BISINDOLES.

10.* SYNTHESIS OF 1,2-(5,5'-DIINDOLYL)ETHANE

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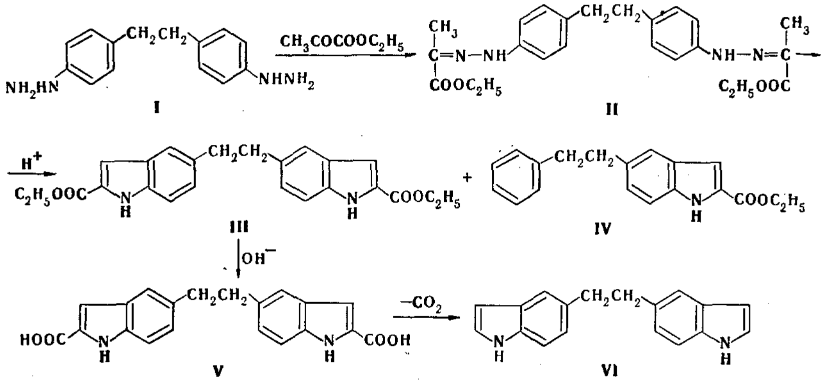
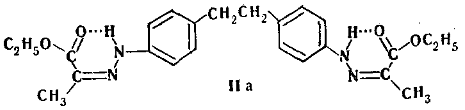
A 2,2'-diethoxycarbonyl derivative of a new bisindole system, viz., 1,2-(5,5'-diindolyl)ethane, was obtained by cyclization of ethyl pyruvate sym-4,4'-diphenyleneethanedihydrazone. 5-(β-Phenylethyl)-2-ethoxycarbonylindole was also isolated in very low yield from the reaction products. Saponification of the 2,2'-diethoxycarbonyl derivative gave the corresponding dicarboxylic acid, the thermal decarboxylation of which leads to the formation of 1,2-(5,5'-diindolyl)ethane. The syn,syn and anti,anti forms of ethyl pyruvate sym-4,4'-diphenyleneethanedihydrazone were also obtained and characterized.

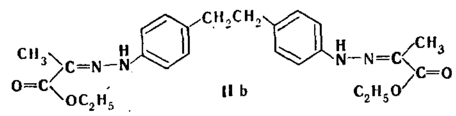
Continuing our research on bisindoles we obtained a new key bifunctional compound, viz., 1,2-(5,5'-diindolyl)ethane (VI) via the scheme



Dihydrazone II was obtained through the corresponding dihydrazine in ~ 50% yield based on the starting diamine. Product II was found to be a mixture of three stereoisomers, from which the syn,syn and anti,anti forms (IIa,b) were isolated by means of column chromatography. According to the PMR spectral data, the mixture also contains the syn,anti isomer (IIc), but we were unable to isolate it in pure form.

A shift of the signal of the proton of the NH group to significantly weaker field (11.9 ppm) as compared with the signal of this proton in the spectrum of anti,anti isomer IIb (7.6 ppm) is observed in the PMR spectrum of isomer IIa in $CDCl_3$; this is due to the participation of the imino proton in the formation of an intramolecular hydrogen bond, which is possible in the case of a syn orientation of the substituent.


IIa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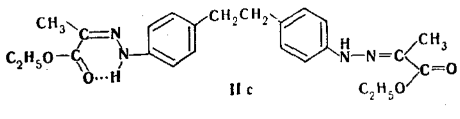
IIc

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*See [1, 2] for Communications 8 and 9.

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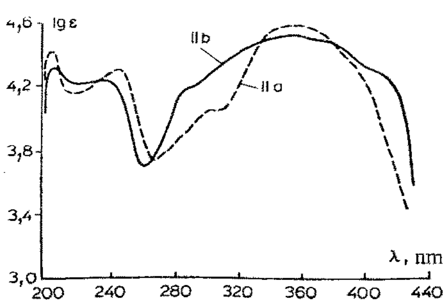


Fig. 1

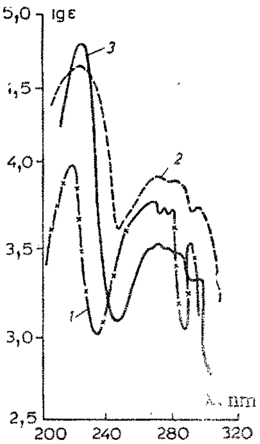


Fig. 2

Fig. 1. UV spectra of ethyl pyruvate sym-4,4'-diphenyleneethane-dihydrazones in ethanol: IIa) syn,syn form; IIb) anti,anti form.

Fig. 2. UV spectra in ethanol: 1) indole; 2) di(5-indolyl)methane; 3)1,2-(5,5'-diindolyl)ethane (VI).

TABLE 1. Parameters of the PMR Spectra of III–VI

Compound	Chemical shifts, δ, ppm									SSCC, J, Hz
	1H	2H	3H	4H	6H	7H	CH_2CH_3	CH_3CH_2	$(CH_2)_2$	
III (d_6-acetone)	9,3 br s	—	7,04 dd	7,45 dd	7,14 dd	7,40 m	4,32 q	1,35 t	3,03 s	$J_{1,3}=2{,}1$; $J_{3,7}=0{,}9$; $J_{4,6}=1{,}6$; $J_{4,7}=0{,}8$; $J_{6,7}=8{,}5$; $J_{CH_3CH_2}=7{,}1$
IV[a] (d_6-acetone)	9,4 br s	—	7,06 dd	7,46 dd	7,14 dd	7,42 d	4,32 q	1,35 t	2,96 br s	$J_{1,3}=2{,}3$; $J_{3,7}=1{,}0$; $J_{4,6}=1{,}4$; $J_{4,7}=0{,}8$; $J_{6,7}=8{,}2$; $J_{CH_2CH_3}=7{,}1$
V[b] (d_6-DMSO), 70°	11,2 br s	—	6,94 d	7,38 d	7,06 dd	7,32	—	—	2,97 s	$J_{4,6}=1{,}7$; $J_{6,7}=8{,}7$
VI (d_6-DMSO), 70°	10,6 br s	7,18 dd	6,27 m	7,30 d	6,91 dd	7,23 dd	—	—	2,95 s	$J_{1,3}=2{,}0$; $J_{1,2}=2{,}4$; $J_{2,3}=2{,}9$; $J_{3,7}=0{,}7$; $J_{4,6}=1{,}7$; $J_{6,7}=8{,}3$

[a] $\delta_{C_6H_5}$ ~ 7.2 ppm. [b] The COOH group gives a broad exchange signal.

A difference in the position of the characteristic absorption bands of the NH and CO groups is observed in the IR spectra of IIa,b (in mineral oil). For syn,syn isomer IIa the absorption band of the NH group is noted at 3260 cm^{-1}, whereas it is observed at 3340 cm^{-1} for anti,anti isomer IIb; the absorption band of the CO group is observed at 1690 and 1740 cm^{-1}, respectively. The shift of the characteristic absorption bands of the NH and CO groups in the spectrum of syn,syn isomer IIa to the lower-frequency region with respect to the analogous bands in the spectrum of anti,anti isomer IIb confirms the existence of an intramolecular hydrogen bond [3].

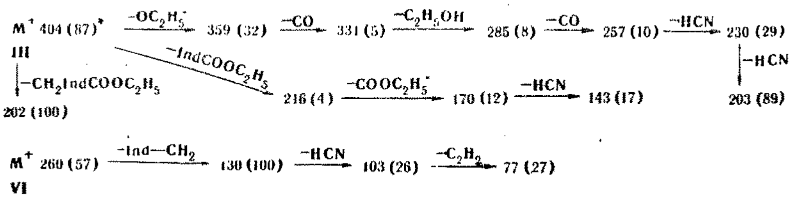
A bathochromic shift of the long-wave absorption maximum and an increase in the absorption intensity for syn,syn isomer IIa, which also indicate the existence of an intramolecular hydrogen bond [4], are observed in the UV spectra (Fig. 1) recorded in ethanol.

Thus the data from the IR, UV, and PMR spectra confirm the syn,syn and anti,anti configurations of the indicated isomers.

The cyclization of the mixture of dihydrazones II was carried out by means of ethyl polyphosphorate. In addition to III, 5-(β-phenylethyl)-2-ethoxycarbonylindole (IV) is formed in 2% yield in the cyclization. We observed the formation of similar reaction products in other cases also [1, 5]; this is explained by splitting out of one hydrazono group as a consequence of decomposition of the azo form of the hydrazone at higher temperature.

The saponification of diester III gave dicarboxylic acid V, the thermal decarboxylation of which leads to the formation of 1,2-(5,5'-diindolyl)ethane (VI).

The structures of III-VI are confirmed by the PMR spectral data (see Table 1). The mass-spectrometrically determined molecular masses of products III and VI correspond to the calculated values, and the character of the subsequent fragmentation does not contradict the proposed structures. The fragmentation of the indicated products under the influence of electron impact proceeds in the same way as the fragmentation of indole and the other bisindoles that we have obtained [1, 5]:



EXPERIMENTAL

Monitoring of the course of the reaction and the purity of the compounds and the determination of the R_f values were accomplished on plates with a fixed layer of Silufol UV-254 silica gel. Silica gel samples with particle sizes ranging from 100 to 250 μm were used as the sorbents. The UV spectra of solutions of the compounds in ethanol were recorded with a Specord spectrophotometer. The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-20 spectrometer. The mass spectrum was recorded with an MKh-1303 spectrometer by direct introduction of the sample into the ion source at an ionizing-electron energy of 50 eV. The PMR spectra were recorded with a Varian CFT-20 high-resolution spectrometer; the chemical shifts were measured relative to tetramethylsilane as the internal standard with an accuracy of 0.01 ppm, while the spin–spin coupling constants (SSCC) were measured with an accuracy of 0.1 Hz.

Ethyl Pyruvate sym-4,4'-Diphenyleneethanedihydrazone (II). A warm (40-45°C) solution of 8.8 g (0.028 mole) of symmetrical 4,4'-dihydrazinodiphenylethane (I) hydrochloride in 300 ml of water was added gradually with stirring to a mixture of 7 g (0.06 mole) of ethyl pyruvate in 20 ml of ethanol and 20 ml of water, during which the solution became turbid, and a yellow crystalline precipitate formed. The mixture was stirred for 1 h, after which it was filtered, and the precipitate was washed with water and dried to give 5.8 g (48%) of a product with mp 156-158°C. Found: C 65.5; H 6.8; N 12.7%. $C_{24}H_{30}N_4O_4$. Calculated: C 65.7; H 6.8; N 12.8%.

For separation of the stereoisomers a 5.8-g sample of hydrazone II was passed through a column filled with silica gel with elution by means of benzene–petroleum ether (2 : 1). The first fraction was worked up to give 0.8 g (14%) of the syn,syn form (IIa) with mp 145-146°C and R_f 0.82 [benzene–acetone (5 : 1)]. IR spectrum: 3260 (NH) and 1690 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 209 (4.56), 245 (4.33), and 204 nm (4.45). PMR spectrum (in chloroform): 11.9 (s, NH), 7.0 (m, Ar), 2.12 (s, CH_3), 4.24 (q, CH_2CH_3), 1.33 (t, CH_3CH_2), and 2.80 ppm (s, $-CH_2CH_2-$); $J_{CH_3CH_2}$ = 7.1 Hz. Subsequent elution of the mixture of hydrazones II with benzene gave 2.0 g (34%) of a mixture of three isomers. The next fraction was the anti,anti form (IIb), which was isolated with benzene–ether (2 : 1) to give 2.4 g (41%) of a product with mp 203-204°C and R_f 0.47 [benzene–acetone (5 : 1)]. IR spectrum: 3340 (NH) and 1740 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 206 (4.36), 241 (4.27), 298.5 (4.19) shoulder, 350.9 (4.51), and 393 nm (4.41) shoulder. PMR spectrum (in chloroform): 7.6 (s, NH), 7.0 (m, Ar), 2.07 (s, CH_3), 4.28 (q, CH_2CH_3), 1.36 (t, CH_3CH_2), and 2.82 ppm (s, $-CH_2CH_2-$); $J_{CH_3CH_2}$ = 7.2 Hz.

1,2-(2,2'-Diethoxycarbonyl-5,5'-diindolyl)ethane (III). A 14.9-g (0.034 mole) sample of hydrazine II was mixed with 150 g of ethyl polyphosphorate, and the mixture was heated slowly with stirring to 80-85°C, during which a temperature jump to 110°C was observed. The reaction mixture was maintained at 90-95°C for 30 min, after which it was cooled and poured into cold water. The precipitate was removed by filtration, washed with water, and dried. Compounds III and IV were separated with a column filled with silica gel by elution with chloroform–carbon tetrachloride (4 : 1). The yield of ester III, with mp 241-242°C and R_f 0.71 [benzene–acetone (5 : 1)], was 6 g (46%). IR spectrum: 3340 (NH) and 1700 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 210 (3.50) shoulder, 225 (3.59), 234 (3.55) shoulder, and 297 nm (3.65). Found: C 70.9; H 6.2; N 7.0%; M^+ 404. $C_{24}H_{24}N_2O_4$. Calculated: C 71.2; H 5.9; N 6.9%; M 404.

5-(β-Phenylethyl)-2-ethoxycarbonylindole (IV). Compound IV was formed as a side product in the synthesis of III. It was purified with a column by means of elution with chloroform–carbon tetrachloride (2 : 1) to give 0.2 g (2%) of a product with mp 136-137°C and R_f 0.66 [benzene–acetone (5 : 1)]. IR spectrum: 3335 (NH) and 1695 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 211 (4.08), 222 (4.06), 235.3 (3.98) shoulder, and 298.5 nm (3.92). Found: C 77.6; H 6.7; N 4.6%. $C_{19}H_{19}NO_2$. Calculated: C 77.8; H 6.5; N 4.8%.

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*Here and subsequently, the m/z values are presented; the values in parentheses are the relative intensities of the ion peaks in percent relative to the maximum peak.

1,2-(2,2'-Dicarboxy-5,5'-diindolyl)ethane (V). A suspension of 1.5 g (0.003 mole) of ester III, 75 ml of ethanol, and 1.1 g (0.019 mole) of KOH was refluxed with stirring for 5-6 h, after which the solution was evaporated. The solid residue was dissolved in water, and the solution was cooled to 5-10°C and acidified with dilute HCl. Product V was removed by filtration, washed with water, and dried to give 1 g (85%) of a substance with mp 277-278°C and R_f 0.44 [ethyl acetate–ether (5 :1)]. IR spectrum: 3455 (NH) and 1710 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 208 (4.72) and 296 nm (4.42). Found: C 68.6; H 5.0; N 8.0%: $C_{20}H_{16}N_2O_4$. Calculated: C 68.9; H 4.8; N 8.0%.

1,2-(5,5'-Diindolyl)ethane (VI). A 1-g (0.002 mole) sample of acid V was heated at 275-295°C in a stream of argon. Compound VI was purified with a column filled with silica gel by elution with benzene–petroleum ether (5 :1). Erlich's solution gave a red coloration with VI. The yield of product with mp 158-159°C and R_f 0.64 [benzene–acetone (5 :1)] was 0.18 g (25%). IR spectrum: 3410 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 228 (4.81), 270 (3.52), 280 (3.51), 288 (3.50), and 296 nm (3.36) (Fig. 2). Found: C 83.1; H 6.3; N 10.7%; M^+ 260. $C_{18}H_{16}N_2$. Calculated: C 83.1; H 6.2; N 10.7%; M 260.

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REACTION OF FISCHER'S BASE WITH o-HYDROXYCINNAMALDEHYDES

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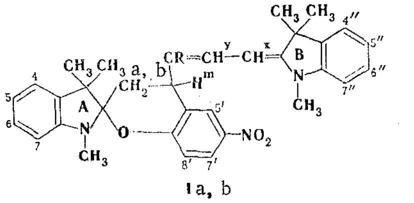
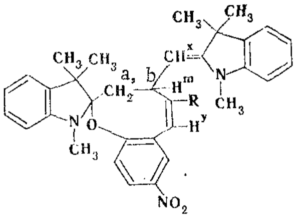
On the basis of a study of the PMR spectra and alternative synthesis it was established that the "dicondensed" products of the reaction of Fischer's base with o-hydroxycinnamaldehydes are not oxocine derivatives, as was previously assumed, but rather are bisindoline spirochromans that are identical to the products of the reaction of vinylogs of Fischer's base with salicylaldehydes.

We have recently reported [1] an unsuccessful attempt to synthesize indoline spirooxocines from vinylogs of Fischer's base and salicylaldehydes. The products of the reaction of these substances were found to be "dicondensed" spirochromans; in particular, Ia was obtained from 5-nitrosalicylaldehyde and 1,3,3-trimethyl-2-(2-butenyl-1-idene)indoline.



Ia, b



II a, b

Ia $R=CH_3$; b $R=H^z$; II a $R=H^z$; b $R=CH_3$

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