Tetrahedron Vol. 42, No. 9, pp. 2417 to 2420, 1986
Printed in Great Britain.

0040–4020/86 $3.00+.00
Pergamon Journals Ltd.

RACEMOSOL: A NOVEL TETRACYCLIC PHENOL FROM BAUHINIA RACEMOSA LAMK.

A.S.R. Anjaneyulu, A.V. Rahgava Reddy and D.S.K. Reddy
School of Chemistry, Andhra University, Waltair, India
and
T. Stanley Cameron and S.P. Roe
Department of Chemistry, Dalhousie University, Halifax, Canada

(*Received in USA* 7 *November* 1985)

Abstract

The isolation of a novel tetracyclic phenol, racemosol, is reported from the hexane extract of the heart-wood of Bauhinia racemosa Lamk. The structure of racemosol has been established as (II) by a study of its chemical and spectroscopic properties and by x-ray analysis.

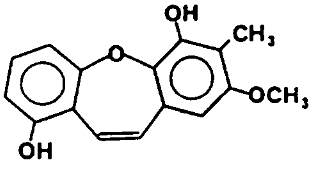
Discussion

Chemical examination of the heart-wood of Bauhinia racemosa Lamk. (fam: Leguminosae, sub fam: Cesalphiniaceae) collected from Araku valley, a forest area of the Visakhapatnam district (India), resulted in the isolation of pacharin(I), a novel phenolic compound of the basic dibenzo-(2,3-6,7) oxepin structure[1]. The heart-wood of the same plant collected from the Paderu area of the Araku valley yielded yet another novel class of phenolic compound, racemosol. The chemical and spectroscopic data, including x-ray analysis, suggest a tetracyclic structure(II) for racemosol. Extraction of the powdered heart-wood with hexane yielded a residue which, on chromatography over a column of silica gel, contained both β-sitosterol and racemosol; the latter being a deep red phenolic substance which is soluble in alkali and crystallises from chloroform as red prisms [m.p. = 202°, $(\alpha)_D$:+64.50°] and identified as $C_{21}H_{24}O_4(M^+340)$. The infrared absorption band at 3400 cm^{-1} suggests the phenolic nature of racemosol, and indicates hydrogen-bonding associated with the hydroxyl groups, since free phenolic hydroxyl O-H stretching vibrations appear near 3600 cm^{-1} as sharp bands. The electronic spectrum of racemosol indicates three maxima at 224 nm (log ε, 4.43), 276 nm (log ε, 3.767) and 430 nm (log ε, 2.278). Ziesel's estimation accounted for one methoxyl. Acetylation ($py+Ac_2O$) of racemosol gave evidence for the presence of two phenolic hydroxyl groups by yielding the diacetate analogue indicated as structure(III), which crystallized as pale yellow needles from methanol [m.p. = 244–246°, $(\alpha)_D$:+30.98°] and identified as $C_{25}H_{28}O_6(M^+424)$. Methylation (CH_2NH_2) of racemosol yielded the dimethylether analogue(IV), which formed as a pale yellow oil and identified as $C_{23}H_{28}O_4(M^+368)$. The fourth oxygen of the molecule which is relatively inert, is present as a cyclic ether.

The ^1H-NMR spectral data for racemosol, its diacetate and dimethylether derivatives are presented in Table 1. The ^1H-NMR (90 MHz) spectrum of racemosol indicates the presence of two aliphatic methyl singlets at 1.30δ and 1.49δ; an aromatic methyl at 1.98δ and an aromatic methoxyl at 3.86δ. The two singlets at 1.60δ and 5.65δ (exchangeable with D_2O) account for the two phenolic protons. The aromatic region indicated only three protons, a singlet for one proton at 6.04δ and a pair of orthocoupled protons as an AB quartet centered at 6.73δ (J=9Hz). There remained seven more protons in the spectrum of racemosol, of which only one appeared for the unique methine proton at 4.45δ as a double doublet (J=12.6Hz); the remaining methylene protons appeared as complex multiplets between 1.18δ and 3.36δ. Subsequent high resolution ^1H-NMR (500MHz) studies of racemosol further resolved the six methylene protons into two sets of related protons. The first set contains two protons, one of which appeared separately at 1.98δ as a double doublet (J=12.6Hz) and the other at 2.41δ as a triplet (J=12Hz); these two protons, coupled to the unique methine proton account for an ABX---AMX system in the molecule, and together with the presence of two aliphatic methyl singlets, collectively support the presence of the 2,2-dimethyl chroman moiety of structure(A) in racemosol. The data thus far accounts for thirteen carbon atoms in racemosol, leaving only an eight carbon fragment (Fig.B) of the molecule to be accounted for, which inherently includes another aromatic ring and a two carbon fragment; the latter incorporates the remaining four aliphatic, nonequivalent, protons which forms the second set (A_2B_2) of related protons. The two protons of C_{12} in the second set appear slightly downfield, one as a doublet at 3.13δ (J=16Hz) and the other as a triplet centered at 2.92δ (J=16Hz). The remaining two protons of the second set on C_{11} are indicated by multiplets at 3.36δ (J=16.6Hz) and 3.18δ (J=16Hz). The aromatic methine protons of the methoxy phenol moiety are indicated by an AB quartet centered at 6.71δ (J=9Hz), while the unique aromatic methine proton of the hydroxy toluene moiety is indicated by a singlet at 6.08δ. The foregoing ^1H-NMR data of racemosol are indicative of a basic skeleton of the type shown in Fig.C, representing a novel structure which has not hitherto been reported from a natural source or synthesized in a laboratory.

The off-resonance ^{13}C-NMR spectral data of racemosol (Table 2) indicates carbon chemical shift assignments which are in accordance with literature values[2,3], and are in agreement with the proposed structure. The basic mass fragments of racemosol and its derivatives are in accordance with the proposed structure, and a fragmentation scheme is shown in Fig. V. In spite of the novelty exhibited by the structure of racemosol in incorporating a cycloheptane ring, it is biogenetically conceivable as a stilbene isoprenyl ether where the end carbon is linked to both aromatic rings of the stilbene part. It is also interesting to note that pacharin(I) isolated from the same plant, yet collected from a different area to that of racemosol, is also a stilbene derivative moulding into a dibenzo(2,3-6,7) oxepin skeleton.

The structure of racemosol has been confirmed by x-ray analysis and the structure is indicated in Fig. VI. Interpretation of the crystal data follows; The torsion angles associated with the atoms of the cycloheptane ring clearly indicates significant distortion of the ring plane. If the hydroxy toluene moiety is assumed as plane 1, the cycloheptane ring as plane 2 and the methoxy phenol moiety as plane 3, then plane 1 and 2 forms an interplane angle of 18.65°, while planes 2 and 3 form an interplane angle of 158.48°, which indicates a trans-configuration of the two aromatic rings relative to the cycloheptane ring. The trans-isomer of racemosol is comparable with the trans-isomer of stilbene, in that this configuration results in longer wavelength absorption bands and higher intensities than the cis-isomer[4]; the rationale for the longer wavelengths is that a more effective Π-orbital overlap occurs in the trans-isomer, thus explaining the electronic band at 430nm imparting the red colouration to racemosol. The C-C bond distances in the aromatic rings [1.38Å] are characteristic of aromatic double bonds [1.335(5)Å][5]. The C-C bond distances in the cycloheptane ring [ca. 1.53Å] are characteristic of single carbon-carbon bonds [1.537(5)Å][5],



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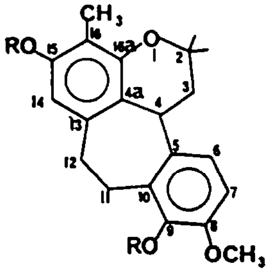
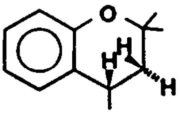


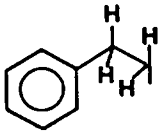
II $R = H$

III $R = COCH_3$

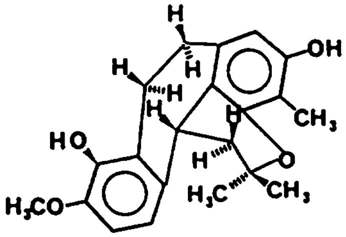
IV $R = CH_3$



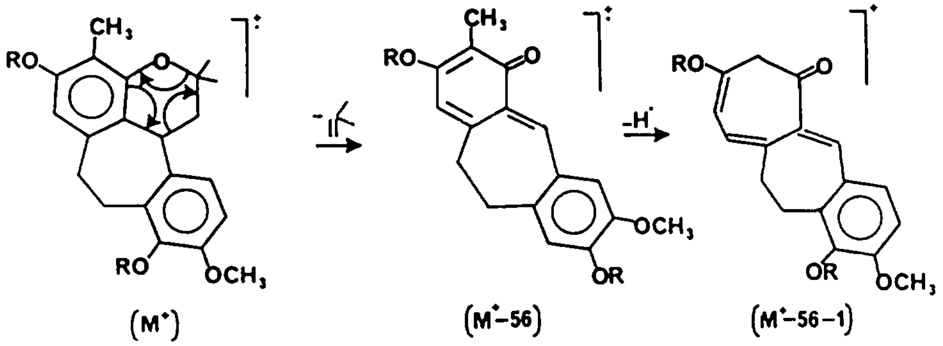
(A)



(B)



(C)



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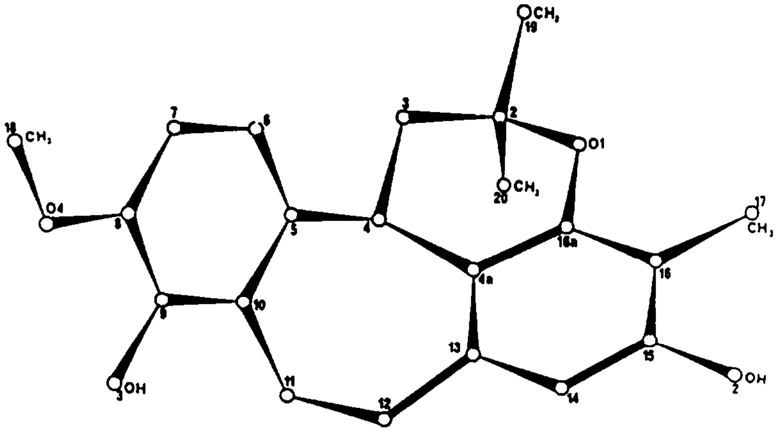

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however, the C–O bond distances in the cyclic ether moiety [1.381Å and 1.455Å] indicate some degree of Π-electron delocalisation over the C–O bonds, as a pure carbonyl bond (C=O) distance is 1.215(5)Å and a paraffinic single C–O bond length is 1.43(1)Å. The features of Π-electron delocalisation into the cyclic ether moiety and the trans-interplane angles are conducive to favourable Π-cloud overlap, and subsequent extension of the Π-system of racemosol; in that, each aromatic moiety of racemosol acts as an auxochrome to the electronic chromophore of the other aromatic moiety of racemosol, resulting in the unusual red colour of this molecule. Inspection of intramolecular distances indicate that the methoxy oxygen atom is involved in weak intramolecular hydrogen bonding with the neighboring phenolic hydrogen, as shown in Fig. VII, which is also indicated in the infrared spectrum of racemosol; the hydrogen bond distance of 2.144Å is significantly less than the sum of the van der waal's radii for hydrogen and oxygen.

Experimental: The heart-wood of *Bauhinia racemosa Lamk.* collected from the Paderu area of the forests of the Araku valley was dried and powdered. The dry powder (2.75 kg) was repeatedly extracted with hexane and methanol. The hexane extract on concentration yielded a residue (3.6 g) which was adsorbed onto silica gel and chromatographed on a column of silica gel eluting with hexane and hexane:benzene mixtures. The first hexane [1-10] and hexane:benzene (92:8)[11-20] fractions gave only an oil (300 mg). The hexane:benzene (85:15)[21-26] and (75-25)[41-46] fractions gave only complex mixtures. The hexane:benzene (82:20)[27-40] fractions yielded β-sitosterol (300 mg)[m.p. = 135-136°, $(\alpha)_D$:-35.0°]. The hexane:benzene (70-30)[47-52] and (60-40)[53-60] fractions yielded a total of 120 mg of racemosol [m.p. = 202.0°]. The subsequent benzene fractions [61-65] yielded a small quantity (20 mg) of complex mixtures.

TABLE I

^{1}H-NMR SPECTRA OF RACEMOSOL AND ITS DERIVATIVES

Proton Assignment	Racemosol (II) 500MHz	90MHz	Racemosoldiacetate (111) 90MHz	Racemosoldimethylether (1V) 90MHz
	(δ)	(δ)	(δ)	(δ)
gem-Me	1.34(3H,s) 1.53(3H,3)	1.30(3H,s) 1.49(3H,s)	1.32(3H,s) 1.53(3H,s)	1.25(3H,s) 1.50(3H,s)
C_{16}-Me	2.03(3H,s)	1.98(3H,s)	1.91(3H,s)	1.80(3H,s)
C_8-OMe	3.86(3H,s)	3.86(3H,s)	3.80(3H,s)	3.58(3H,s)
C_9-OH	4.39(1H,s)	1.60(1H,s)	2.24(3H,s -OCOCH)	3.76(3H,s -OCH)
C_{15}-OH	5.68(1H,s)	5.65(1H,s)	2.36(3H,s -OCOCH)	3.76(3H,s -OCH)
C_{14}-H	6.08(1H,s)	6.04(1H,s)	6.22(1H,s)	5.92(1H,s)
C_6-H C_7-H	6.71(2H,q, J=9Hz)	6.73(2H,q, J=9Hz)	6.95(2H,q, J=9Hz)	6.70(2H,q, J=9Hz)
C_4-H	4.54(1H,dd, J=12.6Hz)	4.45(1H,dd, J=12.6Hz)	4.57(1H,dd, J=12.6Hz)	4.40(1H,dd, J=12.6Hz)
C_3-aH	1.98(1H,dd, J=12.6Hz)			
C_3-eH	2.41(1H,t, J=12Hz)			
C_{11}-aH	3.18(1H,d, J=16Hz)			
C_{11}-eH	3.36(1H,m, J=16.6Hz)	1.8 to 3.36 (6H,m)	1.8 to 3.3 (6H,m)	1.8 to 3.3 (6H,m)
C_{12}-aH	2.92(1H,t, J=16Hz)			
C_{12}-eH	3.13(1H,d, J=16Hz)			

TMS served as the internal standard for the 90MHz spectra while benzene served as the internal standard for the 500MHz spectrum; s:singlet,d:doublet,dd: double doublet,t:triplet,m:multiplet

Characterization of racemosol: Racemosol crystallized as deep red prisms from chloroform [$(\alpha)_D$:64.45° (c, 1.0 in $CHCl_3$)]; it is soluble in alkali giving a yellow colour which reverts to the red colour on acidification. Found: C, 74.20; H, 7.22%. $C_{21}H_{24}O_4$ requires: C, 74.09; H, 7.10%. Electronic spectrum (EtOH)λ_{max}; nm[log ε]:224[4.43], 276[3.767], 430[2.278]. Infrared spectrum (KBr disc)ν_{max}; cm^{-1}:3400, 2900, 1595, 1495, 1405, 1350, 1260, 1220, 1155, 1125, 1100, 1085, 925 and 880. Mass spectrum; m/z[R.A %]:340[M^+17.5], 339[75], 324[15], 322[16], 284[30], 283[100], 268[17], 140[5], 214[8], 212[5], 194[5], 184[6], 166[5], 165[4], 152[3], 142[3], 91[4]. Crystal data: (From single crystal diffractometry : MoK_α,λ=0.7092Å) : $C_{21}H_{24}O_4$, F.W.=340.42, monoclinic, $P2_1/c$, F(000)=728e', a=11.733(2)Å, b=11.691(2)Å, c=13.096(2)Å, =99.89°, V=1296.3Å^3, Z=4, D_c=1.278 g.cm^{-3}, μ=0.94 cm^{-1}.

Intensity data, structure determination and refinement: The crystal used for data collection was of the dimension 0.3x0.2x0.4 mm. The unit cell constants were obtained by least-squares analysis of the diffractometer settings of 25 well centered reflections with 24°<2θ>28°. The data was collected on a CAD-4 diffractometer up to 2θ=46°; intensities of three standard reflections were monitored, and showed no significant variation in intensity during the data collection. Of the 2646 reflections collected, 1506 were found significant ($|F_o| > 2\sigma(|F_o|)$). No absorption corrections were applied. The structure was readily solved by direct methods (MULTAN-80; Germain, Main and Woolfson, 1971)[6]. Refinement was by Full-matrix least-squares methods, minimizing $\Sigma W\Delta F^2$, where $1/W=\sigma^2(|F_o|) + 0.0005\,|F_o|^2$. The hydrogen atoms were determined from a difference-fourier synthesis and included in the refinement. The positional and isotropic temperature factors of the hydrogen atoms were refined for two cycles and then fixed. In the final cycle only the positional and anisotropic temperature factors of the non-hydrogen atoms were refined. The final R value (for observed reflections only) was 0.0398 (R_W=0.0436). The refinement positional coordinates and U_{iso} for all constituent atoms are recorded in Table 3*; the bond angles and bond lengths are recorded in Table 4*, and selected torsion angles are recorded in Table 5.

Racemosoldiacetate: Racemosol (40 mg) in pyridine (2 ml) and acetic anhydride (4 ml) were heated on a steam bath for 4 hrs. The subsequent diacetate derivative crystallized from benzene as pale yellow needles (yield:30 mg)[m.p.=244-246°, $(\alpha)_D$:+30.98°](c, 1.0 in $CHCl_3$). Electronic spectrum (MeOH)λ_{max}; nm: 210, 275. Infrared spectrum (KBr disc)$\nu_{max}cm^{-1}$: 1760, 1610, 1585, 1495, 1440, 1365, 1280, 1130, 1080, 1005, 995, 900, 800, 750. Mass spectrum; m/z [R.A %] : 424[M^+, 50%], 368[67.5], 365[20], 340[11], 339[11], 327[31], 326[15], 325[12], 284[97], 283[100], 269[7.5], 241[7.5], 240[5], 214[7.5], 195[5], 194[5], 168[7.5], 166[6], 164[8], 153[5], 147[5], 118[8], 104[5], 96[5], 90[6.5], 83[20], 81[7.5]. Found: C, 69.98; H, 6.90%. $C_{25}H_{28}O_6$ requires: C, 70.74; H, 6.65%.

Racemosoldimethylether: To a solution of racemosol (40 mg) in DMF (1 ml) and methyliodide (1 ml) was added freshly precipitated silver oxide (1 g) in small portions over a period of one hour; the resulting mixture was kept at room temperature for 24 hrs., then poured into distilled water (15 ml) and extracted with chloroform. The chloroform extract was washed with a dilute KCN solution to remove traces of silver oxide then dried over anhydrous $MgSO_4$. The chloroform was removed by evaporation yielding a pale yellow oil (25 mg). Electronic spectrum (MeOH)λ_{max}; nm: 220, 280. Infrared spectrum ($CHCl_3$); ν_{max} cm^{-1} : 2900, 1590, 1405, 1320, 1270, 1185, 1125, 1080, 920, 890, 820, 750. Mass spectrum; m/z [R.A %] : 368[M^+, 65], 367[5], 353[12.5], 351[12.5], 337[10], 313[35], 311[12.5], 297[7.5], 284[5], 283[24], 184[7.5], 152[5], 121[3], 91[4]. Found: C, 74.80; H, 7.80%. $C_{23}H_{28}O_4$ requires: C, 74.97; H, 7.66%.

TABLE 2

Assignment	Shift(ppm)	Assignment	Shift(ppm)
C-2	73.2678	C-13	137.0773
C-3	22.1816	C-14	109.1531
C-4	38.1561	C-15	152.1707
C-5	135.8804	C-16	107.3950
C-6	128.4352	C-16a	152.4480
C-7	114.6267	C-4a	137.5573
C-8	145.0493	gem-Me	30.3112
			23.3004
C-9	141.8135	Me-Ar	8.1776
C-10	115.6171	MeO-Ar	55.9563
C-11	34.0184		
C-12	32.1037		

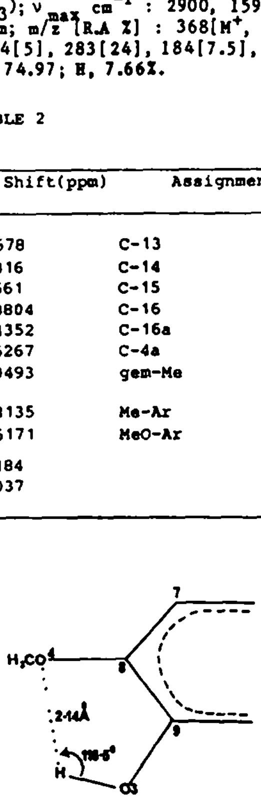

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TABLE 5

Selected Torsion Angles(Å)*	
C(16a)-C(16)-C(15)-C(14)	5.28
C(16)-C(15)-C(14)-C(13)	-4.35
C(15)-C(14)-C(13)-C(4a)	-1.71
C(14)-C(13)-C(4a)-C(16a)	6.22
C(13)-C(4a)-C(16a)-C(16)	-5.31
C(4a)-C(16a)-C(16)-C(15)	-0.39
C(14)-C(13)-C(4a)-C(4)	-173.83
C(14)-C(13)-C(12)-C(11)	-173.17
C(13)-C(12)-C(11)-C(10)	-65.76
C(12)-C(11)-C(10)-C(5)	70.44
C(11)-C(10)-C(5)-C(4)	7.19
C(11)-C(10)-C(5)-C(6)	-173.84
C(10)-C(5)-C(4)-C(4a)	-70.64
C(10)-C(5)-C(4)-C(3)	164.38
C(10)-C(5)-C(6)-C(7)	-0.71
C(10)-C(18)-C(8)-C(7)	-140.32
C(9)-C(8)-C(7)-C(6)	-0.42
C(9)-C(8)-C(4)-C(18)	172.00
C(8)-C(7)-C(6)-C(5)	0.17
C(7)-C(6)-C(5)-C(10)	-0.71
C(7)-C(6)-C(5)-C(4)	178.20
C(6)-C(7)-C(8)-O(4)	-179.26
C(6)-C(7)-C(8)-C(18)	175.94
C(6)-C(5)-C(10)-C(11)	-173.84
C(5)-C(4)-C(4a)-C(13)	44.39
C(4)-C(4a)-C(13)-C(12)	8.02
C(4a)-C(13)-C(12)-C(11)	5.07
C(4)-C(3)-C(2)-O(1)	-63.86
C(3)-C(2)-O(1)-C(16a)	50.33
C(2)-O(1)-C(16a)-C(4a)	-18.39
O(1)-C(16a)-C(4a)-C(4)	-3.49
C(16a)-C(4a)-C(4)-C(3)	-10.06

*; A positive rotation is anticlockwise from atom 1, when viewed from atom 3 to atom 2 in the set atom1-atom2-atom3-atom4

Acknowledgement: The authors are grateful to Dr. A. Sri Krishna and Dr. P. Atchuta Ramaiah for the 500 MHz ^1H-NMR spectrum and the ^{13}C-NMR spectrum respectively and the CDRI, Lucknow for the mass spectra. S.P.R. wishes to thank, and acknowledge the NSERC for grant support.

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*: Tables 3 and 4 have been deposited with the Cambridge Crystallographic Centre.