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## The Terpenoid Amines. I. The Isomeric Thujylamines

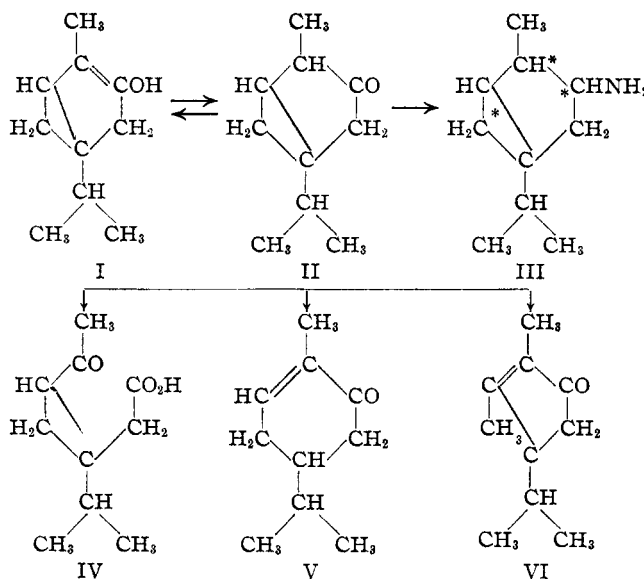
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The purpose of this investigation is to characterize the stereoisomeric amines derivable from the five important dicyclic systems represented by thujone, pinocamphone, fenchone, isofenchone and camphor. The various amines are being studied as to their possible value as resolving agents and as to their suitability as derivatives for the analytical determination of the parent terpenoid substances. The present paper is concerned principally with the isomeric thujylamines, the first family that has been fully characterized thus far.

**The Isomeric Thujylamines.**—Two so-called thujylamines were known when the present work was begun. The more fully characterized amine was first obtained by Semmler<sup>2</sup> by reduction of an oxime, m. p. 51.5°, prepared from dextro-rotatory  $\beta$ -thujone (tanacetone), the principal ketone of tansy oil. The preparation was repeated by Wallach<sup>3</sup> and by Tschugaëff<sup>4</sup> and the amine was reported to have b. p. 195°,  $[\alpha]_D +101^\circ$ .

It formed a sparingly soluble nitrate and very soluble hydrochloride. The second amine was contained in a mixture which Wallach<sup>5</sup> obtained by heating crude levorotatory  $\alpha$ -thujone from thuja oil with ammonium formate and hydrolyzing the resulting formyl derivative. The amine was stated to form a sparingly soluble sulfate but was not completely separated from stereoisomers or from the accompanying fenchylamine.

Wallach<sup>6</sup> later showed that the  $\alpha$ - and  $\beta$ -forms of thujone (II) are interconvertible in the presence of either alkaline or acidic reagents, presumably through the common enol (I). The  $\beta$ -form predominates at equilibrium. Both forms yield the same dextrorotatory thujaketonic acid (IV) upon oxidation. Hence the two thujones have the same configuration except for an interchange of H and CH<sub>3</sub> on the upper ring carbon. Wallach also demonstrated the isomerization of both thujones, by heating with strong acids, into *dl*-carvotanacetone (V) and the so-called *dl*-isothujone (VI).



These transformations were of primary importance for the proposed preparation of the thujylamines (III), which it was hoped to accomplish on a large scale by heating the thujone fraction of thuja oil with ammonium formate-formamide reagent. Although this fraction (b. p. 196–200°,  $\alpha_D -18^\circ$ ) consists largely of  $\alpha$ -thujone, together with some levorotatory fenchone, the  $\alpha$ - $\beta$  isomerization undoubtedly would be induced by prolonged heating in the mildly alkaline reaction mixture and could result in the formation of all four of the diastereoisomeric thujylamines—one antipode from each pair. In addition it was possible that amines derived from *l*-fenchone, *dl*-carvotanacetone and *dl*-isothujone might likewise be formed under the conditions used.

Application of this process, followed by alkaline hydrolysis of the crude formyl derivative, actually gave 55–60% yields of mixed amines, b. p. 193–202°,  $\alpha_D +23^\circ$ . This material was then converted to salts with a variety of acids and these were gradually and completely separated by prolonged fractional crystallization. In this way there were finally obtained five distinct amines for which the principal properties are given in Table I.

(1) Constructed from a thesis submitted by H. L. Dickison in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Vanderbilt University.

(2) Semmler, *Ber.*, **25**, 3343 (1892).

(3) Wallach, *Ann.*, **286**, 91 (1895).

(4) Tschugaëff, *Ber.*, **34**, 2276 (1901).

(5) Wallach, *Ann.*, **272**, 109 (1893).

(6) Wallach, *ibid.*, **336**, 247 (1904).

TABLE I  
 PROPERTIES OF THE AMINES

Amine	B. p., °C.	$\alpha_D^{25}$ <sup>a</sup>	Characteristic salts	M. p., benzoyl deriv., °C.
A	199.6	+27.80°	Sulfate- <i>p</i> -Toluene-sulfonate	73.0
B	193.4	+94.94°	Nitrate-Acid oxalate	131.5
C	196.7	-14.15°	Sulfate-Normal oxalate	94.5
D	202.2	-22.07°	<i>l</i> -Malate-sulfate	Glassy
E	195.3	+22.19°	<i>d</i> -Mandolate- <i>l</i> -Malate	90.2

<sup>a</sup> Rotation for 1 dm. without solvent.

The amine E was identified as (+)-fenchylamine, which had been partially characterized previously. The absence of optically inactive amines excluded the presence of amines derived from *dl*-carvotanacetone or *dl*-isothujone. The four remaining amines were therefore probably the theoretically possible thujylamines.

In a supplementary series of experiments, undertaken in an effort to correlate two of these amines with  $\beta$ -thujone, pure crystalline  $\beta$ -thujoneoxime, m. p. 53°, was reduced with sodium and alcohol and the product converted to salts and fractionated. In this way there were obtained 83.7% of an amine identical with B above, 6% identical with A and 4% identical with D. Aside from a trace of C, no other amines were present. These results confirmed the identification of the four thujylamines and indicated with considerable certainty that A and B were derived from  $\beta$ -thujone while the small amounts of C and D were derived from  $\alpha$ -thujone, whose oxime must have been formed by an inversion occurring during the reduction.

When this work was practically complete, there appeared a paper by Short and Read<sup>7</sup> dealing in part with two thujylamines. One of these, which these authors named *d*-isothujylamine ( $\alpha_D^{12}$  +94.82°), likewise was obtained by reduction of  $\beta$ -thujoneoxime, m. p. 53°, and is clearly identical with the less pure amine previously prepared in the same way by Semmler,<sup>2</sup> Wallach<sup>3</sup> and Tschugaeff<sup>4</sup> and with the amine B described above. The other amine, which was named *l*-thujylamine ( $\alpha_D^{13}$  -24.32°), was obtained by reduction of the crude liquid oxime of  $\alpha$ -thujone and purification through the hydrochloride. This amine was probably present in the impure preparation of Wallach and is identical with the amine D described above. Amines corresponding to A and C were not described.

(7) Short and Read, *J. Chem. Soc.*, 2016 (1938).

In view of the constants and relationships that have now been established for the entire group of four amines, it would seem advantageous to systematize their nomenclature. All four amines as well as both thujones have the same configuration at the junctions of the two rings and hence may be regarded as belonging to the same configurational series. It will not be possible to decide whether this is the *d*- or the *l*-series until a suitable derivative can be correlated with some substance of known configuration. However, in order to name the four diastereoisomers in each series it is proposed that the prefixes  $\alpha$ - and  $\beta$ -, which have long been used for the two natural thujones, be retained in the names of the derived pair of amines and that the prefix iso- be assigned provisionally to that member of each pair which has the higher numerical rotatory power. With the addition of the sign of rotation, the amines A and B then become (+)- $\beta$ -thujylamine and (+)-iso- $\beta$ -thujylamine, respectively, while C and D become (-)- $\alpha$ -thujylamine and (-)-iso- $\alpha$ -thujylamine, respectively. These names are used in the remainder of this paper.

**Characterization of the Amines.**—The four thujylamines and also fenchylamine have been characterized rather completely as free amines and as salts and other derivatives. The most important data are recorded in the Experimental part. In each instance some six or seven of the most readily crystallizable salts were prepared from each amine and the crystal habit, solubility, rotatory power and other constants were carefully determined. It is expected that, should any of the amines be encountered again in other parts of the present program or by other workers, it should be possible to separate and recognize them readily by reason of their sharply distinctive properties.

**Application as Resolving Agents.**—This portion of the program has been studied thus far only incidentally to the separation of the isomeric amines, in the course of which *dl*-mandelic acid and *dl*-malic acid were employed. It was found that *dl*-mandelic acid was resolved readily by either (+)- $\beta$ -thujylamine or (-)- $\alpha$ -thujylamine and that *dl*-malic acid was resolved by (-)-iso- $\alpha$ -thujylamine. Also both of these acids were readily resolved by (+)-fenchylamine. Preliminary experiments have shown further that all of these amines form well crystallized salts with several other types of organic acids and it is ex-

pected that various other resolutions can be carried out. Work is being continued in this direction.

### Experimental

**$\alpha$ -Thujone.**—This was obtained in the crude state by distilling commercial oil of *Thuja occidentalis*,  $\alpha_D -12.8^\circ$ , through a jacketed 60-cm. Vigreux column. The fraction b. p. 196–199° (745 mm.), 78–82° (12 mm.),  $\alpha_D^{25} -18^\circ$  ( $l = 1$ ), was used for the Leuckart synthesis of amines. This fraction (55% of the oil) contained also considerable levorotatory fenchone. Pure  $\alpha$ -thujone is reported<sup>7</sup> to have  $\alpha_D^{18} -19.94^\circ$ .

**$\beta$ -Thujone.**—This was obtained similarly from oil of tansy,  $\alpha_D^{25} +39^\circ$ . The fraction b. p. 80–82° (12 mm.),  $[\alpha]_D^{25} +59.7^\circ$  ( $c = 4$ , ether) was used to prepare the oxime. This fraction (38% of the oil) contained also some  $\alpha$ -thujone and levorotatory camphor. Pure  $\beta$ -thujone is reported to have  $\alpha_D^{25} +72.46^\circ$  ( $l = 1$ ),  $[\alpha]_D +76.16$  in ether<sup>8</sup> and  $[\alpha]_D +77.45^\circ$  in hexane.<sup>8</sup>

**$\beta$ -Thujoneoxime.**—Crude  $\beta$ -thujone (55 g.), hydroxylamine hydrochloride (28 g.) and sodium acetate trihydrate (60 g.) were dissolved in 85% ethanol (600 cc.) and allowed to remain overnight. It was hoped that mild conditions would minimize the oximation of camphor. The alcohol was evaporated and the liquid oxime extracted with benzene and distilled. The principal fraction (65%), b. p. 117–118° (6 mm.),  $[\alpha]_D^{25} +82^\circ$  ( $c = 4$ , methanol), largely solidified after several days. The liquid portion smelled strongly of camphor. The solid was drained by suction and redistilled with rejection of a small forerun. After solidification this process was repeated on the product. The oxime then had m. p. 53°,  $[\alpha]_D^{25} +105.3^\circ$  ( $c = 4$ , methanol). Short and Read<sup>7</sup> report  $[\alpha]_D^{15} +98.14^\circ$  ( $c = 2$ , ethyl alcohol). The observation of these authors that the crystalline oxime could not be made satisfactorily from fractions containing considerable (liquid)  $\alpha$ -thujoneoxime was confirmed. Repeated distillation of material with specific rotation  $+45^\circ$  or less produced only slight enrichment of  $\beta$ -thujoneoxime in the higher boiling fractions. In this connection it was found that oximation of  $\beta$ -thujone in the presence of alcoholic pyridine<sup>10</sup> gave a non-crystallizable liquid of low dextro-rotation. Partial isomerization of the  $\beta$ - to the  $\alpha$ -configuration apparently occurs readily under these conditions.<sup>11</sup>

**Leuckart Synthesis of Mixed Thujylamines.**—Crude  $\alpha$ -thujone (537 g., 3.53 moles) and solid ammonium formate (895 g., 14.2 moles) were heated in a 2-l. flask equipped with an automatic separator arranged to reject the distilled aqueous ammonium carbonate solution and return the ketone. The mixture, which darkened considerably, became homogeneous after two hours and was then heated at 175–185° for seven hours longer. The heating period was purposely made somewhat shorter than usual with the hope that the less reactive fenchone would be incompletely converted. The mixture of crude formyl

derivatives, unchanged ketone and condensation products was extracted with benzene and hydrolyzed by refluxing for eight hours with 285 g. of sodium hydroxide in 3 l. of 85% alcohol. A little water was then added to dissolve sodium formate and most of the alcohol distilled through a long column. The crude amine was then distilled with steam, cautiously neutralized with cold, dilute hydrochloric acid and extracted with benzene to remove neutral volatile substances. The amine was then liberated with alkali, extracted and dried. The benzene was removed through an efficient column and the amine then distilled through a short column. The mixed amines weighed 314 g. (58% yield) and had b. p. 195–201°,  $\alpha_D^{25} +22.53^\circ$  ( $l = 1$ ),  $d_4^{25}$  0.880,  $n_D^{25}$  1.4615.

The volatile neutral material (45 g.) was examined briefly. The main fraction, b. p. 69–75° (12 mm.), had  $\alpha_D^{25} -40.2^\circ$  ( $l = 1$ ) and smelled strongly of fenchone. The non-volatile condensation products remaining after the steam distillation were not examined.

Several additional runs were made as described above, or by substitution of an equivalent amount of 95% formamide for the ammonium formate, with substantially similar results. In preliminary experiments<sup>12</sup> attempts were made to hydrolyze the formyl derivatives with 20% hydrochloric acid in the usual way. In one experiment brief heating, followed by isolation of the amine as described above, gave a 45% yield of mixed amines having  $\alpha_D^{25}$  about  $+15^\circ$ . With longer heating the yield was much smaller. A somewhat similar result was observed by Short and Read.<sup>7</sup> When purified amine, obtained by alkaline hydrolysis, was neutralized exactly with dilute aqueous hydrochloric acid, the solution at once acquired a violet color. This rapidly deepened and changed to black on long standing or brief heating and much of the amine could not be recovered. No similar coloration or decomposition was noted when other acids were used, but care was always taken in the later work to avoid any excess of strong acid. The amine mixture obtained by acid hydrolysis was not used for the experiments described below.

**Fractional Separation of Mixed Amines.**—The combined product of several runs (650 g., b. p. 193–200°,  $\alpha_D^{25} +23.0^\circ$ ,  $n_D^{25}$  1.4650) was separated eventually by the fractional crystallization of a variety of salts. The principal steps in this long and tedious process are outlined below. Full descriptions of the various salts and amines are reserved for a later section.

The mixture was first subjected to a preliminary fractionation as sulfates. The amine was combined with slightly less than the amount of acid calculated for the normal salt in 2 liters of hot water. The dense crystal mass was filtered after cooling and then heated with 500 cc. of water and again filtered after cooling. The amine (270 g.) recovered from these two filtrates was called Fraction IV. The crystalline portion was then boiled with three successive 1-liter portions of water and the solutions filtered at 60° from undissolved solid. The latter was called Fraction I. The warm filtrates on cooling gave crystalline crops. These were combined into Fraction II and the filtrates into Fraction III.

The sulfate fraction I was found to yield almost com-

(8) Mohler and Lohr, *Helv. Chim. Acta*, **20**, 1183 (1937).

(9) Prepared by Mr. Robert Shirey, M.A. Thesis, Vanderbilt University, 1937.

(10) Bachmann and Boatner, *This Journal*, **58**, 2097 (1936).

(11) Bachmann and Barton, *J. Org. Chem.*, **3**, 300 (1938).

(12) Dickison, M.A. Thesis, Vanderbilt University, 1936.

pletely pure amine A, subsequently called (+)- $\beta$ -thujylamine. The very sparingly soluble sulfate was recrystallized in portions from large volumes of water. The amine was then recovered and converted to the *p*-toluenesulfonate, which could be recrystallized more conveniently. The pure salt (195 g.) had  $[\alpha]^{25}_D +27.91^\circ$ . The amine (5.5 g.) recovered from the final mother liquor was combined with that from Fraction II.

Fraction II was converted to the amine (90 g.) and this to the *p*-toluenesulfonate. Brief fractionation gave 20 g. more of the *p*-toluenesulfonate of amine A and mother liquors from which the mixed amines were recovered. Fraction III was also converted to the amine (168 g.) and this to the nitrate. Fractionation gave 24 g. of a characteristic nitrate,  $[\alpha]^{25}_D +70.48^\circ$ , of the amine B, subsequently called (+)-iso- $\beta$ -thujylamine. The residual amine was recovered from the mother liquor and combined with that recovered from Fraction II.

The combined amines were then converted to mandelates by the use of *dl*-mandelic acid. Prolonged fractionation of the crystalline portion finally gave two apparently homogeneous fractions, (a) 65 g. having  $[\alpha]^{25}_D +23.4^\circ$  and (b) 82 g. having  $[\alpha]^{25}_D +1.3^\circ$ . Actually, neither fraction proved to be uniform. The amine recovered from the portion (a) on fractionation as nitrate gave more of the amine B, and the soluble portion of the nitrate series, on conversion to sulfate, gave a new, rather sparingly soluble sulfate having  $[\alpha]^{25}_D +3.47^\circ$ . Alternate crystallization as nitrate and sulfate gave exclusively 14.5 g. of amine A and 16.5 g. of the new amine C, subsequently called (–)- $\alpha$ -thujylamine.

The crystalline mandelate fraction (b) yielded an amine which was then converted to the malate by means of *dl*-malic acid. It was found that the principal constituent resolved *dl*-malic acid, giving a sparingly soluble acid *l*-malate,  $[\alpha]^{25}_D -14.73^\circ$ . In order to obtain the maximum amount of this salt the *dl*-acid was taken in twice the equivalent amount so that at least one equivalent of the *l*-acid was present. The mother liquor gave an amine consisting almost entirely of the amine A. Alternate fractionation as the *p*-toluenesulfonate and malate gave 7 g. of A and 35 g. of the new amine D, subsequently called (–)-iso- $\alpha$ -thujylamine.

The mother liquors of the original mandelate series (containing the unseparated remainder of fractions II and III) gave an amine which was then combined with an excess of *dl*-malic acid. Fractionation gave a small amount of a crystalline malate which was distinctly different from that of the amine D, and a very soluble portion remaining in the mother liquors. A similar behavior had been observed in the meantime with certain parts of Fraction IV (see below). The two malate series were therefore combined and their further fractionation is described later. The crystalline malate proved to be the acid *l*-malate of a fifth amine E, subsequently identified as (+)-fenchylamine.

Since the amines from the sulfate fraction IV distilled over a moderate range, this material was separated into four sub-fractions, (a), (b), (c) and (d), in that order of decreasing volatility. These fractions were examined separately while some of the work described above was still in progress. The fraction (a) (18.3 g.) was combined

with *dl*-malic acid and yielded a little of the crystalline malate of E and mother liquors containing very soluble malates. The amine was recovered from the mother liquors and later converted to oxalates. The fraction (b) (76 g.) was combined with *dl*-mandelic acid and yielded a small crystalline crop. The amine recovered from this was further fractionated as nitrate and gave more of the nitrate of amine B already described. The amines in the mother liquors of the mandelate and nitrate were then combined with *dl*-malic acid. Fractionation gave 36 g. more of the *l*-malate of D. The amines in the mother liquors were later converted to oxalates.

The fraction (c) (144.2 g.) was converted to the *d*-tartrate. The crystalline portions of this series could not be obtained uniform. The amine was therefore recovered from it and fractionated alternately as malate and nitrate. This gave more of the pure *l*-malate of D and the nitrate of B. The amines in the tartrate mother liquors were also combined with *dl*-malic acid and the crystals thus obtained were combined with similar material from the foot of fractions II and III and from IV (a). Fractionation gave 60 g. of the pure acid *l*-malate of (+)-fenchylamine. This salt has no observable rotation, apparently because the rotatory effect of each ion is cancelled. The salt was identical with that prepared from the pure amine and pure *l*-malic acid. This acid had therefore been resolved by fenchylamine.

The amines remaining in the mother liquors of the malate series were combined with similar material already mentioned and with IV (d) (32 g.). This material (all that remained of the original mixture) was then fractionated as oxalates. This gave 55 g. of the pure acid oxalate of B and 36 g. of less pure oxalate of D. The latter was purified by conversion to the *l*-malate. The amines in the mother liquors of the oxalate and malate (about 7 g.) were further separated into small additional amounts of the salts already described. No trace of any other amine was discovered.

In summary, there were obtained as pure amines or salts 137.5 g. of A, 54 g. of B, 34.9 g. of C, 54 g. of D, and 53.6 g. of E. The total (334 g.) is slightly over 50% of the original mixture. With the information now in hand concerning the salts it would undoubtedly be possible to separate a similar mixture much more systematically and with very little loss.

**Amines from  $\beta$ -Thujoneoxime.**—The oxime already described (33.8 g.) was reduced in 550 cc. of absolute alcohol by rapid addition of 47 g. of sodium. This process gave 28.6 g. (92%) of an amine mixture of b. p. 193–195°,  $[\alpha]^{25}_D +75.58^\circ$  ( $c = 4$ , benzene),  $+93.94^\circ$  ( $c = 3.7$ , ethanol). The entire amount was converted to nitrates and brief fractionation gave 32.4 g. of the characteristic nitrate of amine B. The amine recovered from the mother liquors then gave in succession 1.5 g. of the oxalate of B, 3.6 g. of the *p*-toluenesulfonate of A and 2.5 g. of the *p*-toluenesulfonate of D. The residual amine (1.3 g.) was converted to oxalates. Because of the small amount, pure salts were not obtained from this portion but the rotation data and crystalline appearance of the various fractions indicated a trace of the amine C and small additional amounts of A and D. From the weights of all of the salts it was calculated that the original mixture con-

TABLE II  
DERIVATIVES OF THE AMINES

Amine	Derivative	Hydrate <sup>a</sup>	Appearance	M. p., °C.	$[\alpha]^{25}_D$ <sup>b</sup>	Solubility <sup>d</sup>
A	Benzoyl	...	Prisms	73-75	+91.44	...
	Sulfate	...	Hexag. plates	242 d.	+42.77	0.95
	<i>p</i> -T. S. <sup>e</sup>	...	Thick needles	194.7	+27.91	1.07
	H-Oxalate	Mono	Long needles	d.	+36.10	2.08
	Nitrate	Hemi	Massive plates	105	+35.97 <sup>c</sup>	79.30
	<i>d</i> -Mandelate	Di	Thick prisms	80-115	+82.59 <sup>c</sup>	3.96
	<i>l</i> -Mandelate	Mono	Fine needles	120-128	-29.52 <sup>c</sup>	2.84
B	Benzoyl <sup>h</sup>	...	Needles	131.5	+87.74 <sup>g</sup>	...
	H-Sulfate	Mono	Cubes	153 d.	+55.25 <sup>c</sup>	23.4
	<i>p</i> -T. S. <sup>e</sup>	...	Long needles	170-171	+41.60	3.24
	H-Oxalate	Mono	Long needles	167	+62.50	1.26
	Nitrate	...	Prisms	176.9	+70.48	3.04
	?-Malate	?	Irregular	160	+49.84	V. s. <sup>i</sup>
	Perchlorate	...	Prisms	168	+55.47	V. s. <sup>i</sup>
C	Benzoyl	...	Plates	94.5	-12.16	...
	Sulfate	Tetra	Dull plates	243 d.	+ 3.47	1.74
	<i>p</i> -T. S. <sup>e</sup>	...	Glass	.....	.....	...
	N-Oxalate	...	Plates	200-201	.....	0.59
	Nitrate	...	Flat needles	150	+ 2.60	8.32
	H- <i>dl</i> -Malate	...	Fine needles	148.5	+ 1.73	11.50
	<i>d</i> -Mandelate	Mono	Needles	99.5	+65.23 <sup>c</sup>	2.97
D	Benzoyl <sup>h</sup>	...	Glass	.....	.....	...
	<i>p</i> -Nitrobenzoyl <sup>h</sup>	...	Needles	146.5	-51.25 <sup>j</sup>	...
	Sulfate	Mono	Scaly plates	263 d.	-16.66	1.67
	<i>p</i> -T. S. <sup>e</sup>	...	Long needles	198.6	-10.40	2.20
	N-Oxalate	...	Plates	235 d.	-12.37	0.80
	Nitrate	...	Long needles	159-160	-15.18	10.33
	H- <i>l</i> -Malate	...	Thick plates	186-187	-14.73	2.04
E	Benzoyl <sup>i</sup>	...	Plates	90.2	+24.43	...
	Sulfate	?	.....	.....	.....	V. s.
	<i>p</i> -T. S. <sup>e</sup>	Mono	Thick needles	188-189	+ 2.60	6.68
	H-Oxalate	...	Fine needles	165	+ 3.11	5.64
	Nitrate	Hemi	Rhombic plates	190 d.	+ 3.41	13.80
	H- <i>l</i> -Malate	...	Thick prisms	191-193	= 0.0	3.45
	<i>d</i> -Mandelate	...	Thick prisms	190.3	+60.8	2.63

<sup>a</sup> Anhydrous unless otherwise indicated. <sup>b</sup> Values for salts in water; for benzoyl derivatives in methanol. <sup>c</sup> Values taken on the hydrated form. <sup>d</sup> Expressed in grams per 100 g. water at 25 ± 0.5°. <sup>e</sup> *p*-Toluenesulfonate. <sup>f</sup> Rotation value in chloroform. <sup>g</sup> Also  $[\alpha]^{25}_D$  +90.5° (*c* = 1, chloroform). <sup>h</sup> Compare Short and Read, Ref. 7. <sup>i</sup> Compare Wallach, Ref. 14. <sup>j</sup> Very soluble.

tained (at least) 6.0% of A, 83.7% of B, 4.0% of D and a trace of C. It may be noted that the previous separation and characterization of the various amine salts enabled the above separation to be carried out rapidly and almost quantitatively. The separation was facilitated considerably by the absence of fenchylamine.

**Characterization and Analysis.**—Each amine was isolated, in the order already mentioned, as an apparently uniform salt. This was recrystallized to constant properties and decomposed with alkali. The amine was extracted with benzene (sometimes after steam distillation) and distilled and characterized. In each instance the amine was then converted to another salt and the entire process repeated as a check. In no instance did this process or distillation at ordinary or reduced pressures produce any significant change in properties. The distillations under low pressures were made in a flask filled with glass wool with omission of the customary capillary

bubbler, and carbon dioxide was excluded as much as possible at all times.

Each pure amine was then converted to various salts and all of these that could be made to crystallize readily were purified and characterized. The properties thus observed were used as guides for the separation of the remaining mixture. The principal data and analyses are recorded in the following sections and in Table II. Additional data and details are recorded in the original thesis.

(+)-*β*-Thujylamine. (Amine A).—B. p. 199.6°<sup>13</sup> (750 mm.), 77.0° (12 mm.);  $n^{25}_D$  1.4654;  $\alpha^{25}_D$  +27.8° (*l* = 1);  $[\alpha]^{25}_D$  +51.27° (*c* = 3, ethanol), +35.31° (*c* = 5.6, benzene). The amine was purified and analyzed as normal sulfate and *p*-toluenesulfonate.

*Anal.* Calcd. for (C<sub>10</sub>H<sub>19</sub>N)<sub>2</sub>·H<sub>2</sub>SO<sub>4</sub>: SO<sub>4</sub>, 24.38.

(13) All temperatures in this paper were taken with reliable short range thermometers without further correction.

Found:  $\text{SO}_4$ , 24.33. Calcd. for  $\text{C}_{10}\text{H}_{19}\text{N}\cdot\text{C}_7\text{H}_5\text{SO}_4$ : N, 4.31. Found: N, 4.27.

(+)-**Iso- $\beta$ -thujylamine**. (Amine B.)—B. p. 193.4° (737 mm.), 76.8° (11 mm.);  $n_D^{25}$  1.4564;  $d_4^{25}$  0.860;  $\alpha_D^{25} + 94.94^\circ$  ( $l = 1$ );  $[\alpha]_D^{25} + 107.9^\circ$ ,  $+108.4^\circ$  ( $c = 1.6$ , ethanol),  $+103.6^\circ$  ( $c = 3.3$ , benzene). The amine was purified as nitrate and oxalate; analyzed as oxalate.

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{19}\text{N}(\text{COOH})_2$ : N, 5.76. Found: N, 5.76.

This amine has been partially described previously.<sup>2-4</sup> The constants recorded above agree closely with those given for an amine named *d*-isothujylamine by Short and Read.<sup>7</sup>

(-)- **$\alpha$ -Thujylamine**. (Amine C.)—B. p. 196.7° (756 mm.), 77.6° (12 mm.);  $n_D^{25}$  1.4590;  $\alpha_D^{27.5}$   $-14.15^\circ$  ( $l = 1$ );  $[\alpha]_D^{25} - 1.41^\circ$  ( $c = 6.3$ , ethanol),  $-13.25^\circ$  ( $c = 5.8$ , benzene). The amine was purified as sulfate and normal oxalate; analyzed as sulfate.

*Anal.* Calcd. for  $(\text{C}_{10}\text{H}_{19}\text{N})_2\text{H}_2\text{SO}_4$ : N, 6.93. Found: N, 6.87.

(-)-**Iso- $\alpha$ -thujylamine**. (Amine D.)—B. p. 202.2° (748 mm.), 86.2° (15.5 mm.), 81.1° (12 mm.);  $n_D^{25}$  1.4640;  $\alpha_D^{27}$   $-22.07^\circ$  ( $l = 1$ );  $[\alpha]_D^{25} - 23.29^\circ$  ( $c = 2.6$ , ethanol),  $-26.92^\circ$  ( $c = 2.3$ , benzene). The amine was purified as *l*-malate and *p*-toluenesulfonate; analyzed as normal oxalate and acid malate.

*Anal.* Calcd. for  $(\text{C}_{10}\text{H}_{19}\text{N})_2(\text{COOH})_2$ :  $(\text{COOH})_2$ , 22.7. Found:  $(\text{COOH})_2$ , 22.6. Calcd. for  $\text{C}_{10}\text{H}_{19}\text{N}\cdot\text{C}_4\text{H}_5\text{O}_6$ : N, 4.88. Found: N, 4.55.

The properties of this amine agree closely with the one named *l*-thujylamine by Short and Read.<sup>7</sup>

(+)-**Fenchylamine**. (Amine E.)—B. p. 195.3° (730 mm.), 73.4° (11.5 mm.);  $\alpha_D^{27}$   $+22.19^\circ$  ( $l = 1$ );  $[\alpha]_D^{25} + 25.89^\circ$  ( $c = 5$ , ethanol),  $+19.11^\circ$  ( $c = 4.6$ , benzene). This amine was purified as *l*-malate and *d*-mandelate; analyzed as malate.

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{19}\text{N}\cdot\text{C}_4\text{H}_5\text{O}_6$ : N, 4.88. Found: N, 4.85.

This amine and its antipode have been partially characterized by Wallach.<sup>14</sup> Further description of the various isomeric fenchylamines is reserved for a later paper.

**Resolution Experiments.**—It was observed in the course of the separation of the amines that (+)- $\beta$ -thujylamine resolved *dl*-mandelic acid. The process was therefore studied on a larger scale with pure amine. Fractionation

of the salts with the *dl*-acid gave alternate crops with distinctive rotations and crystalline appearance. Both salts were purified quickly by combining similar crops and recrystallizing systematically. The principal constants of these salts already have been given in Table II.

The resolution of *dl*-mandelic acid with (-)- $\alpha$ -thujylamine was studied similarly. The less soluble salt (-B + A type) was purified readily and had  $[\alpha]_D^{25} + 65.23^\circ$  ( $c = 1.2$ , water). The more soluble salt was not purified completely.

Attempted resolution of *dl*-mandelic acid with (+)-iso- $\beta$ -thujylamine gave three successive crystalline crops having specific rotations  $+68.9$ ,  $+61.9$  and  $+48.2^\circ$ , respectively. Since it appeared that prolonged fractionation would be necessary for the resolution, the attempt was abandoned. Somewhat similar results were obtained with (-)-iso- $\alpha$ -thujylamine, except that the fractions were more distinctly different. This resolution has not been completed.

The resolution of *dl*-malic acid with (-)-iso- $\alpha$ -thujylamine was employed in the original separation of this amine from the mixture. In separate experiments the pure amine was combined with two equivalents of *dl*-malic acid. Fractionation readily gave a good yield of the pure acid *l*-malate,  $[\alpha]_D^{25} - 14.78^\circ$  ( $c = 4$ , water). The mother liquor contained principally *d*-malic acid. The identity of this salt was confirmed by its preparation from the amine and pure *l*-malic acid. The much more soluble *d*-malate was not purified. The malates of the other three thujylamines were too soluble for convenient crystallization and the resolutions were not studied.

The use of active fenchylamines as resolving agents has shown that they are probably the most convenient agents yet employed for the resolution of *dl*-malic acid and *dl*-mandelic acid. This work will be described in a later paper.

## Summary

The four diastereoisomeric thujylamines derived from the natural thujones have been prepared and their separation from each other and from fenchylamine described. All of these amines have been characterized fully. A preliminary study of the use of these amines as resolving agents is reported.

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(14) Wallach, *Ann.*, **263**, 140 (1891).