Tetrahedron Letters Vol. 21, pp 2657 - 2660 0040-4039/80/0701-2657$02.00/0

UNUSUAL MACROCYCLIC PYRROLIZIDINE ALKALOIDS FROM PARSONSIA HETEROPHYLLA A. CUNN AND PARSONSIA SPIRALIS WALL. (APOCYNACEAE)[1]

John A. Edgar*,[a] Nigel J. Eggers*,[b] Alan J. Jones,[c] and Graeme B. Russell[d]

[a] C.S.I.R.O. Division of Animal Health, Animal Health Research Laboratory, Private Bag 1, P.O., Parkville, Victoria., 3052 Australia

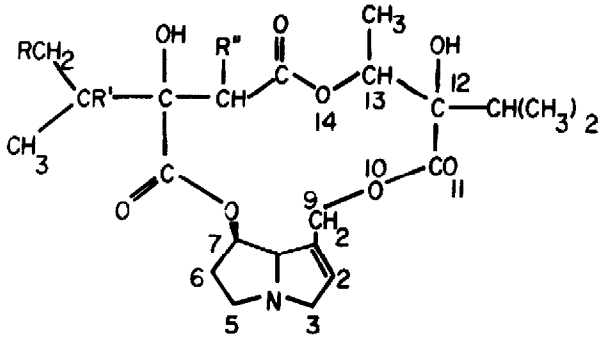
[b] Chemistry Division, DSIR, Private Bag, Petone, New Zealand

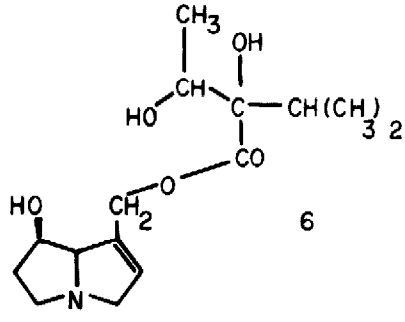
[c] National NMR Centre, Australian National University, Canberra, A.C.T., 2600 Australia

[d] Applied Biochemistry Division, DSIR, Private Bag, Palmerston North, New Zealand

Summary: *A series of 14-membered ring macrocyclic pyrrolizidine alkaloids have been isolated from Parsonsia heterophylla and Parsonsia spiralis.*

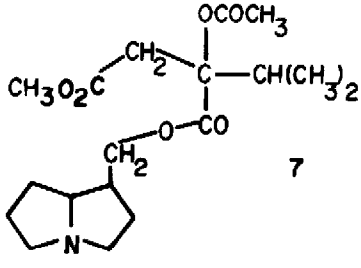
We wish to report the isolation and/or characterisation, in two species of Parsonsia, of (a) a series of unusual macrocyclic pyrrolizidine alkaloids 1-5, incorporating an indicine-type moiety 6 esterified by a series of dicarboxylic acids to complete a novel 14-membered macrocyclic ring system, and (b) a new alkaloid with gross structure 7.





6

1. R=R'=R"=H
2. R=CH_3, R'=R"=H
3. R=R'=H, R"=OH
4. R=CH_3, R'=H, R"=OH
5. R=CH_3, R'=R"=OH



7

Three of the alkaloids, parsonsine 1, $C_{22}H_{33}NO_8$ (micro-analysis and M^+ 439): white orthorhombic plates mp 158° (from benzene, $[\alpha]_D^{20}$ + 19.8° (c, 0.56 in MeOH) and its polymorphic form, mp 198° (from toluene), $[\alpha]_D^{20}$ + 19.7° (c, 0.91 in MeOH),[2,3] heterophylline 2, $C_{23}H_{35}NO_8$ (M^+ 453): mp 190° (from benzene), and 7, (microanalysis and M^+ 355) non-crystalline, $[\alpha]_D^{20}$ + 57.6° (c, 0.38 in MeOH), have been isolated from Parsonsia heterophylla A Cunn. The structure of the dimorphic forms of parsonsine 1, determined by X-ray diffraction, have been presented earlier.[2,3] The structures of the Parsonsia spiralis Wall alkaloids, which include spiraline 3 (M^+ 455), spiranine 4 (M^+ 469) and spiracine 5 as well as 1 and 2 were established by their mass spectra and, in the case of 1 and 2, by comparison and co-chromatography with the purified alkaloids from Parsonsia heterophylla.

The proton nmr spectrum[4] of parsonsine 1 ($CDCl_3$) exhibits the characteristics of a pair of isopropyl groups: doublets at δ 0.84 (J 6.6Hz), 0.98 (J 7.0Hz, $2CH_3$ groups), 1.04 (J 7.1Hz) and corresponding methine septets at δ1.79 and 1.93 (J 7Hz). A methyl doublet at δ1.27 (J 6.7Hz) coupled to a methine quartet at δ5.34 (J 6.4Hz) indicates the presence of the CO-O-CH-CH_3-C function at C13 and the low-field shift of this methine contrasts with that of the secondary alcohol function (ca. δ4) in alkaloids such as 6.[5] A broad singlet at δ5.9 characterises the olefinic methine of the pyrrolizidine ring. In addition a series of AB patterns are observed, in particular, the doublets at δ5.20 and 4.45 (J 12.8Hz) characterising the C9 protons and their non-equivalence in a macrocyclic ring system,[5] but the separation between these doublets (0.75ppm) cannot be used as a criterion of ring size.[6] The electron impact mass spectra of the alkaloids 1-5 show them to be a series of closely related pyrrolizidine alkaloids esterified at both the C7 and C9 hydroxyls. Selective cleavage of the C9 ester linkage of parsonsine 1 by hydrogenolysis (Pt/MeOH) gave, after treatment of the product with diazomethane, a single gcms peak [M^++1(CI), 458] which retained both the amino alcohol and acid moieties thereby confirming the macrocyclic ring system. An analogous product [M^++1(CI), 472] was obtained from heterophylline 2. Vigorous alkaline or acid hydrolysis of 1 gave two acids identified as trachelanthic and 2-isopropylmalic acids by gc-ms comparison of their methyl esters with authentic samples. The basic product of this hydrolysis was identified as retronecine by gc-ms and mixed melting point. Hydrolysis of heterophylline 2 gave a dicarboxylic acid, the dimethyl ester of which gave a mass spectrum interpretable as that of dimethyl-2-sec-butylmalate by comparison with the spectrum of dimethyl-2-isopropylmalate and the published spectrum of the isomeric dimethyl-2-isobutylmalate[7]. Partial hydrolysis of 1 yielded a major product identified as the known alkaloid 6 by gc-ms. This partial structure is incorporated in the alkaloids 1-5 as shown by their mass spectra which exhibit major ions resulting from loss of 143 amu, $C_7H_{11}O_3$, from the molecular ion. This loss corresponds to the expected cleavage of the C9-O10 and C13-O14 bonds.

Note that the failure of parsonsine 1 and heterophylline 2 to form alkylboronate derivatives confirms that the vicinal diol structure present in 6 is unavailable in 1 and 2. However, alkylboronate derivatives of the alkaloids 3-5 are readily formed and mass spectra of these compounds show appropriate M^+ ions and prominent ions resulting from fragmentation at C9-O10 and C13-O14, and the CR'-C bond. The fragmentation at the CR'-C bond is particularly facilitated in the alkylboronate of spiracine 5 and this locates the additional hydroxyl in this molecule.

The proton nmr spectrum of 7 exhibits signals corresponding to an isopropyl group at δ0.97, 0.99, $(CH_3)_2CH$ (J 6.8Hz) and 2.31 $CH(CH_3)_2$ (J 6.8Hz), an acetoxy group at δ2.11 and a methyl ester group δ3.67. In addition a geminal methylene AB pattern at δ2.8, 3.0 (J 14Hz) characterises the C13 methylene attached to the asymmetric centre (C12). Slight non-equivalence of the C9 protons is indicated by the apparent doublets at δ4.1 and 4.2 but this spectral region is congested by the pyrrolizidine ring proton absorptions. The ions at m/e 295 and m/e 296 (weak) in the mass spectrum of 7 indicate loss of the elements of acetic acid (by a McLafferty rearrangement) and a carboxymethyl group respectively. Mild acid hydrolysis of 7 in methanol removed the acetyl group to provide a desacetyl derivative the mass spectrum of which showed facile loss of $CH_2CO_2CH_3$ and $CO_2C_8H_{14}N$ moieties as indicated by the presence of the ions at m/e 240 and 145. These data demonstrate the nature of the methyl ester function and more importantly indicate which carboxyl group (C14) is esterified. Vigorous acid hydrolysis of 7 produced an aminoalcohol and a neutral optically active compound which on base hydrolysis gave 2-isopropylmalic acid, $C_7H_{12}O_5$ (microanalysis): mp 171-173°, $[\alpha]_D^{25}$ - 19.5°, (c, 0.42 in MeOH),[8,9] identical with an authentic sample.[10] The amino alcohol was identified as a 1-hydroxymethyl-pyrrolizidine. The specific rotation $[\alpha]_D^{25}$ + 38° suggests that this alcohol is an approximately equal mixture of the two diastereoisomers, laburnine ($[\alpha]_D^{25}$ + 15°)[11] and lindelofidine ($[\alpha]_D^{20}$ + 72°).[11]

The structures of 1 and 7 have been further verified by complete analysis of the ^{13}C nmr spectra of these compounds and their derivatives.[12]

The unusual macrocyclic pyrrolizidine alkaloids described here are essentially of the acyclic type, eg 6, found previously in other species of Parsonsia[13] and in the Boraginaceae[14] and Eupatorieae[14]. They are however modified by the incorporation of 2-alkylmalic acids, similar to those associated with the pyrrolizidine alkaloids of the Orchidaceae[7,11] so that they resemble in some respects macrocyclic alkaloids, such as trichodesmine, found mainly in the genus Crotalaria[14].

P.spiralis is a newly discovered larval food plant for the danaine butterfly Euploea treitschkei aenea Butler and the larvae of this species sequester the plant alkaloids which can be found, with the metabolite 6, in the adult butterflies[15]. This is the first confirmed example of danaine butterflies obtaining pyrrolizidine alkaloids from a larval food plant and may have relevance

to the origin of the requirement that adult Danainae of other species have for pyrrolizidine alkaloids and their metabolites as defensive and semiochemicals[15,16].

Acknowledgements: We are grateful to Dr. R. Hodges for some of the high resolution mass spectra, Dr N. Galbraith for the CI mass spectra, Mr. A.P. Druce for identification of the Parsonsia heterophylla plant material under herbarium accession number CHC 354426, Botany Division, DSIR, Christchurch, New Zealand and the Honiara Herbarium for the identification of P.spiralis. Our thanks are also due to Mr. P. Hanisch, Dr. R.H. Newman, Mr. S.A. Gwyn and Mr. R. Derrer.

References and Notes

1. This report is the result of independent studies by JAE/GBR and NJE/AJJ. Neither group was aware of the other's interest in the alkaloids of Parsonsia heterophylla until the work was nearing completion.

2. N.J. Eggers and G.J. Gainsford, Cryst.Struct.Commun., 8, 597 (1979).

3. G.J. Gainsford, Cryst.Struct.Commun., in press.

4. Proton nmr spectra were determined at 270MHz using a Bruker HFX-270 spectrometer. Chloroform-d was employed as solvent in all cases and chemical shifts are reported relative to internal TMS.

5. C.C.J. Culvenor and W.G. Woods, Aust.J.Chem., 18, 1625 (1965).

6. D.H.G. Crout, in Chemical Society, London. Specialist Periodical Reports: Alkaloids, 6, 76 (1976).

7. S. Brandänge, B. Lüning, C. Moberg and E. Sjöstrand, Acta Chem.Scand., 25, 349 (1971).

8. W.R. Martin, W.H. Coleman, N.E. Wideburg, R. Cantrell, M. Jackson and F.W. Denison, Biochim. Biophys. Acta, 62, 165 (1962).

9. T. Sai, Agric.Biol.Chem., 32, 522 (1968).

10. M. Yamashita, J.Org.Chem., 23, 835 (1958).

11. S. Brandänge, B. Lüning, C. Moberg and E. Sjöstrand, Acta.Chem.Scand., 26, 2558 (1972).

12. See also N.V. Mody, R.S. Sawhney and S.W. Pelletier, J.Nat.Prod., 42, 417 (1979).

13. J.A. Edgar and C.C.J. Culvenor, Experientia, 31, 393 (1975).

14. L.B. Bull, C.C.J. Culvenor and A.T. Dick, "The Pyrrolizidine Alkaloids", North-Holland, Amsterdam (1968).

15. J.A. Edgar, in preparation.

16. J.A. Edgar, Philos.Trans.R.Soc.London,Ser.B., 272, 467 (1975).

(Received in UK 2 May 1980)