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STEREOCHEMISTRY OF CYCLOPROPYLCARBINYL REARRANGEMENTS

THUJOPSENE–WIDDROL INTERCONVERSION*

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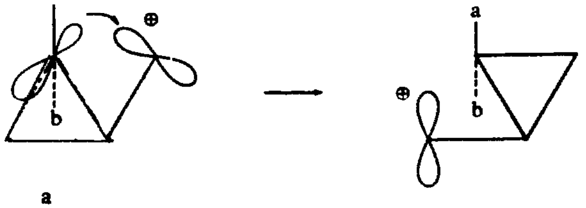
Abstract—The cyclopropylcarbinyl–cyclopropylcarbinyl rearrangement involved in the thujopsene–widdrol interconversion has been shown to proceed with retention of configuration. 7-Bromowiddrol (3) was converted to the 6,7-α-epoxide (4) which, in turn, was reduced with LAD to yield 7β-deuterowiddrol (5). Acid catalyzed rearrangement of 5 gave monodeuterothujopsene (6) and the stereochemistry of the deuterium was determined by NMR spectroscopy. Spectral analysis of the cyclopropane protons was achieved by use of calculated spectra at three fields.

The results establish that the interconversion must involve either the small lobe of the back bond of the cyclopropane ring or a series of 1,2-shifts via a puckered cyclobutonium ion.

For the interconversion of one cyclopropylcarbinyl cation to another such cation, many mechanistic pathways have been postulated.[1] Recent studies of the stereochemical consequences of such a rearrangement have permitted the details of the process to be better defined.[2] Using the stereospecifically deuterium labeled cyclopropylcarbinyl cation derived from bicyclobutane, Wiberg has found that the rearrangements must occur by a direct conversion involving the small lobe of the back bond (Eq. 1) or by a series of 1,2-shifts of the cyclopropane bonds via a puckered cyclobutonium ion as an activated complex (Eq. 2).[2] Simililar results have been reported by Zimmerman[3] and by Hill[4] for the related rearrangement of this cation when incorporated into a bicyclo[3·1·0]hexane ring system.



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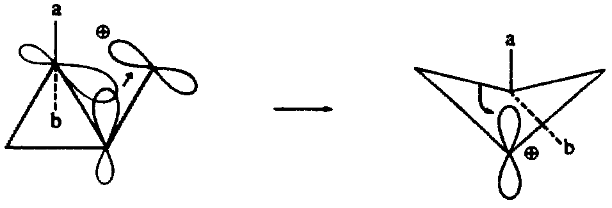

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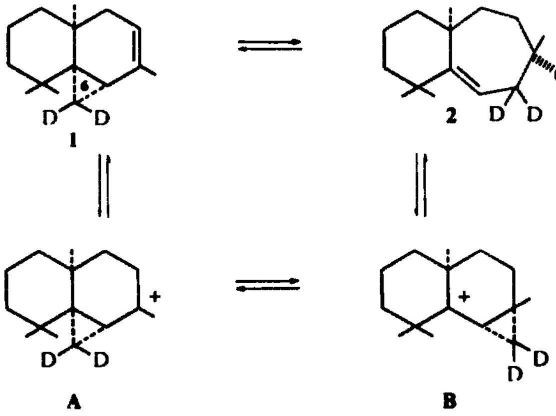
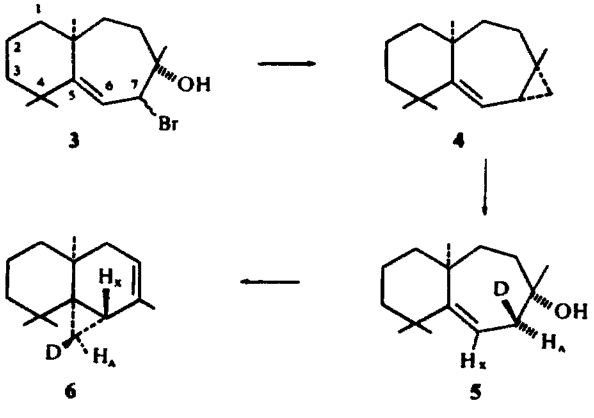
A related series of interconversions of the cyclopropylcarbinyl cation has been found to occur in various sesquiterpenes and steroids,[5-8] and in view of the importance of such rearrangements to the possible biogenetic postulates in these series of materials,[9] the rearrangement of the widely occurring sesquiterpene thujopsene has been restudied.

Previous work on the rearrangement of thujopsene (1) to widdrol (2), using deuterium labeled 1, showed that during the reversible transformation, a skeletal rearrangement had occurred.[8] The overall process can be viewed as proceeding with the formation of ion A which by direct interconversion or by a series of 1,2-bond shifts yields ion B, the direct precursor of 2.



By using thujopsene labeled stereospecifically with one deuterium at C-6, the details of the interconversion of A and B can be evaluated. The preparation of such a specifically labeled species would require a multistep synthesis. However, since the thujopsene–widdrol interconversion is reversible, it is possible to start with a monodeuterated ion analogous to B; this ion can be obtained from the more readily available widdrol labeled stereospecifically at the allylic C-7 position.



Widdrol was brominated with N-bromosuccinimide and the resulting crude bromide (3) upon reaction with 1,5-diazabicyclo[4.3.0.]non-5-ene yielded the epoxide 4; the overall yield was 49%. Although two epimeric bromides are possible, only one epoxide can be formed by the internal displacement by the α-placed hydroxyl group,[10] and the resulting epoxide must have α-stereochemistry. Reduction of the epoxide 4 with LAH gave an almost quantitative yield of widdrol in which the vinylic hydrogen H_X appears in the NMR as a doublet of doublets at δ 5·5 with $J = 8{\cdot}7$ Hz and 5·5 Hz. Reduction of epoxide 4 with lithium aluminum deuteride produced an almost quantitative yield of monodeuterowiddrol 5. From the known stereochemistry of hydride reduction of epoxides and from the NMR spectrum of 5 in which the vinylic hydrogen H_X appears as a doublet with $J_{H_A H_X} = 5{\cdot}5$ Hz, the stereochemistry of deuterium can be assigned β.

The deuterowiddrol 5 was heated under reflux for 20 min in 80% aqueous dioxan which was 0·02M in perchloric acid and during this period approximately 15% of the starting alcohol was converted to a mixture of hydrocarbons. VPC analysis indicated that 60% of the hydrocarbon mixture was thujopsene (6) and the remaining portion of the mixture was composed of at least four other isomeric hydrocarbons, the structures of which have been described elsewhere.[11] The mass spectrum of the deuterothujopsene indicated that no deuterium was lost during the rearrangement. The stereochemistry of the deuterium was assigned by NMR spectroscopy.

Interpretation of the cyclopropyl hydrogen region of the NMR spectrum of monodeuterothujopsene was complicated since the C_4-β-methyl group is highly shielded by the ring current of the cyclopropane ring[12] and appears as a singlet at δ 0·6. Also the band for two other Me groups at δ 1·13 overlaps the other cyclopropyl hydrogen absorption. Thus definite assignments of the coupling patterns of the cyclopropyl hydrogens was not possible at 60 or 100 MHz. However, at 220 MHz,* the peaks due to the two cyclopropyl hydrogens were visible, and with the aid of 220 MHz spectrum

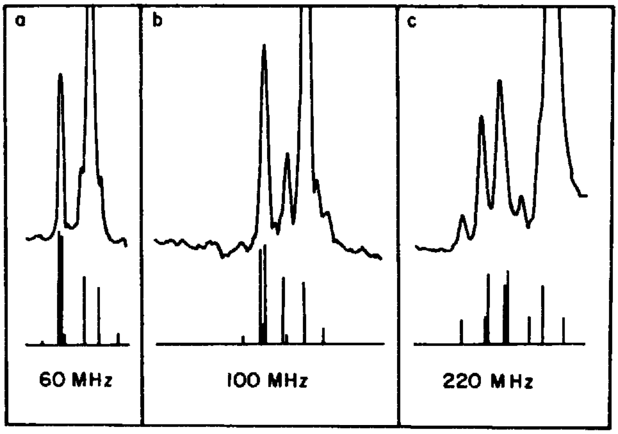


FIG. 1 Calculated and Observed NMR spectra of the Cyclopropyl Hydrogens H_A and H_B of Natural Thujopsene

[a] Taken with Varian T-60 spectrometer.[b] Taken with Varian HA-100 spectrometer.[c] Taken with Varian HA-220 spectrometer. The peak which is off scale in each figure is due to the C_4 β methyl Group.

* 220 MHz NMR was taken with Varian HR220. We wish to thank Dr. George Kotowycz and Dr. Mel Klein of the Chemical Biodynamics Laboratory, University of California, Berkeley, for Spectra.

of dideuterothujopsene, stereochemistry of the deuterium was assigned. The 220 MHz spectra of dideuterothujopsene showed one hydrogen singlet at δ 1·16 and thus permits the assignment of the chemical shift to H_X. At this same field, the monodeuterothujopsene (6) showed two doublets at δ 0·64 and 1·12. Since in the spectrum of the dideutero derivative no signal near δ 0·6 was observable, the signal at δ 0·64 must be assigned to H_A. Furthermore, the coupling constants of these bands of 4·5 Hz showed that H_X and H_A were *trans* to each other on a cyclopropyl ring,[*] as shown in 6 and, thus, the deuterium must be β.

The position and the stereochemistry of the D atom in the monodeuterothujopsene (6) obtained from the rearrangement of the monodeuterowiddrol (5) indicates that the cyclopropylcarbinyl–cyclopropylcarbinyl rearrangement occurs by the pathway given by either Eq. 1 or 2; thus, the large lobe of the back bond of the cyclopropyl ring does not participate in the rearrangement, a result in agreement to those reported earlier in less complicated cases.

With the aid of the NMR data obtained from the monodeutero- and dideuterothujopsene and the computer programs NMRIT and NMREN,[14] the coupling patterns of the cyclopropyl hydrogens of thujopsene, itself, were analyzed. Through a series of computer iterations, the best values for the chemical shifts and coupling constants for H_A, H_B, and H_X were found to be:

$$\begin{array}{llll}
H_A = 0{\cdot}65 & J_{AB} = & -4{\cdot}51 & \text{Hz} \\
H_B = 0{\cdot}61 & J_{AX} = & 4{\cdot}31 & \text{Hx} \\
H_X = 1{\cdot}12 & J_{BX} = & 8{\cdot}65 & \text{Hz}
\end{array}$$

When these values were used with NMRIT program, the calculated spectra for the 60 MHz and 100 MHz were practically identical with what could be seen for the two cyclopropyl hydrogens which were not hidden by the high field methyl signal (Fig. 1). Finally, it should be noted that calculated spectra for 60 MHz and 100 MHz resemble an ABC pattern whereas at 220 MHz, they resemble an ABX pattern.

EXPERIMENTAL

IR spectra were taken with Perkin–Elmer 237 and 337 Infrared Spectrometer. NMR spectra were taken with Varian A-60, Varian T-60, Varian HA-100, or Varian HR-220 spectrometer. Solvent used for NMR was CCl_4 and chemical shifts are given in ppm downfield from internal TMS. Mass spectra were taken on CEC 21–103C.

Widdrol epoxide (4). To a refluxing soln of 5·5 g (24·6 mmole) widdrol in 150 ml CCl_4 under N_2 atomosphere, 4·8 g (25·6 mmole) N-bromosuccinimide (dried overnight at room temp under vacuum) was added while illuminating the mixture with 275 watt General Electric sunlamp. The heating mantle was removed and the sunlamp was left on for an additional 12 min. The soln was cooled in an ice bath, the solid material was filtered and CCl_4 was removed on a rotary evaporator to yield 7·2 g brown oil. The crude bromide was dissolved in 150 ml dry benzene and 3·1 g (25·0 mmole) DBN (1,5-diaza-bicyclo[4.3.0]non-5-ene) was added. The soln was heated at 70° for 10 hr under N_2, cooled, and the ppt was removed by filtration and washed with benzene. The benzene was removed on a rotary evaporator to yield 6·3 g of crude epoxide 4 which contained some DBN (bp 95–98°, 17·5 mm). The epoxide was chromatographed on 100 g of Woelm neutral alumina (act. II). (Prolonged contact of epoxide with alumina appeared to destroy the epoxide.) Elution with 350 ml of hexane gave 3·4 g of oily 4 which was 79% pure by vpc (5 ft × $\frac{1}{4}$ in. KOH, Carbowax 6000, T = 160°); $\nu_{max}^{CCl_4}$ 3060, 1635, 1110, 868 cm^{-1}; NMR (CCl_4) δ 5·64 (1 H, J = 5·5 Hz), 2·78 (1 H, J = 5·5 Hz), 1·25 (3H, s), 1·13 (9 H, s).

[*] *trans* Coupling is between 2·6 and 5·6 Hz while *cis* coupling is between 6·9 and 9·3 Hz.[13]

Monodeuterowiddrol (**5**). A soln of 3·4 g (12·2 mmole) 79% pure **4** in 30 ml dry ether was added dropwise to 300 mg (7·31 mmole) LAD in 225 ml dry ether. The reaction mixture was stirred at room temp for 2 hr, cooled, and cold water was added carefully. The ppt was removed by filtration and washed thoroughly with ether. The ethereal soln was dried over $MgSO_4$ and the ether evaporated to yield 3·41 g crude **5**. VPC examination (5 ft × $\frac{1}{4}$ in. KOH, Carbowax 6000, T = 160°) showed the product to be about 80% pure. The peaks due to non-polar impurities in the starting material were still present and the impurities did not interfere with the reduction of the epoxide. The crude **5** was chromatographed on Woelm neutral alumina (act. II) to yield 2·6 g (95·5%) of crystalline **5**: m.p. 85–87°; $\nu_{max}^{CCl_4}$ 2175 cm^{-1}; NMR (CCl_4) δ 2·45 (1 H, d, $J = 5·5$ Hz), 5·5 (1 H,d, $J = 5·5$ Hz); mass spectra $m/e^{+} = 223$, 98·5% monodeuterated.

Similar treatment of 68 mg (0·29 mmole) 94% pure **4** with LAH gave 67 mg (99%) widdrol.

Monodeuterothujopsene (**6**). To a refluxing soln of 555 mg (2·48 mmole) of **5** in 5 ml of 80% aqueous dioxan under N_2 was added 8·3 μl 70% $HClO_4$aq and the soln refluxed for 20 min. A 5-ml portion of half saturated $NaHCO_3$aq was added to the soln which was cooled to room temp and extracted with hexane. The hexane soln was dried over $MgSO_4$ and the hexane was removed on a rotary evaporator to yield 541 mg of pale yellow crystalline material. VPC analysis (5 ft × $\frac{1}{4}$ in, KOH, Carbowax 6000, $T = 160°$) showed ca. 15% hydrocarbons and 85% starting alcohol **5**. The hydrocarbons were separated from the alcohol by chromatography on alumina. VPC analysis (10 ft × $\frac{1}{4}$ in, 2·5% KOH, 2·5% Carbowax 20M on Chromosorb G, T = 150°) of the hydrocarbon mixture showed 60% monodeuterothujopsene (**6**) which was purified by preparative VPC: ν_{max} 2257, 1675, 1085, 1055 cm^{-1}; NMR on Varian HR-220 (CCl_4) δ 0·64 (1 H, doublet, $J = 4·5$ Hz), 1·12 (1 H, d, $J = 4·5$ Hz): mass spectra $M/e^{+} = 205$, 98% monodeuterated.

REFERENCES

[1] M. Hanack and H. J. Schneider, *Fortschr. Chem. Forsch.*, **8**, 554 (1967).

[2] K. B. Wiberg and G. Szeimies, *J. Am. Chem. Soc.*, **90**, 4195 (1968).

[3] [a] H. E. Zimmerman and D. S. Crumrine, *Ibid.*, **90**, 5612 (1968);
[b] H. E. Zimmerman, D. S. Crumrine, D. Dopp, P. S. Huyffer, *Ibid.*, **91**, 434 (1969).

[4] T. M. Brennan and R. K. Hill, *Ibid.*, **90**, 5614 (1968).

[5] Y. Hikino and P. de Mayo, *Chem. Comm.*, 550 (1965).

[6] J. Tadanier, *J. Org. Chem.*, **31**, 2124 (1966).

[7] S. W. Pelletier, S. Nagahama and Y. Shimizu, *Chem. Comm.*, 727 (1966).

[8] W. G. Dauben and L. E. Friedrich, *Tetrahedron Letters* 1735 (1967).

[9] W. G. Dauben and P. Oberhansli, *J. Org. Chem.*, **31**, 315 (1966).

[10] [a] C. Enzell, *Acta Chem. Scand.*, **16**, 1553 (1962);
[b] C. Enzell, *Tetrahedron Letters* 185 (1962).

[11] W. G. Dauben and L. E. Friedrich, *Abstracts* IUPAC *5th International Symposium on the Chemistry of Natural Products*. F13-p. 296. London, July 8–13 (1968)

[12] S. Forsen and T. Norin, *Acta Chem. Scand.*, **15**, 592 (1961).

[13] W. G. Dauben and W. T. Wipke, *J. Org. Chem.*, **32**, 2976 (1967)

[14] *Computer Programs for Chemistry* (Edited by D. F. DeTar) Vol. 1, pp. 54–116. Benjamin, New York (1968)