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NEW C-6 OXYGENATED ROTENOIDS FROM TEPHROSIA VILLOSA -- VILLOSIN, VILLOSONE, VILLOL AND VILLINOL

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In this communication we report the structure determination of four closely related new phenolic rotenoids -- villosin (IV), villosone (XI), villol (V) and villinol (IX) isolated along with 6a,12a-dehydrosumatrol (villosol) (VII)[1]and 12a-hydroxysumatrol (villosinol) (III)[1] from the pods of <u>Tephrosia</u> <u>villosa</u>.

All the compounds gave positive Rogers-Calamari test[2] and green colour with alcoholic ferric chloride indicating that these are phenolic rotenoids. The UV absorption curves of villosin (IV) and villol (V) are strikingly similar to those of rotenone (I) and villosinol (III)[1] respectively. The UV absorption curve of villinol (IX) resembles that of villosol (VII)[1] and dehydrorotenone (VI). The phenolic hydroxyl group in these rotenoids has been located at C-11 position, chelated to the carbonyl, on the basis of the bathochromic shift of the longer wavelength band in the UV spectra in the presence of aluminum chloride. In the NMR spectra of villosin, villol and villinol the resonances due to isopropenyl dihydrofuran, methoxyl and aromatic protons appear at more or less similar positions as reported for sumatrol (II) and rotenone (I)[3,4] but differ with respect to C-6, C-6a and C-12a protons (Table-I). The B/C ring fusion as <u>cis</u> in villosin (IV) and villol (V) is evident from the characteristic[3,4] signals at 6.85 and 6.74 respectively in their NMR spectra. The H1 in villinol (IX) resonates at 8.40 indicating it to be a 6a,12a-dehydrorotenoid[3,4].

Villosin (IV) $C_{23}H_{22}O_8$, M^+426, mp 133°, IR: ν max $CHCl_3$ 1645 cm^{-1}(C=O), 3425 cm^{-1}(OH), 3575 cm^{-1}(OH) UV:λ max MeOH 257 nm (sh) (3.68) and 298 nm (4.24), formed a diacetate, $C_{27}H_{26}O_{10}$, M^+510, mp 147° and a monomethyl ether with dimethyl sulfate $C_{24}H_{24}O_8$, M^+440, mp 108° indicating the presence of one alcoholic and one phenolic hydroxyl group. Oxidation of villosin with manganese dioxide gave two compounds: 1. dehydrovillosin (VIII), $C_{23}H_{20}O_8$, M^+424, mp 201° and 2. a keto-lactone (XI), $C_{23}H_{18}O_8$, M^+422, mp 268°. Dehydrovillosin on further oxidation with manganese dioxide also furnished the same keto-lactone. This keto-lactone was found to be identical in all

CHEMICAL SHIFTS (δ) OF ROTENOID PROTONS* (TABLE - I)

Compound	H1	H4	H6	H6a	H12a	H5'	H7'	H10	H11	H4'	Me-8'	MeO-2	MeO-3
Rotenone (I)	6.77 (bs)	6.45 (s)	4.15(bd) 4.59(q)	4.90 (m)	3.80	5.22 (t)	5.06(bs) 4.90(bs)	6.50 (d)	7.84 (d)	3.32(q) 2.93(q)	1.77 (bs)	3.79	3.75
Sumatrol (II)	6.86 (bs)	6.44 (s)	4.13(bd) 4.56(q)	4.80 (m)	3.80	5.17 (t)	5.04(bs) 4.90(bs)	6.00 (s)	12.40 (s)(OH)	3.23(q) 2.83(q)	1.74 (bs)	3.80	3.77
Villosin (IV)	6.85 (bs)	6.42 (s)	5.75(d) 3.95(OH)	4.74 (m)	3.95 (d)	-- 5.10(m) --		6.00 (s)	12.50 (s)(OH)	3.15(q) 2.80(q)	1.74 (bs)	3.78	3.74
Villol (V)	6.74 (s)	6.56 (s)	5.74 3.75-- 3.84(OH)	4.73 (m)	4.58 (bs)(OH)	-- 5.20(m) --		6.07 (s)	12.30 (s)(OH)	3.12(q) 2.75(q)	1.78 (bs)	3.84	3.75
** Villosinol (III)	6.40 (s)	6.12 (s)	4.42 ------	5.52(m)	7.36 (bs)(OH)	4.42--5.52(m)		5.97 (s)	12.30 (s)(OH)	3.23(q) 2.74(q)	1.66 (bs)	3.66	3.44
Dehydro- rotenone (VI)	8.47 (s)	6.50 (s)	4.87	--	--	5.20	5.11	6.90 (d)	8.10 (d)	3.27(m)	1.87	4.00	3.87
** Villosol (VII)	8.20 (s)	6.80 (s)	4.51-- 5.50(m)	--	--	4.51--5.50(m)		5.97 (s)	12.30 (s)(OH)	3.25(q) 2.75(q)	1.79 (bs)	3.75	3.25
** Villinol (IX)	8.40 (s)	6.90 (s)	6.10(s) 3.65(OCH_3)	--	--	5.00--5.30(m)		6.50 (s)	12.30 (s)(OH)	3.50-- 2.50(m)	1.86 (bs)	3.95	3.85

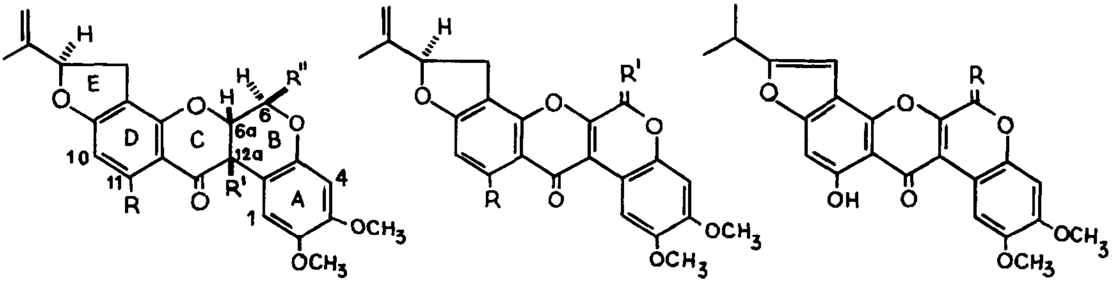
* NMR spectra recorded in $CDCl_3$, 60 MHz.

** Solvent DMSO- D_6

s = singlet, d= doublet, m= multiplet, b = broad.

doublet seen after D_2O exchange. $J_{12a,6a} = 4$ Hz, $J_{6,6a} = 2.75$ Hz (after D_2O exchange) respects with authentic 6a,12a-dehydrosumatrol-6-one (XI) procured by the oxidation of 6a,12a-dehydrosumatrol (VII) with manganese dioxide. Therefore 6-hydroxysumatrol structure (IV) is assignable to villosin.

Villosone (XI), $C_{23}H_{18}O_8$, M^+422, mp 268°, IR: νmax KBr 1650 cm^{-1}(C=O), 1735 cm^{-1}(lactone C=O), 3450 cm^{-1} (OH), UV: λ max Dioxane 264 nm (4.16), 300 nm (4.13) and 348 nm (3.50). The IR and UV data is strikingly similar to that of rotenonone (X)[4](IR: νmax KBr 1630 cm^{-1}, 1740 cm^{-1}, UV: λ max Dioxane 268 nm (4.28), 297 nm (4.20) and 342 nm (3.80). Structure XI (6a,12a-dehydrosumatrol-6-one) has been assigned to villosone by a direct comparison with an authentic sample which was prepared as described above.



(I) R,R',R'' = H
(II) R = OH; R',R'' = H
(III) R,R' = OH; R'' = H
(IV) R, R'' = OH; R' = H
(V) R, R', R'' = OH

(VI) R = H, R' = H,H
(VII) R = OH; R' = H, H
(VIII) R = OH; R' = H, OH
(IX) R = OH, R' = H, OCH_3
(X) R = H; R' = O
(XI) R = OH; R' = O

(XII) R = O
(XIII) R = H, OH

Villol (V) $C_{23}H_{22}O_9$, M^+ 442, mp 223°, IR: νmax $CHCl_3$ 1645 cm^{-1}(C=O), 3400–3450 cm^{-1}(OH), UV: λ max MeOH 230 nm (4.23), 275 nm (sh) (4.03) and 300 nm (4.21), formed a triacetate $C_{29}H_{28}O_{12}$, M^+ 568, mp 124°. Villol is inert towards oxidation with manganese dioxide, a feature noticed in 12a-hydroxysumatrol (III) and other 12a-hydroxyrotenoids[5]. Dehydration of villol with phosphorus pentoxide in benzene[6] followed by chromatography of the resulting crude product gave isovillosone (XII), identical with an authentic sample procured by the acid catalysed isomerization of villosone (XI). We consider that villol (V) is first converted to dehydroisovillosin (XIII) (by dehydration as well as isomerization) which undergoes auto-oxidation to isovillosone (XII). Further, it is interesting to note that dehydrovillosin (VIII) when treated with phosphorus pentoxide in benzene, followed by chromatography, also gave isovillosone, possibly by a similar sequence of reactions. These considerations lead to structure V (6,12a-dihydroxysumatrol) for villol.

Villinol (IX) $C_{24}H_{22}O_8$, M^+ 438, mp 200°, IR: νmax KBr 1660 cm^{-1}, (C=O) 3500 cm^{-1}(OH), UV: λ max MeOH 222 nm (4.12), 278 nm (4.18) and 320 nm (3.84), formed a monoacetate $C_{26}H_{24}O_9$, M^+ 480, mp 170°, Three methoxyl groups are observed in the NMR spectrum of villinol (Table-I). Methylation of dehydrovillosin (VIII) with methyl iodide-silver oxide in acetone (2 hours reflux) gave a monomethyl ether which was found to be identical with natural villinol Therefore the structure IX (6-methoxy-6a,12a-dehydrosumatrol) is assignable to villinol.

The coupling constant $J_{6a,12a}$= 4 Hz in villosin (IV) (rotenone $J_{6a,12a}$= 4Hz[4,7]) shows that the B/C ring junction is *cis*. A study of vicinal coupling constants in villosin between C-6, C-6a and C-12a protons from molecular models using Karplus equation[8] and comparison with observed value, $J_{6a,6}$= 2.75 Hz (Table-1) suggest that the C-6 hydroxyl may be β-oriented and the ring B assumes a boat conformation. Further, models suggest that such a β-oriented hydroxyl group does not interact with the π-system of ring A in the boat form whereas such interactions are possible in the half-chair form of ring B. In the latter case the observed coupling constant should have been 2.518 (dihedral angle H-6a-12a-H 42° and H-6a-6-H 55°) on the basis of calculations from Karplus equation[8]. In contrast ring B in rotenone is reported to have half-chair conformation[4,7]. In villol (V) also $J_{6a,6}$= 2.75 Hz was observed, indicating it may have a similar ring B conformation as in villosin. A comparison of NMR, ORD and CD data of these new rotenoids with rotenone (I) dehydrorotenone (VI) and rotenonone (X) suggest that villosin (IV) has 6aS, 12aS, 6S and 5'R, villosone (XI) 5'R, villol (V) 6aS, 12aS, 6S and 5'R and villinol (IX) 6S and 5'R absolute configuration. Satisfactory elemental analysis were obtained for all new compounds. The mass spectral fragmentation pattern of IV, XI, V and IX is in accordance with the rotenoid skeleton.

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