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THE SYNTHESIS OF PROPTEROL, A NOVEL 1,3-DIARYLPROPAN-2-OL FROM *PTEROCARPUS MARSUPIUM*

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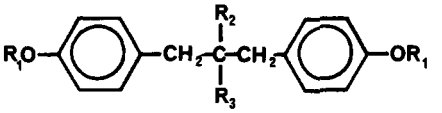
Pterocarpus marsupium Roxb. (Leguminosae), a large tree indigenous to the forests of central and peninsular India, has a long history of folkloric use as a medicinal in the treatment of various infections, fever, diarrhea, and diabetes (1-3). Previous research has established the genus *Pterocarpus* to be a rich source of polyphenolic compounds (4), and recently, the isolation and identification of ten phenols from the heartwood of this plant was reported by our laboratories (3). These compounds were diverse but structurally-related and included the stilbene, pterostilbene; the chalcone, isoliquiritigenin; the dihydroxychalcone, pterosupin; the flavanones, liquiritigenin and (2*S*)-7-hydroxyflavanone; the flavones, 5-deoxykaempferol and 7,4′-dihydroxyflavone; the benzofuranone, marsupsin; the simple phenols *p*-hydroxybenzaldehyde and (−)-3-(*p*-hydroxyphenyl)-lactic acid; and an incompletely characterized phenolic compound designated PM-33 (3).

The present paper describes the synthesis of PM-33, the structure of which was previously established as 1,3-bis-(4-hydroxyphenyl)-propan-2-ol (**1**) on the basis of spectral data with the trivial name pterosupol being given to this compound (5). A recent publication on propterol (**1**) (6), in which its structure was determined by a consideration of physicochemical data and both Jones and potassium-permanganate oxidation of propterol dimethyl ether (**2**), revealed the identity of propterol with pterosupol and prompts us to record our findings, particularly the synthesis of propterol (**1**).



1 $R_1=R_2=H$; $R_3=OH$
2 $R_1=CH_3$; $R_2=H$; $R_3=OH$
3 $R_1=CH_3$; $R_2+R_3=O$

PM-33 was isolated as an optically inactive substance, mp 171°,[1] whose melting point and spectral properties (uv, ir, ^1H nmr, ^{13}C nmr) are identical to those of propterol (**1**) (6). Synthesis of propterol (**1**) was achieved via dimerization of 4-methoxyphenylacetyl chloride (prepared by treatment of 4-methoxyphenylacetic acid with thionyl chloride in dry C_6H_6) with triethylamine (7) to afford a ketene dimer. Hydrolysis of this dimer *in situ* in alkaline solution afforded 1,3-bis-(4-methoxyphenyl)-propan-2-one (**3**) (7) which was converted to 1,3-bis-(4-methoxyphenyl)-propan-2-ol (**2**) by reduction with sodium borohydride in MeOH (8). Finally, demethylation of **2** with boron tribromide (9) afforded 1,3-bis-(4-hydroxyphenyl)-propan-2-ol (**1**) which was identical to propterol by direct comparison (uv, ir, ^1H nmr, ^{13}C nmr, ms, mp, co-tlc).

The occurrence of 1,3-biphenyl-propan-2-ols, a rare class of simple flavonoids, appears to have been limited

[1]The mp of 314-315° given by Maurya *et al.* (3) is erroneous.

to the genus *Virola* (Myristicaceae) (virolanols A, B and C) (10, 11) until this time. To our knowledge, propterol is the first example of a compound of this class outside of the genus *Virola* and is unusual in its symmetrical aromatic hydroxylation. None of the three synthetic biphenylpropanoids (**1, 2, 3**) possessed antimicrobial activity when screened against a standard set of microorganisms using the agar dilution streak method (12).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Melting points were taken on a Fisher-Johns apparatus and are uncorrected. The uv spectra were obtained on a Perkin-Elmer model 552A recording spectrophotometer in MeOH, and the ir spectra were determined on a Perkin-Elmer model 257 recording spectrophotometer in KBr pellets. The ^{1}H-nmr spectra were recorded on a Hitachi-Perkin-Elmer model R-24 high resolution spectrometer (60 MHz) or on a Bruker WH-90 spectrometer (600.6 MHz) in $CDCl_3$ (with/without deuterated MeOH) with TMS as the internal standard and chemical shifts reported in δ (ppm) units. THe ^{13}C-nmr spectra were recorded on a JEOL FX-90Q spectrometer (22.5 MHz) in the same solvents. The low resolution mass spectra were taken with a Finnigan EI Mass Spectrometer, Spectrel Electronics, interfaced with a Finnigan Incos Data System, Extranuclear Laboratories, Inc. The high resolution mass spectrum was obtained on a Varian MAT, Model CH-5 spectrometer. Thionyl chloride, triethylamine, C_6H_6, and CH_2Cl_2 were obtained from Fisher Scientific, Pittsburgh, PA, and were distilled immediately prior to use. Boron tribromide, 4-methoxyphenylacetic acid, and sodium borohydride were obtained from Aldrich Chemical Company, Milwaukee, WI. Silicic acid (100 mesh) (Mallinckrodt) and silica gel G (Camag) were used for column chromatography.

PREPARATION OF 1,3-BIS-(4-METHOXYPHENYL)-PROPAN-2-ONE (**3**) (7).—To 4-methoxyphenylacetic acid (50 g) in dry C_6H_6 (500 ml) was added freshly distilled $SOCl_2$ (60 ml) and the mixture refluxed for 4 h. The C_6H_6 was evaporated, and the resulting 4-methoxyphenylacetyl chloride (pale yellow oil) was dissolved in Et_2O (500 ml) and Et_3N (60 ml) added dropwise over a period of 1 h. The resulting mixture was stirred overnight, partitioned with H_2SO_4 (2%) (1000 ml) to remove amine salts, and the Et_2O was evaporated. The resulting residue was treated with KOH (2%) (700 ml) and the mixture heated on a steam bath for 1 h. The mixture was cooled in ice, extracted with Et_2O (1000 ml), the Et_2O layer rinsed with H_2O (500 ml), dried (anhydrous Na_2SO_4), filtered, and evaporated to a residue (19.6 g). Chromatography of this residue in C_6H_6 (50 ml) over silicic acid (300 g) and elution with C_6H_6 (600 ml) afforded a mixture of products. Continued elution with C_6H_6 (2500 ml) gave 1,3-bis-(4-methoxyphenyl)-propan-2-one (**3**) as a solid which crystallized from hot MeOH as pale yellow plates (6.7 g) (16% yield), mp 84°; uv λ max (MeOH) 285 nm (sh) (log ε 3.10), 276 (3.29), and 227 (4.27); ir ν max (KBr) 1703 cm^{-1}, 1610, 1580, 1510, and 820; ^{1}H nmr ($CDCl_3$) δ 3.61 (s, 4H, CH_2), 3.85 (s, 6H, OCH_3), 6.81 (d, 4H, J=9Hz, Ar*H*) and 7.07 (d, 4H, J=9Hz, Ar*H*); ^{13}C nmr, ($CDCl_3$) 50.0 (C-7+C-7′), 55.2 (OCH_3), 114.1 (C-2+C-6 and C-2′+C+6′), 126.1 (C-4+C-4′), 130.5 (C-3+C-5 and C-3′+C-5′), 158.6 (C-1+C-1′), and 206.2 (C-8) (13-15); ms M^+ *m/z* 270 (66%) for $C_{17}H_{18}O_3$, 148 (21), 121 (100), 106 (13), 91 (34), and 77 (67).

PREPARATION OF 1,3-BIS-(4-METHOXYPHENYL)-PROPAN-2-OL (**2**).—To a solution of 1,3-bis-(4-methoxyphenyl)-propane-2-one (**3**) (2.0 g) in MeOH (300 ml) was added $NaBH_4$ (1.0 g) portionwise over 1 h with stirring (8). The resulting solution was stirred for 3 h, evaporated, and the residue dissolved in HCl (10%) (100 ml) and partitioned with Et_2O (100 ml) twice. The Et_2O extracts were combined, dried (anhydrous Na_2SO_4), filtered, and the filtrate evaporated to afford a crystalline mass which was recrystallized from petroleum ether-$CHCl_3$ (50:1) to afford 1,3-bis-(4-methoxyphenyl)-propan-2-ol (**2**) (1.73 g) (86%) as white needles, mp 57°; uv λmax (MeOH) 283 nm (log ε 3.43), 276 (3.51), and 226 (4.35); ir ν max (KBr) 3500 cm^{-1}, 1610, 1580, 1510, 1100, and 820; ^{1}H nmr, ($CDCl_3$, TMS, 60 MHz) δ 2.71 (m, 4H, $2CH_2$), 3.77 (s, 6H, $2OCH_3$), 3.98 (m, 1H, *CH*OH), 6.83 (d, 4H, J=9Hz, Ar*H*); and 7.14 (d, 4H, J=9Hz, Ar*H*); ^{13}C nmr ($CDCl_3$, TMS) 42.4 (C-7+C-7′), 55.1 (OCH_3), 73.7 (C-8), 113.9 (C-2+C-6 and C-2′+C-6′), 130.3 (C-3+C-5 and C-3′+C-5′), 130.6 (C-4+C-4′), 158.2 (C-1+C-1′) (13-15); ms M^+ *m/z* 272 (14%) for $C_{17}H_{20}O_3$, 254 (5), 151 (28), 133 (4), 122 (100), 121 (54), 107 (17), 91 (27), 77 (22).

PREPARATION OF 1,3-BIS-(4-HYDROXYPHENYL)-PROPAN-2-OL (PROPTEROL) (**1**).—To a solution of 1,3-bis-(4-methoxyphenyl)-propan-2-ol (**2**) (1.0 g) in freshly distilled CH_2Cl_2 (100 ml) and cooled to −80° was added BBr_3 (1.0 ml) in freshly distilled CH_2Cl_2 (20 ml) (9). The mixture was allowed to slowly warm to room temperature over 12 h while stirring. The mixture was then stirred with H_2O (100 ml), the CH_2Cl_2 layer removed, and the remaining H_2O par-

titioned with Et_2O (100 ml). The CH_2Cl_2 and Et_2O layers were combined, dried (anhydrous Na_2SO_4), filtered, and evaporated. The resulting residue was treated with NaOH (2N) (100 ml), partitioned with Et_2O (100 ml), and the alkaline solution acidified with HCl (6N) and again partitioned with Et_2O (100 ml) twice. The acidic Et_2O layers were combined, dried (anhydrous Na_2SO_4), filtered, and the filtrate evaporated to afford a residue (735 mg). Chromatography of this residue over silica gel in C_6H_6-Me_2CO-HOAc (90:30:0.1) and collection of 20 ml fractions afforded propterol (**1**) (140 mg) (16%) from fractions 14-16. Propterol crystallized from $CHCl_3$-MeOH as fine white needles, mp 171°; λ max (MeOH) 285 nm (sh) (log ε 3.42), 278 (3.54), and 226 (4.23); ir ν max (KBr) 3420 cm^{-1} 3260, 3130, 2925, 2905, 1612, 1595, 1510, 1450, 1432, 1418, 1375, 1340, 1320, 1295, 1235, 1172, 1100, 1080, 1025, 1015, 945, 935, 928, 808, and 740; ^1H nmr ($CDCl_3$+CD_3OD, TMS, 600.6 MHz) δ 2.73 (dd, 2H, J_{gem}=14Hz, J_{trans}8.1Hz, ArCH_2), 2.85 (dd, 2H, J_{gem}=14Hz, J_{cis}=4.4Hz, ArCH_2), 4.02 (m, 1H, *CH*OH), 6.85 (d, 4H, *J*=8.5Hz, Ar*H*), and 7.16 (d, 4H, *J*=8.5Hz, Ar*H*); ^{13}C nmr ($CDCl_3$+CD_3OD, TMS) 41.9 (C-7+C-7′), 73.8 (C-8), 114.9 (C-2+C-6 and C-2′+C-6′), 129.6 (C-4+C-4′), 130.0 (C-3+C-5 and C-3′+C-5′), and 154.8 (C-1+C-1′) (13-15)[2]; ms M^+ *m/z* 244 (19%) (calculated 244.1100 and measured 244.1096 for $C_{15}H_{16}O_3$), 137 (18), 119 (14), 108 (68), 107 (100), 91 (27), and 77 (26). The synthetic material was identical to the natural product by direct comparison (uv, ir, ^1H nmr, mp).

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[2]Comparison with the spectrum of 1,3-biphenyl-propan-2-ol prepared by reduction ($NaBH_4$) of 1,3-biphenyl-propan-2-one (dibenzylketone) (Aldrich Chemical Company, Milwaukee, WI).