

MONOTERPENOIDS — VI^a

ON THE OPTICAL PURITY OF (+)-CAR-3-ENE FROM *PINUS ROXBURGHII*, AND THE SOURCE OF RACEMIZATION OF (-)-MENTHOL DERIVED THEREFROM^b

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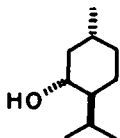
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Abstract — It is shown that (+)-car-3-ene occurring in the oleoresin from *Pinus roxburghii* is optically pure. It is also demonstrated that in the production of (-)-menthol from (+)-car-3-ene by the MRC process, partial racemization of (-)-menthol has its origin at the stage of (+)-isoterpinolene.

In the production of (-)-menthol (2) from (+)-car-3-ene (1) by MRC Process¹, (+)-isolimonene (3) and (+)-isoterpinolene (4) are important intermediates. Since, (-)-menthol produced by this process is racemized to the extent of some 10-12%, the present investigation was undertaken to determine the source of this racemization.



1



2



3



4

Optical Purity of (+)-Car-3-ene

Many monoterpenes occur in nature partially or fully racemized²; an extreme case is that of α -pinene which seldom occurs in nature in optically pure form.³ Car-3-ene occurs in nature in (+), (-), and (+)-forms.^{2c} It was important, in the first instance, to determine the optical purity of (+)-car-3-ene as isolated from *Pinus roxburghii* Sarg. syn. *P. longifolia* Roxb.

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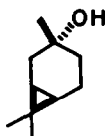
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Table 1. Comparison of $\{\alpha\}_D$ of (+)-Car-3-ene of different sources

No.	Source	$\{\alpha\}_D$ (neat, t°)
1	<i>Pinus silvestris</i> (Poland) ⁴	+ 17.1° (20°)
2	<i>P. silvestris</i> (Sweden) ⁵	+ 17.6° (25°)
3	<i>P. ponderosa</i> ⁶	+ 18.1° (20°, ?)
4	<i>P. roxburghii</i> ⁷	+ 17.32° (20°)
5	<i>P. roxburghii</i> (our sample)	+ 17.2 ± 0.2° (25°)

A reference to Table 1 shows that (+)-car-3-ene from diverse sources has a spread of $\{\alpha\}_D$ values, which may be meaningful as far as optical purity is concerned, or simply may be a reflection of ultra-trace impurities or subjective experimental error. This situation was clarified as follows.

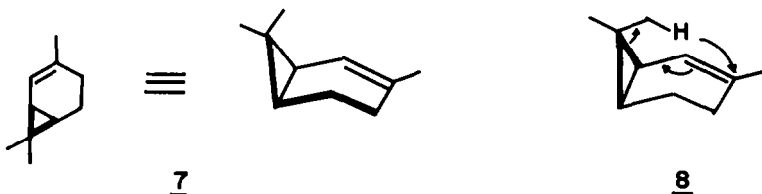
(+)-Car-3-ene from *Pinus roxburghii* was epoxidised (ACOOH) to furnish the known⁸ (+)-3 α ,4 α -epoxycarane (5), which on LAH reduction gave in over 90% yield the tertiary alcohol 6 as per the reported procedure.⁹ A part of this product was carefully fractionated to get 100% GLC pure product and its specific rotation noted $\{(\alpha)_D^{30} + 23.6^\circ$ (neat)}. Another portion was converted into its crystalline *p*-nitrobenzoate and crystallized to constant m.p. (m.p. 113-114°). The crystalline ester was saponified and the product fractionated to get 100% GLC pure cut and its optical rotation determined $\{(\alpha)_D^{30} + 23.8^\circ$ (neat)}. Since the two values are, within experimental error, identical, it follows that the starting carene (ex. *P. roxburghii*) is optically pure.

56

Racemization of (+)-Isoterpinolene

In the MRC process for the production of (-)-menthol, (+)-car-3-ene (1) is first equilibrated with its Δ^2 -isomer (7) under basic conditions.¹⁰ Since (+)-car-3-ene separated from this equilibrium mixture (1:7 :: 3:2) has its $\{\alpha\}_D$ unchanged, there cannot be any racemization at this stage. This was anticipated. At the next stage, thermal reorganization (8) of (+)-car-2-ene proceeds by a symmetry-allowed process to generate (+)-isolimonene (3).¹¹ No racemization is

expected in this process. To establish that no overlap of any catalytic pathway with the sigmatropic rearrangement (8) occurs, thermal isomerization of pure (+)-car-2-ene was investigated at various temperatures (240-400°) in a variety of reactors (glass tubular reactor packed with glass helices or SS wire-mesh, sealed glass ampule at 240-260°, or SS autoclave at 240-260°). The specific rotation of (+)-*trans*-isolimonene (3), thus obtained, was the same $\{[\alpha]_D^{25} + 21.0^\circ \pm 1^\circ (\text{neat})\}$ for all the samples. This reinforced the contention that there can be no racemization at this stage.



In the next step, (+)-isolimonene (3) is isomerized to (+)-isoterpinolene (4). This is achieved by exposure of 3 to deactivated high-surface-sodium-on-alumina.¹² Isomerization is essentially quantitative, and the product contains, besides 4 (~90%), its 3,8-isomer (9; ~7%) and *p*-cymene (~3%). GLC pure isoterpinolene (4), thus obtained (from pure isolimonene), had $\{[\alpha]_D^{25} + 66.7^\circ (\text{neat})\}$. This value is different from two values reported in the literature: $\{[\alpha]_D^{20} + 63^\circ (\text{CHCl}_3)\}$ ¹³, $+ 49.1^\circ (\text{neat})$ ¹⁴. This situation was clarified as follows:



GLC pure isoterpinolene on ozonolysis followed by CrO_3 oxidation¹⁵ furnished, as the main product, α -methylglutaric acid, which was repeatedly crystallized to get pure (-)- α -methylglutaric acid (10, R=H; m.p. 86-88°, $\{[\alpha]_D^{25} - 24.71^\circ (\text{EtOH})\}$). Esterification (CH_2N_2) furnished optically pure ester (10, R=Me; $\{[\alpha]_D^{25} - 24.85^\circ (\text{neat})\}$). Another portion of ozonolysis-oxidation product was esterified (CH_2N_2) and then precision-fractionated to get GLC pure α -methylglutarate. This product had $\{[\alpha]_D^{25} - 22.5^\circ (\text{neat})\}$. From this it can be inferred that isoterpinolene is racemized to the extent of 10%. This then establishes the source of racemization in the synthesis of (-)-menthol from (+)-car-3-ene. From this it also follows that optically pure (+)-isoterpinolene should have $\{[\alpha]_D^{25} + 74.1^\circ (\text{neat})\}$.

Racemization of isoterpinolene, during its preparation from isolimonene, can occur through two possible pathways depicted in Fig. 1. In the present context, pathway 1 is considered unimportant, since generation of 13 should be far more facile in comparison to that of ion 11, more so because isomerization of isolimonene (3) to isoterpinolene (4) should be a kinetically-controlled process.¹⁶ Pathway 2 envisages racemization of isoterpinolene *via* its 3,8-isomer (9). This implies greater racemization of 3,8-isomer as compared to that of isoterpinolene,

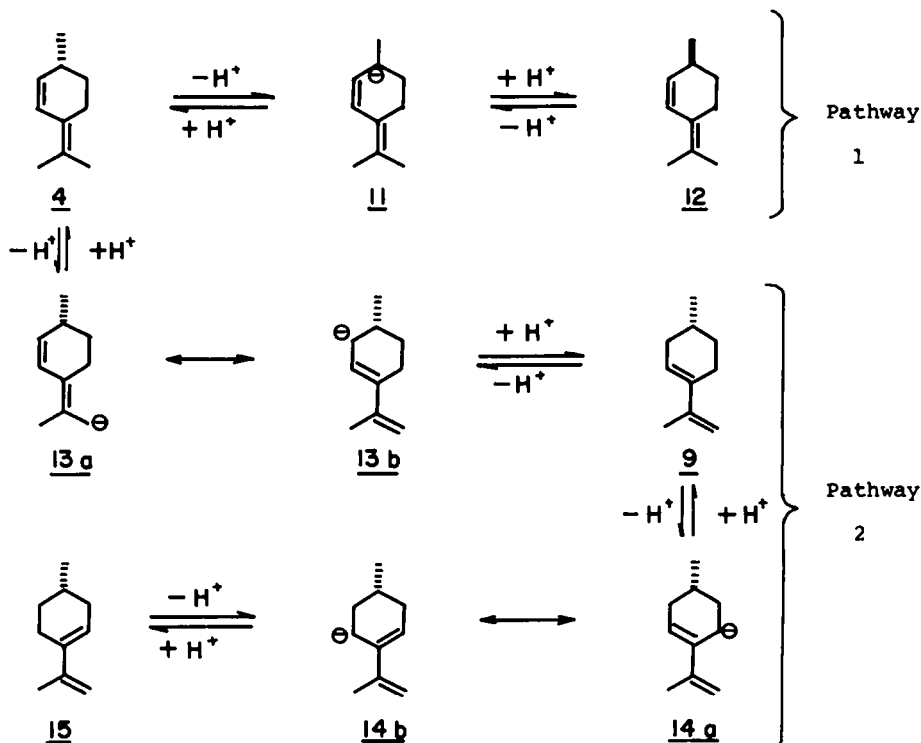


Fig. 1. Possible modes for racemization of isoterpinolene

since in isomerization of 3,8-isomer to isoterpinolene (4) the large excess of 9 will compete with small proportions of 15. To check this point, the 3,8-isomer formed as a co-product during isomerization of isolimonene to isoterpinolene was isolated in GLC pure state and was found to have $[\alpha]_D^{25} + 128.9^\circ$ (CHCl_3). The maximum specific rotation reported for (+)-mentha-3,8-diene (9) in the literature¹³ is $+159.0^\circ$ (CHCl_3), from which it follows that our sample of 3,8-isomer must have been racemized to the extent of some 19%. This, then supports the contention that during production of (+)-isoterpinolene from (+)-isolimonene, partial racemization had occurred *via* pathway 2. This also implies that racemization of 9 is a slower process than its isomerization to 4. This may be expected when one compares the structure of ions 14 and 13.

E X P E R I M E N T A L

M.ps and b.ps are uncorrected. Light petroleum refers to fraction b.p. 60-80°. All solvent extracts were finally washed with brine and dried (Na₂SO₄).

Precision fractionation was carried out using Adiabatic Annular Teflon Spinning-band Distillation Unit, supplied by Nester/Faust Manufacturing Corporation, Newark, USA.

Following instruments were used for spectral/analytical data: Schmidt + Haensch electronic polarimeter model Polatronic 1; Perkin-Elmer model 267 Infrared Spectrophotometer; Perkin-Elmer model R32 (90 MHz) NMR spectrometer; Hewlett-Packard 5712A and 7624A Gas Chromatographs (Al columns, 180 cm x 0.6 cm; 10% Carbowax 20M on 60-80 mesh Chromosorb W; carrier gas, H₂).

(+)-Car-3-ene used in the following experiments was 100% GLC pure, having $[\alpha]_D^{25}$ in the range + 16.98° to + 17.46° (neat).

(+)-cis-Caran-3-ol (6)

cis-Caran-3,4-epoxide^{8c} (19.0 g) in dry ether (100 ml) was reduced with LAH (5.0g) in ether (70 ml) as reported in an earlier procedure⁹, to get crude 6 (18.0g), b.p. 90-95°/20 mm (GLC purity, 88%). This was precision fractionated to get 100% (GLC) pure *cis*-caran-3-ol (6): d_4^{30} 0.9754, n_D^{35} 1.4705, $[\alpha]_D^{30}$ + 23.6° (neat).

A mixture of crude LAH reduction product (16.0 g), *p*-nitrobenzoyl chloride (27.5 g) and dry pyridine (40 ml) was stirred at 100° for 2 hr, and worked up to get the crude ester (31.4 g, m.p. 102-105°). This was repeatedly crystallized from light petroleum to a constant m.p. (113-114°; 24.6g). IR (CCl₄): 1725, 1300, 1255, 1115 and 1105 cm⁻¹. ¹H-NMR (CCl₄): δ Me-C (3H, s, 0.97; 3H, s, 1.01; 3H, s, 1.55 ppm), Ar-H (4H, ABq, 8.16 ppm).

The above pure ester (24.0 g) was saponified with methanolic KOH to get 6 (12.0g) of 98% GLC purity. This was carefully fractionated to furnish caranol of 100% GLC purity: d_4^{30} 0.9786, n_D^{35} 1.4710, $[\alpha]_D^{30}$ + 23.8° (neat).

(-)-α-Methylglutaric acid from (+)-isoterpinolene

(+)-Isoterpinolene {20g; GLC purity 100%, n_D^{25} 1.5028, d_4^{25} 0.8494, $[\alpha]_D$ + 66.7° (neat)} in acetone (100 ml) was exposed to ozonized oxygen (3.23g O₃ per hr; 2 l O₃ + O₂/min) at -10° to -15° for 4.5 hr (+ve excess O₃ test). The reaction mixture was diluted with cold (-5°) acetone (200 ml), and oxidized by Jones' reagent (stock soln: CrO₃ 133.5g, conc H₂SO₄ 115 ml and H₂O 200 ml; 60 ml, introduced dropwise with slow stirring and cooling), while maintaining the reaction

temp at 10-20°. The reaction mixture was worked up in the usual manner to get an acid fraction as a viscous material (17.7 g). Several batches of isoterpinolene were ozonized-oxidized in this manner.

The crude acid (29.1 g) was esterified with CH₂N₂ (18.0g, 500 ml ether) to get a distilled product (b.p. 75°/1mm, 19.5g) of 88% GLC purity. This was fractionated to furnish 100% GLC pure ester: $n_D^{25^\circ}$ 1.4239, $d_4^{25^\circ}$ 1.0535, $\{\alpha\}_D^{25^\circ}$ -22.5° (neat).

Another batch of crude acid (30.6 g) was seeded and kept at 5° for 24 hr, and the crystallized brownish white material (12.9g, m.p. 67-71°) collected. This on four crystallizations from benzene gave a product (9.9g, m.p. 81-83°), which was repeatedly recrystallized from ether + light petroleum to constant m.p. to get pure 10 (R=H; 7.6g), m.p. 86-88°, $\{\alpha\}_D^{25^\circ}$ -24.71° (EtOH, c 5%). {Lit.¹⁷, m.p. 82.5-83°, $\{\alpha\}_D^{25^\circ}$ -21.7° (EtOH)}. Pure acid, thus obtained, was esterified (CH₂N₂) to get 100% GLC pure ester (10, R = Me), $n_D^{25^\circ}$ 1.4238, $d_4^{25^\circ}$ 1.0500, $\{\alpha\}_D^{25^\circ}$ -24.85° (neat).

REFERENCES AND NOTES

- ¹ (a) Sukh Dev, Proceedings of 11th IUPAC International Symposium on Chemistry of Natural Products, Vol. 4, part 1, p. 433, Bulgarian Academy of Sciences, Golden Sands, 1978; (b) Sukh Dev, Proceedings of International Symposium on Medicinal and Aromatic Plants, p. 77, Central Institute of Medicinal and Aromatic Plants, Lucknow, 1983; (c) P.Z. Bedoukian, Perfumer and Flavorist 8(2), 5 (1983).
- ² (a) H. Erdtman in Chemical Plant Taxonomy (Editor: T. Swain), p. 93, Academic Press, New York, 1963; (b) V. Plouvier, Phytochemistry 5, 955 (1966); (c) Sukh Dev, A.P.S. Narula and J.S. Yadav, CRC Handbook of Terpenoids, Vol. II, CRC Press, Boca Raton, Florida, 1982.
- ³ D.V. Banthorpe, B.V. Charlwood, and M.J.O. Francis, Chem. Rev. 72, 126 (1972).
- ⁴ V. Herout, Coll. Czech. Chem. Comm. 15, 381 (1950).
- ⁵ G. Vidmark, Acta Chem. Scand. 9, 925 (1955).
- ⁶ R.T. O'Connor and L.A. Goldblatt, Analyt. Chem. 26, 1726 (1954).
- ⁷ Y.-R. Naves, Bull. Soc. Chim. Fr. 554 (1959).
- ⁸ (a) B.A. Arbuzov and B.M. Mikhailov, J. Prakt. Chem. 127, 1 (1930); (b) P.J. Kropp, J. Am. Chem. Soc. 88, 4926 (1966); (c) V.S. Joshi, N.P. Damodaran and Sukh Dev, Tetrahedron 24, 5817 (1968).
- ⁹ K. Gollnick, S. Schroeter, G. Ohloff, G. Schade, and G.O. Schenck, Liebigs Ann. 687, 14 (1965).
- ¹⁰ (a) G. Ohloff, K.H. Schulte-Elte and W. Giersch, Helv. Chim. Acta 48, 1665 (1965); (b) W. Cocker, P.V.R. Shannon and P.A. Staniland, J. Chem. Soc. (C) 41, (1966); (c) S.P. Acharya and H.C. Brown, J. Am. Chem. Soc. 89, 1925 (1967).
- ¹¹ (a) G. Ohloff, Tetrahedron Lett. 3795 (1965); (b) K. Gollnick and G. Schade, Tetrahedron 22, 123 (1966).
- ¹² A.N. Misra, M.R. Sarma, R. Soman and Sukh Dev, Indian Patent 146086 (1979).
- ¹³ J.H. Brewster and H.O. Bayer, J. Org. Chem. 29, 116 (1964).
- ¹⁴ H. Horiuti, H. Otuki and O. Okuda, Bull. Chem. Soc. Japan 14, 501 (1939).
- ¹⁵ A.S. Narula and Sukh Dev, Tetrahedron Lett. 1733 (1969).
- ¹⁶ Under thermodynamic control the major product is p-mentha-1,3-diene, rather than isoterpinolene: A. Ferro and Y.-R. Naves, Helv. Chim. Acta 57, 1141 (1974).
- ¹⁷ E. Berner and R. Leonardsen, Liebigs Ann. 538, 1 (1939).