The Mechanism of the Rearrangement of Pinonic Acid into Homoterpenyl Methyl Ketone.

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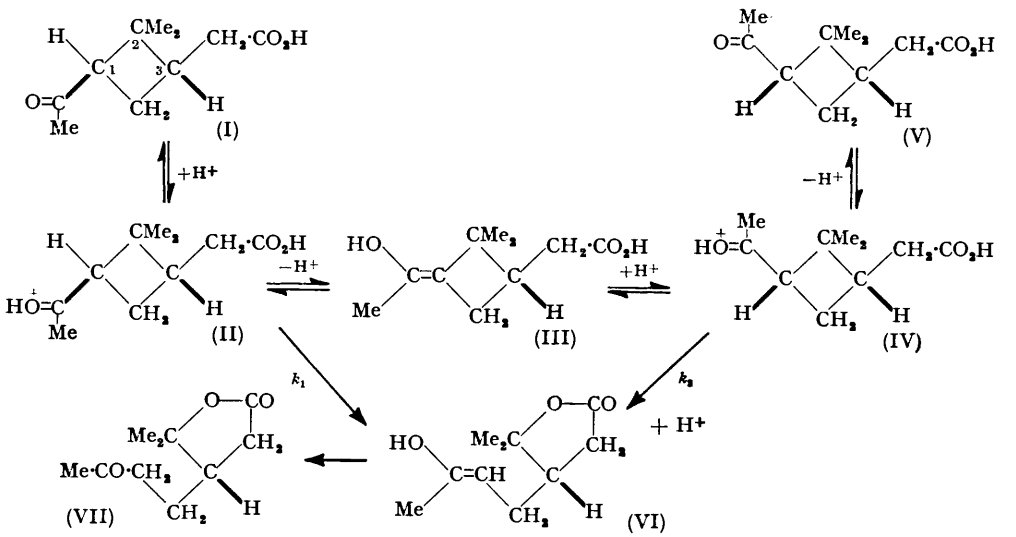
The rearrangement of pinonic acid (I) to homoterpenyl methyl ketone (VII) requires relatively strong acid-catalysis. The rearrangement of (±)- and of (+)-*trans*-pinonic acid, in monochloroacetic acid at 100°, is of the first-order with regard to pinonic acid. A partial conversion into *cis*-pinonic acid occurs in the acidic solution, but this isomer also rearranges to homoterpenyl methyl ketone.

An intramolecular mechanism, represented in (IX), is proposed for the rearrangement.

Pinonic acid (I), on being heated with 50% sulphuric acid, is converted in high yield into homoterpenyl methyl ketone (VII) (Baeyer, *Ber.*, 1896, **29**, 326); the (+)- and the (−)-form of this compound have been obtained from (+)- and (−)-pinonic acid (Barbier and Grignard, *Bull. Soc. chim. France*, 1910, **7**, 548). The structure of homoterpenyl methyl ketone has been ascertained by degradation (Tiemann and Semmler, *Ber.*, 1895, **28**, 1778) and by synthesis (J. Owen and Simonsen, *J.*, 1932, 1424).

The data relating to the degradation and synthesis of pinonic acids (Baeyer, *Ber.*, 1896, **29**, 3, 1909; Perkin and Simonsen, *J.*, 1909, **95**, 1176; Gallas and Montañeš, *Anal. Fis. Quím.*, 1930, **28**, 1196; Grandperrin, *Ann. Chim.*, 1936, **6**, 5; Guha, Ganapathi, and Subra-



manian, *Ber.*, 1937, **70**, 1505; Rao, *J. Indian Chem. Soc.*, 1943, **20**, 97) yield no decisive evidence on geometrical configurations, mainly owing to the use (largely unavoidable) of reagents which catalyse enolisation, leading to geometrical isomerisation. The assignment of geometrical configurations to (+)- and (±)-pinonic acids made by Simonsen and L. N. Owen (" The Terpenes," University Press, Cambridge, 1949, Vol. II, p. 147)—that the solid acids are *trans* and the liquid acids *cis*—has been adopted. The opposite configurations have been used by Delépine and Badoche (*Compt. rend.*, 1952, **235**, 1455), but no essential alteration to the mechanisms which have been deduced (below) becomes necessary if these authors' configurations are adopted.

The essential step in the conversion of (I) into (VII) is the rearrangement of an aceto-*cyclo*butylacetic acid to a keto-γ-lactone. Reaction schemes postulating the intermediate tertiary alcohol (VIII) have been proposed (Simonsen and Owen, *op. cit.*, p. 117; Delépine and Badoche, *loc. cit.*), but no experimental evidence for its occurrence has been adduced.

$$\begin{array}{c} \mathrm{CMe_2{\cdot}OH} \\ | \\ \mathrm{COMe{\cdot}CH_2{\cdot}CH_2{\cdot}CH{\cdot}CH_2{\cdot}CO_2H} \end{array}$$
(VIII)

In experiments preliminary to rate-measurements, the percentage conversion of pinonic acid into homoterpenyl methyl ketone, in acid solvents at 100° for stated times, has been determined; the results are collected in Table 1. In a number of instances the keto-lactone was converted into its 2 : 4-dinitrophenylhydrazone, of which the yield (based on the pinonic acid) is given in the last column.

It is apparent from Table 1 that the strongly acidic media, phosphoric, trichloroacetic, and 99% formic acids, cause rapid rearrangement, that acetic acid is ineffective, and that monochloroacetic and 90% formic acids occupy an intermediate position.

The rearrangement proceeds smoothly, and no by-products have been encountered; prolonged heating in phosphoric acid effects a breakdown of homoterpenyl methyl ketone which is to be described later.

TABLE 1. *The conversion of* (±)-*pinonic acid into* (±)-*homoterpenyl methyl ketone.*

Expt. no.*	Acid	Quantity	Time (hr.)	Yield (%) of homoterpenyl methyl ketone: direct	from 2 : 4-dinitrophenylhydrazone
1	Acetic	4·0 g.	4·5	Nil	—
2	Formic (90%)	4·0 g.	4·5	55	51
3	Formic (99%)	to 10 ml.	2	73	—
4[a]	Monochloroacetic	4·0 g.	3·5	17	15
5	,,	to 10 ml.	9	58	—
6	,,	to 10 ml.	30	95	—
7	Trichloroacetic	4·0 g.	4·5	100	94
8	Phosphoric (*d* 1·72)	4·0 ml.	5 min.	95	92
9[b]	Formic (90%) containing $H{\cdot}CO_2Na$	4·0 g. 0·53 g.	4·5	1	1
10[c]	Monochloroacetic containing $CH_2Cl{\cdot}CO_2Na$	to 10 ml. 1·80 g.	9	5	4

* 1·00 G. of (±)-pinonic acid in each expt.

[a,b,c] 0·74, 0·85, 0·85 G. of pinonic acid recovered, respectively.

An acid containing 0·1 molecular proportion of its sodium salt was used as solvent in two experiments (9, 10; cf. 2, 5); in each instance the yield of homoterpenyl methyl ketone was markedly depressed, and 85% of the pinonic acid was recovered. This effect is ascribed to the lowering of hydrogen-ion concentration by the buffering action of the salts.

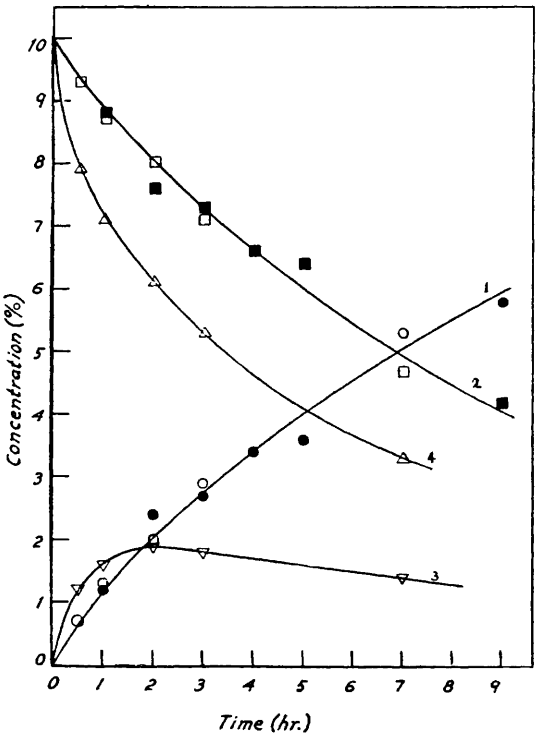
Kinetic Measurements.—Monochloroacetic acid was selected for use in a kinetic study of the conversion of (±)- and of (+)-pinonic acid into (±)- and (+)-homoterpenyl methyl ketone. The rate of rearrangement at 100° was determined by isolation of the keto-lactone after the recorded intervals (see Figure). The plot of $\log_{10}$ [pinonic acid]$^{-1}$ *versus* time is linear, and yields a first-order rate constant $k = 9{\cdot}9 \times 10^{-2}$ hr.$^{-1}$.

When solutions of (+)-pinonic acid in monochloroacetic acid at 100° were studied polarimetrically, a considerable change in rotatory power was observed before conversion into homoterpenyl methyl ketone had proceeded very far. This mutarotation was found to be due to a partial conversion of (+)-*trans*- into (−)-*cis*-pinonic acid; the oxime of the latter was prepared from the pinonic acid recovered from "mutarotated" solutions. In addition, the oxime of (±)-*cis*-pinonic acid was prepared from pinonic acid recovered from the rate-experiments with (±)-*trans*-pinonic acid.

The specific rotations (*c*, 5 in $CHCl_3$) of the specimens of optically active pinonic acid recovered from the kinetic experiments were determined. The corresponding value is known for (+)-*trans*-pinonic acid: $[\alpha]_{5893}$ +92·4° (present observation; Delépine and Badoche, *Ann. Chim.*, 1950, **5**, 153, record $[\alpha]_{5893}$ +95°), and for (−)-*cis*-pinonic acid: $[\alpha]_{5893}$ −81·5° (*idem, loc. cit.*), whence were calculated the proportions of these isomers in the above specimens of pinonic acid. The concentrations of total, *trans*-, and *cis*-pinonic acid are plotted *versus* time in the Figure.

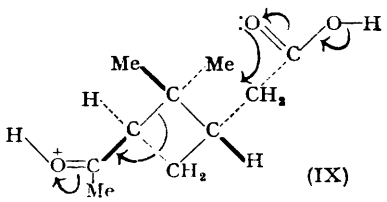
The Mechanism of Rearrangement, and of trans–cis-*Isomerisation.*—The mechanism of the conversion of *trans*- into *cis*-pinonic acid is probably identical with that for the acid-catalysed racemisation of ketones CHRR'·CO·R" (Bartlett and Stauffer, *J. Amer. Chem. Soc.*, 1933, **55**, 4992; 1935, **57**, 2580; Ingold and Wilson, *J.*, 1934, 773). When this mechanism is applied to *trans*- and *cis*-pinonic acid (I—V), the inversion of configuration at $C_{(1)}$ results in the appropriate geometrical isomerisation.

During the first 1·9 hours *cis*-pinonic acid accumulates in the system more rapidly than does homoterpenyl methyl ketone, and, from tangents drawn at the origin to curves 3 and 1, the rate constant for *trans*-acid ⟶ *cis*-acid is approximately twice that for *trans*-acid ⟶ keto-lactone.



Rearrangement and isomerisation of trans-*pinonic acid in monochloroacetic acid at* 100°.
(1) Homoterpenyl methyl ketone, ○
(2) Total pinonic acid, □
(3) *cis*-Pinonic acid, ▽
(4) *trans*-Pinonic acid, △
" Open " points were determined with (+)-*trans*-pinonic acid, and " solid " points with (±)-*trans*-pinonic acid.

The mechanism of the rearrangement of pinonic acid to homoterpenyl methyl ketone is, most probably, that shown in formulæ (I—VII). (The geometrical configurations given to the ethylenic groups of the enols have no significance.) The act of conversion of the *cyclo*butane into the lactone ring is the rearrangement of the protonated *trans*- or *cis*-pinonic acid (II or IV). Models of these molecules show the carboxyl group to be well placed to enter into a replacement reaction at $C_{(2)}$. The steric relations, together with the tautomeric electron movements whereby rearrangement occurs, are represented in (IX).


(IX)

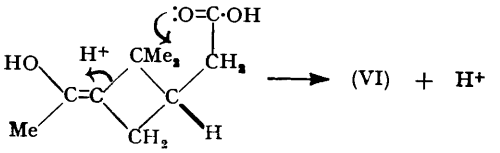
It has been found, above, that the rate of formation of homoterpenyl methyl ketone is proportional to the total concentration of (*trans*- + *cis*-)pinonic acid, and it is inferred from this result that the rate constants k_1 and k_2, relating to (II) and (IV) respectively, do not differ appreciably.

Three apparently possible mechanisms, briefly described below, have been considered and rejected.

The rate of formation of homoterpenyl methyl ketone is, as has been stated, proportional to the concentration of (*trans*- + *cis*-)pinonic acid : were the *trans*-acid (or its proton

adduct) the sole precursor, then the curve for the formation of the keto-lactone (curve 1) would show an initial rapid fall in slope, and were the *cis*-acid (or its proton-adduct) the sole precursor, this curve would have a sigmoid form.

A tenable mechanism is that postulating the enol (III) as the sole presursor to the keto-lactone:



This is considered less probable than the mechanism adopted above, because it involves the taking up of a proton at a point ($C_{(1)}$) from which a proton has earlier been released to form the enol.

Experimental

Rotations are for *l*, 2·0 unless otherwise stated.

The proportions of α- and β-pinene in specimens of (−)- and (+)-pinene from American and Portuguese turpentines were estimated by determination of the rotatory dispersions $[\alpha]^{25}_{5461}/[\alpha]^{25}_{5893}$ and $[\alpha]^{25}_{5461}/[\alpha]^{25}_{5780}$, and comparison of these values with the Tables given by Fuguitt, Stallcup, and Hawkins (*J. Amer. Chem. Soc.*, 1942, **64**, 2978). A mixture containing 97·5% of α- and 2·5% of β-pinene was then made which had b. p. 156—158°, $[\alpha]^{20}_{5893}$ −0·54°; this material (748 g.) was oxidised by Delépine's method (*Bull. Soc. chim. France*, 1936, **3**, 1369) except that chloroform was replaced by methylene chloride as extractant; it yielded (±)-*trans*-pinonic acid (336 g., from benzene), m. p. 103—104°, which on recrystallisation from hot water had m. p. 105° [semicarbazone, prisms (from ethanol), m. p. 217° (decomp.); Ruzicka and Pontalti (*Helv. Chim. Acta*, 1924, **7**, 494) record m. p. 208°].

Ammonium (±)-*trans*-pinonate, on reaction with *S*-benzylthiuronium chloride, yielded *S-benzylthiuronium* (±)-trans-*pinonate*, flakes (from ethanol), m. p. 152° (decomp.) (Found: S, 9·0. $C_{18}H_{26}O_3N_2S$ requires S, 9·15%).

The following method was used for the preparation of all pinonic acid oximes: (±)-*trans*-Pinonic acid (1·00 g.) was dissolved in a solution of potassium hydrogen carbonate (0·55 g.) in water (2·0 ml.); a solution of hydroxylamine hydrochloride (0·42 g.) in water (1·0 ml.) was added and the whole was shaken. The oxime separated and solidified; it was crushed, filtered off, washed with water, and dried *in vacuo* (H_2SO_4). It (0·85 g.), on recrystallisation from ethanol, yielded prisms (0·55 g.), m. p. 152° (decomp.) (Baeyer, *Ber.*, 1896, **29**, 24, records m. p. 150°).

(+)-α-Pinene (68·0 g.), b. p. 154·5—156°, $[\alpha]^{20}_{5893}$ +47·0°, on similar oxidation gave (+)-*trans*-pinonic acid (17·3 g.; isolated by fractional crystallisation from ether), m. p. 68—69°, $[\alpha]^{24}_{5893}$ +92·4° (*c* 5·443 in $CHCl_3$). Its oxime, needles from ethanol–water (1 : 4), had m. p. 135·5°, $[\alpha]^{20}_{5893}$ +51·7° (*c*, 5·102 in $CHCl_3$) (Found: C, 60·2; H, 8·7; N, 7·3. Calc. for $C_{10}H_{17}O_3N$: C, 60·3; H, 8·6; N, 7·05%). Delépine (*loc. cit.*) records m. p. 128°.

(±)-*Homoterpenyl Methyl Ketone*.—The following preparation is based on the brief description given by Baeyer (*loc. cit.*). (±)-*trans*-Pinonic acid (6·0 g.) was heated with aqueous sulphuric acid (50%; 60 g.) at 100° for 30 min., and the solution was poured into water (150 ml.). The product was salted out with ammonium sulphate and extracted with chloroform; the extract was washed and dried (Na_2SO_4), and the solvent distilled. The crystalline product (5·4 g.) yielded, on recrystallisation from the minimum of boiling ether, (±)-homoterpenyl methyl ketone (3·4 g.), prisms, m. p. 60·5°. Its semicarbazone, hexagonal plates from methanol, had m. p. 206—207°; J. Owen and Simonsen (*J.*, 1932, 1424) record m. p. 206—207°. Its 2 : 4-*dinitrophenylhydrazone*, orange needles from ethanol, had m. p. 163·5° (Found: C, 53·1; H, 5·6; N, 14·9. $C_{16}H_{20}O_6N_4$ requires C, 52·7; H, 5·55; N, 15·4%).

Rearrangement in the acidic solvents of Table 1. (±)-*trans*-Pinonic acid (1·00 g.) was heated at 100° in the solvent, and for the time, stated in the Table; water (100 ml.) was then added and the whole was made slightly alkaline (to methyl red) with ammonia and extracted with methylene chloride (25, 20, 15, 10, 10 ml. portions successively); the extract was washed with water (2 × 25 ml.) and distilled (water forms an azeotrope with methylene chloride). The homoterpenyl methyl ketone was dried at 100° (30 min.) or *in vacuo* at ordinary temperature.

Unconverted pinonic acid was recovered from the extracted aqueous solution by acidification with hydrochloric acid and extraction as above.

(These procedures for the isolation of the keto-lactone and pinonic acid were used in the rate-measurements, below.)

The preparation of the 2 : 4-dinitrophenylhydrazone of (±)-homoterpenyl methyl ketone was standardised as follows : to a solution of the keto-lactone (1·00 g.; reagents proportional to the actual weight were taken) in warm propan-2-ol (15 ml.), 2 : 4-dinitrophenylhydrazine (1·1 g.) was added; the solution was boiled, and addition of a few drops of concentrated hydrochloric acid then precipitated the derivative; further propan-2-ol (15 ml.) was added, and the suspension was cooled and filtered. The 2 : 4-dinitrophenylhydrazone was washed with propan-2-ol (30 ml.), dried at 120°, and weighed. Its m. p. and mixed m. p. were determined. In a control experiment (±)-homoterpenyl methyl ketone (0·50 g.) gave 0·95 g. (95%) of the derivative.

Rate of rearrangement. Monochloroacetic acid was fused, and 0·05 mol. of concentrated aqueous sodium hydroxide was cautiously added; distillation then gave a main fraction having b. p. 101—102°/25 mm. The liquid was allowed to solidify to the extent of about 90% and the remaining liquid was drained off and discarded; the solid was re-melted and the process repeated; the acid so purified had equiv. 94·31 (Calc. for $CH_2Cl{\cdot}CO_2H$: equiv., 94·50).

(±)-*trans*-Pinonic acid (1·00 g.) was weighed into a 10-ml. graduated flask and dissolved in monochloroacetic acid at 80°; the solution was made up to the mark, the flask was sealed with a Polythene cap, and thereafter immersed in a steam-bath for the time(s) recorded in the Figure; homoterpenyl methyl ketone was then isolated as described above. The quantities of keto-lactone formed by rearrangement of (±)- and (+)-pinonic acid, together with those calculated from the first experimental point ($t = \frac{1}{2}$ hr.) by use of the first-order rate-constant $k = 9{\cdot}9 \times 10^{-2}$ hr.$^{-1}$, are as follows :

t (hr.)		½	1	1	2	2	3
Pinonic acid		+	+	±	+	±	+
Homoterpenyl methyl ketone	isolated (g.)	0·07	0·13	0·12	0·20	0·24	0·29
	calc. (g.)	same	0·11	0·11	0·20	0·20	0·27
t (hr.)		3	4	5	7	9	
Pinonic acid		±	±	±	+	±	
Homoterpenyl methyl ketone	isolated (g.)	0·27	0·34	0·36	0·53	0·58	
	calc. (g.)	0·27	0·34	0·40	0·51	0·60	

Specimens of pinonic acid recovered from the rate-experiments were combined and washed with ethanol, whereby they were separated into (±)-*trans*-pinonic acid, m. p. and mixed m. p. 102°, and a liquid mixture of this acid and the (±)-*cis*-isomer. This mixture was converted into the mixed oximes, from which, by fractional crystallisation from ethanol, there were isolated (±)-*cis*-pinonic acid oxime, m. p. 171° [Delépine (*loc. cit.*) records m. p. 168°], and also the more soluble *trans*-oxime, as prisms, m. p. 151° alone and when mixed with the specimen above.

(+)-*Homoterpenyl Methyl Ketone.—Mutarotation of solutions of pinonic acid in monochloroacetic acid.* A solution of (+)-*trans*-pinonic acid [(i), (ii) 1·000 g.; (iii), (iv) 1·750 g.] in monochloroacetic acid (to 10 ml. at 80°) was placed in a 1-dm. jacketed polarimeter tube with sealed end-plates, maintained at 100° by steam passing freely through the jacket. The rotatory power of the solution was determined at intervals (Table 2); the first reading was made within 5 min. of the preparation of the solution.

The liquid mixture of (+)-*trans*- and (−)-*cis*-pinonic acids (6·3 g.) recovered from these

TABLE 2.

	Time (min.) :	0	5	10	20	30	40	60	80	100
(i)	α^{100}_{5893}	5·46°	5·18°	4·92°	4·50°	4·10°	3·87°	3·46°	3·18°	3·02°
(ii)	α^{100}_{5893}	5·53	5·24	4·99	4·54	4·18	3·90	3·44	3·21	3·04
(iii)	α^{100}_{5893}	9·34	8·85	8·39	7·69	6·88	6·65	5·92	5·41	5·10
(iv)	α^{100}_{5893}	9·55	9·07	8·67	7·90	7·33	6·82	6·05	5·52	5·18
	Time (min.) :	120	140	150	180	195	210	230	240	
(i)	α^{100}_{5893}	2·94°	2·89°	2·89°	—	2·89°	2·91°			
(ii)	α^{100}_{5893}	2·92	2·87	2·87	—	2·87	2·88			
(iii)	α^{100}_{5893}	4·87	4·77	4·73	4·67°	—	—	4·67°	4·67°	
(iv)	α^{100}_{5893}	4·93	4·78	4·71	4·65	—	4·63	4·69	4·69	

polarimetric experiments was heated with thrice its volume of phosphoric acid (*d* 1·72) for 10 min. at 100°. The product (5·95 g.), isolated as described for the (±)-keto-lactone, was

recrystallised from ether and yielded (+)-homoterpenyl methyl ketone (3·5 g.), m. p. 46·5°, $[\alpha]_{5893}^{20}$ +58·6° (*c* 5·271 in $CHCl_3$), $[\alpha]_{5893}^{100}$ +45·5° (*c*, 5·612 in $CH_2Cl{\cdot}CO_2H$) and $[\alpha]_{5893}^{100}$ +45·8° (*c*, 10·000 in $CH_2Cl{\cdot}CO_2H$; the rotation was unchanged after 4 hr. at 100°); it gave a 2 : 4-*dinitrophenylhydrazone*, orange needles (from ethanol), m. p. 168·5° (Found : C, 53·0; H, 5·7; N, 15·5%). Both Barbier and Grignard (*loc. cit.*) and Delépine and Badoche (*Compt. rend.*, 1952, **235**, 1069) record m. p. 47° for (+)-homoterpenyl methyl ketone.

Rate of rearrangement. Five determinations (cf. Figure) of the conversion of (+)-*trans*-pinonic acid into (+)-homoterpenyl methyl ketone, with recovery of unconverted pinonic acid, were carried out by the method described for the (±)-keto-lactone. The specific rotation (*c*, 5 in $CHCl_3$) of the recovered pinonic acid was determined :

Reaction-time (hr.)	0·5	1	2	3	7
$[\alpha]_{5893}^{t}$	+66·7°	+57·4°	+47·0°	+43·4°	+39·7°
t	22°	22°	21°	20°	22°

The specimens of (+)-keto-lactone isolated during these rate-experiments were combined (1·60 g.), dissolved in hot water (20 ml.), treated with charcoal to remove methyl red, extracted with methylene chloride, and twice recrystallised from ether–light petroleum (b. p. 40—60°); the (+)-homoterpenyl methyl ketone formed prisms (0·57 g.), m. p. 46—47°, $[\alpha]_{5893}^{17}$ +59·6° (*c*, 5·013 in $CHCl_3$).

The specimens of semisolid pinonic acid recovered from the above rate-experiments were pressed on filter paper; the solid was removed and the paper extracted with methylene chloride. The extract yielded a liquid acid (2·16 g.) which was converted into its oxime (1·72 g.); after extraction with boiling ether there remained a product (0·69 g.), m. p. 195°, which by repeated recrystallisation from hot ethanol yielded (−)-*cis*-pinonic acid oxime, prisms, m. p. 199·5—200°, $[\alpha]_{5893}^{20}$ −34·3° (*l*, 4; *c*, 0·437 in ether) (Found : C, 60·5; H, 8·7; N, 7·2%). For this oxime Delépine (*loc. cit.*) records m. p. 192° and $[\alpha]_{5893}$ −29·5° (in ether).

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