Tetrahedron, 1964, Vol. 20, pp. 67 to 70. Pergamon Press Ltd. Printed in Northern Ireland

THE ABSOLUTE CONFIGURATION OF OCCIDENTALOL

H. ZIFFER*, T. J. BATTERHAM*, U. WEISS* and E. VON RUDLOFF†

(*Received* 19 *August* 1963)

Abstract—A study of the optical rotatory dispersion curves of occidentalol and an unsaturated ketone derived from tetrahydrooccidentol indicate that the absolute stereochemistry of the hydrogen and methyl group at the ring junction is $\beta\beta$. The absolute stereochemistry of the isopropanol group is suggested as being most probably β.

THE structures of occidentalol (I) and occidol (II), the principal constituents of the essential oil of the wood of *Thuja occidentalis L.*, have been elucidated by Nakatsuka and Hirose.[1] Later work by von Rudloff and Erdtman[2] has shown that the stereochemistry at the ring junction of occidentalol is *cis* ($\alpha\alpha$ or $\beta\beta$). The arguments presented here, concerning the absolute stereochemistry at the ring junction, are, however, independent of the previous chemical evidence and consider all possible configurations.

The optical rotatory dispersion (ORD) curve of I (Fig. 1) shows an intense positive Cotton effect, proving that the diene system must be skewed in the sense of a right-handed helix.[3] Dreiding models show that this can be the case if the configurations of the 5 (H) and 10 (CH_3) groups at the ring junction are $\beta\beta$; $\alpha\alpha$; or $\beta\alpha$, but not if it is $\alpha\beta$. Further work on the ketonic oxidation products from tetrahydrooccidentalol has shown one of them to be the α,β-unsaturated ketone (IV) [λ_{max} 242 mμ ($\varepsilon = 6300$), calculated 244 mμ;[4] ν(CO) carbonyl absorption at 1670 cm^{-1}] rather than a saturated ketone as first assumed.[2] The ORD curve of this material can be used to distinguish between the 5β, 10β configuration and the two other possibilities (5α, 10α and 5β, 10α) on the basis of the chirality of the conjugated chromophore.[5] Models show that only the first case, with a 10β methyl group, could give a negative Cotton effect whereas the other two cases, with the opposite configuration at C_{10}, should produce positive Cotton effects, provided the conformations of unsaturated ketones in the 10-methyl decalin series are essentially the same as those of the 3-keto-Δ^4 steroids. As it was not possible to determine independently the conformation of IV, an analogous α,β-unsaturated ketone of known absolute configuration was prepared and its ORD curve

---

* National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Public Health Service, Department of Health, Education and Welfare, Bethesda, Maryland.

† National Research Council of Canada, Prairie Regional Laboratory, Saskatoon, Saskatchewan, Canada.

[1a] T. Nakatsuka and Y. Hirose, *Bull. Agric. Chem. Soc., Japan* **20**, 215 (1956);

[1b] Y. Hirose and T. Nakatsuka, *Ibid.* **23**, 140 (1959).

[2] E. von Rudloff and H. Erdtman, *Tetrahedron* **18**, 1315 (1962).

[3] A. Moscowitz, E. Charney, U. Weiss and H. Ziffer, *J. Amer. Chem. Soc.* **83**, 4661 (1961).

[4] L. F. Fieser and M. Fieser, *Steroids* p. 19. Reinhold, New York (1959).

[5] C. Djerassi, R. Records, E. Bunnenberg, K. Mislow and A. Moscowitz, *J. Amer. Chem. Soc.* **84**, 872 (1962).

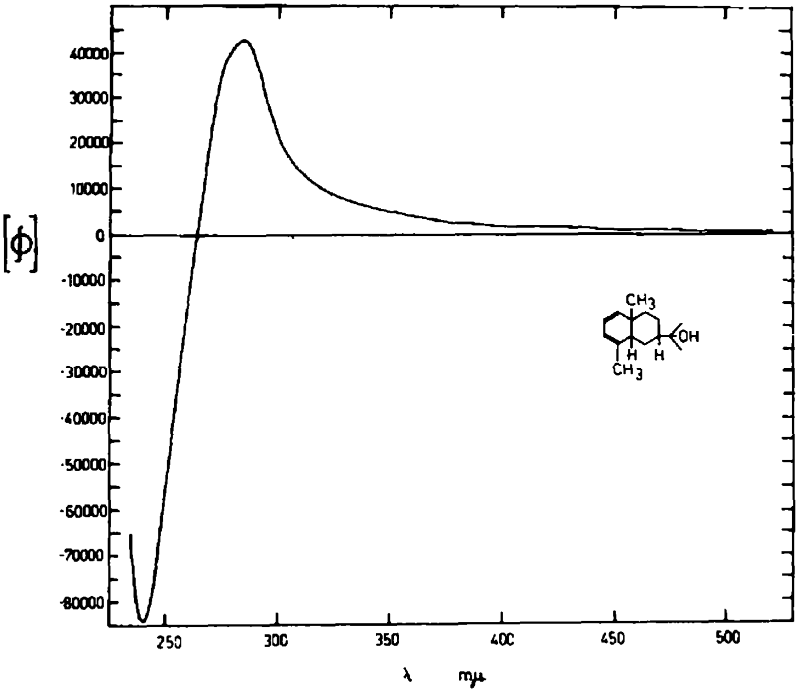


Fig. 1. Optical rotatory dispersion curve of occidentalol.

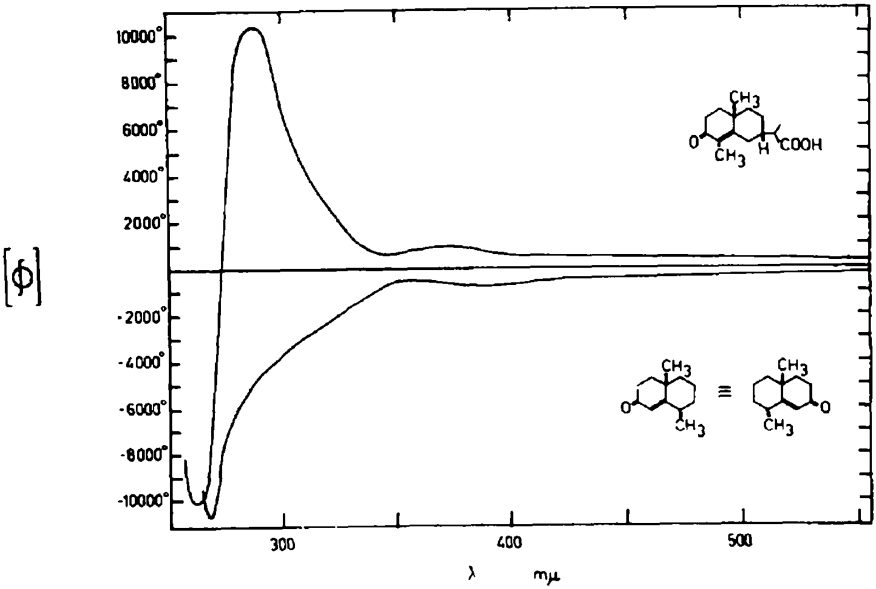
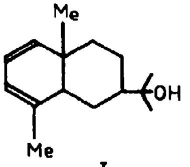


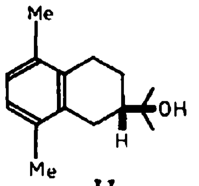
Fig. 2. Optical rotatory dispersion curves of unsaturated ketones.

compared with that of IV. The compound chosen was V, a reduction product of α-santonin, whose absolute configuration has been determined by Bruderer *et al.*[6] The mirror-image relationship of the ORD curves from the two unsaturated ketones (Fig. 2) indicated that the configuration of the C_{10}-methyl group in IV must be β.[7] It therefore follows that the configuration of the hydrogen at C-5 must be β and that the absolute configuration at the ring junction is the one shown in Formula VI.

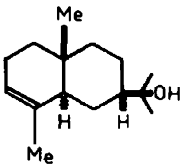
There remains the problem of the stereochemistry of the 2-hydroxy isopropyl group. The NMR spectra (both 60 Mc and 100 Mc) of I were carefully examined but unfortunately the signals from the C5 and C7 protons were not separated clearly enough from the remainder of the spectrum to give an unequivocal answer. However, there is nothing in the NMR spectrum which would contradict a β configuration, which appears likely since in the limited number of natural eudesmol-like compounds investigated thus far, the isopropyl group is always *cis* to the C_{10} methyl group. Furthermore, this group had been proven[8] to be β-orientated in II, the other main constituent of the oil of *Thuja occidentalis*. While a close biogenetic connection between I and II has not been experimentally established, their co-occurrence in the



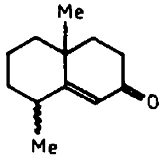
I



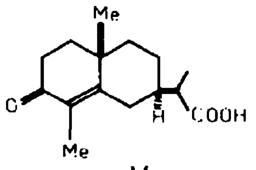
II



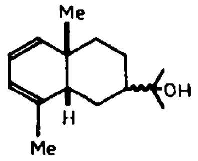
III



IV



V



VI

---

[6] H. Bruderer, D. Arigoni and O. Jeger, *Helv. Chim. Acta* **39**, 858 (1956).

[7] The absorption maximum of V occurs at 250 mμ, i.e. at 8 mμ toward longer wavelength than that of IV, and therefore the Cotton effect is also shifted approximately 10 mμ to longer wavelength.

[8] M. Nakazaki, *Bull. Chem. Soc., Japan* **35**, 1387 (1962).

same plant in approximately equal amounts, and their respective structures, certainly suggest a precursor-product relationship, or their formation from common intermediates. In either case, the biosynthetic events are not likely to involve C_7. Consequently, the known β-orientation of the 2-hydroxyisopropyl group in II makes it probable that this group in I is likewise β-orientated.

Since the preparation of this manuscript, Mislow and Moscowitz[9] have reported on the basis of a conformational analysis of occidentalol that the 2-hydroxyisopropyl group is β orientated.

EXPERIMENTAL

Crude tetrahydrooccidentalol, m.p. 81–84° (approx. 90% pure, GLC analysis; 140 mg) was dissolved in acetic acid (1 ml). A drop of 5% aq. H_2SO_4 was added and the mixture heated on a steam bath (80–85°) for 10–15 min. To this was added with stirring chromium trioxide (125 mg) in water (1 ml) and acetic acid (2 ml) over 30 min and the mixture heated for a further 30 min. Excess oxidant was reduced by addition of methanol (0·1 to 0·2 ml) and the solution was cooled, made alkaline (NaOH) and extracted with ether. The ethereal solution was separated, dried (Na_2SO_4) and the solvent evaporated to give the total neutral product (120 mg). GLC analysis showed this to be a mixture of 3 hydrocarbons (50%), unreacted tetrahydrooccidentalol (15%) and an unsaturated ketone (15%). The latter was isolated practically pure by preparative GLC. (Found: C, 80·51; H, 10·35%. Calc. for $C_{12}H_{18}O$: C, 80·85; H, 10·18%). No crystalline oxime, semicarbazone, or 2,4-dinitrophenylhydrazone was obtained.

---

[9] K. Mislow and A. Moscowitz, *Tetrahedron Letters* 699 (1963).