Phytochemistry, 1974, Vol. 13, pp. 2281 to 2284. Pergamon Press. Printed in England.

STRUCTURE OF CHINENSIN: A NEW LIGNAN LACTONE FROM *POLYGALA CHINENSIS**

SHIBNATH GHOSAL, RAMABALLAV P. S. CHAUHAN and RADHEY S. SRIVASTAVA
Pharmaceutical Chemistry Research Laboratory, Department of Pharmaceutics,
Banaras Hindu University, Varanasi, India

(*Received* 21 *November* 1973)

Key Word Index—*Polygala chinensis*; Polygalaceae; chinensin; lignan lactone; structural analysis.

Abstract—Chinensin, a 1-aryl-2,3-naphthalide lignan, was isolated from *Polygala chinensis*. Chemical transformation and UV, IR, PMR and MS evidence established its structure as 6,7-methylenedioxy-1-(3′,4′-dimethoxyphenyl)-3-hydroxymethylnaphthalene-2-carboxylic acid lactone. The lignan has not been encountered before in nature or prepared synthetically.

INTRODUCTION

MEMBERS of the genus *Polygala* (family Polygalaceae) are well known for synthesizing a variety of chemical constituents, e.g. polyoxygenated xanthones,[1,2] lignans[3–5] and triterpenes,[6] a number of which exhibit significant biological activity. Previous phytochemical investigation[5] of *P. chinensis* yielded two acyclic and one cyclic lignan lactones, suchilactone (**2**), chisulactone (isomeric with suchilactone), and helioxanthin (**3**), from the petrol and EtOH extracts of the whole plants. Further examination of the petrol extracts afforded a new arylnaphthalide lignan in addition to the previous three. In this paper, we provide evidence for the structure of this compound, which we name chinensin, as the 1-aryl-2,3-naphthalide lignan (**1**).

RESULTS AND DISCUSSION

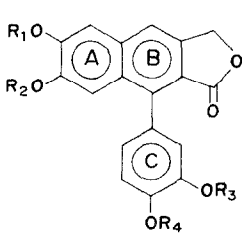
Extraction of whole plants with petrol followed by crystallization and column chromatography of the extractives afforded four crystalline lignans, chinensin (**1**), suchilactone (**2**),[5] helioxanthin (**3**),[5] and chisulactone.[5] Extraction of the defatted plant material with EtOH gave a further crop of chinensin (total yield, 0·1%) plus two other new lignans, chinensinaphthol, m.p. 285–286° (yield, 0·14%) and chinensinaphthol methyl ether, m.p. 257–258° (yield, 0·07%). In addition, two minor lignans and two polyoxygenated benzophenones were obtained by preparative chromatography and derivatization. The plant materials, collected in three lots, were separately extracted and processed. Only minor qualitative but essentially quantitative variations in the chemical constituents were observed. It is of

* Part II in the series "Chemical Constituents of the Polygalaceae". For Part I see Ref. 5.

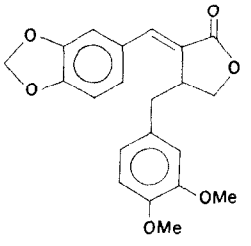
[1] MORON, J., POLONSKY, J. and POURRAT, H. (1967) *Bull. Soc. Chim. France* 130.
[2] DREYER, D. L. (1969) *Tetrahedron* **25,** 4415.
[3] POLONSKY, J., MORON, J. and POURRAT, H. (1962) *Bull. Soc. Chim. France* 1722.
[4] TAKIURA, K. and HOND, S. (1964) *Yakugaku Zasshi* **84,** 1223.
[5] GHOSAL, S., KUMARSWAMY, C., CHAUHAN, R. B. S. and SRIVASTAVA, R. S. (1973) *Phytochemistry* **12,** 2550.
[6] PELLETIER, S. W., ADITYACHAUDHURY, N., TOMAZ, M., REYNOLDS, J. J. and MECHOULAM, R. (1965) *J. Org. Chem.* **30,** 4234.

interest that when the yield of suchilactone decreased the yields of chinensin, chinensinaphthol, and chinensinaphthol methyl ether increased. This observation could have a bearing on the biogenesis of the arylnaphthalene lignan lactones from acyclic precursors involving dehydrogenation (at C_3, C_4) followed by cyclization. Simulated biogenetic transformation of an acyclic lignan into 1-aryl-2,3-naphthalide lignan (diphyllin), involving a cyclic peroxide, has been reported by Horii *et al.*[7]

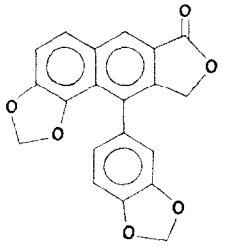
Empirical analyses and MW determination (M^+) established that chinensin had a molecular formula $C_{21}H_{16}O_6$. It gave a bluish–green Labat test (methylenedioxy group), a deep purple colour with conc. H_2SO_4 and a brilliant blue UV fluorescence on TLC plates (reminiscent of arylnaphthalene lignans). Chinensin exhibited UV absorption maxima at λ 220, 250, 258, 290–295 *sh*, 310, 350 nm (log ϵ, 4·22, 4·45, 4·58, 4·09, 4·10, 3·44) and major IR absorption bands at ν 1765, 1756 (aromatic γ-lactone), 1628, 1605, 1588 (aromatic ring), 940 (methylenedioxy), 798 cm^{-1} (1,2,4-trisubstituted aromatic ring), which were closely similar to those of taiwanin-C (**4**),[8] λ_{max} 217, 223, 251 *sh*, 257, 294, 305, 350 nm (log ϵ, 4·30, 4·29, 4·60, 4·64, 3·99, 3·96, 3·70); ν_{max} 1763, 1740, 935 cm^{-1} and dehydrodimethyl-α-retrodendrin (**5**),[8] λ_{max} 213–223, 249, 257, 286–295, 313, 346 nm (log ϵ, 4·37, 4·52, 4·66, 3·86, 3·94, 3·69); ν_{max} 1767, 1755, 932 cm^{-1}, indicating the presence of an 1-aryl-2,3-naphthalide chromophore system in its molecule.



(**1**) $R_1 + R_2 = -CH_2-$; $R_3 = R_4 = Me$
(**4**) $R_1 + R_2 = R_3 + R_4 = -CH_2-$
(**5**) $R_1 = R_2 = R_3 = R_4 = Me$



(**2**)



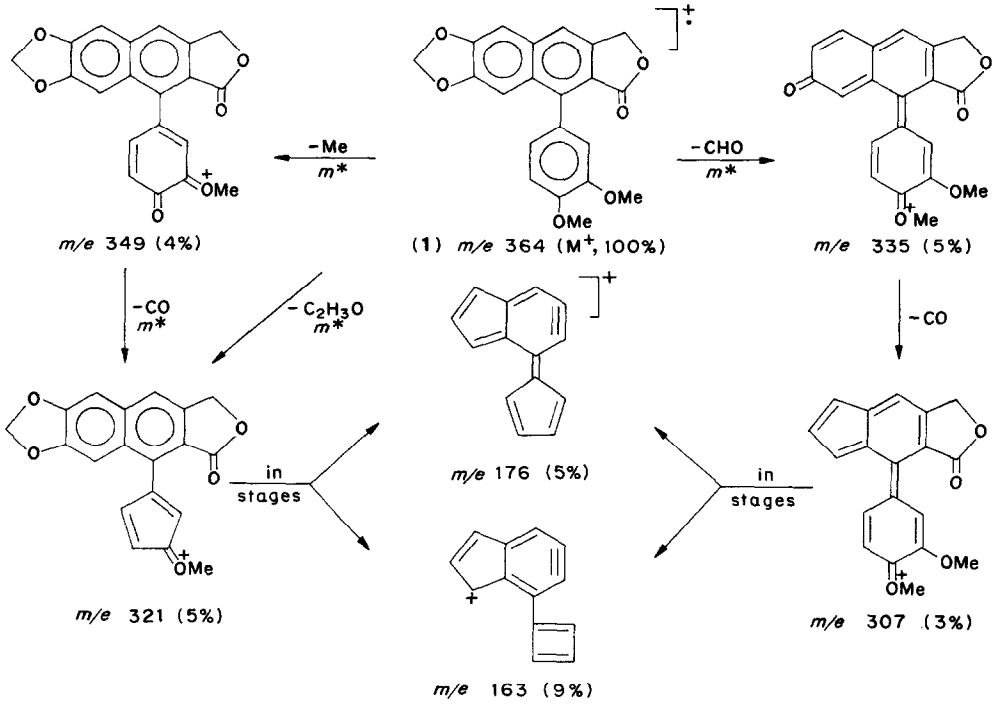
(**3**)

The PMR spectrum of chinensin displayed two methoxyl signals at δ 3·85 and 3·96 which were ascribed to the two C-ring methoxyls (C_3' and C_4'). The alternative location of the methoxyl groups at the C_6 and C_7 positions was ruled out on the basis of the observation[9] that $\Delta\delta$ for A-ring methoxyls would be $>0·2$ ppm. The signal due to the lactone methylene protons appeared at δ 5·34 (doublet, J 1 Hz), indicating it as a 1-aryl-2,3-naphthalide lignan.[10] The remaining signals appeared at δ 6·08 (2H, singlet), 6·88 (1H, singlet), 6·90 (3H, ABX multiplet), 7·22 (1H, singlet), and 7·72 (1H, broad singlet) which were associated with a methylenedioxy (C_6,C_7) and six aromatic protons (C_8, C_2', C_5', C_6', C_5, C_4, respectively). The absence of any aromatic proton signal $>7·72$ ppm also supported the *retro* disposition of the lactone ring.[11]

Evidence for the presence of the lactone ring was obtained from $LiAlH_4$ reduction of chinensin which yielded the corresponding diol, $C_{21}H_{20}O_6$.

[7] HORII, Z., OHKAWA, K. and IWATA, C. (1971) *Chem. Pharm. Bull. Japan* **20**, 624.
[8] LIN, Y.-T., LO, T.-B., WANG, K. T. and WEINSTEIN, B. (1967) *Tetrahedron Letters* 849.
[9] STEVENSON, R. and HOLMES, T. L. (1971) *J. Org. Chem.* **36**, 3450.
[10] HORII, Z., TSUJIUCHI, M. and MOMOSE, T. (1969) *Tetrahedron Letters* 1079.
[11] KLEMM, L. H., GOPINATH, K. W., HSU, D., KELLY, F. W., TROD, E. and MCGUIRE, T. M. (1966) *Tetrahedron* **22**, 1797.

The MS fragmentation of chinensin resembled that of helioxanthin (**3**) in which each oxygen-containing carbon was lost in turn;[12] either the methylenedioxy or one of the methoxyl groups of chinensin could initiate this cleavage. Scheme 1 illustrates one possible fragmentation pathway for chinensin. The formation of the significant fragment ion species was substantiated by metastable ions (m*).



SCHEME 1. MASS FRAGMENTATION PATTERN OF CHINENSIN (**1**).

Further evidence in favour of structure (**1**) for chinensin was obtained by oxidation. Mild oxidation of chinensin gave 3,4-methylenedioxy-6-(3',4'-dimethoxy-benzoyl)-benzoic acid. The product was identified by MS and by conversion with CH_2N_2 to the corresponding keto ester.[13] More drastic oxidation of chinensin gave veratric acid together with other products.

It is concluded that chinensin is 6,7-methylenedioxy-1-(3',4'-dimethoxyphenyl)-3-hydroxymethylnaphthalene-2-carboxylic acid lactone (**1**). The structure is thus isomeric with that of justicidin-B[14] in which the position of the alkoxyl groups (two methoxyl and methylenedioxy) are reversed. The co-occurrence of 1- and 4-aryl-2,3-naphthalide lignans (**1** and **3**), in *Polygala chinensis*, is biogenetically significant, since neither of these two types of lignan is usually found in the same species.

EXPERIMENTAL

M.ps are uncorrected. UV spectra were measured in EtOH, IR spectra as mulls in mineral oil and PMR spectra were determined using a 60 MHz instrument in $CDCl_3$ with TMS as internal standard. MS were recorded at

[12] BURDEN, R. S., CROMBIE, L. and WHITING, D. A. (1969) *J. Chem. Soc.* (*C*) 693.
[13] GOVINDACHARI, T. R., SATHE, S. S., VISWANATHAN, N. and SRINIVASAN, M. (1969) *Tetrahedron* **25**, 2815.
[14] MUNAKATA, K., MARUMO, S., OHTA, K. and CHEN. Y. -L. (1967) *Tetrahedron Letters* 3821.

70 eV using a direct inlet. TLC was carried out on silica gel G with $CHCl_3$ as the solvent. Spots were detected by fluorescence and with I_2 vapour.

Extraction of Plant material. Polygala chinensis L. was collected, in three lots, from Varanasi during August 1971 to September 1973. Voucher specimens have been kept at the Pharmaceutical Chemistry Research Laboratory, Department of Pharmaceutics, Banaras Hindu University. Whole plants were air dried, finely powdered and extracted (Soxhlet) with petrol and then with EtOH (30 hr each). The extractives were processed separately according to a previously described method.[5]

Isolation of chinensin (1). Petrol extractives of the plant (3·2 kg) afforded a yellow solid (9·3 g) on standing at 20° for about a week. Preliminary purification was accomplished by recrystallization from EtOH when colourless needles (3·7 g), consisting of a mixture of suchilactone, (R_f 0·78) and chinensin (R_f 0·66) were obtained. The compounds were separated by column chromatography on silica gel. Petrol, C_6H_6 and $CHCl_3$ (5 l. each) were used as eluents. Chinensin was eluted in the later C_6H_6 and early $CHCl_3$ eluates. After evaporation, repeated crystallization of the residue from MeOH–$CHCl_3$ afforded chinensin as a single entity (0·54 g), R_f 0·66, m.p. 220–221°; $[\alpha]_D^{25}$ 0 ($CHCl_3$); IR: ν_{max} 1765, 1756, 1628, 1605, 1588, 1518, 1505, 1420, 1406, 1382, 1335, 1260, 1252, 1236, 1208, 1182, 1160, 1140, 1042, 1028, 940, 898, 885, 798, cm^{-1}; MS: (rel. intensity) 365 ($M^+ + 1$, 20%, substantiated by a peak at *m/e* 182·5), 364 (M^+, 100), 349 (4, *m** 364→349, 334·8), 335 (5, *m** 364→335, 308·5), 321 (5, *m** 364→321, 283·0; 349→321, 295·5), 307 (3), 305 (7), 289 (6), 277 (5), 249 (4), 233 (3), 219 (5), 205 (5), 204 (3), 176 (5), 163 (9). (Found: C, 69·98; H, 4·62. $C_{21}H_{16}O_6$ requires: C, 69·23; H, 4·39).

$LiAlH_4$ reduction of chinensin. To a stirred slurry of $LiAlH_4$ (0·3 g) in Et_2O (40 ml), was added a soln of chinensin (0·158 g) in Et_2O (40 ml) over a period of 30 min. Stirring was continued for 2 hr and the mixture was kept at 20° for 18 hr. It was then diluted with Et_2O (100 ml) and excess reagent destroyed by successive addition of H_2O and aq. NaOH soln (15%). The organic layer was separated and worked up in the usual way when chinensin diol was obtained as a colourless powder (0·118 g). It crystallized from $(Me)_2CO$–MeOH as needles, m.p. 182–184°; $C_{21}H_{20}O_6$; IR: ν_{max} 3350 (*br*, OH), 1628, 1605, 1585, 1522, 1505, 1418, 1255, 1208, 1182, 1148, 1042, 1025, 945, 890 cm^{-1}; MS: *m/e* 368 (M^+, 100), 353 (M–Me, 5), 350 (M–H_2O, 8), 339 (M–CHO, 3), 338 (M–CH_2O, 2), 325 (M–C_2H_3O, 5), 321 (M–H_2O–CHO, 8), 320 (M–H_2O–CH_2O, 9). (Found: C, 68·02; H, 5·2. $C_{21}H_{20}O_6$ requires: C, 68·46; H, 5·43).

Mild oxidation of chinensin. To a stirred boiling soln of chinensin (1·8 g) in $(Me)_2CO$ (100 ml), $KMnO_4$ (3·5 g) was added over a period of 1 hr. The mixture was refluxed for a further 1 hr and the solvent removed. The residue was suspended in H_2O, acidified with dil. H_2SO_4 and treated with $NaHSO_3$ until all the MnO_2 had dissolved. The dull yellow solid obtained was collected by filtration. It was digested with aq. NaOH (2%, 50 ml), filtered, cooled, acidified and extracted with $CHCl_3$ (3 × 50 ml). The solvent was removed and the residue dissolved in a minimum vol. of MeOH. Chromatographed on a silica gel column using C_6H_6, C_6H_6–$CHCl_3$ and $CHCl_3$ for elution. The $CHCl_3$ eluates afforded 3,4-methylenedioxy-6-(3',4'-dimethoxybenzoyl)-benzoic acid as colourless crystals (0·058 g), m.p. 208–211°; $C_{17}H_{14}O_7$; MS: *m/e* 330 (M^+, 52%), 315 (5), 300 (3), 255 (18), 242 (12), 176 (16), 165 (100). A portion of compound was dissolved in MeOH and treated with excess ethereal CH_2N_2. The product crystallized from $(Me)_2CO$–hexane as colourless needles, m.p. 179–181°; $C_{18}H_{16}O_7$; IR: ν_{max} 1710, 1662, 1605, 1598, 932 cm^{-1}; MS: *m/e* 344 (M^+, 18%), 329 (7), 314 (5), 313 (6), 285 (7), 180 (5), 165 (100). The physical properties of the compound were identical to those of methyl-3,4-methylenedioxy-6-(3',4'-dimethoxybenzoyl)-benzoate.[13]

Oxidation of chinensin. A mixture of chinensin (0·32 g), aq. KOH (2 N, 25 ml) and aq. $KMnO_4$ (2 g, 25 ml) was heated at 100° for 4 hr. The reaction mixture was cooled and the $KMnO_4$ removed with EtOH. After the usual work up the product was dissolved in $CHCl_3$ (2 ml) and chromatographed on a silica gel column (20 × 1·4 cm). Elution with C_6H_6–$CHCl_3$ gave veratric acid (18 mg), m.p. and mm.p. 178–180°; superimposable IR spectra; MS: *m/e* 182 (M^+), 167, 162, 150, 138, 137, 104.

Acknowledgements—The authors are grateful to Professor G. B. Singh, Department of Chemistry, Banaras Hindu University, Dr. B. C. Das, CNRS, Gif-Sur-Yvette, France, Dr. Nitya Nand, CDRI, Lucknow, for obtaining the spectra, and to Dr. C. S. P. Rao, Department of Botany of this University, for confirming the identity of the plant materials.