

Notizen

Sesquiterpenoids, 53¹⁾

Structure of „Tetrahydroatractylon Monooxide“

Hiroshi Hikino

Pharmaceutical Institute, Tohoku University,
Aoba-yama, Sendai, Japan

Received December 28, 1977

Sesquiterpenoide, 53¹⁾

Konstitution von „Tetrahydroatractylon-monooxid“

Das 1924 durch Hydrierung von Atractylon (1) und Aufbewahren des Produkts an der Luft erhaltene „Tetrahydroatractylon-monooxid“ wurde in seiner Konstitution aufgeklärt und ist das dimere Peroxid 3.

In 1924, *Takagi* and *Hongo* isolated a crystalline oxide, atractylon (1), from the rhizomes of what they considered to be originating from *Atractylis ovata* Thunberg, as part of their chemical investigation of the constituents of the crude drug „Jutsu“, now identified as being prepared from the rhizomes of *Atractylodes* spp.²⁾ Atractylon was hydrogenated over platinum in acetic acid to give the hexahydro derivative which on standing afforded a crystalline derivative 3. It was deduced that this derivative was saturated and had no primary or secondary hydroxyl nor a carbonyl group, and the two oxygen atoms in the molecule were thus concluded to be ethereal in nature. The derivative 3 was shown not to be a peroxide since treatment with iodide in an acidic medium gave no iodine. Therefore, it was designated as tetrahydroatractylon monooxide and considered to have one more oxygen atom as well as four extra hydrogen atoms as compared with the parent substance atractylon. The structure of atractylon was elucidated as being a sesquiterpenoid represented by formula 1 later in 1962³⁾. The structure of the derivative 3, the so-called “tetrahydroatractylon monooxide”, has remained unknown. The purpose of the present work was to clarify the structure of this interesting derivative.

Hydrogenation of atractylon (1) over platinum in acetic acid resulted in the consumption of 3 mol of hydrogen to yield hexahydroatractylon (2) which might be a stereoisomeric mixture. Inspection of the ¹H NMR spectrum, however, indicated that 2 consisted of one main stereoisomer, though its stereochemistry could not be specified.

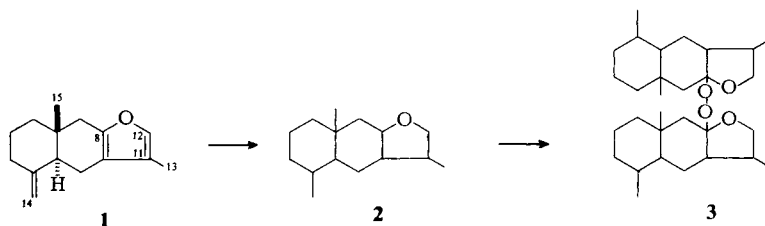
Standing in air of the hexahydro derivative (2) without further purification furnished the crystalline derivative 3 as reported. Its molecular formula was formerly postulated to be C₁₄H₂₂O₂ as the most probable one²⁾. Elemental analysis, now carried out, is in accord with the composition C₁₅H₂₄O₂. Because the IR spectrum disclosed no hydroxyl or carbonyl band, both the oxygen atoms in the molecule must be involved in oxide linkages. The ¹H NMR spectrum resembled that of hexahydroatractylon (2) and exhibited one methyl singlet and two methyl doublets which are allocated to C-15, and C-13 and C-14 hydrogens, respectively, but signals for only two hydrogens on oxygen-bearing carbon at $\delta = 3.51$ and 4.14. Double resonance experiments established the presence of the partial structure $-\text{O}-\text{CH}_2-\text{CH}-\text{CH}_3$ which must be allotted to C-12, C-11,

¹⁾ Part. 52: H. Hikino and K. Aota, *Phytochemistry* **15**, 1265 (1976).

²⁾ S. Takagi and G. Hongo, *Yakugaku Zasshi* **44**, 539 (1924).

³⁾ H. Hikino, Y. Hikino, and I. Yosioka, *Chem. Pharm. Bull.* **10**, 641 (1962); **12**, 755 (1964).

and C-13 in the eudesmane skeleton. The noticeable fact was, therefore, the missing of the signal for the hydrogen on the oxygen-carrying carbon C-8, which is present at $\delta = 3.32$ in the spectrum of the hexahydro derivative (2). In the ^{13}C NMR spectrum, the signals for 13 carbons were present in the saturated carbon region as expected. In the carbonyl carbon region, the signal for a secondary carbon carrying oxygen (C-12) appeared at $\delta = 73.0$ and, further, the signal for a quaternary carbon bearing two oxygens occurred at a lower-field region ($\delta = 113.2$). These observations indicated that the hydrogen at C-8 in the hexahydro derivative (2) was replaced by an oxygen function in the derivative 3. However, since the substance possesses no hydroxyl group as revealed by its IR spectrum, the newly formed C–O linkage at C-8 must constitute an oxide moiety. This requirement could be met only if the derivative were a dimer (3).



The molecular weight of the compound, formerly determined by means of cryoscopic method to be 220.0²⁾, was newly determined by means of two methods. The vapor pressure equilibrium method gave the molecular weight 458, and the mass spectrum disclosed the molecular ion peak at $m/e = 474$, demonstrating that the derivative 3 has the molecular formula $\text{C}_{30}\text{H}_{50}\text{O}_4$ with which the results of the elemental analysis are also consistent. The structure is thus deduced to be represented by formula 3. This was further confirmed by high resolution mass spectroscopy. The spectrum exhibited no molecular ion peak in this case, but displayed peaks at $m/e = 237.1869$ for $\text{C}_{15}\text{H}_{25}\text{O}_2$ and 221.1909 for $\text{C}_{15}\text{H}_{25}\text{O}$ at the heavy end, which are compatible with the proposed structure 3. It is concluded, therefore, that the derivative 3 is formed not during hydrogenation of attractylon (1) but during standing of hexahydroattractylon (2) in air. Formation of a dimeric peroxide from a tetrahydrofuran on standing seems to have no precedent in this group of substances.

Although the stereochemistry of compound 3 is still unknown, it can be concluded that dimerization through oxygen molecule occurred between the two hexahydro derivatives of the same stereochemistry since no heterogenous nature does occur in the ^1H and ^{13}C NMR spectra of the dimer.

Thanks are due to *Analytical Laboratories*, this Institute, to *Analytical Laboratories, Department of Chemistry*, this University, and to *JEOL Ltd.* for mass and NMR spectra measurement and microanalysis, to *Corona Electric Ltd.* for molecular weight determination, and to Dr. *Y. Hikino*, Dr. *C. Konno*, and Mrs. *M. Mikami*, this Institute, for technical assistance.

Experimental Part

Abbreviations: s = singlet, d = doublet, t = triplet, q = quarter, m = multiplet, and dd = doublet of doublets.

Dodecahydro-3,3',5,5',8a,8a'-hexamethyl-9a,9a'-dioxymbis(naphtho[2,3-b]furan) ("tetrahydroattractylon monooxide") (3): Attractylon (1) (3.0 g) in AcOH (20 ml) was hydrogenated over PtO_2 (50 mg) at room temperature, consuming 955 ml H_2 (standard state). After filtration, evaporation, and ether extraction, the product (2.0 g) was chromatographed over alumina (40 g). Fractions eluted with light petroleum gave hexahydroattractylon (2) as colorless oil (1.6 g). — IR (CCl_4 , cm^{-1}):

1032 (oxide). — ^1H NMR (60 MHz, CCl_4): $\delta = 0.92$ (3H, d, $J = 7$ Hz, CH_3 -14), 0.97 (3H, d, $J = 7$ Hz, CH_3 -13), 0.97 (3H, s, CH_3 -15), 2.4 (1H, m, 11-H), 3.32 (1H, m, 8-H), 3.6–4.0 (2H, m, 12- H_2).

2 on standing at room temperature for 1 month deposited colorless crystals which were crystallized from ethyl acetate giving 3 as colorless needles, m. p. 177–178.5°C (uncorr.). — MS (low resolution): $m/e = 474$ (M^+), 237, 221, 205; MS (high resolution): $m/e = 237.1869$ (calcd. for $\text{C}_{15}\text{H}_{25}\text{O}_2$ 237.1856), 221.1909 (calcd. for $\text{C}_{15}\text{H}_{25}\text{O}$ 221.1907). — IR (KBr, cm^{-1}): 1058, 1012 (oxide), 915 (peroxide?). — ^1H NMR (100 MHz, CDCl_3 , systematic numbering): $\delta = 0.89$ (6H, d, $J = 6$ Hz, 5- and 5'- CH_3), 0.95 (6H, s, 8a- and 8a'- CH_3), 0.97 (6H, d, $J = 5$ Hz, 3- and 3'- CH_3), 2.72 (2H, ddq, $J = 9, 8,$ and 5 Hz, 3- and 3'-H), 3.51 (2H, dd, $J = 10$ and 8 Hz, 2- and 2'-H), 4.14 (2H, dd, $J = 9$ and 8 Hz, 2- and 2'-H). — ^{13}C NMR (25 MHz, CDCl_3): $\delta = 11.9$ (q), 15.0 (q), 17.1 (t), 20.4 (q), 25.0 (t), 33.3, 33.6, 33.9, 34.7 (s), 42.6 (t), 44.6 (d), 46.0 (d), 48.9 (t), 73.0 (t), 113.2 (s).

$\text{C}_{30}\text{H}_{50}\text{O}_4$ (474.7) Calcd. C 75.90 H 10.62 Found C 76.05 H 10.43

[457/78]