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MANASSANTINS A/B AND SAUCERNEOL: NOVEL BIOLOGICALLY ACTIVE LIGNOIDS FROM SAURURUS CERNUUS

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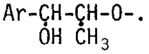
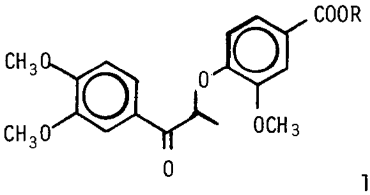
Abstract: From the extract of Saururus cernuus two toxic principles, manassantins A and B and a related substance, saucerneol, were isolated. They have novel dineolignan or sesquineolignan type structures. Although toxic, manassantin A showed potential neuroleptic activity.

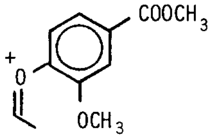
The alcoholic extract of Saururus cernuus (N.O. saururaceae), commonly known as lizard's tail, was found to be toxic to mice when injected. Fractionation based on toxicity gave a mixture of lignoids[1] from which two major toxic principles named manassantins A and B, and a related but relatively nontoxic lignoid named saucerneol have been isolated and their structures elucidated.

Manassantin A, $C_{42}H_{52}O_{11}$,$[\alpha]_D$-100, λ_{max} (log ε) in ethanol: 2.35 (4.62) and 280 nm (4.16); ν in KBr: 3500, 1610, 1590 cm^{-1}; δ ($CDCl_3$) 0.67, 0.78, d, J 6Hz, 2 CH-C$\underline{H}_3$; 1.10, 1.20, d, J 6Hz, 2 C$\underline{H}_3$CH-O; 2.30, m, 2 C$\underline{H}$-CH_3; 3.86, s, 6 OCH_3; 4.10, m, 2 CH_3C$\underline{H}$-O; 4.57, 4.70, d, J 8Hz, 2 Ar-C$\underline{H}$-OH; 5.40, 5.50, d, J 6Hz, 2 Ar-C$\underline{H}$-O- and 6.70-7.05, m, 12 arom. H. The compound decomposed in the mass spectrometer without providing a useful mass spectrum. Acetylation gave a diacetate, $C_{46}H_{56}O_{13}$ (ν 1735 cm^{-1}, δ 2.20, s, 6H). Significant downfield shifts of the doublet, possibly due to Ar-CH-OH from δ 4.57, 4.70 to δ 6.00, 6.10 and of the CH_3C$\underline{H}$-O multiplet from δ 4.10 to 4.53 suggested close proximity of the two functions as for e.g.,  $\text{Ar-}\underset{OH}{CH}\text{-}\underset{CH_3}{CH}\text{-O-}$.

Permanganate oxidation of manassantin A gave veratric acid, 3,4-dimethoxyphenylglyoxylic acid and the acid 1 whose methyl ester 1a, $C_{20}H_{22}O_7$ (M^{+}374) gave the following spectral data: λ_{max} 285, 307 nm; ν 1690, 1660 cm^{-1}; δ 1.70, 1.81, d, J 7Hz, 3H; 4.86, s, 12H; 5.53, q, J 7Hz, 1H; 6.83, m, 2H and 7.67, m, 4H. Fission of the molecular ion into two major fragments was indicated by the ions m/e 165 (base peak, $(OCH_3)_2C_6H_3CO^+$) and m/e 209, represented by 2. The structure of 1a was established through synthesis based on O-alkylation of methyl vanillate with 2'-bromo-3,4-dimethoxy propiophenone[2]



1, R = H
1a, R = CH$_3$



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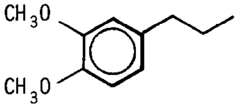
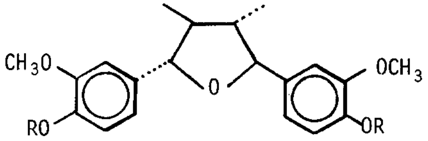
Catalytic dehydrogenation (5% Pd/C, oxydiethanol) of manassantin A led to the formation of two products: 3,4-dimethoxyphenylpropane 3 and a phenolic compound 4, which on methylation, gave the known neolignan, galbelgin[3] 5

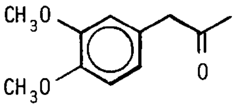


3



4, R = H
5, R = CH$_3$

Reaction of manassantin A with acid (p-toluenesulfonic acid in benzene), also yielded two products: 3,4-dimethoxyphenyl acetone[4] 6 and a phenolic component 7 which, on methylation, formed the known lignoid derivative, cyclogalbelgin[3] 8.



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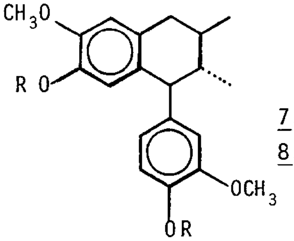
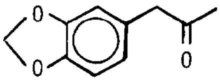


7, R = H
8, R = CH$_3$



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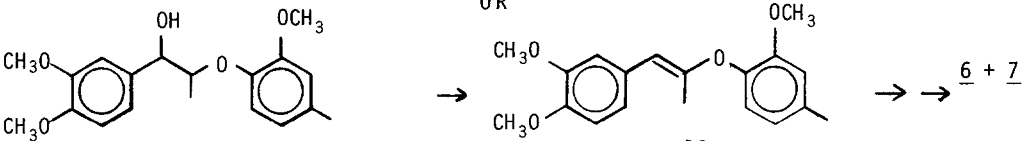

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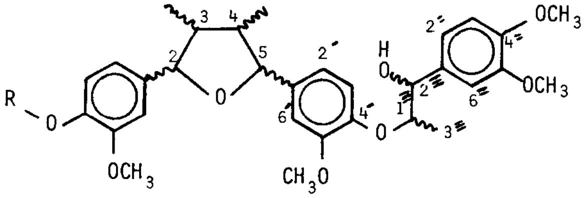
The above degradative and spectral data support the assignment of structure 9 for manassantin A. Formation of 6 and 7 presumably proceeds via dehydration to an enol ether 10 followed by hydrolysis and the well known acid-mediated isomerization of the tetrahydrofuran fragment to 7. As is required by structure 9, quantitative analysis of the acid-transformation products showed a 2:1 ratio for 6 and 7. ^{13}C NMR spectral data of the compound shown in Table 1 were in complete agreement with the structure 9, on the basis of published chemical shifts of closely related lignoid compounds.[5-7] The spectrum suggested that in addition to the obvious symmetry resulting from the dimeric nature of the molecule, which would have shown 21 unique carbons, there was another element of symmetry, because, only 18 unique carbon types were seen in the fully decoupled spectrum.

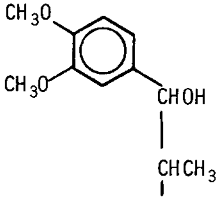
Table 1. ^{13}C NMR Spectrum of Manassantin A*

Chemical shift	Assignment	Carbon #
14.7	$CH \cdot \underline{C}H_3$	6,7
16.8	$O\text{-}CH \cdot \underline{C}H_3$	3'''L,R
44.0	$\underline{C}H\text{-}CH_3$	3,4
55.7	$O\text{-}\underline{C}H_3$	
78.1	$O\text{-}\underline{C}H\text{-}CH_3$	1'''L,R
83.2,83.6	$\text{-}O\text{-}\underline{C}H\text{-}Ar, HO\text{-}\underline{C}H\text{-}Ar$	2,5,2'''L,R
110.1,111.8,118.4, 118.6,119.8	$\underline{C}H$ (Aromatic)	2',5',6'L,R;2",5",6",L,R
132.6,136.2,146.3,148.7 148.9,150.4	$\underline{C}$ (Aromatic)	1',3',4'L,R;1",3",4",L,R

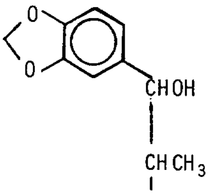
*All values given as ppm downfield from TMS. Spectrum in $CDCl_3$. All assignments supported by off-resonance decoupling data. L and R stand for the carbons to the left and right of the central tetrahydrofuran ring.



9, R =



11, R =



13, R = H

Manassantin B, $C_{41}H_{48}O_{11}$, $[\alpha]_D$-99, resembled 9 closely in its physical and spectral properties. Its ^1H NMR spectrum differed from that of 9 only by the presence of an additional singlet at δ 5.85, 2H and by the decrease in the intensity of the methoxyl signal from 18H to 12H. This suggested the replacement of one of the terminal dimethoxphenyl units by a methylenedioxy unit as shown in 11. In agreement with this structure, 11 gave on treatment with acid, two ketones 6 and 12 along with 7 in the ratio of 1:1:1.

Saucerneol, a phenolic lignoid, $C_{31}H_{38}O_8$, $[\alpha]_D$-52.3 also showed spectral properties similar to those of 9 and 11. Its ^1H NMR spectrum differed from that of 9 only in the integral ratios: e.g., the upfield/downfield doublets due to $CH\text{-}C\underline{H}_3$ as well as the Ar-CH-O-/Ar-CH-OH groups showed a ratio of 2:1 instead of 1:1 as found in 9. Also, the ratio OCH_3/arom. H was 1.33 instead of 1.5. Acetylation gave a diacetate, $C_{35}H_{42}O_{10}$, whose spectral data: 1735, 1760 cm^{-1}; δ 2.00, s, 3H; δ 2.30, s, 3H, suggested the presence of one alcoholic and one phenolic hydroxyl. When treated with acid, saucerneol gave one mole each of 6 and 7, which led to the assignment of structure 13 for the compound.

Manassantins A and B represent members of a new class of lignoids named dineolignans, in which four phenylpropanoids are joined together. Although the component systems: the 7-O-7'/8-8' and the 8-O-4' type neolignans are known separately, a combination of the two is not known. Similarly, saucerneol represents a member of a new class of neolignans named sesquineolignans. A few examples of such di- and sesquilignans have been described[8,9] but the present compounds represent the first members of the neolignan series. The stereochemistry of the three compounds is being studied. Although detailed studies on the biological activity of the toxic principles of manassantins A and B will be published elsewhere,[10] when administered to mice at sublethal doses, they showed potential neuroleptic activity. The compounds were named on the basis of this activity[11].

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10. K.V. Rao and F.M. Alvarez, to be published.
11. The name 'manassantin' is derived from the Sanskrit: manas = mind and santi = peace or, taken together, peace of mind.

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