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CONVULSANT ALKALOIDS FROM DIOSCOREA DUMETORUM

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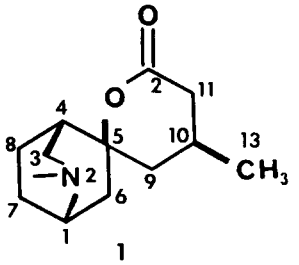
Abstract: Investigation of the West African medicinal yam Dioscorea dumetorum Pax has resulted in the isolation and stereostructural elucidation of the previously reported dihydrodioscorine as well as the new alkaloid dumetorine.

The yam Dioscorea dumetorum has a rich history of medicinal use among the African peoples[1]. Folk medicine has used the yam extracts as a phytotherapeutic agent for treatment of diabetes[2], as a topical anesthetic[1], as well as in arrow poisons[1]. Initial investigation began of D. dumetorum after a poisoning case was reported in Ibadan, Nigeria[3,4]. The study revealed a convulsive alkaloid[5] **1** with the formula $C_{13}H_{21}NO_2$. Comparison of the i.r. of **1** with the i.r. of the hydrogenation product of dioscorine **2** ($C_{13}H_{19}NO_2$), an alkaloid obtained from Dioscorea hispida Dennst[6], indicated that they were closely related. However, the melting points of the picrate, methiodide and hydrochloride derivatives of **1** and the hydrogenation product of **2** were dissimilar, which was attributed to the mixture of stereoisomers resulting from the hydrogenation of **2**.[3]



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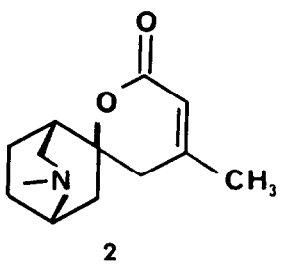

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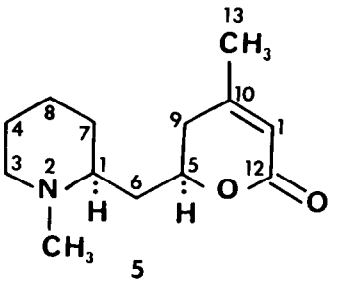


5

Tubers of Dioscorea dumetorum Pax were collected from wild plants growing in secondary forest clearings around Uturu in Okigwe County of Imo State between September and November 1982. The peeled tubers were reduced into thin slices and dried at 40° for two days. The dried plant material was comminuted to a coarse powder. 1kg of each sample of plant material was extracted with petroleum spirit (b.p 40-60°), chloroform and methanol using a soxhlet. The extracts were filtered and evaporated to dryness under reduced pressure. Column chromatography of the petroleum spirit extractive (186g) on silica gel (Kieselgel 60 PF 254 + 366 Merck) eluted with benzene and benzene-ethanol (9:1, 8:1, 6:1, 4:1) gave

three compounds. The chloroform extractive (35g) was separated by preparative thin layer chromatography (on silica gel GF 254, using benzene/ethanol 9:1, chloroform/acetone 1:1 as solvent systems) to yield four compounds, two of the compounds were polar and Dragendorff positive while the less polar ones were identified as diosgenin and β-sitosterol (by co-TLC, m.s., and ^{1}H n.m.r.).

Dihydrodioscorine **1**, $[\alpha]_D^{18}$-42.2° (C,3.4 in $CHCl_3$)[3] $C_{13}H_{21}NO_2$ (m/z 223.158; calc 223.157), oil, has a band in its i.r. (film, 1730cm^{-1}) spectrum consistent with the presence of a δ-lactone. The ^{1}H n.m.r. (C_6D_6, 300MHz) shows the presence of a secondary methyl [δ 0.50 (d=7Hz)] and a tertiary N-methyl [δ 2.04(s)]. The ^{13}C n.m.r. ($CDCl_3$) indicates that **1** is closely related to **2** based on similarity of chemical shifts (See Table 1). The results of two-dimensional n.m.r. experiments (COSY)[7,8] are tabulated in Table 2. This allowed all proton assignments to be made and confirmed the structure as shown. The absolute configuration was determined using the method of molecular rotation additivities between dioscorine **2**[9] and the models 2-oxo-4-methyl tetrahydropyran **3**[10] and 2-oxo-4,6,6-trimethyltetrahydropyran **4**[11] as shown in Table 3. This strongly suggests that C-10 has the S configuration as depicted.

Table 1. ^{13}C Assignments for Dihydrodioscorine **1**, Dioscorine **2**[16], and Dumetorine **5**.

Atom	**1**[a]	**2**[2]	**5**[b]	**5**[a]
C-1	52.1 d	52.4 d	59.7 d	58.9 d
C-3	53.6 t	53.8 t	‡56.7 t	‡56.2 t
C-4	34.7 d	35.2 d	†25.5 t	†24.9 t
C-5	‡83.9 s	81.6 s	73.8 d	73.3 t
C-6	†37.5 t	39.6 t	*35.1 t	*35.0 t
C-7	20.7 t	20.3 t	‡30.4 t	‡29.9 t
C-8	‡19.3 t	19.5 t	†24.2 t	†23.4 t
C-9	†40.4 t	40.9 t	*37.9 t	*37.4 t
C-10	‡23.5 d	155.9 s	156.4 s	156.9 s
C-11	‡42.4 t	116.5 d	116.7 d	115.8 d
C-12	171.4 s	165.1 s	161.4 s	164.0 s
C-13	21.4 q	23.3 q	22.3 q	22.3 q
N-CH_3	42.4 q	42.6 q	59.7 d	42.3 q

a = $CDCl_3$ b= C_6D_6 ‡ or * means interchangable within columns.

Table 2. ^{1}H Assignments for Dihydrodioscorine **1** and Dumetorine **5** in C_6D_6.

Atom	**1**	**5**
1-H	2.18	2.15
3-H	1.97, 2.51	1.96, 2.63
4-H	1.30	1.51, 1.15-2.0
5-H	-	4.18
6-H	1.65, 1.78	1.35,1.55
7-H	1.22, 1.30	1.30, 1.95
8-H	1.72, 2.11	1.94, 1.15-2.0
9-H	0.87, 1.96	1.15-2.0 (2H)
10-H	1.38	-
11-H	1.28, 1.57	5.67
13-H	0.50	1.24
N-CH_3	2.04	2.10

Dumetorine **5**, $[\alpha]_D^{28}$ + 40° (C,0.021 in $CHCl_3$), $C_{13}H_{21}NO_2$ (m/z 223.158; calc 223.157), oil, has bands in its i.r. (film, 1710 cm^{-1}) spectrum suggestive of an α,β-unsaturated δ-lactone. The ^1H n.m.r. (C_6D_6, 300MHz) shows the presence of two methyl singlets, an ene methyl (δ 1.24) and an N-methyl (δ 2.10). Also observed was a highly coupled methine next to oxygen (δ 4.18), the equatorial proton of a methylene next to nitrogen [δ 2.63, (bd = 14 Hz)], and a broad ene proton consistent with substitution α to a carbonyl (δ 5.67). The ^{13}C n.m.r. ($CDCl_3$) supported the presence of a α,β-unsaturated ester [(C-10, δ 156.9(s), C-11, δ 115.8(d), C-12, δ 164.0(s) and C-5, δ 73.7(d)] as well as an N-methyl (δ 42.3) and a methyl attached to an ene (δ 22.5). Also observed were a methine [δ 58.9(d)] and a methylene [δ 56.2(t)] next to nitrogen. All other peaks were methylenes [δ 23.4, 24.9, 29.9, 35.0 and 37.4, all (t)], suggesting the spiro-lactone observed in **2** was not present in **5**, and that the carbon backbone differs between the two compounds (see Table 1).

The results of two-dimensional ^1H n.m.r. experiments (COSY)[7,8] are tabulated in Table 2. This allowed for assignment of most of the protons. Of interest is the connectivity of 5-H (δ 4.18) to 6-H(2H, δ 1.30, 1.95), which in turn are coupled to 1-H (δ 2.15). This established that the δ-lactone is attached to an N-methyl piperidine ring. The protons 3-H(1H, δ 2.63) and 1-H (1H, δ 2.15) were heteronuclearly decoupled to show that they were indeed a methylene and a methine next to nitrogen, respectively[12]. This further verifies that the δ-lactone is attached to the piperidine ring at C-1 as depicted. The relative and absolute configurations of **5** were determined using the molecular rotation additivity method, with N-methyl conine **6**[13], parasorbic acid **7**[14] and massoilactone **8**[15] as models. Examination of Table 4 clearly rules out all possible stereoisomers except the 1-S, 5-R dumetorine (derived from R-N-methyl coniine and S-parasorbic acid or S-massoilactone). The fact that the configuration at C-1 is S in **5** and **2** indicates that they follow similar biosynthetic pathways[16].

Table 3. Determination of the Absolute Stereochemistry of Dihydrodioscorine **1** using Molecular Rotation Additivities.

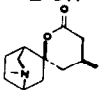
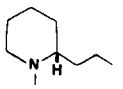
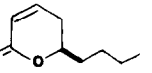
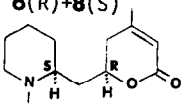
	$[\alpha]_d^t$ (deg)	$[M]_D^t$ (deg)
2 	-23.5	-52
4-S 	-45.4	-64
3-S 	-30.3	-35
2+4S		-116
2+3S		-87
2+4R		+12
2+3R		-17
1 	-42.2	-94

Table 4. Determination of Absolute Stereochemistry of Dumetorine **5** using Molecular Rotation Additivities.

		$[\alpha]_D^t$ (deg)	$[M]_D^t$ (deg)
6-S		+81	+114
7-R		-209	-234
8-R		-93	-156
6(S)+**7**(R)			-120
6(S)+**8**(R)			-42 } -81
6(S)+**7**(S)			-348
6(S)+**8**(S)			-270 } -309
6(R)+**7**(R)			+348
6(R)+**8**(R)			+270 } +309
6(R)+**7**(S)			+120
6(R)+**8**(S)			+42 } +81
5		+40	+89

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