

STUDIES IN THE SANTALOL SERIES. PART I. SEPARATION OF THE SANTALOLS AND THE SANTALENES

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The alcohols, α - and β -santalols have been isolated from East Indian sandalwood oil and their physical constants determined. The process has been treated mathematically and several graphs and tables drawn in this connection furnish now an easy method of finding out the composition of a sample of sandalwood oil. Both α - and β -santalene of a high degree of purity have also been obtained and the probable optical rotations of the pure compounds determined by mathematical calculations.

East Indian sandalwood oil, which is obtained from the heart of wood of *Santalum album*, contains near about fourteen chemical substances comprising alcohols, aldehydes, ketones, hydrocarbons, etc. (Simonsen, "Terpene." Vol. II, p. 544). The main bulk of the oil comprises two sesquiterpene primary alcohols ($C_{15}H_{24}O$), α - and β -santalols, and in fact they form almost the entire amount of the higher boiling fraction of the oil. The main constituents of the lower boiling fractions are two isomeric sesquiterpenes ($C_{15}H_{24}$), α -santalene and β -santalene. The other ingredients *viz.* acids, aldehydes, etc. form only a comparatively minor part (*cf.* Parts IV and V of this series).

It has been established through the classical researches of Semmler (*Ber.*, 1910, 43, 1893), Ruzicka (*Helv. Chim. Acta*, 1935, 18, 355) and Simonsen (*J. Chem. Soc.*, 1935, 309) that both α -santalol and α -santalene are tricyclic compounds possessing a long side-chain and an ethylenic linkage; whereas the corresponding β -compounds are bicyclic, containing two double bonds in their molecules.

The acidic, aldehydic and ketonic ingredients can be easily separated in the form of their derivatives. The separation of the main constituents of sandalwood oil *viz.* the two santalols and the two santalenes is, however, attended with difficulties and could not be successfully effected by earlier workers (Schimmel & Co. Report. 1910, Oct., p.113; Semmler, *Ber.*, 1910, 43, 445; Paolini and Divizia, *Atti. R. Acad. Lincei*, 1914, 23, 226).

The Hydrocarbons.

The boiling points of α - and β -santalene lie close to each other, the former boiling at $118^{\circ}/7$ mm. and the latter at 127° under the same pressure. The difficulty in separation is further augmented by the similarity of their general characteristics and when they are distilled, one comes invariably mixed up with the other isomeride. Moreover, β -santalene is a highly *l*-rotatory compound, whereas the α -isomeride has been shown by us to possess a feeble *d*-rotation (according to previous workers it is slightly *l*-rotatory, Schimmel & Co., *loc. cit.*). Evidently, even a trace of the highly *laevo*-rotatory β -compound affects the optical purity of its α -isomeride to a great extent and *vice versa*.

Alcohols.

What has been described about the properties of the hydrocarbons hold equally well in the case of the alcohols. Thus α -santalol is a feebly *d*-rotatory compound, b.p. 148°/5 mm. and the corresponding β -isomeride is a highly *l*-rotatory compound, b.p. 158°/5 mm.

Recently Simonsen has isolated the santalols (Simonsen, *loc. cit.*) in a pure state by repeated fractionations and has determined their physical properties, but, unfortunately, no exhaustive description is made about the details of this important separation. As we were in need of some pure α -santalol for comparison with our synthetic variety, we had to undertake the problem of separation of the two santalols as also of the two santalenes.

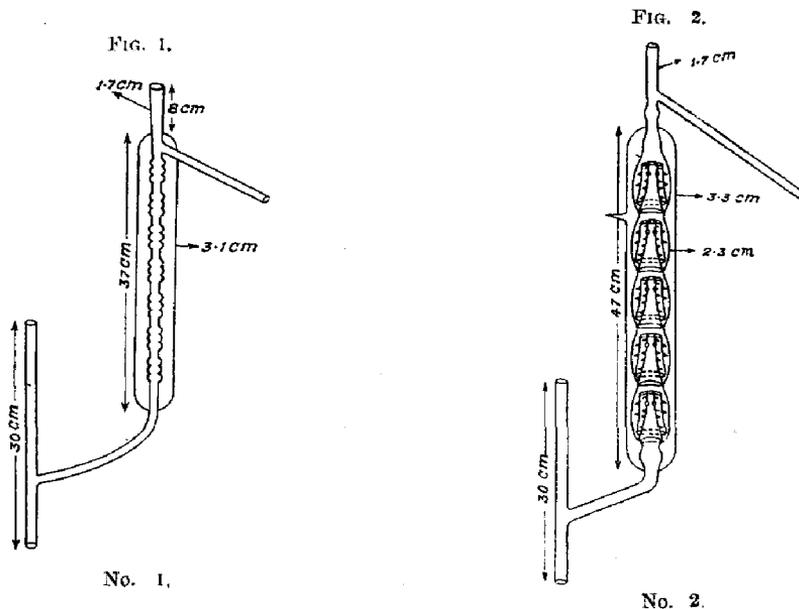
The separation of the santalenes is rendered even more difficult due to their presence in very small quantities (only 4 to 6%) in the sandalwood oil. Anyway, by repeated fractionations through two special types of fractionating columns, it has been possible to isolate α - and β -santalol in a state of absolute purity and their physical constants have been determined. As one of the Indian States (Mysore) at present commands the major supply of this commodity, the whole process has been exhaustively treated. Several graphs and tables drawn in this connection, by way of correlating the quantities of their ingredients with the unsaturation number and the corresponding optical rotations, furnish now an easy and a mechanical method of determining the composition of a santalol mixture in a more or less correct measure.

Samples of α - and β -santalene of about 90% purity have also been isolated. As the amount of substance at our disposal was not quite adequate, further purification beyond this limit was not possible; but our samples were purer than the samples of the hydrocarbons isolated by earlier workers. It has also been possible to determine the probable optical rotations of pure α - and β -santalene with the help of some mathematical calculations.

The course of separation was followed by a polarimeter and by measuring the amount of unsaturation with percamphoric acid (Milas and McAlevy, *J. Amer. Chem. Soc.*, 1933, 55, 349). Obviously the pure β -compound will have an unsaturation value of "Two", whereas that for the α -compound will be "One". By this method, the composition of a santalol or santalene mixture could be determined to a degree of reasonable accuracy.

For the actual process of separation two columns were used, one of which (No. 1) has been devised by Bradfield (*J. Soc. Chem. Ind.*, 1935, 54, 6r) and the other (No. 2) by us. The first one was primarily used in the case of the santalols and for the earlier fractionations of the santalenes; the final stages of the separation of these hydrocarbons being carried with the help of the second column. The special features of the columns are the outer jackets. In each case the space between the outer jacket and the inner tube was evacuated with the mercury diffusion pump to 10^{-6} mm. of mercury and sealed properly. The introduction of an outer jacket serves the purpose of a thermos flask and reduces the transference of heat due to

radiation to a minimum. The column No. 1 is particularly suitable for the fractionation of viscous liquids like the sesquiterpene alcohols; whereas the second one is

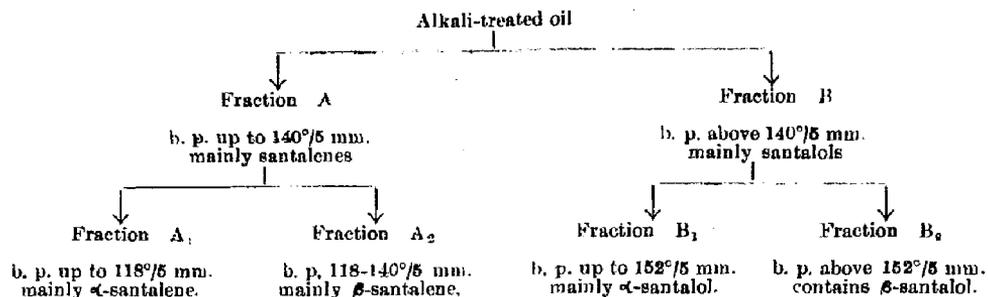


more effective for the fractionation of the less viscous and comparatively low boiling compounds like the hydrocarbons.

The rate of distillation was so regulated that only one drop of liquid distilled per second. For maintaining an inert atmosphere and particularly for facilitation of the stirring of the liquids, dry and pure carbon dioxide was drawn through the liquid under treatment. A metal-bath was used as the source of heat. The method of treatment which has been followed in this paper is expected to be helpful in the case of separation of ingredients of other essential oils. The fractionating columns used in this investigation may also be useful in other difficult separations.

EXPERIMENTAL

A sample of Government-certified sandalwood oil from the Mysore Sandalwood Oil Factory was saponified by boiling for $\frac{1}{2}$ hour with 3% alcoholic potash solution. The oil was precipitated by pouring into excess of water, extracted with ether and washed thoroughly with water to remove the last trace of alkali. After drying and removal of ether, the residual oil was subjected to vacuum distillation under 5 mm. pressure and divided into two fractions. The lower boiling fraction contained the santalenes and the higher boiling fraction contained the santalols. The two fractions were then further subdivided as shown below :



All the fractions A_1 , A_2 , B_1 , B_2 , were then repeatedly fractionated for the isolation of the pure substances and will be described separately and individually.

Isolation of α -Santalol.

Fraction B_1 was repeatedly fractionated at 5 mm. pressure and the portion coming just at $147-148^{\circ}/6$ mm. was collected; anything coming above and below this temperature being collected separately.

The gradually changing unsaturation numbers and the corresponding optical rotations of the same fraction, distilled repeatedly at $147-148^{\circ}/5$ mm. for 21 times, have been shown in Table I. It is evident that in the case of the santalols a constant boiling point does not necessarily mean that the distillates are identical.

The results have also been plotted graphically (Fig 3).

TABLE I

No of distillation.	Observed rotation in degrees α_{D}^{20}	Observed unsaturation number.	No. of distillation.	Observed rotation in degrees α_{D}^{20}	Observed unsaturation number.
1	-16.8	1.285	12	+4.0	1.05
2	-13.8	1.245	13	+4.8	...
3	-11.0	...	14	+5.4	...
4	-9.5	1.20	15	+6.1	1.02
5	-6.1	...	16	+6.62	...
6	-3.0	1.13	17	+7.2	1.01
7	-1.2	...	18	+7.8	...
8	0.0	...	19	+8.31	...
9	+1.0	1.08	20	+8.79	...
10	+2.1	...	21	+9.02	1.00
11	+3.15	...			

The two santalols show a tendency of coming over as a constant boiling mixture at $152^{\circ}/5$ mm. Great care should, therefore, be taken during the earlier period of fractionations.

The proportion of α - and β -santalol, in any arbitrary mixture, was calculated from the corresponding unsaturation number with the help of the following simple algebraic calculations :

Let in any mixture, percentage of α -santalol be x ,

Therefore, percentage of β -santalol should be $100-x$.

Now a β -santalol molecule³ contains two double bonds and α -santalol molecule contains one double bond.

Therefore, the total amount of unsaturation is proportional to $x \times 1 + (100-x)2$.

Therefore, the average unsaturation value which may be determined with percamphoric acid

$$U = \frac{x \times 1 + (100-x)2}{x + 100 - x}$$

On simplification x (percentage of α -santalol) = $200 - U$.

Percentage of β -santalol is obtained by difference.

The results correlating the relation between the unsaturation number and percentage of α -santalol-rich mixture have⁴ been shown in Table II.

TABLE II

No.	Unsaturation number.	α 5780.	Percentage unsaturation.	Percentage of α -Santalol from rotation.	Percentage of β -Santalol from unsaturation.	Percentage of β -Santalol from rotation.
1	1.285	- 16.8	71.5	69.6	28.5	30.4
2	1.246	- 13.8	75.5	73.11	24.5	26.8.9
3	1.20	- 9.5	80.0	78.16	20.0	21.85
4	1.131	- 3.0	86.9	85.79	13.1	14.21
5	1.08	+ 1.0	92.0	90.49	8.0	9.41
6	1.06	+ 4.0	95.0	94.1	5.1	5.9
7	1.021	+ 6.1	97.9	96.48	2.1	3.52
8	1.01	+ 7.2	99.0	97.77	1.0	2.23
9	1.00	+ 9.0	100.0	99.88	0.0	0.12

The results have been plotted graphically (Fig. 4.). In Table II the calculated results showing the relationship existing between the percentage and the corresponding optical rotations have also been tabulated; Landolt's law of mixture being applied for these calculations. The law states that if P_1 parts of a liquid of specific rotation $[\alpha_1]_D$ be mixed with P_2 parts of another liquid of $[\alpha_2]_D$ and if the specific rotation of the mixture be $[\alpha_m]_D$, then

$$[\alpha_m]_D = \frac{P_1[\alpha_1]_D + P_2[\alpha_2]_D}{P_1 + P_2}$$

In this investigation only pure samples of oil (without any solvent) were used in the polarimetric tube. It has actually been determined that rotation of pure α -santalol

is $\alpha_{5780} = +9.02$, and that of β -santalol $\alpha_{5780} = -76.10$. Therefore, applying these

FIG. 3.

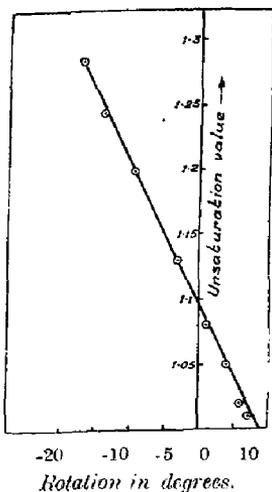


FIG. 4.

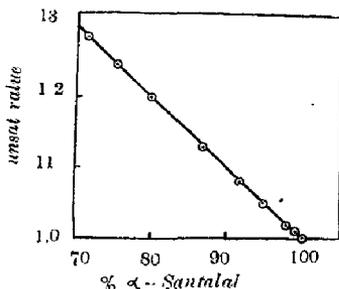
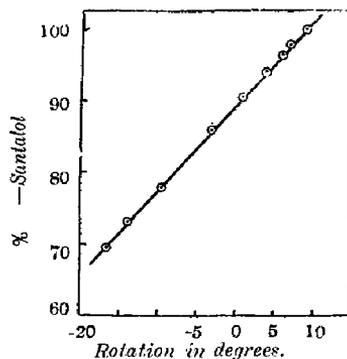


FIG. 5.



data in the above equation an approximate composition of a mixture can be easily calculated. These results have also been plotted graphically (Fig. 5).

Comparison of the Unsaturation-percentage and the Percentage-rotation Graphs.

For determining the composition of a santalol-mixture the unsaturation-percentage graph is more reliable. The composition, as determined from the percentage-rotation graph may not be entirely accurate due to two reasons: *viz.* (i) during the long course of distillation differential racemisation of the two santalols may take place; (ii) Landolt's law of mixture may not be accurate in case of substances containing hydroxyl groups, which have been shown by different workers to have a tendency towards association and inter-influence (Ramsay and Shields, *Z. physikal. Chem.*, 1893, 12, 431). The difference in the densities of the two santalols will also slightly affect the results. It is worth mentioning in this connection that in spite of the facts cited above, the results are found to be fairly accurate. It appears from Table II that a slight difference really exists between the results of composition as calculated from the unsaturation numbers and the corresponding optical rotations, the difference decreasing with the decreasing percentage of β -santalol. It is not improbable that the presence of the α - and β -variety together may have some slight inter-influence on the rotations of each other.

The unsaturation-percentage graph is of course free from these anomalies, the unsaturation number of a substance being very little affected under ordinary circumstances. From a study of these graphs it is now possible to determine the purity of

α -santalol samples isolated by earlier workers. Semmler's sample, having an optical rotation of $+1^\circ$, thus contained near about 10% β -santalol as impurity.

Properties of α -Santalol.—B.p. $148^\circ/5$ mm.; 145.4 mm.; $\alpha_{5780} = +9.02^\circ$; $\alpha_{5460} = +10.4^\circ$; $n_D^{25} = 1.5016$; $d_{25}^{25} = 0.977$; $[R_L]_D = 66.4$. Calc. $C_{15}H_{24}O \sqrt{1} = 65.93$. Exaltation is in conformity with the existence of a cyclopropane ring. Strychnine salt of hydrogen phthalate, m.p. 146 .

Isolation of β -Santalol.

Fraction B_2 was repeatedly fractionated through column No. 1 and the portion coming at $156-158^\circ/5$ mm. was collected. The unsaturation number and the corresponding polarimetric readings have been tabulated below (Table III). The optical rotation $\alpha_{5780} = -61.6^\circ$, and the corresponding unsaturation number "1.843" became constant after 19 distillations corresponding to 84.3% β -santalol. Pure β -santalol was then prepared from it by the application of chemical operations (Simonsen, *loc. cit.*, Paolini and Divizia, *loc. cit.*) as stated (*vide infra*).

TABLE III

No. of distillation,	Rotation in degrees α_{5780}	Unsaturation number.	No. of distillation.	Rotation in degrees α_{5780}	Unsaturation number.
1	-26.0	1.423	11	-53.63	...
2	-30.1	...	12	-55.0	1.761
3	-34.0	1.524	13	-58.3	...
4	-38.21	...	14	-57.41	...
5	-41.3	1.614	15	-68.3	1.805
6	-44.22	...	16	-59.0	...
7	-47.1	1.68	17	-59.7	...
8	-49.25	...	18	-60.6	...
9	-50.95	1.72	19	-61.6	1.843
10	-52.31	...			

The above results have been plotted graphically (Fig. 6) and the graph extended to a point indicating the unsaturation number "2", which is the value for that of pure β -santalol. The optical rotation corresponding to this point should be the rotation of pure β -santalol. In fact the value (-75°) thus obtained tallies fairly well with the value $\alpha_{5780} = -76.1^\circ$ actually determined.

Isolation of pure β -Santalol.—The impure β -santalol, obtained as above, was converted into acid phthalate in the usual way and this was then converted into the strychnine salt by boiling in alcoholic solution with the requisite amount of strychnine. The salt on fractional crystallisation and subsequent hydrolysis and

distillation furnished pure β -santalol having an unsaturation number "2" and $\alpha_{5780} = -76.1^\circ$.

As in the case of α -santalol, the relationship existing between the percentage proportion and unsaturation value has been shown in Table IV, and the results

FIG. 6.

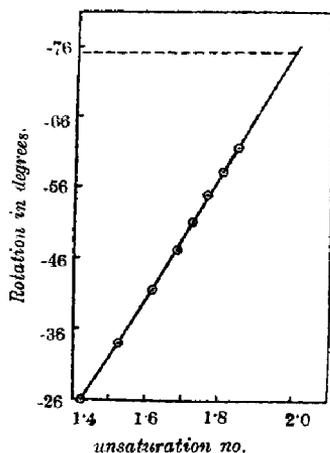


FIG. 7.

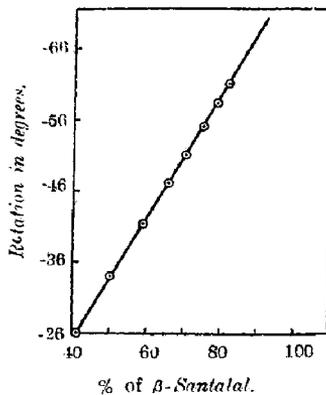
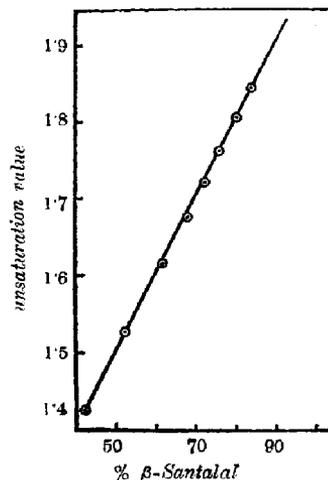


FIG. 8.



plotted graphically in Fig. 7. Similarly, the results of percentage-proportion and the corresponding optical rotations have also been arranged in the same table. The results have also been plotted in Fig. 8.

TABLE IV.

No.	Unsaturation number.	α_{5780} in degrees	Percentage unsaturation.	Percentage of β -Santalol from rotation.	Percentage of unsaturation.	Percentage of α -santalol from rotation.
1	1.425	-26.0	42.5	41.08	57.5	58.92
2	1.524	-34.0	52.4	50.69	47.6	49.41
3	1.614	-41.8	61.4	59.16	38.6	40.84
4	1.68	-47.1	68.0	65.96	32.0	34.04
5	1.72	-50.96	72.0	70.48	28.0	29.52
6	1.761	-55.0	76.1	75.24	23.9	24.76
7	1.806	-58.8	80.6	79.12	19.6	20.88
8	1.849	-61.1	82.3	82.4	15.7	17.6

The arguments offered to explain the discrepancies in the composition as determined from the unsaturation value and optical rotations in the case of α -santalol are equally applicable in this case also.

Properties of β -Santalol.—B.p. 157°/5 mm., 15°/3 mm. d_{25}^{25} , 0.9719; n_D^{25} , 1.5102; $[R_L]_D = -67.7$; Calc. $C_{15}H_{24}O \sqrt{2} = 67.66$; $\alpha_{5780} = -76.1^\circ$; $\alpha_{5480} = -87.4^\circ$.

Isolation of α -Santalene

Fraction A₁ was subjected to three preliminary fractional distillations and the fraction boiling at 113-118°/5 mm. was treated in the usual way successively with saturated bisulphite solution and with phthalic anhydride to remove the aldehydic and ketonic as also the alcoholic impurities. The treated oil was then distilled over sodium and the distillate, thus obtained, was fractionated repeatedly through the column No. 2 and the portion coming at 113-115°/5 mm. was collected. Optical rotations and unsaturation numbers were noted as previously.

TABLE V

No. of distillation.	Rotation in degrees α_{5780}	Unsaturation number.	Percentage of α -santalene from unsaturation.	Percentage of β -santalene
12	-0.91	1.177	88.3	11.7
16	+2.6	1.07
17	+2.06	1.07	93.0	7.0

From the above results, the probable optical rotations of pure α - and β -santalene have been determined by calculation, as follows, the percentage-proportion as determined from the unsaturation value having been taken to be correctly applicable in the case of the determination of percentage-proportion from optical rotation as well.

When there is 88.3% α -santalene and 11.7% β -santalene

$$\alpha_{5780} = -0.91,$$

and when there is 93% α -santalene and 7% β -santalene

$$\alpha_{5780} = +2.06.$$

Therefore, if X be the optical rotation of pure α -santalene and Y that of pure β -santalene then

$$\frac{93X + 7Y}{93 + 7} = +2.06 \text{ and } \frac{88.3X + 11.7Y}{88.3 + 11.7} = -0.91$$

Solving X (probable α_{5780} of pure α -santalene) = +6.48°

Y (probable α_{5780} of pure β -santalene) = -56.6°

The results may also be obtained graphically. Among the earlier workers, the purest sample of α -santalene isolated by Schimmel & Co. (*loc. cit.*) had an optical rotation $\alpha_D = -3^\circ$.

As the amount of material at our disposal was rather limited and also because the santalenes are present in the oil to the extent of only about 4.6% it has not been possible to study them as exhaustively as in the case of the santalols. Moreover, the tendency of the hydrocarbons to accompany each other during

fractionations is far more well pronounced than in the case of the alcohols. Besides there being no chemical process of purification available for the isolation of the hydrocarbons, the figures attributed to the optical rotations of the α - and β -santalenes may not be entirely correct.

Properties of author's Sample of α -Santalene.—B.p. $117^{\circ}/7$ mm.; $\alpha_{5780} = +2.06$; $d_4^{20} = 0.9102$; $n_D^{20} = 1.4900$; $[R_L]_D = 64.91$; $C_{15}H_{24} \sqrt{1} = 64.4$. Exaltation is in conformity with the existence of cyclopropane ring. Probable optical rotation of pure variety $\alpha_{5780} = +6.48^{\circ}$. This result is of course open to slight variation.

Isolation of pure β -Santalene

Fraction A_2 was subjected to three preliminary fractions and the portion coming at $121-25^{\circ}/5$ mm. was purified from impurities as in the case of α -santalene and then fractionated repeatedly through column No 2 at $123-24^{\circ}/5$ mm. When the optical rotation (α_{5780}) and the corresponding unsaturation number came to -49.9° and 1.88 respectively, no further purification was possible. This corresponded to 88% β -santalene.

Properties.—B.p. $125^{\circ}/7$ mm.; $\alpha_{5780} = -49.9^{\circ}$; $n_D^{20} = 1.4941$; $d_4^{20} = 0.8940$; $[R_L]_D = 66.4$; Calc. for $C_{15}H_{24} \sqrt{2} = 66.136$. Probable optical rotation of pure variety $\alpha_{5780} = -56.6^{\circ}$. This result is also open to slight variation.

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