

SENSITIZED PHOTOOXIDATION OF THUJOPSENE: SYNTHESIS OF THUJOPSADIENE

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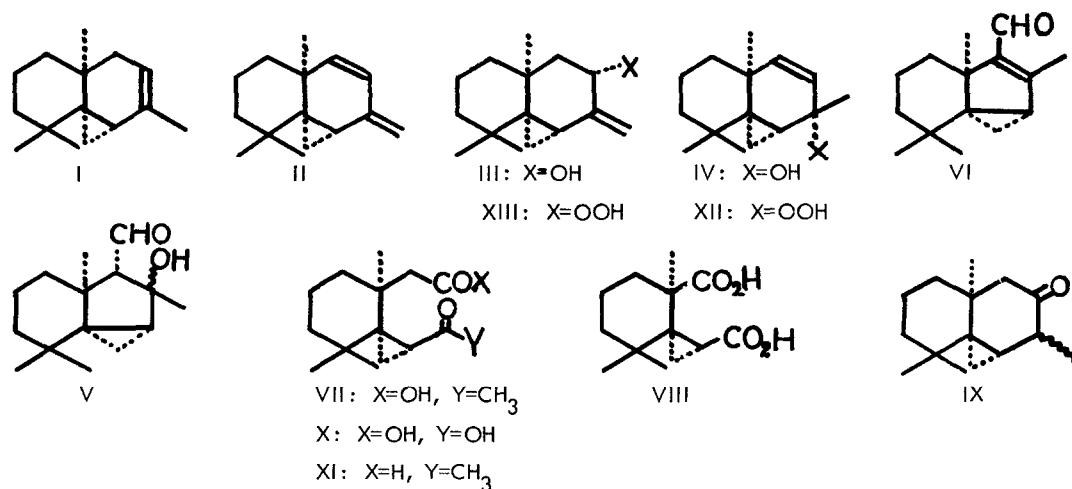
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Although the sensitized photooxidation of various types of organic compounds have been studied extensively by a number of workers (1), the known examples of reactions of compounds having a cyclopropane in the α position to an olefinic linkage are limited, as far as we know, to the following three cases: (-)cis- Δ^2 -carene (2), (+)- Δ^3 -carene (3) and (+) α -thujene (4). In these cases, the cyclopropyl group remained unchanged and photooxidation occurred stereospecifically from the opposite side of the cyclopropane ring, yielding the corresponding allyl alcohols. We have investigated the similar reaction of thujopsene, a tricyclic sesquiterpene with an α -cyclopropyl olefinic system. The results described herein throw light on the conformation of thujopsene and also accomplish a formal total synthesis of thujopsadiene, a natural thujopsane sesquiterpene recently isolated from Biota orientalis (5).

A methanolic solution of thujopsene (I) was irradiated by a 500 watt tungsten lamp in the presence of a small amount of methylene blue under oxygen atmosphere (6). After reduction with sodium sulphite, the reaction mixture was separated by silica gel chromatography and/or preparative thin layer chromatography to give four new products (II, III, IV, V) in addition to the following two known compounds obtained before by the chemical degradation of I; viz. the unsaturated aldehyde (VI) (7,8), 8% yield and the keto carboxylic acid (VII), 5% yield { δ 0.71 (3H, s), 0.99 (3H, s), 1.25 (3H, s), 2.33 (3H, s), 2.03 (1H, d, $J=13$) } (9).



The structures of the new compounds were determined in the following way. The hydrocarbon (II), colorless liquid, b.p. 115°/10 mm, obtained in 15% yield, has a 1,3-disubstituted diene system [$\lambda_{\text{max}}^{\text{MeOH}}$ 235 m μ ($\epsilon=23800$), δ 4.63 (H_A), 4.80 (H_B), 5.03 (H_C), 5.68 (H_D), $J_{\text{CD}}=10.2$, $J_{\text{CB}}=1.2$, $J_{\text{AB}}=2.3$, $J_{\text{DE}}=1.7$]. The NMR spectrum also exhibits the presence of cyclopropane hydrogens [δ 0.5-1.0 (2H, m), 1.91 (H_E, m)] and a methyl signal (δ 0.70) which is affected by the diamagnetic anisotropy of the cyclopropane ring as in I (10), besides two other methyl signals (δ 1.08 and 1.19). Permanganate oxidation of II yielded known bisnordicarboxylic acid (VIII) (9).

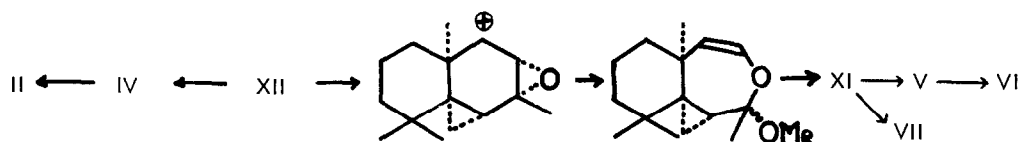
The allyl alcohol (III), m.p. 83.5-85°, isolated in 27% yield, has a secondary hydroxyl group [ν 3450, 1110 cm⁻¹, δ 4.07 (1H, dd, $J=9.5, 7.5$)], a vinylidene group [ν 1635, 890 cm⁻¹, δ 4.97 (1H, br.), 5.17 (1H, br.)] and three methyl groups (δ 0.60s, 1.04s, 1.12s). By cold mineral acid, III was converted to the saturated ketone (IX), colorless liquid, [oxime, m.p. 132-3°] (11) which contained a newly generated secondary methyl group [δ 1.23 (3H, d, $J=7$)] (12). Permanganate oxidation of III afforded the known nordicarboxylic acid (X) (9). Configuration of the hydroxyl group in III was assigned from the molecular rotation difference $\Delta[\Phi]=+157^\circ$ of III [$\Delta[\Phi]^{25}=-58.3^\circ$] and its *p*-nitrobenzoate, m.p. 147-8°, [δ 0.64 (Me, s), 4.97 (1H, br. s), 5.71 (1H, t, $J=8.0$), 8.17 (4H, s), $\{\Phi\}_D^{25}+98.8^\circ$] and the positive sign of the Cotton effect ($\theta_{328}+680$) in CD curves of the nitrobenzoate (13).

The second allyl alcohol (IV), m.p. 93-95°, isolated in 17% yield, showed the presence of a *cis* double bond [δ 5.23 (1H, mdd, $J=10.2, 1.8$), 4.93 (1H, d, $J=10.2$)] and a tertiary hydroxyl group [ν

3450 cm^{-1} , δ 1.91 (1H, OH)) with the cyclopropane group unchanged (δ_{Me} 0.65s, 1.07s, 1.16s, 1.40s). IV is unstable and changed to II upon silica gel chromatography or by distillation (100°/3 mm). The α -orientation of the hydroxyl group in IV was assigned by analogy with III.

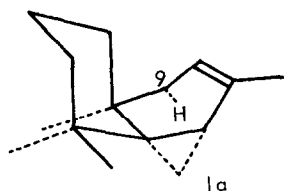
The hydroxyaldehyde (V), m.p. 75-76.5°, was obtained in 15% yield and its IR (ν 3580, 1730 cm^{-1}) and NMR spectra [δ 0.57 (3H, s), 1.00 (3H, s), 1.21 (3H, s), 1.57 (3H, s), 1.98 (1H, d, $J=2.0$), 9.79 (1H, d, $J=2.0$)] disclosed the presence of a hydroxyl group and an aldehyde group on a tertiary carbon, besides four methyl groups (14). V was easily converted to VI by alumina chromatography.

The compounds V, VI and VII are apparently secondary products formed during isolation, the most probable precursor being the ketoaldehyde (XI). In fact, an aldehyde was detected by TLC immediately after the reduction, but this changed to V and VI rapidly. The reaction pathway leading to these products can be visualized by the following scheme (15), the allylic hydroperoxide (XII) being preferred to a hypothetical dioxetane derivative (16).



From this mechanistic consideration, as well as the experimental fact described above, all the reaction products II-VII are shown to be formed from XII, except III which originates from another hydroperoxide (XIII).

The reaction rate of I was found to be larger in the presence of methylene blue than with eosin yellow. However, the ratio of yields of the products III/II+IV+V+VI+VII (XIII/XII) remains constant (ca 1/2) with both sensitizers, although the yield of each product originating from XII varies according to the isolation procedure. A cyclic mechanism has been proposed for this type of reaction and the preferred abstraction of an axial allylic hydrogen over methyl hydrogens by singlet oxygen was clearly



demonstrated (2,4,17). In view of the small ratio of XIII/XII, it is concluded that the α -side of thujopsene is less hindered in spite of the presence of cyclopropane ring and the 9 α -hydrogen is axially oriented, defining the preferred conformation of I as Ia. This conformation is in agreement with the one deduced by the study of circular dichroism (18).

II was proved to be identical (19) with natural thujopsadiene recently isolated by Nakatsuka *et al* (5). Since the total synthesis of I has been achieved (20), the photochemical process provides a formal total synthesis of II. Concomitant occurrence of I and II (21) and the mildness of the condition of the photochemical process suggest this process be in fact a biosynthetic pathway of II.

References and Footnotes

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- 21) Spectral similarity of II with the "Hydrocarbon VI", isolated from Cupressus funebris by O. Motl and S.K. Pakniker (Coll.Czech.Chem.Comm., 33, 1939 (1968) was noted by Professor T. Nakatsuka (private communication).