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3-HYDROXY-9-METHOXY AND 3-METHOXY-9-HYDROXYPTEROCARPANS

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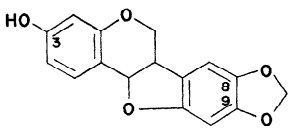
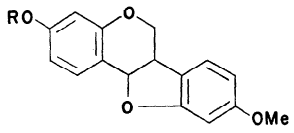
Key Word Index—*Dalbergia stevensonii*; *Andira inermis*; Leguminosae; pterocarpans; synthesis.

Abstract—(±)-3-Hydroxy-9-methoxy and 9-hydroxy-3-methoxypterocarpans have been synthesised and characterized as their acetates. Extraction of *Dalbergia stevensonii* affords, among other products, a mixture of laevorotatory and racemic 3-hydroxy-9-methoxy and 3-hydroxy-8,9-methylenedioxypterocarpans. It is suggested that the '3-hydroxy-9-methoxypterocarpan' isolated from *Andira inermis* was a similar mixture.

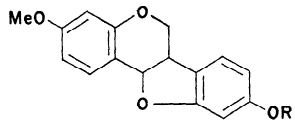
SOME 10 years ago, the isolation of two pterocarpans and the isoflavone, biochanin A from *Andira inermis* Wright H. B. K. was reported.[1] One of the pterocarpans was readily identified as 3-hydroxy-8,9-methylenedioxypterocarpan (I),* and the second, which was obtained in poor yield, was subsequently compared[2] with synthetic racemic 3-hydroxy-9-methoxypterocarpan (IIa). The m.p. of the racemate was considerably higher than that of the optically active natural product. While the IR spectra in Nujol or KBr of the racemic compound and of the naturally occurring species differed in detail, the IR spectra in $CHCl_3$ appeared to be identical. It was concluded that the natural product was 3-hydroxy-9-methoxypterocarpan (IIa).



(I)



(IIa) R = H
(IIb) R = COMe



(IIIa) R = H
(IIIb) R = COMe

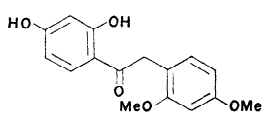
Harper *et al.*[3] subsequently isolated a number of pterocarpans from *Swartzia madagascariensis*, and showed that one of these possessed the structure (IIa), mainly on the basis of NMR spectral comparison. Harper pointed out that there were 'serious discrepancies' between the IR spectra of the pterocarpan from *Andira inermis* and that from *Swartzia madagascariensis* which remained unaccounted for.

* The numbering adopted is that recommended by Harper *et al.*[3]

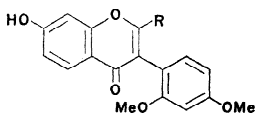
[1] W. COCKER, T. DAHL, C. DEMPSEY and T. B. H. McMURRY, *J. Chem. Soc.* 4906 (1962).
[2] W. COCKER, T. B. H. McMURRY and P. A. STANILAND, *J. Chem. Soc.* 1034 (1965).
[3] S. H. HARPER, A. D. KEMP, W. G. E. UNDERWOOD and R. V. M. CAMPBELL, *J. Chem. Soc.* C, 1109 (1969).

We had none of the original sample of the extractive from *Andira inermis*, and so we decided to resynthesise 3-hydroxy-9-methoxypterocarpan and to synthesise 9-hydroxy-3-methoxypterocarpan (IIIa) for comparison purposes.

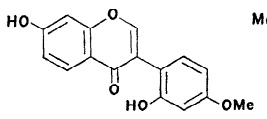
The synthesis of 3-hydroxy-9-methoxypterocarpan (IIIa) followed the route already described[2] with minor modifications. 2,4-Dimethoxybenzaldehyde was prepared from resorcinol dimethyl ether by a Vilsmeyer reaction[4] rather than the Gattermann procedure.[5] The ethoxalylation procedure[6] of the deoxybenzoin (IV)[2] afforded the ethyl ester (Va) which was hydrolysed by one equivalent of 0·3% Na_2CO_3 in aqueous acetone (7:1) at 90° for 4 hr. The corresponding acid (Vb) was decarboxylated. Partial demethylation of (Vc) was achieved using aluminium chloride in acetonitrile[7] to give 7,2′-dihydroxy-4′-methoxyisoflavone (VI) which under standard procedures[2,8] afforded the pterocarpan (IIa), characterized as its acetate (IIb).



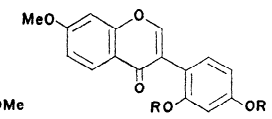
(IV)



(Va) R = CO_2Et
(Vb) R = CO_2H
(Vc) R = H



(VI)



(VIIa) R = Me
(VIIb) R = H

9-Hydroxy-3-methoxypterocarpan (IIIa) has already been synthesized[8] but not characterized. 7,2′,4′-Trimethoxyisoflavone (VIIa)[7,8] was demethylated with 50% HBr[9] to give 2′,4′-dihydroxy-7-methoxyisoflavone (VIIb), which was reduced with borohydride followed by acid to give the pterocarpan (IIIa) as an oil, which was characterized as its acetate (IIIb). The NMR spectra of (IIb) and (IIIb) proved to be quite different, and that of (IIb) is identical with the spectrum of the pterocarpan acetate prepared by Harper.

The question remains as to the identity of the product isolated from *Andira inermis*.[1] We believe that this was mainly 3-hydroxy-9-methoxypterocarpan but contained other pterocarpans with a higher oxygen content. Some light on the problem is shed by extractives from *Dalbergia stevensonii* Standl which afforded, among other products[10] a mixture of two laevorotatory pterocarpans which co-occur with their racemates. The optically active compounds could be separated from the racemates by fractional crystallization, but separation of the optically active mixture could only be achieved by very careful TLC of the acetates, affording 6a*R*,11a*R*-3-acetoxy-9-methoxypterocarpan and 6a*R*,11a*R*-3-acetoxy-8,9-methylenedioxypterocarpan in the ratio 2:1. The MS of the mixture of isoflavans obtained by hydrogenolysis of the pterocarpans confirmed the position of the substituents. It is probable that *Andira inermis* afforded a similar mixture, and indeed it was impossible by IR spectroscopy alone to detect the difference between the mixture and pure 3-hydroxy-9-methoxypterocarpan. Table 1 records the physical properties of the known pterocarpans (see Ref. 11). Where a pterocarpan has been isolated in several studies the highest m.p. is recorded.

[4] A. C. JAIN, P. O. SARPAL and T. R. SESHADRI, *Indian J. Chem.*, **4**, 223 (1966).
[5] D. J. CRAM, *J. Am. Chem. Soc.* **70**, 4240 (1948).
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[8] H. SUGINOME and T. IWADARA, *Bull. Chem. Soc. Japan* **39**, 1535 (1966).
[9] See T. H. SIMPSON and J. L. BEETON, *J. Chem. Soc.* 4065 (1954); R. C. SHAH, V. V. VIRKAR and K. VENKATERAMAN, *J. Indian Chem. Soc.* **19**, 135 (1942).
[10] D. M. X. DONNELLY, J. THOMPSON and W. B. WHALLEY, unpublished results.
[11] W. D. OLLIS, in *Recent Advances in Phytochemistry*, Vol. 1, p. 354, Appleton–Century–Crofts, New York (1968).

TABLE 1. PHYSICAL PROPERTIES OF KNOWN PTEROCARPANS

Compound	Racemate m.p. (°)	Ref.	6αR,11αR m.p. (°)	$[\alpha]_D$($CHCl_3$)	Ref.
3-Hydroxy-9-methoxypterocarpan	195–197	2	127·5–128·5	−234°	17
3-Acetoxy-9-methoxypterocarpan	107–108	2	120–121	−181°	3,17
3,9-Dimethoxypterocarpan	123–125	12,13	83–85	−225°	3,13,17
3-Hydroxy-8,9-methylene-dioxypterocarpan	194–195	13–15	175–177	−240°	1,3
3-Acetoxy-8,9-methylene-dioxypterocarpan	159–160	14	176–177·5	−178°	1,3,17
3-Methoxy-8,9-methylene-dioxypterocarpan	185–186	13,14,16	163–164	−220°	1,3

EXPERIMENTAL

IR spectra were measured on a Perkin–Elmer Infracord 137, UV spectra for ethanol solutions and NMR spectra at 60 MHz on Perkin–Elmer R.10 and R.12 instruments. MS were measured on a Hitachi–Perkin–Elmer RMS.4 instrument.

3-Hydroxy-9-methoxypterocarpan (IIa) has m.p. 195–197° (lit.[2] 194–195°) IR ν_{max} ($CHCl_3$) 3300, 1620, 1600, 1490 and 1016 cm^{-1}, NMR τ [$CDCl_3$–$(CD_3)_2SO$] 6·4 (*m*, 2H), 6·23 (3H, OMe), 5·75 (*m*, 1H), 4·45 (br. *d*, *J* 7 Hz, 1H), 3·3–3·7 (*m*, 4H), 2·82 (*d*, *J* 8 Hz, 1H), 2·65 (*d*, *J* 8 Hz, 1H) and 0·8 (1H, OH).

3-Acetoxy-9-methoxypterocarpan (IIb) had m.p. 107–108° (lit.[2] 105–106°) IR ν_{max} ($CHCl_3$), 1760, 1620, 1600, 1150, 1025, 957 and 900 cm^{-1}. NMR τ ($CDCl_3$) 7·73 (3H, MeCOO), 6·4 (*m*, 2H), 6·23 (3H, OMe), 5·70 (*m*, 1H), 4·48 (br. *d*, *J* 8 Hz, 1H), 3·50 (*m*, 2H), 3·25 (*d*, *J* 2 Hz, 1H), 3·20 (*d. d*, *J* 8 Hz and 2 Hz, 1H), 2·88 (*d*, *J* 8 Hz, 1H) and 2·44 (*d*, *J* 8 Hz, 1H).

2′,4′-Dihydroxy-7-methoxyisoflavone (VIIb). 7,2′,4′-Trimethoxyisoflavone (VIIa)[7,8] (800 mg) was refluxed in 50% aq. HBr (100 ml) for 20 min. The solution was poured on to ice, and chromatography of the solid on a silica column afforded 2′,4′-dihydroxy-7, methoxyisoflavone (200 mg), m.p. 210–211° (lit.[7] 212°), I.R. ν_{max} (Nujol) 3500, 1625, 1607, 1550, 1045 and 1020 cm^{-1}. NMR τ [$(CD_3)_2SO$] 6·10 (3H, OMe), 2·9–3·8 (*m*, 5H) 2·05 (*d*, *J* 8 Hz, 1H), 1·82 (OH), 0·82 (OH) and 0·70 (1H).

9-Acetoxy-3-methoxypterocarpan (IIIb). $NaBH_4$ (200 mg) in EtOH (5 ml) was added dropwise to the dihydroxymethoxyisoflavone (180 mg) in tetrahydrofuran (5 ml), and the mixture set aside for 60 hr. Acetone (5 ml) was added to destroy excess borohydride. The solvent was removed and the residue acidified with 10% HCl. The mixture was extracted with $CHCl_3$ and chromatographed on silica to give 9-hydroxy-3-methoxypterocarpan as an oil. Acetylation (Ac_2O-pyridine) afforded after chromatography on silica, 9-acetoxy-3-methoxypterocarpan, as leaflets, m.p. 117–118° (Found: C, 68·9; H, 4·95. $C_{18}H_{16}O_5$ requires: C, 69·2; H, 5·2%). IR ν_{max} (Nujol) 1760, 1610, 1587, 1087, 1040, 1020, NMR τ ($CDCl_3$) 7·72 (3H, MeCOO), 6·3 (*m*, 2H), 6·2 (3H, OMe), 5·75 (*m*, 1H), 4·48 (br. *d*, *J* 7 Hz, 1H) 3·45 (*m*, 4H), 2·80 (*d*, *J* 8 Hz, 1H) and 2·60 (*d*, *J* 8 Hz, 1H).

9-Hydroxy-3-methoxypterocarpan (IIIa). The above acetate (10 mg), EtOH (1 ml) and aq. ammonia (1 ml) was heated for 20 min. The product from EtOH–H_2O was 9-hydroxy-3-methoxypterocarpan (1 mg) as leaflets, m.p. 63–64° (M^+ *m/e* 270) IR ν_{max} ($CHCl_3$) 3590, 1621, 1610 (sh), 1588, 1090 and 1040 cm^{-1} NMR τ [$CDCl_3$ + $(CD_3)_2SO$)] 6·45 (*m*, 2H), 6·23 (OMe), 5·80 (*m*, 1H), 4·48 (br. *d*, *J* 8 Hz, 1H), 3·30–3·60 (*m*, 4H), 2·93 (*d*, *J* 8 Hz, 1H), and 2·58 (*d*, *J* 8 Hz, 1H).

Isolation of (±),(−)-*3-hydroxy-9-methoxypterocarpan and* (±), (−)-*3-hydroxy-8,9-methylenedioxypterocarpan from* Dalbergia stevensonii *Standl.* The finely ground heartwood (3 kg) was exhaustively extracted with hot *n*-hexane and MeOH in the cold. The residue from the MeOH extract was subsequently extracted with hot benzene. A solid (50 mg) was deposited from the *n*-hexane extract and on crystallization with benzene afforded a non-crystalline mixture (m.p. 180–181°) of (±)-3-hydroxy-9-methoxypterocarpan (m.p. 194°, lit.[2] 194–195°) and (±)-3-hydroxy-8,9-methylenedioxypterocarpan (m.p. 194°, lit.[13] 194–195°). MS *m/e* 284 (rel. int. 18), *m/e* 270 (rel. int. 100). $C_{16}H_{12}O_5$ requires: M^+ 284; $C_{16}H_{14}O_4$ requires: M^+ 270

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[14] S. SHIBATA and Y. NISHIKAWA, *Chem. Pharm. Bull. Tokyo* **11**, 167 (1963).
[15] K. FUKUI, M. NAKAYAMA and H. TSUZUKI, *Experientia* **24**, 536 (1968).
[16] E. SPÄTH and J. SCHLÄGER, *Chem. Ber.* **73**, 1 (1940).
[17] E. MACKAWA and K. KITAO, *Wood Res.* **50**, 29 (1970).

In the NMR spectrum of the mixture, the relative intensities of methoxyl to methylenedioxy peaks indicated a ratio of 1:1. An aliquot (20 g) of the C_6H_6 extract was chromatographed (800 g silica, Merck) using $CHCl_3$ $CHCl_3$–Me_2CO [19:1; 9:1; 4:1] as eluting solvents. The fraction eluted with $CHCl_3$ yielded, among many other compounds,[10] an oil (70 mg), which an addition of MeOH, precipitated the racemates (10 mg) (see above). The residue (60 mg), from evaporation of the filtrate, was acetylated [Ac_2O (10 ml): pyridine (0·5 ml)], and afforded a mixture (2:1) of 6α*R*,11α*R*-3-acetoxy-8,9-methylenedioxypterocarpan and 6α*R*,11α*R*-3-acetoxy-9-methoxypterocarpan as needles from MeOH, m.p. 154–166°,* $[\alpha]_D^{21}$ −188·5° ($CHCl_3$). Separation by triple development [light petrol. (b.p. 60–80°): EtOAc, 7/3] on TLC gave (Band i) 6α*R*,11α*R*-3-acetoxy-9-methoxypterocarpan as needles from MeOH, m.p. 119–120° (lit.[3,17] 122–123, 120–121°), $[\alpha]_D^{21}$ −182° ($CHCl_3$) [M^+ *m/e* 312 (60%), 270 (100%)]. Band (ii) afforded 6α*R*,11α*R*-3-acetoxy-8,9-methylenedioxypterocarpan as needles from EtOAc, m.p. 176° (lit.[1] 178°) $[\alpha]_D^{21}$ −177° ($CHCl_3$).

Hydrogenolysis of a mixture of (−)-3-*acetoxy*-8,9-*methylenedioxypterocarpan and* (−)-3-*acetoxy*-9-*methoxypterocarpan.* A mixture (30 mg) of 6α*R*,11α*R*-3-acetoxy-8,9-methylenedioxypterocarpan and 6α*R*,11α*R*-3-acetoxy-9-methoxypterocarpan, Pd–C (50 mg) and H_2SO_4 (1 drop) in EtOH (10 ml) was stirred in an atmosphere of H_2 at 80° for 3 hr. The catalyst and solvent were removed. The crude mixture of isoflavans was acetlyated [Ac_2O (5 ml); pyridine (0·5 ml)] at room temp. for 12 hr. Purification by TLC (3% EtOAc–C_6H_6) afforded, 7,2′-diacetoxy-4′,5′-methylenedioxyisoflavan (A) and 7,2′-diacetoxy-4′-methoxyisoflavan (B) as lustrous plates (EtOH) (13 mg), m.p. 154–155°, MS (A) M^+ 370 (20%), *m/e* (%) 328 (55), 286 (21), 164 (100), 163 (70) 151 (25); (B) M^+ *m/e* 356 (18), 314 (20), 272 (13), 150 (53), 137 (24), 135 (18).

7,2′-*Diacetoxy*-4′,5′-*methylenedioxyisoflavan* (3 mg) was isolated by TLC of the above mixture (13 mg) [Developer 3% EtOAc–C_6H_6; 6×] m.p. 160–161° (M^+ *m/e* 370), τ ($CDCl_3$) 7·71, 7·77 (*s*, 2 × 0.$COCH_3$), 3·98 (*s*, O.CH_2O). [(±)-7,2′-Diacetoxy-4′,5′-methylenedioxyisoflavan m.p. 138–139°].[14]

Acknowledgements—We are grateful to the S.R.C. for a studentship (EM) and the Department of Education of the Republic of Ireland for a maintenance award (JCT). We wish to thank V. Delaney for technical assistance.

* The m.p. of the 'mixture' from *Andira inermis* was 148–150°.[1]