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SYNTHESIS AND CHARACTERIZATION OF BISINDOLE-7,7'- DICHLORO-2,2'-DIETHOXYCARBONYL-5,5'- BIS-1*H*-INDOLE

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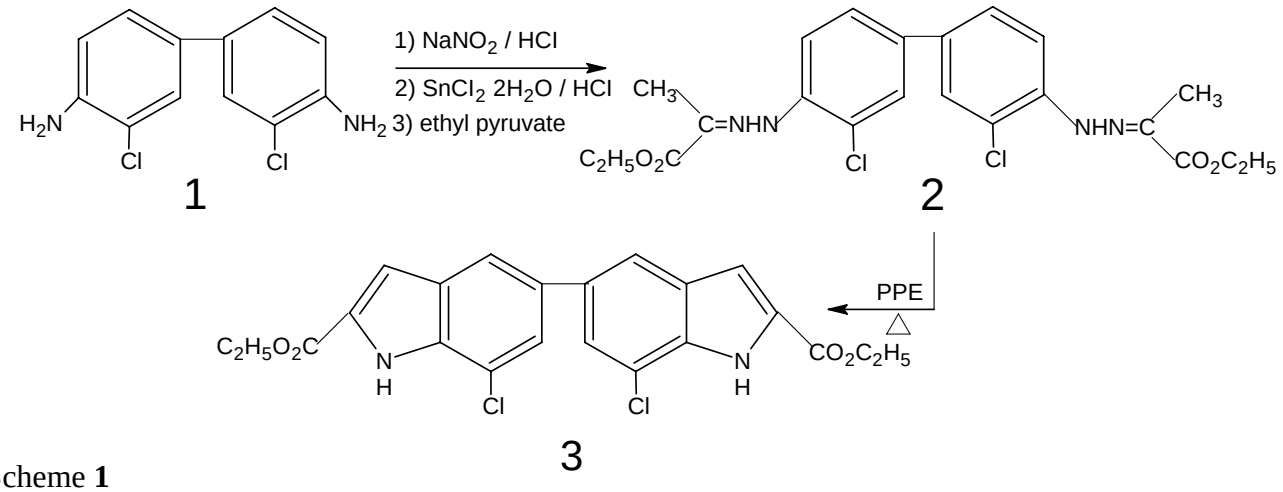
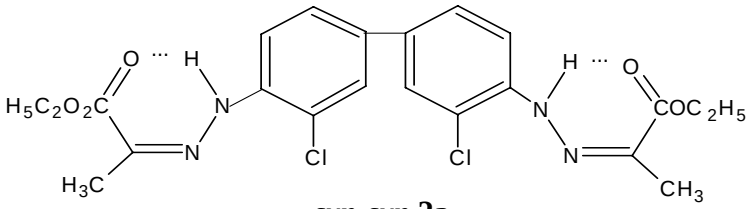
Abstract–3,3'-Dichlorobenzidine is used for the preparation of 7,7'-dichloro-2,2'-diethoxycarbonyl-5,5'-bis-1*H*-indole. This was accomplished by converting the diamine to the diazonium salts. Reduction of this diazonium salts afforded dihydrazine which was condensed with ethyl pyruvate to give dihydrazone that is separated on column chromatography to provide the following isomers: *syn-syn*, *syn-anti* and *anti-anti*. Cyclization of the dihydrazone using polyphosphate ester gave 7,7'-dichloro-2,2'-diethoxycarbonyl- 5,5'- bis-1*H*-indole.

Bisindoles have been a subject of numerous studies and a number of their preparations, for example the cyclization of diamide, [1, 2] condensation, [3, 4] and the reduction of diisotines, [5] have been reported. However, the easiest and the most economic way to prepare unsubstituted α,β-bisindoles is still the Fischer indole synthesis.[6,7] This method has been largely used.[8-11] It is used to prepare 7,7'-dichloro-2,2'-diethoxycarbonyl-5,5'-bis-1*H*-indole (**3**). Treatment of the diamine (**1**) with $NaNO_2$ in the presence of hydrochloric acid, followed by reduction with $SnCI_2.2H_2O$ /HCI gave dihydrazine, which was condensed with ethyl pyruvate to give dihydrazone (**2**) as a mixture of three geometric isomers, which were easily separated on column chromatography. Cyclization of dihydrazone (**2**) using PPA, H_2SO_4/CH_3COOH, $ZnCI_2$, and C_2H_5OH/HCI gave poor yields. The use of polyphosphate ester at high temperature (160-170°C) gave the bisindole (**3**) which was isolated on column chromatography, with a 15% yield, Scheme (**I**).

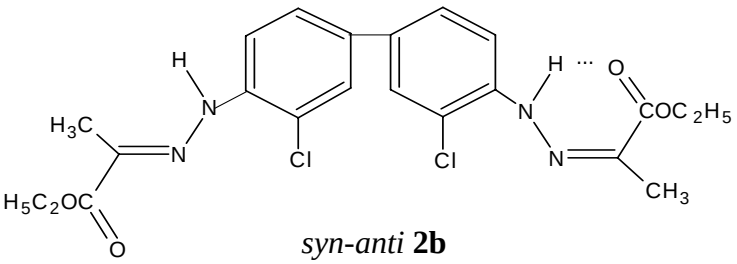


Scheme **1**

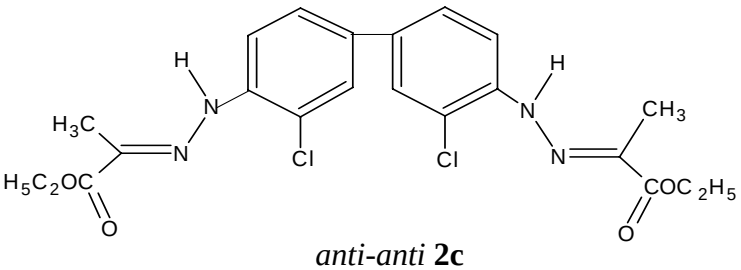
The presence of both electron attractive groups on the aromatic dihydrazones derivatives and hydrogen bond in *syn* isomer may have helped in the separation of *syn-syn*, *syn-anti* and *anti-anti* isomers (**2a,b,c)**, Scheme (**2**).



syn-syn **2a**



syn-anti **2b**



anti-anti **2c**

Scheme **2**

The structure of dihydrazone (**2a,b,c**) and 7,7'-dichloro-2,2'-diethoxycarbonyl-5,5'-bis-1*H*-indole (**3**) were confirmed by ^{1}H-NMR, IR and MS spectra. The results are summarized in Table (**I**).

Table (**1**): Spectral Data for isomers of dihydrazone (**2**) and bisindole (**3**)

compounds	Yield %	mp °C	IR cm^{-1} NH	IR cm^{-1} CO	UVnm λ_{max}	^{1}H-NMR NH(s)
syn-syn **2a**	13.3	177	3358	1725	213	12.32
					368	
syn-anti **2b**	18.3	167	3358	1708	209	12.31
			3456	1723	365	8.08
anti-anti **2c**	25	235	3456	1728	210	8.06
					353	
bisindole **3**	15	271	3308	1708	265	9.09
					299	

The IR spectrum of *syn-anti* (**2b**) showed two absorption bands at 1723 and 1708 cm^{-1} corresponding to the carbonyl groups, and two bands at 3358 and 3456 cm^{-1} of the N-H groups and these prove that this isomer is unsymmetrical, this was further confirmed by H-NMR spectrum, which showed two chemical shifts at 12.31 and 8.08 ppm corresponding to the proton of N-H of the same *syn-anti* (**2b**)**.** However, a single peak appeared in both *syn-syn* (**2a**) and *anti-anti* (**2c**) at 1725 and 1728 cm^{-1} of the carbonyl groups as well as 3358 and 3456 cm^{-1} of the N-H respectively. From our studies we came to a conclusion that electron attractive groups on aryl hydrazones does not help cyclization unless a high temperature is applied, and this leads to the craking of hydrazones and breaking down of the catalyst (PPE). The reason for the differences in the H-NMR chemical shifts, IR and UV-vis absorption is due to the presence of hydrogen bonding in the isomer *syn*.

EXPERIMENTAL

All melting points were determined with a kofler-type hot-stage apparatus and are uncorrected. IR spectra were measured on a Shimadzu - FTIR-8300 on KBr . ^{1}H-NMR spectra were run on Bruker-400MHz in $CDCI_3$. For column chromatography silica gel 60(70-230 mesh). Thin Layer Chromatography (TLC) -UV-250.

3.3’-Dichloro-4.4’-diphenylenedihydrazone of ethyl pyruvate (2)

A mixture of 30 mL of water, 3.3’-dichlorobenzidine dihyrochloride (**1**) (3 g, 9.2 mmol), and 10 mL of concentrated hydrochloric acid was cooled to 0-4°C. To this was added a solution of sodium nitrite (2 g,

28.9 mmol) in 10 mL water, dropwise. This mixture was added slowly to a solution of tin dichloride (14 g, 62 mmol) in 13 mL of concentrated hydrochloric acid at 0-4°C. Having finished this addition the mixture was stirred at the same temperature. This mixture was left for another overnight in the fridge. After filtration of the precipitate, it was diluted with 800 mL of hot water (60°C). Then, sodium acetate was added until a pH 3-4. This solution was filtered again and the filtrate was left to cool to 45°C, to this filtrate was added ethyl pyruvate (3 mL, 27 mmol) in isopropanol 10 mL with continuous stirring until a yellow precipitate appeared, This precipitate was filtered, dried and weighed to yield **2** (3.45 g, 80%), which was separated on column chromatography to provide the following three fractions.

Fraction one (***syn-syn*** **2a**)

Eluted benzene, yield: 13.3%. Recrystallization from hexane (mp 177°C). R_f = 0.69 (4/1 benzene: hexane). *Anal*. Calcd for $C_{22}H_{24}CI_2N_4O_4$; C: 55.11, H: 5.01, CI: 14.82, N: 11.69. Found; C: 55.09, H: 5.01, N: 11.71, CI: 14.80. IRν_{max} cm^{-1} (KBr): 3358 (NH), 1725 (C=O).^{1}H-NMR ($CDCI_3$, 400 MHz) δ:1.30 (3H t, *J*=7.12 Hz, $OCH_2C\underline{H}_3$), 2.13 (3H, s, =C-$C\underline{H}_3$), 4.26 (2H, q, *J*=7.12 Hz, $OC\underline{H}_2CH_3$), 7.36 (d, *J*=8.75 Hz, C^5-H), 7.41 (dd, *J*=8.75 and 1.85 Hz, C^6-H), 7.58 (d, *J*=1.85 Hz, C^2-H), 12.31 (s, N-H). UV λ_{max} (log ε): 213(5.37), 281(4.89), 368(5.19).

Fraction two (*syn-anti* 2b)

Eluted benzene, yield: 18.3 %, Recrystallization from hexane (mp 167°C). R_f =0.64 (2/1, benzene: hexane). *Anal*. Calcd for $C_{22}H_{24}CI_2N_4O_4$; C: 55.11, H: 5.01, CI: 14.82, N: 11.69. Found; C: 55.11, H: 5.01, CI: 14.81, N: 11.65. IRν_{max} cm^{-1} (KBr): 3358, 3456 (NH), 1708, 1723, (C=O). ^{1}H-NMR ($CDCI_3$, 400 MHz) δ:1.29 (3H, t, *J*=7.12 Hz, $OCH_2C\underline{H}_3$), 2.08 (3H, s, =C-$C\underline{H}_3$), 4.22 (2H, q, *J*=7.12 Hz, $OC\underline{H}_2CH_3$), 7.32 (d, *J*=8.50 Hz, C^5-H), 7.39(dd, *J*=8.50 and 1.90 Hz, C^6-H), 7.56 (d, *J*=1.90 Hz, C^2-H), 8.08 (s, N-H), 1.31 (3H', t, *J*=7.12 Hz, $OCH_2C\underline{H}_3$), 2.11 (3H', s, =C-CH_3), 4.24 (2H', q, *J*=7.12 Hz, $OC\underline{H}_2CH_3$), 7.36 (d, *J*=8.50 Hz, C^5-H'), 7.40 (dd, *J*=8.50 and 1.90 Hz, C^6-H'), 7.58 (d, *J*=1.90 Hz, C^2-H'), 12.31 (s, N-H'). UV λ_{max} (log ε): 209 (5.29), 280 (4.75), 365 (5.14).

Fraction three (*anti-anti* 2c)

Eluted (2:1 benzene-acetone), yield: 25 %. Recrystallization from hexane (mp 235 °C). R_f = 0.69 (2/1 benzene: acetone). *Anal*. Calcd for $C_{22}H_{24}CI_2N_4O_4$; C: 55.11, H: 5.01, CI: 14.82, N: 11.69. Found; C: 55.15, H: 5.01, CI: 14.85, N: 11.66. IRν_{max} cm^{-1} (KBr): 3456 (NH), 1728 (C=O). ^{1}H-NMR ($CDCI_3$, 400 MHz) δ:1.30 (3H, t, *J*=7.12 Hz, $OCH_2C\underline{H}_3$), 2.12 (3H, s, =C-$C\underline{H}_3$), 4.24 (2 H, q, *J*=7.12 Hz, $OC\underline{H}_2CH_3$), 7.35 (d, *J*=8.75 Hz, C^5-H), 7.40 (dd, *J*=8.75 and 1.85 Hz, C^6-H), 7.57 (d, *J*=1.85 Hz, C^2-H), 8.06 (s, N-H). UV λ_{max} (log ε): 210(5.37), 278(4.73), 353(4.76).

7.7'-Dichloro-2.2'-diethoxycarbonyl-5,5'-bis-1*H*-indole (3)

To a PPE (polyphosphate ester) 50 g was added dihydrazones (**2)** (3 g, 6, 26 mmol), the mixture was stirred until it becomes homogeneous, and then heated to 160-170°C for 7 min. This was left to cool

down to rt. Then, it was decanted in 300 mL of cold water. The precipitate was filtered, dried, and purified on column chromatography, over slica gel using benzene to give (0.43 g, 15 %) (mp 271-273°C), which were recrystallized from hexane. R_f = 0.63 (6/1 benzene: acetone). *Anal*. Calcd for $C_{22}H_{18}N_2O_4Cl_2$; C: 59.45, H: 4.05, CI: 15.76, N: 6.30. Found; C: 59.49, H: 4.05, CI: 15.70, N: 6.25. IRν_{max} cm^{-1}: 3308 (NH), 1708 (C=O). ^{1}H-NMR ($CDCI_3$, 400 MHz) δ:1.46 (3H, t, *J*=6.86 Hz, $OCH_2C\underline{H}_3$), 4.48 (2H, q, *J*=6.86 Hz, $OC\underline{H}_2CH_3$), 7.32 (d, *J*= 1.35 Hz, C^3-H), 7.63 (d, *J*= 1.47 Hz, C^4-H), 7.81 (d, *J*=1.47 Hz, C^6-H), 10.62 (s, N-H). UV λ_{max} (log ε): 265(4.33), 299(3.23). MS (EI): m/z (%) = 444 (100) [M^+], 398 (76.99), 352 (66.56), 325 (14.25), 289 (14.57), 261 (09.58), 226 (21.34), 172(01.40).

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