BISINDOLES.

28.* SYNTHESIS OF 7,7'-DIMETHYL-5,5'-BIS-1H-INDOLE

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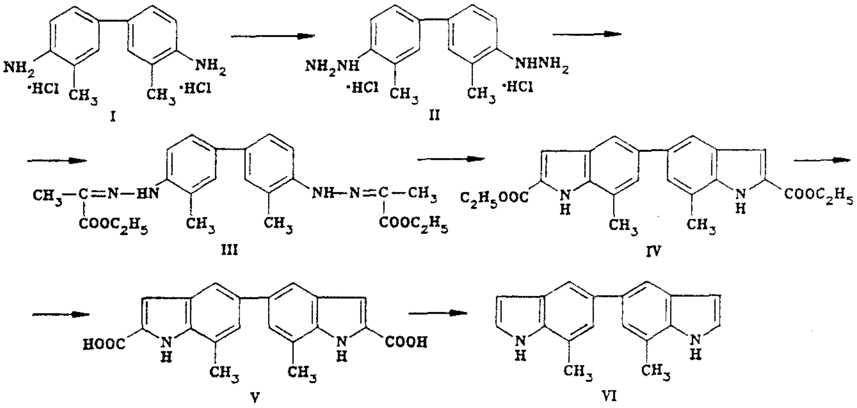
Cyclization of the 3,3'-dimethyl-4,4'-diphenylendihydrazone of ethyl pyruvate in polyphosphoric ester gave 7,7'-dimethyl-2,2'-dicarbethoxy-5,5'-bis-1H-indole which was hydrolyzed and decarboxylated to give 7,7'-dimethyl-5,5'-bis-1H-indole.

The synthesis of unsubstituted bisindoles which are directly linked via benzene ring carbon atoms have been described in [2, 3]. With the aim of studying the effect of a donor substituent on the formation of the bisindole we have synthesized 7,7'-dimethyl-5,5'-bis-1H-indole (VI) as shown:



Diazotization of diamine I followed by reduction of the diazonium salt gave the dihydrazine dihydrochloride II. Condensation of II with ethyl pyruvate gives ethyl pyruvate 3,3'-dimethyl-4,4'-diphenylendihydrazone (III), cyclization of which in polyphosphoric ester gives the diester IV. Hydrolysis of (IV) and decarboxylation of the resultant acid V forms VI (Tables 1 and 2).

Dihydrazone III is a mixture of syn-syn (IIIa), syn-anti (IIIb), and anti-anti (IIIc) forms which were separated.

In the IR spectrum (in chloroform) of the syn-syn isomer IIIa the absorptions of the NH and CO groups are shifted to low frequency of the corresponding bands in the anti-anti isomer IIIc by 110 and 25 cm^{-1}. This results from the participation of the groups in the formation of intramolecular hydrogen bonds in this syn-syn orientation. In the syn-anti isomer IIIb the two bands for the NH and CO groups occur in pairs at 3400, 3290, 1715, and 1690 cm^{-1} due to the isomers' unsymmetrical configuration.

The UV spectra (in ethanol) showed characteristic bathochromic shifts in the absorption bands of those isomers which have an intramolecular bond. The shift in the long wavelength band for the syn-syn isomer IIIa is 32 nm and for the syn-anti isomer IIIb 21 nm.

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*For Communication 27 see [1].

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TABLE 1. PMR Spectra of IIIa-c

Compound	Chemical shift (in $CDCl_3$), δ, ppm								Spin-spin coupling, J, Hz
	2-H, d	5-H, d	6-H, dd	NH, s	CH_3—Ar, s	CH_2—CH_3, d	CH_3—CH_2, t	C—CH_3, s	
IIIa	7,33	7,61	7,42	12,18	2,33	4,30	1,38	2,20	$J_{56}=8,4$; $J_{26}=1,8$; $J_{Et}=6,9$
IIIb	7,33; 7,33	7,61; 7,64	7,41; 7,45	7,56; 12,18	2,32; 2,33	4,30; 4,33	1,37; 1,40	2,13; 2,20	$J_{56}=J_{5'6'}=8,4$; $J_{26}=J_{2'6'}=1,8$; $J_{Et}=J_{Et'}=6,9$
IIIc	7,34	7,65	7,45	7,57	2,32	4,34	1,40	2,14	$J_{26}=1,5$; $J_{56}=8,4$; $J_{Et}=7,3$

TABLE 2. PMR Spectra of IV-VI

Compound	Chemical shift (in acetone-d_6), δ, ppm					Spin-spin coupling, J, Hz
	1-H, br.s	3-H	4-H	6-H	CH_3, s	
IV*	10,62	7,24 d	7,77 s	7,46 s	2,65	$J_{13}=1,8$; $J_{Et}=6,9$
V**	10,65	7,28 d	7,80 d	7,49 d	2,68	$J_{13}=1,8$; $J_{4,6}=1,1$
VI***	10,21	6,51 dd	7,67 s	7,27 s	2,57	$J_{13}=1,8$; $J_{12}=2,6$; $J_{23}=2,9$

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*δ 4.37 (q, CH_2–CH_3), 1.38 ppm (t, CH_3–CH_2).

**COOH broad exchanged signal.

***δ 7.31 ppm (dd, 2-H).

The PMR spectrum of the syn-syn isomer IIIa shows a low field shift of the NH proton signal when compared with the anti-anti isomer IIIc due to its participation in H bond formation. The syn-anti isomer IIIb shows two NH proton signals.

It was found that the configuration of the starting dihydrazone has practically no effect on the yield of the bisindole because of the severity of the cyclization reaction conditions (120-130°C).

Introduction of donor groups into the ortho position of the diaminodiphenyl causes only an insignificant increase (up to 4%) in the indolization stage yield.

EXPERIMENTAL

The reaction course and compound purity were monitored by TLC on Silufol UV-254. Column chromatography was carried out on 100-250 mesh silica gel. IR spectra were recorded on a UR-20 instrument, UV spectra on a Specord spectrophotometer (in ethanol), mass spectra on a Ribermag R 10-10B spectrometer, and PMR spectra on a WP-200-SY instrument using TMS as internal standard.

Elemental analytical data for C, H, and N and M^+ (mass spectral) agreed with those calculated.

Isomeric 3,3'-Dimethyl-4,4'-diphenylendihydrazones of Ethyl Pyruvate (III, $C_{24}H_{30}N_4O_4$). A solution of $NaNO_2$ (8 g, 115 mmole) in water (20 ml) was added slowly with stirring to a solution of 3,3'-dimethyl-4,4'-diaminodiphenyl I (10 g, 47 mmole), in water (150 ml), and concentrated HCl (60 ml) which had been cooled to –5°C. The diazo solution formed was stirred for 30 min and poured into a solution of stannous chloride (80 g, 353 mmole) in concentrated HCl (125 ml) which had also been cooled to –5°C. The product was stirred for 4 h at 0°C and, next day, the precipitate was filtered off, dissolved in water (1.5 liter) and adjusted to pH 3 using sodium acetate. The precipitate was filtered off and ethyl pyruvate (15 ml) in isopropanol (35 ml) was added to the filtrate. The reaction product was stirred for 1 h and the precipitate filtered off, washed with water, and dried to give a mixture of the isomeric dihydrazones III (73%). Three grams were separated on a silic gel column using benzene.

First Fraction (syn-syn isomer IIIa). Yield 0.2 g (7%), mp 129-130°C, R_f 0.67 (benzene-hexane 1:2). IR Spectrum,(in chloroform): 3290 (NH), 1690 cm^{-1} (CO). UV Spectrum, λ_{max} (log ε): 231 (4.08), 263 (4.09), 391 nm (4.64).

Second Fraction (syn-anti isomer IIIb). Yield 1.1 g (36%), mp 152-153°C, R_f 0.45 (benzene). IR Spectrum (in chloroform): 3290, 3400 (NH), 1690, 1710 cm^{-1} (CO). UV Spectrum: 231 (4.26), 258 (4.24), 380 nm (4.61).

Third Fraction (anti-anti isomer IIIc). Yield 0.2 g (10%), mp 180°C, R_f 0.8 (benzene-acetone 2:1). IR Spectrum (in chloroform): 3400 (NH), 1710 cm^{-1} (CO). UV Spectrum: 231 (4.22), 250 (3.94), 359 nm (4.69).

7,7'-Dimethyl-2,2'-dicarbethoxy-5,5'-bis-1H-indole (IV, $C_{24}H_{24}N_2O_4$). Polyphosphoric ester (40 g) was added to dihydrazone III (5 g, 11 mmole) and stirred for 30 min at 120-130°C. After cooling, the reaction product was poured onto ice, the precipitate filtered off, washed, and dried. Column chromatography (silica gel, benzene) gave the diester IV (0.5 g, 11%) with mp 224-225°C, R_f 0.52 (benzene-acetone 6:1). IR Spectrum (in chloroform): 3475 (NH), 1715 cm^{-1} (CO). UV Spectrum: 244 (4.56), 2.76 (4.62), 304 nm (4.64).

7,7'-Dimethyl-2,2'-dicarbethoxy-5,5'-bis-1H-indole (V, $C_{20}H_{16}N_2O_4$). NaOH (1 g, 25 mmole) was added to a mixture of diester IV (0.8 g, 1.98 mmole), water (20 ml), and isopropanol (23 ml) and stirred under reflux for 2 h. The solution was cooled, diluted with water (52 ml), and acidified with concentrated HCl to pH 1. The precipitated solid was filtered off, washed with water, and dried to give V (0.61 g, 88%) with mp 253-254°C and R_f 0.57 (benzene-acetone 2:1). IR Spectrum (in Vaseline mull): 3340-3455 (NH), 1690 cm^{-1} (CO). UV Spectrum: 265 (3.49), 241 (3.36), 301 nm (3.38).

7,7'-Dimethyl-5,5'-bis-1H-indole (VI, $C_{18}H_{10}N_2$). Compound V (0.1 g, 0.2 mmole) was heated until evolution of CO_2 ceased. The reaction product was cooled, extracted with acetone, and column chromatographed on silica gel using benzene to give VI (0.02 g, 28%) with mp 160-161°C and R_f 0.81 (benzene). IR Spectrum (in Vaseline mull): 4500 cm^{-1} (NH). UV Spectrum (in methanol): 219 (4.55), 250 (4.83), 304 nm, sh (3.97).

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