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Proof of the Configuration at C_4 of Guaioxide

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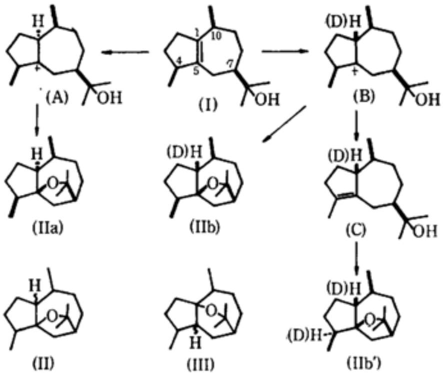
Recent communications[1,2] on the structure of guaioxide have prompted us to report our results on this problem. Our attention to the structure of this compound has been drawn by isolation of two new sesquiterpene oxides ($C_{15}H_{26}O$) from "San-shion" of *Ligularia* genus (probably *L. sibirica*).[3] These oxides which we conventionally called LB and LC are both isomeric to guaioxide. One (LC) of these recently turned out to be identical with liguloxide.[4]

Guaioxide has been isolated from guaiac wood oil by Bates and Slagel.[5] They reported that acid treatment of guaiol (I) gave guaioxide for which the structure II or III was suggested. Later Ledoux *et al.*[6] assigned the structure IIa to guaioxide, provided that the hydroxyl group adds to the double bond at C_1—C_5 in *trans* manner, and that no isomerization occurs at the other centers (I→A→IIa). Ishii *et al.*[1] recently deduced the structure IIb for guaioxide in which the hydrogen at C_1 and the ether bridge are both β-oriented. One of the most probable courses of formation of guaioxide might be a migration of the double bond at C_1—C_5 to the position C_4—C_5 with addition of proton at C_1 from β-side followed by *srans* addition of the hydroxyl group (I→B→C→IIb′). Hence use of deuteriated acid in cyclization of guaiol (I) is expected to give information on the mechanism of formation of guaioxide and on the stereochemistry at C_4.



Guaiol (I) gave guaioxide-d_1 when treated with sulfuric acid-d_2 in acetic acid-d_1. The mass spectrum of deuteriated guaioxide shows a molecular ion peak at m/e 223, and the NMR spectrum is essentially the same with that of non-deuteriated guaioxide, showing no change in the region of methyl signals. One deuterium atom introduced is, therefore, located at C_1.

This result eliminates the possibility of any acid-catalyzed isomerizations of the double bond (*e.g.* I→B→C→IIb′) during the formation of guaioxide, and establishes that guaioxide has the same configurations at C_4, C_7 and C_{10} as those of guaiol, although no evidence is given as to the ring junction. The above result firmly confirms the 4β-methyl configuration which was previously given for guaioxide by Ishii *et al.*[1] on the basis of generally accepted considerations for microbial hydroxylation.

With Ishii's conclusion[1] admitted, guaioxide should be formed by the route I→B→IIb. *Cis* addition of hydroxyl group would be due to the

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[1] H. Ishii, T. Tozyo and H. Minato, *Chem. Commun.*, **1968**, 649.

[2] C. Ehret and G. Ourisson, *Bull. Soc. Chim. France*, **1968**, 2629.

[3] F. Patil, G. Ourisson, Y. Tanahashi, M. Wada and T. Takahashi, *ibid.*, **1968**, 1947.

[4] H. Ishii, T. Tozyo and H. Minato, *Chem. Commun.*, **1968**, 106. The structure of liguloxide was recently shown to be 4-epiguaioxide: H. Ishii, T. Tozyo and H. Minato, *Chem. Commun.*, **1968**, 1534.

[5] R. B. Bates and R. C. Slagel, *Chem. & Ind.*, **1962**, 1715.

[6] P. Ledoux, B. P. Vaterlaus and G. Chiurdoglu, *Bull. Soc. Chim. Belges*, **75**, 551 (1966); P. Ledoux, *Ing. chim.*, **48**, 24 (1966).

conformational stability of an intermediate cation B in comparison with cation A. This evidence is important in view of the structural studies of the remaining oxide (LB) which are in progress in our laboratory and in the Shionogi Research Laboratory.[7]

Experimental

Treatment of Guaiol with Sulfuric Acid-d_2 in Acetic Acid-d_1. Guaiol (957 mg) was dissolved in 99% acetic acid-d_1 (CIBA Ltd. ; 19 g) containing sulfuric acid-d_2 (13 μl). The solution was left at room temperature (13—15°C) for 72 hr. Repeated chromatographies (eluted with petroleum ether) of the crude reaction product (763 mg) over silica gel, then over alumina, gave a hydrocarbon mixture (437 mg) and a colorless oil (41 mg). The latter, having the same retention time in VPC with that of guaioxide, showed essentially the same IR and NMR spectra with those of guaioxide respectively, and gave rise to a molecular ion peak at m/e 223 on its mass spectrum (measured using the Hitachi Mass Spectrometer, RMU-6D Type).

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[7] Private communication from Dr. H. Ishii.