Revision of the Stereochemistry of Liguloxide and Related Compounds

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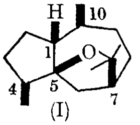
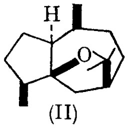
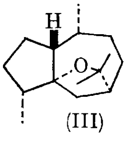
OUR previous work on guaioxide[1] together with that of Tanahashi,† who gave decisive evidence for the β-configuration of the C(4)-Me group, has established its absolute configuration as that shown in (I). Hence 1-epiguaioxide, recently prepared by Ehret and Ourisson,[2] should be represented by formula (II), which would be expected to correspond to the antipodal structure of 10-epiliguloxide (III).[3] The compounds, however, were found not to be enantiomorphic by comparison of their i.r. and n.m.r. spectra. This requires the correction of the stereochemistry of 10-epiliguloxide and thus that of liguloxide itself (IV).[3]



(I)



(II)



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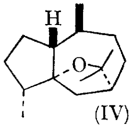
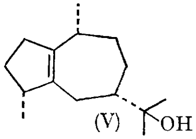
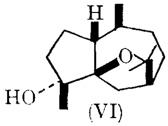


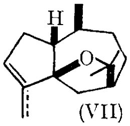
(IV)



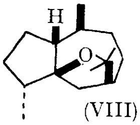
(V)



(VI)



(VII)



(VIII)

We deduced[3] the stereoformula (IV) for liguloxide from the fact that BF_3-treatment of 10-epiliguloxide led to the formation of (+)-guaiol (V), on the assumption that in this reaction no inversion would have occurred. Since formula (III) is no longer applicable to 10-epiliguloxide we were forced to consider the possibility that, in the BF_3-reaction, inversion might take place at C(4), the nearest asymmetric centre to a terminal position of the oxido-bridge to be opened. If this were true, the structure of liguloxide would differ only in the configuration of the oxido-bridge from the structure of guaioxide (I). Because we cannot chemically change the configuration of the oxide bridge, we have prepared various epimers of liguloxide or guaioxide differing in the configuration at C(1), C(4), and C(10), by microbial hydroxylation on these positions; we can thus correlate liguloxide with guaioxide, whose absolute configuration is now confirmed.[1]

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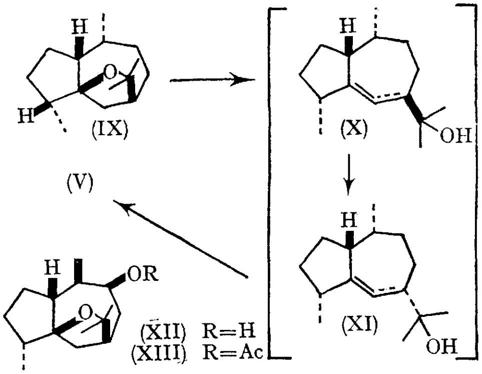
† Tanahashi treated guaiol with [$^2H_2$]sulphuric acid in [^{2}H]acetic acid to give a deuteriated guaioxide, mass spectrum M 223. This means that there is no acid-catalyzed isomerization of the double bond during the formation of guaioxide, and thus establishes that guaioxide has the same 4β-Me group as guaiol (personal communication from Dr. Y. Tanahashi of the University of Tokyo).

Treatment of 4α-hydroxyguaioxide (VI)[1] with thionyl chloride and pyridine gave a mixture of dehydrated compounds (VII), which were catalytically hydrogenated to yield a 2 : 1 mixture of guaioxide (I) and 4-epiguaioxide (VIII).

We found, unexpectedly, that the i.r. spectrum of 4-epiguaioxide is identical with that of liguloxide. Also the m.p., $[\alpha]_D$, and retention times of both compounds were comparable, and liguloxide and 10-epiliguloxide consequently proved to have the stereochemistry shown in (VIII) and (IX), respectively. Therefore inversion had taken place at C(7) and not at C(4), in the BF_3-treatment of 10-epiliguloxide (Scheme). The bulky axial isopropyl group at C(7) in (X) would epimerize to the equatorial conformation of (XI), and then give (+)-guaiol (V).

Since the two other constituents of *L. fischeri*, liguloxidol and liguloxidol acetate, have been interrelated,[3] they too must contain a β-oriented oxido-bridge. The configuration of the C(9)-hydroxy-group in liguloxidol must also be β and not α, because its assignment is based on the presence of intramolecular hydrogen bonding between this hydroxy-group and the ether oxygen atom.[3] Liguloxidol and liguloxidol acetate consequently have the absolute configurations (XII) and (XIII), respectively. From these revised structures, the conformation of 9-oxoliguloxide is (XIV); this is confirmed by the o.r.d. determination,[3] showing a negative Cotton curve ($a = -76$), and by the fact[3] that lithium aluminium hydride reduction of the ketone produced predominantly liguloxidol.

Liguloxide and related compounds are now shown to have the 7β-isopropyl configuration common to essentially all guaiane-type sesquiterpenes.



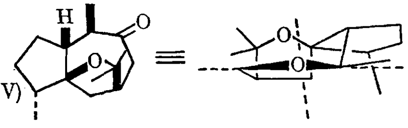
(IX)

(X)

(XI)

(V)

(XII) R=H
(XIII) R=Ac



(XIV)

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[1] H. Ishii, T.Tozyo, and H. Minato, *Chem. Comm.*, 1968, 649.
[2] C. Ehret and G. Ourisson, *Bull. Soc. chim. France*, 1968, 2629.
[3] H. Ishii, T. Tozyo, and H. Minato, *Chem. Comm.*, 1968, 106.