

SECOWITHAMETELIN, A WITHANOLIDE OF *DATURA METEL* LEAVES*

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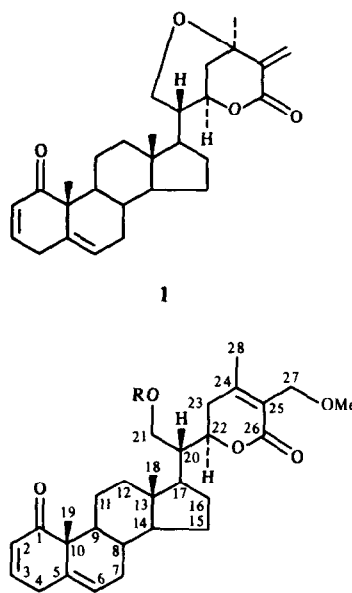
Abstract—A new withanolide, secowithametelin, has been isolated from the leaves of *Datura metel* and its structure determined as (20*R*,22*R*)-1-oxo-21-hydroxy-27-methoxy-witha-2,5,24-trienolide on the basis of chemical and detailed spectral analysis.

INTRODUCTION

Datura metel (Solanaceae), a common medicinal plant, is widely distributed in India [1]. While the presence of alkaloids in the plant was reported as early as 1903 [2, 3], the first publication [4] reporting the occurrence of a withanolide in the leaves of this plant appeared in early 1987 which was, however, followed by several other publications from two different laboratories with similar reports [5–9].

Our continued search for new withanolides from this plant has now resulted in the isolation of a withanolide from the chloroform extract of the dried leaves. It has been designated secowithametelin from a comparison of its structural features with the previously reported withametelin (1). Secowithametelin (2) $C_{29}H_{40}O_5$ (M^+ at m/z 468), mp 190°, $[\alpha]_D^{25} + 28.53^\circ$ ($CHCl_3$), showed IR absorption bands at 3490, 1684 and 1718 cm^{-1} assignable, respectively, to hydroxyls, enone and α,β -unsaturated δ -lactone groupings. Like a typical withanolide [10], it showed a single absorption maximum at 222.8 nm ($\epsilon = 14040$) in the UV region indicating the presence of an enone and an α,β -unsaturated δ -lactone chromophore. Three olefinic hydrogen signals discernible in its ^1H NMR spectrum at δ 6.73 (1H, *ddd*, $J = 10, 5.5, 2.5\text{ Hz}$), 5.85 (1H, *dd*, $J = 10, 2.5\text{ Hz}$) and 5.53 (1H, *d*, $J = 6\text{ Hz}$) revealed the presence of a steroidal 2,5-diene-1-one system, as is present in withametelin. It also showed, like typical 20-H withanolides [11], the diagnostic double triplet at δ 4.49 ($J = 12, 4\text{ Hz}$) for the carbinyl hydrogen at C-22, which in turn suggested that the side chain of secowithametelin is not bicyclic like withametelin. In addition to signals for two angular C-methyls (δ 0.75; 1.23 for 18- and 19-methyls) and an allylic methyl (δ 2.08), the ^1H NMR spectrum of secowithametelin showed signals for two oxymethyl ($-\text{CH}_2-\text{O}-$) groupings around δ 3.94 (2H, *m*) and 4.24 (2H, AB *q*). Of these two methylenes, the one appearing as multiplets around δ 3.94 was readily recognised as C-21 hydroxymethyl [4] from its splitting pattern as well as from its downfield shift to δ 4.36 in the

spectrum of its acetate derivative (2a). The other methylene was obviously placed at C-27 bound to a methoxyl function; the non-equivalence of the two hydrogens of this allylic methylene giving rise to an AB pattern is considered to be due to its anisotropic environment [12]. The ^1H NMR parameters of the three olefinic hydrogens and the angular methyls of secowithametelin were found to be in perfect agreement with those of withametelin and it was thus inferred that the same carbocyclic moiety is present in both the molecules. This assumption was further substantiated from a comparison of their ^{13}C NMR spectra which revealed that the resonance signals for C-1 to C-19 of withametelin were also discernible in the spectrum of secowithametelin almost at the same positions relative to the TMS signal (Table 1). That the two molecules differ only in their side chains became obvious from their NMR spectral analysis. In the



2 R = H
 2a R = Ac

*Part 17 in the series on withasteroids. For part 16 see ref. [4].

Table 1 ^{13}C NMR spectral assignments of compounds **1** and **2** (CDCl_3)

C	1	2
1	204.5 s	204.4 s
2	128.0 d	127.9 d
3	145.0 d	145.5 d
4	33.4 t	33.5 t
5	135.9 s	135.9 s
6	124.5 d	124.6 d
7	30.7 t	30.8 t
8	33.2 d	33.3 d
9	42.8 d	42.9 d
10	50.4 s	50.5 s
11	23.6 t	23.8 t
12	39.6 t	39.2 t
13	42.5 s	42.3 s
14	56.0 d	56.1 d
15	24.0 t	24.3 t
16	26.5 t	27.2 t
17	47.6 d	46.2 d
18	12.7 q	12.3 q
19	18.9 q	19.0 q
20	39.9 d	45.3 d
21	60.4 t	59.5 t
22	75.8 d	77.9 d
23	33.2 t	32.7 t
24	69.2 s	157.6 s
25	138.9 s	123.2 s
26	165.2 s	165.9 s
27	129.7 t	65.7 t
28	25.6 q	20.6 q
-OMe	—	58.4 q

^{13}C NMR spectrum, secowithametelin showed signals for two sp^2 carbons of a tetrasubstituted olefin as a part of an unsaturated δ -lactone at $\delta 157.6$ s and 123.2 s. It also showed signals for two oxymethylenes at $\delta 65.7$ t and 59.5 t, in addition to two other oxycarbons signals at $\delta 77.9$ d and 58.4 q for C-22 and the methoxy carbon, respectively. In its mass spectrum, secowithametelin showed the molecular ion peak at m/z 468 which, by loss of MeOH, showed the base peak at m/z 436 corresponding to the molecular ion peak of withametelin (**1**) and all the peaks below m/z 436 were virtually identical in both the spectra. Based on these spectral data and from the observed positive Cotton effect at 253 nm, $[\theta] +13538$, signifying the (22*R*)-configuration, secowithametelin was formulated as **2**. The carbon resonance signals shown in Table 1 also support the proposed structure.

Chemical evidence in support of this structure came from the conversion of withametelin (**1**) to secowithametelin (**2**) by methanolysis of the allylic ether linkage, methanol acting as a nucleophile in a $\text{S}_{\text{N}}2'$ type reaction. When a solution of withametelin in methanol was treated with perchloric acid and left overnight at room temperature the major product in the reaction mixture was secowithametelin which was isolated by chromatography

over silica gel. The derived compound was found to be indistinguishable from the naturally occurring secowithametelin (mp, IR, ^1H NMR)

EXPERIMENTAL

Isolation of secowithametelin Dried and pulverised plant material (10 kg) was defatted with petrol (60–80°) and extracted with CHCl_3 . Chromatography of the CHCl_3 extract (150 g) over silica gel and elution with petrol–EtOAc (3:1) yielded secowithametelin (**2**) (80 mg) as white plates from the petrol–EtOAc mixture, mp 190° $[\alpha]_{\text{D}} +28.53^\circ$ (CHCl_3 , c 0.75). ^1H NMR [100 MHz, CDCl_3] δ 6.73 (ddd, $J=10, 5.5, 2.5$ Hz, H-3), 5.85 (dd, $J=10, 2.5$ Hz, H-2), 5.53 (d, $J=6$ Hz, H-6), 4.49 (dt, $J=12, 4$ Hz, H-22), 4.24 (AB q, $J=12$ Hz, $\Delta\nu$ 16 Hz, H₂-27), 3.94 (m, H₂-21), 3.38 (s, -OMe), 2.08 (s, H₃-28), 1.23 (s, H₃-19), 0.75 (s, H₃-18). Monoacetate (**2a**) m/z 510 $[\text{M}]^+$, ^1H NMR [100 MHz, CDCl_3] δ 0.76 (s, H₃-18), 1.24 (s, H₃-19), 2.08 (s, H₃-28 and -OAc), 3.40 (s, -OMe), 4.22 (AB q, $J=12$ Hz, H₂-27), 4.36 (m, H₂-21), 4.50 (dt, $J=14, 4$ Hz, H-22), 5.60 (br d, H-6), 5.88 (dd, $J=10, 2.5$ Hz, H-2), 6.78 (ddd, $J=10, 5.5, 2.5$ Hz, H-3).

Transformation of withametelin (1) to secowithametelin (2). A soln of withametelin (100 mg) in MeOH (15 ml) was treated with a few drops of HClO_4 and left overnight at ambient temp. The reaction product on chromatography over silica gel furnished white plates of secowithametelin (60 mg) from petrol–EtOAc (3:1) eluates.

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