Structure of Liguloxide, Liguloxidol, and Liguloxidol Acetate, Sesquiterpenes of Antipodal Guaiane Type

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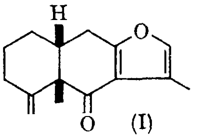
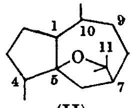
We previously reported[1] the isolation of ligularone (I), an eremophilane-type sesquiterpene, from the aerial part of ***Ligularia Fisheri*** Turcz. We have also isolated three other sesquiterpenes of antipodal guaiane type, which were named liguloxide (II), liguloxidol (III) and liguloxidol acetate (IV) respectively.

Liguloxide (II), $C_{15}H_{26}O$, has m.p. 36°, $[\alpha]_D$ $-52{\cdot}8°$, and on dehydrogenation it gave guaiazulene. The i.r. spectrum of liguloxide shows no carbonyl or hydroxyl absorption. The n.m.r. spectrum displays two doublets centred at τ 9·13 and 9·07 [Me on C(4) and C(10)], and also two singlets at τ 8·84 and 8·68 [Me on C(11)], but no signals below τ 7·7, which means that liguloxide is a guaiane sesquiterpene having a ditertiary ether linkage between C(11) and C(1) or C(5).

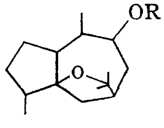
Liguloxidol (III), $C_{15}H_{26}O_2$, a colourless oil, $[\alpha]_D$ $-36{\cdot}8°$, was shown to be a hydroxy-derivative of liguloxide, by its oxidation with Jones reagent to yield a ketone (V), m.p. 115°, ν_{max} 1702 cm.$^{-1}$, indicating that the hydroxyl group in (III) is secondary and present in the seven-membered ring. Heating liguloxidol with methanesulphonyl chloride and pyridine gave two dehydrated compounds [(VI) and (VII)]. Hydrogenation of (VI), which contains a –CH=CH– group (n.m.r. spectrum), led to the formation of liguloxide (II), demonstrating that liguloxidol has the same structure as (II) except for an additional hydroxyl group. The hydroxyl group should be located at C-9 because the other dehydrated compound (VII) possesses a –CMe=CH– grouping (n.m.r. τ 8·35, 3H).



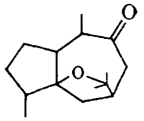
(I)



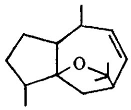
(II)



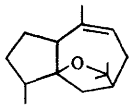
(III) R=H
(IV) R=Ac



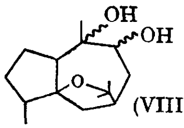
(V)



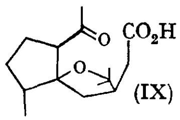
(VI)



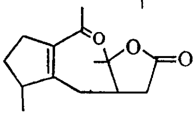
(VII)



(VIII)



(IX)



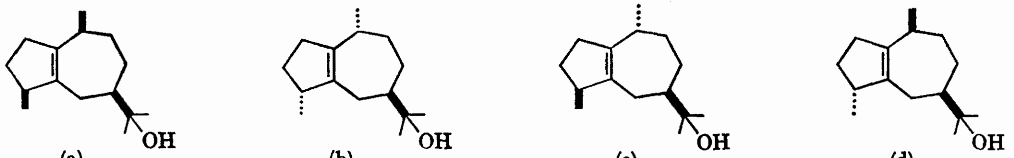
(X)

Hydrogenation of (VII) gave a 1 : 1 mixture of liguloxide and 10-epiliguloxide, $C_{15}H_{26}O$, a colourless oil, $[\alpha]_D$ $-3{\cdot}5°$.

Osmium tetroxide oxidation of (VII) afforded a

(a) (b) (c) (d)

(II)



(a) (b) (c) (d)

(XI)

1 : 1 mixture of *cis*-diols (VIII), which were successively oxidized with periodic acid and Jones reagent to form a keto-acid (IX), $C_{15}H_{24}O_4$, m.p. 96°. In the n.m.r. spectrum of (IX), there appears an active methine signal at τ 6·72 as a triplet (J = 9 c./sec.),[2] suggesting that the ethereal oxygen in (IX), thus in turn in (II), links to C(5) and not to C(1).

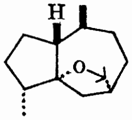
Acid treatment of (IX) produced a keto-lactone (X) in 70% yield. This compound (X) shows absorptions at 253 mμ (ϵ 6640);[3,4] 1765 (γ-lactone), 1672, and 1605 cm.$^{-1}$ ($\alpha\beta$-unsaturated ketone); and no peaks due to vinyl proton or vinyl methyl group in the n.m.r. spectrum, thus agreeing with the assigned structure. The formation of (X) as a single major product also supports the structure (II) for liguloxide.

Liguloxide can be represented by one of the relative configurations (IIa, b, c or d),† and thus its ether-cleaved compound is one of the stereoisomers (XIa, b, c or d), in which (XIa) alone is a known substance, guaiol.[5]

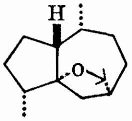
Treatment of liguloxide with boron trifluoride in acetic anhydride in the presence of lithium iodide[6] furnished, after hydrolysis and extensive chromatography, a guaiol-type compound (XIc), $C_{15}H_{26}O$, a colourless oil, ν_{max} 3560 and 3400 cm.$^{-1}$ (OH), n.m.r. τ 9·06, 9·03, 8·95, 8·93 [Me on C(4) and C(10)], 8·82 Me on C(11)] and no vinyl proton signals. This compound differs from guaiol (XIa) in gas chromatographic behaviour. Then, 10-epiliguloxide was also treated in the same manner giving rise to a crystalline compound, $C_{15}H_{26}O$, m.p. 89—90°, $[\alpha]_D$ +28·6° (±2·4°), which proved to be the enantiomer of guaiol,‡ m.p. 89—90°, $[\alpha]_D$ −31·2° (±0·7°), by comparison of the i.r. spectrum and retention time.

These facts corroborated the absolute configuration of liguloxide as (XII) and that of 10-epiliguloxide as (XIII) respectively, except for the assignment at C(1). The decision on the stereochemistry at C(1) was possible from studies of liguloxidol and the ketone (V).

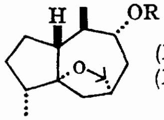
Examination of the i.r. spectrum of liguloxidol taken in dilute solution revealed the presence of a strong intramolecular hydrogen bonding, confirming the hydroxyl group in liguloxidol to be α-oriented as shown in (XIV).



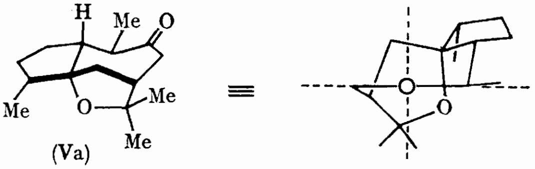
(XII)



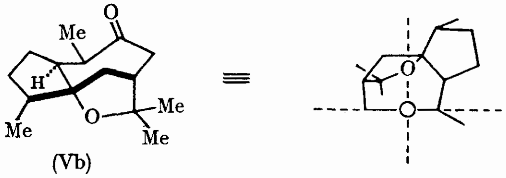
(XIII)



(XIV) R=H
(XV) R=Ac



(Va)



(Vb)

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† This is not the place to consider the question on stereochemistry at C(1).

‡ Purchased from Polak & Schwarz's Essence-Fabriken, New York.

Considering that the ketone (V) is stable to alkali, *i.e.* the methyl group on C(10) is equatorial-like, it can be restricted within two conformations (Va and b), the former carrying 1β-hydrogen while the latter 1α-hydrogen. The o.r.d. determination of (V) showed a negative Cotton curve ($a = -76$), the amplitude agreeing with a value (above 60)[7] expected from (Va), and not with a value (below 60)[7] expected from (Vb). Furthermore, that lithium aluminium hydride reduction of (V) predominantly produced liguloxidol (9α-hydroxyliguloxide) is applicable only to the conformer (Va): if the ketone were the alternative (Vb), attack of the reagent would occur from less hindered α-side, thus giving 9β-hydroxyliguloxide. These results led to the establishment of the absolute configurations (XII), (XIII), (XIV), and (XV) for liguloxide, 10-epiliguloxide, liguloxidol, and liguloxidol acetate§ respectively.

Since 10-epiliguloxide was found to differ from guaioxide[8] by comparison of their spectra and retention times,¶ the antipodal structure of (XIII) for guaioxide should be removed out of the four possible structures,[8b] although the American and Belgian authors took it to be most probable. Studies to establish the structure of guaioxide are now in progress in our laboratory.

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§ $C_{17}H_{28}O_3$, m.p. 85°, $]\alpha]_D$ $-52{\cdot}0°$, ν_{max} 1735 and 1240 cm.$^{-1}$.

¶ We are grateful to Dr. P. Ledoux for his kind donation of a sample of guaioxide.

[1] H. Ishii, T. Tozyo, and H. Minato, *Tetrahedron*, 1965, **21**, 2605.

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[3] W. M. Schubert and W. A. Sweeney, *J. Amer. Chem. Soc.*, 1955, **77**, 2297.

[4] H. Hikino, K. Meguro, Y. Sakurai, and T. Takemoto, *Chem. and Pharm. Bull.* (*Japan*), 1966, **14**, 1241.

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[6] R. D. Youssefyeh and Y. Mazur, *Tetrahedron Letters*, 1962, 1287.

[7] C. Beard, C. Djerassi, J. Sicher, F. Sipos, and M. Tichy, *Tetrahedron*, 1963, **19**, 919.

[8] (a) R. B. Bates and R. C. Slagel, *Chem. and Ind.*, 1962, 1715; (b) P. Ledoux, B. P. Vaterlaus, and G. Chiurdoglu, *Bull. Soc. chim. belges.*, 1966, **75**, 551; (c) M. V. Kadival, M. S. R. Nair, and S. C. Bhattacharyya, *Tetrahedron*, 1967, **23**, 1241.