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STRUCTURES OF CONTORTADIOL (AGATHADIOL), CONTORTOLAL (AGATHOLAL), AND HYDROXYEPIMANOOL (EPITORULOSOL)*

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In a recent paper (2) we reported on the isolation and proof of structure of the new diterpene, 13-epimanool (I),**** from the benzene extract of the bark of lodgepole pine (Pinus contorta Dougl.). At the same time we reported on the isolation of three further new diterpenes, hydroxyepimanool, contortadiol, and contortolal, the latter being isolated in the form of its semicarbazone. We suggested that these compounds might have the structures $\Delta^{8(20),14}$-labdadiene-13α,18-diol, $\Delta^{8(20),13}$-labdadiene-15,18-diol, and 15-hydroxy-$\Delta^{8(20),13}$-labdadien-18-al respectively.

We now wish to present evidence that the correct structures of these diterpenes are identical to those postulated except that all are epimeric at C-4 (i.e., the "18" in the systematic names above should be replaced with "19").

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* Previous paper in this series: "Triterpenes of Pine Barks: Identity of Pinusenediol and Serratenediol" (1).

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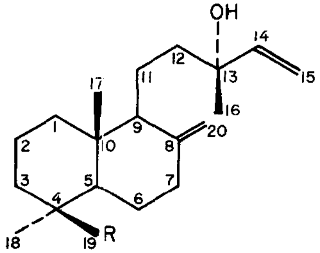
*** Maintained at Madison, Wis., in cooperation with the University of Wisconsin.

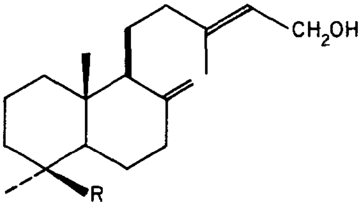
**** 13-Epimanool is also a major constituent of the oleoresin of Larix decidua (3).

Thus hydroxyepimanool is II (13-epitorulosol), contortadiol is identical to agathadiol (III), and contortolal (IV) should be renamed agatholal.



I EPIMANOOL (R = CH_3)

II EPITORULOSOL (R = CH_2OH)



III AGATHADIOL (R = CH_2OH)

IV AGATHOLAL (R = CHO)

As has been pointed out by Gough (4), our own data, especially the position of the AB quartet of the 4-CH_2OH in the n.m.r. (5), favored oxidation at the C-19 methyl rather than at the C-18 methyl. Our original preference for C_{18} oxidation, however, was based mainly on two grounds. First, axial oxidation at C-19 had not yet been observed in any diterpenes of the genus *Pinus*, equatorial oxidation at C-18 being the usual observation, and at that time no case had been reported of the cooccurrence of both these oxidation patterns. Second, direct comparison of agathadiol (6) and contortadiol led us to the conclusion that, although these compounds were very similar, they were not identical since they gave different patterns on gas-liquid chromatography (2-1/2% SE-30 on 70/80 Anakrom ABS at 206°) and on mass spectroscopy. However, the melting points (undepressed on admixture), optical rotation, ultraviolet and infrared spectra, and behavior in various thin layer chromatographic systems were identical. We have since also compared the n.m.r. spectra and found them to be identical (7).

Our biogenetic reasonings became untenable when Henrick and Jefferies (8) found diterpene acids with both an 18-COOH and a 19-COOH to cooccur in the resin of Ricinocarpus stylosus. This was followed by several other examples (4), concluding with the demonstration that elliotinoic acid from Pinus elliottii, for which we had suggested a structure, correct except for an 18-COOH group (2), was actually identical with communic acid containing a 19-COOH group (9). Repetition of the gas chromatographic comparison of agathadiol and contortadiol showed that those peaks due to decomposition varied according to the method of injection, and that their behavior was in fact identical. Finally, the mass spectral comparison of agathadiol and contortadiol was repeated. As before, the spectra were very similar but with a few marked differences. To our surprise those peaks which had differed in the original mass spectral determinations were now identical, and repeated runs were not completely superimposable. This indicated that we undoubtedly had both thermal and ionic fragmentation taking place, leading to difficulty in obtaining replication of repeat runs. This sensitivity to thermal fragmentation has recently been discussed (10). Therefore, by every test, agathadiol and contortadiol are identical, and the latter name should be dropped. Thus lodgepole pine is the first species in which agathadiol has been found to occur naturally. We have also found it, together with 13-epitorulosol, in jack pine bark.*

We had previously shown (2) that hydroxyepimanool and torulosol (6) had similar ultraviolet, infrared, n.m.r., and mass spectra,** somewhat similar melting points and optical rotation, and the same R_f on thin layer chromatography. We have also observed them to behave identically on gas chromatography on SE-30. This is completely analogous to the comparison of manool

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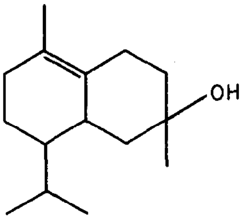
* A paper on the benzene extractives of the bark of jack pine (Pinus banksiana Lamb.) should be completed within a year.

** The mass spectra of manool, epimanool, torulosol, hydroxyepimanool, and related diterpenes have been discussed by Enzell and Ryhage (11).

and epimanool which appear identical by these tests, but which, however, were shown to be definitely different by comparison of their 3,5-dinitrobenzoates. Hydroxyepimanool and torulosol were shown to be different by a dramatic depression of the mixed melting point in addition to minor differences in the physical and spectral properties. Hydroxyepimanool was subjected to allylic rearrangement analogous to the procedure used by Enzell on torulosol (6). There was obtained, in addition to the expected triene alcohol, a good yield of agathadiol identical with authentic agathadiol by all of the tests used previously. Therefore, hydroxyepimanool is 13-epitorulosol (19-hydroxy-13-epimanool), II. The agreement between $\Delta[M]_D$ (manool → epimanool) +57° and $\Delta[M]_D$ (torulosol → epitorulosol) +37° is now as expected (2).

Crude contortolal was reduced with lithium aluminum hydride to also yield authentic agathadiol thus proving it to be IV. Therefore, the name of this compound should more logically be agatholal rather than contortolal.

During an unsuccessful attempt to obtain agatholal 3,5-dinitrobenzoate from the crude contortolal fraction, we did isolate a pure crystalline ester, m.p. 153.5-154.5, $[\alpha]_D^{22}$ -38°, whose analysis showed it to be the ester of an alcohol, $C_{15}H_{26}O$. The n.m.r. spectrum in deuterochloroform (Varian A-60) showed typical isopropyl methyl doublets at τ 9.10 and 9.22 (J = 6-1/2 c.p.s.), a sharp singlet at τ 7.76 for a methyl on the carbon carrying the 3,5-dinitrobenzoate group, a sharp singlet at τ 8.30 for a vinylic methyl, and no vinylic protons. These data suggest that the compound could be the 3,5-dinitrobenzoate of a cadinol (shown below) similar to δ-cadinol (12) but with the double bond in the exocyclic tetrasubstituted position as was originally suggested for δ-cadinol (13).



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