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THE STRUCTURE OF THE LIPID PORTION OF THE ANTIBIOTIC PRASINOMYCIN

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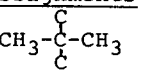
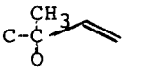
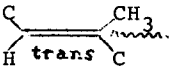
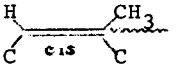
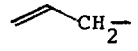
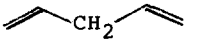
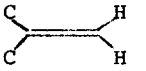
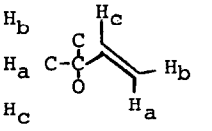
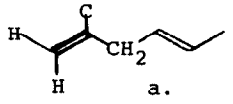
The isolation and characterization of a new group of phosphorus-containing antibiotics, the prasinomycins, has been previously reported.[1] Comparison of the biological, physical, and chemical properties of the prasinomycins with the recently described antibiotics, moenomycin,[2] 11,837 RP,[3] and 8036 RP[4] indicated that all are closely related. A recent publication by Tschesche et al[5] on the structure of the lipids obtained by hydrolysis of moenomycin prompts us to present our evidence for the structures of the lipids derived from prasinomycin.

Hydrolysis of either the individual prasinomycins or the mixture of prasinomycins with 1 N HCl at 100° for 30 minutes yields a chloroform-soluble oil that can be resolved by silica gel TLC (benzene:$CHCl_3$:MeOH::8:1:) to give an alcohol I (R_f 0.68), a second alcohol II (R_f 0.80), and a hydrocarbon fraction III (R_f 0.95). Alcohol II, after molecular distillation, was shown by elemental analysis and high resolution mass spectrometry to have the molecular formula $C_{25}H_{42}O$. It exhibits bands in the IR ($CHCl_3$) at 3600 $cm.^{-1}$ (OH), 1690-1600 $cm.^{-1}$ (C=C), 1360 and 1375 $cm.^{-1}$ (doublet suggesting CH_3-C-CH_3), 990, 970, 920, and 890 $cm.^{-1}$ (terminal methylene and terminal vinyl). Alcohol II is optically inactive and has no absorption above 210 mu (no conjugated double bonds). The hydroxyl function is probably tertiary,since it is not acetylated on treatment with acetic anhydride in pyridine.

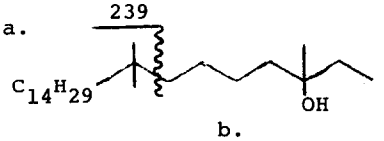
The pmr spectrum of alcohol II in $DCCl_3$ at 60 MH_z is assigned as follows:

Number of Protons	Chemical Shifts (τ)	Signal Pattern	Assignments
6	9.03	Singlet	
3	8.72	Singlet	
6	8.39	Broad Singlet	
3	8.31	Broad Singlet	
8	7.7-8.1	Multiplet	
2	7.31	Broad Doublet, $J=7H_z$	
2	5.30	Broad Singlet	
4	4.6	Multiplet	Vinyl Protons
1	4.90	Quartet, $J=10H_z$, $J=2.5H_z$	
1	4.75	Quartet, $J=17H_z$, $J=2.5H_z$	
1	4.07	Quartet, $J=17H_z$, $J=10H_z$	

Field decoupling by irradiation at 100 MH_z in the region of the diallylic methylene protons (7.3 τ) shows only one change in the vinyl proton region, namely, the collapse of the broad singlet at 5.30 τ to a sharp singlet and a small shoulder, thus indicating that the diallylic methylene protons are coupled to the terminal methylene function as in a.



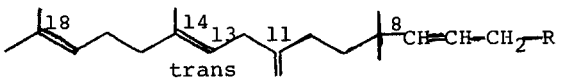
a.

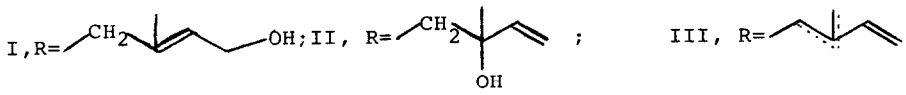


b.

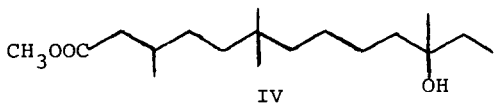
Alcohol II on hydrogenation with PtO_2 in acetic acid consumes five equivalents of hydrogen to give a saturated alcohol $C_{25}H_{52}O$. The mass spectrum of this saturated alcohol shows prominent peaks 368 (M^+), 353(M-15), 351 (M-17), 350 (m-18), 339 (M-29), 239, 238, 197, and 196,in addition to peaks at lower masses including m/e 73 (base)  The relatively intense peaks at m/e 239 and m/e 238 suggest that the gem dimethyl group is on the eighth carbon atom from the end of the molecule bearing the tertiary alcoholic function as in b.

Among various structures that can be drawn to fit the above data is structure II.

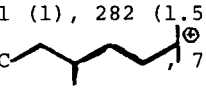
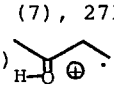




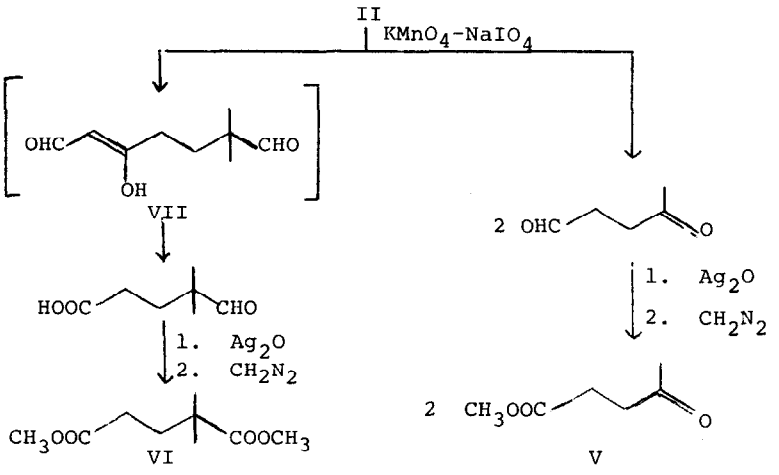
That II is indeed the correct structure for alcohol II was confirmed by two degradation schemes. Alcohol II on reduction with PtO_2 in 95% EtOH consumes four equivalents of hydrogen after 4 hours to give octahydro II. Ozonolysis of octahydro II followed by hydrolysis of the ozonide, further oxidation with Ag_2O, and finally treatment with diazomethane yields the methyl ester IV ($C_{18}H_{36}O_3$) of a C_{17} hydroxy acid;



IV

ir: 3300-3600 $cm.^{-1}$ weak hydroxyl absorption, 1730 $cm.^{-1}$ intense carbonyl pmr: 3H(s) @ 6.28 τ (CH_3O), 2H (m) @ 7.80 τ (-CH_2-COO), 3H(s) @ 8.82 τ (CH_3-C(CH)-O), 12H complex pattern @ 8.85-9.18 τ (4 CH_3-C). Mass spectrum of a gas chromatographed sample: m/e 300 (1) M^+, 281 (1), 282 (1.5), 285 (7), 271 (27), 269 (5), 253 (16), 239 (45), 171 (70) CH_3OOC  , 73 (100)  . The isolation of a hydroxy ester of a C_{17} acid places the double bond in octahydro II, and therefore the most hindered double bond in alcohol II, at the thirteenth and fourteenth carbon atoms from the end of the molecule bearing the hydroxyl group.

Finally, oxidation of alcohol II with $KMnO_4$-$NaIO_4$ in t-BuOH-H_2O and K_2CO_3, followed by Ag_2O oxidation and subsequent treatment with diazomethane, yields methyl levulinate (V) and 2,2-dimethylglutaric acid dimethyl ester (VI), isolated by gas chromatography. Methyl levulinate was identified by comparison of its mass spectrum and retention times on two different columns with those of an authentic sample. The diester VI arising by oxidation of the intermediate enolic dialdehyde VII was identified as 2,2-dimethylglutaric acid dimethyl ester by comparison of its pmr and mass spectra with those of an authentic sample.



Alcohol I,through spectral measurements (ir, pmr, uv, high resolution mass spectrometry) and elemental analyses of itself, its monoacetate, and its decahydro derivative,is clearly the isomeric primary allylic alcohol I. Similar analyses on the hydrocarbon fraction indicate that it is a mixture of isomers (III) resulting from dehydration of alcohol I or II.

The structures I, II, and III,derived above for the lipids obtained by hydrolysis of prasinomycin,are identical to those reported for the moenomycin lipids, moenocinol, isomoenocinol, and moenocene,by Tschesche et al, who determined their structures by a different procedure.

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References

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2. Farbwerke Hoeschst, Irish Patent 1001/65 (1965).
3. Rhone-Poulenc, Belgian Patent 653,168 (1965).
4. Rhone-Poulenc, South African Patent 65/6204 (1966).
5. R. Tschesche, F. X. Crock, and I. Duphorn, Tetrahedron Letters No. 24, 2905 (1968) and references therein.