The Preparation of Optical Isomers in the Camphor Series, and Investigation of their Melting Point Curves.

THESIS

submitted for the degree of Ph.D.

by

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INTRODUCTORY.

Towards the end of last century great interest was aroused in the question of the recognition of racemic compounds, as opposed to inactive mixtures, of optical isomers. Various physical properties of the active and inactive forms were investigated in the endeavour to find a convenient and suitable criterion. Differences of solubility and melting point of the active and inactive forms were at first reckoned as evidence of compound formation, but later proved indeterminate. The most satisfactory among the earlier experiments were those of Walden [Ber. 1896, 1692], who compared a number of substances of somewhat varied nature and concluded that "....... Every inactive (d.l.) "substance can be considered to be a true racemic "compound if it has a different crystal form and "different density from the d. or l. components....." Kipping and Pope [J.C.S. 1897, 989], working along similar lines, went a step further, and pointed out that a third type of inactive (d.l.) substance could and did exist, the pseudoracemate. At the close of /

of their paper they stated "...... there is only "one method at present of really practical use for "the characterising of solid racemic compounds, "namely, that based on the determination of the "crystalline forms of the optically active and "externally compensated materials, ... the "crystallographic constants are not always determin-"able with ease and completeness; hence the establish-"ment of other criteria of racemism is a matter of "considerable importance."

Parallel with these investigations on crystalline solids, Ladenburg [Ber. 1895, 163 and 1991], among others, experimented with the possibility of obtaining racemic compounds in the liquid state, and from heat absorption on mixing d. & l. coniine, which occurred without change in specific gravity, concluded that a liquid racemic compound was formed. He also put forward [Ber. 1894, 3065] a general criterion for distinguishing racemates, whether liquid or solid, but this met with immediate criticism by Kipping and Pope, and was modified by Ladenburg [J.C.S. 1899, 466] to read "...... Determine the "solubility of the substance without and with the "addition /

"addition of a small quantity of one of the optical "components at the same temperature and in the same "solvent. If the solubilities are different, the "substance is a racemic compound, if the same, it "is a mixture." As was pointed out by several workers, this method is usually successful when dealing with two solid active components, though in some cases it requires also a determination of the optical rotations of the solutions in question. Roozeboom [Ber. 1899, 2172] criticised it from the standpoint of the Phase Rule, and showed that it breaks down completely when dealing with liquid isomers, though adequate in the case of solid components.

The most outstanding contribution to the theoretical working out of the whole problem is due to Roozeboom [Zeits. Phys. Chem. 1899, 494], who applied the Phase Rule to all possible cases of mixtures of two optical isomers. He found that a satisfactory method of distinguishing between the three possible types of inactive (d.l.) substance, namely, the racemic compound, pseudoracemic mixed crystals, and the inactive conglomerate or mixture was /

was to determine completely -

(a) the solubility diagram

or (b) the freezing-point diagram,

for the system of two optical isomers. Bruni, working independently, published [Gazzetta 1900, 30 1 35] a general method almost identical with that of Roozeboom, applying the solubility diagram as a criterion for the recognition of racemic compounds. This added weight to the conclusions reached by Roozeboom, and these became generally accepted by all workers in this field.

A great number of experiments were set on foot to apply these principles to various optical isomers, and, among a number of workers, the most exhaustive enquiry was carried out by Adriani [Zeits. Phys. Chem. 1900, 453], who utilised principally the melting point curve method outlined theoretically by Roozeboom. From this a satisfactory conclusion can be reached for temperatures in the vicinity of the melting point. For lower temperatures crystallographic methods have to be resorted to. The paper gives a summary of the knowledge then held of racemic substances in solid, liquid, and gaseous state. Various fresh substances have been since investigated /

investigated from time to time, and in every case the results have been found in complete agreement with the principles laid down by Roozeboom.

The question of the existence of racemic compounds in the liquid state, and in solution, has given rise to much controversy, and so far it may be said that the number of instances in which the existence of a racemic liquid has been definitely proved is very small, though it seems probable from the laws of equilibrium that a small proportion of racemic liquid must exist in the vicinity of the melting point. At other temperatures it may be completely dissociated into the active components. Similarly, in concentrated solutions, racemic compounds probably exist to a limited extent, but break down into the d.& l. isomers with increasing dilution. A brief summary of the principal methods used to investigate this problem may be of interest.

Ladenburg adhered to his solubility method in spite of all criticism, and in 1911 [Ber. 44, 676], again offered it as a criterion. Van der Linden [Ber. 1911, 963], and Kruyt [Ber. 1911, 995], showed once again that in the light of the Phase Rule /

Rule it is quite inadmissible. The other property on which Ladenburg based some of his conclusions regarding the existence of liquid racemates was that of heat of mixing of d.& l. isomers without change in specific gravity. While this has been adversely criticised by several workers, it has not been definitely disproved, and in some cases may give a correct indication of the formation or partial formation of a liquid racemate. In 1910 he determined [Ber. 43, 2374] the freezing point curve for mixtures of d.& l. pipecoline, and this would indicate the existence of a racemic compound.

Bruni & Padoa [Atti. R. Accord Lincei 1902 ii 212] studied the cryoscopic behaviour of dimethyl esters of diacetyltartaric and racemic acids in various solvents, and concluded "...... it would "seem that in presence of an excess of an active "compound, the corresponding racemic compound can "exist as such in solution".

Kremann [Monat 1904, 1215 et seq.] carried out a great number of determinations of melting point curves, chiefly of phenols and amines, and in the cases in which a compound was formed, worked out the degree of dissociation at its melting point. Findlay and Hickmans [J.C.S. 1907, 905] applied this to the case /

case of the menthyl mandelates where partial racemism occurs, and were able to calculate the degree of dissociation of the racemic compound at its melting point, i.e. the percentage of racemic compound existing there in the liquid state.

Dunstan & Thole utilised viscosity determinations as a criterion. Thole [J.C.S. 1913, 19] gives a full summary of previous work, and concludes "......... In most cases inactive (d.l.) "liquids and solutions are merely conglomerates. .... "In certain instances proof has been afforded of the "existence in solution and in the liquid state of "racemic compounds. ...... In the cases where "racemic existence in solution has been substantiated, "dissociation is very considerable, even at fairly "high concentrations in a comparatively non-dissociat- "ing solvent." Considerations of molecular surface energy, i.e. determinations of density and surface tension, were employed by Mitchell & Smith [J.C.S. 1913, 489], while Vanzetti [Atti.Accad Lincei 22 II 477] measured the heat of formation of liquid racemates.

Conflicting results have been reached with many of the above methods, since they all depend on the /

the measurement of some physical property of the liquid or solution which may or may not be entirely constitutive. Hence some care has to be taken in attaching importance to results obtained by any one of these methods. That outlined by Kremann, and applied by Findlay & Hickmans [loc. cit.] to optical isomers, depending on the determination of the melting point curve as suggested by Roozeboom, would seem to be the most definite and conclusive way of deciding whether a racemic compound exists in the liquid state, and, if so, to what extent it is dissociated with the d. and l. components.

Such then was the position when the present investigations were begun. Roozeboom's theoretical methods had been fully substantiated in practice. A number of isolated examples of racemic compounds and pseudoracemic mixed crystals were available, see Findlay "The Phase Rule" Edition V, pp. 175-178. for a summary. So far no case had been found in which the d. and l. isomers behaved as a simple mixture. No systematic arrangement of these isolated cases had been attempted. Accordingly, a series of substances were taken, with a sequence of /

of chemical groups, and their melting point curves investigated. For convenience, and because a considerable number of the compounds required had been prepared at some earlier date, the camphor series was chosen, and the dextro and laevo isomers of the following substances were prepared in a pure state:-

Borneol	Alcohol
Camphor	Ketone
Camphoric Acid	Acid
Camphoric Anhydride	Anhydride
Ortho Methyl Camphoric Ester	Acid Ester
Bornyl Hydrogen Phthalate	Acid Ester
Pinene	Hydrocarbon
Camphene	Hydrocarbon

It was hoped that some regular tendency to the formation of any of the three possible types might be connected up with the presence of some particular grouping in the molecule, and hence that some generalisation might be arrived at which would apply to all substances containing the same grouping. Also it was hoped to obtain some further information with regard to racemic compounds in the liquid state in view of the small number of cases in which their existence has been definitely proved.

PREPARATION of OPTICAL ISOMERS.

Since the substances were to be used to determine melting points, special care was taken to obtain the dextro and laevo forms in as pure a state as possible. A Schmidt and Haensch instrument was used in all polarimetric measurements, which were carried out in a two decimetre tube at ordinary temperature using sodium light. c denotes the number of grams of substance dissolved in 100 c.c. of solution. All temperatures have been corrected for emergent stem, and comparisons made with a Standard Thermometer.

BORNEOL.

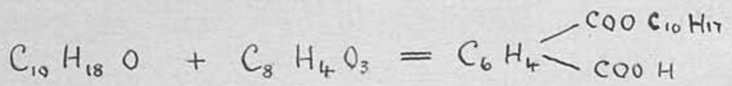
Laevo borneol.

This substance was obtained from the British Drug Houses Limited. After one recrystallisation from light petroleum ether, it melted at 207°C and gave a rotation of $[\alpha]_D^{14.5} = -36.52^{\circ}$ in toluene solution with $c = 11.5$. A second sample gave $[\alpha]_D^{14.5} = -36.81^{\circ}$, while Haller gives $[\alpha]_D = -37.1^{6}$. This, however, was not sufficiently pure for our purpose, so a lengthy purification was begun. The general method is due to Haller [C.R. 1889, 108, 456], see /

see also Pickard and Littlebury [J.C.S. 1907, 1974]. After suitable modifications, that finally adopted was as follows:-

Conversion into l-bornyl hydrogen phthalate.

By mixing l-borneol and phthalic anhydride in the proportions required by the equation



$$C_{10}H_{18}O + C_8H_4O_3 = C_6H_4\begin{cases}COOC_{10}H_{17}\\COOH\end{cases}$$

and warming in an Erlenmeyer flask at 130°C for two hours, l-bornyl hydrogen phthalate was formed. When the temperature had risen to 130°C, the contents of the flask melted, and the flask was then corked. When the reaction was complete, the liquid was poured, while still hot, into a large volume of a hot solution of sodium carbonate. The bornyl hydrogen phthalate usually dissolved almost at once - if not, the solution was kept warm until it did. On cooling and extraction with petroleum ether, the unchanged borneol and any normal phthalate formed were removed in the ethereal layer. The aqueous layer was acidified with concentrated hydrochloric acid; frothing occurred as carbon dioxide was liberated. The l-bornyl /

l-bornyl hydrogen phthalate which separated was extracted with ether, excess of ether distilled off, and the product recrystallised from boiling benzene. It gave a rotation of $[\alpha]_D^{14.5} = -55.1^\circ$ with c = 10 in absolute alcohol.

Formation of the l-menthylamine salt.

This was now coupled up with l-menthylamine hydrochloride, prepared from l-menthol supplied by Macfarlan, which gave a rotation of $[\alpha]_D^{19} = -50.0^\circ$ with c = 10 in absolute alcohol. By conversion of this via l-menthone, and l-menthone oxime, l-menthylamine hydrochloride was obtained. Details of this preparation were as follows:-

(a) Preparation of l-menthone.

45g crystallised menthol were added to a solution of 60g potassium bichromate (1 mol.) and 50g concentrated sulphuric acid (2½ mol.) in 300g water, which was brought to 30°C. The menthol blackened on the surface owing to the formation of a chromium compound. It was necessary only to shake vigourously to complete the reaction. The temperature rose of its own accord, and at 53°C the black compound suddenly decomposed to a brown mass from which the menthone separated. The temperature rose to /

to about 55°C in half an hour. For smaller quantities heat may be required, or corresponding cooling for larger ones. The solution was allowed to cool, and extracted with ether. The ethereal solution was washed with water and dilute sodium hydroxide until almost colourless. It was purified further by steam distillation, and subsequent extraction with ether.

(b) Conversion to 1-menthone oxime.

Twenty parts 1-menthone (1 mol.) were dissolved in 2½ times the quantity of 90% alcohol, and twelve parts of hydroxylamine hydrochloride (1.3 mol.) added, along with rather more than the calculated quantity of sodium bicarbonate. The reaction was complete in the cold in a day. The oxime formed separated as an oil on the addition of water. If sufficiently pure it may solidify, but in this case it did not, and so was separated by extraction with ether. The oil remaining after the ether had been distilled off did not solidify easily, but gave crystals most readily from a solution in dilute alcohol, which was cooled in ice. When pure it crystallised easily, and melted at 59.5°C

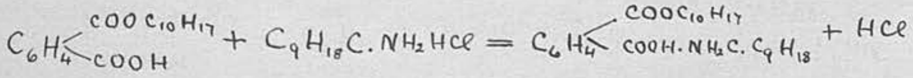
(c) Reduction to l-menthylamine hydrochloride.

[Wallach & Kuthe Ann. 276 300].

10g l-menthone oxime were dissolved in 75 c.c. absolute alcohol (if possible, water free). At small intervals 15g of roughly cut metallic sodium were added to the boiling liquid. The separation of crystalline sodium alcoholate was thereby avoided. Meanwhile absolute alcohol (in all 60 c.c.) was added gradually to the reacting solution. When all the sodium had dissolved, the solution was carefully diluted with water, and the product steam distilled. At first practically only alcohol passed over. As soon as a turbidity showed in the distillate, the process was interrupted. The distillate was acidified with concentrated hydrochloric acid, and evaporated to dryness on the water bath, when solid l-menthylamine hydrochloride was obtained. It gave a rotation of $[\alpha]_D^{19} = -37.5^\circ$ with $c = 3$ in water. This would indicate that it consisted almost entirely of the laevo variety of the four possible partial racemates. Tutin and Kipping [J.C.S. 1904 65] isolated the laevo form from the mixture in which it is /

is the chief constituent, got by reduction of l-menthone oxime, and gave its rotation as $[\alpha]_D = -36.6^\circ$ with $c = 2.5$ in water.

L-bornyl hydrogen phthalate was heated with the requisite quantity of potassium carbonate in a large volume of water, when solution occurred in half an hour. After cooling, a solution which contained the quantity of l-menthylamine hydrochloride required by the equation



$$C_6H_4\begin{matrix}COOC_{10}H_{17}\\COOH\end{matrix} + C_9H_{18}C.NH_2HCl = C_6H_4\begin{matrix}COOC_{10}H_{17}\\COOH.NH_2C.C_9H_{18}\end{matrix} + HCl$$

was added with stirring. The compound separated as a pasty mass, which soon hardened. After filtering it was dissolved in methyl alcohol, the solution diluted somewhat with water, and allowed to cool, when l-menthylamine l-bornyl hydrogen phthalate crystallised out. By three further crystallisations from dilute methyl alcohol, the pure l-menthylamine salt was obtained. This gave a rotation of $[\alpha]_D^{14.5} = -41.20^\circ$ with $c = 5$ in methyl alcohol. Haller [loc. cit.] gives $[\alpha]_D = -52.8^\circ$.

X divergent

Hydrolysis of Pure l-menthylamine Salt.

This /

This was easily effected by dissolving in rather more than the minimum quantity of alcohol, adding an equal volume of dilute hydrochloric acid, and boiling on the water bath under a reflux for one hour. The product was poured into water, when pure l-bornyl hydrogen phthalate separated out. It was filtered off, and recrystallised from boiling benzene. . The aqueous filtrate was extracted with ether - after its bulk had been considerably reduced by evaporation - to remove traces of phthalate, and evaporated to dryness. The solid l-menthylamine hydrochloride obtained was used to convert a further quantity of l-bornyl hydrogen phthalate. The recrystallised purified l-phthalate melted at 163°C and gave a rotation of $[\alpha]_D^{14.5} = -56.1^\circ$ with c = 10 in absolute alcohol. Haller [loc. cit.] gives $[\alpha]_D = -58.27^\circ$. This purified l-bornyl hydrogen phthalate was used in the determination of the phthalate melting point curve.

Hydrolysis of Pure l-bornyl hydrogen phthalate.

This was carried out by dissolving in potassium methoxide (15%), adding a quarter of that bulk of methyl alcohol, and warming on the water bath. When hot, a volume of water equal to that of the methyl alcohol /

alcohol was added. The solution was boiled under a reflux for five hours, then poured into a large volume of water, when pure l-borneol separated out. When cold, this was filtered off, dried, and recrystallised from light petroleum ether. The pure l-borneol thus obtained melted at 207.2°C, and gave a rotation of $[\alpha]_D^{14.5} = -37.50^\circ$. A similar purification was carried out on a second sample of l-borneol. Pure l-borneol having a rotation of $[\alpha]_D^{19} = -37.65^\circ$ was obtained. Haller [loc. cit.] gives $[\alpha]_D = -37.61^\circ$. The pure l-borneol so obtained was used in the determination of the curve for d & l borneols, and also as the starting material in the preparation of l-camphor, l-camphoric acid, l-camphoric anhydride, and l-ortho methyl camphoric ester.

? toluene as solvent

p.10 −37.1°

Dextro borneol was obtained from British Drug Houses Limited. The product obtained, on crystallisation from light petroleum ether separated in large crystalline plates. These melted at 206°C, and gave a rotation of $[\alpha]_D^{14.5} = +29.88^\circ$ with c = 8 in toluene. For pure d-borneol Haller gives $[\alpha]_D = +37.77^\circ$. While the crystals obtained looked pure enough, the discrepancy in the rotation is obvious, and /

and seems to be accounted for by the fact that the recrystallised substance does not consist of pure d-borneol, but really of mixed crystals of d-borneol and l-isoborneol. This was recognised in earlier years, [McKenzie J.C.S. 1907 1225], but does not seem to be generally known since [Lowry [J.C.S. 1925 614] employs d-borneol of low rotation, $[\alpha]_D^{20} = +26.88^\circ$ with c = 22.855 in benzene, under the impression that it is pure.

McKenzie [loc. cit.] obtained pure d-borneol from these mixed crystals by boiling with zinc chloride in benzene for three hours. In our case this method gave d-borneol with a rotation of $[\alpha]_D^{19} = +32.81^\circ$ with c = 8 in toluene. On boiling for a further period of three hours the rotation of the final product rose to $[\alpha]_D^{19} = +35.0^\circ$. Prolonged experiments with various times of boiling up to twenty hours did not yield d-borneol with a rotation over $[\alpha]_D = +35.0^\circ$. The method finally adopted was therefore as follows:-

100g of the commercial product once recrystallised from petroleum ether were dissolved in 80g of hot benzene, and boiled with 50g of zinc chloride for

six /

six hours. By this process the l-isoborneol splits off water and is converted into camphene, while the d-borneol is unchanged. The resulting product yielded d-borneol most readily by shaking up in a separating funnel with very dilute hydrochloric acid and more benzene. Some solid which separated at first dissolved in the dilute hydrochloric acid. The upper layer was separated, most of the benzene distilled off, and the remaining product poured into a crystallising basin. The d-borneol so obtained was recrystallised from petroleum ether. It gave a rotation of $[\alpha]_D^{19} = +35.0^\circ$ with c = 8 in toluene.

For complete purification it was necessary to use the l-menthylamine salt conversion, the details being similar to those for the purification of l-borneol. D-bornyl hydrogen phthalate was recrystallised from glacial acetic acid, and had a melting point of 161.4°C. The rotation was not tried. Haller [loc. cit.] gives $[\alpha]_D = +56.7^\circ$. The l-menthylamine d-salt was recrystallised four times from acetone, and so obtained in a pure state. Hydrolyses /

Hydrolyses were carried out as in the case of the laevo variety. The pure d-borneol obtained gave a rotation of $[\alpha]_D^{16} = +37.1^\circ$ with c = 8 in toluene, and had a melting point of 206.5°C.

CAMPHOR.

Laevo camphor was obtained in a pure state using the pure l-borneol prepared as above as starting material. [Aschan, Acta Soc. Scientiarum Fennicae, Tom XX1 No. 5].

To 15g pure l-borneol were added 190g concentrated nitric acid (d = 1.42), and product heated for two hours at about 100°C in a flask fitted with a long air condenser ground into the neck, as in the initial stage of preparation of camphoric acid. The solution was then made just alkaline with sodium carbonate and steam distilled. The l-camphor so obtained was recrystallised from benzene. Yield = 10g. It melted at 177.7°C, and gave a rotation of $[\alpha]_D^{16} = -43.61^\circ$ with c = 16.51 in absolute alcohol. Beckmann [L.A. 250 253] gives $[\alpha]_D = -44.22^\circ$.

An earlier method of oxidising l-borneol with bichromate /

bichromate solution was tried, but in every case a product resulted which gave too high a melting point. On investigation it was evident that by this method a solid solution of l-camphor and l-borneol resulted. These can give any melting point between 178° & 206.5°C

<u>Dextro Camphor</u> was supplied by Macfarlan as Camphor Ang. On recrystallisation from alcohol a product was obtained which melted at 178.6°C, and gave a rotation of $[\alpha]_D^{16} = +44.20°$ with c = 16.51 in absolute alcohol. Beckmann [loc cit.] gives $[\alpha]_D = +44.22°$. This was employed in experiments without further purification.

CAMPHORIC ACID.

<u>Laevo camphoric acid</u> was prepared from the pure l-borneol obtained above. [Aschan, Acta Soc. Scientiarum Fennicae, Tom XXI No. 5].

40g l-borneol were placed in an R.B. flask which was provided with a long glass tube ground into the neck to act as an air condenser. 500g concentrated nitric acid (d = 1.42) were poured in quickly, and the vessel cooled in a basin of water in the fume cupboard. After a minute or so a vigourous evolution of nitrous fumes occurred. When this was over /

over, the mixture was heated on a small electric air bath, carefully for two hours corresponding to the change from borneol to camphor, then more strongly at 100 - 110°C for fifty hours. On cooling, l-camphoric acid crystallised out, was filtered off, and washed with cold water. By concentration of the filtrate a further yield of acid was obtained. For purification of this crude acid, it was dissolved in 10% sodium hydroxide, and the small quantity of unchanged camphor filtered off. To remove the last trace of this, the solution was extracted with ether, and the aqueous layer acidified in the cold with concentrated hydrochloric acid. L-camphoric acid separated in the form of fine white powdery crystals, melting at 182.5°- 183°C, and giving $[\alpha]_D^{16} = -45.41°$ with $c = 8.24$ in absolute alcohol. Further purification was effected by the anhydride transformation (for details see the case of the d-acid below). On reconverting to the acid, a poor yield was obtained, 7.5g yielding 3.5g acid, which, however, was in a pure state, and melted at 187.5°C. It gave a rotation of $[\alpha]_D^{16} = -48.12°$ with $c = 8.24$ in absolute alcohol.

Dextro/

Dextro Camphoric Acid was obtained in a pure state by purifying the d-camphoric acid supplied by the British Drug Houses Limited, or directly from their camphoric anhydride. The acid supplied, after one crystallisation from aqueous alcohol, gave $[\alpha]^{16}_{D} = +47.15^{\circ}$ with $c = 8.24$ in absolute alcohol, and melted at 177- 179°C. It was purified by the anhydride transformation [Aschan, loc. cit.].

68g (1 mol.) of perfectly dry recrystallised camphoric acid were mixed with 136g. (4 mol.) of acetic anhydride and 34g. of sodium acetate, and the whole heated on a water bath for five hours with occasional shaking, and then poured into a large volume of water. The d-camphoric anhydride which separated was filtered off, washed with water, and twice recrystallised from boiling alcohol. It separated out in fine needles.

? fused

Yield?

The yield obtained in every case was low. A better yield was obtained by converting the acid to anhydride using acetyl chloride as dehydrating agent, but the latter method yields acetyl chloride along with the anhydride, so that it is very difficult to purify the product.

The /

The reconversion to the acid was effected by boiling in aqueous solution with the molecular quantity of potassium carbonate. Complete solution occurred in rather more than half an hour. The solution was then allowed to cool; (if solid separated the whole was boiled up for a further period) and the solution was extracted with plenty of ether. The aqueous layer was acidified with concentrated hydrochloric acid, when d-camphoric acid separated. Two recrystallisations from hot water gave a pure acid, which melted at 187.6°C, and had a rotation of $[\alpha]_D^{17} = +47.6^\circ$ with c= 8.24 in absolute alcohol. From the anhydride supplied by the British Drug Houses Limited the pure d-acid obtained melted at 188.2°C, and gave $[\alpha]_D^{17} = +47.75^\circ$ with c = 8.24 in absolute alcohol.

CAMPHORIC ANHYDRIDE.

Laevo Camphoric Anhydride was obtained in the purification of l-camphoric acid. After two recrystallisations from boiling alcohol, it melted at 222.9°C, and gave a rotation of $[\alpha]_D^{16} = +3.2^\circ$ with c = 4 in benzene. No recorded rotation could be found. It is curious that the anhydride of strongly laevorotatory camphoric acid should give a small dextro /

dextro rotation. The name laevo camphoric anhydride is retained in these experiments.

Dextro Camphoric Anhydride.

This was obtained in the purification of d-camphoric acid. After two recrystallisations from boiling alcohol it melted at 223.8°C, and gave a rotation of $[\alpha]_D^{17} = -3.1^\circ$ with c = 4 in benzene. Marsh [Chem. News 60, 307] gives $[\alpha]_D = -3.7^\circ$. In these experiments this anhydride is known as the dextro anhydride.

ORTHO METHYL CAMPHORIC ESTER.

Laevo Camphoric Ester.

Several methods of preparation were available. In the first instance that by Walker [J.C.S. 1892, 1088] was employed, using as starting material pure l-camphoric anhydride.

A weighed quantity of sodium was dissolved in methyl alcohol, the solution of sodium methoxide cooled, and to it gradually was added the calculated quantity of l-camphoric anhydride (1 mol. to 1 at. sodium). The anhydride was previously powdered, and the temperature kept low by cooling in water. The reaction took place with the disengagement of a considerable /

considerable amount of heat, the anhydride being rapidly attacked, and the sodium methyl camphorate falling out after a time as a white finely crystalline precipitate. After the mixture had remained for some hours at the ordinary temperature, the methyl alcohol was distilled off, and the solid pure white residue dissolved in water, in which it is very soluble. The aqueous solution was acidified, and the oil which separated removed, washed with a little water, and dried. The oil obtained in the early experiments stood for several months before crystals separated, but later batches crystallised after seeding with a crystal of the l-ester. They did not separate if a crystal of the d-ester was added to them.

The ester first prepared melted sharply at 86°C, but gave no rotation with plane polarised light. It must have become racemised at some stage in the process. Later the laevo ester was obtained. It melted at 73.5°C, and showed a rotation of $[\alpha]_D^{15} = -52.95^\circ$ with c = 10 in absolute alcohol. No recorded rotation could be found to compare this with.

This ester was also obtained by acting on l-camphoric acid dissolved in methyl alcohol with dry hydrochloric /

hydrochloric acid gas, which was passed in for about two hours. The di-ester was also formed in this process. Purification was effected by pouring into water, dissolving the oil which separated in alkali in the cold, and extracting the solution with ether to remove di-ester. Hydrochloric acid was added to the aqueous layer to precipitate the hydrogen ester, and the solution extracted with a large quantity of petroleum ether. This was distilled off, and the l-ortho methyl camphoric ester remained ~~as~~ an oil. Crystallisation was effected as in the case of the l-ester obtained in the first method. Once fairly pure crystals had been obtained, they could be recrystallised very easily, and formed well shaped crystals. Titration of crystals in 10 c.c. of a 10% solution of alcohol with baryta as in the case of the d-acid below gave 12.40 c.c. required.
12.58 c.c. Theoretical.

Dextro Camphoric Ester.

This was prepared in an exactly similar manner to the l-ester. Both of the above methods were employed, starting from pure d-camphoric anhydride or the acid obtained therefrom. The oil first obtained /

obtained solidified partly after some months. By pressing on a porous tile and crystallising from petroleum ether, crystals were obtained. These melted at 63°C, but successive recrystallisations raised the melting point to 72°C, 75°- 76°C, and finally to 76°C, the melting point of the pure d-ester. It gave a rotation of $[\alpha]_D^{15} = +51.95^\circ$ with c = 10 in absolute alcohol. Haller [C.R. 114, 1516] gives a melting point of 75°- 76°C, with $[\alpha]_D = +51.52^\circ$.

An analysis was effected by dissolving 2.5g. of the ester in 25 c.c. alcohol, and titrating 10 c.c. of the solution with standard baryta solution.

No. of c.c.'s required = 12.40 c.c.

No. of c.c.'s calculated for d-ester = 12.58 c.c..

An analysis carried out on the oil form of the d-ester gave exactly comparable results to that done with the crystals.

For 7.027g. ester, 33.01 c.c. alkali were required.

Theoretical 32.82 c.c. alkali.

BORNYL /

BORNYL HYDROGEN PHTHALATE.

The laevo and dextro forms of this were prepared in the course of purification of laevo and dextro borneols, and utilised after one recrystallisation from their respective solvents, benzene and glacial acetic acid. See under Borneol, pages 16&19

PINENE.

There would seem to be no very effective way of purifying pinene. A number of investigators have endeavoured to find a solid compound which would yield up the pinene unchanged, but most, as e.g. the one formed with picric acid, give camphene on further treatment. The only method which can be used is that of repeated distillation in steam, a little carbonate being added to the pinene before starting, followed by drying and careful fractionation. The rotation finally reached would seem to depend on the original source of the sample of pinene. Great variations are reported, see Landolt "Das Optische Drehungsvermogen" , Second Edition, p. 555-557.

Laevo /

Laevo Pinene - From Three different sources,
1, 11, and 111.

Sample 1 was obtained from Kahlbaum. Before treatment it gave a rotation of $\alpha = 99.30^\circ$, the density being .8856, whence $[\alpha]_D^{18} = -56.07^\circ$. $l = 2$
After purification two fractions were obtained, A. and B.

A boiled at 158-159°C Rotation = 112.07°
Density = .8698 $[\alpha]_D = -64.43^\circ$

B boiled at 159-162°C Rotation = 114.47°
Density = .8696 $[\alpha]_D = -65.81^\circ$.

Further purification yielded a main fraction which boiled at 157.8° - 159.8°C. The rotation was 115.64°, Density = .8665, whence $[\alpha]_D^{15} = -66.73^\circ$. This, however, gave no sharp setting or melting point when these were tried in a test tube cooled in a bath of solid carbon dioxide and alcohol, and therefore was useless for our purpose.

Sample 11 was obtained from British Drug Houses Limited, The initial rotation was $\alpha = 61.17^\circ$, Density = .8682; whence $[\alpha]_D^{15} = -35.23^\circ$. On purification the main fraction boiled at 160°C, rotation was $\alpha = -65.18^\circ$, Density = .8674; whence $[\alpha]_D^{15} = -37.58^\circ$.

This /

This gave a sharp melting point at -63°C, the point being determined by thermoelectric measurements as in the curve for d. and l. pinenes.

Sample 111, was obtained from crude French turpentine oil. It gave an initial rotation of $\alpha = -18\frac{1}{4}^{\circ}$. After being steam distilled three times, dried, and fractionated, the following fractions were obtained:-

Approximate values of their rotations are shown alongside.

Boiling Point.	Rotation
156°- 159°C	$-17\frac{1}{4}$
159°- 162°C	-19
162°- 166°C	$-20\frac{1}{2}$
166°- 169°C	-21
169°- 172°C	$-20\frac{3}{4}$
172°- 176°C	-19
176°- 178°C	$-16\frac{3}{4}$

A large quantity of the crude oil was fractionated, and the portion boiling between 156° and 167°C was collected. From one gallon of the oil 800 c.c. of this fraction were obtained. This was steam distilled, dried, and fractionated. Four separate portions /

portions were collected; 157° - 159°C; 159°-162°C; 161°- 163°C; 163°- 165°C. It was hoped to purify some of these further, and so obtain a sample of l-pinene which would do for the purpose in hand, but no sample gave any indication of having a sharp melting point. Hence the idea of obtaining pure l-pinene from crude French turpentine oil was given up.

The laevo pinene of Sample 11 was used in all experiments.

Dextro Pinene. From two sources 1 and 11.

Sample 1 was obtained from Kahlbaum. Before treatment it gave a rotation of $\alpha = +78.65^\circ$; Density = .8665, whence $[\alpha]_D^{15} = +45.38^\circ$. After fractionation the three portions obtained gave -

A boiled at 155°- 156° C; Rotation $= +81.04^\circ$;
Density =..8635; whence $[\alpha]_D = +46.92^\circ$.

B boiled at 156°- 157°C; Rotation $= +80.25^\circ$;
Density = .8630; whence $[\alpha]_D = +46.49^\circ$.

C boiled at 157°- 162°C; and gave an approximate rotation of $[\alpha]_D = +45.5^\circ$.

After purification the main portion boiled at 156°C, and gave a rotation of $\alpha = +80.38^\circ$; Density .8590; whence $[\alpha]_D^{15} = +46.80^\circ$. It gave a sharp melting /

melting point at $-64^{\circ}C$, the point being determined by thermoelectric measurements as in the curve of d and l-pinenes. The setting point was also tried, but as the liquid super-cooled persistently in spite of vigorous stirring, it was not found possible to determine the setting point accurately.

Sample 11 was obtained from rectified oil of turpentine. After steam distillation, drying, and fractionation, the following fractions were obtained;-

Boiling Point.	Rotation.
157-160°C	12.3°
160-163°C (a)	13.8°
160-163°C (b)	15.2°
163-165°C	20.3°

It was hoped to arrive at a good sample of d-pinene from these, but no indication of a sharp melting point was given by any of the fractions. Hence the dextro pinene of sample one was used in all experiments.

CAMPHENE /

CAMPHENE.

Laevo Camphene.

This was prepared from the pure l-pinene obtained as above. The directions followed were those given in Fischer's Laboratory Manual of Organic Chemistry. Successive quantities of 100g. of laevo pinene which had been thoroughly dried, were placed in a small round bottom flask, and dried hydrochloric acid gas passed in at a fairly rapid rate continuously for about two hours. The flask was embedded in ice to which a little salt had been added. As the reaction proceeded, the temperature rose, and further quantities of salt had to be added. The best temperature for the reaction is from 5° to 15°C. When the pinene was saturated, pinene hydrochloride separated as a semi-solid mass. The flask was disconnected, corked, and cooled to -10° to -15°C for half an hour, the contents then filtered off with suction, and pressed out on a porous tile. A small additional quantity was obtained by cooling the filtrate for a second time.

The crude product was dissolved in 40 c.c. of warm alcohol, cooled to -5°C, with stirring to avoid the /

the formation of a solid mass, filtered off and pressed out as above. 50 grams of white crystalline pinene hydrochloride of melting point 120°C were obtained from each 100g. of pinene.

The conversion of this product into camphene was accomplished by heating with potassium phenolate. 95g. phenol were melted in a 200 c.c. round bottom flask and 38g. crushed potassium hydroxide added. The mixture became hot, and the alkali dissolved. The flask was connected with a condenser for distillation, a thermometer being inserted in the vapour above the mixture, and heated carefully over a wire gauze to distil off the water formed in the reaction. When the temperature had risen to 180°C, the flask was allowed to cool somewhat, disconnected, and 50g. of pinene hydrochloride added in two portions, the second after the first reaction had subsided. A long upright air condenser was fitted to the flask, and the contents heated carefully till the initial somewhat violent reaction was over. Thereafter the mixture was kept boiling for two to three hours with frequent shaking. The flame was then temporarily removed, and the flask fitted for ordinary distillation /

distillation as before, an air condenser being employed. Heating was continued, when almost pure camphene passed over from 150° to 160°C; above that temperature it became more and more contaminated with phenol, and the distillation was stopped when a drop of the distillate gave no turbidity in a solution of sodium hydroxide. The distillate was shaken with dilute sodium hydroxide, and cooled in ice, when the camphene separated in solid lumps. It was filtered off, washed with water, melted in a small flask, and poured off from the aqueous layer. This was repeated with addition of a few pieces of calcium chloride, and the camphene fractionated in a small fractionating column, using an air condenser. Pure l-camphene passed over at 160.5°C. It melted at 44°C, and gave a rotation of $[\alpha]_D^{15} = -77.15^\circ$ with c = 10 in absolute alcohol. For earlier rotations see Landolt "Das Optische Drehungsvermogen," second edition, p. 554 - 555.

Dextro Camphene.

This was prepared in an exactly similar way from pure d-pinene. It boiled at 160°C, and melted rather higher than the laevo camphene at 46°C. Its /

Its rotation was $[\alpha]_D^{15} = +72.8^\circ$ with $c = 11.7$ in absolute alcohol.

Both laevo and dextro camphenes are exceptionally volatile, and great care had to be taken to avoid exposing them to the air for any length of time.

DETERMINATION OF CURVES.

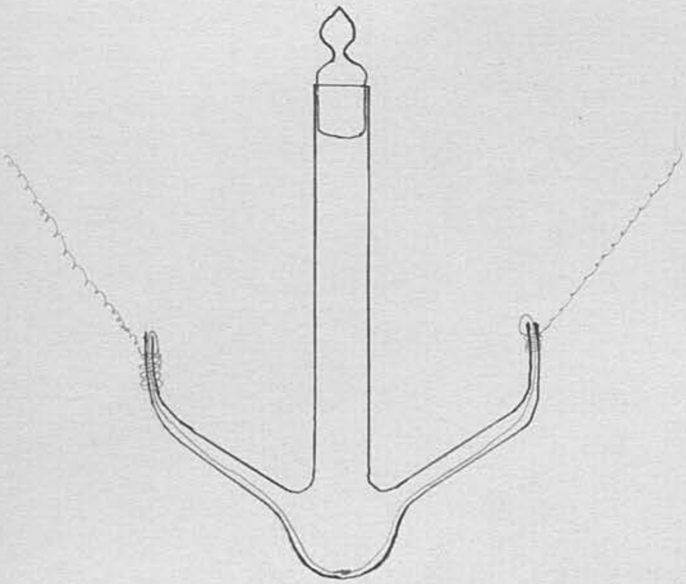
Owing to the difficulty of obtaining the pure dextro and laevo isomers in large quantity, some method of investigating the curves had to be devised which would permit of the use of small quantities of the materials. Moreover, since the borneol for example does not melt till 206°C., yet boils as low as 212°C.,and is consequently very volatile at its melting point, the determinations of the melting point curve required to be done in a closed tube. This made the arrangement for stirring a problem of considerable magnitude. As the temperatures ranged from -60 to 220°C., it was not easy to obtain accurate thermometers which would cover all the range. The use of a thermocouple suggested itself, and was gradually developed, so as to harmonise with the other requirements of the case.

THE TUBE.

The determinations accordingly were carried out in a specially prepared tube. A bulb was blown on the end of a glass tube 6in. long and ½in.diameter. Two side tubes 3in. long and 1/8th in./

in.diameter were sealed in at the opposite sides of the bulb. Two lengths of wire, one of copper, Standard Wire Gauge 30, the other of constantin, Standard Wire Gauge 33, were joined with hard solder, and inserted through the side tubes so that the join of the two wires occupied the foot of the tube in the bulb. Copper and Constantin were chosen since they could be easily obtained and gave a large E.M.F. for small changes of temperature. With the wires in this position the ends of the side tubes were heated and drawn off so that the glass collapsed on to the wire and effected a complete seal. In spite of what might have been expected to the contrary, no trouble was experienced from the expansion of the wire in different amount to the glass; this seal was never a breaking point for the tube. The wires were bent back from the point where they emerged from the side tube, and given a number of turns round the glass, so that the strain of continual bending just at the point of emergence from the glass seal was reduced and the "life" of the thermocouple prolonged. A glass stopper was ground into the mouth of the tube.

A diagram of the tube follows:-



THE THERMOCOUPLE.

The junction of the copper and constantin wires inside the tube, in all cases except pinene, acted as the hot junction of the thermocouple. A similar join of two other pieces of the copper and constantin wires was effected, and placed in a suitable holder to form the cold junction. The temperature was kept steady at 0°C. for several hours by immersing this junction in an "ice-mush" in a test tube which was placed in a vacuum vessel filled with ice and water. This "ice-mush" was obtained by freezing distilled water, and cutting down the piece of ice formed with a razor blade. In the actual experiments the constantin wires from the /

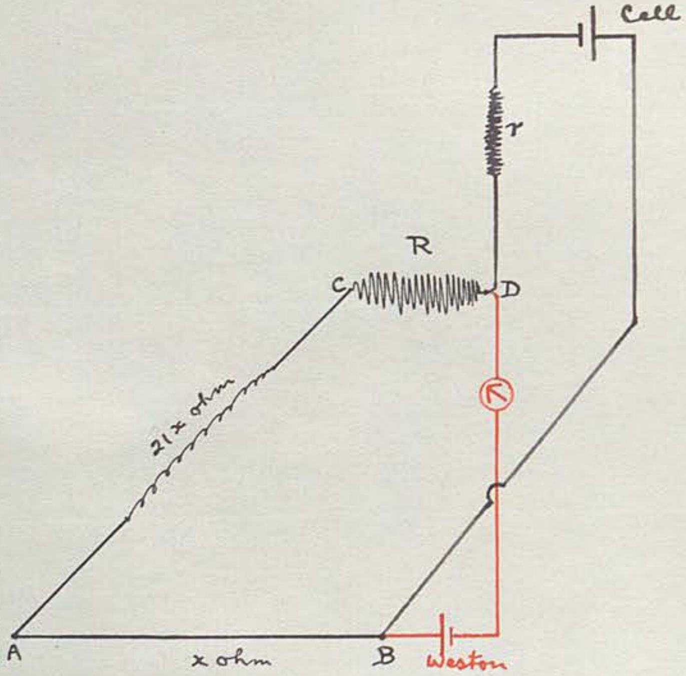


Fig 1

the two junctions were twisted together, the join being kept in ice, while the copper wires from both were led to the potentiometer.

THE POTENTIOMETER.

This was a Cambridge and Paul instrument of the enclosed pattern. Twenty one bobbins each of the same resistance as the Bridge Wire are arranged in series. In this way a considerable range of E.M.F. can be measured without any alteration in the instrument. A method of measuring accurately very small voltages was used, as outlined in Watson's Textbook of Practical Physics, for diagrams of connections see opposite page.

The general lay out of the apparatus is shown diagrammatically in Fig. 1. AB is the bridge wire of resistance x ohms, AC contains the 21 coils each of resistance x ohms, and R is a large resistance placed between C and D. For the purpose of this explanation BACD can be reckoned as the actual "Bridge". To the ends of this bridge an accumulator is connected, but in this circuit a resistance r is interposed, which is of such a magnitude as to reduce the voltage between B and D from 2.2 v to 1.019 v.

In /

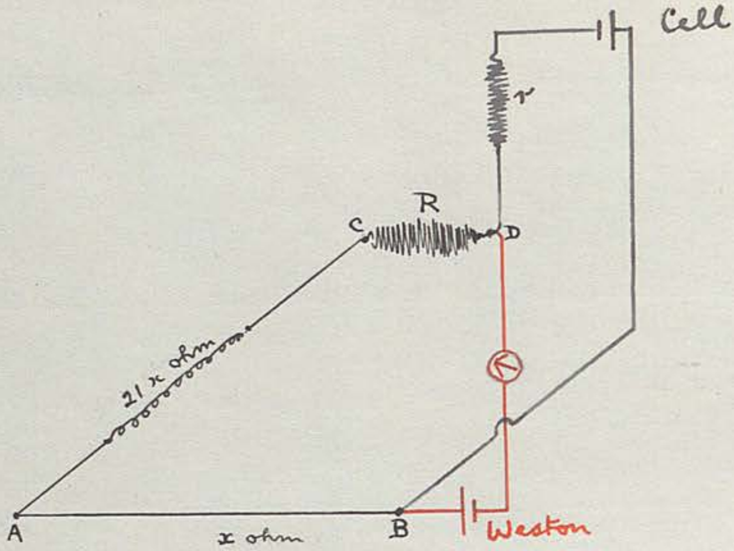

Cell
r
R
C
D
21 x ohm
A
x ohm
B
Weston

Fig 1

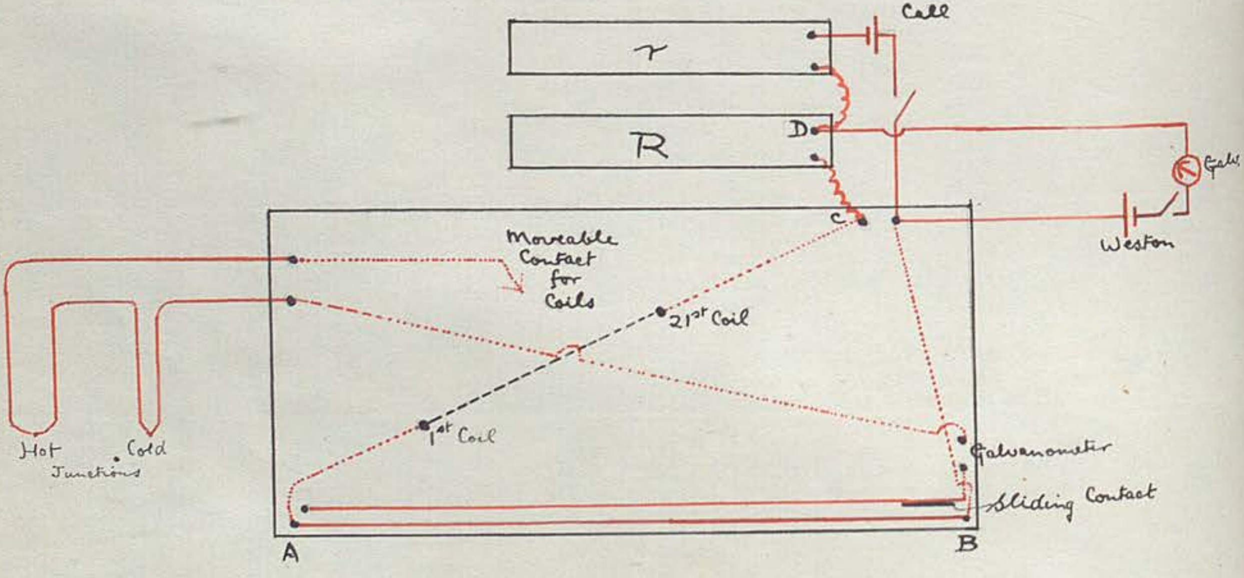

Cell
r
R
D
Galv.
C
Weston
Moveable Contact for Coils
21st Coil
1st Coil
Galvanometer
Sliding Contact
Hot
Cold
Junctions
A
B

Fig 2

In order to find out the value of r, a Weston cell with a galvanometer in circuit is connected to B and D. r is then adjusted so that no deflection is shown in the galvanometer. In this way by frequent testing with the Weston cell a constant fall of potential between B and D was maintained. R was calculated so that

$$\frac{x}{22x + R} = \frac{1}{1019}$$

i.e. so that the bridge wire (and each of the coils) took 1/1019 of the total fall of potential.
i.e. 1/1019 of 1.019 v. = .001 v.. Hence each large division on the Bridge (scale 100 half cms.) represented .00001 v., and each small division represented 1x10^{-6} v.. 22x was determined experimentally to be 51 ohms, hence R = 2312 ohms. In this way a fall of potential of 22x.001 v. = .022 v. was maintained between C and B.

The measurement of the E.M.F. of the thermocouple was accomplished as shown in Fig. 2, where the actual potentiometer is represented, the dotted lines in red indicating wires in the interior of the instrument. From the fall of potential in the coils and the bridge wire, a sufficient amonnt was /

was tapped off equal to the E.M.F. developed by the thermocouple, the point of balance being determined on a very sensitive mirror galvanometer connected to the terminals shown in diagram. Accuracy in reading to 1×10^{-5} v. was obtained with this instrument.

CONVERSION TO DEGREES CENTIGRADE.

The relationship between the E.M.F. of the thermocouple and the actual difference of temperature between the junctions is not absolutely linear, but for small ranges of temperature the error introduced by regarding it as such is negligible. In general then for each curve, two substances were chosen which melted at steady temperatures, one at either end of the range of the melting point curve. These melting points were determined (a) with each thermocouple

(b) with an accurate thermometer.

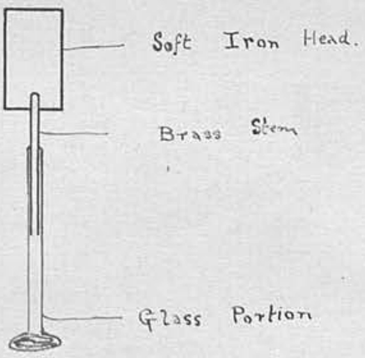
This thermometer was corrected for emergent stem and compared with a standard thermometer. Hence two fixed temperatures were expressed as bridge readings for each thermocouple, and from these a gradient calculated, which was valid for that range of /

of temperature, and enabled E.M.F. measurements to be converted into degrees. In practice it was found that 100 divisions of the scale on the bridge did not correspond exactly to .001 v.; but that 94 divisions really acted as the end of the bridge. Hence all readings on the scale were increased by 6.4%. This, of course, did not apply to that portion of the E.M.F. measured by the coils. Owing to the high temperature necessary in several of the curves, some variations were observed in the values obtained for the thermocouples in the early readings. Accordingly, all tubes before calibration were kept for 24 hours at 150°- 200°C.. In this way more constant values for the temperature were obtained.

STIRRING.

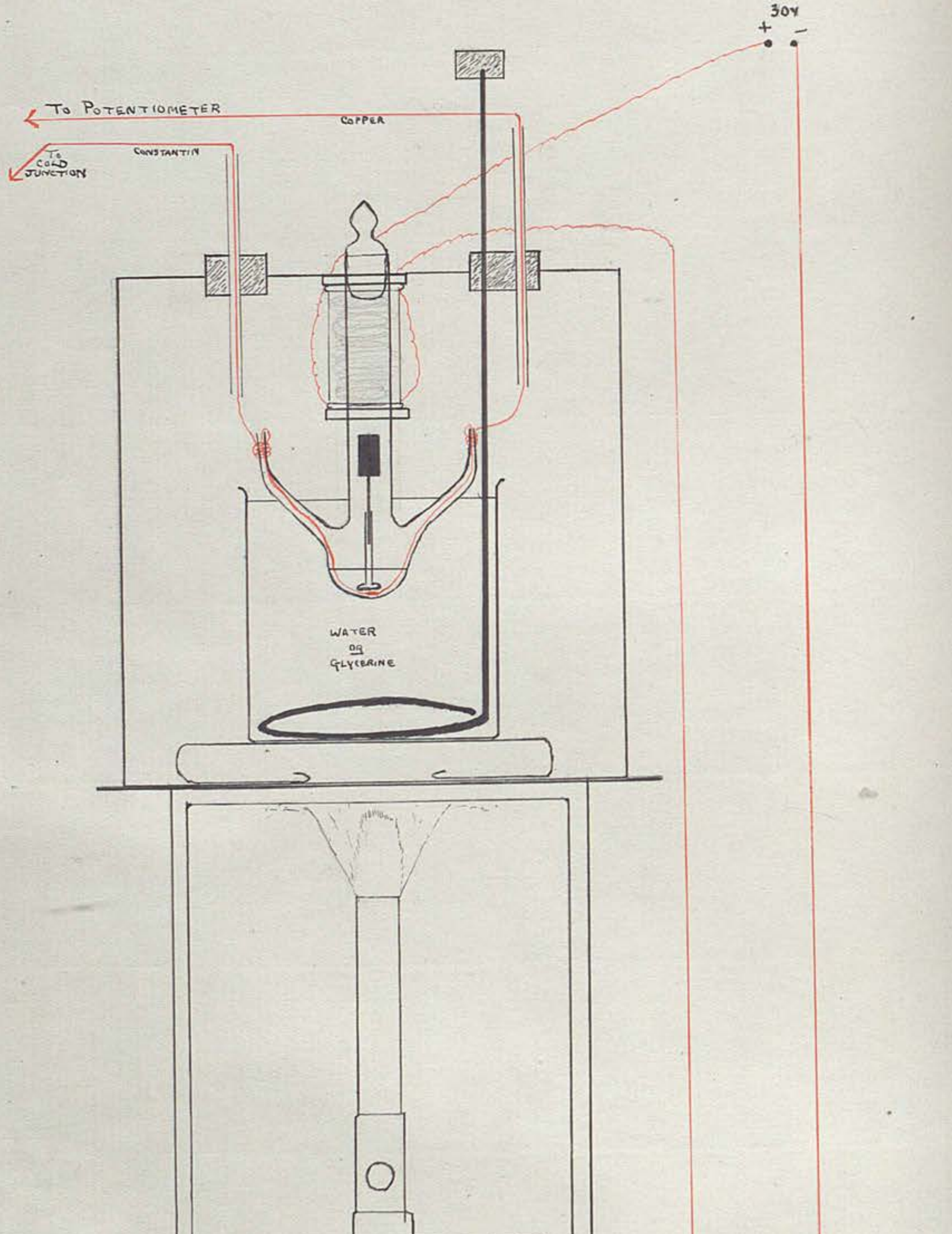
It was essential in all determinations to have efficient stirring. Two types of stirrer were employed. A was used when dealing with substances volatile at their melting points, as for /

Type A

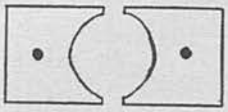


for example borneol, when the determination had to be carried out in a tube completely closed;B was used for the remainder, as for example pinene, when loss by volatilisation was negligible. In the case of the type A , the stirring was accomplished by an electro magnetic stirrer.

A small rod of soft iron ½in. long and ¼in. diameter was fitted with a short brass stem 1in. long. A length of glass tubing was selected of internal diameter such that the brass stem fitted it tightly. Short lengths of 1½-2in.were cut and a large blob of glass melted on the end of each length. For each experiment one of these was pushed on to the brass stem of the soft iron head;this was placed inside the tube, and constituted the internal portion of the stirring arrangement. Two small bobbins of 5 ohms resistance, made of enamelled copper wire, were fitted with cores of soft iron and screwed on to a plate of the same material, which had a hole in the centre to allow of the passage of the melting point tube. At the other end of the bobbins two pieces of soft iron were screwed in to act as the magnetic poles, and of such a shape that they fitted close/


30V
+
−
TO POTENTIOMETER
COPPER
TO COLD JUNCTION
CONSTANTIN
WATER
OR
GLYCERINE

close to the tube. See diagram.



All the determinations which employed this type of stirring were carried out in a bath of glycerine or water, according to the requirements of the case, which was contained in an air oven fitted with a mica window at back and front and illuminated from behind. The bobbins were screwed into, and so suspended from the top of this oven, and the melting point tube passed up through the middle, the final position being one in which the soft iron head of the stirrer inside was about half an inch below the lower end of the bobbins outside. The thermocouple wires were passed up through two holes in the roof of the oven in glass tubes held in position by corks. A potential of 30 volts was applied to the bobbins, contact being made and broken regularly when required by a tapping key in the circuit, which could be depressed by hand. The internal stirrer alternately jumped up to the bobbins, and fell back by its own weight as contact was made and broken. This gave very efficient stirring when setting points were being /

being determined, and fairly good in the case of melting points.

Type B was a glass stirrer, simply a rod which had been flattened at the end to as wide a diameter as the melting point tube would allow. It was worked by hand.

BORNEOL.

The calibration of the thermocouples was carried out with

d-borneol melting at 206.5°C
and
d-camphor melting at 178.6°C

the temperatures being measured on an Anschütz Thermometer, and corrected. A stirrer of type A was used in all experiments.

The heating was carried out in a glycerine bath in the air oven. A large bunsen was employed in the earlier stages, but was replaced by an ordinary one when the temperature of melting was approached, and the latter turned out just before melting occurred. Air cooling prevented the temperature from rising much above the melting point. Great care had to be taken that this did not occur, since if kept at a temperature more than one degree above its melting point the borneol began to decompose, a brown mass being formed.

The melting point of the borneol was tried, but no very definite point was found, either as a steady point during the melting of the solid or as the /

the point where the last trace of solid disappeared. Some indication was given, however, of the probable setting point, which was accurately determined on cooling. A point was always found at which the temperature remained constant for a brief period of time, and in some cases it rose to a steady value. This rise does not seem to have been generally observed in the determination of such setting points, and it is probably due to the sensitiveness of the thermocouple to slight and momentary changes of temperature, as opposed to the comparatively slowly acting thermometer.

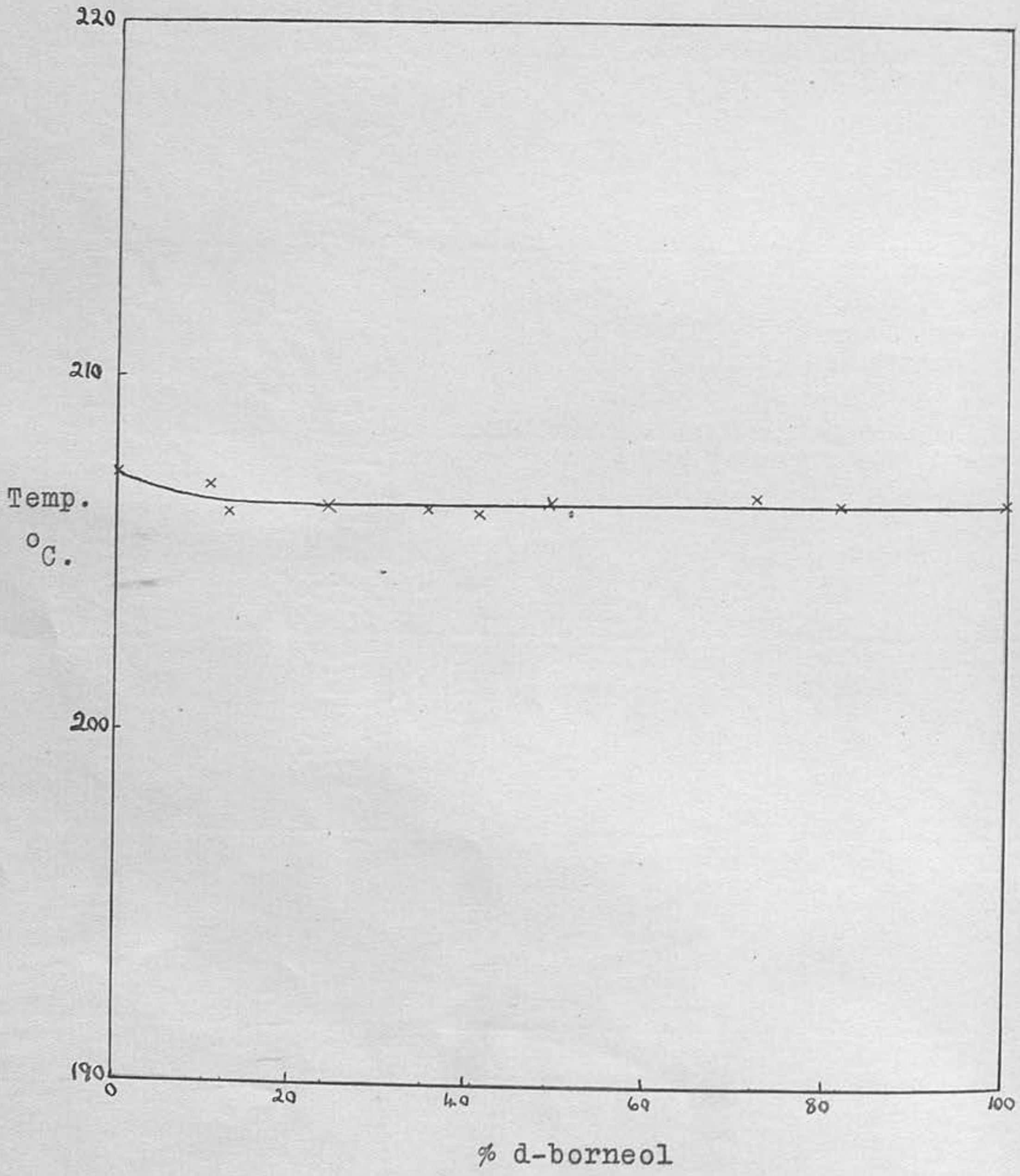
With due precautions to avoid heating too high, it was possible to repeat the setting point of each mixture two or three times, but thereafter the temperature of solidification became lower and lower, and a brownish colour was developed. The tube had then to be cleaned out, dried, and a fresh sample employed. These mixtures were prepared in a weighing bottle, and brushed into the tube with a camel hair brush, over a sheet of glazed paper. Very small quantities of the substance could be employed, only about .3 to .5 grams being necessary.

As the tubes were heated up to 200°C. from the ordinary temperature, a considerable pressure was developed inside, and this was released just before the melting point was taken.

The table of setting points is shown alongside of the curve on the next page.

DEXTRO AND LAEVO BORNEOLS.

SETTING POINT CURVE.



DEXTRO and LAEVO BORNEOLS.

% d-borneol	Setting Point in °C
100.00	206.5
81.30	206.4
72.04	206.6
49.48	206.4
40.75	206.0
35.40	206.2
24.06	206.2
12.35	206.1
10.45	206.8
0.00	207.2

CAMPHOR.

The calibration of the thermocouples was carried out with

d-borneol melting at 206.5°C
and
d-camphor melting at 178.6°C

the temperatures being measured on an Anschutz Thermometer, and corrected. A stirrer of type A was used in all experiments.

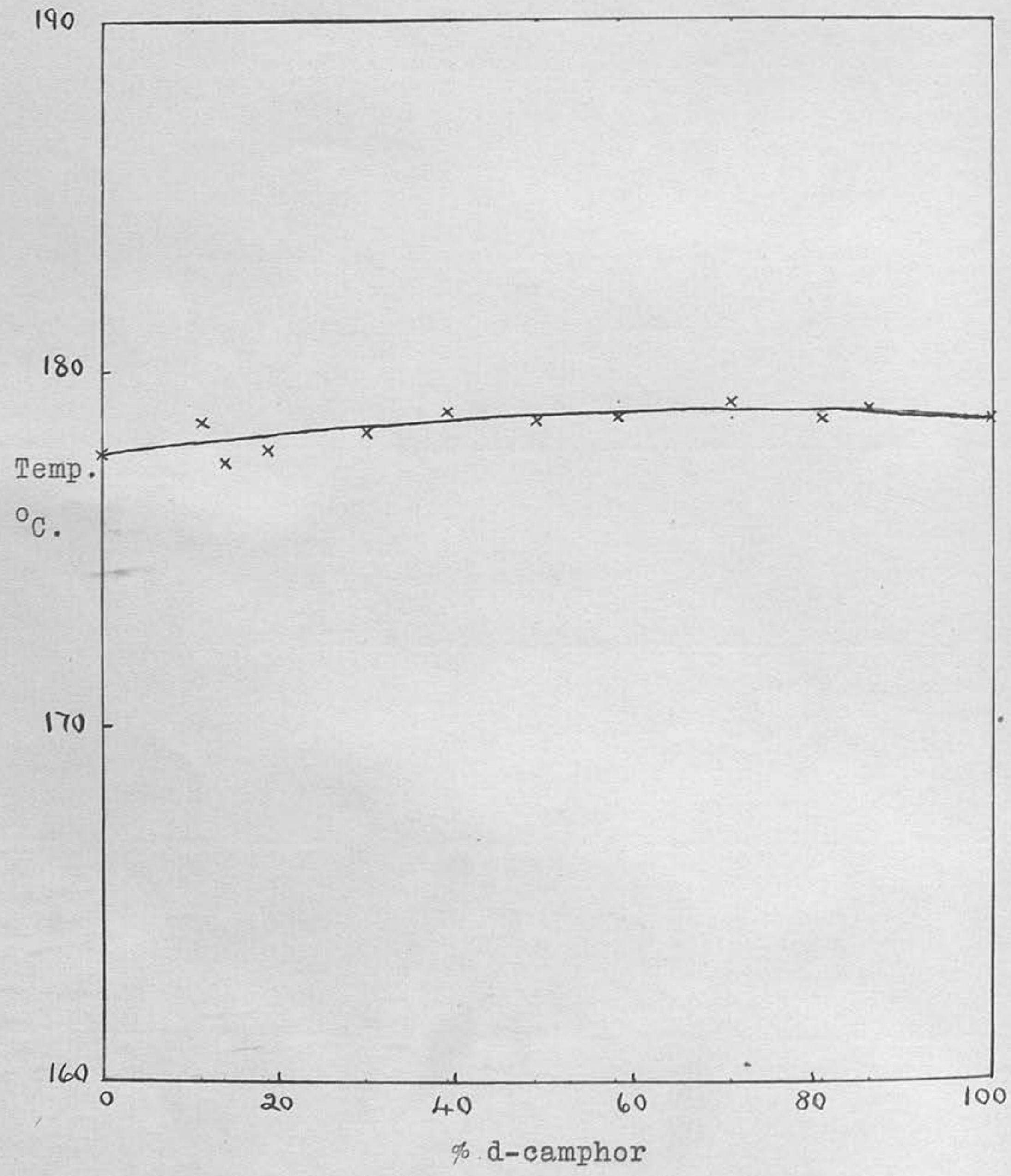
This determination was carried out in an exactly similar way to that of d-borneol. Here, also, slow decomposition occurred if the temperature rose more than about one degree above the melting point. Each mixture served only one point on the curve, a fresh start being made each time.

The melting point did not give a satisfactory value, so the setting point was determined as in the case of borneol.

The values of the setting points for various percentages of d- and l- isomers are shown in the table and graph on the next page.

DEXTRO AND LAEVO CAMPHORS.

SETTING POINT CURVE.



DEXTRO and LAEVO CAMPHORS.

% d-camphor	Setting Point in °C
100.00	178.6
86.2	178.8
81.0	178.6
70.8	179.1
57.9	178.7
48.7	178.6
39.3	178.8
30.1	178.3
19.1	177.8
13.8	177.4
11.3	178.5
0.0	177.7

D-BORNEOL and D-CAMPHOR

This curve had already been worked out by [Vanstone J.C.S. 1909, 597]. The d-borneol which he employed , however, was not pure(see note under the preparation of d-borneol) . It melted at 208.6°C and gave a rotation of $[\alpha]$ =+27.66°. Moreover, the determination was not done in a closed tube, so that some loss by volatilisation was almost certain to occur. The temperature measurements by the thermocouple are probably more accurate than those carried out by Vanstone. Accordingly it was decided to re-determine the curve, using pure d-borneol and pure d-camphor.

The calibration of the thermocouple was carried out with

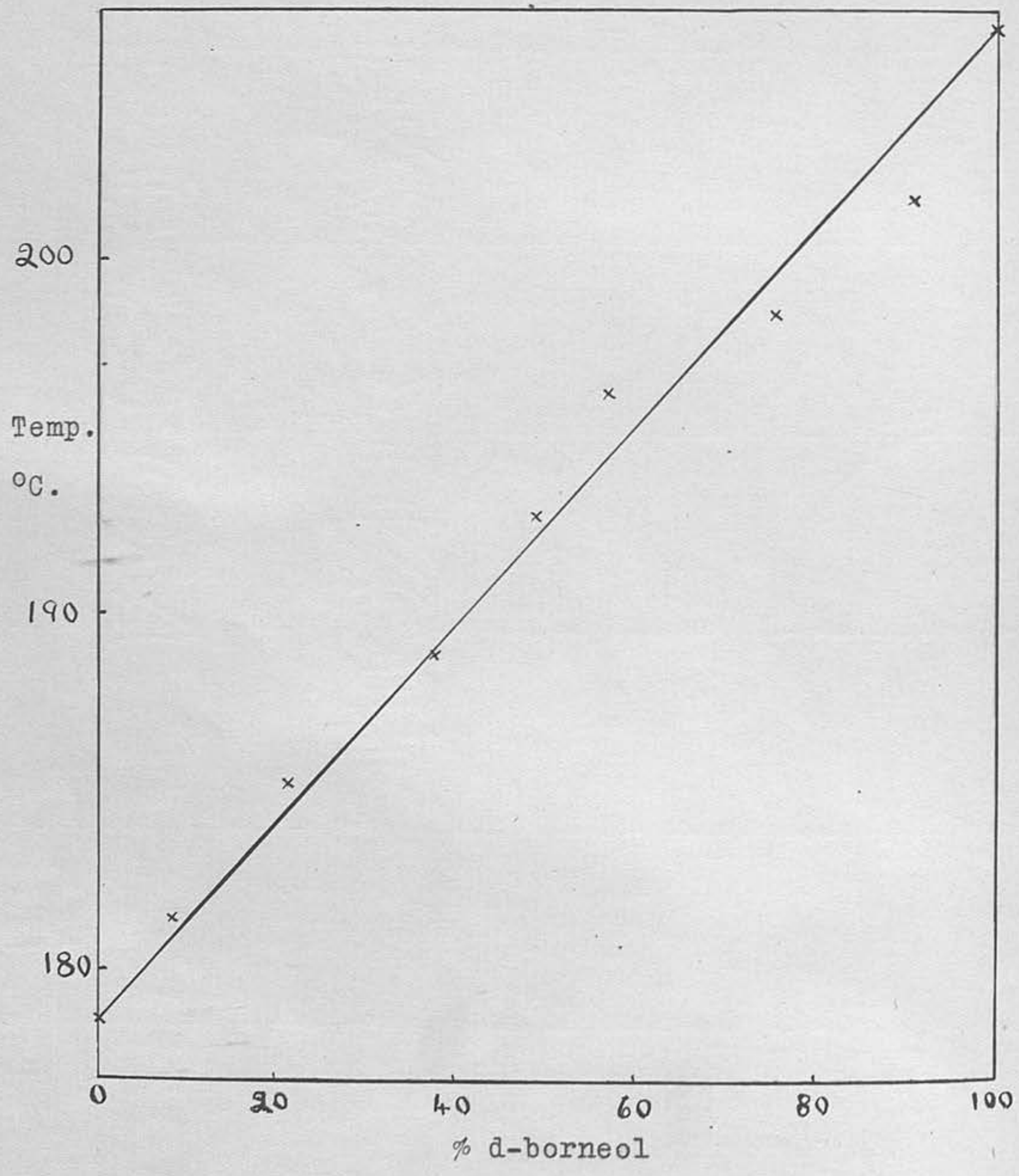
d-borneol melting at 206.5°C .
and
d-camphor melting at 178.6°C.

the temperatures being measured on an Anschutz Thermometer, and corrected. A stirrer of type A was used in all experiments.

The procedure was exactly the same as in the two previous cases, the setting point curve being determined. The graph and table are shown on the next page.

DEXTRO BORNEOL AND DEXTRO CAMPHOR.

SETTING POINT CURVE.



DEXTRO BORNEOL and DEXTRO CAMPHOR.

% d-borneol	Setting Point in °C
100.0	206.5
90.4	201.7
75.7	198.5
57.3	196.2
49.0	192.7
37.8	188.9
21.3	185.3
8.4	181.4
0.0	178.6

CAMPHORIC ACID.

The calibration of the thermocouple was carried out with

d-borneol	melting at	206.5°C
	and	
d-camphor	melting at	178.6°C

the temperature being measured on an Anschutz Thermometer, and corrected. Frequent recalibration was necessary owing to slight changes in the thermocouples due to a slow action of the camphoric acids on the metals. A stirrer of type A was used in all experiments.

This curve was more difficult to determine than any of the ones already dealt with. The camphoric acid when melted decomposed with great readiness, though in this case no charring was to be seen, and it was not possible to get a setting point after melting once, far less to repeat the melting point after cooling and reheating. It was therefore necessary to start every mixture afresh, heat it up carefully, and take the point at which it melted for the first time. The mixing was not so good as when a setting point of a melted mixture was to be determined. The melting point obtained on heating was /

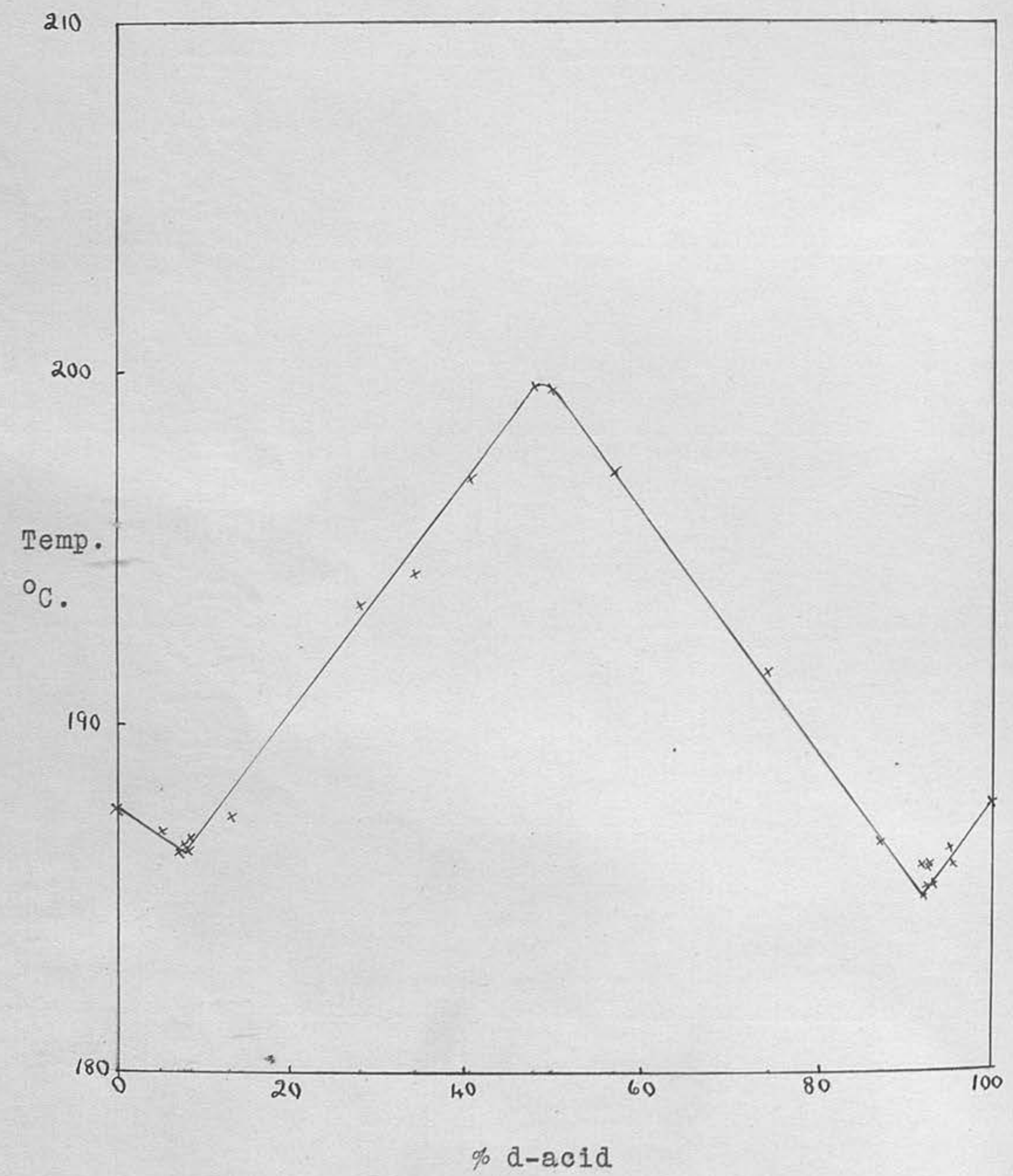
was indicated usually by a fall of temperature, followed by a brief steady interval, and then a further rise as the solid disappeared. This short steady interval was the point taken, as no steady point was observed when the last trace of solid disappeared.

The table and melting point curves are shown on pages 64-65.

Equal quantities of d and l acids were accurately weighed out, mixed, and recrystallised together from aqueous alcohol. Racemic acid was obtained of melting point 202.6°C., rather over 2° higher than that found in the curve for a 50%, 50% mixture of d and l. This difference is probably due to some trace of decomposition in the latter case. A melting point curve was determined for mixtures of d and r acids, in an exactly similar way to the above d and l acids. The results are shown on pages 66-67.

DEXTRO AND LAEVO CAMPHORIC ACIDS.

MELTING POINT CURVE.

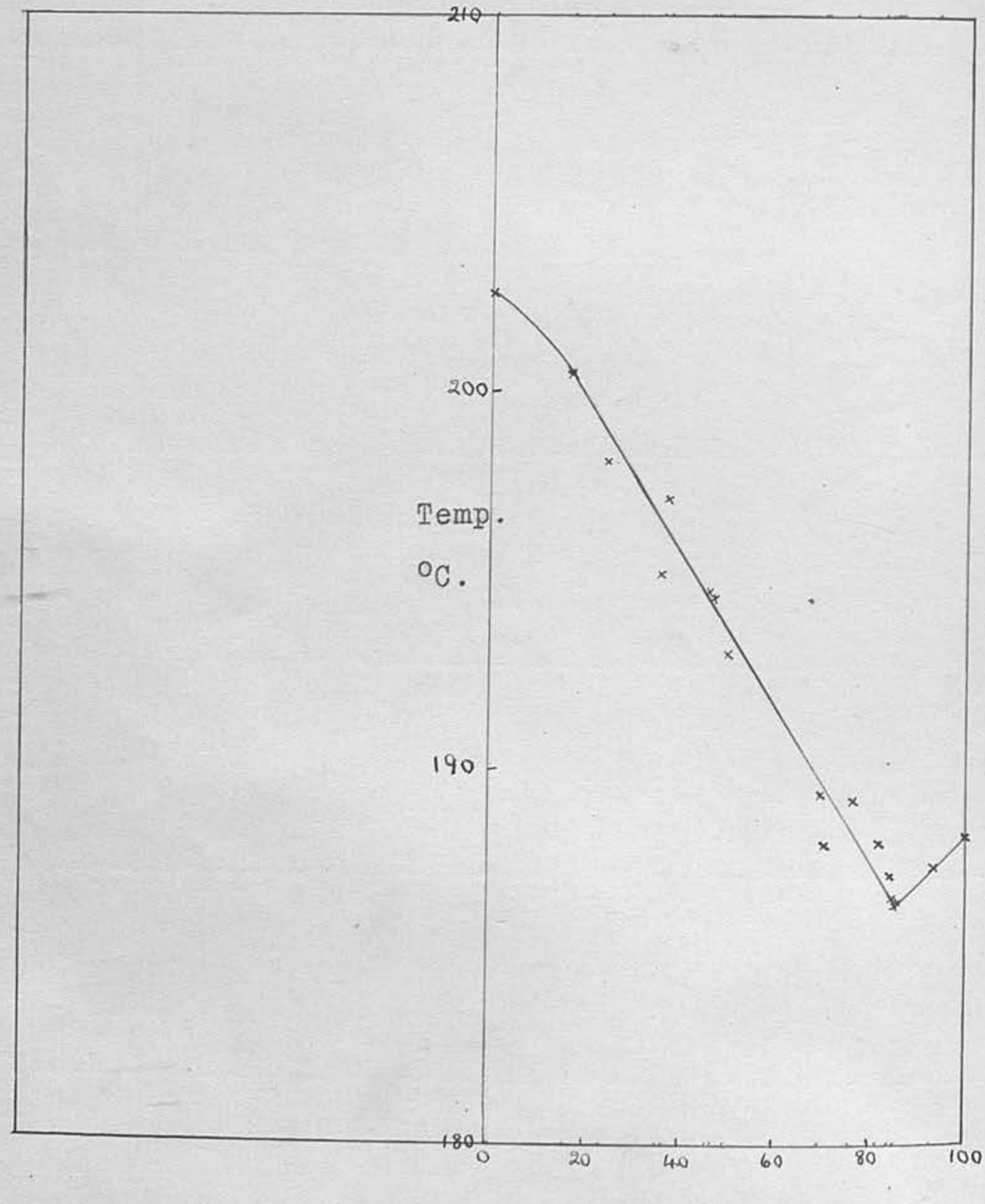


DEXTRO and LAEVO CAMPHORIC ACIDS.

% d-acid	M.P.in °C	% d-acid	M.P.in °C
100.00	187.6	49.83	199.5
95.40	185.9	47.86	199.6
95.10	186.3	40.70	196.9
93.47	185.4	34.43	193.4
92.70	185.9	28.10	193.3
92.30	185.8	13.40	187.3
92.26	185.2	8.87	186.7
92.15	185.8	8.43	186.3
92.10	185.0	8.03	186.5
91.80	185.0	7.35	186.2
87.30	186.5	5.47	186.8
74.40	191.3	0.00	187.5
56.94	197.2		

DEXTRO AND RACEMIC CAMPHORIC ACIDS.

MELTING POINT CURVE.



DEXTRO and RACEMIC CAMPHORIC ACIDS.

% d-camphoric acid	Melting Point in °C
100.00	188.2
93.48	187.3
85.70	186.5
85.40	186.4
84.27	186.5
84.04	187.1
81.72	187.2
75.57	189.1
69.62	187.9
69.38	189.3
49.17	193.1
46.91	194.5
45.77	194.7
36.39	197.1
35.19	195.1
23.63	198.1
16.01	200.5
0.00	202.6

CAMPHORIC ANHYDRIDE.

The calibration of the thermocouples was carried out with

d-camphoric anhydride melting at 223.8°C

and

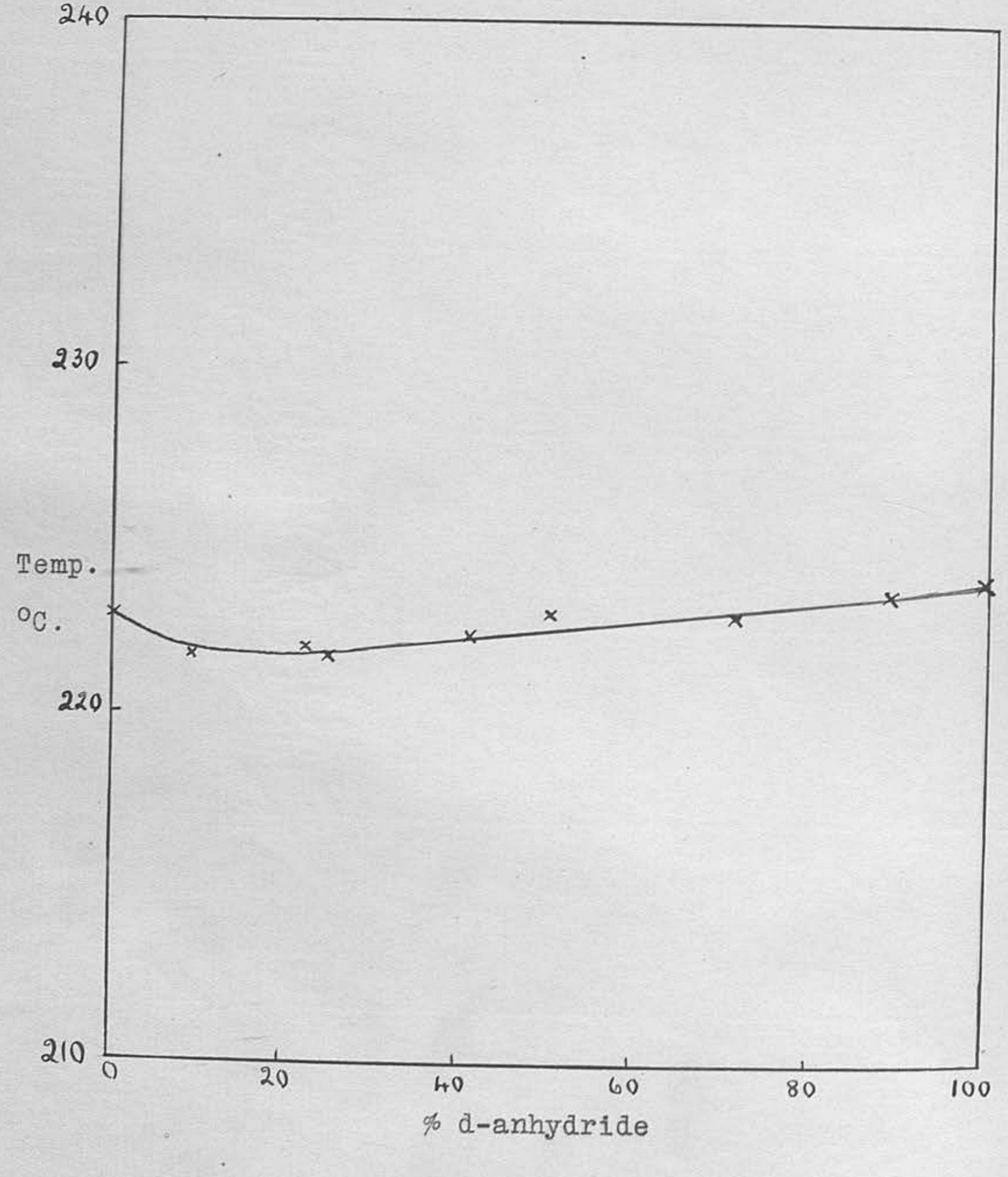
d-borneol melting at 206.5°C

The temperature of the melting of the anhydride was found on an accurate thermometer, and that of the borneol on an Anschutz Thermometer, and both corrected. A stirrer of type A was used in all experiments.

The curve was determined in a similar way to that of borneol. The setting point was taken, though the melting point gave an almost identical value. Decomposition of the melted anhydride, if any, was very slow, and each point could be repeated several times, and so accurately located. The results are given on the next page.

DEXTRO AND LAEVO CAMPHORIC ANHYDRIDES.

SETTING POINT CURVE.



DEXTRO and LAEVO CAMPHORIC ANHYDRIDES.

% d-camphoric acid anhydrides	Setting Point in °C
100.00	223.8
88.80	223.5
71.62	222.8
50.24	222.9
41.37	222.2
25.00	221.6
22.14	221.9
9.43	221.7
0.00	222.9

ORTHO METHYL CAMPHORIC ESTER.

The calibration of the thermocouples was carried out with

dinitrobenzene	melting at	90.50°C
	and	
diphenyl	melting at	68.70°C

The temperatures were measured on an accurate thermometer reading from 50° to 100°C., in 1/10ths. and corrected. A stirrer of type B was used in all experiments.

At the much lower temperature of melting of the ester, a closed tube was not necessary. The glycerine bath was replaced by one of water. It was not found possible to determine a setting point curve, not because of decomposition, but on account of the tendency of the ester to form an oil on cooling. Repeated determinations of the melting point were possible, and these were carried out on each mixture.

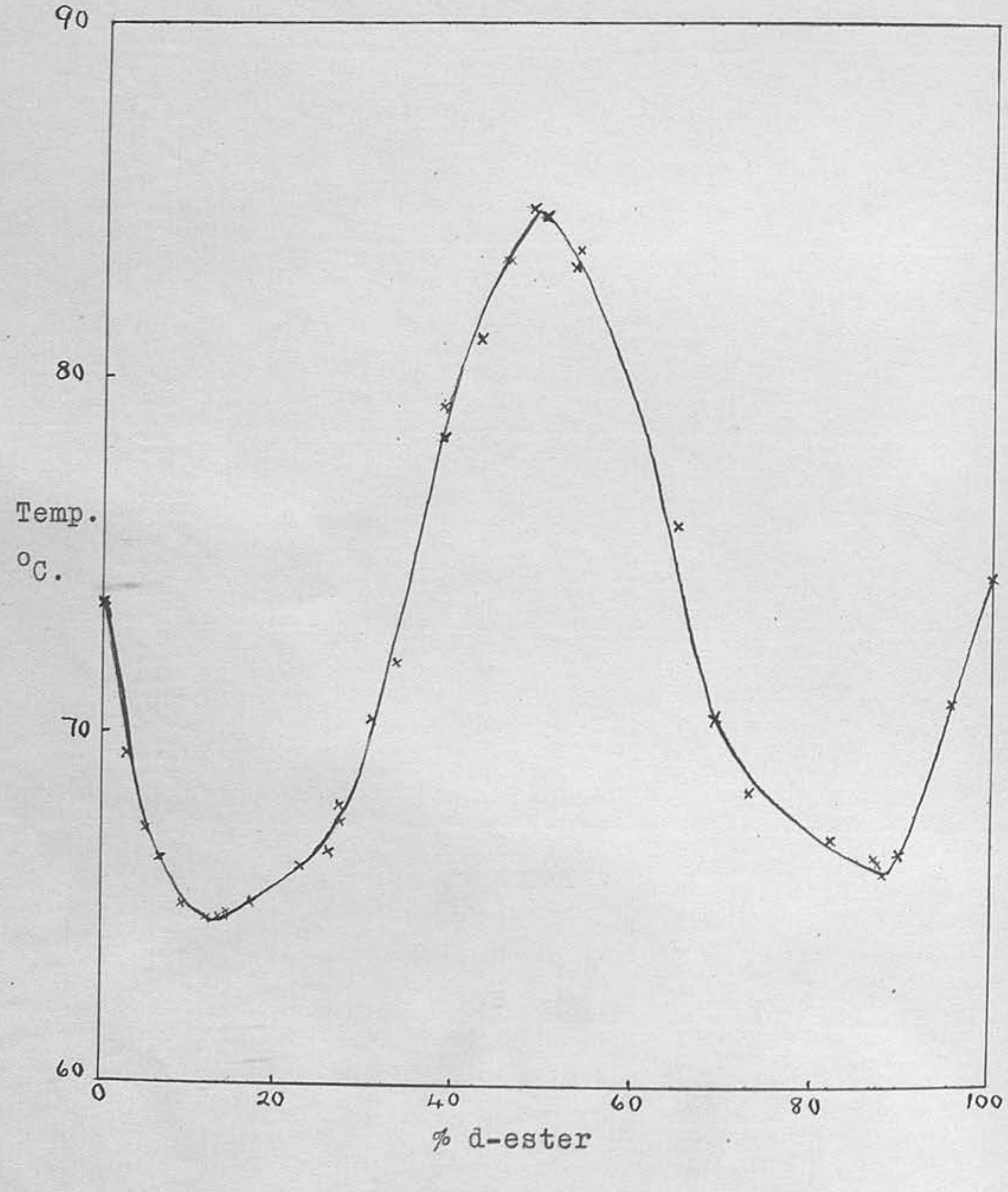
In the actual experiment a weighed quantity of one of the isomers, say d-ester, was placed in the tube, and the latter put in position. The water bath was then heated up. As in the case of the acid, the melting point was indicated by a slight fall of temperature, a brief steady interval, followed by a more /

more rapid rise as the solid disappeared. As soon as the steady interval was completed, the hot water of the bath was syphoned off and replaced by cold. In this way the time of solidification was shortened. If the ordinary rate of cooling was adhered to, the oil form of the ester was maintained for a considerable period of time. This determination of the melting point was repeated two or three times, or until constant results were obtained. A quantity of the l-ester was then added to the tube in situ, and the melting point of the mixture determined. A further quantity of the l-ester was added thereafter, and so on, till the whole curve was completed. Confirmatory results were obtained by starting from the opposite end. The curve and table are shown on the next page.

In the course of preparation of the l-ester, some became racemised, This was used to determine a melting point curve for d and r ester. The procedure was exactly the same as above. The results are shown on pages 75-76.

DEXTRO AND LAEVO METHYL CAMPHORIC ESTERS.

MELTING POINT CURVE.

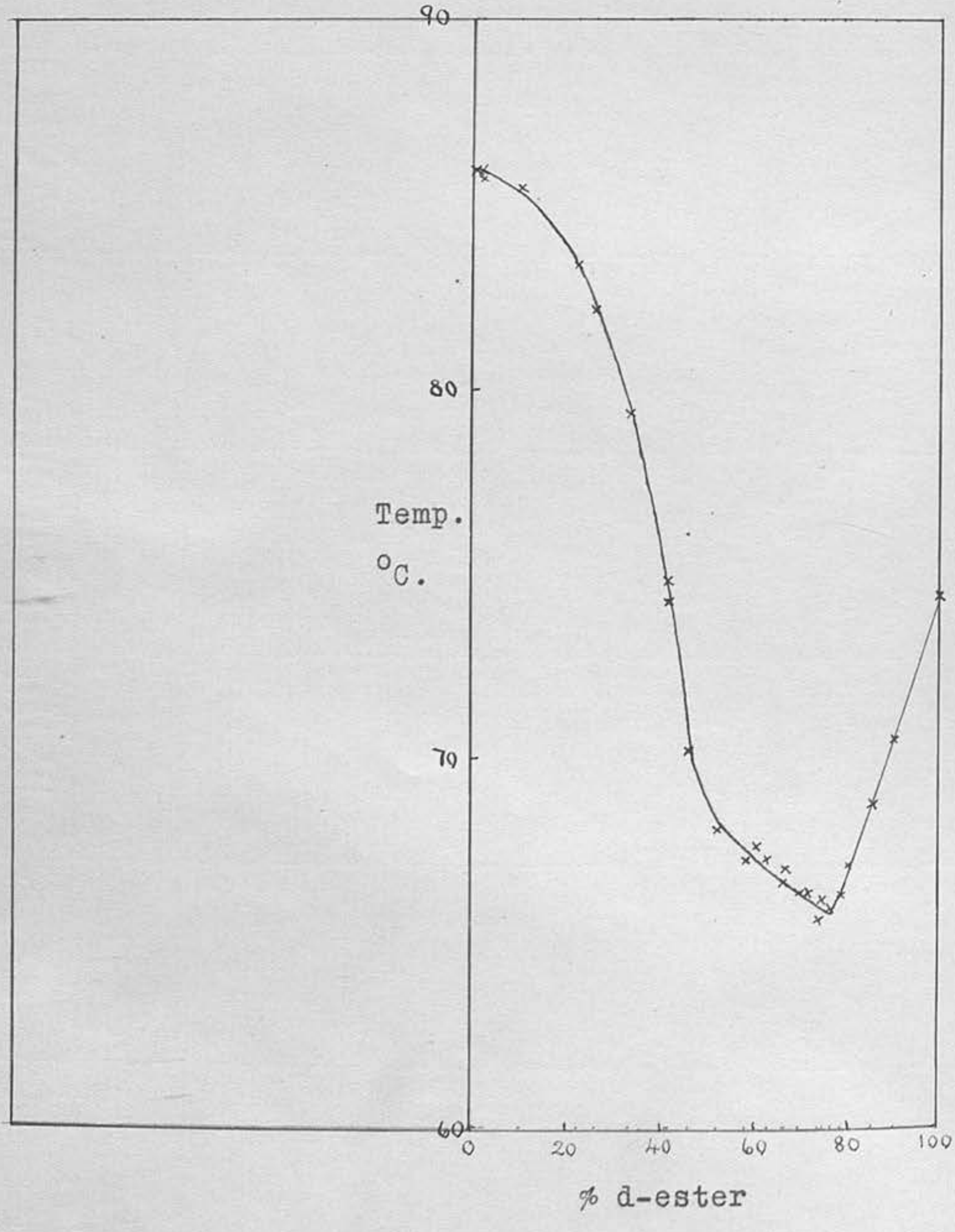


DEXTRO and LAEVO METHYL CAMPHORIC ESTERS.

% d-ester	M.P.in °C	% d-ester	M.P.in °C
100.00	74.3	38.43	79.1
95.58	70.8	38.39	78.3
89.65	66.5	33.30	71.9
88.00	65.9	30.71	70.4
87.40	66.2	27.42	67.4
86.90	66.4	27.18	67.9
82.20	66.9	25.84	66.5
73.24	68.3	22.55	66.1
69.50	70.3	17.00	65.0
64.58	75.9	14.34	64.8
53.85	83.6	14.10	64.7
53.45	83.1	13.38	64.7
49.86	84.6	12.00	64.6
48.63	84.8	9.39	65.0
45.96	83.4	6.19	66.3
45.66	83.4	4.79	67.1
42.43	81.0	2.52	69.3
		0.00	73.5

DEXTRO AND RACEMIC METHYL CAMPHORIC ESTERS.

MELTING POINT CURVE.



DEXTRO and RACEMIC METHYL CAMPHORIC ESTERS.

% d-ester	M.P.in °C	% d-ester	M.P.in °C
100.00	74.4	58.00	67.2
90.28	70.5	51.61	68.0
85.10	68.7	46.51	70.2
80.04	67.0	41.53	74.2
78.94	66.2	33.32	79.2
75.81	65.9	26.01	82.2
74.28	66.2	22.56	83.3
73.08	65.6	9.90	85.5
69.54	66.3	1.43	85.7
66.58	67.0	1.41	85.9
66.18	66.6	0.00	85.9
63.05	67.3		
60.24	67.6		

BORNYL HYDROGEN PHTHALATE.

The calibration of the thermocouples was carried out with

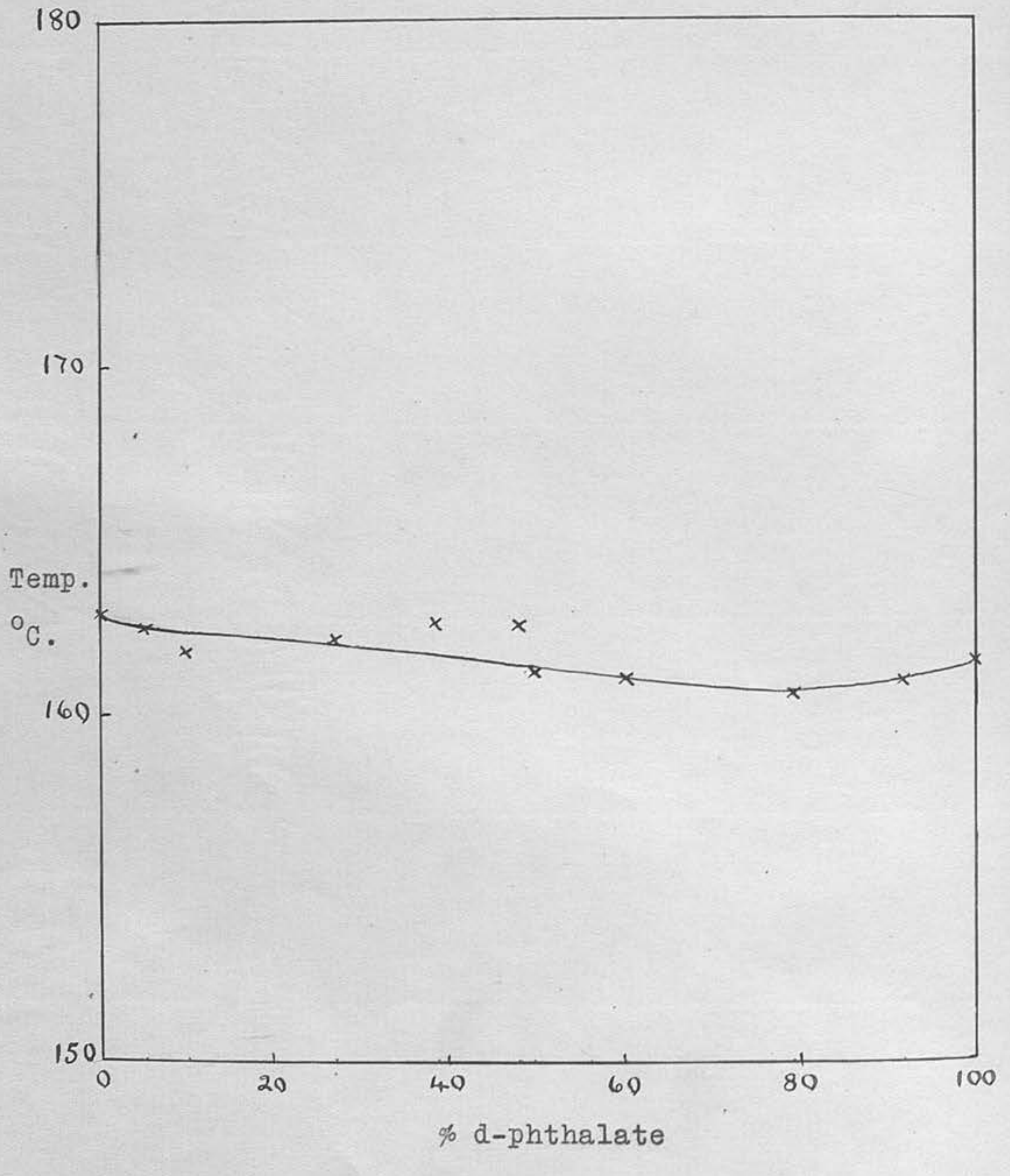
d-camphor	melting at	178.6°C
and		
d-bornyl hydrogen phthalate	melting at	161.4°C

the temperatures being measured on an Anschutz Thermometer, and corrected. A stirrer of type A was used in all experiments.

This curve was carried out in a similar way to that of camphoric acid, a glycerine bath being used to heat up the tube. As in the case of the acid, decomposition of the melted substance occurred very readily. The melting point at the first time of heating was taken. The tube was then cleaned out, and used in the determination of a fresh mixture. Somewhat variable results were obtained, but their range was too small to leave any doubt as to the real nature of the curve. The table and the graph are shown on the next page.

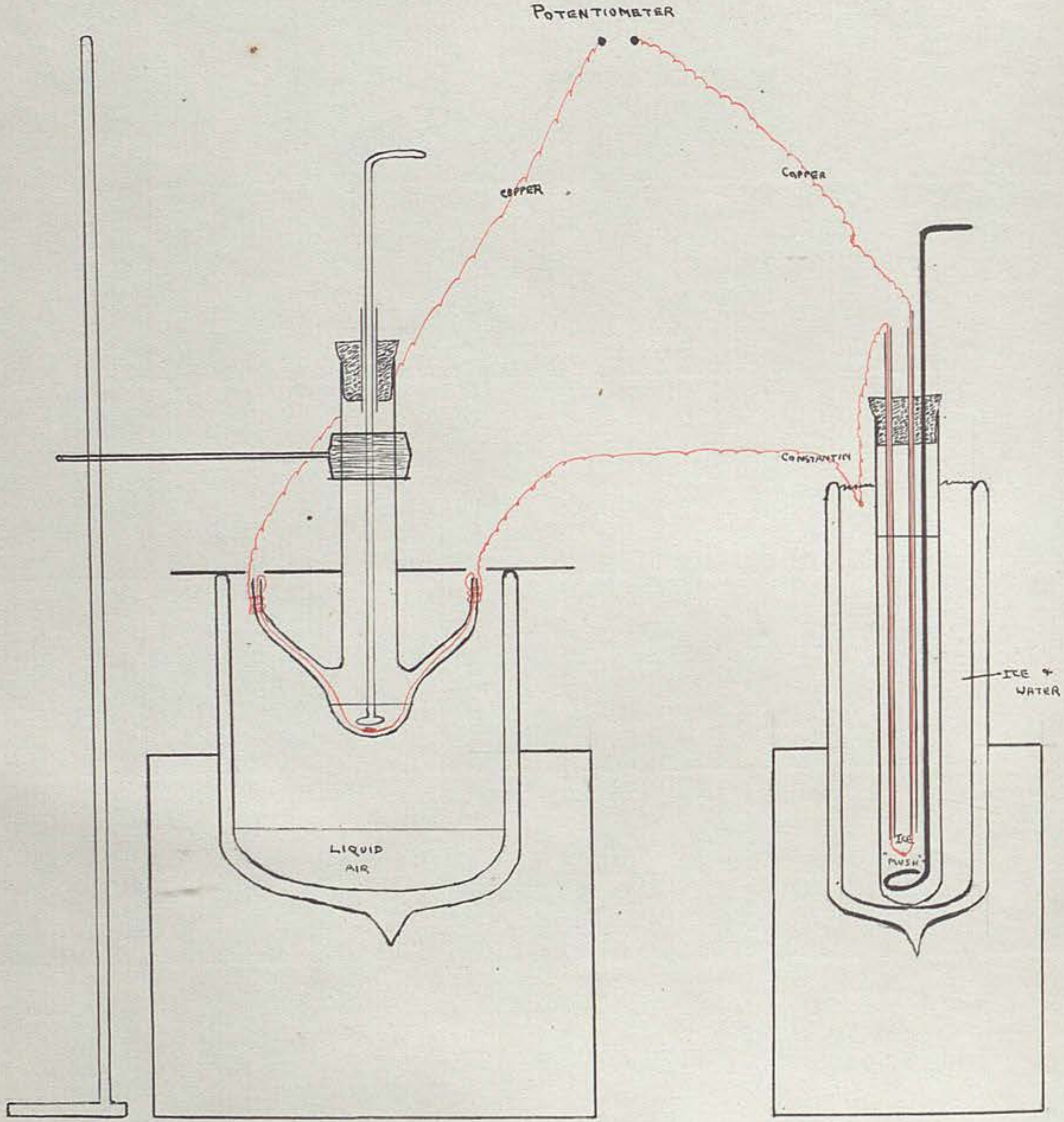
DEXTRO AND LAEVO BORNYL HYDROGEN PHTHALATES.

MELTING POINT CURVE.



DEXTRO and LAEVO BORNYL HYDROGEN PHTHALATES.

% d-phthalate	Melting Point in °C
100.00	161.4
91.60	160.8
78.90	160.5
60.00	169.9
49.65	161.1
48.08	162.5
38.55	162.5
27.00	162.1
9.74	161.7
5.27	162.3
0.00	162.8


POTENTIOMETER
COPPER
COPPER
CONSTANTIN
ICE + WATER
LIQUID AIR
ICE "MUSH"

PINENE.

The low temperature necessary for the determination of this curve was obtained by immersing the tube in a bath of liquid air, contained in a vacuum vessel. The junction at 0°C. thus became the "hot" junction, so that the direction of the flow of current in the thermocouple circuit was reversed.

Owing to the large range of temperature over which the curve extends, the calibration of the thermocouples was difficult. Further, no accurate thermometer was available for those temperatures. Accordingly several pure substances were taken, and their freezing points determined in the thermocouples. The corresponding values of temperature were taken from the freezing points of the pure substances as given in the latest edition of Landolt-Bornstein Tabellen. The following were chosen -

Diethylaniline	freezing point	- 38.1°C
Chloroform	freezing point	- 63.3°C
Toluene	freezing point	- 94.5°C
Ethyl Alcohol	freezing point	-114.2°C

The /

The relationship between the E.M.F. of the thermocouple and the temperature could not be assumed to be a linear one for this large range without some considerable error. The gradient of the thermocouple decreased continuously over the range. From the values obtained with the above substances, a series of values of the gradient for every ten degrees range of temperature was calculated. These were used in converting the bridge readings into degrees Centigrade. A stirrer of type B was used in all experiments.

The freezing point of pinene was first tried in a bath of solid Carbon Dioxide and alcohol, but no definite point could be obtained owing to the large amount of supercooling.

The method finally adopted to measure the melting point was as follows:-

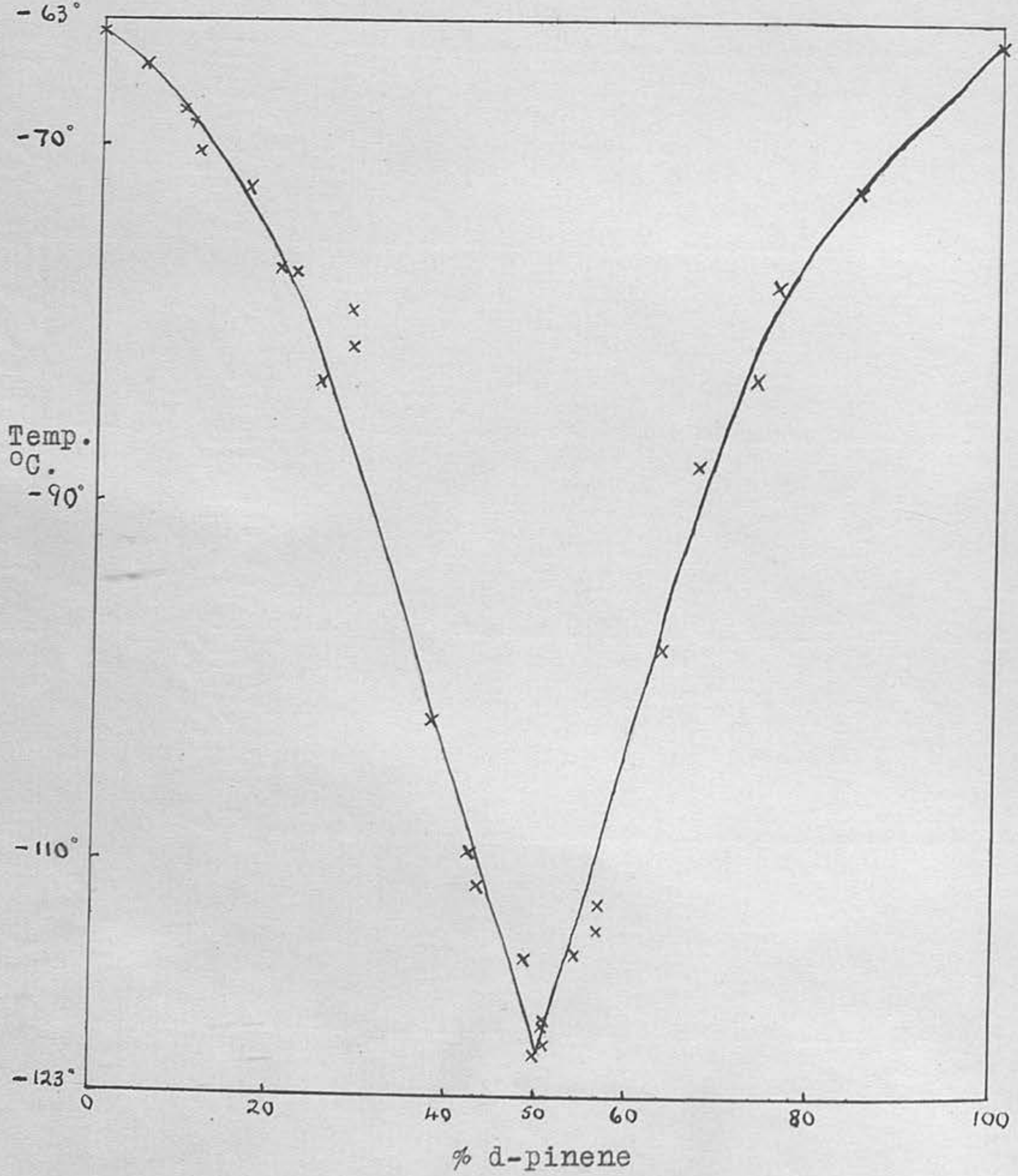
A weighed quantity of one of the isomers, say, d-pinene, was introduced from a weighing pipette into the tube, and the latter set in position in the vacuum vessel, which contained liquid air to the depth of about one inch. The stirrer was inserted, and the bulb of the melting point tube immersed in the liquid air, until all the pinene had /

had solidified. The tube was then raised, so that the bulb remained within the vacuum vessel, but was above the liquid. In this position the temperature rose slowly until the melting point was reached, when it remained steady for a short time, and then continued to rise once more. Each determination was repeated two or three times, or until constant results were obtained.

A small quantity of l-pinene was then added, and the melting point of the mixture determined, and so on till the curve was completed. The results are shown on the next page.

DEXTRO AND LAEVO PINENES.

MELTING POINT CURVE.



DEXTRO and LAEVO PINENES.

% d-pinene	M.P.in °C	% d-pinene	M.P.in °C
100.00	-64.1	43.30	-111.3
84.49	-72.5	42.34	-109.5
75.78	-77.7	38.09	-101.9
73.66	-82.8	28.85	- 79.6
67.12	-87.7	28.84	- 81.2
63.57	-98.1	25.44	-83.2
56.72	-112.4	22.17	- 77.1
56.58	-113.8	20.14	- 76.7
53.99	-115.1	16.92	- 72.2
50.65	-120.2	11.46	- 70.3
50.60	-118.7	10.21	- 68.8
50.36	-119.3	9.36	- 68.0
49.45	-120.8	4.95	- 65.4
48.50	-115.4	0.00	- 63.1

CAMPHENE.

The calibration of the thermocouples was carried out with

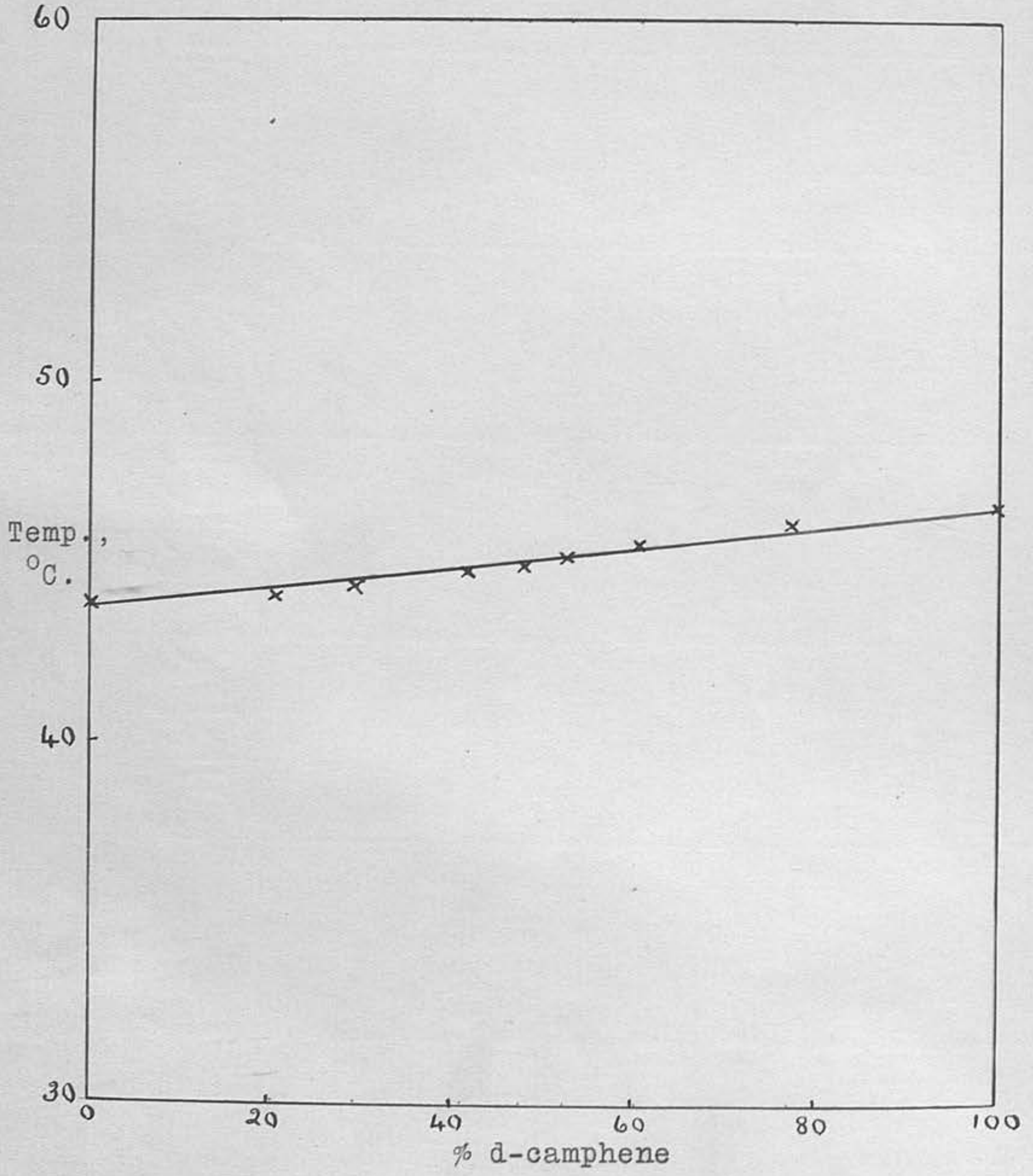
Urethane	setting point	47.75°C
	and	
Salol	setting point	41.64°C

the temperatures being measured on an accurate thermometer reading from 0°C to 50°C. in 1/10ths. and corrected. A stirrer of type A was used in all experiments.

In spite of its low temperature of melting, camphene is very volatile, so a closed tube had to be used, Heating was done on the water bath in the air oven. No decomposition of camphene in the liquid state was observed; the setting point could be repeated any number of times. The melting point was practically the same, but could not be found with such great accuracy. When the setting point had been determined for one of the isomers, successive quantities of the other were added to it, and hence the curve completed. The table and curve are shown on the next page.

DEXTRO AND LAEVO CAMPHENES.

SETTING POINT CURVE.



DEXTRO and LAEVO CAMPHENES.

% d-camphene	Setting Point in °C
100.00	46.5
77.20	46.0
60.55	45.4
52.86	45.0
48.02	44.8
41.55	44.6
29.79	44.2
20.72	43.9
0.00	43.7

DISCUSSION of RESULTS.

The results fall naturally into three divisions -

(a) The curves obtained for

d-& l- borneol	(p. 54)
d-& l- camphor	(p. 57)
(d-borneol & d-camphor)	(p. 60)
d-& l- camphoric anhydride	(p. 69)
d-& l- bornyl hydrogen phthalate	(p. 78)
d-& l- camphene	(p. 87)

are all of the same type, namely, a close approximation to the straight line joining the melting points of the pure substances. This indicates that the mixtures of all these d- & l- isomers form a <u>continuous series of mixed crystals</u>. It is not possible from these data to say whether a racemic compound exists or not, since if it were formed and gave mixed crystals with the d- or l- components, the same type of curve would be obtained. The inactive substance is a pseudoracemic mixed crystal. Vanzetti [Atti Accad. Lincei 22 II 479], using a calorimetric method, found that inactive camphor at ordinary temperatures /

temperatures was a solid solution of the two components, which shows that the pseudoracemate can exist at least at temperatures ranging from 20°to 180°C.

(b) With

d-& l- camphoric acid (p. 64).

d-& l- ortho methyl camphoric ester (p. 73).

the curves consist of three portions, with a eutectic point near each end, and a maximum for the middle portion at the 50:50 mixture. This indicates clearly the formation of a <u>racemic compound</u>. The sharpness of the turning point at the temperature of melting of the racemate gives an indication of the amount of dissociation which occurs [Findlay & Hickmans, J.C.S. 1907, 905]. In both cases it would seem that this is comparatively small, and hence that a large percentage of the racemic compound exists as such in the liquid state. Racemic camphoric acid can only have a brief period of existence owing to decomposition, but with the ester the liquid racemate would seem to be quite stable. The acid curve confirms one obtained earlier by Centnerzwer [Zeit. Phys. Chem. 1899, 29 715]

(c) /

(c) In the case of Pinene(page 84) the curve consists of two portions which descend steeply, and show a very low point of intersection at the 50:50 mixture. This indicates that the inactive substance is a simple mixture of d-& l- pinene, the "inactive conglomerate" of Roozeboom. It seems to be the first melting point curve of this type obtained for optical isomers, and confirms the result suggested for pinene from differences in rotation in various solvents by Pope and Peachey [J.C.S., 1899, 1111] and by Mitchell and Smith [J.C.S., 1913, 489] from considerations of molecular surface energy.

It should be mentioned that the above conclusions apply to temperatures in the vicinity of those investigated. They may, or may not, hold for other temperatures. For a complete investigation of the system supplementary methods would have to be resorted to.

The majority of the curves obtained are of the mixed crystal type. This seems generally to be of the most frequent occurence, probably because the dextro and laevo substances are so similar that in many /

many cases they are able to replace each other in crystals without essential alteration in the crystal structure, as is the case with isomorphous solids. It is difficult to understand why d-& l-camphene form mixed crystals while d-& l-pinene give a simple mixture. In view of the very exceptional occurrence of this type of inactive mixture at higher temperatures, it may be that the reason is connected with the low melting point of pinene. The two cases in which a compound is formed occur with substances containing a carboxyl group, camphoric acid and acid ester. A similar result might have been expected with bornyl hydrogen phthalate, where however the acid group is in the inactive part of the molecule. Dunstan and Thole [J.C.S., 1910, 1249], from viscosity determinations found that inactive (dl) octyl hydrogen phthalate was not a racemic compound, which is in agreement with the pseudoracemic nature of inactive bornyl hydrogen phthalate.

Some of the results obtained by earlier investigators may supplement the above instances. Little progress was made until it was recognised that crystallographic differences alone between active

and /

and inactive forms were not a sufficient criterion for the recognition of a racemic compound. Much of the earlier work of Walden, and of Kipping & Pope, did not yield conclusive results on account of this, though the latter [J.C.S. 1895, 388] found that r-& d- bromo-camphor and r-& d- chloro-camphor formed a continuous series of mixed crystals. Centnerzwer [Zeit. Phys. Chem. 1899, 29, 715] determined a number of melting point curves of various acids and esters, as for example, d-& i- chlorosuccinic acid, d-& l- isocamphoric acid, d-& l- methyl mandelic ester, and in every case showed that the inactive substance was a racemic compound. Adriani [Zeit. Phys. Chem. 1900, 33, 453] found that dimethyl tartaric ester, diacetyl tartaric ester, and phenylglycollic acid formed racemic compounds, while inactive camphoroxime (at the temperature of melting), carvoxime and benzoyl tetrahydroquinaldine were pseudoracemic mixed crystals.

A general review of the position with regard to racemates and pseudoracemates was given by Landrieu in 1922 [Bull. Soc. Chim., 31, 1234].

He /

He advanced the view that if a dextro or laevo isomer is dissociable, as for example in the case of an acid or salt, it will most probably form a racemic compound, the ions occupying the nodes of the crystal lattice; it may also form mixed crystals. If, on the other hand, the active substance is non-dissociable, as for example an anhydride, it will form only mixed crystals. The curves obtained for the camphor series are in complete agreement with this statement.

A survey of all the results which have been found hitherto indicates that the most commonly occurring type of inactive (dl) substance is the pseudoracemic mixed crystal. With polar compounds, however, as for example acids, there seems little doubt that a racemic compound is generally formed. This is in line with the possibility of ionisation with these substances as suggested by Landrieu. From another point of view it seems evident that the dextro and laevo isomers which form racemic compounds with each other are those with the greatest tendency to associate themselves.