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THE STRUCTURES AND CONFIGURATIONS OF LARIXOL AND LARIXYL ACETATE

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From the oleoresin of European larch (Larix europaea D.C.) H. Wienhaus et al. (1,2) isolated a compound which they named larixyl acetate ($C_{22}H_{36}O_3$; m.p. 82°; $[\alpha]_D$ +67°)[+]. On hydrolysis this compound furnished a diterpenoid diol named larixol ($C_{20}H_{34}O_2$; m.p. 101°; $[\alpha]_D$ +57°). Recently Shmidt et al. (3) reported that larixol and not larixyl acetate was one of the main neutral constituents of the oleoresin of Siberian larch (L. sibirica Ledb.).

In an abstract from a meeting Haeuser (4) briefly summarizes some data concerning the structure of larixol. He proposes that larixol should be the 6-hydroxy derivative of manool. On the bases of this structure the mass spectrum of larixol has recently been discussed (5).

The NMR spectrum[++] of larixol provides clear indications for

[+] All rotations are measured in chloroform solutions.

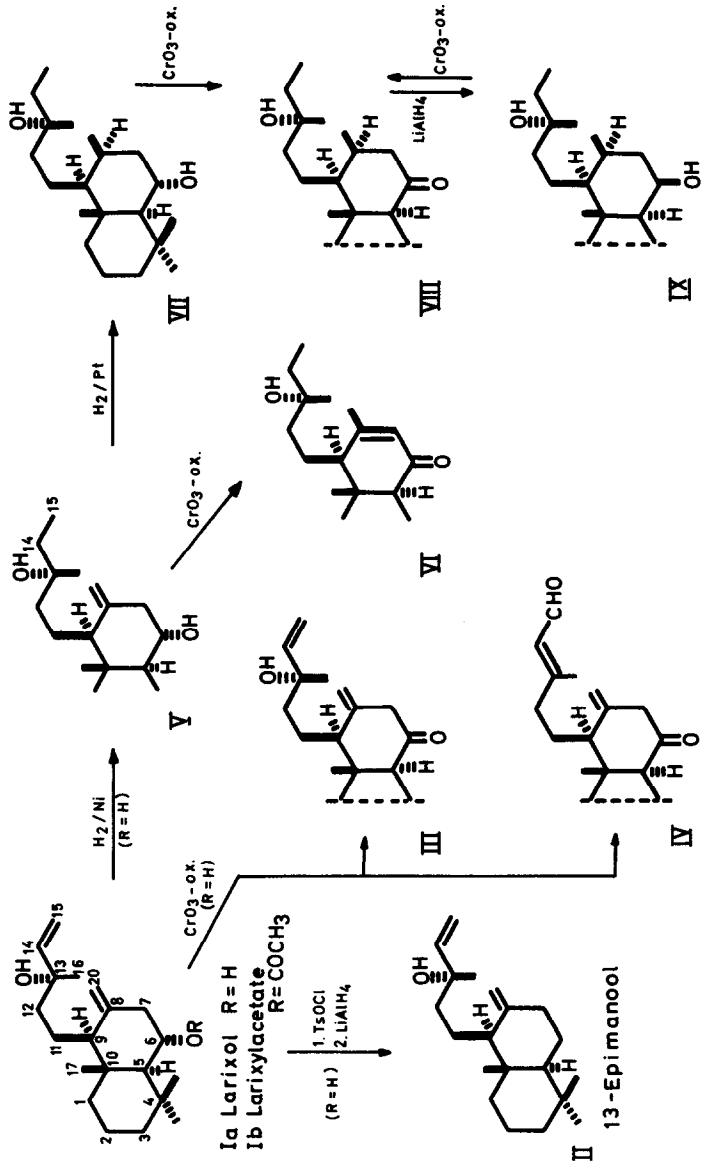
[++] The NMR spectra are recorded on a Varian A60 instrument (60Mc/s) using carbon disulphide solutions. The chemical shifts are from tetramethylsilane (internal standard).

the fact that it is a manool (or 13-epimanool) derivative possessing an additional secondary hydroxyl group. The ABC-patterns due to the C(14)- and C(15)-protons are very similar in the spectra of larixol and manool. The two broad signals due to the protons of the C(20)-methylene group at 4.55 and 4.79 ppm are shifted to lower field compared to manool (4.45 resp. 4.75 ppm).

The proton of the secondary carbinol atom ($\geq$C<u>H</u>-OH) of larixol has its resonance position at 3.67 ppm. In larixyl acetate the corresponding signal appears at 4.88 ppm. Larixyl acetate is thus the monoacetate of larixol in which the secondary hydroxyl group is acetylated. On treatment with equimolecular amounts of acetyl chloride in pyridine larixol gave larixyl acetate in an almost quantitative yield. Under similar conditions the corresponding mono-p-nitrobenzoate (I, R = $-COC_6H_4NO_2$; $C_{27}H_{37}O_5N$; m.p. 131-132°; $[\alpha]_D$ +61°) was formed. The corresponding diacetate $C_{24}H_{38}O_4$; m.p. 117°; $[\alpha]_D$ +36°) could be prepared from larixol or larixyl acetate using acetyl chloride under conditions previously describes (6).

Since 13-epimanool (II) (7) has been found to be one of the main constituents of the oleoresin of <u>L. europaea</u> (8) it was believed that larixol (Ia) is of the 13-epimanool type. The difference in molecular rotations between manool/14,15-dihydromanool ($\Delta[M]_D$ -15°, 13-epimanool / 14,15-dihydro-13-epimanool ($\Delta[M]_D$ -55°) and larixol/14,15-dihydrolarixol ($\Delta[M]_D$ -43°) provides indications for the 13-epi-configuration of larixol (Ia).

On treatment with an equimolecular amount of p-toluenesulphonyl chloride in pyridine larixol furnished a mono-p-toluenesulphonate which, however, was not very stable. It was therefore treated with an excess of lithium aluminium hydride in boiling ether without any preceeding purification. The main product from this hydride reduction was separated by chromatography on alumina and was identified as 13-epimanool (II) (m.p. 35-38°; $[\alpha]_D$ +48°) by a direct comparison (mixed m.p. and IR) with an authentic sample. The identity was further confirmed by com-


Ia Larixol R = H
Ib Larixylacetate R = COCH3
(R = H) 1. TsOCl 2. LiAlH4
II 13-Epimanool
CrO3-ox. (R = H)
H2/Ni (R = H)
III
IV
V
CrO3-ox.
VI
H2/Pt
VII
CrO3-ox.
VIII
LiAlH4
IX

parisons of the corresponding 3,5-dinitrobenzoates (7) and of the p-nitrobenzoate (m.p. 141-142°, $[\alpha]_D$ +47°). This settles the structure Ia of larixol except for the position and relative configuration of the secondary hydroxyl group.

The Jones oxidation of Ia under standardized conditions (9) furnished mainly two products. The broad singlet at 2,66 ppm in the NMR spectrum belongs to two protons within a homoconjugated system, which proves the arrangement of the C-atoms 6, 7 and 8 as indicated in the molecul III. Based on the intensity of the absorption in the vinyl region the ketoalcohol III is the minor part of the oxidation products. The main product exhibits a α,β-unsaturated aldehyd grouping (doublet at 9,9 ppm) in the side chain (sharp singlet at 2,1 according to a methyl group (C 16) on conjugated system) and represents the structure IV. The IR absorption bands at 1720 and 1673 agrees with the carbonyl group in 6 and 15 position, respectively. A strong absorption at 890 cm^{-1} ($>$=CH_2) and weaker ones at 912 and 990 cm^{-1} (vinyl) indicates likewise the proportion of III and IV.

Hydrogenation of larixol (Ia) using a Raney-nickel catalyst furnished 14,15-dihydrolarixol (V, $C_{20}H_{36}O_2$, m.p. 110-111°, $[\alpha]_D$ +43°). Jones oxidation of V yielded a crude mixture from which an oily α,β-unsaturated hydroxy-ketone VI could be separated by chromatography on alumina. The IR spectrum of the product exhibits bands at 3 500 (broad, -OH), 1 670 and 1 625 ($>$C=C-CO) cm^{-1}, but no bands characteristic of an exocyclic methylene group ($>$C=CH_2, 3100 and 890 cm^{-1}). The UV spectrum of the product has a maximum at 240 mμ. Thus the 8,20-double bond isomerizes during the oxidation or isolation procedures in 7,8-position. This experiment shows that larixol can be either the 6- or 11-hydroxy derivative of 13-epimanool, the former alternative being more consistent with the ultraviolet data of the hydroxy-ketone VI.

Nuclear magnetic spectral data provide evidence for a 6α-hydroxyl grouping in larixol. The signal at 3.67 ppm is assigned to the axial

6β-proton and reveals couplings to the axial 5α- and 7α-protons (J 10 cps) and to the equatorial 7β-proton (J 5 cps). Due to the deshielding of the C(8)-C(20) double bond and the 6α-hydroxyl group the equatorial 7β-proton signal appears at a low field (2.51 ppm). This proton is coupled to the axial 6β-proton (J 5 cps) and to the 7α-proton (J 12 cps). The signals due to the 18- and 19-methyl groups of larixol (0.92 and 1.09 ppm respectively) appear at lower field than those of the corresponding groups of 13-epimanool (0.78 and 0.86 ppm, respectively). Particularly the 19-methyl signal is shifted downfield. This must be due to the deshielding effect of the 6α-hydroxyl group.

The configuration of the 6-hydroxyl group of larixol is confirmed by the following chemical experiments (cf. also Ref. 4). Hydrogeneation of larixol (Ia) using a platinum catalyst yielded tetrahydrolarixol (VII, $C_{20}H_{38}O_2$, m.p. 123-124°, $[\alpha]_D$ +53°). A mild chromic acid oxidation (9) of VII gave the ketone (VIII, $C_{20}H_{36}O_2$, m.p. 67-68°, $[\alpha]_D$ +46°) which on reduction with lithium aluminium hydride gave the alcohol (IX, $C_{20}H_{38}O_2$, m.p. 89-90°, $[\alpha]_D$ +26°). This alcohol could be oxidized back to the ketone VIII. Alcohol IX must therefore be the 6-epimer of tetrahydrolarixol (VII). Hydride attack from the less hindered α-side of the ketone VIII leads to the alcohol IX which thus must have the 6β-configuration. Accordingly tetrahydrolarixol (VII) has the 6α-configuration.

The results presented above settle the relative and absolute configuration of larixol (Ia) and larixyl acetate (Ib).

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