Tetrahedron Letters No. 26, pp 2291 - 2294, 1974. Pergamon Press. Printed in Great Britain.

PENNSYLVANINE AND PENNSYLVANAMINE, TWO NEW DIMERIC ISOQUINOLINE ALKALOIDS[1]

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(Received in USA 21 March 1974; received in UK for publication 20 May 1974)

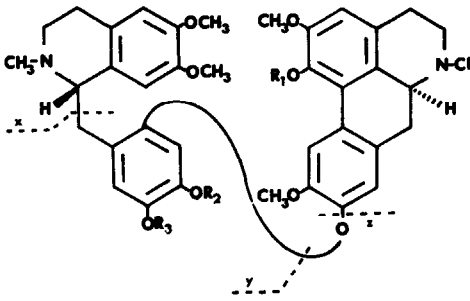
The *in vivo* tumor inhibitory activity of thalicarpine (3)[2,3] now chosen for clinical trial, prompts us to report the characterization of two new potential tumor inhibitors pennsylvanine (1) and pennsylvanamine (2), phenolic analogs of 3, obtained from the giant meadow rue, *Thalictrum polygamum* Muhl. (Ranunculaceae), which is endemic throughout Pennsylvania.

Pennsylvanine (1), $C_{40}H_{46}N_2O_8$, $[\alpha]_D^{24}$ +131° (c = 0.7, MeOH), a major alkaloid of the plant, was obtained as crystals mp 112-113° (ether). The uv spectrum, λ_{max}^{MeOH} 284, 304 and 320sh nm (log ε 4.26, 4.18 and 4.05), was reminiscent of that for thalicarpine (3) and showed both a hyperchromic effect and a bathochromic shift to $\lambda_{max}^{MeOH-OH^-}$ 284, 311 and 320sh nm (log ε 4.32, 4.29 and 4.15). The major fragments in the mass spectrum of 1, m/e 682 (M^+), 476 (M^+ - x), 340 (M^+ - y), 324 (M^+ - z), and 206 (x^+, base), were identical with those in the spectrum of the related monophenolic aporphine-benzylisoquinoline dimer thalidoxine (4).[4] Diazomethane O-methylation of 1 afforded (+)-thalicarpine (3). Assignment of the phenolic function of pennsylvanine (1) to C-5" in the benzyl ring was confirmed by analysis of the nmr data for pennsylvanine acetate (5), $C_{42}H_{48}N_2O_9$, mp 137-138° (ether), obtained by treatment of 1 with Ac_2O in pyridine. Whereas acetylation of the C-4" phenol in thalidoxine (4) gave rise to a 0.1-0.2 ppm upfield shift of the C-8 aporphine aromatic proton due to shielding by the acetate carbonyl,[5] no such upfield shift was observable in the spectrum of 5.

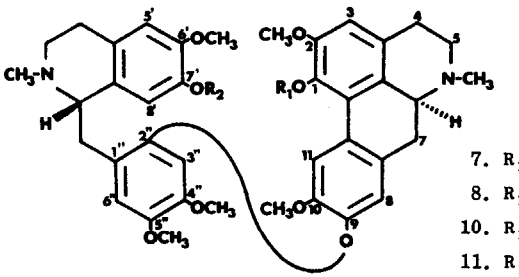
The second alkaloid, pennsylvanamine (2), $C_{39}H_{44}N_2O_8$, $[\alpha]_D^{25}$ = +119° (c = 0.94, MeOH), was obtained as fine needles, mp 128-129° (acetone-ether), or prisms, mp 107-108° (ether). The uv spectrum, λ_{max}^{MeOH} 276sh, 284, 297sh and 312sh nm (log ε 4.07, 4.17, 4.11 and 4.06), showed a pronounced bathochromic shift to $\lambda_{max}^{MeOH-OH^-}$ 292, 315 and 352 nm (log ε 4.10, 3.98 and 3.82), suggestive of a C-1 phenolic aporphine.[6] The mass spectrum of pennsylvanamine (2), m/e 668 (M^+), 462 (M^+ - x), 326 (M^+ - y), 325 (M^+ - y - H), 309 (M^+ - z - H) and 206 (x^+, base), indicated an aporphine-benzylisoquinoline dimer with a phenolic hydroxyl on the benzyl ring and another phenolic function on the aporphine. The aporphine phenol must be at C-1 because of the absence of a high field methoxyl signal near δ3.70 in the nmr spectrum.[4]

Table 1. NMR Spectral Data for Phenolic Analogs of Thalicarpine and their Acetate Derivatives (δ)

	N-Methyls		Methoxyl Groups							Aromatic Protons							Acetate Methyl		
			C-7'	C-1	C-5"	C-4"	C-6'	C-2	C-10	C-8'						C-11	C-1		C-7'
Thalictropine (7)	2.47	2.50	3.58	-	3.78	3.78	3.82	3.88	3.92	6.20	6.55	6.55	6.55	6.59	6.67	8.18	-	-	-
Thalictropine acetate (8)	2.45	2.47	3.58	-	3.78	3.78	3.82	3.84	3.92	6.18	6.50	6.53	6.55	6.60	6.63	7.60	2.34	-	-
Thalidoxine (4)	2.47	2.48	3.57	3.70	3.75	-	3.78	3.88	3.90	6.23	6.50	6.50	6.50	6.57	6.77	8.15	-	-	-
Thalidoxine acetate (9)	2.57	2.61	3.54	3.67	3.70	-	3.84	3.85	3.90	6.13	6.40	6.54	6.54	6.60	6.87	8.14	-	2.25	-
Pennsylvanine (1)	2.46	2.50	3.58	3.71	-	3.79	3.82	3.90	3.92	6.22	6.52	6.56	6.59	6.62	6.76	8.18	-	-	-
Pennsylvanine acetate (5)	2.50	2.53	3.58	3.70	-	3.71	3.83	3.88	3.91	6.23	6.51	6.57	6.61	6.63	6.87	8.20	-	2.29	-
Thalictrogamine (12)	2.49	2.52	-	-	3.79	3.83	3.83	3.92	3.96	6.40	6.53	6.58	6.58	6.58	6.77	8.18	-	-	-
Thalictrogamine diacetate (13)	2.49	2.51	-	-	3.80	3.80	3.76	3.84	3.91	6.43	6.51	6.53	6.62	6.62	6.66	7.60	2.34	-	2.19
Pennsylvanamine (2)	2.47	2.53	3.60	-	-	3.80	3.83	3.92	3.94	6.25	6.55	6.55	6.58	6.58	6.80	8.20	-	-	-
Pennsylvanamine diacetate (6)	2.50	2.52	3.59	-	-	3.70	3.83	3.86	3.88	6.25	6.53	6.57	6.61	6.68	6.90	7.63	2.33	2.28	-
Thalmelatine (10)	2.42	2.48	-	3.72	3.79	3.79	3.79	3.88	3.95	6.43	6.52	6.55	6.60	6.60	6.68	8.18	-	-	-
Thalmelatine acetate (11)	2.49	2.52	-	3.71	3.80	3.80	3.76	3.90	3.92	6.45	6.54	6.58	6.61	6.61	6.65	8.19	-	-	2.19



1. $R_1=R_2=CH_3$, $R_3=H$
2. $R_1=R_3=H$, $R_2=CH_3$
3. $R_1=R_2=R_3=CH_3$
4. $R_1=R_3=CH_3$, $R_2=H$
5. $R_1=R_2=CH_3$, $R_3=CH_3CO$
6. $R_1=R_3=CH_3CO$, $R_2=CH_3$
9. $R_1=R_3=CH_3$, $R_2=CH_3CO$



7. $R_1=H$, $R_2=CH_3$
8. $R_1=CH_3CO$, $R_2=CH_3$
10. $R_1=CH_3$, $R_2=H$
11. $R_1=CH_3$, $R_2=CH_3CO$
12. $R_1=R_2=H$
13. $R_1=R_2=CH_3CO$

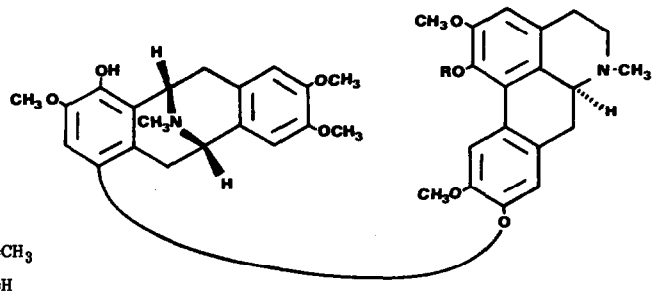
Treatment of pennsylvanamine (2) with Ac_2O in pyridine afforded the diacetate 6, $C_{43}H_{48}N_2O_{10}$, mp 147-148° (ether). The signal for the aporphine C-11 proton was now shifted upfield to δ7.63, consonant with the presence of a C-1 acetate function.[7] No other aromatic proton had undergone an upfield shift so that the phenolic function on the benzyl ring of pennsylvanamine (2) must be situated at C-5". Diazomethane O-methylation of 2 yielded an easily separable 1:1 mixture of (+)-thalicarpine (3) and (+)-thalictropine (7).[7]

The structural assignment for any new phenolic analog of (+)-thalicarpine can now be derived from the combination of uv, nmr and mass spectral data for the alkaloid and its acetate. Mass spectroscopy will readily detect the phenol(s) on any of the three large moieties of the alkaloid: aporphine, isoquinoline and benzyl ring. The relevant nmr chemical shifts have been summarized in Table 1, and some of the more useful generalizations for specifically locating the phenolic function(s) have been listed in Table 2.

An interesting recent development has been the isolation in this Laboratory of two other dimeric alkaloids, pennsylpavine (14) and pennsylpavoline (15). These are the first aporphine-pavine dimers known, and it is tempting to speculate that in the plant pennsylvanine (1) and pennsylvanamine (2) may act as precursors to 14 and 15, respectively.[10]

Table 2. Diagnostic Spectral Features for Phenolic Analogs of Thalicarpine

	Phenol at	Observed Data for Parent Phenol	Observed Data for Acetate Derivative
Aporphine	C-1	C-1 methoxyl signal at δ3.71 absent. Strong bathochromic shift in uv spectrum with base.[8]	Aporphine H-11 signal shifted upfield to ≈ δ7.60. Acetate methyl signal at ≈ δ2.34.
Aporphine	C-2	A single methoxyl signal will appear below δ3.85 assignable to C-10.[9]	C-1 methoxyl signal originally near δ3.71 will be shifted to slightly higher field. No significant shift of aporphine H-11 signal.[9]
Aporphine	C-10	A single methoxyl signal will appear below δ3.85 assignable to C-2.[9]	Aporphine H-11 signal will be shifted downfield to ≈ δ8.30. Acetate methyl signal near δ2.20.[9]
Isoquinoline	C-6'	Highfield C-7' methoxyl signal at ≈ δ3.58. H-8' signal at ≈ δ6.23.	
Isoquinoline	C-7'	Highfield C-7' methoxyl signal at ≈ δ3.58 absent. H-8' signal at ≈ δ6.4 rather than δ6.2.	H-8' signal near δ6.4 essentially unchanged. Acetate methyl signal at δ2.19.
Benzyl Ring	C-4"	Aromatic proton at ≈ δ6.80. H-8' signal near δ6.23. No distinct bathochromic shift in uv spectrum with base.	Lowest field aromatic proton at ≈ δ6.90. Signal at ≈ δ6.23 unchanged. Aporphine H-8 signal shifted upfield to ≈ δ6.40. One methoxyl signal shifted upfield to ≈ δ3.70.
Benzyl Ring	C-5"	Aromatic proton at ≈ δ6.80. H-8' signal near δ6.23. Bathochromic shift in uv spectrum with base.	Lowest field aromatic proton at ≈ δ6.90. No upfield shift of aromatic proton signals. One methoxyl signal shifted upfield to ≈ δ3.70.



14. R=CH_3

15. R=H

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1. This work was supported by grant HL-12971 from the National Institutes of Health. Nmr spectra are in $CDCl_3$ at 60 MHz. All compounds were analyzed by means of high resolution mass spectroscopy. For a recent review on the aporphine-benzylisoquinoline dimers see M. Shamma, "The Isoquinoline Alkaloids", Academic Press, New York (1972), p. 232.
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8. This spectral pattern is also observed for the related dimer fetidine: M.P. Cava and K. Wakisaka, Tetrahedron Lett., 2309 (1972).
9. The expected data for the C-10 phenol was extrapolated from that observed for monomeric aporphines and for the pakistanine series of aporphine-benzylisoquinoline alkaloids, M. Shamma, J.L. Moniot, S.Y. Yao, G.A. Miana and M. Ikram, J. Amer. Chem. Soc., 95, 5742 (1973).
10. The chemistry of 14 and 15 will be described in a separate paper. Conclusive proof regarding the biogenesis of 14 and 15 can come only from in vivo experiments using labeled precursors.