

γγγ-Trichloro-β-hydroxybutyric acid.

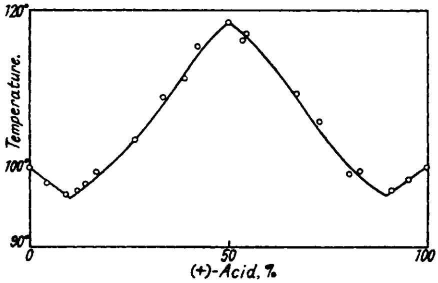
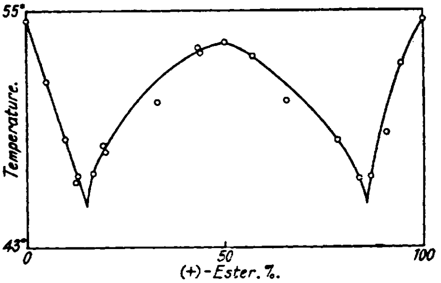


FIG. 3.

Methyl mandelate.



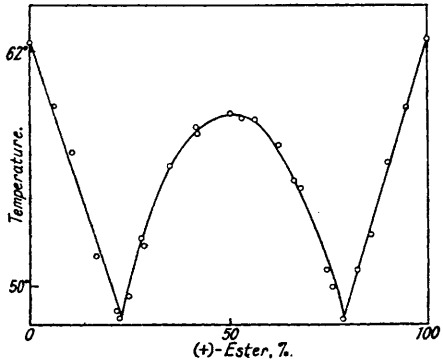


FIG. 2.

Methyl ester of γγγ-trichloro-β-hydroxybutyric acid.

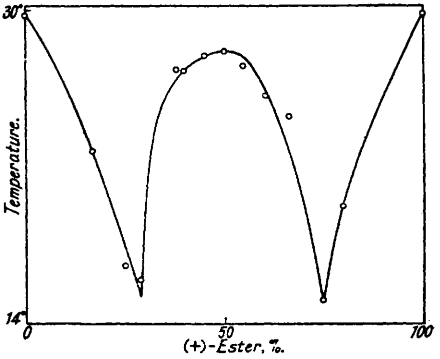


FIG. 4.

Ethyl mandelate.

In dealing with the esters of mandelic acid, hand stirring by means of a glass rod was used, and it was found more convenient to standardise the thermocouples as follows. The bulb of a standard thermometer was immersed in water, contained in the m.-p. tube, and the temperature of the thermometer, duly corrected for emergent stem, and the corresponding potentials were read off. M. p.'s were taken in each case, but in dealing with the ethyl esters special precautions were necessary, since in order to induce crystallisation they had to be cooled in ice-water. Under such conditions, the esters took up moisture from the air, and so gave a low m. p. It was, therefore, found essential to dry the esters in a desiccator between each determination of the m. p.

TABLE III.

Methyl mandelate.

(+)-Ester, %.	Temp.	(+)-Ester, %.	Temp.
0·0	54·4°	50·0	53·3°
4·8	51·2	57·0	52·6
9·1	48·5	66·1	50·3
13·0	46·1	78·8	48·4
13·0	46·4	83·7	46·7
16·7	46·5	87·2	46·8
20·0	48·2	91·1	48·8
20·0	47·9	95·3	52·0
33·3	50·2	100·0	54·4
42·9	52·8		

TABLE IV.

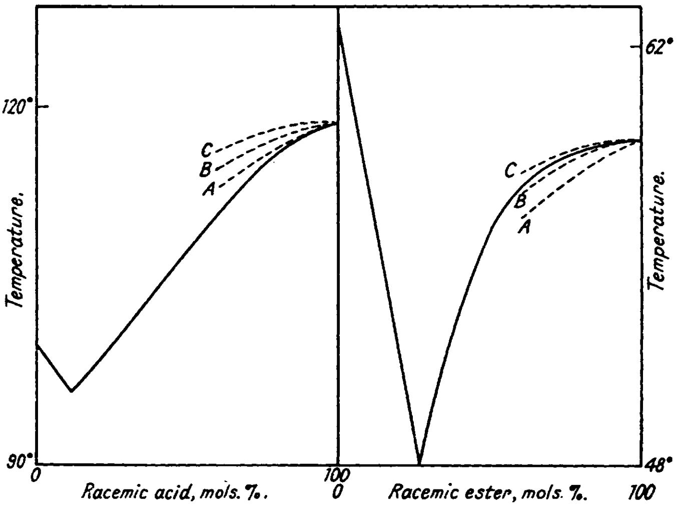
Ethyl mandelate.

(+)-Ester, %.	Temp.	(+)-Ester, %.	Temp.
0·0	29·8°	50·0 (*r*-Ester)	28·1° 28·0
16·7	22·9		
25·0	17·0	54·4	27·2
28·6	16·1	60·0	25·8
33·3	24·4	66·7	24·7
37·5	27·1	75·0	15·2
40·0	27·1	80·0	20·1
45·4	27·7	100·0	29·8

In both cases the type of curve obtained (Figs. 3 and 4) shows that a racemic compound is formed.

Analysis of Experimental Curves.—The curves are symmetrical, and for purposes of analysis half of the experimental curves were drawn, the molar percentages of the racemate being plotted against the m. p.'s. The shape of the curve near the m. p. of the racemate indicates the degree of dissociation of the racemic compound. If definite percentages of dissociation are assumed, Kremann (*Monatsh.*, 1904, **25**, 1215) has shown how the shape of the curve may be found. By using this criterion, the m. p.'s of the different mol.-fractions for γγγ-trichloro-β-hydroxybutyric acid were calculated for 10%, 15%, and 20% dissociation.

FIG. 5. FIG. 6.



γγγ-Trichloro-β-hydroxybutyric acid. *Methyl ester of γγγ-trichloro-β-hydroxybutyric acid.*

Curve.	Mol.-fraction (x) =	0·0.	0·2.	0·4.
A	t for 10%	118·3°	116·2°	112·6°
B	t for 15%	118·3	117·3	114·5
C	t for 20%	118·3	117·8	115·8

The curves A, B, and C are drawn in Fig. 5. The experimental curve lies near the curve A, and the dissociation of the racemate was taken to be 10%. Similar calculations for the other substances examined gave the following results :

Methyl γγγ-trichloro-β-hydroxybutyrate (see Fig. 6).

Curve.	Mol.-fraction (x) =	0·0.	0·2.	0·4.
A	t for 10%	58·8	57·8	56·1
B	t for 15%	58·8	58·3	57·0
C	t for 20%	58·8	58·5	57·6

Dissociation of racemic ester, 16%.

Methyl mandelate (see Fig. 7).

Curve.	Mol.-fraction (x) =	0·0.	0·2.	0·4.
A	t for 10%	53·3	52·1	50·1
B	t for 15%	53·3	52·7	51·1
C	t for 20%	53·3	53·0	51·9

Dissociation of racemic ester, 20%.

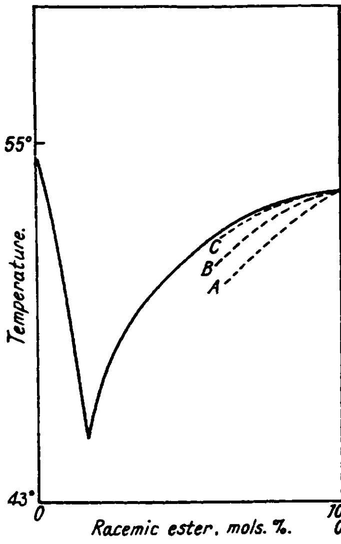
Ethyl mandelate (see Fig. 8).

Curve.	Mol.-fraction (x) =	0·0.	0·2.	0·4.
A	t for 10%	28·0	26·7	24·6
B	t for 15%	28·0	27·4	25·7
C	t for 20%	28·0	27·7	26·8

Dissociation of racemic ester, 20%.

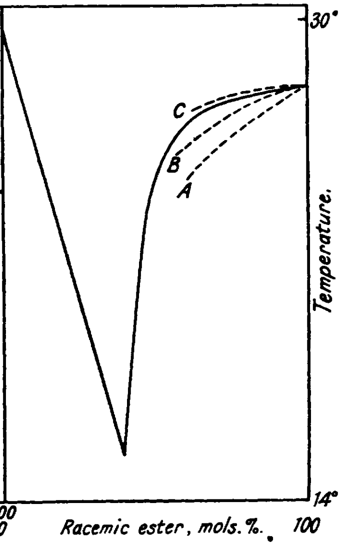
The degree of dissociation of the racemate may also be calculated by a formula worked out by van Laar, though, as Kremann has shown, the value so obtained is generally 2—3 times as great as that given by the graphical method. This observation has been confirmed in the present instances, and also for camphoric acid and methyl hydrogen camphorate (Ross and Somerville, *loc. cit.*). In some cases van Laar's formula gives values corresponding to almost complete dissociation of the racemate, a result which is not in conformity with the shape of the experimental curves. It is reasonable, therefore, to assume that the graphical method gives more reliable data for the degree of dissociation of the racemate.

FIG. 7.



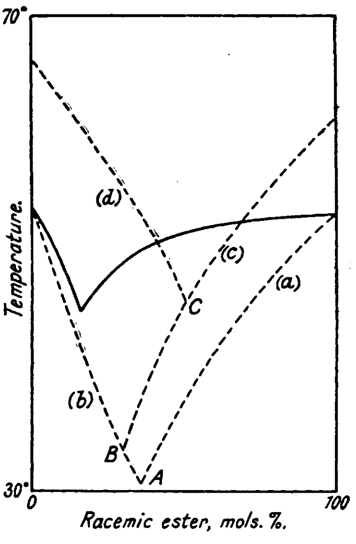
Methyl mandelate.

FIG. 8.



Ethyl mandelate.

FIG. 9.



Methyl mandelate.

Attempts have been made to apply the equation for " ideal solutions," *viz.*, $dT/dx = RT^2/Lx$, to the lowering of m. p. of optical isomerides. The values given by this equation have been worked out in the case of methyl mandelate, and the results are shown in Fig. 9. If the above equation is applied directly to the lowering of the observed m. p. of the racemic and of the active ester [curves (*a*) and (*b*)] the eutectic point given by the intersection of these two curves (point *A*) is much lower than the observed eutectic. The main difficulty in the application of this equation is due to the dissociation of the racemic ester. If we take the value of the dissociation from Kremann's criterion, we can calculate what the m. p. of the undissociated racemate would be. The curve (*c*) would then show the lowering of the m. p. of the undissociated racemate, and the eutectic point would be the point *B*, which again is much lower than the observed eutectic point. It has been found, however, that when two active isomerides form a racemic compound the active forms are themselves associated. If we assume that the active forms are associated to the same extent as the (+)- and (—)-forms are associated in the racemic compound, we get curves (*c*) and (*d*) for the lowering of m. p., which give a eutectic point approximating closely to the observed value. The difference between the observed and the calculated eutectic percentage composition may be explained by the fact that the experimental curve is drawn for molar percentages of racemate and active ester. In the other cases investigated, the theoretical curves for "ideal solutions" give the best agreement with the observed eutectic temperature, though a difference is generally observed between the theoretical and the observed eutectic percentage composition.

The author thanks the Carnegie Trust for a Teaching Fellowship and for a grant for material.

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[*Received, December* 19*th*, 1935.]