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PALLIDOL, A RESVERATROL DIMER FROM *CISSUS PALLIDA*

MUSHTAQ A. KHAN, SHAH G. NABI, SATYA PRAKASH and ASIF ZAMAN*

Department of Research in Unani Medicine and Department of Chemistry, Aligarh Muslim University, Aligarh-202001, India

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Key Word Index—*Cissus pallida*; Vitaceae; stemwood; stilbene dimer; ^{13}C NMR; structure determination.

Abstract—Pallidol, a new 3,5,4'-trihydroxystilbene dimer, isolated from the stemwood of *Cissus pallida* is assigned the structure 5,11-*p*-hydroxyphenyl-2,4,8,10-tetrahydroxydibenzo[a, e]tetrahydropentalene on the basis of spectral evidence.

INTRODUCTION

Resveratrol and polymeric products derived from it exhibit marked antifungal activity. In the context of our work on the stilbenes of *Gnetum ula* [1-3] and the reported presence of resveratrol oligomers in the Dipterocarpaceae [4-8], Vitaceae [9, 10] and Gnetaceae [11, 12] we studied the phenolic constituents of *Cissus pallida* and succeeded in isolating a new resveratrol dimer, pallidol. The structural elucidation of this compound forms the subject of the present paper.

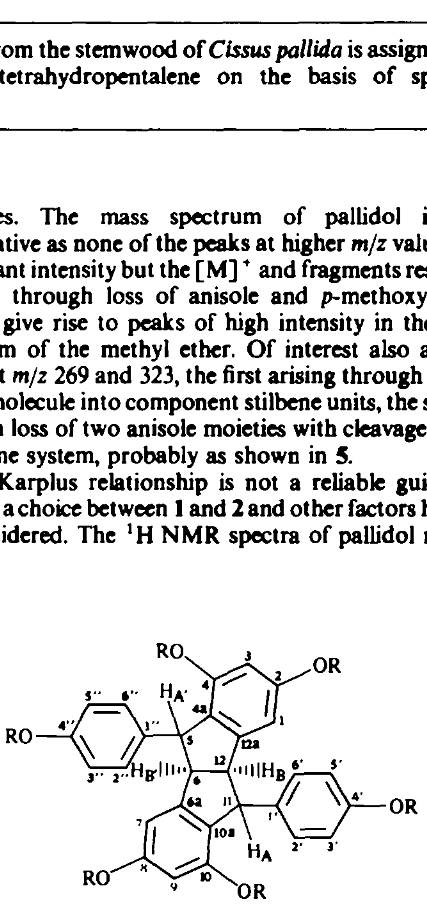
RESULTS AND DISCUSSION

Pallidol, molecular formula $C_{28}H_{22}O_6$, $[M]^+$ m/z 454.14022, was obtained as an amorphous powder which melted with decomposition above 300°. Its IR spectrum showed strong hydroxyl absorption and it readily gave a crystalline methyl ether **3**, $C_{34}H_{34}O_6$, $[M]^+$ m/z 538, and an acetate **4**, $C_{40}H_{34}O_{12}$, $[M]^+$ at m/z 706. The ^{1}H NMR spectra of these derivatives were consistent with the presence of six phenolic hydroxyl groups.

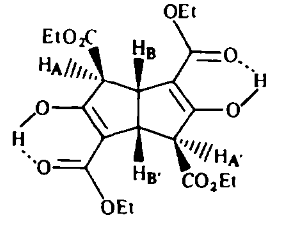
The ^{1}H NMR spectrum of pallidol in DMSO-d_6 shows the presence of 12 aromatic protons which must belong to two sets, one consisting of eight and the other of four protons, to account for the AA'BB' quartet centred at δ6.77 and the *meta* coupled doublets at 6.46 and 6.13. Of the four singlets in the spectrum the two at 8.65 (4H) and 8.39 (2H) obviously represent resonances of the phenolic hydroxyls but assignment of the other two at 4.43 (2H) and 3.74 (2H) is not immediately apparent. The UV absorption of the compound and its derivatives does not show any further conjugation of the benzenoid rings and is typical of phenols.

The above data clearly establish the presence of two resorcinol and two phenol moieties in pallidol and its molecular formula is satisfied if four methine groups are included in the structure. As in the case of the aromatic protons resonances of the methine hydrogens also overlap so as to give rise to two singlets. Pallidol must, therefore, have a symmetrical structure and formulae **1** and **2** alone fulfil this requirement. The singlet at 4.43 is now readily assigned to the benzylic and that at 3.74 to the bridgehead methines. The mass spectrum of pallidol is not informative as none of the peaks at higher m/z values has significant intensity but the $[M]^+$ and fragments resulting from it through loss of anisole and *p*-methoxybenzyl groups give rise to peaks of high intensity in the mass spectrum of the methyl ether. Of interest also are the peaks at m/z 269 and 323, the first arising through fission of the molecule into component stilbene units, the second through loss of two anisole moieties with cleavage of the pentalene system, probably as shown in **5**.

The Karplus relationship is not a reliable guide for making a choice between **1** and **2** and other factors have to be considered. The ^{1}H NMR spectra of pallidol methyl



1 R = H; Ar (eq); $H_{A,A'}$ (ax)
2 R = H; Ar (ax); $H_{A,A'}$ (eq)
3 R = Me
4 R = Ac



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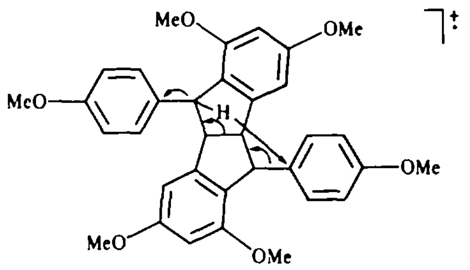
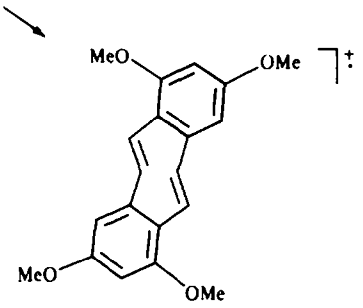
*To whom correspondence should be addressed.



3 m/z 538 (100%)



5 m/z 323 (30%)

ether and its acetate show that resonances of two methyls occur at abnormally high values. This can only happen if the aryl groups are not free to rotate, and in the preferred conformation, two methyl groups come within the shielding zone of the benzene rings. Since models indicate substantial hindrance to free rotation whether the aryl groups are axial or equatorial, shielding of methyls alone does not provide a sufficient basis for stereochemical assignments. However, the accompanying paramagnetic shift of the singlet of C-6, C-12 hydrogens from 3.74 in pallidol to 3.93 in its methyl ether and 4.168 in its acetate can occur only if the aryl groups are equatorial, that is on the same side as the bridgehead hydrogens, and conversion to derivatives produces a change in their conformation.

In lignans, for example eudesmin, lirioresinol-B and piperitol [13–15], which have a similar [3.3.0]bicyclooctane ring system, the conformation of equatorial aryl groups is such as to place the opposite methylene hydrogens [13] in the deshielding zone of the benzene rings. In pallidol methyl ether the C-4 and C-10 methoxyls are roughly in the same plane but are shielded. Models show that the conformation which would have led to deshielding of methyls is not feasible for pallidol due to repulsive interaction between C-4, C-10 substituents and the *ortho*-aryl hydrogens. If the reasonable assumption is made that the bulkier the substituent the larger would be the departure from this conformation to one in which the two methyl groups are progressively shielded and the bridgehead methines deshielded, the chemical shift differences observed in the spectra of pallidol, its methyl ether and acetate become understandable. Thus, whereas in the methyl ether the C-4 and C-10 methyl resonances appear at 3.55, an upfield shift of 0.25 from the normal value of 3.80, the methyls of the acetate groups at these positions suffer a much larger shift of 0.60.

NMR data on saturated dibenzopentalene derivatives is not available in the literature but **6** is a close enough model for comparison [16]. Like pallidol it has a C_2 axis of symmetry and the ^{1}H NMR spectrum therefore exhibits two (2H) triplets for the four carbocyclic protons. The triplets result from long range coupling in which $J_{AB} \sim J_{AB'} = 2.7$ Hz, exactly the pattern of coupling observed in the 100 MHz spectrum of pallidol acetate. The resolution enhanced 300 MHz spectrum shows the signal as a double doublet $J_{AB} = 3.7$ and $J_{AB'} = 2.6$ Hz. Long range coupling of this magnitude across five bonds is uncommon but has been observed in homoallylic systems [17]. Homobenzylic coupling has also been reported but J values are smaller, ~ 0.5 Hz [18]. The enhanced coupling in the present case is probably due to the contribution of the σ bonds of the strained ring system. It is difficult to be certain of the exact reason for the transformation of the methine singlets of pallidol to double doublets in the acetate but since there is no indication of splitting in the methyl ether spectrum molecular distortion is unlikely and perturbation due to proximity of carbonyl groups is probable.

The ^{13}C NMR spectrum of pallidol, as required by the symmetrical structure **1** assigned to it, shows only 12 signals eight of which can be assigned to the fused ring system and the remaining four to the two phenol moieties. The chemical shifts given in Table 1 are in close agreement with values reported for the resveratrol trimer capalliferol-A [19]. A surprising feature of pallidol is its lack of optical activity, the first instance of the kind among polystilbenes although there are examples among lignans [20, 21]. The most likely mechanism for the biogenesis of pallidol, by analogy with that suggested for capalliferol-A [19], is oxidative coupling of two resveratrol units as shown in Scheme 1.

EXPERIMENTAL

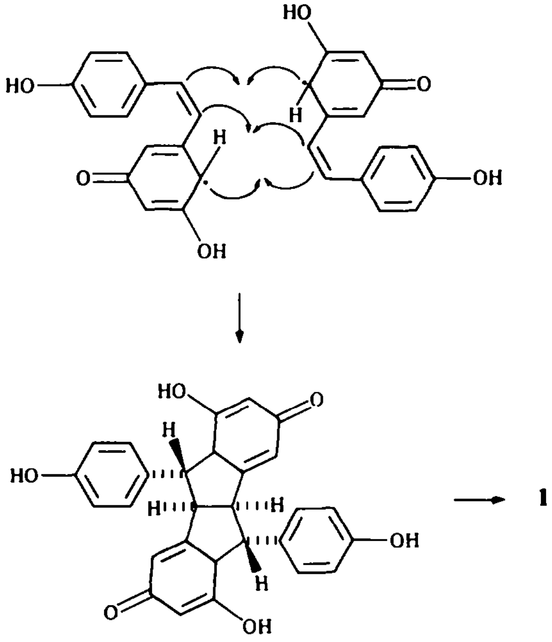
Mps are uncorr. CC was carried out with silica gel (BDH, 60–120 mesh) and TLC with silica gel GF-254 (E. Merck). ^{1}H NMR spectra were recorded at 60, 90, 100 and 300 MHz for

Table 1. ^{13}C NMR chemical shifts of pallidol (1) and its acetate (4)

Assignment	1 (DMSO-d_6)	4 ($CDCl_3$)
C-1	102.2 (*d*)	115.3 (*d*)
C-2	154.4 (*s*)	147.9* (*s*)
C-3	101.7 (*d*)	115.0 (*d*)
C-4	158.2 (*s*)	151.1* (*s*)
C-4a	122.1 (*s*)	133.5 (*s*)
C-5	52.7 (*d*)	55.8 (*d*)
C-6	59.2 (*d*)	61.1 (*d*)
C-6a	148.9 (*s*)	147.5 (*s*)
C-7	102.2 (*d*)	115.3 (*d*)
C-8	154.4 (*s*)	147.9* (*s*)
C-9	101.7 (*d*)	115.0 (*d*)
C-10	158.2 (*s*)	151.1* (*s*)
C-10a	122.1 (*s*)	133.5 (*s*)
C-11	52.7 (*d*)	55.8 (*d*)
C-12	59.2 (*d*)	61.1 (*d*)
C-12a	148.9 (*s*)	147.5 (*s*)
C-1′	136.5 (*s*)	140.7 (*s*)
C-2′	128.1 (*d*)	128.6 (*d*)
C-3′	115.2 (*d*)	121.9 (*d*)
C-4′	155.4 (*s*)	149.6* (*s*)
C-5′	115.2 (*d*)	121.9 (*d*)
C-6′	128.1 (*d*)	128.6 (*d*)
C-1″	136.5 (*s*)	140.7 (*s*)
C-2″	128.1 (*d*)	128.6 (*d*)
C-3″	115.2 (*d*)	121.9 (*d*)
C-4″	155.4 (*s*)	149.6* (*s*)
C-5″	115.2 (*d*)	121.9 (*d*)
C-6″	128.1 (*d*)	128.6 (*d*)
$\underline{Me}CO$		19.9 (*q*)
		20.9 (*q*)
		21.0 (*q*)
$Me\underline{C}O$		167.6 (*s*)
		168.8 (*s*)
		169.2 (*s*)

In δ values from TMS (100 MHz, in DMSO-d_6 and $CDCl_3$). SFORD multiplicities in parentheses.

*Values may be interchanged but those given here are considered to be the most likely.



Scheme 1. Possible mechanism for the biogenesis of pallidol.

solns in DMSO-d_6 and $CDCl_3$. ^{13}C NMR were measured at 100 MHz. MS were recorded at 70 eV.

Plant material. Cissus pallida was collected near Hyderabad in South India and a reference specimen has been deposited in the Department of Botany, Osmania University, Hyderabad.

Isolation of pallidol (1). Air dried stem wood (10 kg) was extracted twice with EtOH and the solvent evapd *in vacuo*. The residue was taken up in H_2O and extracted with EtOAc in a liquid–liquid extractor. The EtOAc soluble fraction (50 g) was chromatographed over silica gel and elution with EtOAc–C_6H_6 (3:2) afforded a brown solid (2 g) which was purified by further chromatography yielding 1 as amorphous powder, $C_{28}H_{22}O_6$, $[M]^+$ *m/z* 454 (observed value 454.14022; calculated value 454.1415), mp > 300° (decomp.); $[\alpha]_D$ 0° (MeOH); UV λ_{max}^{MeOH} 284 nm; IR ν_{max}^{KBr} cm^{-1}; 3350 (br), 1605, 1510, 1240, 1125, 835; ^1H NMR (100 MHz, DMSO-d_6): δ3.74 (2H, *br s*, H-6, 12), 4.43 (2H, *br s*, H-5, 11), 6.13 (2H, *d*, $J = 2$ Hz, H-1, 7), 6.46 (2H, *d*, $J = 2$ Hz, H-3, 9), 6.63 (4H, *d*, $J = 9$ Hz, H-3′, 5′, 3″, 5″), 6.90 (4H, *d*, $J = 9$ Hz, H-2′, 6′, 2″, 6″), 8.39 (2H, *s*, exchangeable on addition of D_2O, 2 × OH), 8.65 (4H, *s*, exchangeable on addition of D_2O, 4 × OH); ^{13}C NMR: see Table 1; MS *m/z* (rel. int.): 454 (20) $[M]^+$, 359 (30), 263 (20), 171 (30), 119 (30).

Pallidol hexamethyl ether (3). A mixture of 1 (0.1 g), K_2CO_3 (5 g) and MeI (5 ml) was refluxed in dry Me_2CO (100 ml) for 3 hr to give 3 which crystallized from MeOH as colourless plates (0.07 g), $C_{34}H_{34}O_6$, $[M]^+$ *m/z* 538, mp 150°; IR ν_{max}^{nujol} cm^{-1}: 1590, 1505, 1460, 1165, 1140, 1030, 835; ^1H NMR (60 MHz, $CDCl_3$): δ3.55 (6H, *s*, 2 × OMe), 3.71 (6H, *s*, 2 × OMe), 3.80 (6H, *s*, 2 × OMe), 3.93 (2H, *br s*, H-6, 12), 4.55 (2H, *br s*, H-5, 11), 6.23 (2H, *d*, $J = 2$ Hz, H-1, 7), 6.64 (2H, *d*, $J = 2$ Hz, H-3, 9), 6.75 (4H, *d*, $J = 9$ Hz, H-3′, 5′, 3″, 5″), 7.05 (4H, *d*, $J = 9$ Hz, H-2′, 6′, 2″, 6″); MS *m/z* (rel. int.): 538 (100) $[M]^+$, 430 (95), 417 (55), 399 (65), 323 (30), 269 (35), 121 (75).

Pallidol hexaacetate (4). Acetylation of 1 (0.1 g) with pyridine–Ac_2O (1:1) by the usual procedure afforded 4 which crystallized from $CHCl_3$–petrol as colourless needles (0.08 g), $C_{40}H_{34}O_{12}$, $[M]^+$ *m/z* 706, mp 126–127°, $[\alpha]_D$ 0° ($CDCl_3$); IR ν_{max}^{nujol} cm^{-1}: 1760, 1620, 1600, 1440, 1380, 1220, 1030; ^1H NMR (300 MHz, $CDCl_3$): δ1.68 (6H, *s*, 2 × OAc), 2.276 (6H, *s*, 2 × OAc), 2.286 (6H, *s*, 2 × OAc), 4.168 (2H, *dd*, $J = 3.7, 2.6$ Hz, H-6, 12 i.e. $H_{B,B'}$), 4.448 (2H, *dd*, $J = 3.7, 2.6$ Hz, H-5, 11, i.e. $H_{A,A'}$), 6.766 (2H, *d*, $J = 2.07$ Hz, H-1, 7), 6.884 (2H, *d*, $J = 2.05$ Hz, H-3, 9), 7.049 (4H, *d*, $J = 8.46$ Hz, H-3′, 5′, 3″, 5″), 7.154 (4H, *d*, $J = 8.55$ Hz, H-2′, 6′, 2″, 6″); MS *m/z* (rel. int.): 706 (25) $[M]^+$, 664 (70), 622 (90), 580 (100), 538 (90), 496 (50), 454 (30), 359 (85), 227 (40), 107 (70).

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REFERENCES

1. Prakash, S., Ahmad, J. and Zaman, A. (1981) *Phytochemistry* **20**, 1455.
2. Prakash, S., Wizarat, K., Zaman, A., Joshi, B. S, Gawad, D. H. and Likhate, M. A. (1983) *Indian J. Chem.* **22B**, 101.
3. Prakash, S., Khan, M. A., Khan, K. Z. and Zaman, A. (1985) *Phytochemistry* **24**, 622.
4. Coggon, P., Janes, N. F., King, F. E., King, T. J., Molyneux, R. J., Morgan, J. W. W. and Sellars, K. (1965) *J. Chem. Soc.* 406.
5. Sultanbawa, M. U. S., Surendrakumar, K., Wazeer, M. I. and Bladon, P. (1981) *J. Chem. Soc. Chem. Commun.* 1204.
6. Samaraweera, U., Sotheeswaran, S. and Sultanbawa, M. U. S. (1982) *Phytochemistry* **21**, 2585.
7. Sotheeswaran, S., Sultanbawa, M. U. S., Surendrakumar, S. and Bladon, P. (1983) *J. Chem. Soc. Perkin Trans.* 1, 699.
8. Sotheeswaran, S., Sultanbawa, M. U. S., Surendrakumar, S., Balasubramaniam, S. and Bladon, P. (1985) *J. Chem. Soc. Perkin Trans.* 1, 159.
9. Langcake, P. and Pryce, R. J. (1977) *Experientia* **33**, 151.
10. Pryce, R. J. and Langcake, P. (1977) *Phytochemistry* **16**, 1452.
11. Lins, A. P., Riebeiro, M. N., Gottlieb, O. R. and Gottlieb, H. E. (1982) *J. Nat. Prod.* **45**, 754.
12. Lins, A. P., Gottlieb, O. R. and Gottlieb, H. E. (1982) *An. Asoc. Quim. Argent.* **70**, 257.
13. Atal, C. K., Dhar, K. L. and Pelter, A. (1967) *J. Chem. Soc.* (*C*) 2228.
14. Briggs, L. H., Cambie, R. C. and Couch, R. A. F. (1968) *J. Chem. Soc.* (*C*) 3042.
15. Pelter, A., Ward, R. S., Rao, E. V. and Sastry, K. V. (1976) *Tetrahedron* **32**, 2783.
16. Camps, P. (1974) *Tetrahedron Letters* **46**, 4067.
17. Jackmann, L. M. and Sternhell, S. (1969) *Applications of NMR Spectroscopy in Organic Chemistry*, p. 320. Pergamon Press, Oxford.
18. Jackmann, L. M. and Sternhell, S. (1969) *Applications of NMR Spectroscopy in Organic Chemistry.* Pergamon Press, Oxford.
19. Sultanbawa, M. U. S., Surendrakumar, S. and Bladon, P. (1980) *J. Chem. Soc. Chem. Commun.* 619.
20. Hostetler, F. D. and Seikel, M. K. (1969) *Tetrahedron* **25**, 2325.
21. Ray, A. B., Chattopadhyay, S. K., Kumar, S., Kanno, C., Kiso, Y. and Hikino, H. (1985) *Tetrahedron* **41**, 209.