Tetrahrdron Letters No. 30, pp 2607 - 2610, 1975. Pergamon Press. Printed in Great Britain.

TOBACCO CHEMISTRY 36.

ABSOLUTE CONFIGURATION OF TOBACCO THUNBERGANOIDS.

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(Received in UK 2 June 1975; accepted for publication 9 June 1975)

The structures of the thunbergane type diterpenoids were first established in 1962 by Dauben, Thiessen and Resnick,[1] and Kobayashi and Akiyoshi[2] for the hydrocarbon cembrene obtained from *Pinus* species, and by Roberts and Rowland[3] for α- and β-4,8,13-duvatriene-1,3-diols (1 and 2) isolated from *Nicotiana tabacum* L. Subsequently, further thunberganoids have been isolated from tobacco leaves and tobacco smoke, as well as from other sources,[4-6] and the gross structures and chemical interrelationships of these tobacco constituents elegantly elucidated by Roberts *et al*.[3,7-9] However, the configurational assignments have been difficult to ascertain because of the conformational flexibility of the macrocyclic ring.

A large number of the volatile and organoleptically important[10] tobacco constituents can be viewed as degradation products of thunberganoids[11-13] and in five of these compounds the chiral centre carrying the isopropyl group has been shown to possess the *S*-configuration, *i. e.* (2*S*)-5-oxo-2-isopropylhexanoic acid,[14] solanone ((5*S*)-2-methyl-5-isopropyl-1,3*E*-nonadien-8-one),[14,15] norsolanadione ((5*S*)-5-isopropyl-3*E*-nonene-2,8-dione),[16] (7*S*)-10-oxo-4ξ-methyl-7-isopropyl-5E-undecen-4-olide,[15] and (6*S*)-3-methyl-6-isopropyl-9-oxo-2*E*,4*E*-decadienoic acid.[17] Consequently, we have suggested that the postulated thunberganoid precursors should have *S*-configuration at the corresponding carbon atom.[15] In order to check this and to clarify the absolute configuration of the tobacco thunberganoids we have subjected α-5,8-oxido-3,9(17),13-duvatrien-1-ol (3) to X-ray diffraction analysis and β-4,8,13-duvatriene-1,3-diol (2) to ozonolytic degradation.

The relative configuration of the hydroxyether 3, which crystallizes in the orthorhombic space group $P2_12_12$ with a=21.925(5), b=8.851(2) and c=9.824(3) A, Z=4, was established by an X-ray direct phase determination procedure (Fig. 1). X-ray intensity data were collected with a computer-controlled PW 1100 diffractometer, and the structure was refined to an *R*-value of 8.7 with anisotropic thermal parameters assigned for all non-hydrogen atoms. Location of hydrogen atoms and further refinement is in progress; full details of the X-ray analysis will be published elsewhere.

Ozonolysis of the diol 2 followed by reductive work-up[15] yielded 4-oxopentanal and (2*S*)-5-oxo-2-isopropylhexanal (4).[18] The latter was identical to the corresponding ketoaldehyde similarly obtained from solanone,[15] and hence established the 1*S*-configuration of the diol 2.

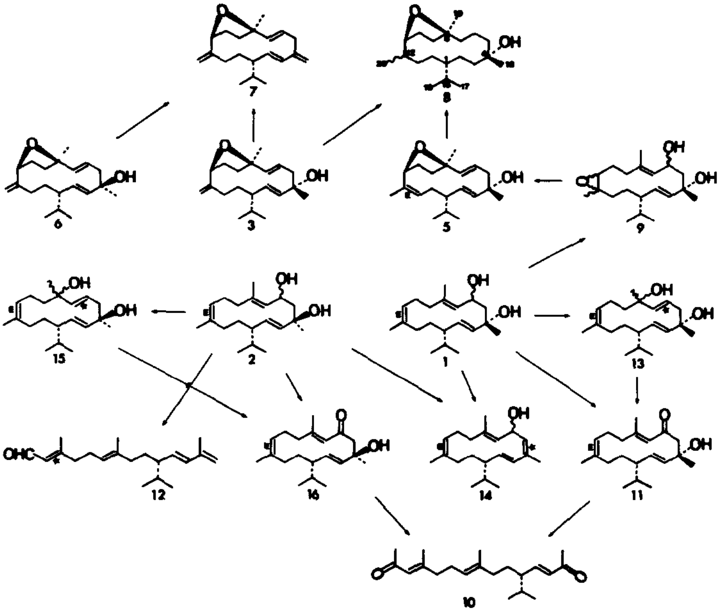
Since the hydroxyether 3 has been correlated[8] with the diol 2 (*vide infra*), the present determinations established the absolute stereochemistry of the former as (1*S*,4*S*,8*R*,11*S*)-8,11-epoxy-2*E*,6*E*,12(20)-thunbergatrien-4-ol (3).

The absolute configurations of the other two hydroxyethers 5 and 6 isolated from tobacco[8] could be deduced from these data since the hydroxyether 3 has been correlated on the one hand to the hydroxyether 6 *via* the ether 7, and on the other to the hydroxyether 5 *via* the perhydro-hydroxyether 8. Thus the two tobacco isolates can be formulated as (1*S*,4*R*,8*R*,11*S*)-8,11-epoxy-2*E*,6*E*,12(20)-thunbergatrien-4-ol (6) and (1*S*,4*S*,8*R*,11*S*)-8,11-epoxy-2*E*,6*E*,12*E*-thunbergatrien-4-ol (5), since the *E*-configuration of the disubstituted double bonds, previously based on IR-data,[8] and of the trisubstituted double bond of the latter compound has recently been established in this laboratory by LIS proton NMR studies.[19]

The last-mentioned hydroxyether 5 has been correlated to the naturally occurring diol 1 *via* the epoxide 9, and this diol 1 in turn converted to the acyclic dione 10 by retro-aldol condensation of the intermediate ketol 11.[3] Moreover, the diols 1 and 2 have been interrelated by dehydration to the mono-ol 14,[9] and the latter diol also converted to the aldehyde 12 by 1,3-glycol cleavage[20] and to the dione 10 *via* the ketol 16.[3] Since the 2,3- and 7,8-double bonds in the diols 1 and 2 and the ketols 11 and 16, the three double bonds in the dione 10, and the 6,7- and 11,12-double bonds in the aldehyde 12 have been assigned the *E*-configuration on the basis of IR and ^{1}H NMR results,[20,21] these compounds which have all been encountered in tobacco, can be described as (1*S*,4*S*)-2*E*,7*E*,11*E*-thunbergatriene-4,6ξ-diol (1), (1*S*,4*R*)-2*E*,7*E*,11*E*-thunbergatriene-4,6ξ-diol (2), (1*S*,4*S*)-2*E*,7*E*,11*E*-thunbergatrien-4-ol-6-one (11), (11*S*)-11-isopropyl-4,8-dimethyl-3*E*,7*E*,12*E*-pentadecatriene-2,14-dione (10), (10*S*)-3,7,13-trimethyl-10-isopropyl-2ξ,6*E*,11*E*,13-tetradecatetraen-1-al (12), and (1*S*,4*R*)-2*E*,7*E*,11*E*-thunbergatrien-4-ol-6-one (16). The identity of the dehydration products prepared from the diols 1 and 2 implies the same relative configuration of the C(6) atoms in these diols. These assignments were verified by ozonolysis of the ketol 11, prepared by oxidation of the diol 1, and of the diketone 10, generated from the ketol 11 on standing, to ascertain that the retro-aldol condensation had occurred without epimerization at C(1). Both compounds gave pure (2*S*)-5-oxo-2-isopropylhexanal (4) exhibiting the same rotatory power as the specimen of this compound generated from the diol 1.[18]

Since the 4,6-diols 1 and 2 have also been converted to the corresponding 4,8-diols 13 and 15 by allylic rearrangement on acidic alumina,[7] these tobacco compounds can now be assigned the structures (1*S*,4*S*)-2*E*,6ξ,11*E*-thunbergatriene-4,8ξ-diol (13) and (1*S*,4*R*)-2*E*,6ξ,11*E*-thunbergatriene-4,8ξ-diol (15) respectively.

It is of interest that all the naturally occurring thunberganoids depicted in Scheme 1 have the same 1*S*,2*E*-configuration and that cembrene from *Pinus* species,[1,2] claimed to be present in tobacco leaves under the influence of enzyme-blocking agents,[22] has the same absolute configuration,[1,23] (1*S*)-2*E*,4*Z*,7*E*,11*E*-thunbergatetraene, as the present compounds and constitutes a probable precursor of the latter. The prefixes 'α-' and 'β-' previously employed to distinguish the two series correspond to the 4*S*- and 4*R*-configurations respectively.



SCHEME 1: Chemical interrelationships of tobacco thunberganoids (1-3,5,6,10-16). Double bonds marked with '*E*' are *trans*, although here more conveniently portrayed as *cis*, and those labelled '★' are of undetermined configuration.

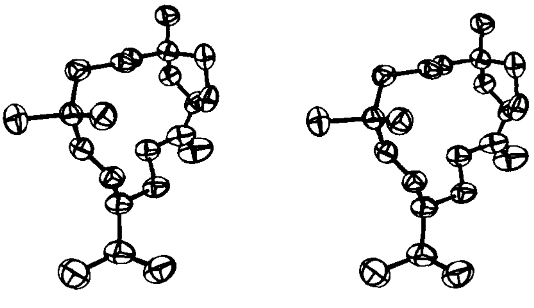


FIG. 1: Stereoscopic view of (1*S*,4*S*,8*R*,11*S*)-8,11-epoxy-2*E*,6*E*,12(20)-thunbergatrien-4-ol (3).

Acknowledgements: The authors are indebted to Miss Ann-Marie Eklund for skilful technical assistance, ing. Kerstin Karlsson for chromatography, Dr. Douglas Austin for providing the tobacco extract, Dr. A. Zane, United States Tobacco Co., Tennessee, for mass spectra, Swedish Natural Science Research Council for financial support, and Professor Peder Kierkegaard for his active and stimulating interest in the X-ray work.

REFERENCES AND NOTES.

1. W. G. Dauben, W. E. Thiessen and P. R. Resnick, *J. Am. Chem. Soc.*, **84**, 2015 (1962).
2. H. Kobayashi and S. Akiyoshi, *Bull. Chem. Soc. Japan*, **35**, 1044 (1962); *ibid.* **36**, 823 (1963).
3. D. L. Roberts and R. L. Rowland, *J. Org. Chem.*, **27**, 3989 (1962).
4. A. J. Weinheimer, R. E. Middlebrook, J. O. Bledsoe, W. E. Marsico and T. K. B. Karns, *Chem. Commun.*, 384 (1968).
5. M. B. Hossain, A. F. Nicholas and D. van der Helm, *Chem. Commun.*, 385 (1968).
6. K. Nakanishi in *Natural Products Chemistry* (K. Nakanishi, T. Goto, S. Ito, S. Natori and S. Nozoe, eds.), *Kodanska Ltd., 1974, Tokyo*.
7. R. L. Rowland and D. L. Roberts, *J. Org. Chem.*, **28**, 1165 (1963).
8. R. L. Rowland, A. Rodgman, J. N. Schumacher, D. L. Roberts, L. C. Cook and W. E. Walker, Jr., *J. Org. Chem.*, **29**, 16 (1964).
9. D. L. Roberts and W. A. Rohde, *Tobacco Science*, **16**, 107 (1972).
10. R. B. Griffith, R. R. Johnson and A. D. Quinn, *U. S. Patent* 3,174,485, March 23 (1965).
11. E. Demole and D. Berthet, *Helv. Chim. Acta*, **55**, 1866 (1972).
12. A. J. Aasen and C. R. Enzell, *Beitr. z. Tabakforschung*, in press.
13. R. R. Johnson and J. A. Nicholson, *J. Org. Chem.* **30**, 2918 (1965).
14. T. Fukuzumi, H. Kaneko and H. Takahara, *Agr. Biol. Chem.*, **31**, 607 (1967).
15. A. J. Aasen, J. R. Hlubucek and C. R. Enzell, *Acta Chem. Scand.*, in press.
16. A. J. Aasen and C. R. Enzell, *Acta Chem. Scand.*, in press.
17. A. J. Aasen, C. R. Enzell and T. Chuman, *Agr. Biol. Chem.*, in press.
18. Optical activities:

Compound	*c*, $CHCl_3$	λ(nm) 589	578	546	436	365
2$^+$	0.53	+165.3°	+172.8°	+198.9°	+363.4°	+624.9°
11$^+$	0.5	+118.4°	+123.6°	+143.6°	+265.2°	
10$^+$	0.4	+ 9.5°	+ 10.0°	+ 12.0°	+ 26.0°	
4§ from **2**	0.4	+ 49.5°	+ 53.0°	+ 63.0°	+149.5°	+404.5°
4 from **11**	0.5	+ 50.0°	+ 52.8°	+ 63.2°	+151.6°	+412.4°
4 from **10**	0.48	+ 47.9°	+ 51.3°	+ 62.1°	+147.5°	+400.8°

$^+$ Lit.[3] for **2**, **11** and **10** (589 nm): +162°, +112° and 0° respectively. §Lit.[16]: +47.8° (589), +50.7° (578), +61.4° (546), +146.6° (436), +400.8° (365).

19. A. J. Aasen, S.-O. Almqvist, T. Nishida, J. R. Hlubucek and C. R. Enzell, *Acta Chem. Scand.*, in press.
20. J. L. Courtney and S. McDonald, *Tetrahedron Letters*, 459 (1967).
21. A. Zane, *Phytochemistry*, **12**, 731 (1974).
22. W. W. Reid, *Biochem. J.*, **100**, 13P (1966).
23. M. G. B. Drew, D. H. Templeton and A. Zalkin, *Acta Cryst.*, **B25**, 261 (1969).