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Synthesis of Novel Spiro 1,3 – Dioxanes And Study of Their Biological and Liquid Crystalline Properties

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Abstract: ***It is proposed to synthesize the spiro 1,3 – dioxane systems and to examine the antimicrobial and liquid crystalline properties. Pentaerythritol and 4-hydroxy-3-methoxy-benzaldehyde were condensed to form the dibenzal derivative (VIII) and it is tested for antibacterial activity, the minimum inhibitory concentrations were determined and the data is presented . Further compound VIII was converted to the corresponding esters by treating with long chain fatty acid chlorides to form the corresponding esters. All the spiro 1,3-dioxane derivatives exhibited liquid crystal properties. The textures were photographed at mesophase region. Further the dibenzal derivative was tested for antibacterial activity, the minimum inhibitory concentrations were determined and the data is presented. This is the first report of Spiro 1,3-dioxanes, exhibiting antibacterial properties.***

Keywords: Spiro 1,3 – dioxanes , dibenzal derivative, antibacterial activity, mesophase, liquid crystal properties.

1. Introduction

Natural products containing medium or large ring ethers (cyclic ethers) are wide spread and show wide spectrum of biological activities[1]. In recent years the number of methods available for the construction of cyclic ethers, rather inaccessible by classical methods are examined[2.3].

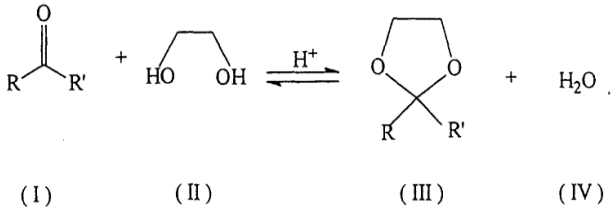
In the cyclic ethers, 1,3 – dioxane, 1,4-dioxane compounds and their derivatives played a vital role in the organic reactions as solvents and also wide variety of applications in the organic chemistry. Compounds containing 1,3 – dioxane, 1,4-dioxane etc., acts as corrosion inhibitors and low temperature heat-transfer fluids, stable to aqueous buffers over a wide range of concentrations[4]. 1,3-dioxane derivatives were used as carpet linings and in paper coating industry[5]. Various applications of 1,3-dioxane derivatives were noted in the literature [6,7,8].

In continuation of our studies on biological activities and liquid crystal properties of different Heterocyclic compounds, it is proposed to synthesize spiro 1,3-dioxane derivatives and examine their biological and liquid crystalline behaviour.

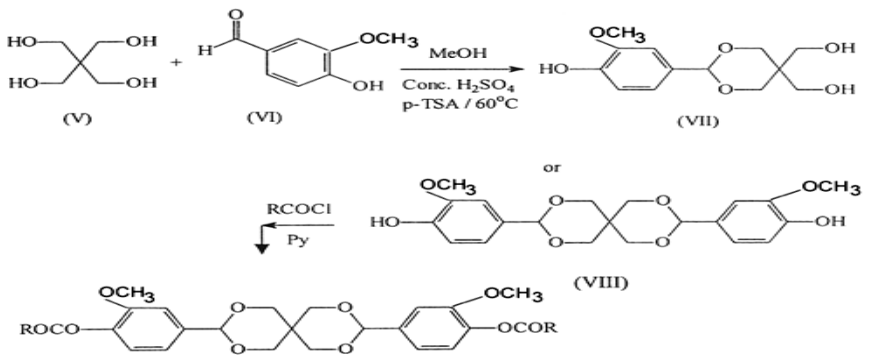
Synthesis of 3,9 – Bis -(4-hydroxy -3-methoxy phenyl) – 2,4,8,10, - tetraoxa spiro [5,5]- undecane (VIII):

Condensation of carbonyl compound (I) and diol (II) lead to form cyclic acetal or ketal (III) under acid catalyzed conditions **(Scheme-I)**[9]. It is an equilibrium reaction normally performed in non-aqueous media with removal of water from the reaction mixture[10].

It is proposed to synthesize a spiro compound through the formation of cyclic ketal. 4 - Hydroxy – 3- methoxy benzaldehyde (VI) was condensed with the molar proportions of pentaerythritol (V) in presence of benzene and catalytic amount of p-TSA **(Scheme-II)** was added and the reaction mixture was azeotropically refluxed for 60 hrs., for completion of the reaction. After usual work up, yielded the corresponding cyclic ketal .



Scheme – I



R = C_nH_{2n+1}, n = 7 (X), 11 (XI), 13 (XII), 15 (XIII), 17 (XIV).

Scheme – II

Table 1

Compound No.	*^{1}H NMR spectral data*	*^{13}C NMR spectral data*
X	δ 0.84 (t,6H, 2XCH_3), 1.22-1.38(br.s,20H, 10 x CH_2),2.2-2.32 (t, 4H, 2 x $OCOCH_2$), 3.84 (s,6H, OCH_3), 3.96 (m,8H, OCH_2), 5.21 (S,2H, C_3-H), 6.6-7.1 (m,6H, aromatic).	14.19 (CH_3), 22.26,24.32,28.2 – 29.97, 32.4 (CH_2), 35.32 ($OCOCH_2$), 55.34 (OCH_2), 56.16 (OCH_3), 106.19(C_3), 110.2, 113.3, 114.74, 120.8 127.1, 147.6 (aromatic), 177.18, 193.26 (COO).
XI	δ 0.9 (t, 6H, 2 x CH_3), 1.1-1.3 (br.s, 36H, 18 x CH_2) 2.25 – 2.48 (t, 4H, 2 x $OCOCH_2$), 3.81 (s, 6H, OCH_3) 3.9 (m,8H, OCH_2), 5.2 (s,2H, C_3-H), 6.7 – 7.3 (m,6H, aromatic).	14.16 (CH_3), 22.19,24.32,28.2 – 29.79, 31.6 (CH_2), 35.32 ($OCOCH_2$), 55.88 (OCH_2), 56.12 (OCH_3), 106.11 (C_3), 110.2, 113.9, 114.86, 120.9, 127.3, 148.6 (aromatic), 179.13, 192.28 (COO) .
XII	δ 0.8 (t,6H, 2 x CH_3), 1.1-1.3 (br.s, 44H, 22 x CH_2), 2.3 (t,4H, 2 x $OCOCH_2$), 3.8 (s, 6H, OCH_3), 3.9 (m,8H, OCH_2), 5.3 (s, 2H, C_3-H), 6.7-7.3 (m,6H, aromatic).	14.18 (CH_3), 22.16, 24.26, 28.1-29.82, 32.1 (CH_2), 35.32 ($OCOCH_2$), 55.89 (OCH_2), 56.12 (OCH_3), 106.57 (C_3), 111.23, 114.24, 121.1, 127.3, 128.14, 128.96, 131.74, 142.91, 149.1 (aromatic), 179.84, 190.97 (COO) .
XIII	δ 0.95 (t, 6H,2xCH_3), 1.2 – 1.4 (s, 52H, 26 x CH_2), 2.25-2.45 (t,4H, 2 x $OCOCH_2$) 3.86 (s, 6H, OCH_3), 3.92 (m, 8H, OCH_2), 5.4 (s, 2H, C_3-H), 6.4–7.12 (m,6H, aromatic).	14.17 (CH_3), 22.29, 24.72, 27.96-28.94 , 32.15 (CH_2), 35.42 ($OCOCH_2$), 55.92 (OCH_2), 56.76 (OCH_3), 106.12 (C_3), 110.31, 114.67, 122.3, 128.16, 132.44, 141.41, (aromatic), 177.49, 189.99 (COO).
XIV	δ 0.89 (t, 6H, 2 x CH_3), 1.32–1.53 (br.s, 60H, 30 x CH_2), 2.12-2.33 (t, 4H, 2 x $OCOCH_2$), 3.8 (s, 6H, OCH_3), 5.21 (s, 2H, C_3-H), 6.6-7.19 (m, 6H, aromatic).	14.57 (CH_3), 22.28, 24.62, 28.96-29.48, 32.15 (CH_2), 35.32 ($OCOCH_2$), 55.62 (OCH_2), 56.96 (OCH_3), 106.17 (C_3), 110.95, 114.80, 122.6, 128.2, 132.64, 141.31 (aromatic), 174.59, 189.99 (COO).

During this reaction, formation of monobenzal (VII) is also possible, when the reaction performs at 35^{O}C [10,11]. Formation of dibenzal (VIII) predominates over the room temperature[10]. Dibenzal was crystallized from methanol as pale yellow crystalline compound, m.p. 188-191^{o}C and analyzed for $C_{21}H_{24}O_8$. IR spectrum showed the absorption bands at 3384, 2941, 2862, 1022 cm^{-1} were in agreement with the structure. ^{1}H nmr spectrum showed the peaks at δ3.3, 3.55, 3.85, 4.55 (assigned to methlyene protons adjacent to oxygen), 5.32 (benzalic proton), 3.7 (s,6H, OCH_3), 6.7 – 6.95 (m, Aromatic protons), 9.1 (s, phenolic proton). The above data was in agreement with the expected values. Furher ^{13}C nmr spectrum showed the characteristic signals at 55.52 (OCH_3), 69.45, 69.94 (exocyclic OCH_2), 101.47 (C_3), 110.05,114.81, 118.88, 129.62,147.15, 146.88 (aromatic carbons). Thus the formation of compound VIII as dibenzal is characterized.The IUPAC name for the compound VIII was proposed with the aid of ref. no. 12.

Synthesis, characterization and liquid crystal properties of 3,9 – Bis -(4-acyloxy -3-methoxy phenyl) – 2,4,8,10, -tetraoxa spiro [5,5]- undecanes (X – XIV):

The compound (VIII) was alkoxylated[13] with long chain fatty acid chlorides (RCOCl ; R = C_nH_{2n+1} , n = 7, 11, 13, 15, 17) in presence of pyridine under anhydrous conditions. After usual work up, yielded the corresponding dibenzal esters X to XIV respectively. The spectral details of the compounds X to XIV are given in the following **Table – I**.

The I.R. spectrum of compound XII , showed the absorption at ν_{max} 2931,2363, 1731 (>C=O), 1046 cm^{-1} (C-O-C ether st). ^{1}H nmr spectrum of the compound showed the signal at δ0.8 (t, CH_3 protons), δ1.1 – 1.3 (br. s, CH_2 protons), δ2.3 (t, -$OCOCH_2$ protons), δ3.8 (s,6H, OCH_3), 3.9 (s,-O-CH_2 protons), δ5.3 (s, benzalic protons), δ6.7-7.3 (m, aromatic protons). Further ^{13}C nmr spectrum showed the characteristic signals at 14.18 (CH_3), 22.16, 24.26, 28.1-29.82, 32.1(CH_2), 35.32 ($OCOCH_2$), 55.89 (exocyclic CH_2), 56.12 (OCH_3), 106.57 (C_3), 111.23 to 149.1 (aromatic carbons), 179.84, 190.97 (COO), confirming the formation of compound 3,9 –Bis-(3-methoxy-4-myristoyloxy phenyl) – 2,4,8,10 – tetraoxaspiro-[5,5]-undecane (XII). Similarly, the other dibenzal estrers i.e. , X, XI, XIII and XIV are well in agreement with the expected values.

After characterization of these dibenzal esters, the liquid crystalline properties were observed by using polarizing microscope. The textures were photographed during the mesophase region (Fig. 1& 2).Further, the mesophase region was confirmed by Differential Scanning Calorimeter (DSC) at a rate of 1^{O}C/min and the thermograms were recorded .The mesophase region and heat energy changes were presented in the following **Table – II**. The above results indicate that the dibenzal esters showed above room temperature liquid crystal properties with no effect on the increasing of the chain.

Table 2: Phase Transition temperatures (mesophase region) and heat of transition of the compounds X to XIV

S. No	Compound No.	Temp. in ^{o}C crystal- mesophase	ΔH J/g
1	X	32.9 – 43.4	159.4
2.	XI	34.8 – 50.9	152.7
3.	XII	45.2 – 78.5	136.9
4.	XIII	52.8 – 69.1	131.5
5.	XIV	51.3 – 70.6	128.9

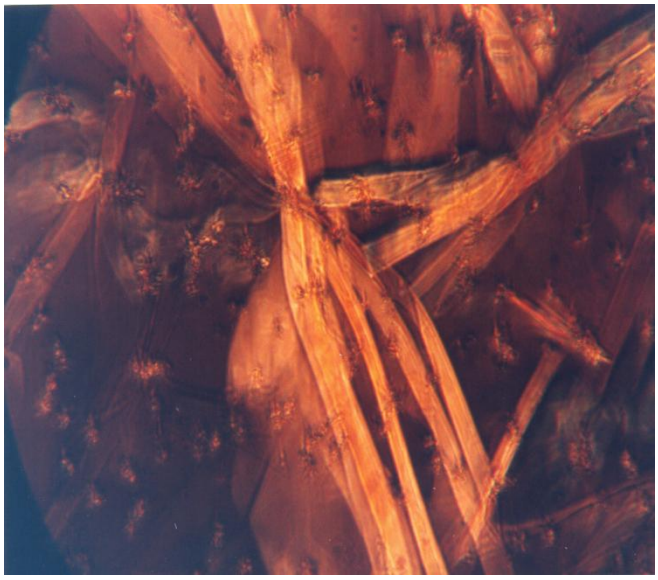


Figure 1: Texture photographed on cooling the mesophase of compound XI.

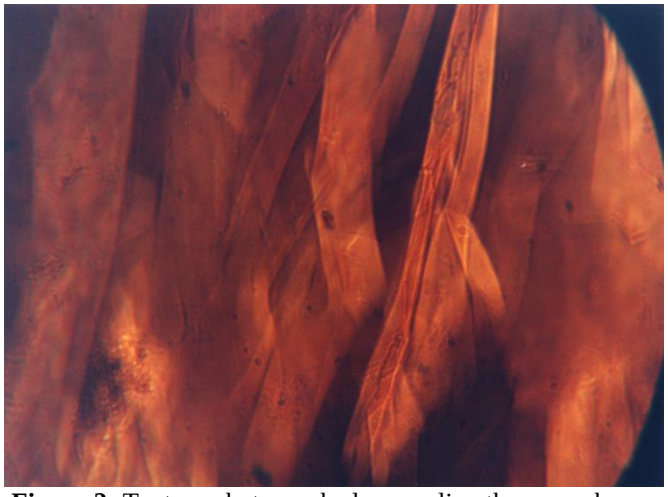


Figure 2: Texture photographed on cooling the mesophase of compound XII

Biological activity studies of the synthesized 3,9 – Bis -(4-hydroxy -3-methoxy phenyl) – 2,4,8,10, - tetraoxa spiro [5,5]- undecane (VIII): Literature survey revealed that cyclic ethers, 1,3 - dioxanes posses a wide variety of biological activities. In continuation of our studies, we have investigated the antibacterial activity studies.

The compound **VIII** was tested for antibacterial activity against Gram – positive bacteria, Bacillus subtilis, Bacillus pumilis, Enterococcus faecalis, Streptococcus faecalis and Micrococcus luteus and Gram – negative bacteria Pseudomonas marginalis, Escherichia coli, Proteus vulgaris and Klebsiella pneumoniae at concentrations of 20, 50, 100 and 200 µg/ml. The cultures of organisms grown over night at 37^{O}C, were used for testing the antibacterial activity which was checked by employing cup plate method. Nutrient agar medium (Himedia, India) was dissolved in water and pH was adjusted to 7.0. This was then distributed in 20ml quantity in boiling tubes; they were then plugged tightly with non-absorbent cotton and sterilized in an autoclave. The bacterial culture (50µl) was then added aseptically to the agar medium maintained at 45^{O}C, mixed well and poured immediately in sterilized petriplates. Test solutions of different concentrations of compound **(VIII)** were prepared in DMSO. After hardening, cups of 8mm diameter each were cut into agar and 50µl test solutions of varying concentrations (20, 50, 100 & 200 µg/ml) were placed in these cups. The plates were incubated at 37^{o}C for 24 hours and the diameter of inhibition zone was measured in mms. Solvent DMSO alone was kept as control, which did not have any inhibition zone. The activity was compared with standard antibiotic Benzyl Penicillin, (manufactured by Alembic Ltd., Vadodara, India), crystallized from MeOH and the antibacterial activity inhibition zones of the compound VIII were presented in the **Table – III**.

Table 3: Antibacterial Activity Inhibition Zones (mm)

Bacteria Name	Benzyl Penicillin	Compound VIII Concentration (µg/ml)			
		20	50	100	200
Gram Positive Bacteria					
Bacillus subtilis	25	-	14	16	20
Bacillus Pumilus	24	13	16	20	21
Enterococcus faecalis	22	-	14	19	20
Streptococcus faecalis	20	-	-	15	19
Micrococcus luteus	19	-	11	13	17
Gram Negative Bacteria					
Pseudomonas marginalis	21	-	12	16	18
Escherichia Coli	23	-	-	11	16
Proteus vulgaris	24	14	20	21	24

2. Results & Discussion

The results show that compound VIII showed antibacterial activity against all the Nine organisms. The minimum inhibition concentration (MIC) was 20µg/ml against Bacillus Pumilus, where as it was 50 µg/ml for remaining organisms, except E. Coli and S. faecalis. Compound (VIII) almost equally active as Benzyl Pencillin at 200µg/ml level against Proteus vulgaris. Our studies once again proved that, spiro 1,3 dioxanes are biologically active compounds. This is the first report in recent years, on the compound VIII structural analogues exhibiting anibacerial acivity. This is the first report of Spiro 1,3-dioxanes, exhibiting antibacterial properties.

3. Conclusion

A series of spiro 1,3-dioxanes were prepared and the parent molecule(VIII) exhibiting antibacterial properties . The dibenzal esters X– XIV were showing liquid crystalline properties . The above results indicate that the spiro dibenzal esters showed above room temperature liquid crystal properties with no effect on the increasing of the chain.

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Author Profile

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