Indole is an important moiety in many biologically active compounds. A large number of synthetic indoles are well recognised by their biological activities. In particular, specifically substituted indoles serve as valuable synthons for the synthesis of natural products and also for pharmacologically active compounds. As a consequence, there is a steady demand for novel synthetically versatile novel indole derivatives. Some bisindole derivatives have been known to possess important biological activities. Recently, a number of natural products containing bisindole moiety have been isolated and have attracted chemist’s attention, not only because of their novel chemical architecture but also due to their diverse pharmacological activities. In continuation of our interest in bisindole derivatives, bridged bi/thriheterocycles and chemoselectivity of indole dicarboxylates towards hydrazine hydrate, herein, we report the chemoselectivity of bisindole tetracarboxylate towards hydrazine hydrate and synthesis of a novel bridged tetracarboxylate containing 1,1’-bisindole derivative. This paper is also aimed at reporting the antimicrobial activities and establishing the conformation of all the 1,1’-bisindolylenethanes.

The preparation of diethyl 5,5’-dihydroxy-2,2’-dimethyl-1,1’-(ethane-1,2-diyl)di-(1H-indole)-3,3’-dicarboxylate 3 has been patented by Wortek and Lukasiewicz in 1974, but the yield was very low. In this report, we disclose the modified one-pot synthesis of bisindole dicarboxylate 3 with improvement in the yield.

A convenient precursor, ethane diylidimino bridged diester 1 was prepared by the condensation of ethyl acetocacetate with ethylenediamine. Compound 1 on condensation with 1,4-benzoquinone under Nenitzescu conditions yielded N,N’-(ethanediyl) bridged bisindole diester 3. This diester 3 was treated separately with methyl iodide and ethyl chloroacetate by refluxing in anthydrate acetone in the presence of anhydrous K$_2$CO$_3$ to secure the corresponding O-methylated and O-(ethylenecarbonylmethyl)ated derivatives 4 and 5 respectively. When diethyl 5,5’-bis(ethylenecarbonylmethyl)-2,2’-dimethyl-1,1’-(ethane-1,2-diyl)di(1H-indole)-3,3’-dicarboxylate 5 was allowed to react with hydrazine hydrate produced exclusively the diethyl 5,5’-bis(hydrazinocarbonylmethyl)-2,2’-dimethyl-1,1’-(ethane-1,2-diyl)di(1H-indole)-3,3’-dicarboxylate 6 instead of the expected tetracarboxyldi hydrazide 7, and this revealed the chemoselectivity of indole tetracarboxylate towards hydrazine hydrate. Further, this dicarboxyldi hydrazide 6 was reacted with acetyl acetone to procure a novel...
bridged tetraheterocycle, diethyl 5,5'-bis(2,5-dimethylpyrrol-1-ylaminocarbonylmethoxy)-2, 2'-dimethyldiethyldi (1H-indole)-3,3'-dicarboxylate 8 (Schemes I and II). Structures of all the compounds were established from their spectral data and elemental analyses.

Although, the chemoselectivity of indole dicarboxylates and diacetylinetoles was studied in our earlier reports, herein, for the first time we are reporting the chemoselectivity of bisindole tetracarboxylate 5 towards the nucleophilic attack of hydrazine hydrate.

The observed resistance of C3,3'-carbethoxy groups towards nucleophilic attack of hydrazine hydrate may be explained by the canonical form B of bisindole carboxylate (Figure 1) wherein the π-electrons of indole nitrogen are delocalised on the oxygen of C3,3'-ester group thereby reducing the double bond character of C3,3'-ester carboxyls.

Further, an additional support to the observed resistance of C3,3'-ester function was adduced by reacting diethyl 5,5'-dimethoxy-2,2'-dimethyl-1,1'- (ethane-1,2-diyl)di(1H-indole)-3,3'-dicarboxylate 4 with excess of hydrazine hydrate in refluxing ethanol in the presence of 4-dimethylaminopyridine (DMAP) catalyst, which gave back the starting material 4.

The C3-methyl signals of indoles generally appear in the range δ 2.60 to 2.70 in their 1H NMR spectra. These signals are observed upfield in the bisindolylethanes 3, 4, 5, 6 and 8 in the range of δ 1.96 to 2.02 because of the thermodynamically stable staggered conformation shown in Figure 2, wherein the
C$_{2,2'}$-methyls lying in the axis of the aromatic rings experience the diamagnetic shielding effect of the ring current.

**Antimicrobial Screening.** All the compounds (3, 4, 5, 6 and 8) were screened for their antibacterial activity against *E.coli* and *B.cirroflagellosus* using Norfloxacin as standard and for antifungal activity against *C.albicans* and *A.niger* using Griseofulvin as standard. Nutrient agar was used as culture medium. Test solution was prepared by dissolving 1 mg of test compound in 1mL of DMF, and 0.1 mL of this solution was used for testing by using cup-plate method$^{17,18}$. The zones of inhibition formed were measured in mm. All the compounds showed weak to moderate activity.

**Experimental Section**

**General.** Melting points were measured in uniform.

**Table I—Antibacterial and Antifungal activities of compounds 3-8**

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Zone of Inhibition</th>
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<tbody>
<tr>
<td></td>
<td>E.Coli</td>
</tr>
<tr>
<td>3</td>
<td>++</td>
</tr>
<tr>
<td>4</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
</tr>
</tbody>
</table>

- = inactive, + = weakly active (12-16 mm), ++ = moderately active (17-21 mm)
+++ = highly active (22-30 mm).
open capillaries and are uncorrected. All solvents were distilled prior to use. IR (KBr): Perkin-Elmer 530, 681 and 1710 (FTR). 1H NMR (DMSO-d$_6$, $6$ ppm): Bruker 250 MHz Spectrometer, TMS as an internal reference; FAB mass spectrum: DI Varian 5 on UIC 002002 Spectrometer. Elemental analysis: Heraus CHN-rapid analyser. 1,4-Benzoquinone was prepared by oxidising hydroquinone. Diethyl 3',(ethane-1,2-diyldimino) dibutene-1 was prepared according to our earlier report.

**Diethyl 5, 5'-dihydroxy-2, 2'-dimethyl-1, 1'-(ethane-1, 2-diyl)dil(1H-indole)-3', 3'-dicarboxylate 3.** To a homogeneous solution of 1,4-benzoquinone 2 (16.2 g, 0.15 mole) in anhydrous acetone (300 mL) was added diethyl 3,3'- (ethane-1,2-diyldimino)dibutene-1 (21.37 g, 0.075 mole). The reaction mixture was heated to reflux for 2.5 hr. The excess of solvent was removed under diminished pressure, and the residue was washed with methanol and left overnight at room temperature. The separated solid was filtered, washed with methanol and dried. Recrystallisation from dioxane yielded 15.31 g of 3 (22 %). mp > 300°C; IR (KBr):1639 (C$_5$t-C=O), 3296 (C$_5$t-OH); 1H NMR (DMSO-d$_6$): 1.29 (t, J=7.4 Hz, 6H, C$_3$t-C)-COOCH$_2$-CH$_2$I), 1.98 (s, 6H, C$_2$2'-CH$_3$), 4.16 (q, J=7.4 Hz, 4H, C$_4$t-C00-C=CH$_2$-CH$_2$I), 4.47 (s, 4H, >N=CH$_2$-CH$_2$-N), 6.61 (dd, J=8.7 Hz and 2.2 Hz, 2H, C$_6$s'-H), 7.24 (d, J=8.7 Hz, 2H, C$_7$s'-H), 7.34 (d, J=8.7 Hz, 2H, C$_8$s'-H) and 8.73 (s, 2H, C$_6$s'-OH), disappeared on D$_2$O exchange; Anal. Caled for C$_{26}$H$_{24}$N$_2$O$_8$: C, 52.21; H, 4.95; N, 7.65%. Found: C, 52.33; H, 5.21; N, 7.59%.

**Diethyl 5, 5'-dimethoxy-2, 2'-dimethyl-1, 1'-(ethane-1, 2-diyl)dil(1H-indole)-3', 3'-dicarboxylate 4.** To the well stirred homogeneous solution of 3 (4.36 g, 0.01 mole) in anhydrous acetone (100 mL) were added methyl iodide (7.06 g, 95 mole) and anhydrous K$_2$CO$_3$ (7.47 g). The reaction mixture was heated with stirring for 50 hr and filtered while hot. The solvent was removed under reduced pressure and the residue triturated with ethanol. The solid was washed with ethanol and dried. Recrystallisation from dioxane yielded 2.60 g of 4 (53 %) mp 230-31°C.

**Diethyl 5, 5'-bis(ethoxycarbonylmethoxy)-2, 2'-dimethyl-1, 1'-(ethane-1, 2-diyl)dil(1H-indole)-3', 3'-dicarboxylate 5.** To a homogeneous solution of 3 (3.46 g, 0.01 mole) in anhydrous acetone (100 mL) were added ethyl chloroacetate (4.88 g, 0.04 mole), anhydrous K$_2$CO$_3$ (7 g) and KI (0.1 g). The reaction mixture was heated to reflux for 40 hr, and filtered while hot. The solvent was removed under reduced pressure and the residue was crystallised from ethanol. Recrystallisation from ethanol gave 4.20 g of 5 (66 %). mp 271-272°C.

**Diethyl 5, 5'-bis(hydrazinocarbonylmethoxy)-2, 2'-dimethyl-1, 1'-(ethane-1, 2-diyl)dil(1H-indole)-3', 3'-dicarboxylate 6.** To a homogeneous solution of 5 (1.27 g, 0.002 mole) in ethanol (50 mL) were added hydrazine hydrate (99 %) (1.85 g, 0.036 mole), and a catalytic quantity of pyridine (2 drops). The reaction mixture was heated at reflux on boiling water-bath for 20 hr. The separated carboxydrazide was filtered, washed with ethanol and dried. Recrystallisation from dioxane yielded 1.09g of 6 (90 %), mp 148-49°C.

**Diethyl 5, 5'-bis(2,5-dimethylpyrrole-1-yl-amino-carbonylmethoxy)-2, 2'-dimethyl-1, 1'-(ethane-1, 2-diyl)dil(1H-indole)-3', 3'-dicarboxylate 8.** To a sus-
pension of the carboxyhydrate 6 (0.608 g, 0.001 mole) in absolute ethanol (25 ml) were added acetonil.
acetone (0.34 g, 0.003 mole) and glacial acetic acid (1 ml). The reaction mixture was heated on boiling wa­
tery bath for 5 h. The solvent was removed under reduced pressure to half of its original volume and poured in to ice cold water (50 ml). The separated solid was collected by filtration, washed with water and dried. Recrystallisation from dioxane yielded 0.562 g of 8 (74 %), mp 266-67°C,

IR (KBr): 1695 (C₃,₃' -COOCH₂-CH₃), 1.96 (s, 12H, C₃,₃'-CH₃ of bisindole and 2,5-CH₃ of pyrrole ring), 4.22 (q, J=7.4 Hz, 4H, C₃,₃'-COO-CH₂-CH₃), 4.58 (s, 4H, >N-C₃H₂-N < ), 4.80 (s, 4H, C₃,₃'-OCH₂CONH-pyrrole), 5.64 (5', 4H, >N-C₃H₂-N < ), 6.92 (dd, J=8.7 Hz and 2.2 Hz, 2H, C₈,₈'-H), 7.38 (d, J'=2.2 Hz, 2H, C₈,₈'-H), 7.60 (d, J'=2.2 Hz, 2H, C₈,₈'-H), 11.0 (s, 2H, amide NH, exchangeable with D₂O); FAB MS : m/z 764 (M' 18%), 765 (M' 9), 719 (4), 613 (6), 460 (22), 329 (53), 307 (100), 289 (77).Anal. Caled for C₄₂H₃₈N₈O₈: C, 66.30; H, 5.83; N, 12.62%. Found: C, 66.19; H, 5.97; N, 12.69%.

Acknowledgements
A S S is grateful to Karnatak University, Dharwad and CSIR, New Delhi, for the award of a research fellowship and senior research fellowship, respectively. The authors also thank Dr L. R. Subramanian, University of Tübingen, Germany for providing spectral data.

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