Asian Journal of Chemistry Vol. 5, No. 2 (1993), 340–347

Synthesis and Evaluation of Bisphenol-C and its Derivatives as Potential Antimicrobial and Antifungal Agents

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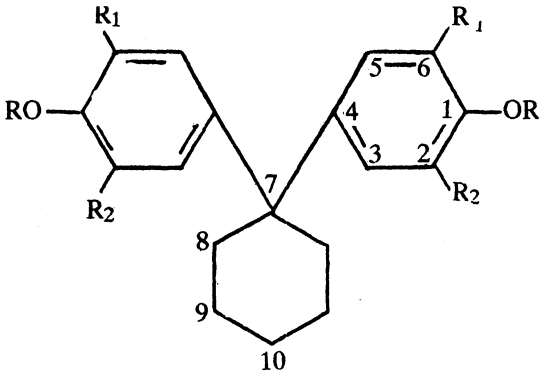
1,1′-Bis(4-hydroxy phenyl) cyclohexane [bisphenol-C] and its derivatives have been synthesised and screened for their potential antimicrobial and antifungal activities against different strains of bacteria and fungi. Some of the compounds are significantly active against *B. subtilis* (**1–7, 9** and **10**), *S. pyogens* (**1** and **4**) and *A. niger* (**2, 3, 7, 8** and **10**). The nitro compounds are the most active as antifungal agents.

INTRODUCTION

Bisphenols are well known for their industrial applications such as dyes and drug intermediates[1,2], varnishes[3], constituents of veterinary medicines and fungistates[4], antioxidants, plasticizers and intermediate many-fields[5–7] and in control of coccicidial infection[8]. Bisphenols are also industrially important in the preparation of thermally stable polymers and epoxy resins[9–11]. In the present communication synthesis of bisphenol-C and its derivatives Type (I) by Friedal-Craft condensation has been reported. Structures of the bisphenol-C derivatives are supported by elemental and spectral studies and the compounds have been screened for their antibacterial and antifungal activities.



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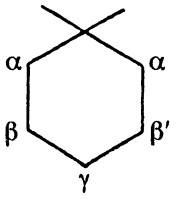

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EXPERIMENTAL

All the chemicals used were of laboratory grade and were purified prior to use. All melting points were determined in open capillary and are uncorrected. The purity of compounds was checked by TLC using Silicagel-G (Siscochem) and HPLC by LKB Pharmacia (Sweden) HPLC-2150 pump. Column: RP-8 Ultrapack Pharmacia, 1.28 Ab, range λ_{max} 278. C and H analyses were carried out with Coleman analyser. Halogen estimation was carried out by Carius method and nitrogen estimation was carried out by Kjeldahl's method. IR (KBr), UV (Methanol), ^{1}H NMR, ^{13}C NMR spectra were scanned on a Shimadzu DR–1, Shimadzu-160; XL-100 A (100.1 MHz) using deutero dimethyl sulfoxides as solvent and TMS as internal standard, and Varian CFT-20, respectively. Mass spectra were scanned on a Varian Mat CH-7 mass spectrometer.

1,1′-Bis (4-hydroxy phenyl) cyclohexane [Bisphenol-C] and its derivatives were synthesised as reported in our previous publications[12–14]. Chlorination of bisphenol-C derivatives was carried out according to the reported method[15].

1,1′-Bis (3,5-dinitro, 4-hydroxy phenyl) cyclohexane [Bisphenol-C] (**7**). Bisphenol-C was suspended in water (25 ml) and the nitrating mixture (nitric acid : sulphuric acid 2 : 1 v/v) added portion wise (112.5 ml) with vigorous shaking and heated at 70°C for 3 hrs. The oily product was poured in crushed ice, filtered, washed with water repeatedly and dried at 50°C. The product was charcolized in methanol solution and again recrystallised from methanol solution four times.

1,1′-Bis (3-methyl, 5-nitro, 4-hydroxy phenyl) cyclohexane (**8**) was prepared according to the above mentioned method. The product was charcolized and purified repeatedly from acetic acid solution.

Acetylation of 1 and 2

Acetylation of **1** and **2** was carried out by taking (0.01 mol) each in acetic anhydride (20 ml) in presence of sodium acetate (2 gm). The reaction reflux time was 2 hrs. The crude solid was collected, washed with water and dried at room temperature. Product was charcolized and repeatedly recrystallised from water methanol.

RESULTS AND DISCUSSION

The physical data of compounds **1–12** are reported in Table 1. The elemental compositions of all the compounds were found to be in good agreement with the theoretical values. The purity of all the compounds was checked by TLC and HPLC in benzene-methanol and methanol solvent system, respectively (Table 1). The TLC of all the compounds showed single spot and HPLC also showed single peak except in compounds **4**, **7** and **8**. The bromo compound (**4**) gave two peaks which may be due to either trace impurities or a mixture of di and mono substituted compounds. Similarly nitro compounds (**7** and **8**) also gave three peaks indicative

TABLE 1
PHYSICAL DATA OF BISEPHENOL-C DERIVATIVES.

Compd.	Substituents			Yield (%)	M. pt. (°C)	Analysis						R_f (solvent)[a]	R_t HPLC (minute)
	R	R_1	R_2			% Bromine Found	% Bromine Calcd.	% Chlorine Found	% Chlorine Calcd.	% Nitrogen Found	% Nitrogen Calcd.		
1*	H	H	H	80	186							0.214 (A)	5.8
2	H	CH_3	H	80	186							0.357 (A)	5.8
3	H	CH_3	CH_3	75	193							0.785 (B)	6.2
4	H	Br	Br	85	137	54.21	54.76					0.473 (B)	4.8, 5.5
5	H	Cl	Cl	70	185			34.63	34.98			0.518 (B)	5.8
6	H	CH_3	Cl	70	181			19.19	19.35			0.598 (B)	5.8
7	H	NO_2	NO_2	60	89					12.18	12.5	0.586 (C)	4.5, 6.0, 6.7
8	H	CH_3	NO_2	64	85					7.21	7.22	0.866 (C)	3.6, 3.8, 5
9	CH_2COOH	H	H	70	185							0.476 (B)	5.7
10	CH_2COOH	CH_3	H	68	190							0.612 (B)	5.8
11	$COCH_3$	H	H	78	80							0.748 (B)	6.0
12	$COCH_3$	CH_3	H	75	110							0.782 (B)	6.4

* %Carbon — Found: 80.41, Calcd.: 80.59; % Hydrogen — Found: 6.91, Calcd.: 7.46

a A benzene–methanol (95 : 5 v/v);
B benzene–methanol (85 : 15 v/v) and
C benzene–methanol (80 : 20 v/v)

of either traces of impurities or di and mono nitro compounds. However ^{13}C NMR of compound **4** gave four signals due to aromatic carbons which indicates disubstitution. The spectral data of all the compounds (**1–12**) are reported in Table 2. The mass spectral data of the compounds **1** and **2** are reported in Table 2. In

TABLE 2
SPECTRAL DATA OF BISPHENOL-C DERIVATIVES

Compd.	UV absorption maxima (nm)	Characteristic IR peaks (cm^{-1})	m/e
1	278.4, 230.2	3580, 1615, 1505, 1445, 1350	a
2	278.8, 216.2	3520, 1608, 1500, 1470, 1335, 1295	b
3	277.2, 213.8	3510, 2920, 2850, 1600, 1300, 1236	
4	300, 225	3440, 1540, 1460, 1312, 1236, 560	
5	278, 231	3560, 1610, 1500, 1360, 1236, 640	
6	279, 216	3510, 1604, 1500, 1240, 630	
7	427.5, 363.5, 239	3500, 1630, 1545, 1320, 825	
8	216	3430, 1615, 1566, 1346	
9	278, 231	3200, 1620, 1594, 1508, 1360, 1236, 1008	
10	279.2, 216.4	3510, 3390, 1604, 1500, 1466, 1400, 1240, 1028	
11	229.8	3050, 1750, 1600, 1470, 1200	
12	273.8, 266.8, 219	3090, 1750, 1620 1460, 1210	

a: 56, 57 (base peak), 69, 71, 81, 83, 85, 91, 97, 99, 111, 125, 251, 268 (M), 269 (M + 1).
b: 56, 71, 82, 91, 105, 107, 110, 145, 165, 181, 253 (base peak), 244, 282, 296 (M), 298 (M + 2).

Table 2 the characteristic IR peaks are reported besides normal models of vibrations. ^1H NMR and ^{13}C NMR spectral data of the compounds **1–16** and **9–10** are reported in Tables 3 and 4, respectively. As cyclohexyl ring contains ten protons out of which four (α-CH_2) protons are identical and remainder six (β and γ-CH_2) protons are also identical. The signal due to α-CH_2 protons and $\beta + \gamma$-CH_2 protons appeared approximately at the same position in all the compounds. The signal of $-CH_3$ protons in the compounds **2, 3, 6** and **10** overlapped with α-CH_2 protons. The NMR spectrum of the compound **6** gave doublet due to methyl and α-CH_2 protons. The compounds **5** and **6** were scanned on 200 MHz NMR spectrometer and remaining compounds were scanned on 100.1 MHz NMR spectrometer. The overlapping of $-CH_3$ and α-CH_2 protons was detected on a 200 MHz NMR spectrometer. In Table 3, besides chemical shift the multiplicities and coupling constants of all the compounds are incorporated. The signal due to $-CH_2$ protons of the substituent group ($-CH_2COOH$) of the compounds **9** and **10** appeared at δ3.35. ^{13}C NMR technique gave information regarding numbers of asymmetric carbons in a molecule. ^{13}C NMR spectra of the compounds **1, 3–5** and **9** gave four signals due to aromatic ring carbons for which C_2, C_6 and C_3, C_5 carbons are identical. The cyclohexyl ring has four types of carbons viz. one tertiary carbon, two α-CH_2 carbons, two

TABLE 3

^{1}H NMR DATA OF BISPHENOL-C DERIVATIVES

Compd.	Substituents			Chemical shift					
	R	R_1	R_2	–OH	–COOH	–Ar	–CH_2/–CH_2 + –CH_3	B + –CH_2	–CH_2–
1	H	H	H	8.5 s	—	6.6–6.9 m J = 9	2.1 s	1.45 s	—
2	H	CH_3	H	8.99 s	—	6.65–6.97 m J = 9	2.09 s	1.43 s	—
3	H	CH_3	CH_3	7.88 s	—	6.8 s	2.11 s	1.41 s	—
4	H	Br	Br	9.7 s	—	7.46 s	2.15 s	1.41 s	—
5*	H	Cl	Cl	9.11 s	—	7.05–7.02, 6.66–6.65 d J = 6 d J = 2	2.13 s	1.41 s	—
6*	H	CH_3	Cl	8.96 s	—	7.35, 6.92, 7–6.865, 6.84, 6.64 s s d J = 2 d J = 2 d J = 5.4	2.11–2.05 d J = 12	1.41 s	—
9	CH_2COOH	H	H	—	9.1 s	7.05, 6.65 d J = 9 d J = 9	2.12 s	1.42 s	3.35 s
10	CH_2COOH	CH_3	H	—	8.94 s	7.38, 6.92, 6.84, 6.68, 6.60 s s d J = 3 s s	2.06 s	1.41 s	3.35 s

*Scanned on 200 MHz

TABLE 4

^{13}C NMR DATA OF BISPHENOL-C DERIVATIVES.

Compd.	Substituents			Chemical shift, ppm										$R_1C(CH_3)$	$C(CH_2)$
	R	R_1	R_2	C_1	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}		
1	H	H	H	152.88	113.12	125.84	137.57	–	–	42.48	35.09	24.30	20.39	–	–
2	H	CH_3	H	151	112.67	123.12	137.58	127.09	121.41	42.31	35.18	24.41	21.01	14.59	–
3	H	CH_3	CH_3	150.5	123.47	126.45	139.40	–	–	43.78	36.74	26.06	22.06	17.02	–
4	H	Br	Br	148.76	112.12	130.48	141.92	–	–	44.37	35.90	25.45	22.38	–	–
5	H	Cl	Cl	154.56	114.80	127.53	139.1	–	–	44.1	36.7	25.9	22.5	–	–
6	H	CH_3	Cl	152.67	115.11	123.06	138.12	129.1	125	43.54	36.68	25.45	22.73	16.42	–
9*	CH_2COOH	H	H	154.77	114.98	127.69	139.25	–	–	44.27	36.79	26.09	22.71	–	21
10*	CH_2COOH	CH_3	H	152.87	114.4	128.65	139.31	123.31	124.98	44.1	36.92	26.21	22.82	16.55	**

*The signal due C(COOH) overlapped with C_1

**The signal due $C(CH_2)$ over lapped with C_{10}

β-CH_2 carbons and one γ-CH_2 carbon. The compounds **2**, **6** and **10** gave six signals due to aromatic ring carbons and four signals due to cyclohexyl ring carbons. The substituent carbon C(CH_3) gave separate signal at about 15–17 ppm. The signal due to C(CH_2) carbon of compound **10** overlapped with C_{10}. In compounds **9** and **10** C(COOH) carbon and C_1 gave the lone signal that means signal due to C(COOH) overlapped with the C_1 carbon of phenyl ring. Thus the structures of all the compounds were confirmed by spectral data.

Antibacterial and Antifungal Activities

All the compounds (**1–12**) were screened for their antibacterial and antifungal activities against different strains of gram +ve bacteria and gram –ve bacteria such as *E. coli*, *K. pneumoniae*, *B. subtilis* and *S. pyogens* and against fungi such as *A. niger* and *S. cerevicie* by using cup-plate method[16]. The solvent used was DMF and the sample concentration was 25 μg. All the compounds and standard drug samples such as Ampicillin (R_1), Sulfanilamide (R_2), Dapson (R_3), Chloramphenicol (R_4) and Norfloxacin (R_5) were tested in duplicate. The zones of inhibition of all the compounds are reported in Table 5, along with standard drug

TABLE 5
ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY OF BISPHENOL-C DERIVATIVES AND STANDARD DRUGS

Compd.	Zone of inhibition in mm.					
	Antibacterial (24 hrs.)			Antifungal (48 hrs.)		
	E. coli (–ve)	*K. pneumoniae* (–ve)	*B. subtilis* (+ve)	*S. pyogens* (+ve)	*A. niger*	*S. cerevicie*
1	10	14	23	17	13	15
2	13	16	21	16	20	13
3	10	16	20	15	21	14
4	15	13	15	17	25	17
5	10	13	22	15	16	10
6	11	14	23	14	18	12
7	10	13	19	16	23	12
8	10	10	10	13	31	10
9	12	14	25	13	17	10
10	11	10	21	14	21	13
11	11	11	11	14	17	11
12	11	11	10	13	10	15
R_1	14	22	14	16	27	13
R_2	14	15	13	21	20	16
R_3	14	14	12	17	19	—
R_4	17	12	12	16	20	14
R_5	28	22	26	22	24	—

R_1–Ampicillin, R_2–Sulfanilamide, R_3–Dapson, R_4–Chloramphenicol, R_5–Norfloxacin
For DMF zone of inhibition is 10–11 mm.

samples. From Table 5 it could be revealed that most of the compounds are mild to moderately active against different strains of bacteria and fungi. However, significant antibacterial activity is observed in the case of the compounds **1–7, 9** and **10** against *B. subtilis*, **1** and **4** against *S. pyogens*. The significant antifungal activity is observed in case of the compounds **2, 3, 7, 8** and **10** against *A. niger*. The compound **8** is the most active antifungal against *A. niger*, while it is inactive as an antibacterial.

ACKNOWLEDGEMENT

Authors are thankful to Head, Department of Chemistry for providing research facilities and also thankful to the Head RSIC Bombay, Chandigarh, Madras and CDRI Lucknow for spectral studies.

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(*Received*: 10 September 1991; *Accepted*: 15 June 1992) AJC–442