THESIS, WITH ADDITIONAL PAPER, PRESENTED BY

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TO MY MOTHER.

I am deeply indebted to my supervisor, Professor T. S. Patterson, for his advice and assistance.

I acknowledge gratefully the receipt of a Mackay Smith Scholarship from the University of Glasgow, and a Research Scholarship from the Carnegie Trust.

The majority of the (micro) nitrogen determinations were carried out by Mr. J. M. L. Cameron, of the Organic Chemistry Department of this University. The remainder of the analyses quoted were due to Dr. G. Weiler, of Oxford.

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THE RECIPROCAL SOLVENT INFLUENCE OF SOME OPTICALLY ACTIVE COMPOUNDS.

Introduction.

1. When an optically active substance (say dA) is dissolved in, or mixed with, an inactive liquid it is in general found that its specific rotation has undergone alteration: nor is the volume of the mixture exactly equal to the combined volumes of the unmixed constituents. Similarly it is to be expected that when dA is mixed with an active liquid (say dB) neither the rotations nor the volumes of the components will be exactly additive. The same considerations will apply to the mixture of dA with the antimere lB. In the case of the mixtures dA, dB and dA, lB the following questions naturally arise:-

(i) What proportion of the change in rotation on mixture is to be attributed to each component?

(ii) Does dA affect the rotation of dB and lB to a varying degree and, conversely, is dA differently affected by dB and lB?

(iii) Is the volume change the same in each case?

The object of my research has been firstly to obtain data for some cases where reciprocal solvent influence was considerable and secondly to find out what inferences, if any, could be drawn as to the difference or identity of the solvent influence of the d- and l- forms of one compound upon an independent optically active compound. The latter object involved answering, if possible, the questions tabulated above.

The experimental work carried out fell naturally into three parts. These were:-

(i) Rotational and density measurements of mixtures of l-nicotine and with ethyl d-tartrate, racemate and mesotartrate.

(ii) Rotational and density measurements of mixtures of l-nicotine with iso-butyl d-tartrate, l-tartrate, racemate and mesotartrate.

(iii) Accurate and delicate density measurements of mixtures of l-menthyl acetate with d- and l- iso-butyl tartrates.

2. The results of the research may be cursorily summarised as follows:-

(i) A considerable mutual solvent effect was shown, as far as optical rotation was concerned.

(ii) The proportion of the change in rotation which should be attributed to each component could only be derived on the assumption that there was no asymmetric solvent effect - e.g. that the effect of dA on dB and lB was identical, while dA was also affected identically by dB and lB.

(iii) There was no evidence that such an asymmetric solvent effect (as defined above) actually existed, but on the other hand no experiment could be devised which would prove its absence.

(iv) In the case of the density measurements of mixtures of l-menthyl acetate with d- and l- iso-butyl tartrates only an extremely small density difference was observed. I would be very reluctant to claim that such a small difference was outside the limits of experimental error.

Historical.

The work which had previously been carried out upon mixtures of optically active compounds can be divided into two parts: the consideration firstly of the optical rotations and secondly of various other physical properties.

3. Biot (Comptes R. 1836, 2, 542) made observations upon the artificially produced anomalous dispersion of a mixture of turpentine and oil of lemon, and also attempted (Annales de Chim. et de Phys. 1852, [iii] 36, 405-489) to prepare a liquid which would have the same rotatory power for all colours of light by dissolving d-camphor in l-turpentine. In the latter paper a formula was developed (see § 13) which gave the observed rotation of a mixture in terms of the specific rotation of its constituents (loc. cit. p. 467). The specific rotation of the turpentine was observed, while that assigned to homogeneous camphor was obtained by extrapolation from acetic acid solutions. (Annales, same volume, p. 306). Although the calculated and observed rotations were in good agreement, Biot was of the opinion that the calculated rotation of such mixtures should not, in general, be exactly equal to the observed rotations (Comptes R. 1852, 35, 619). von Wyss (Annalen der Phys. und Chem. 1888, 33, 568) showed that the anomalous dispersion of a natural turpentine could be imitated

by a mixture of the so-called d- and l- turpentines, which were, probably, d-limonene and l-pinene (Lowry, Optical Rotatory Power, 1935, 109). Using Biot's formula, he found differences between the calculated rotation of the mixtures and the observed values: these he attributed to variations in temperature during the series of observations.

4. Landolt (Optical Rotation of Organic Substances, translated by Long, 1902, p. 240-243) gave formulae for a mixture of two active substances, and for the system comprising two active bodies dissolved in an inactive solvent. The first of these (see § 13) is identical in content with that of Biot.

Landolt mentioned the work of Hammerschmidt (*Inaug. Dissert. Rostock 1889, apparently never published in any journal), who found no difference between calculation and observation in the case of right and left rotating turpentine, only a very slight difference in the case of cane sugar and grape sugar in water, and a somewhat greater difference in the case of d-camphor and l-santonin dissolved in chloroform.

5. It must be observed that the polarimetric observation of the inversion of cane sugar depends on the absence of mutual solvent effect between sucrose, fructose and glucose. This has been investigated by Hönig and Jesser (*Zeit. für

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* An asterisk attached to a reference implies, here and throughout, that I have not been able to consult the original.

Rubenzucker-Ind. 1888, 1037) and especially by Ost (Ber. 1891, 24, 1636). Hammerschmidt (loc. cit.) and Creydt k/ ·^ (*Zeit. fur Rubenzucker-Ind. 1887, 153) found that cane sugar and raffinose had no mutual solvent effect in water.

6. H. O. Jones (Proc. Cambridge Phil. Soc. 1906, 14, 27-29) examined the rotations of d- and l- camphor, and also d- and l- impure/ camphoroxime in d-pinene and dextro-rotatory amyl bromide. Jones mixed a solution containing an active solute in an active solvent with a similar solution containing the antimere of the first solute in the same concentration: he then subtracted the observed rotation of the mixture from those shown by the unmixed solutions. The results were taken as the rotatory power of the d- and l- isomers in the active solvent. As these were identical, Jones concluded that the rotatory power of d- and l- isomerides were identical in active solvents. While, as I will attempt to show in paragraphs 18 to 26 , this conclusion does not ~~necessarily~~ follow, it is most probably correct.

Jones's paper is a short one, and the treatment cursory: but it does not appear to have been published elsewhere in an extended form.

No further references to the optical rotation of mixtures of optically active compounds have been found.

7. van't Hoff was the first to state openly that the solubilities of a pair of antimeres might not be identical in an active solvent (The Arrangement of Atoms in Space, translated Eiloart, London 1898, p. 12; *Lagerung der Atome im Raume, Braunschweig 1894, p. 30). Meyerhoffer (Gleichgewichte der Stereomeren, p. 54) reported a correspondence between himself and van't Hoff in the year 1893: the latter then stated that Le Bel had already carried out research on the subject, while Pasteur had considered the question even earlier.

8. Tolloczko found that aqueous racemic acid was not selectively extracted by active amyl alcohol: nor was r-mandelic acid extracted selectively from a strong solution of fructose by means of ether (Zeit. Phys. Chem. 1896, 20, 412). Goldschmidt and Cooper found the solubility of d- and l- carvoxime in active limonene to be identical (Zeit. Phys. Chem. 1898, 26, 711). Cooper found the solubilities of NaH-d- and l- tartrates to be identical in aqueous d-glucose (* American Chemical Journal, 1900, 23, 255). Jones found identical solubilities for d- and l- camphor, d- and l- camphoroxime in d-pinene and dextrorotary amyl bromide (Proc. Cambridge Phil. Soc. 1906, 14, 27). Ranken and Taylor found the presence of cane sugar had the same effect upon the electrical conductivity, viscosity and density of aqueous solutions of (i) d-, dl- and l- potassium tartrates and (ii) d-, dl- and l- tartar emetics; although they considered

that the measurements for the dl- compounds indicated the existence of racemic ions or molecules. (Proc. of Roy. Soc. of Edinburgh, 1907, 27, 172)

8. Pasteur (Annales de Chim. et de Phys. 1853 (iii) 38, 461) was able to isolate a crystalline compound from ammonium hydrogen l-malate and ammonium hydrogen d-tartrate, but could not obtain a similar compound from the l-malate and l-tartrate.

McKenzie and his collaborators found that when l-malic acid was added to solutions of alkali dl-tartrates crystals of alkali hydrogen racemate with a small admixture of alkali hydrogen d-tartrate were deposited (1,2). When d-malic acid was used the l-tartrate was predominant in the crystals deposited (3). Although 15 other optically active acids were tested, malic acid alone caused optical activation (2).

When potassium hydrogen racemate was crystallised from aqueous l-malic acid, the d-tartrate was deposited in slight excess (1). This apparently indicated a difference in solubility between the d- and l- tartrates: it has however been found that no such difference existed, and that the activation observed was probably due to the formation and subsequent decomposition of molecular compounds of l- KH malate with d- and with l- KH tartrates (4).

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(1) McKenzie, J.C.S. 1915, 107, 440.
(2) McKenzie & Walker, J.C.S. 1922, 121, 349.
(3) McKenzie, Plenderleith & Walker, J.C.S. 1923, 123, 2875.
(4) McKenzie & Christie, Biochem. Zeit. 1935, 277, 122.

9. Ebert and Kortüm (Ber. 1931, 64, 342) considered that the optical activity of a substance A could only be observed when the rate of transformation of the two enantiomorphous forms $Ad \rightleftharpoons Al$ was small. If this rate of transformation was large, a liquid racemate Adl could only be recognised as such (i.e. as a mixture of two antimeres) when it was possible - perhaps through the influence of a third optically active substance Bd - to alter the ratio $\frac{Ad}{Al}$ from the value 1 to another value $\neq 1$. This alteration would show itself fundamentally through a rotational change, whereby the new optical activity would show peculiar magnitudes and anomalies (Cotton Effect) in that portion of the spectrum in which the longest wavelength absorbtion band of the molecule lay.

The fundamental idea - that a racemate might give rise to an "induced" rotation when dissolved in an active solvent - is of interest. Ebert and Kortüm considered only the possibility of the active solvent upsetting the equilibrium between the d- and l- forms of the racemate, but induced optical activity would also result if the active solvent had a different solvent effect upon the two antimeres.

Ebert and Kortüm found no difference in the solubility of d- and l- potassium hydrogen tartrates in water containing mannitol, or of d- and l- camphor-sulphonic acids in benzene solutions of d- or l- camphor. No differences in the change of surface tension of d- and l- camphor sulphonate solutions were observed on the addition of active pinene, camphor, menthol, menthone, menthene, dimethyl-camphoric ester, propyl tartrate or menthyl acetate.

The authors were of the opinion that any difference in solubility must be extremely small.

10. Schröer, however, claimed that he had demonstrated such a difference. (Ber. 1932, 65, 966).

"With d- and l- carvone as solvents, dl-mandelic acid as the solute and water as the immiscible solvent, carvone solutions of the racemic mandelic acid extracted successively by repeated washings with H_2O yielded specimens of mandelic acid with a small but certain activity which decreased in successive fractions, passed through zero and underwent a reversal of sign. According to theory this reversal should occur, as it does, when the inactive solvent has extracted half of the solute from the active solvent. A similar experiment with limonene as the active solvent gave negative results." (Chemical Abstracts, 26, 4228).

Schröer was of the opinion that the difference in solubility had been well established. "Sicher, wenn auch recht klein". The method used to demonstrate this small effect may best be judged by an example. 200g. of dl-mandelic acid in 800ccs. of d-carvone were shaken as a first extraction with 1000ccs. of water. Of the mandelic acid 38g. passed into the water. The litre of solution thus obtained was boiled down to 12c.cs. and the mandelic acid which separated found by test to be inactive. The mother liquor gave a rotation of -0·66° when examined in a 189mm. tube. Using l-carvone under similar circumstances the rotation was positive.

11. Timmermans has investigated the melting points of mixtures of independent optically active compounds. Starting from the work of Roozeboom and others, on the melting points of mixtures of, say, dB and lB, Timmermans extended the work to the freezing-point curves of mixtures of dA with (i) dB and (ii) lB. His work was published in the Bull. soc. chim. Belgique, but two summaries (Rec. trav. chim. des Pays-bas: 1929, 48, 890 and 1932, 51, 585) have been consulted. In the majority of cases it was found that the freezing-point diagrams of dA with dB and with lB were identical, a eutectic or a series of mixed crystals being given in both cases. The compound dA thus behaved as if inactive towards dB and lB: it had no selective action upon the crystallization of dB or lB. Timmermans believed that the prevalence of this behaviour made comprehensible the repeated failure to observe any difference in the solubility of two antimeres in an optically active solvent. In some cases (notably in the case of tartaric and malic acid derivatives) the freezing-point diagram for dA mixed with dB differed entirely from that for dA

mixed with lB: in the one case a eutectic, and in the other the formation of an equimolecular (pseudo-racemic) compound, was indicated. e.g. l-methyl malate formed an equimolecular compound with d-methyl tartrate, and gave only a eutectic mixture with l-methyl tartrate. Timmermans suggested that in such cases the compounds giving a eutectic mixture should be regarded as having the same configuration, while those which combine have opposite configurations.

There is no indication that Timmermans ever examined the optical rotation of such mixtures.

Previous work may be roughly summed up as follows:-

I. Very few rotational data have been recorded, and none in cases where a considerable mutual solvent effect was to be expected.

II. In spite of repeated failures to demonstrate any difference between the systems ~~of~~ dA.dB and dAlB, both Timmermans and Schröer claim to have done so.

Theoretical.

12. It will be understood from the historical summary which has just been presented that any theoretical consideration of the rotation shown by mixtures of optically active compounds cannot be obtained, ready made, from the literature. To guide me in my work I have endeavoured to consider the question to some extent. I am fully conscious that my arguments may suffer from my lack of experience; I set them out nevertheless, since otherwise my conclusions would rest largely upon dogmatic statements of opinion.

The Recognition of a Mutual Solvent Effect.

13. Landolt (Trans. Long. 1902, p. 240) gave a formula for mixtures of two active liquids. "If the mixture consists of

p_1 parts by weight of one body of specific rotation $[\alpha]_1$

p_2 parts by weight of the other body of specific rotation $[\alpha]_2$

then the specific rotation of the mixture, $[\alpha]_m$, will be given by

$$[\alpha]_m = \frac{p_1[\alpha]_1 + p_2[\alpha]_2}{p_1 + p_2} \text{"} \quad . \quad . \quad . \quad . \quad . \quad (i)$$

It is, however, difficult to see what meaning - other than a purely arithmetical one - is to be attributed to the term $[\alpha]_m$. Biot (Annales de Chim. et de Phys, 1852, [iii] 36, 467) did not make direct use of the term $[\alpha]_m$. He gave

$$\alpha_m = d_m l \left(\varepsilon_1[\alpha]_1 + \varepsilon_2[\alpha]_2\right) \quad . \quad . \quad . \quad (ii)$$

where α_m was the observed rotation of the mixture (of density d_m) in a tube of length 1 dm; ε_1, and ε_2 were the proportions ($\varepsilon_1 + \varepsilon_2 = 1$) by weight of the substances present of specific rotations $[\alpha]_1$ and $[\alpha]_2$.

This formula may be used in the form

$$\alpha_m \text{ (100mm.)} = d_m \frac{p_1[\alpha]_1 + p_2[\alpha]_2}{100} \quad . \quad . \quad . \quad . \quad \text{(iii)}$$

or $$\alpha_m \text{ (100mm.)} = \frac{v_1\alpha_1 + v_2\alpha_2}{100} \quad . \quad . \quad . \quad . \quad \text{(iv)}$$

where d_m = density of mixture.

p_1, p_2 = weight percentages of components.

v_1, v_2 = volume percentages of components.

$[\alpha]_1$, $[\alpha]_2$ = specific rotations of unmixed components.

α_1, α_2, = observed rotations (100mm) of unmixed components.

These four formulae are precisely identical in content, and represent accurately the rotation to be expected when two liquids mix without exerting any physical influence upon each other.

In general, however, a contraction in volume is observed upon mixture, and the Biot-Landolt formulae hold only when no volume change takes place. It seems to me theoretically sounder to follow the ideas of Guye, and make allowance for the effect of volume changes by the use of $\sqrt[3]{d}$.

It must be observed that while formulae (i) to (iii) are identical under all circumstances, (iv) is only identical with (i), (ii) & (iii) if no volume change takes place upon mixture.

14. I have actually compared the observed rotation of a 100mm. tube of the mixture, α_m , with the rotation suffered by a ray of light passing successively through the two components of the mixture in separate tubes of such lengths that a light-ray traverses the same number of molecules of each sort as before.

15. If no volume change occurs, this conception is precisely expressed by Biot's formula, and to carry out the comparison I have calculated the rotation to be expected by means of formula (iii) or (iv), using, in the case of (iii), the calculated density, d_c,* of the mixture in place of the

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* Calculated density $= \dfrac{w_1 + w_2}{\dfrac{w_1}{d_1} + \dfrac{w_2}{d_2}} = \dfrac{d_1 d_2 (w_1 + w_2)}{w_1 d_2 + w_2 d_1}$

where w_1, w_2, are the weights and d_1, d_2 the densities of the unmixed components.

density actually found, d_f. I thus obtained the rotation to be expected if no change in volume took place.

Let us suppose that a contraction has actually occured. Then a light ray passing through a 100mm. tube of the mixture will traverse $\frac{\sqrt[3]{d_f}}{\sqrt[3]{d_c}} = \sqrt[3]{\frac{d_f}{d_c}}$ times as many molecules as formerly, and to ensure comparison in the terms of § 14 the rotation just calculated on the assumption that a volume change did not exist must be multiplied by the factor $\sqrt[3]{\frac{d_f}{d_c}}$. In short, I have made use of the formula:-

$$\alpha, \text{ mixture } (100\text{mm.}) = \sqrt[3]{\frac{d_f}{d_c}} \; \frac{v_1\alpha_1 + v_2\alpha_2}{100}$$

$$\text{or} \qquad = d_c\sqrt[3]{\frac{d_f}{d_c}} \; \frac{p_1[\alpha]_1 + p_2[\alpha]_2}{100}$$

The Possibility of two Antimeres having a Different Solvent Effect upon an Independent Active Solute.

16. It would be of very considerable interest to prove or

disprove this possibility. As will have been seen from the historical introduction, in only one case have two antimeres been found to have different solubilities in an optically active solvent (E. Schröer, Ber. 1932, 65, 966), and the effect, when found, was very small. No other example of similar asymmetric action has been found. It is therefore a priori likely that any asymmetric solvent effect is very small.

I have been able to think of three main methods whereby an asymmetric solvent effect might be recognised, but I have been unable to devise any experiment which would definitely show the solvent effects to be identical within the limits of experimental error.

Definitions. Taking the active substances A and B, the various isomers are referred to as dA, lA, dlA, etc. The solvent effect of, for example, dA upon lB is indicated by $S\frac{dA}{lB}$, and the expression $S\frac{dA}{lB} = S\frac{lA}{lB}$ means that dA and lA have precisely the same influence upon the rotation of lB. In this analysis the independent optically active substance is taken as lB, and A provides the antimeres. This renders possible an easy application of the theory to practice (l-nicotine or l-menthyl acetate as lB, tartaric esters as dA, dlA, lA.)

17. The three methods are:-

(a) By an inspection of the shape of the curve of observed rotation obtained when dA is replaced gradually by lA, the proportion of lB remaining unaltered.

(b) Through the possibility that, when lB is added to the racemate dlA, the latter will show an induced activity great enough to be recognised either by apparently altering the rational dispersion coefficient of lB, or, in some special cases, by an anomaly of the Cotton Effect type.

(c) In those special cases where A shows anomalous dispersion, the cutting-points of the T-R curves (for various colours of light) of dA can be compared with the corresponding cutting points obtained for a solution of dA in lB. The latter values would be obtained by making the assumption that:

Observed Rotation of dA in lB
= Observed Rotation of dA-lB mixture, less
the observed rotation of lB in dlA.

If the cutting points obtained in these two ways did not correspond, the assumption was unjustified, and an asymmetric solvent effect indicated if the difference is greater than the normal variation of cutting-point values in different solvents.

18. Detailed Consideration of Method (a) above.

We are here dealing with mixtures in which the proportions of A and B remain constant. The only variable factor is the configuration of A; while B remains lB throughout, A is gradually altered from dA → dlA → lA. In short, the observed rotation of a mixture containing definite proportions of A and B is plotted against the percentage of lA in the A used, from dA → dlA → lA.

Précis of Argument.

(i) The rotation due to lB is first considered, and it is shown that this may, or may not, change in a linear manner as dA → lA, when S $\frac{dA}{lB} \neq$ S $\frac{lA}{lB}$.

(ii) The rotation due to A must change linearly, unless S $\frac{dA}{dA} \neq$ S $\frac{lA}{dA}$: and S $\frac{dA}{dA}$ has been found, experimentally, to be equal to S $\frac{lA}{dA}$.

Thus if a non-linear change is shown, S $\frac{dA}{lB} \neq$ S $\frac{lA}{lB}$.

Consideration of the Solvent Influences at Work.

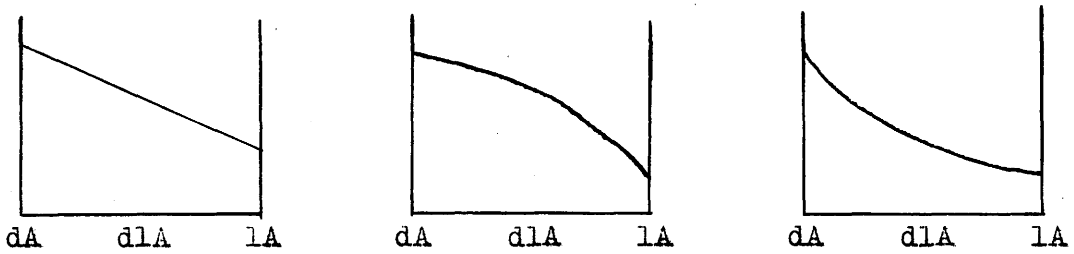
19. On lB. Any given lB molecule will always be surrounded by the same proportions of A and B molecules. But the A molecules will change steadily from all dA to all lA.

Therefore, if S $\frac{dA}{lB}$ = S $\frac{lA}{lB}$, the rotation due to lB will remain unchanged, unless the argument is invalidated by the existence of racemic molecules of dlA.

But if S $\frac{dA}{lB} \neq$ S $\frac{lA}{lB}$ the rotation due to lB must change.

The position is exactly analogous to that of an optically active compound (here lB) in a mixed solvent (here dA and lA). The most probable curves would seem to be:-

FIGURE I.



(i) (ii) (iii)

20. **Summary:** The rotation due to lB must, if $S\frac{dA}{lB} = S\frac{lA}{lB}$, remain unchanged throughout.

If $S\frac{dA}{lB} \neq S\frac{lA}{lB}$, change as dA → lA. The change may be either rectilinear or curvilinear.

It will be observed at once that if the curvilinear changes (ii) or (iii) take place, then the rotation shown by lB when mixed with dlA will **not** be the arithmetical mean of the rotations due to lB in dA and lA, taken separately. If the straight line change (i) holds, then the asymmetric solvent effect $S\frac{dA}{lB} \neq S\frac{lA}{lB}$, though present, will not thus make its presence evident.

Consideration of the Rotation due to A.

21. If there are no asymmetric solvent effects ($e.g.$ $S\frac{lB}{dA} = S\frac{lB}{lA}$ and $S\frac{dA}{dA} = S\frac{lA}{dA}$) then the rotation will change linearly as dA → lA.

It can be assumed that $S\frac{dA}{dA} = S\frac{lA}{dA}$. This assumption - that the rotation due to a dA molecule is the same, whether it is surrounded by dA or lA molecules - is one which has not, to my knowledge, been openly questioned. It is, however, not self-evident, and can be investigated experimentally by observing the rotation of dA in dlA. Pope and Peachey (J.C.S. 1899, *75*, 1117) were of the opinion that if the specific rotation of an active compound dissolved in its own racemate was not the same as that exhibited in the ~~homologous~~ homogeneous state, then the existence of racemic molecules was indicated. [Meyerhoffer (Gleichgewichte der Stereomeren, p. 17) did not agree with this conclusion.] In any case, Pope and Peachey found the specific rotation of l-tetrahydroquinaldine and l-pinene to be unaltered on solution in the corresponding dl-compounds.

I have examined experimentally the mixtures I and II, which were closely analagous to the nicotine-*iso*-butyl tartrate mixtures. The specific rotation of the *iso*-butyl d-tartrate was identical

	I.	II.	
$\underline{\mathrm{Iso}}\mathrm{Bu}_2\mathrm{d}\bar{\mathrm{T}}$, p =	49·968	23·301)	) 49·933
$\mathrm{IsoBu}_2\mathrm{dl}\bar{\mathrm{T}}$, p =	——	26·632)	
Pyridine, p =	50·032	50·067	

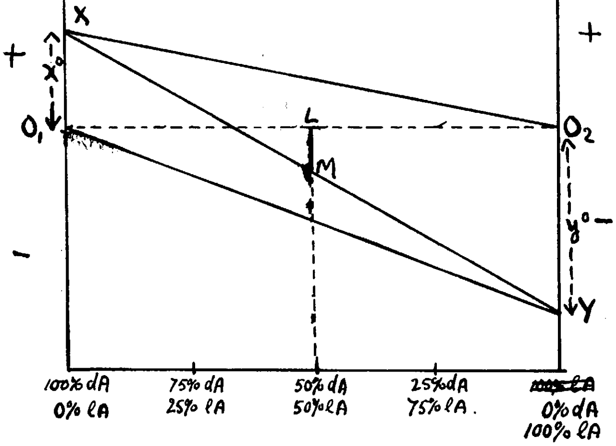
in I and II. Details in § 53, L; page 77.

The assumption that $S\frac{dA}{dA} = S\frac{lA}{dA}$ has thus experimental justification, and it is only necessary to consider the rotation due to A as dA → lA, when $S\frac{lB}{dA} \neq S\frac{lB}{lA}$ and $S\frac{dA}{dA} = S\frac{lA}{dA}$.

22. It must first be observed that although the proportion of dA molecules changes from 100°/₀ → 0°/₀, there should be no change in rotation due to change in concentration. For whatever the proportion of dA in the mixture, any individual dA molecule has the same number of lB molecules in its environment. The only change is that due to a replacement of dA molecules by lA molecules, and this, since $S\frac{dA}{dA}$ is assumed equal to $S\frac{lA}{dA}$, cannot affect the rotation. Exactly the same applies to the lA molecules.

Therefore, as we pass from 100°/₀ dA → 0°/₀ dA, the rotation due to dA changes from a value x° to 0°. The decrease must be linear, since there is no change due to concentration change: the fall in rotation is due solely to the decrease in the number of dA molecules present, and the rotation must be directly proportional to that number.

FIGURE 2.



Similarly, the rotation due to lA changes linearly from 0° to y°. The rotation due to A, as a whole, is found by the addition of the values of corresponding points on the lines XO_2 and YO_1, i.e. by XY. (Fig. 2)

23. It must be noted (i) That since XY is obtained by the combination of two straight lines, it must itself be a straight line. Thus although $S\frac{lB}{dA} \neq S\frac{lB}{lA}$, there is no deviation from lineality as $dA \rightarrow dlA \rightarrow lA$.

(ii) Since $S\frac{lB}{dA} \neq S\frac{lB}{lA}$, therefore $O_1X \neq O_2Y$. Thus XY does not pass through 0° at the 50-50 mixture (dlA). The racemate, dlA, has an induced rotation (LM) when dissolved in lB.

24. If $S\frac{dA}{dA}$ were not equal to $S\frac{lA}{dA}$, then a deviation might well arise. The question may naturally be asked why $S\frac{dA}{dA} \neq S\frac{lA}{dA}$ should cause a deviation from lineality, while $S\frac{lB}{dA} \neq S\frac{lB}{lA}$ does not. This is the case since, while a dA molecule is always surrounded by a constant number of lB molecules, the number of lA molecules in its environment varies from 0°/o to 100°/o of the surrounding A molecules. Thus the influence of lB on an individual dA molecule is always the same, whether there be many or few dA molecules in the mixture as a whole. But the influence of lA on a dA molecule is great when the mixture contains but few dA molecules and small when dA preponderates.

If no independent optically active substance were present, I am of the opinion that the deviation would take the shape of a symmetrical curve, inflected at the middle (racemate) point. When lB is added the position is complicated, and I am gradually forced from reasoning into guesswork. It is therefore fortunate that, experimentally, $S\frac{dA}{dA} = S\frac{lA}{dA}$.

25. Summary. The rotation due to A must change linearly if:-

(i) $S\frac{lB}{dA} = S\frac{lB}{lA}$ and $S\frac{dA}{dA} = S\frac{lA}{dA}$

or (ii) $S\frac{lB}{dA} \neq S\frac{lB}{lA}$, but $S\frac{dA}{dA} = S\frac{lA}{dA}$.

If $S\frac{dA}{dA} \neq S\frac{lA}{dA}$, linear change is improbable, but this has been shown by experiment to be unlikely.

26. These arguments can, I think, be applied practically. The possible asymmetric solvent effects are

(i) $S\frac{dA}{dA} \neq S\frac{lA}{dA}$ and $S\frac{lA}{lA} \neq S\frac{dA}{lA}$.

These are found to be absent by direct experiment, when lB (as Nicotine) is replaced by Pyridine. I see no reason whatever why they should suddenly come into existence when Nicotine is present. (§ 21).

(ii) $S\frac{lB}{dA} \neq S\frac{lB}{lA}$. In this case, though the racemate dlA would have a rotation induced by the presence of lB, the rotation due to A would change linearly as dA → lA. (§§22,23).

(iii) $S\frac{dA}{lB} \neq S\frac{lA}{lB}$. In this case a non-linear rotational change might occur, but need not necessarily do so. (§§ 19, 20).

Thus I come to the conclusion that if the observed rotation of the mixture lB.dlA is not the arithmetical mean of the rotations of the mixtures lB.dA and lB.lA, then $S\,\frac{dA}{lB} \neq S\,\frac{lA}{lB}$. If, on the other hand, the observed rotation is equal to the arithmetical mean it is still possible that $S\,\frac{dA}{lB} \neq S\,\frac{lA}{lB}$. This observation affords no information as to the identity or difference of $S\,\frac{lB}{dA}$ and $S\,\frac{lB}{lA}$*.

27. Detailed Examination of the Second Method.

I have pointed out (§§ 22,23) that if $S\,\frac{lB}{dA} \neq S\frac{lB}{lA}$ the racemate dlA will have an activity when mixed with lB. I originally thought that this might show itself through an apparent alteration of the rational dispersion coefficient of lB, but analysis shows this to be unlikely.

Précis of Argument.

(i) By a consideration of the characteristic diagram of dA (or lA) (Patterson J.C.S. 1916, 109, 1176-1203) it is shown that:-

$$\frac{\text{Observed Induced Rotation for } Hg\ y}{\text{Observed Induced Rotation for } Hg\ g} = \text{Rational Dispersion coefficient } \frac{[\alpha]_y}{[\alpha]_g} \text{ for dA.}$$

(ii) This being so, if dA and lB have the same rational

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* Contrast the opinion of Jones, §6.

dispersion co-efficient, the value determined for the rational dispersion co-efficient of 1B in d1A will be unaltered, whether d1A contributes an induced rotation or not.

(iii) The rational dispersion co-efficients of the substances examined were:-

(a) Nicotine 0·867 (Homogeneous, and in various solvents)
(b) Ethyl Tartrate 0·87 (Homogeneous)
(c) *Iso*-butyl Tartrate 0·85 - 0·86 (Homogeneous*)

These values are roughly the same, hence the rational dispersion co-efficient of (a) will be little affected by any induced rotation in the racemates of (b) and (c).

It may be mentioned that by "Observed Induced Rotation" I mean the actual rotation which would be observed if we were able to eliminate the rotation due to 1B. The rational dispersion co-efficient $\frac{[\alpha]\ 5790}{[\alpha]\ 5461}$ has been considered: for other colours the argument would be similar.

28. Consider the characteristic diagram of dA for λ =5461 and λ = 5790, as given below (fig. 3). The rotations for H_g gr (λ = 5461) are plotted as abscissae. The differences of the specific rotations of H_g y (λ = 5790) from those observed for Hg gr under identical conditions are plotted as ordinates, giving the line YZD_y. When, for example, the specific rotation for H_g gr is OD_g, that for H_g y is $OD_g - D_gD_y$.

The specific rotation for 1A under identical conditions will be numerically the same as for dA, but the sign of the

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* And 0.86-0.87 in quinoline, calculated from the same rational zero.

rotation will be reversed. If, then, we plot $-[\alpha]$ for lA we will obtain exactly the same diagram as by plotting $+[\alpha]$ for dA.

29. If the racemate dlA shows an induced rotation in the presence of lB, its two components dA and lA must be maintained in different states through the action of lB. If $[\alpha d]$ and $[\alpha l]$ are the specific rotations of these components, $+[\alpha d]$ and $-[\alpha l]$, must both lie on the characteristic diagram of dA. Also, since both components are present in the same tube in identical concentration, the observed rotations will be $K[\alpha d]$, and $K[\alpha l]$. [Since $[\alpha] = \frac{100\alpha}{lpd}$ and $K[\alpha] = \alpha$ by definition above, $K = \frac{lpd}{100}$ where p is the percentage of dA or lA; hence $K = \frac{Pd}{200}$ for a 100m.m. tube where P is the percentage by weight of the racemate.] The observed induced rotation will be the sum of these, that is $K[\alpha d] + K[\alpha l]$, or $K\left([\alpha d] - (-[\alpha l])\right)$. Thus, if the specific rotations of dA and lA (as $+[\alpha d]$, and $-[\alpha l]$) are plotted on the characteristic diagram of dA, the observed induced rotation will be K times the numerical value of the point for dA minus the numerical value of the point for lA.

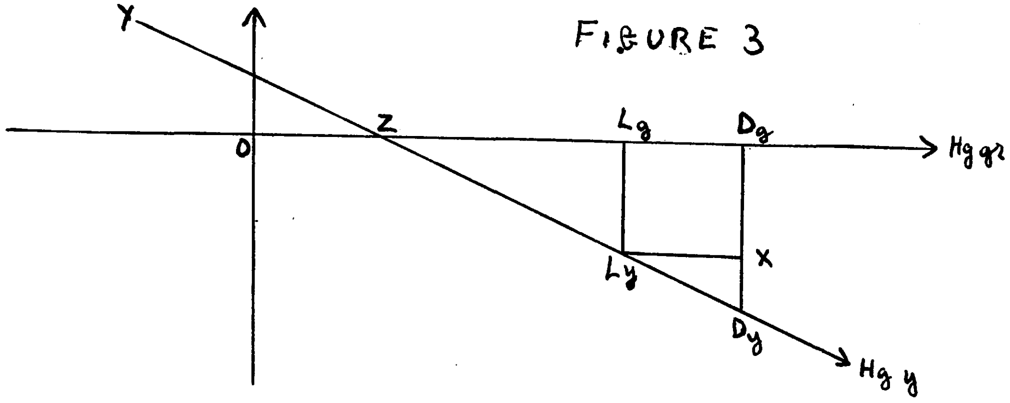


FIGURE 3

30. Geometrically, if L_g and L_y represent the specific rotations of 1A for green and yellow light, while D_g and D_y represent those of dA, then the observed induced rotation is $K\ (OD_g - OL_g)$ for green and $K\ \ (OD_g - D_gD_y) - (OL_g - L_gL_y)$ for yellow.

Hence the ratio

$$\frac{\alpha y}{\alpha g} = \frac{K\ [(OD_g - D_gD_y) - (OL_g - L_gL_y)]}{K\ [OD_g - OL_g]}$$

$$= \frac{OD_g - OL_g - D_gD_y + L_gL_y}{L_gD_g}$$

$$= \frac{L_gD_g - XD_y}{L_gD_g} = \frac{L_yX - XD_y}{L_yX} \quad (L_yX \text{ is drawn } \parallel^{el} \text{ to } OD_g)$$

Now the rational dispersion co-efficient for A is $\dfrac{ZD_g - D_gD_y}{ZD_g}$.
And the triangles ZD_gD_y and L_yXD_y are equiangular and similar.

Therefore $\dfrac{L_yX - XD_y}{L_yX} = \dfrac{ZD_g - D_gD_y}{ZD_g}$

or $\dfrac{\text{Observed Induced Rotation for } Hg_{\,y}}{\text{Observed Induced Rotation for } Hg_{\,gr}} = $ Rational Dispersion Coefficient $\dfrac{[\alpha]_y}{[\alpha]_g}$ for dA.

31. Hence, unless the rational dispersion co-efficients of dA and 1B differ widely, there will be no appreciable effect on the observed rational dispersion co-efficient of 1B when mixed with

dlA, even if the induced optical activity of dlA is large.

Proof.

If $[\beta]_y$, $[\beta]_g$ are the specific rotations of lB, reckoned from the rational zero, then $\frac{[\beta]_y}{[\beta]_g}$ is the rational dispersion co-efficient. dlA now superposes observed induced rotations of α_y, α_g. In calculating anew the specific rotation of lB, α_y and α_g will be multiplied by the constant k ($k = \frac{100}{lpd}$, where p = percentage of lB). The specific rotations of lB reckoned from the rational zero thus become $[\beta]_y + k\alpha_y$ and $[\beta]_g + k\alpha_g$, and the rational dispersion co-efficient

$$\frac{[\beta]_y + k\alpha_y}{[\beta]_g + k\alpha_g} \quad . \; . \; . \; . \; . \; . \; . \; (i)$$

It has just been shown that $\frac{\alpha_y}{\alpha_g}$ = Rational dispersion co-efficient of dA. If this is equal to the rational dispersion coefficient of lB, then

$$\frac{\alpha_y}{\alpha_g} = \frac{[\beta]_y}{[\beta]_g} \quad . \; . \; . \; . \; . \; . \; . \; (ii)$$

From (i) and (ii) it can be shown by simple algebra that the new rational dispersion coefficient (i) is precisely equal to the old value, $\frac{[\beta]_y}{[\beta]_g}$.

32. It is, of course, always possible that dA and lA might be maintained in such different states that they did not lie upon

the same characteristic diagram. This would invalidate the foregoing argument. Since, also, my argument might itself be faulty, I evaluated a number of rational dispersion coefficients for nicotine in ethyl racemate and *iso*-butyl racemate. These show a close agreement with the previously determined values of Patterson and Fulton (J.C.S., 1925, **127**, 2441).

33. Another possibility, of limited application only, has occured to me in connection with a possible induced activity of dlA in presence of lB. Ebert and Kortüm were of the opinion that if lB altered the ratio $\frac{dA}{lA}$ from the value 1, anomalies of the Cotton effect type would be shown. The effect might possibly be shown through an asymmetric solvent effect of lB, apart altogether from any alteration in the ratio $\frac{dA}{lB}$. If a coloured racemate is dissolved in an inactive solvent the unequal absorption of right and left circularly polarised light and the consequent elliptical polarisation of one isomer is compensated by the equal and opposite effect of its antimere. But when the inactive solvent is replaced by a colourless active one, the two components dA and lA may be maintained in different states by its presence, and an induced circular dichroism and ellipticity may result. If a coloured racemate, dissolved in a colourless optically active solvent, were to show elipticity, then it would seem to me to indicate definitely either (i) An asymmetric solvent effect exerted by

1B or (ii) An alteration of the ratio $\frac{dA}{lA}$ from the value 1; and if dA were a stable substance, not easily racemised, the second possibility could be ruled out.

The third method (§ 17,c) does not, as far as I can see, lend itself to analytical discussion, and I cannot usefully enlarge upon the statement given there.

34. There remains to be considered the question of the density measurements. The question at issue is a simple one, in theory. Is the density of a mixture of dA and lB precisely the same as that of a mixture of lA and lB of the same composition? In the case of the menthyl acetate - iso-butyl tartrate mixtures the densities have been plotted against the composition of the mixtures and, in addition, the Molecular Solution Volume of the iso-butyl compounds have been evaluated. The experimental methods employed to give an accurate comparison within the limits of experimental error will be explained in due course.

35. Summary of Theoretical Work.

(A). The recognition of a mutual solvent effect has been considered. It has been proposed that the observed rotation of a mixture should be compared with the rotation suffered by a ray of light traversing the same number of molecules of each sort in separate tubes as were formerly traversed in the mixture. The formula of Biot (which could be written in various forms) expressed this conception perfectly if no volume change took place upon mixture. It was proposed to make allowance for volume changes by multiplying the calculated rotation by $\sqrt[3]{\frac{d\ \text{found}}{d\ \text{calc.}}}$

(B). The possibility of two antimeres having a different effect upon an independent optically active solute (and vice-versa) was next examined. By a consideration of the various solvent effects involved it was shown that this might become apparent through the observed rotation of the mixture lB - dlA not being equal to the mean of the mixtures lB - dA and lB - lA: and in general through the rotation changing in a non-linear fashion when dA was replaced by lA, while the ratio $\frac{(dA + lA)}{lB}$ was kept constant. (§ 18 to § 26). These conceptions seemed also to show that the racemate dlA would in such cases have an induced rotation, as its constituents would no longer have numerically equal rotations (§ 22-23). Use of the characteristic diagram led me to the opinion that this induced rotation would have no appreciable effect upon the rational dispersion co-efficient of lB. (§ 27-31). Anomalies of the Cotton effect type might, however, be produced. (§ 33).

If the absence of this kind of asymmetric solvent effect was assumed, the rotation of dA (or lA) in lB could be calculated. If the T-R curves so found were consistent with the known behaviour of dA in inactive solvents (eg. with regard to cutting points of curves in cases of anomalous dispersion), the absence of asymmetric solvent effects could be inferred.

(C). If racemic molecules of dlA were present to an appreciable extent, the arguments set out above would possibly be invalid. I have assumed that the liquid tartrate racemates could be regarded simply as mixtures of the d- and l- forms, an assumption which is supported by the majority of the literature on the subject. The special case of <u>iso</u>-butyl dl-tartrate is considered later (§ 50), and it is found that a density difference formerly attributed to the existence of racemic molecules is in fact non-existent.

(D). Density measurements, it was held, could be arranged to give a direct comparison between the mixtures dA - lB and lA - lB, and differences greater than experimental error would show that some asymmetric solvent effect was present.

General Outline of Experimental Work: Findings.

36. The following 11 mixtures were made up, and the rotation examined for 6 colours of light at 5 temperatures between 0° and 100°: densities were also observed.

			l-Nicotine p =	§ 53,
		92·12	7·88	A
Ethyl d-tartrate	p =	66·67	33·33	B
		39·81	60·19	C
		92·12	7·88	D
Ethyl dl-tartrate	p =	66·67	33·33	E
		39·80	60·20	F
Ethyl mesotartrate	p =	39·80	60·20	G
<u>Iso</u>-butyl d-tartrate	p =	39·80	60·20	H
<u>Iso</u>-butyl l-tartrate	p =	39·80	60·20	I
<u>Iso</u>-butyl dl-tartrate	p =	39·80	60·20	J
<u>Iso</u>-butyl mesotartrate	p =	39·80	60·20	K

(The full results are given on pages 66 to 76.)

With the sole exception of the ethyl tartrate, the purity of the compounds used was thoroughly satisfactory. This matter will be referred to when the experimental work is considered in detail: it need only be stated here that all comparisons were made with T-R curves experimentally determined for the ethyl tartrate used, and hence I do not think that the impurity affects in any way the conclusions reached.

37. Attention may first be drawn to the mutual solvent effect shown in nicotine - ethyl *d*-tartrate mixtures, for green light, λ = 5461. Full results for $\lambda =_{s}$ 5461 and 4359 are tabulated on pages 78&79.

Nature of Mixture						
Nicotine.	p=7·88°/o		p=33·33°/o		p=60·19°/o	
Temperature	0°	100°	0°	100°	0°	100°
Calculated rotation α, 100mm.	-12·82°	-2·47°	-73·1°	-62·2°	-131·1°	-119·8°
Observed rotation α, 100mm.	- 5·44°	+0·85°	-52·3°	-53·6°	-112·5°	-111·5°
Observed exceeds calculated by:-	+ 7·38°	+3·32°	+20·8°	+ 8·6°	+ 18·6°	+8·3°

On mixture heat was evolved and a slight contraction took place. Allowance was made for this contraction when the calculated rotation was evaluated (§ 15): the change introduced was trivial, being only 0·3 - 0·4°/o of the calculated rotation.

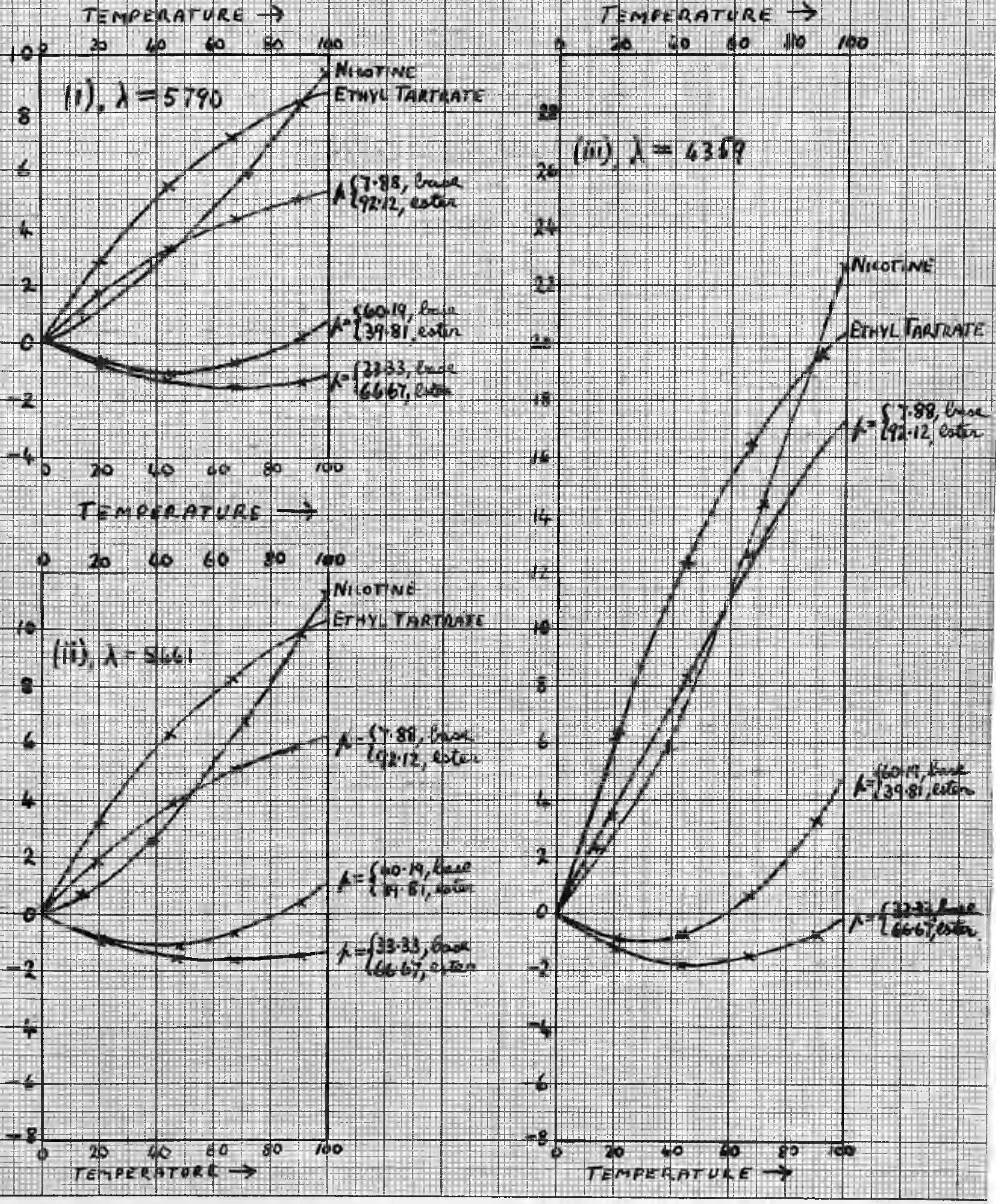
When the difference between observation and calculation was plotted against the composition of the mixture in question, it was seen that the mutual solvent effect was numerically greatest when the two constituents were present in approximately equimolecular proportions (nicotine, p = 44·03).

38. While both ethyl tartrate and nicotine have rising Temperature - Observed Rotation curves, those of the 67-33 ~~33-67~~ and 40-60 ~~60-40~~ mixtures showed a definite minimum which apparently moved towards lower temperatures as the wavelength of the light diminished or the proportion of nicotine was increased. To exhibit in a convenient manner the shape of these curves I have plotted the change in observed rotation shown by nicotine, ethyl tartrate and the three mixtures on warming from 0° to 100° - i.e. α^t(100mm.) - α^0(100mm.) has been plotted from 0° → 100°.

If mutual solvent influence were entirely absent, the curves plotted for the mixtures would lie between those of the ester and the base. As fig. 4 shows, this was far from being the case.

FIGURE 4.

$\alpha^{t}(100\,mm) - \alpha^{0}(100\,mm)$ in degrees.



CHANGE IN OBSERVED ROTATION
ON WARMING, 0° → 100°
NICOTINE — ETHYL d-TARTRATE MIXTURES.

39. Full details are given below of the mutual solvent effect at 73° in the case of the iso-butyl tartrate - nicotine mixtures.

Ester, p = 39·80; Base, p = 60·20.

Nature of Mixture.	l-nicotine d-*iso*-butyl tartrate			l-nicotine l-iso-butyl tartrate		
Density, calculated	0·9914			0·9914		
" found	1·0001			1·0006		
$\sqrt[3]{\frac{d_f}{d_c}}$	1·0029			1·0031		
Colour of light,	5790	5461	4357	5790	5461	4359
Calculated rotation if no volume change took place. α, 100mm.						
Contributed by ester	+7·1	+9·0	+11·7	-7·1	-9·0	-11·7
" " base	-107·1	-123·7	-225·1	-107·1	-123·7	-225·1
Total, A.	-100·0	-114·7	-213·4	-114·2	-132·7	-236·8
A × $\sqrt[3]{\frac{d_f}{d_c}}$	-100·3	-115·0	-214·0	-114·6	-133·1	-237·5
Observed rotation α, 100mm.	- 92·4	-107·0	-198·8	-118·6	-136·4	-242·9
Observed exceeds calculated by	+ 7·9	+8·0	+15·2	- 4·0	- 3·3	- 5·4

The mutual solvent effect was positive in the case of the dAlB mixture, and negative for the lAlB mixture. Hence it was apparent that a mixture could be prepared which would show little or no sign of mutual solvent influence (approximately nicotine, p = 60·2; d- ester, p = 11·6; l- ester p = 28·2 - for green light at 73°).

I do not consider this to be of physical significance. It represents merely the arithmetical compensation of one solvent effect by the other: the compensation very possibly does not hold over a range of colours and almost certainly does not hold over a range of temperatures.

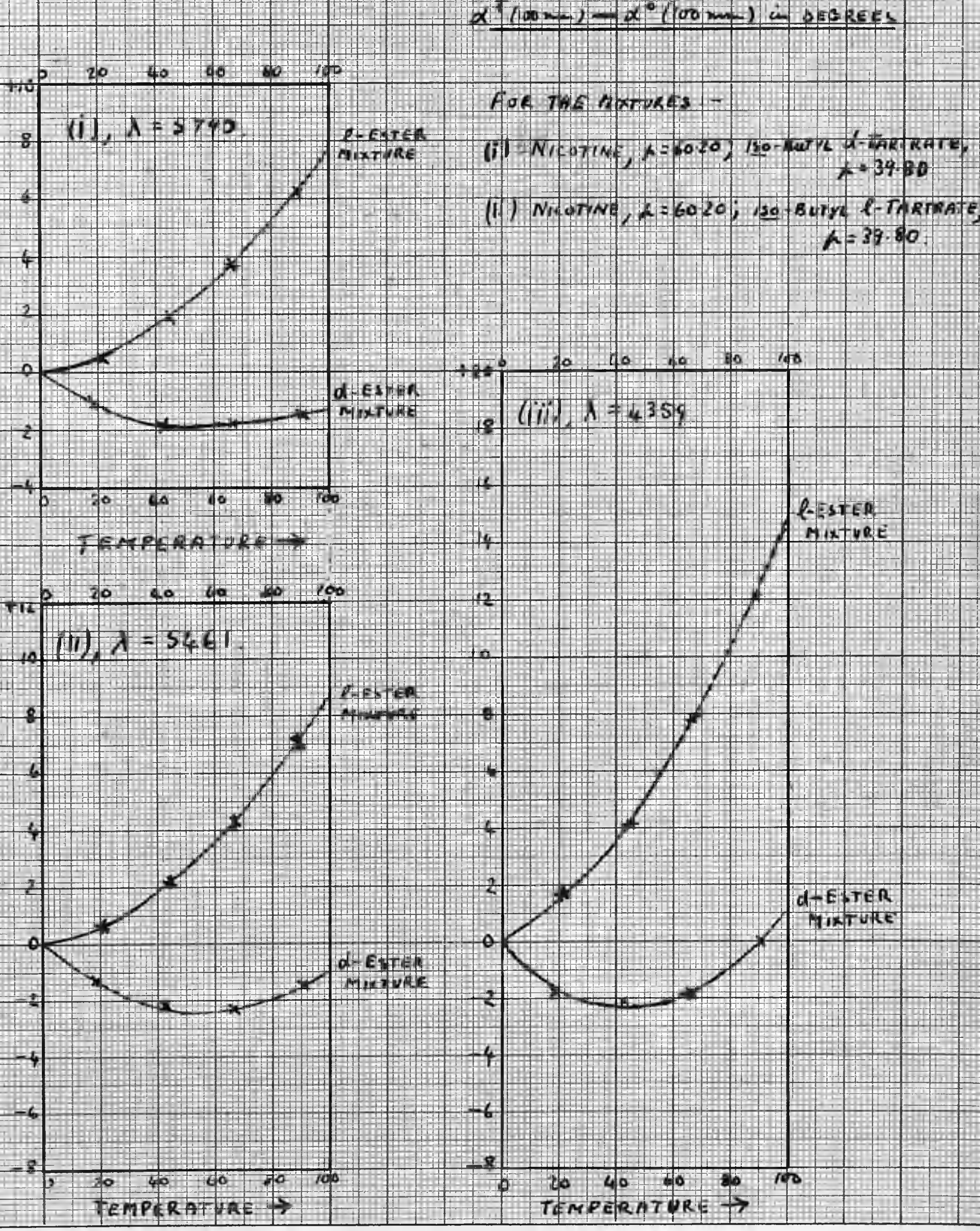
40. To exhibit the shape of the Temperature - Observed Rotation curves ($\alpha^t - \alpha_0$) has again been plotted (fig. 5). A minimum was apparent in the case of the dAlB mixture, and the full set of curves (r_1 to v) showed that this again moved towards lower temperatures as the wavelength of the light decreased.

41. While little more can be done than point out the existence of a mutual solvent effect, it can at least be said that the curves obtained were fully consonant with the following ideas.

(i) That the tartrate esters, on solution in nicotine, had their Temperature-Rotation curves displaced towards the right (higher temperature) region of the general T-R curve (fig. 6).

(ii) That the effect of the esters upon nicotine was analogous to that produced by a fall in temperature.

FIGURE 5



$\alpha^t(100\,mm) - \alpha^0(100\,mm)$ in DEGREES

FOR THE MIXTURES —

(i) = NICOTINE, p = 60·20; ISO-BUTYL d-TARTRATE, p = 39·80

(ii) NICOTINE, p = 60·20; ISO-BUTYL l-TARTRATE, p = 39·80.

CHANGE IN OBSERVED ROTATION, ON WARMING, 0° → 100°
i.e. $\alpha^t(100\,mm) - \alpha^0(100\,mm)$
MIXTURES OF NICOTINE WITH d- and l- ISO-BUTYL TARTRATES.

42. If asymmetric solvent effects are absent, then the observed rotation of dA when dissolved in lB is given by:- Observed Rotation of dAlB, minus observed Rotation of dlAlB (§17.c).

From the results so obtained, the specific rotations of ethyl d-tartrate and iso-butyl d-tartrate in nicotine were calculated. The curves obtained for yellow, green and violet light are given in figures 7 and 8, and these are the graphical expression of the opinion stated in § 41, (i)

The curves are not abnormal. As the proportion of nicotine was increased, the T-R curve of the ethyl tartrate was displaced from the region efg of the general curve to the region of the maximum, ghi. *Iso*-butyl tartrate lies normally nearer to the maximum point than the ethyl ester.*

For this reason the *iso*-butyl compound exhibited the more distant region ik of the general T-R curve.

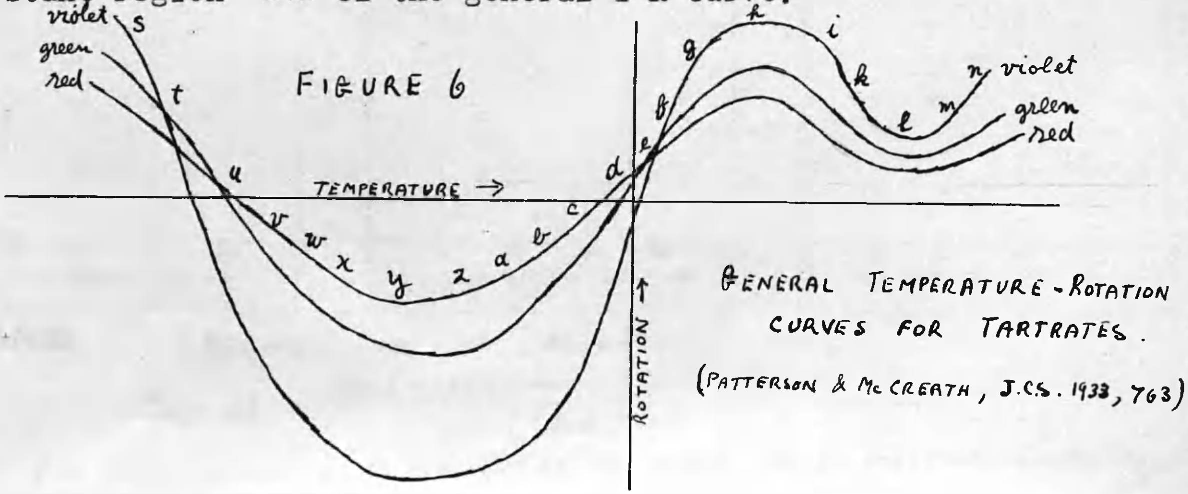


FIGURE 6

GENERAL TEMPERATURE-ROTATION CURVES FOR TARTRATES.

(PATTERSON & McCREATH, J.C.S. 1933, 763)

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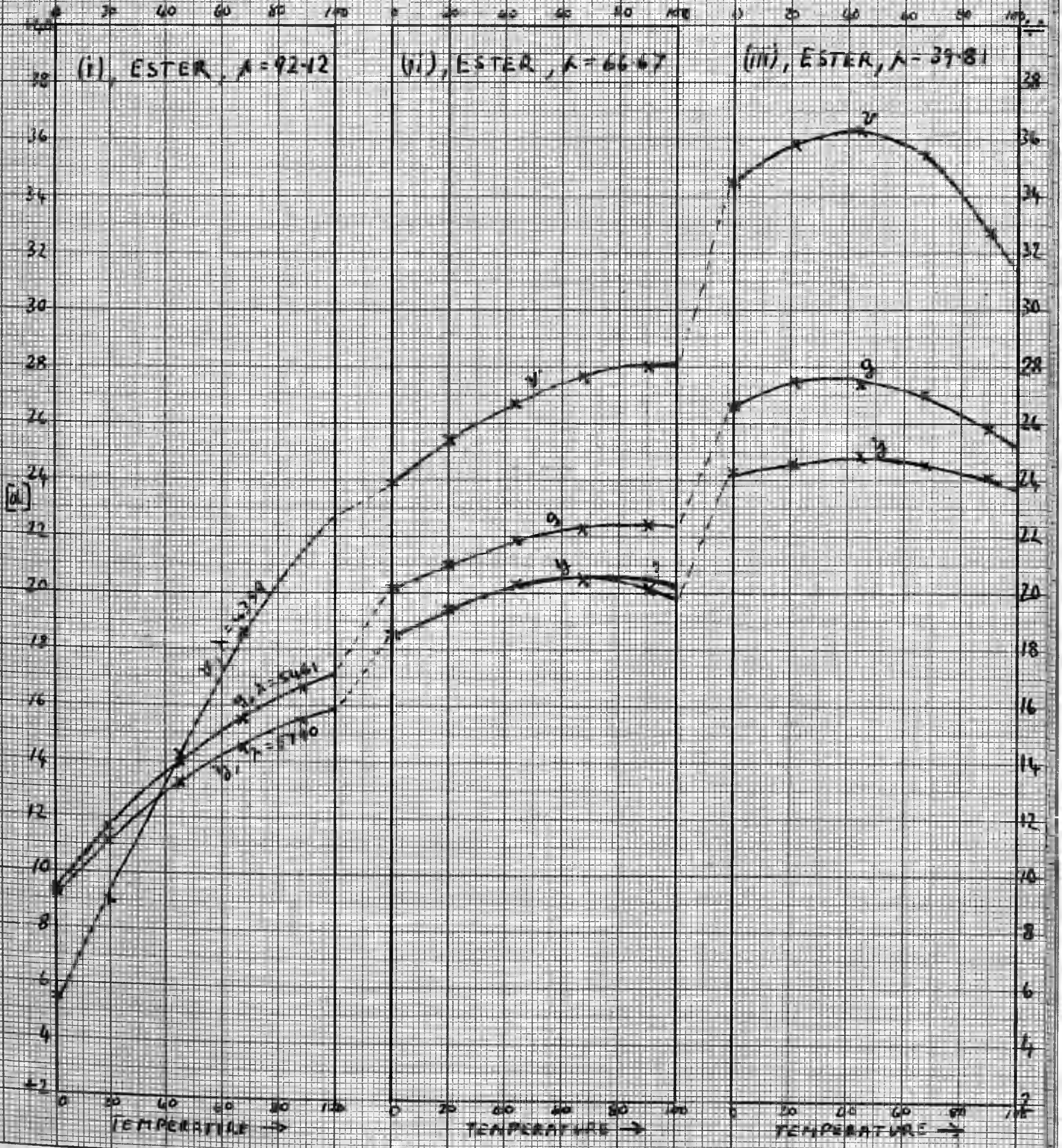
* When both esters are examined in a homogeneous condition at the same temperature.

FIGURE 7

SPECIFIC ROTATION OF ETHYL TARTRATE IN NICOTINE.



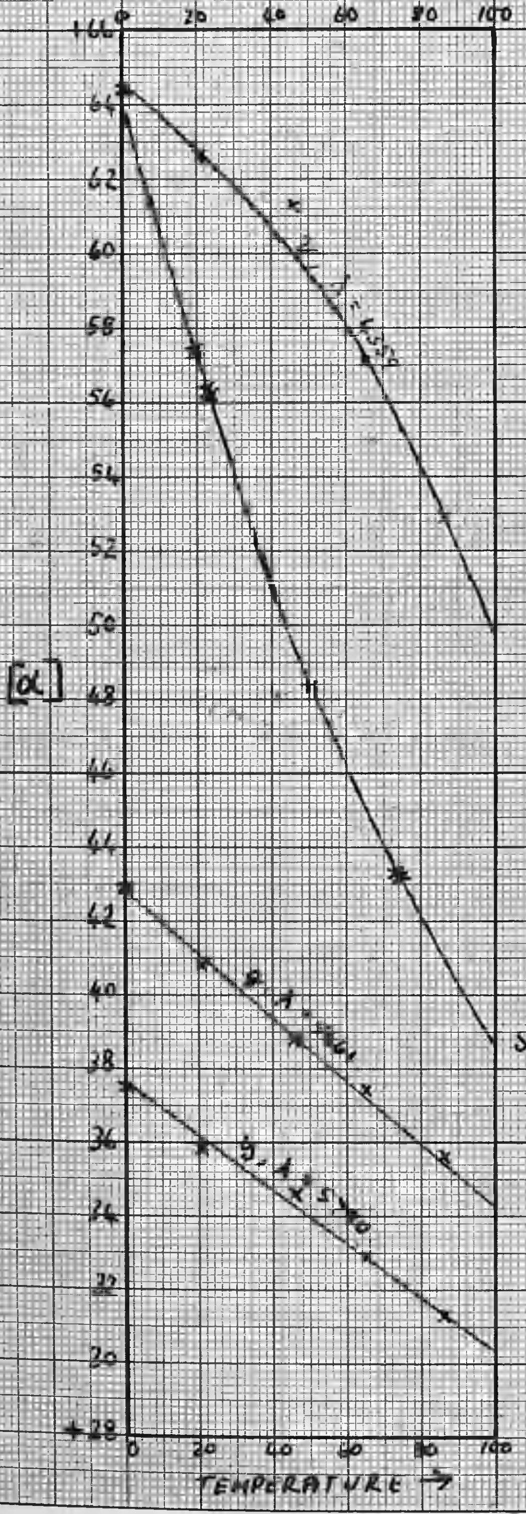
DERIVED ON THE ASSUMPTION THAT:-

$$[\alpha],\, dA = \frac{100\left[\alpha\,(dA.lB \text{ MIXTURE}) - \alpha\,(dlA.lB \text{ MIXTURE})\right]}{l\,p\,d}$$

FOR COMPARABLE dAlB and dlAlB MIXTURES, UNDER IDENTICAL CONDITIONS.

FIGURE 8

SPECIFIC ROTATION OF ISO-BUTYL d-TARTRATE IN NICOTINE



IT MUST BE EMPHASISED THAT THE SPECIFIC ROTATIONS PLOTTED IN FIGURES 7 and 8 ARE DERIVED FROM THE DIFFERENCE OF TWO VERY MUCH LARGER NUMBERS (ESPECIALLY IN FIGURES 7(ii), 7(iii) and 8). ALSO, IF THE ROTATION OF THE NICOTINE WAS IN ANY WAY DIFFERENT IN THE dA lB and dlA lB MIXTURES, SUCH A DIFFERENCE WOULD AFFECT THE CALCULATED SPECIFIC ROTATION OF THE ESTER.

THUS THE SPECIFIC ROTATIONS CANNOT BE EXPECTED TO BE OF THE SAME DEGREE OF ACCURACY AS THOSE DIRECTLY DETERMINED IN AN INACTIVE SOLVENT.

BEARING THESE FACTS IN MIND, THE CURVES SEEM TO REPRESENT, SATISFACTORILY ENOUGH, THE PROBABLE ROTATIONS OF THE TARTRATE ESTERS IN NICOTINE.

SPECIFIC ROTATION, FOR GREEN LIGHT ($\lambda = 5461$) OF ISO-BUTYL d-TARTRATE IN PYRIDINE
$p = 49{\cdot}968$.
(FOR COMPARISON).

DERIVED ON THE ASSUMPTION THAT:-

$$[\alpha], dA = \frac{100\,[\alpha(dA\,lB \text{ MIXTURE}) - \alpha(dlA\,lB \text{ MIXTURE})]}{l\,p\,d}$$

FOR COMPARABLE dA lB and dlA lB MIXTURES, UNDER IDENTICAL CONDITIONS.

The Existence or Absence of Asymmetric Solvent Effects.

43. The fact that the T-R curves of ethyl and iso-butyl tartrate (derived as explained in § 42) were not abnormal is in itself an argument against asymmetric solvent effects.

When the full curves of specific rotation of ethyl tartrate were plotted, the cutting points for various colours of light could be determined in the case of the nicotine $p = 7{\cdot}88°/_{o}$ mixture. In comparison with the results for homogeneous ethyl tartrate:-

Specific rotations at which Violet, (λ =4359) cuts

	r_1	r_2	y	g	b
In derived curve	9·4	10·9	12·6	13·9	15·8
In Et_2T used	9·5	11·1	12·8	14·4	17·4

With the exception of the v/b value, the agreement is fairly close, and the differences are not large enough to indicate any abnormal solvent effect: they are little, if any, greater than those which might normally be expected. Patterson, for example, (J.C.S. 1916, 109, 1148) gave the cutting points observed for iso-butyl-d-tartrate in two different concentrations in S-tetrachlorethane. These were:-

<u>Iso</u>-butyl d-tartrate in S-tetrachlorethane

Specific Rotations at which violet (4359) cuts:-

	b	g	y	r_2	r_1
p = 48·15	17·8	13·5	11·8	9·7	8·0
p = 33·362	17·0	13·5	12·0	10·2	8·4

It will be seen that the cutting points did not correspond exactly, even in this simpler case.

44. In the case of the iso-butyl tartrate mixtures an experimentally sounder line of attack was open. It has already been shown that if the observed rotation of the mixture dlA.lB was not the mean of the rotations found for the dAlB and lAlB mixtures, then $S\frac{dA}{lB} \neq S\frac{lA}{lB}$ (§ 26). At the same time it was pointed out that agreement, if found, did not prove the absence of such an asymmetric solvent effect.

An extremely close agreement was actually found. In my first experiments where <u>iso</u>-butyl racemate of M.P. 57°-58° (the number quoted in the literature) was used, there was a discrepancy which was ultimately traced to the fact that <u>iso</u>-butyl racemate does not melt at 57°-58°, but at 63° when pure. With pure <u>iso</u>-butyl racemate the divergencies previously observed disappeared.

Agreement between rotational measurements for mixtures of d-, dl- and l- *iso*-butyl tartrates and nicotine (p = 60·200 ± 0·004). The results at a temperature of 0° are as observed. Those at 45° and 90° are taken from graphs.

Colour of light, λ	Temp.	0° α,100mm.	45° α,100mm.	90° α,100mm.
6716	Average of d- & l-	-75·50	-75·6	-74·0
	Found, for dl-	-75·40	-75·5	-73·3
6234	Average of d- & l-	-89·09	-89·25	-87·1
	Found, for dl-	-89·20	-89·2	-87·1
5790	Average of d- & l-	-106·74	-106·8	-104·35
	Found, for dl-	-106·45	-106·6	-104·2
5461	Average of d- & l-	-123·15	-123·25	-120·3
	Found, for dl-	-123·03	-123·1	-120·2
4916	Average of d- & l-	-159·44	-158·95	-155·05
	Found, for dl-	-159·88	-159·6	-155·5
4359	Average of d- & l-	-224·51	-223·45	-218·65
	Found, for dl-	-224·65	-224·5	-218·3
Average difference (dl- exceeds average by		0·03°	0·18°	-0·14°

45. There remains to be considered the rotation of nicotine in the racemates and mesotartrates. For the reasons set out in §§ 27 - 32, I did not expect that, even if asymmetric solvent effects were present, the rotational dispersion coefficient of the nicotine would be altered. This was, however, calculated, with the results given below:-

Rational Dispersion Co-efficient of Nicotine $\frac{[\alpha]_y}{[\alpha]_g}$

Using a rational zero of +3°.

Solvent	Ethyl Racemate	Ethyl Mesotartrate	*Iso*-butyl Racemate	*Iso*-butyl Meso-tartrate	Previously found in various solvents. Patterson & Fulton. J.C.S. 1925. 127, 2441.
Highest value.	0·8694	0·8652	0·8700	0·8694	-
Lowest value	0·8650	0·8628	0·8652	0·8678	-
No. of determinations	15	5	5	5	-
Average	0·8676	0·8640	0·8680	0·8687	0·8674

With the exception of the Ethyl Mesotartrate solution, there is a close agreement between the present and previous values.

In the following figure the specific rotation of nicotine in ethyl racemate (3 concentrations), ethyl mesotartrate, *iso*-butyl racemate and *iso*-butyl mesotartrate is plotted for λ = 5461 between 0° and 100°. (The curves for other colours of light are precisely analogous). (Fig. 9).

It will be seen that the rotation of the nicotine was raised in the absolute sense, while the slope of the curve became steeper. In particular it can be observed that there was a difference between the action of the racemates and meso-compounds, the rotation being higher in the absolute sense in the latter. The shape of the

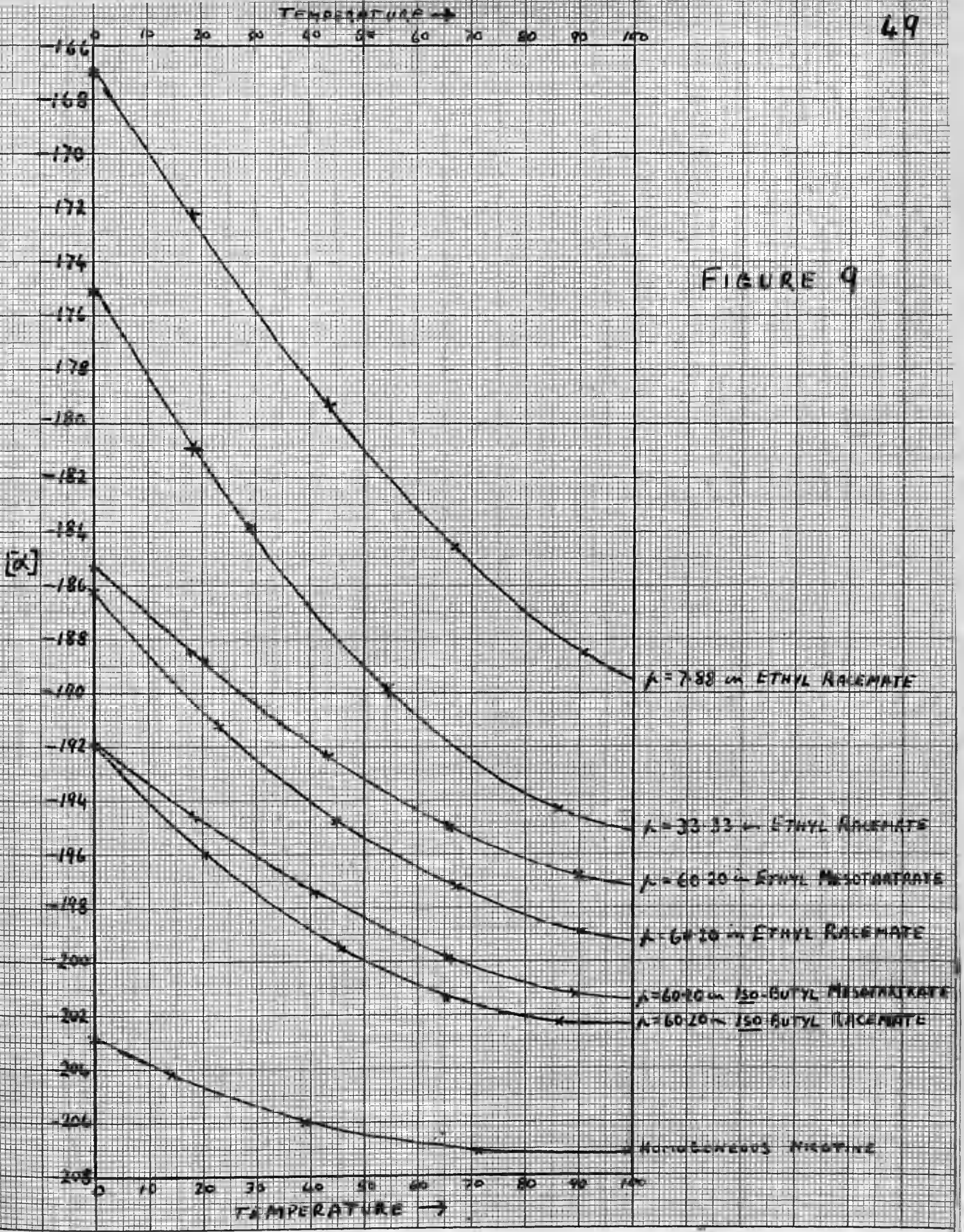


FIGURE 9

THE SPECIFIC ROTATION OF NICOTINE
IN RACEMIC and MESO ESTERS, FOR GREEN LIGHT.
$\lambda = 5461$.

curve is different, an effect particularly well shown in the case of the iso-butyl compounds. Since it has been reported (Wolf, Trans. Faraday Soc. 1930, 26, 319) that the dipole moment of ethyl mesotartrate is greater than that of ethyl d- or l- ~~racemate~~ tartrate, these observations may be of interest in connection with the relation of the dipole moment of a solvent to the specific rotation of the solute.

It also is apparent that the rotation of the nicotine was less affected by the iso-butyl than by the ethyl compounds. For example, Nicotine, p = 60·20 had $[\alpha]_y^{\circ}$ = - 191·9° in iso-butyl racemate and mesotartrate, and $[\alpha]_g^{\circ}$ = - 186·2°, -185·3° in ethyl racemate and mesotartrate, respectively. Even if allowance was made for the fact that the molecular concentration of the nicotine was greater in the case of the iso-butyl compounds, a slight but definite difference remained. Nicotine, p= 65·80 in ethyl racemate, contains the ester and base molecules in the same proportions as nicotine, p = 60·20 in iso-butyl racemate. From a concentration graph I obtained the following results:-

	In Ethyl Racemate	In Iso-butyl Racemate	Difference.
$[\alpha]_y^{\circ}$	-164° ± 1°	-166·1°	2°
$[\alpha]_g^{\circ}$	-189° ± 1°	-191·9°	3°
$[\alpha]_v^{\circ}$	-346° ± 1°	-350·3°	4°

Density Determinations.

46. In the case of the iso-butyl compounds it was found by actual experiment that the densities of the d- and dl- compounds were (in the liquid state) exactly alike (§ 50). The following comparison was then drawn up:-

Differences in density between mixtures of d-, l-, dl- amd i- <u>iso</u>-butyl tartrates ($p = 39{\cdot}800 \pm 0{\cdot}004$) in nicotine. A straight line was drawn from $d_4^{0} = 1{\cdot}0653$ to $d_4^{100} = 0{\cdot}9761$: the following are the divergencies from this line shown by the various observations.

Mixture of Nicotine p = 60·20 with:		Temp.	Divergence. (Units in 4th place)
Taken with 5 c.cs. quartz pyknometer	d- Ester	17·5	± 0
		18·4	- 5
		42·4	± 0
		66·5	+ 1
		90·7	- 1
	dl- Ester	17·3	- 1
		20·6	± 0
		46·0	+ 2
		65·2	± 0
		86·2	+ 1
Taken with 1·5 c.cs glass pyknometer	l- Ester	21·2	+ 9
		44·8	+ 4
		66·5	+ 1
		89·3	+ 6
	i- Ester	18·5	+ 30
		41·0	+ 37
		65·8	+ 41
		89·3	+ 46

It can be seen that there was a very close agreement between the d- and dl- mixtures, and that both the density and co-efficient of expansion showed an alteration when the mseo-compound was used. There was also a slight difference in the case of the l-compound. To this, however, I do not attach much importance in view of the fact that the same pyknometer was not used throughout; and the accuracy of the 1·5ccs. pyknometer, while amply sufficient for calculating specific rotations, is not satisfactory for work of this type. It may be noted that by chance readings were taken at 66·5° for both d- and l- compounds, and the densities found were exactly identical.

These results did however suggest that it would be of value to repeat and extend some work upon the same problem which had previously been carried out by Professor T. S. Patterson.

47. Samples of *iso*-butyl d-tartrate and *iso*-butyl dl-tartrate were prepared and purified with special care. A series of mixtures containing just over 5°/o of the solid ester were made up in menthyl acetate, and examined in a 30ccs. pyknometer. (In each case five or six determinations of the contents weight of the pyknometer were made over the temperature range 19·7° - 20·3°, and the weight at 20° calculated by interpolation.)

The results obtained may be conveniently summarised as follows:-

Percentage of:-

	l-menthyl acetate	d-iso $Bu_2\overline{T}$	l-iso $Bu_2\overline{T}$	D^{20}_{4}	Molecular Soln. Volume of <u>iso</u>-butyl compound.
1	100	-	-	0·925340	
2	95·0056	4·9944		0·931982	242·89
3	94·5991	5·4009		0·932533	242·86
4	94·6021	5·3979		0·932516	242·93
5	94·6002	5·3998		0·932524	242·91
6	94·6011		5·3989	0·932530	242·86
7	94·6010		5·3990	0·932530	242·86
8	94·5995		5·4005	0·932535	242·85
9	94·6020	5·3980		0·932519	242·92

In my opinion, the error in the percentages given is less than ± 0·001, and each individual density is correct to ±0·00001, equivalent to an error in the contents weight at 20° of 0·3mg. It can be seen that, experimentally, the density determinations are self-consistent to this degree: when the centre of gravity of the D^{20}_{4} determinations Nos. 3,4,5 and 9 is joined to the D^{20}_{4} determination No.2, the maximum divergence from the line thus found is shown by No.3. (= + 0·000008). A full account of the precautions taken to obtain this degree of accuracy is given later (§ 56).

Discussion of Results.

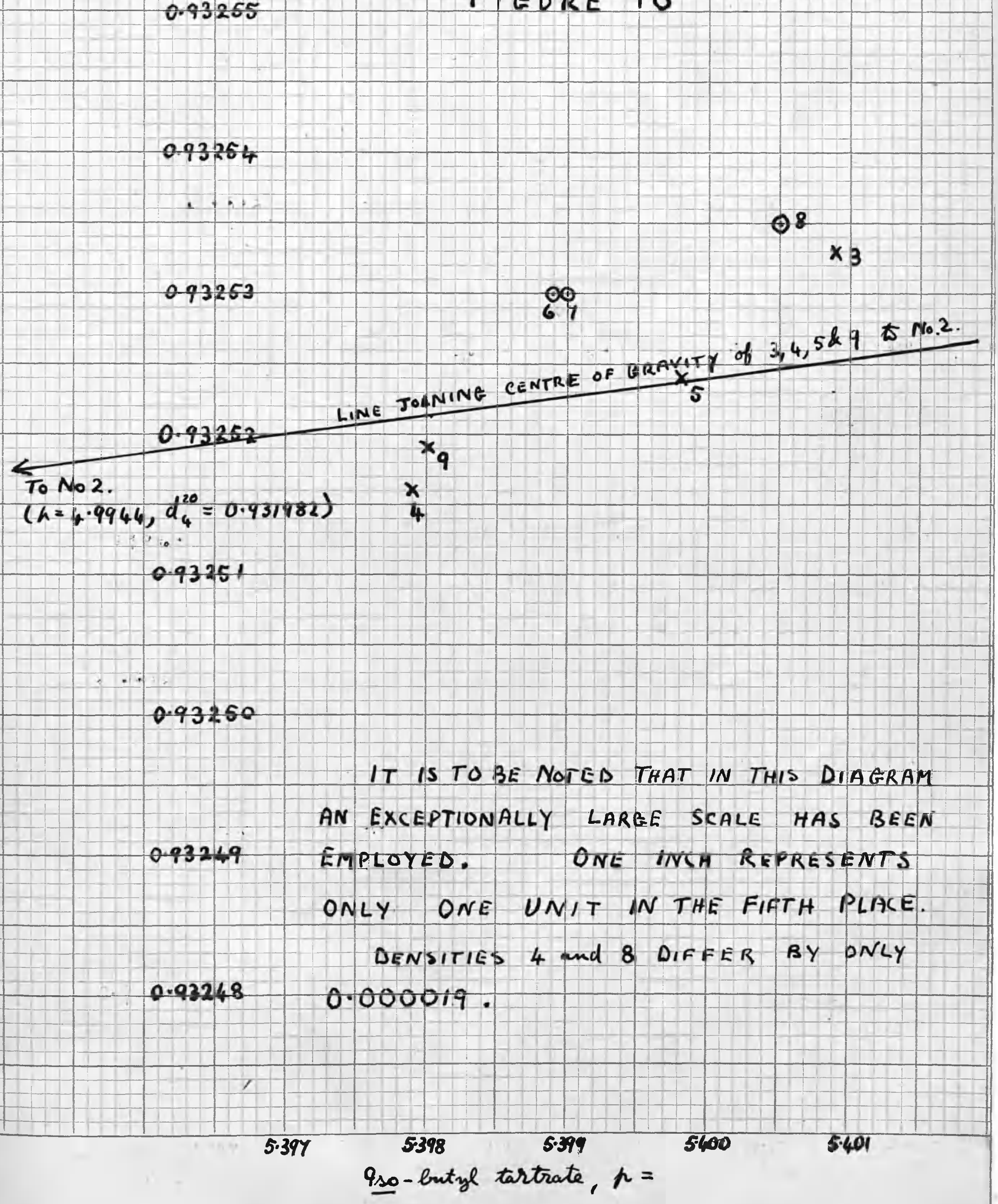
When the D^{20}_{4} determinations were plotted against the percentages of the iso-butyl compounds present, it could be seen that the solutions of the l-compound had a slightly greater density than the solutions of the d-compound (Fig. 10). The molecular solution volumes were (i) l-compound (242·86, 242·86 and 242·85 Average = 242·86) and (ii) d-compound (242·89, 242·86, 242·93, 242·91 and 242·92, Average - 242·90).

The actual density difference observed (0·000008) was extremely small, and was less than the experimental error in determining one density. An attempt was made to carry out similar determinations in a symmetric solvent: for if the density difference actually observed was due to asymmetry it should have disappeared in a symmetric solvent. Several determinations in iso-butyl alcohol showed that (possibly on account of its greater volatility) an equal standard of accuracy could not be obtained.

If any density difference due to asymmetry existed, it must have been extremely small - most probably less than 1 in the 5th place. The molecular solution volumes of the d- and l-compounds agreed also to 1 part in 5,000.

This is, of course, the most that can be said, unless a difference definitely greater than experimental error - say 2 or 3 units in the 5th place - had been found.

FIGURE 10



IT IS TO BE NOTED THAT IN THIS DIAGRAM AN EXCEPTIONALLY LARGE SCALE HAS BEEN EMPLOYED. ONE INCH REPRESENTS ONLY ONE UNIT IN THE FIFTH PLACE.

DENSITIES 4 and 8 DIFFER BY ONLY 0·000019.

ISO-BUTYL TARTRATES IN MENTHYL ACETATE.

Results, with dextro-compound, X.
" " laevo-compound, ⊙.

48. Concise Summary of the Experimental Findings.

It has been found that:-

(i) Mixtures of ethyl tartrate and iso-butyl tartrate with nicotine exhibited a considerable mutual solvent effect, which was most marked in the case of the ethyl tartrate - nicotine mixtures. The changes in rotation which could be attributed to alterations in density were in comparison trivial. An entire change in the shape of the Temperature - Observed Rotation curves was produced.

These changes were consonant with the view that nicotine displaced the T-R curves of tartrate esters towards the right (higher temperature regions) ~~for~~ of the general T-R curve, and that the esters raised (in the absolute sense) the rotation of nicotine, giving at the same time more steeply falling T-R curves.

(ii) While it cannot be stated that asymmetric solvent action has been disproved, an examination of the rotations of mixtures of nicotine in d-, l- and dl- iso-butyl tartrates afforded no sign whatever of its existence. According to my theoretical reasoning, such an effect would have been indicated if the observed rotation of the dl-mixture had not been the mean of those shown by the d- and l- mixtures.

(iii) Iso-butyl racemate melts, when pure, at 63° - 64° and has in the liquid state the same density as the active form.

Arguments in favour of the existence of racemic molecules in the liquid state based upon density measurements of the racemate of M.P. 58° are incorrect. (See § 50, below).

(iv) The rational dispersion co-efficient of nicotine dissolved in ethyl racemate, <u>iso</u>-butyl racemate, ethyl mesotartrate and iso-butyl mesotartrate showed a good agreement with the value previously determined, although the value in ethyl mesotartrate was unaccountably low. The rotation of nicotine in these solvents was raised in the absolute sense, and the T-R curves dropped more steeply. A slightly higher rotation was shown in both mesotartrates than in the corresponding racemates. The specific rotation was lower in the iso-butyl than in the ethyl compounds. Even when mixtures containing equal molecular proportions of the ester and base were considered, the rotation remained lower in the <u>iso</u>-butyl solvent.

(v) The densities of mixtures of <u>iso</u>-butyl d- and l- tartrates ($p = 5{\cdot}4$) with menthyl acetate showed a difference of less than one in the 5th place, which was of the same order as the experimental error. The difference is not, in my opinion, large enough to be significant.

In general it may be said that in the case of tartrate esters and nicotine or menthyl acetate there is no apparent sign of any definite and measureable asymmetry in the relation of the solvent to the solute.

Experimental Details.

The Compounds used.

49. Ethyl Tartrate, Racemate, Mesotartrate.

These were prepared by the constant esterification method of Frankland and Aston (J.C.S. 1901, 79, 517). It was found necessary to employ wooden corks in the apparatus. When rubber corks were used, sulphur was dissolved by the refluxing of the alcohol, even when no "bloom" was apparent upon the corks used. Ethyl tartrate was found to dissolve sulphur, which volatilised with the ester and passed over with the earlier fractions on distillation. The solubility of sulphur in the ester was extremely small in the cold (much less than 1 in 500), though somewhat more when warm. Thus a contaminated distillate developed a milky opacity on cooling: if sufficient sulphur was present crystalline needles finally separated. The impurity had little, if any, effect upon the rotation of the ethyl tartrate, but the opacity rendered it unfit for polarimetry. This phenomenon of opalesence had already been observed in this laboratory, though not previously investigated. The most satisfactory method of purification was by dissolving the contaminated ester in benzene, and then shaking with mercury until all the sulphur was precipitated as sulphide. (Patterson & Lamberton, Chemistry & Industry, 1934, 53, 363).

It was also found that the use of sulphuric acid as a catalyst was undesirable. No abnormality was observed during the esterification, but when ethyl tartrate containing even a small quantity of the acid was distilled the rotation of the later fractions was increased by the production of some impurity. In the final preparations quantities of sulphuric acid varying between 0·4 and 4 g. were used to each 100 g. of acid. The preparations were allowed to stand over an excess of barium carbonate to remove the catalyst before distillation.

In the case of the ethyl racemate this procedure, judged by the density determined, was successful. After two careful distillations at 2 - 3mm. pressure:-

Density Found.	Previous Values.
$d_4^{20} = 1{\cdot}2050$.	$d_4^{20} = 1{\cdot}2052$ (for $Et_2 d\text{-}\bar{T}$) Patterson, J.C.S. 1916, <u>109</u>, 1160.
$d_4^{25} = 1{\cdot}1999$	$d_4^{25} = 1{\cdot}1986$ Perkin, J.C.S. 1887, <u>51</u>, 363.
$d_4^{99} = 1{\cdot}1256$	$d_4^{99} = 1{\cdot}1246$ Kühn, Ber, 1928, <u>61</u>, 486.

In the case of the ethyl d-tartrate two careful distillations at 2 - 3mm. gave a sample of α_{5461}^{20} (100mm.) = $+10{\cdot}18^\circ$; previous values were $+9{\cdot}40^\circ$ (Patterson, J.C.S. 1916, <u>109</u>, 1160), $+9{\cdot}48^\circ$ (Lowry, J.C.S. 1922, <u>121</u>, 537) and $+9{\cdot}51^\circ$ (Rule, J.C.S. 1933, 1222). The dansity d_4^{20}, was 1·2037, as against 1·2052 (Patterson, loc. cit.), 1·2036 (Winther Z. Phys. Chem. 1902, <u>41</u>, 174) and

1·2028 (Lowry, loc. cit).

As this state of affairs was not improved by careful vacuum distillation, it was decided to carry out some projected experiments with this material, repeat these with a scrupulously pure ester if any abnormality were observed, and proceed for further work to the crystalline _iso_-butyl tartrates, which could be easily obtained in a state of undoubted purity. It can be said in extenuation that the actual impurity was almost certainly a compound of high rotation, present only in small quantity: during investigation a specimen of "ethyl tartrate" with as high a rotation as $\alpha_{8}^{17\cdot5} = +36\cdot2^\circ$ was obtained. The conditions which govern the production of this impurity (possibly diethyl-diethoxy-succinate) are still uncertain.

In conclusion it may be said that in the preparation of these esters:-

(i) Rubber corks must be avoided during the esterification, though these cause no harm during the distillation of the ester.

(ii) Sulphuric acid as a catalyst must not be used.

(iii) Very little air must be permitted to pass through the tartrate during the distillations, or oxidation of the ester will result (see supplementary paper on "green ethyl tartrate".)

Ethyl Mesotartrate, was prepared by the constant esterification method from mesotartaric acid which, when dehydrated, had M.P. = 143°. The reaction mixture from the constant esterification apparatus was evaporated to a syrup, seeded with solid ethyl mesotartrate which had been obtained by the vacuum distillation of a small portion, and extracted with benzene. [A considerable amount of benzene insoluble matter (probably $H_2\overline{M}$ and some $EtH\overline{M}$) was thus recovered: this would have been lost by decomposition had the crude product been distilled.] Crystallisation of the ester from carbon disulphide did not improve the melting point, but vacuum distillation gave a solid of freezing point 57°. The M.P. was 57°, with slight preliminary softening at 54°. Kühn and Wagner-Jauregg gave M.P. 55° (Ber. 1928, <u>61</u>, 503).

50. The <u>iso</u>-butyl esters were prepared by the Fischer-Speier method, washed with water to remove <u>iso</u>-butyl alcohol and hydrochloric acid, and crystallised from benzene until pure. Three crystallisations were usually required: the pure product was then distilled at 5 - 8mm. to fit it for polarimetric work by the removal of dust and fibres of filter paper. Petroleum ether (60°-80°) is a more suitable solvent when small quantities are prepared: the solubility of these esters in cold petroleum ether is small.

The following observations were made:-

	Iso-butyl-			
	d-tartrate	l-tartrate	dl-tartrate	i-tartrate
Setting (solidification) points*.	72·7°	72·7°	63·0-63·1°	81·5°
Solubility in benzene. g. in 100g. C_6H_6	62	-	80	17
Densities determined, Combustion results, etc.	$d_4^{80\cdot8}$ =1·0265	-	$d_4^{67\cdot6}$ =1·0386	Not previously prepared. B.P. was 176° - 178° at 12mm. Found, C = 55·27°/o H = 8·48°/o Calc. C = 54·92°/o H = 8·46°/o
	$d_4^{90\cdot3}$ =1·0178	-	$d_4^{77\cdot7}$ =1·0294	
	$d_4^{91\cdot1}$ =1·0171	-	$d_4^{85\cdot6}$ =1·0222	
	$d_4^{94\cdot5}$ =1·0138	-	$d_4^{96\cdot4}$ =1·0122	
Rotation in Benzene. p = 10·0173	$[\alpha]_{5461}^{20}$ =+32·90°	-	-	
Rotation in pyridine p = 6·856 - 6·943	$[\alpha]_{5461}^{20}$ =+67·65°	-67·69°	-	
p = 49·968	$[\alpha]_{5461}^{20}$ =+57·20°	-	-	-

[*The thermometer used for the setting point determinations was calibrated by observing the setting point of pure naphthalene - 80·1°. Francis & Collins, J.C.S. 1936, 138.]

By inter- and extra- polation from the densitied determined:-

	d-cpd.	dl-cpd.
D_4^{80}	1·0272	1·0273
D_4^{100}	1·0090	1·0090

Campbell (J.C.S. 1929, 1116) gave:-

D_4^{80}	1·0213	1·0160
D_4^{100}	1·0178	1·0124

It may be noted that (i) the low solubility of the mesotartrate in benzene as compared with the racemate might provide a method whereby a pure mesotartrate could be prepared from mesotartaric acid residues containing racemic acid, and (ii) the close agreement between the densities of the molten d- and dl- compounds invalidated one of the arguments brought forward by Campbell in favour of the existence of liquid racemates. Since the M.Pts. recorded by Campbell were 70° and 58°, it would seem that the density difference found was due to the impurity of the esters examined.

51. The nicotine was purified by means of the zinc chloride double salt, $C_{10}H_{14}N_2$, 2HCl, $ZnCl_2$, H_2O. (Lowry & Lloyd, J.C.S. 1929, 1381). The rotation and density showed a very close agreement with the previous results of Jephcott (i), Patterson & Fulton (ii), Lowry & Singh (iii) Lowry & Lloyd (iv).

(i) J.C.S. 1919, <u>115</u>, 104.
(ii) J.C.S. 1925, <u>127</u>, 2439.
(iii) Comptes R. 1925, <u>181</u>, 910.
(iv) J.C.S. <u>1929</u>, 1772.

Distillation was carried out in an atmosphere of nitrogen at 10 - 15 mm. pressure. After the distillation had been completed atmospheric pressure was restored by the admission of nitrogen instead of air. During the later work with the iso-butyl esters the distillate was shaken up vigorously before removal from the nitrogen-filled receiver. This saturation with nitrogen at atmospheric pressure greatly improved the keeping properties of the nicotine. This treatment, preceeded by careful drying and distillation, gave a specimen of $\alpha_g^{20} = -206{\cdot}2°$. After keeping for 6-7 weeks in a corked bottle filled to the neck, the rotation had only fallen to $\alpha_g^{20} = -206{\cdot}1°$; and the liquid showed no colouration whatever.

52. The rotation measurements were taken by means of the apparatus designed by Patterson (J.C.S. 1927, 1717). In the case of those mixtures containing a considerable proportion of nicotine, a stream of nitrogen was passed into the side arm of the polarimeter tube to prevent oxidation. Except where otherwise stated, a 5 ccs. quartz pyknometer was used for the density measurements. The colours of light used were:-

	r_1	r_2	y	g	b	v
λ =	6716	6234	5790	5461	4916	4359 Å

53. Ethyl Tartrate used.

α, 100 mm.

Temp.	d_4^t	r_1	r_2	y	g	b	v
0°	1·2237*	6·86	7·23	7·32	6·98	4·67	-2·54
20·2°	1·2035	8·94	9·64	10·11	10·21	9·09	3·70
44·6°	1·1793	10·76	11·77	12·70	13·25	13·16	9·73
66·7°	1·1571	11·88	13·18	14·40	15·24	15·94	13·89
90·1°	1·1335	12·66	14·15	15·64	16·73	18·00	17·08

[α]

0°	1·2237*	5·61	5·91	5·98	5·70	3·82	-2·08
20·2°	1·2035	7·43	8·01	8·40	8·48	7·55	3·08
44·6°	1·1793	9·13	9·98	10·76	11·24	11·15	8·23
66·7°	1·1571	10·27	11·39	12·45	13·18	13·78	12·00
90·1°	1·1335	11·17	12·48	13·80	14·78	15·89	15·08

All rotations are positive, unless specially marked

Density * is by extrapolation.

53A.

Ethyl Tartrate - Nicotine Mixture.

Nicotine, p = 7·88.

α, 100 m.m.

Temp.	d_4^t	r_1	r_2	y	g	b	v
0°	1·2087*	-0·87	-1·91	-3·52	-5·44	-10·63	-23·1
19·5°	1·1901	+0·28	-0·51	-1·84	-3·50	- 8·36	-19·7
45·1°	1·1645	+1·36	+0·81	-0·21	-1·55	- 5·66	-14·8
67·3°	1·1426	+2·01	+1·63	+0·78	-0·33	- 3·96	-10·6
88·7°	1·1210	+2·53	+2·18	+1·48	+0·50	- 2·47	—

Density marked * by extrapolation.

53. B.

Ethyl Tartrate - Nicotine mixture.

Nicotine, $p = 33·33$.

α, 100 m.m.

Temp.	d^t_4	r_1	r_2	y	g	b	v
0°	1·1621*	30·35	36·50	44·40	52·30	71·10	105·6
20·1°	1·1421	30·88	37·15	45·15	53·18	72·08	106·8
43·9°	1·1191	31·30	37·60	45·65	53·78	72·63	107·4
67·6°	1·0962	31·55	37·85	45·88	53·90	72·58	107·1
90·7°	1·0735	31·40	37·73	45·75	53·75	72·08	106·4

All Rotations are <u>Negative</u>.

Density* by extrapolation.

53. C.

Ethyl Tartrate - Nicotine mixture.

Nicotine, p = 60·19

α, 100 m.m.

Temp.	d^t_4	r_1	r_2	y	g	b	v
0°	1·1066*	67·85	81·03	96·90	112·50	148·18	212·10
21·3°	1·0871	68·38	81·43	97·60	113·28	148·73	212·95
44·4°	1·0664	68·35	81·75	97·98	113·55	149·43	212·80
67·8°	1·0450	68·73	81·58	97·63	113·18	149·33	211·48
90·4°	1·0240	67·75	80·88	96·70	112·15	147·48	208·90

All Rotations are Negative.

Density marked * by extrapolation.

53. D.

Ethyl Racemate - Nicotine Mixture.

Nicotine, p = 7·88

α, 100 m.m.

Temp.	d^t_4	r_1	r_2	y	g	b	v
0°	1·2092*	9·79	11·59	13·73	15·92	20·80	29·22
18·8°	1·1921	9·91	11·72	13·99	16·18	21·11	29·51
44·0°	1·1676	10·09	11·94	14·27	16·51	21·46	29·93
66·9°	1·1443	10·08	12·06	14·44	16·65	21·65	30·19
90·7°	1·1202	10·19	12·07	14·41	16·64	21·52	29·88

[α], of Nicotine.

Temp.	d^t_4	r_1	r_2	y	g	b	v
0°	1·2092*	102·8	121·6	144·1	167·0	218·3	306·8
18·8°	1·1921	105·5	124·7	148·9	172·2	224·7	314·2
44·0°	1·1676	109·6	129·8	155·0	179·3	233·2	325·2
66·9°	1·1443	111·8	133·8	160·0	184·6	240·1	334·9
90·7°	1·1202	115·4	136·8	163·2	188·5	243·9	338·5

All rotations are Negative

Density marked * by extrapolation.

53. E.

Ethyl Racemate - Nicotine mixture.

Nicotine, p = 33·33.

α, 100 m.m.

Temp.	d^t_4	r_1	r_2	y	g	b	v
0°	1·1635*	41·08	49·13	58·68	67·88	88·70	124·1
19·0°	1·145 *	42·38	50·08	59·78	69·08	90·13	126·0
29·2°	1·1346	42·18	50·38	60·25	69·48	90·50	126·6
54·2°	1·1093	43·15	51·18	60·58	70·18	91·30	127·3
86·3°	1·0783	43·08	50·75	60·43	69·85	91·10	126·7

[α]

0°	1·1635*	105·9	126·7	151·4	175·1	228·8	320·0
19·0°	1·145 *	111·1	131·2	156·7	180·9	236·1	330·2
29·2°	1·1346	111·6	133·2	159·4	183·8	239·4	334·9
54·2°	1·1093	116·9	138·6	164·0	189·9	247·1	344·4
86·3°	1·0783	119·9	141·4	168·0	194·3	253·4	352·6

Densities marked * by extrapolation.

All rotations are Negative.

53.F.

Ethyl Racemate - Nicotine mixture.

Nicotine, p = 60·20.

α, 100 m.m.

Temp.	d^t_4	r_1	r_2	y	g	b	v
0°	1·1077*	75·65	90·03	107·55	124·20	161·60	227·28
23·0°	1·0869	76·43	90·78	108·30	125·13	162·23	228·13
44·8°	1·0669	76·65	90·73	108·35	125·13	162·48	228·13
67·4°	1·0461	76·28	90·25	107·68	124·28	160·65	225·58
90·2°	1·0253	75·20	89·10	106·35	122·75	156·90	222·68

[α]

Temp.	d^t_4	r_1	r_2	y	g	b	v
0°	1·1077*	113·4	135·0	161·2	186·2	242·3	340·8
23·0°	1·0869	116·8	138·8	165·5	191·2	247·9	348·6
44·8°	1·0669	119·4	141·3	168·7	194·8	252·9	355·2
67·4°	1·0461	121·1	143·3	170·9	197·2	255·0	358·1
90·2°	1·0253	121·9	144·4	172·3	198·9	254·2	360·7

All Rotations are Negative.

Density * by extrapolation.

53 G.

Ethyl Mesotartrate-Nicotine mixture.

Nicotine, p = 60·197

α, 100 m.m.

Temp.	d^t_4	r_1	r_2	y	g	b	v
0°	1·1116 *	75·98	89·63	107·30	124·00	160·68	226·68
17·8°	1·0953 *	-	-	-	124·28	160·95	-
20·5°	1·0928	76·18	90·10	107·50	124·13	-	226·93
43·4°	1·0723	75·90	90·05	107·65	124·15	161·10	226·03
66·1°	1·0516	75·58	89·45	106·88	123·43	159·55	224·55
89·9°	1·0297	74·78	88·58	105·80	121·98	157·33	221·58

$[\alpha]$

0°	1·1116 *	113·6	134·0	160·3	185·3	240·1	338·8
17·8°	1·0953 *	-	-	-	188·5	244·1	-
20·5°	1·0928	115·8	137·0	163·4	188·7	-	345·0
43·4°	1·0723	117·6	139·5	166·8	192·3	249·6	350·1
66·1°	1·0516	119·4	141·3	168·8	195·0	252·0	354·7
89·9°	1·0297	120·7	142·9	170·6	196·8	253·7	357·4

All Rotations are Negative

Densities marked * by extrapolation. Densities taken with a 5 cc. quartz pyknometer. M.P. of Ethyl Mesotartrate = 57°.

53. H.

Iso-Butyl d-Tartrate - Nicotine Mixture.

Nicotine, p - 60•200.

α, 100m.m.

Temp.	d_4^t	r_1	r_2	y	g	b	v
0°	1•0653*	63•30	74•93	90•55	104•85	137•43	197•33
18•4°	1•0484	64•23	75•88	91•68	106•18	139•08	199•15
42•4°	1•0275	64•73	76•68	92•40	107•05	138•90	199•40
66•5°	1•0061	64•93	76•83	92•38	107•13	139•65	199•25
90•7°	0•9842	64•55	76•25	92•08	106•38	138•28	197•33

Density * by extrapolation. All Rotations are Negative. Rotation of Nicotine used, $\alpha_g^{20} = -205\cdot9^\circ$. M.P. of Iso-butyl d-Tartrate = 73°; Rotation, $[\alpha]_g^{20} = +32\cdot90^\circ$ in Benzene, c = 10•0173. Densities taken with a 5 ccs. quartz pyknometer.

Additional results:-

Two other mixtures gave.

Nicotine, p = 60•201, of $\alpha_g^{20} = -206\cdot1$:-

$\alpha_g^{17\cdot5} = -106\cdot05^\circ$, $d_4^{17\cdot5} = 1\cdot0497$.

Nicotine, p = 60•198, of $\alpha_g^{20} = -206\cdot1$

$\alpha_g^{16\cdot0} = -106\cdot43$.

53.I.

Iso-Butyl 1-Tartrate-Nicotine Mixture.

Nicotine, p = 60·201.

α, 100m.m.

Temp.	d_4^t	r_1	r_2	y	g	b	v
0°	1·0658*	87·70	103·25	122·93	141·45	181·45	251·68
21·2°	1·0473	87·23	102·85	122·40	140·85	179·53	250·03
44·8°	1·0258	86·50	101·85	121·03	139·25	178·38	247·58
66·5°	1·0061	85·13	100·15	119·20	137·13	176·80	243·90
89·3°	0·9862	83·48	98·00	116·75	134·35	171·68	239·65

Density * by extrapolation. All Rotations are Negative.

Rotation of Nicotine used, α_g^{20} = -205·8°. M.P. of Iso-Butyl 1-Tartrate used = 73°.

Densities taken with a 1·5ccs. glass pyknometer.

53. J.

Iso-butyl Racemate - Nicotine Mixture.

Nicotine, p = 60·200

α, 100 m.m.

Temp.	d_4^t	r_1	r_2	y	g	b	v
0°	1·0653*	75·40	89·20	106·45	123·03	159·88	224·65
20·6°	1·0470	75·75	89·45	106·68	123·50	159·98	225·10
46·0°	1·0245	75·38	89·30	106·60	123·05	159·40	224·53
65·2°	1·0071	74·48	88·45	105·75	122·10	157·83	222·03
86·2°	0·9885	73·85	87·38	104·48	120·50	156·00	218·90
					[α]		
0°	1·0653*	117·6	139·1	166·1	191·9	249·4	350·3
20·6°	1·0470	120·2	141·9	169·2	196·0	253·9	357·2
46·0°	1·0245	122·3	144·8	172·9	199·5	258·4	364·1
65·2°	1·0071	122·8	145·9	174·4	201·4	260·3	366·2
86·2°	0·9885	124·0	146·7	175·4	202·3	261·9	367·5

Additional Results:- $\alpha_g^{17\cdot6} = -123\cdot48$; $\alpha_y^{19\cdot9} = -106\cdot88$;
$d_4^{17\cdot3} = 1\cdot0498$.

All Rotations are negative. Density * by extrapolation.

All densities taken with a 5 ccs. quartz pyknometer.

Relation of Nicotine used, $\alpha_g^{20} = -205\cdot8°$. M.P. of Iso-butyl Racemate = 63°

53. K.

Iso-butyl Mesotartrate - Nicotine Mixture.

Nicotine, p = 60·196.

α, 100 m.m.

Temp.	d_4^t	r_1	r_2	y	g	b	v
0°	1·0680*	75·70	89·50	106·98	123·50	160·15	225·83
18·5°	1·0518	75·80	89·13	106·83	123·25	159·80	224·63
41·0°	1·0325	75·35	88·95	106·25	122·75	159·08	223·60
65·8°	1·0107	74·53	88·28	105·38	121·60	156·93	220·90
89·3°	0·9902	73·85	86·98	103·90	119·93	154·73	217·20
					[α]		
0°	1·0680*	117·6	139·1	166·2	191·9	248·8	351·0
18·5°	1·0518	119·8	140·8	168·9	194·6	252·4	354·8
41·0°	1·0325	121·2	143·1	170·9	197·4	256·0	359·7
65·8°	1·0107	122·5	145·1	173·2	199·9	257·9	363·1
89·3°	0·9902	123·9	145·9	174·3	201·2	259·6	364·5

All Rotations are Negative. Density * by extrapolation.

Rotation of Nicotine used, $\alpha_g^{20} = -206 \cdot 1^\circ$

M.P. of Iso-butyl mesotartrate = 82°

Densities taken with a 1·5 ccs. pyknometer.

53. L.

Specific rotation of Iso-butyl d-tartrate

(A) In mixture

d-tartrate, p = 49·968

pyridine, p = 50·032

(B) In mixture,

d-tartrate, p = 23·301

dl-tartrate, p = 26·632 49·933

pyridine, p = 50·067

Temp.	$[\alpha]_g$.	Temp.	$[\alpha]_g$.
19·5°	+57·35	19·7°	+57·21
22·5°	56·34	22·6°	56·33
23·2°	56·09	23·5°	56·04
50·6°	48·32	72·8°	43·62
73·8°	43·32	74·2°	43·33
74·3°	43·23		

Whence

	$[\alpha]_g^{23\cdot 0}$	$[\alpha]_g^{74\cdot 0}$
in (A	+56·16	+43·28
in (B	+56·20	+43·37

The difference shown is extremely small: therefore,

experimentally, $S\frac{dA}{dA} = S\frac{lA}{dA}$.

Extent of Mutual Solvent Influence.

Nicotine and Ethyl d-Tartrate.

Temperature 0°

Nature of Mixture, nicotine,	p = 7·88°/o		p = 33·33°/		p = 60·19°/o	
Density of Mixture, found	1·2087		1·1621		1·1066	
calc.	1·2056		1·1505		1·0973	
$\sqrt[3]{\frac{d_f}{d_c}}$	1·0008		1·10033		1·0028	
Colour of light,	5461	4359	5461	4359	5461	4359
Calculated Rotation α, 100mm (if no volume change took place) Contributed by ester	+6·34	-2·31	+4·4	-1·6	+2·5	-0·9
Contributed by base	-19·15	-35·06	-77·3	-141·5	-133·2	-243·7
Total, A	-12·81	-37·37	-72·9	-143·1	-130·7	244·6
$B = A \times \sqrt[3]{\frac{\text{density found}}{\text{density calc.}}}$	-12·82	-37·40	-73·1	=143·6	-131·1	-245·3
Observed Rotation of mixture α_m, as found, C.	-5·44	-23·1	-52·3	-105·6	-112·5	-212·1
D = C - B (observed exceeds calculated by)	+7·4	+14·3	+20·8	+38·0	+18·6	+33·2

Temperature 100°

Nature of Mixture, Nicotine,	p = 7·88		p = 33·33		p = 60·19	
Density of Mixture, Found.	1·1093		1·0648		1·0154	
Calc.	1·1075		1·0577		1·0096	
$\sqrt[3]{\frac{d_f}{d_c}}$	1·10055		1·0022		1·0019	
Colour of light,	5461	4359	5461	4359	5461	4359
Calculated Rotation, α, 100mm (if no volume change took place).						
Contributed by ester	+15·63	+16·4	+10·8·	+11·3	+6·1	+6·5
Contributed by base	-18·11	-32·9	-72·9	-132·7	-125·7	-228·8
Total, A	-2·48	-16·5	-62·1	-121·4	-119·6	-222·3
B = A × $\sqrt[3]{\frac{\text{density found}}{\text{density calc.}}}$	-2·48	-16·5	-62·2	-121·7	-119·8	-222·7
Observed rotation of mixture, α_m, as found, C.	+0·85	-5·2	-53·6	-105·5	-111·5	-207·2
D = C-B (observed exceeds calculated by)	+3·33	+11·3	+8·6	+16·2	+8·3	+15·5

The Densities of the Solutions of

(i) *iso*-butyl d-tartrate
(ii) *iso*-butyl l-tartrate

in Menthyl Acetate.

55. Menthyl acetate was prepared by the treatment of l-menthol with acetyl chloride (Tchugaeff, Ber. 1898, 31, 363). The rotation and density were in agreement with the results of Pickard and Kenyon (J.C.S. 1915, 107, 46).

The preparation and properties of the *iso*-butyl esters have already been detailed. (§ 50).

56. Method employed in Density Measurements.

A bath of some 16 litres capacity was fitted with an efficient stirrer and a large gas thermostat. At slightly above room temperature constancy to 0·01° was easily obtained. The pyknometer, of 31·3770 ml. capacity at 20°, was calibrated over the temperature range 18°-25°. Conductivity water which had just been boiled was used. Two separate sets of observations, the first of 7 and the second of 4 determinations, showed an excellent agreement.

The line which represented the true volume at various temperatures was found by the centre of gravity method (W.N. Bond, Probability and Random Errors, Arnold & Co., London 1935, p. 89 et seq.) In brief, the observational-data were divided into two groups, equal or differing only by one.

The centre of gravity of each group was found, and the junction of these two points gave the required line. While theoretically not so accurate as the tedious method of least squares, this procedure eliminated any personal error in estimating the best position of the line required. In eleven determinations, the greatest difference from the final line was only 0·0005g. or 1 in 62,750, while the error in the estimated capacity at 20° must be much less.

The weighings were carried out with standarised weights upon a good Bünge balance. The temperature of the balance case and the barometric pressure were observed at the time of each weighing, and the weights observed corrected to vacuo.

[It may be mentioned that a change of 1cm. in barometric pressure, if not allowed for, alters an observed density by 16 parts in the sixth place; while 1° change in temperature produces an error of 4 in the sixth place. In a series of determinations such errors might amount to more than 5 units in the 5th place in extreme cases].

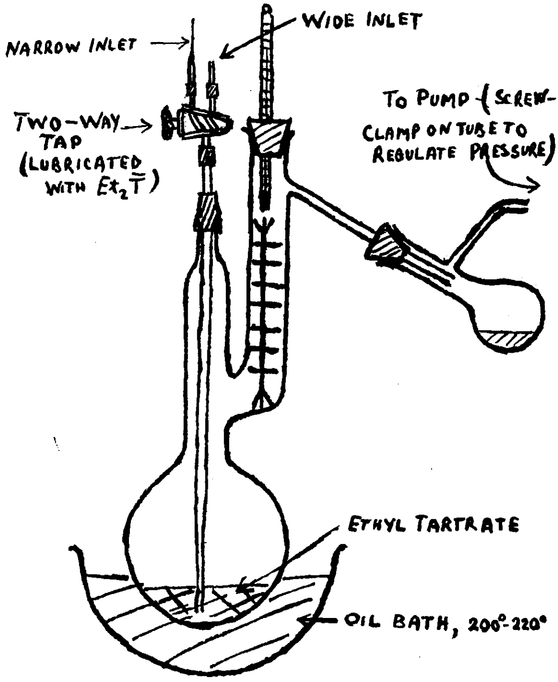
Precisely similar precautions were observed while determining the density of the menthyl acetate and the 8 solutions examined. In these cases the weight of the pyknometer contents at 20° were determined by the centre of gravity method from the observed data, and the density, d_4^{20}, then calculated.

In all 47 separate determinations were made, every one of which lay within 0·4 mg. (1 part in 73,000) of the lines drawn.

THE NATURE OF GREEN ETHYL TARTRATE.

1. <u>Historical</u>. Lowry and Cutter (J.C.S. 1922, <u>121</u>, 537) observed that a sample of carefully distilled ethyl tartrate showed a yellow colouration, which disappeared on standing. They were of the opinion that this colour indicated the purity, rather than the impurity, of the ester; and thought that it might be due to "reversible anhydride formation". In reference to this Patterson (J.C.S. 1922, 121, 1042) mentioned that a similar phenomenon had often been observed by him in samples of ethyl tartrate. It could be produced by the passage of air through the hot ester, and passed over with the first portion of the distillate upon careful fractionation. It was suggested that the colour (referred to by Patterson as green) was due to an oxidation product produced by the action of the air on the hot ester.

2. Various experiments were carried out with the object of concentrating the impurity as far as possible. Of these the most successful was by the alternate aeration and distillation of the ester. About 250g. of ethyl



ROUGH DIAGRAM – NOT TO SCALE

tartrate were heated to a temperature of 200° in the apparatus shown. Air at atmospheric pressure was sucked through the hot ester for some 5 minutes. The two-way tap was then turned to the narrow inlet: the pressure in the flask thus diminished, and a small first fraction, which was highly coloured (brownish-yellow) was very carefully distilled off. This process was repeated some 20 times, until about 150g. of distillate had been collected.

3. This was redistilled and a small quantity (7g.) of a colourless liquid was first collected (A). This, which boiled at about 30° at 20mm., was redistilled at atmospheric pressure. The temperature rose steadily to 180°, when decomposition set in. The fraction up to 140° was colourless, optically inactive, and gave a strong positive reaction with the fuchsine aldehyde reagent. It has not been further investigated.

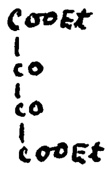
The 2nd fraction (B) of the main distillate consisted of 35g. of strongly coloured (greenish-yellow) material. Three further fractions (92g. in all) were distilled off; C, 25g, greenish; D, 25g, almost colourless; E, 42g, colourless.

Fraction B showed a rotation 15°/o less than that of the later fractions. It gradually lost most of its colour on standing for a month in a stoppered flask, though the colour returned on heating. The colour was immediately destroyed by the addition of a drop of water to 0·5c.cs. of the product.

4. The suggestion (for which I thank Professor G. T. Morgan) was investigated that glyoxal - which has a yellow-green colour in the monomolecular state - might be responsible for the colouration. It was found that when a 1°/o solution of glyoxal in colourless ethyl tartrate was heated a green colour developed, and that the colouration faded on cooling. The similarity of the phenomenon to that observed in the case of natural "green ethyl tartrate" led to the employment of 2.4.dinitrophenylhydrazine as a reagent: this proved to be the crucial point of the research.

5. The production of glyoxal itself from ethyl tartrate seemed, however, to be much less likely than the production of ethyl diketosuccinate (I). A sample of this compound was prepared from the sodium salt of dihydroxy-tartaric acid by the Fischer-Speier method (Anschütz & Parlatto, Ber. 1892, 25,1976). In the homogeneous state it forms a red oil, but when added

I



$$\begin{array}{c} COOEt \\ | \\ CO \\ | \\ CO \\ | \\ COOEt \end{array}$$

in small quantity to pure ethyl tartrate a colour indistinguishable from that of fraction B was produced.

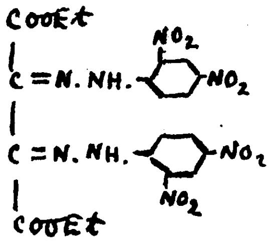
That the colouration was in fact due to the diketosuccinate was proved by the following experimental work.

6. To 4•84g. of "green ethyl tartrate" (fraction B) were added 10ccs. of absolute alcohol, followed by 70ccs. of Brady's reagent ($2\frac{1}{2}$°/o of 2.4 dinitrophenylhydrazine, $12\frac{1}{2}$°/o of sulphuric acid, 85°/o absolute alcohol, by weight). After a few moments an orange precipitate (1•11g.) was thrown down.

If this were wholly the 2.4 dinitrophenylhydrazone of ethyl diketosuccinate, the diketo ester would be present in fraction B to the extent of 8 - 9°/o. It must be remembered that the colour had been concentrated in this fraction by intensive aeration and careful distillation: in ordinary samples of coloured ethyl tartrate the proportion present must be much smaller.

The precipitate, which could be crystallised from glacial acetic acid or chloroform, formed lemon-yellow needles after five crystallisations from chloroform. On analysis C=42•57°/o, H = 3•25°/o, N = 20•12°/o.

II



$C_{20}H_{18}O_{12}N_8$, requires C = 42•69°/o
H = 3•22°/o
N = 19•94°/o

The first crystallisation contained also a small quantity of bright red crystals which could not be isolated for further examination. The chloroform solution was optically inactive.

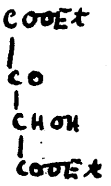
The synthetic specimen of ethyl diketosuccinate gave under the same circumstances an apparently identical product which had C = 42·55°/o, H = 3·34°/o, N = 19·76°/o, after two crystallisations from glacial acetic acid. Calc., as before, C = 42·69°/o, H = 3·22°/o, N = 19·94°/o.

This compound, the bis 2.4dinitrophenylhydrazone of diethyl diketosuccinate (II), had, unfortunately, no definite melting point. It decomposed gradually at 180°-200°.

In contrast to these results the action of 2.4 dinitrophenylhydrazine sulphate upon "glyoxal green" ethyl tartrate gave a precipitate which was darker in colour, practically insoluble in glacial acetic acid, and did not melt below 280°.

7. Astin & Riley (J.C.S. 1934, 845) have found that after oxidising ethyl tartrate with selenium dioxide ethyl ketohydroxysuccinate (III) could be isolated.

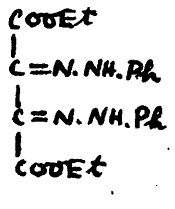
III



$$\begin{array}{l} COOEt \\ | \\ CO \\ | \\ CHOH \\ | \\ COOEt \end{array}$$

This compound, on treatment with aqueous phenylhydrazine acetate gave not the mono, but the bisphenylhydrazone (IV). It is therefore probable that if the ketohydroxysuccinate (III) were responsible for the colouration, it would

IV



$$\begin{array}{l} COOEt \\ | \\ C{=}N.NH.Ph \\ | \\ C{=}N.NH.Ph \\ | \\ COOEt \end{array}$$

give the bis-2:4 dinitrophenylhydrazone already isolated (II). Astin & Riley (loc. cit.) have, however, found that the ketohydroxysuccinate is colourless: it cannot therefore be the active agent in "green ethyl tartrate".

It remains, logically, possible that the hydrazone II might be derived from the colourless ketohydroxysuccinate III, while the colour of the green tartrate was due not to the diketo compound I, but to some entirely different substance. This seems to me extremely unlikely in view of the fact that a synthetic "green ethyl tartrate", indistinguishable in appearance from fraction B*, had been produced by the addition of the diketo compound to colourless ethyl tartrate.

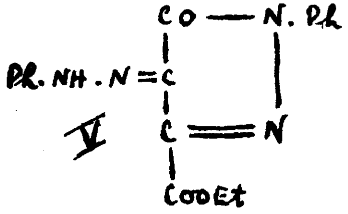
---

* In addition to the precipitation reactions mentioned, fraction B, synthetic "green ethyl tartrate" and ethyl diketosuccinate all reduced Fehlings solution. The last two results were somewhat unexpected, but they are plausible, since Fenton has found (J.C.S.1898,73, 480) that the salts of dihydroxy tartaric acid, e.g. $\left(\begin{matrix}\mathrm{COONa}\\ |\\ \mathrm{C(OH)_2}\\ |\end{matrix}\right)_2$, reduced Fehlings solution.

On the other hand the synthetic green tartrate and ethyl diketosuccinate gave negative results with the fuchsine aldehyde reagent, while the natural green tartrate gave a moderate positive result. This was probably due to incomplete separation from fraction A, which exhibited it strongly.

Colourless ethyl tartrate gave no reaction in either case.

8. As a corroboration of these experiments use was made of the formation of a pyrazole from the bis-phenylhydrazone of ethyl diketosuccinate, as observed by Anschutz & Parlatto (Ber. 1892, 25, 1979). Fraction B on treatment with phenylhydrazine acetate in aqueous solution, gave a pasty yellow precipitate, which, on boiling with glacial acetic acid, and then dilution with water, yielded an orange precipitate. After two crystallisations from alcohol the ring compound V was obtained as felted orange needles, identical with that described by Anschütz & Parlatto, Astin & Riley.


V

The 4-phenylhydrazone of ethyl 4.5-diketo-1-phenyl-4.5-dihydro-pyrazole-3-carboxylate.

M.P. 153°-154°.

The melting point was not depressed by admixture with a synthetic specimen prepared from ethyl diketosuccinate.

N, found = 16·61°/o, calc. = 16·67°/o.

Experiments with Homologous Esters.

9. Methyl tartrate and *iso*-butyl tartrate showed the phenomenon of colouration on the passage of air, though only a weakly coloured specimen of the former could be obtained, owing to decomposition.

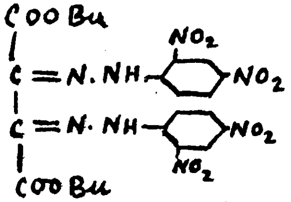
In the case of *iso*-butyl tartrate the colouration could be removed by crystallisation from benzene, and was concentrated to some extent in the tartrate obtained from the mother liquors. An attempt was made to concentrate the colouration in a manner similar to that used with the ethyl ester but without a rod and disc fractionating column. 60g. of *iso*-Butyl tartrate were aerated and distilled at 200°-210° about 12 times. On redistillation a small first fraction (0·5g.) of a colourless liquid separated, then 23g. of moderately "green" ester, and finally 25g. of colourless ester. The concentration was not so effective as in the case of the ethyl ester.

10. *Iso*-butyl diketosuccinate was prepared from sodium dihydroxy tartrate and *iso*-butyl alcohol by the method of Anschütz & Parlatto (loc. cit.). The substance obtained was a viscous red oil, B.P. 109°-112° at 3mm. It was not analysed as such since v. Auwers reported (Ber. 1918, *51*, 1121) that the corresponding ethyl diketosuccinate could not be obtained pure by distillation. Its identity was, however, amply confirmed by the formation of derivatives.

2:4 dinitrophenylhydrazine sulphate gave the bis 2:4 dinitrophenylhydrazone of di-*iso*-butyl diketosuccinate (vi), which was lemon yellow in colour, and decomposed about 180°. It crystallised from glacial acetic acid. (N, found = 18·10°/o

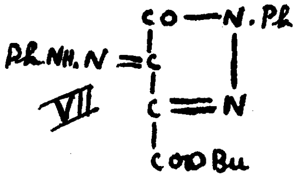
Calc. for

VI



N = 18·13°/o.

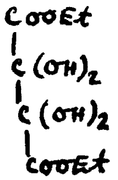
Phenylhydrazine acetate in boiling glacial acetic acid, followed by precipitation with water and crystallisation from EtOH, gave felted orange needles of, presumably, the pyrazole (vii) M.P. = 127°-128°. Found, C =65·78°/o, H = 5·60°/o, N = 15·16°/o.
Calculated C = 65·90, H = 5·55, N = 15·38°/o.

VII


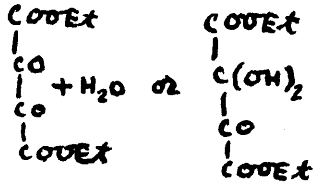
[It is possibly of interest to point out that whereas the plain phenylhydrazones were rapidly converted into the ring compounds by boiling acetic acid, the 2·4 dinitrophenylhydrazones were apparently entirely unaffected (normal combustion results after crystallisation from glacial acetic acid).]

The addition of water gave a colourless insoluble oil which, on evaporation at room temperature, yielded a white solid. This was crystallised from carbon bisulphide, M.P. 87°-90°.

Anschütz & Parlatto (loc. cit.) found that the colour of ethyl diketosuccinate disappeared on the addition of water: they attributed this to the formation of ethyl tetrahydroxysuccinate (viii), which was not, however, isolated in the solid state.

VIII

$$\begin{array}{l}COOEt\\ |\\ C(OH)_2\\ |\\ C(OH)_2\\ |\\ COOEt\end{array}$$

On the other hand, Wahl (Bull. Soc. Chim. 1908, [4] 3, 24) found that ethyl diketosuccinate lost its colour on standing, and deposited colourless crystals of the monohydrate (ix).

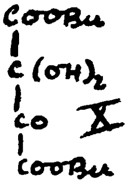
IX

$$\begin{array}{l}COOEt\\ |\\ CO\\ |\\ CO\\ |\\ COOEt\end{array} + H_2O \text{ or } \begin{array}{l}COOEt\\ |\\ C(OH)_2\\ |\\ CO\\ |\\ COOEt\end{array}$$

While it must be clearly understood that the white solid from *iso*-butyl diketosuccinate has not been rigorously purified owing to a shortage of material, yet it may be mentioned that the combustion results were closer to the theory for the ketohydroxy compound (x) than the tetrahydroxy compound (xi).

Found. C = 53·0°/o H = 7·0°/o

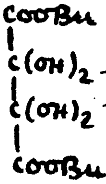
Calc. for (x) C = 52·1°/o H = 7·3°/o

Calc. for (xi) C = 49·0°/o h = 7·5°/o



$COOBu-C(OH)_2-CO-COOBu$

X



$COOBu-C(OH)_2-C(OH)_2-COOBu$

XI

When either this white solid, or the original *iso*-butyl-diketosuccinate were added to hot colourless *iso*-butyl tartrate, the colouration of the green ester was exactly imitated.

11. When "green *iso*-butyl tartrate" prepared by aeration was treated with 2.4 dinitrophenylhydrazine sulphate in alcohol a small quantity of the yellow bis-phenylhydrazone (vi) was produced. N, found = 18·37°/o, calc. for $C_{24}H_{26}O_{12}N_8$, 18·13°/o.

5g. of the green *iso*-butyl ester were boiled for 15 minutes with 0·5g. of phenylhydrazine acetate in glacial acetic acid. The orange coloured solid (mainly iso-butyl tartrate) obtained by precipitation with water was, after drying, crystallised from carbon disulphide, and the *iso*-butyl tartrate which separated filtered off. The mother liquor was evaporated and after two recrystallisations from methylated spirit, yielded a few mg. of orange felted needles, M.P. 127°-128°, identical with a synthetic specimen of the iso-butyl pyrazole (vii).

Phenylhydrazine acetate and pure iso-butyl tartrate under similar conditions also gave rise to a colouration (presumably due to decomposition of the acetate), but this latter was water soluble and on precipitation pure iso-butyl tartrate was recovered.

12. It may finally be mentioned that (i) In the case of every reaction of a green tartrate a control experiment with the colourless ester was also carried out: these were uniformly negative. (ii) The bis 2.4 dinitrophenylhydrazones presumably exist in syn-, anti- & amphi- forms [Cf. the three isomers found by Anschütz & Pauly (Ber. 1895, 28, 64) in the case of the phenylhydrazones], but the precise form of the compounds isolated is immaterial from the point of view of the present work.

13. Summary. It will be seen from the evidence just presented that the colouration produced by the aspiration of air through hot tartrate esters is almost certainly due to the oxidation of a small portion of the ester to the corresponding diketosuccinate: the reactions taking place are not, however, confined solely to this simple oxidation, and in particular a more volatile substance, probably aldehydic, is also produced.