BISINDOLES.

26.* SYNTHESIS OF 7,7-DICHLOROBIS(5-INDOLYL)METHANE

Dzh. Zegkhugkh, D. O. Kadzhrishvili,
Sh. A. Samsoniya, N. N. Suvorov,
and N. Z. Kedelashvili

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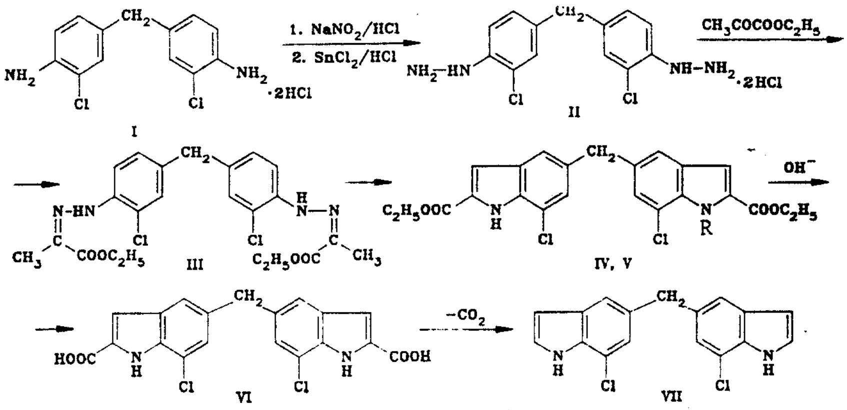
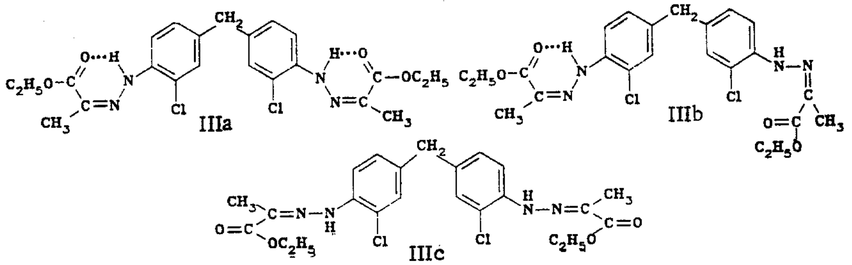
7,7'-Dichloro-2,2'-dicarbethoxybis(5-indolyl)methane has been synthesized by cyclization of the 3,3'-dichloro-4,4'-diphenylmethanedihydrazone of ethyl pyruvate. Subsequent hydrolysis and decarboxylation of the corresponding diacid gave the unsubstituted 7,7'-dichlorobis(5-indolyl)methane. The syn-syn, syn-anti, and anti-anti forms of 3,3'-dichloro-4,4'-diphenylmethanedihydrazone of ethyl pyruvate have been separated and characterized.

In [2] the synthesis of bis(5-indolyl)methane was reported. With the aim of synthesizing chlorobisindoles we have prepared 7,7'-dichlorobis(5-indolyl)methane by the following scheme:



IV R=H; V R=C$_2$H$_5$

Diazotization of 3,3'-dichloro-4,4'-diaminodiphenylmethane dihydrochloride (I) and reduction of the resulting diazonium salt with stannous chloride led to the corresponding dihydrazine II. Without separation this was then condensed with ethyl pyruvate to give 3,3'-dichloro-4,4'-diphenylmethane dihydrazone (III), which is a mixture of three geometrical isomers. The mixture was separated by column chromatography to give the syn-syn (IIIa), syn-anti (IIIb), and anti-anti (IIIc) forms:



The PMR spectrum of isomer IIIa shows an NH proton signal shifted to low field (12.31 ppm) when compared with the corresponding signal in IIIc (8.05 ppm) due to the formation in IIIa of intramolecular hydrogen bonds with the syn orientation of the substituents (Table

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*For Communication 25, see [1].

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TABLE 1. PMR Spectra of Compounds IIIa-c in $CDCl_3$

Compound	Chemical shift, δ, ppm								Spin spin coupling, Hz
	2-H, d	5-H, d	6-H, dd	CH_2, s	NH, s	CH_2CH_3, q	CH_3CH_2, t	CH_3, s	
IIIa	7,09	7,54	7,04	3,82	12,31	4,31	1,37	2,13	$J_{26}=1,83$; $J_{56}=8,41$; $J_{CH_2CH_3}=6,95$
IIIb	7,09	7,54	7,03	3,83	12,31	4,31	1,37	2,18	$J_{26}=J_{2'6'}=2,20$; $J_{56}=8,71$;
	7,08	7,60	7,07		8,05	4,32	1,35	2,14	$J_{5'6'}=8,77$; $J_{CH_2CH_3}=$ $=J_{(CH_2CH_3)'}=6,94$
IIIc	7,09	7,60	7,08	3,84	8,05	4,32	1,38	2,14	$J_{26}=1,83$; $J_{55}=8,77$; $J_{CH_2CH_3}=6,94$

1). The contrasting IIIb is the non-symmetrical syn-anti isomer as evidenced by the shift of one of the amine protons to significantly lower field (12.31 ppm) than the other (8.05 ppm).

The UV spectra of isomers IIIa-c taken in ethanol show long wavelength maxima at 357, 337, and 326 nm respectively, i.e., the syn-syn form shows a bathochromic shift of 31 nm from the anti-anti and 20 nm from the syn-anti forms. The IR spectrum of the syn-syn isomer taken in chloroform showed absorption bands at 3260 cm^{-1} (NH) and 1690 cm^{-1} (CO) which were shifted to low frequency of the corresponding bands for the same groups in the anti-anti isomer (3365 and 1725 cm^{-1} respectively). Isomer IIIb shows two absorption bands for each of these groups, i.e., NH at 3265 and 3365 cm^{-1} and CO at 1690 and 1715 cm^{-1}.

Indolization of dihydrazone III was carried out in polyphosphate ester to give IV together with a small yield of 1-ethyl-7,7'-dichloro-2,2'-dicarbethoxybis(5-indolyl)methane (V). Formation of this N-ethyl derivative is probably due to alkylation of the amino nitrogen of the dihydrazone by decomposition products of the polyphosphate ester and subsequent cyclization.

Hydrolysis of diester IV gave diacid VI which is decarboxylated to form 7,7'-dichlorobis(5-indolyl)methane (VII).

The PMR spectrum of the heterocycle VII (Table 2) showed a low field shift of all protons when compared with the analogous protons in bis(5-indolyl)methane and indole due to the electron acceptor effects of the chlorine atoms. The greatest deshielding occurred for the 6-proton whose signal was found (7.45 ppm) to low field of the 4-proton (7.09 ppm). In the PMR spectra of indole and bis(5-indolyl)methane the order of these signals is reversed [3].

EXPERIMENTAL

IR spectra were recorded as paraffin mulls on a UR-20 instrument and UV spectra on a Specord spectrophotometer for ethanol solutions. PMR spectra were measured on a Varian CFT-20 (80 MHz, internal standard TMS) and mass spectra on a NERMAG's R-10-10B with direct sample introduction into the ion source and an electron ionization energy of 70 eV. The course of the reaction and purity of the products were monitored by TLC on Silufol UV-254 plates.

Isomers of Ethyl Pyruvate 3,3'-Dichloro-4,4-diphenylmethanedihydrazone (III). A mixture of compound I (10 g, 29 mmole), concentrated HCl (40 ml), and water (20 ml) was cooled to −5°C and a solution of sodium nitrite (5 g, 72 mmole) in water (10 ml) was added so that the temperature did not exceed 0°C. The formed diazo solution was stirred for 1 h, poured into a cooled (−10°C) solution of stannous chloride (34 g, 150 mmole) in concentrated HCl (60 ml) such that the temperature of the reaction mixture did not exceed −5°C, and stirred for 3 h at 0°C. The precipitate was filtered off, dissolved in water (2 liters), heated to reflux and the pH adjusted to 4 with sodium acetate. The precipitated salts were filtered off, the filtrate was cooled and ethyl pyruvate (8.4 ml) in isopropanol (8 ml) added with vigorous stirring. The product was stirred for 2 h and the precipitated solid filtered off, washed with water and dried to give a mixture of isomers of dihydrazone III (12 g, 82%). Four grams were separated on a silica gel column (100/250 micron) using benzene.

The first fraction was the syn-syn form (IIIa) in 0.1 g (3%) yield with mp 193-194°C and Rf 0.77 (benzene-hexane, 1:1). IR spectrum (in chloroform): 3265 (NH), 1690 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 241 (4.18), 307 (3.99), 357 nm (4.49). Found: N 11.9; Cl 14.6%. $C_{23}H_{26}Cl_2N_4O_4$. Calculated: N 11.4; Cl 14.4%.

TABLE 2. PMR Spectra of Compounds IV, VI, and VII

Compound	Chemical shift, δ, ppm (acetone-D_6)					Spin spin coupling, Hz
	1-H, br.s	3-H	4-H.d	6-H.d	CH_2, s	
IV*	10,95	7,23 d	7,29	7,58	4,17	$J_{13}=1{,}83$; $J_{46}=1{,}47$; $J_{CH_2CH_3}=6{,}95$
VI**	11,84	7,50 s	7,14	7,23	4,06	$J_{46}=1{,}46$
VII***	10,45	6,51 dd	7,09	7,45	4,13	$J_{13}=2{,}19$; $J_{23}=3{,}0$; $J_{46}=1{,}10$

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*CH_2CH_3 4.33 ppm (q) and 1.35 (t) respectively.
**COOH, broad exchangeable signal, DMSO-D_6 solvent.
***2H 7.38 ppm (d).

The next fraction was the syn-anti form (IIIb) in 1.2 g (30%) yield with mp 190-191°C and R_f 0.47 (benzene). IR spectrum (in chloroform): 3265, 3365 (NH), 1690, 1715 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 235 (4.20), 299 (4.24), 337 nm (4.47). Found: N 11.5; Cl 14.7%.

The final fraction was the anti-anti form (IIIc) in 1.4 g (34%) yield with mp 167-168°C and R_f 0.80 (benzene-acetone, 10:1). IR spectrum (in chloroform): 3365 (NH), 1715 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 231 (4.14), 300 (4.40), 326 nm (4.55). Found: 11.6; Cl 14.2%.

7,7'-Dichloro-2,2'-dicarbethoxybis(5-indolyl)methane (IV) and 1-ethyl-7,7'-dichloro-2,2'-dicarbethoxybis(5-indolyl)methane (V). A mixture of compound III (2 g, 4 mmole) and polyphosphoric ester (20 g) was held with vigorous stirring at 160-180°C, cooled, and poured onto ice. The precipitate was filtered off, dried, and purified by column chromatography on silica gel (100/250 micron) using benzene to give the ester IV (0.7 g, 38%) with mp 203-204°C and R_f 0.7 (benzene-acetone, 8:1). IR spectrum: 3325 (NH), 1725 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 215 (4.52), 238 (4.68), 298 nm (4.58). Found: C 60.6; H 4.8; Cl 16.0; N 6.2%. M^+ 458. $C_{23}H_{20}Cl_2N_2O_4$. Calculated: C 60.1; H 4.4; Cl 15.5; N 6.2%, M 458 (^{35}Cl).

The yield of V was 0.03 g (2%) with mp 139-140°C with R_f 0.45 (benzene). IR spectrum: 3330 (NH), 1725 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 210 (4.68), 239 (4.82), 300 nm (4.69). PMR spectrum (acetone-D_6): 10.94 (NH); 7.23 (1H, d, 3-H, J_{13} = 2.19 Hz); 7.27 and 7.28 (1H, d, 4-H, and 1-H, d, 6-H, J_{46} = 2.93 Hz); 7.56 (1H, s, 3'-H); 7.28 and 4.57 (1H, d, 4'-H and 1H, d, 6'-H, $J_{4'6'}$ = 2.93 Hz); 4.14 (2H, s, CH_2 bridge); 4.36 and 1.37 (2H, q, $COO\underline{CH_2}CH_3$) and 3H, t, $\underline{CH_3}CH_2$, $J_{CH_2CH_3}$ = 7.31 Hz); 5.01 and 1.40 ppm (2H, q, CH_2N and 3H, t, CH_3CH_2N, $J_{CH_2CH_3}$= 6.95 Hz). Found: C 61.8; H 5.1; Cl 14.4%, M^+ 486. $C_{25}H_{24}Cl_2N_2O_4$. Calculated: C 61.6; H 4.9; Cl 14.6%. M 486 (^{35}Cl).

7,7-Dichloro-2,2'-dicarboxybis(5-indolyl)methane (VI). A suspension of IV (2.2 g, 5 mmole) in isopropanol (20 ml) was added to a solution of NaOH (1 g) in water (35 ml) and refluxed for 2 h. The solution was cooled, filtered, and acidified to pH 1 with conc. HCl. The precipitated solid was filtered, washed with water, and dried to give VI (1.9 g, 96%) with mp 280°C (decomp.) and R_f 0.64 (benzene-acetone, 2:3). IR spectrum: 1690 (CO), 3410-3480 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 236 (4.49), 297 nm (4.53). Found: C 56.2; H 2.9; Cl 17.3; N 6.5%. $C_{19}H_{12}Cl_2N_2O_4$. Calculated: C 56.5; H 2.9; Cl 17.6; N. 6.9%.

7,7'-Dichlorobis(5-indolyl)methane (VII). Compound VI (1 g, 2.4 mmole) was heated for 2 min at 280°C, the reaction product cooled, extracted with acetone, and purified on a silica gel column (100/250 micron) using benzene to give VII (0.42 g, 52%) with mp 171-172°C and R_f 0.5 (benzene-hexane, 2:1). IR spectrum: 3440 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 231 (4.70), 276 (4.10), 289 (4.07), 301 nm (3.87). Found: C 64.3; H 4.1; Cl 22.5; N 8.4%. $C_{17}H_{12}Cl_2N_2$. Calculated: C 64.7; H 3.8; Cl 22.5; N 6.8%. Mass spectrum [m/z (data for chlorinated ions reported for the ^{35}Cl isotope), relative intensity, %] 314 (79) (M), 313 (10) (M-H), 278 (16) (M-H-Cl), 243 (100) (M-H-2Cl), 216 (4) (M-H-2Cl-HCN), 189 (7) (M-H-2Cl-2HCN), 164 (62) (M-IndCl).

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