BISINDOLES.
30.* ACID CONDENSATION OF BISINDOLES WITH AROMATIC ALDEHYDES AND THE SYNTHESIS OF NEW INDOLE-CONTAINING POLYAMINES

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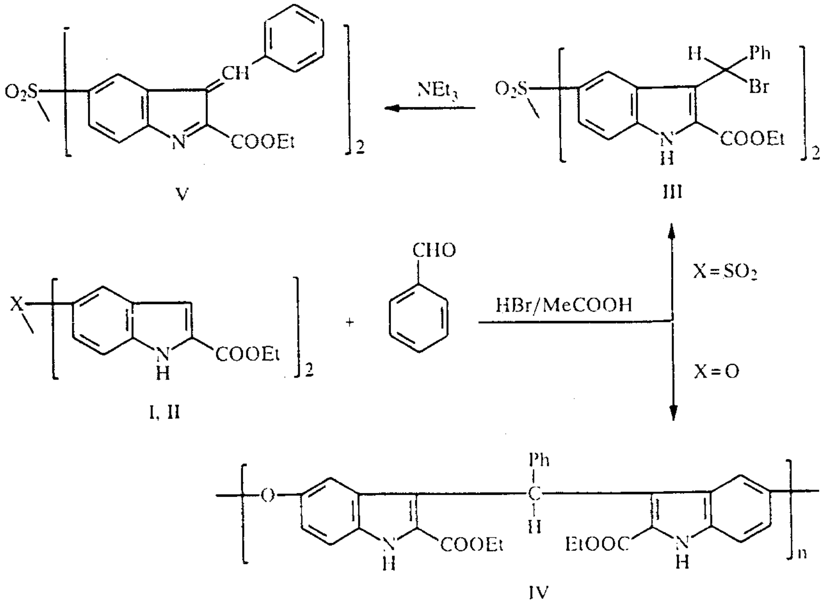
Reaction of 2,2′-diethoxycarbonyl-bis(5-indolyl)sulfone with benzaldehyde gave an active dibromide – 2,2′-diethoxycarbonyl-3,3′-di(bromobenzyl)bis(5-indolyl)sulfone; derivatives of di(bisindolyl)phenylmethane have been prepared by condensation of 2,2′-diethoxycarbonyl-bis(N-methyl-5-indolyl)sulfone with benzaldehyde and p-methoxybenzaldhyde. On the basis of the active dibromides, for the first time polyamines have been prepared which have indole rings in the macromolecular chain where the bonding of the indolyl fragments takes place via the β-position.

In the search for routes to polymers of different types having indole fragments in the macromolecular chain which, as a result, can be converted to polymeric analogs of biologically active substances, our attention was drawn to the previously reported [2, 3] 2,2′-diethoxy-carbonyl-bis(5-indolyl) oxide (I) and 2,2′-diethoxycarbonyl-bis(5-indolyl)sulfone (II). The existence of unsubstituted β-positions in compounds I and II gave rise to the possibility, by analogy with [4, 5], of preparing β-substituted compounds which could act as monomers in the preparation of macromolecular compounds.

We have studied the condensation of benzaldehyde with sulfone (II) and oxide (I) in acetic acid saturated with HBr. A reaction based on sulfone II gave 2,2′-diethoxycarbonyl-3,3′-di(bromobenzyl)bis(5-indolyl)sulfone (III), and on oxide I, a polycondensation product IV with reduced viscosity 0.11 dl/g.



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*For communication 29, see [1].

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The formation of different reaction products III and IV from the diesters I and II can be explained by the different electronic characteristics of the bridging groups $-O-$ and $-SO_2-$ since quantum chemical calculations of bis(5-indolyl)-oxide and bis(5-indolyl)sulfone show that replacing the $-SO_2-$ group by oxygen results in a higher electron density at the β-position of the pyrrole ring [2, 3].

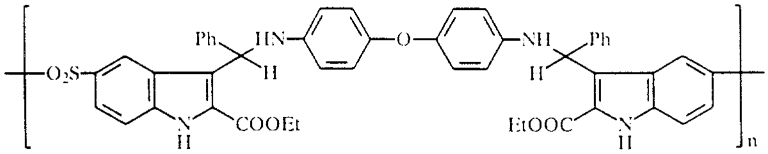
Thus, in the present case the direction of the reaction is determined by the nature of the bridging group in the bisindole. Increase in the electron density in the 3,3′ positions leads to the formation of a polymer and its reduction to a 3,3′-benzylidene derivative.

The dibromide III is a stable, easily crystallized compound. On melting, HBr separates. Under the action of triethylamine it loses two molecules of HBr and is converted into the yellow, highly reactive indolenin – 2,2′-diethoxycarbonyl-3,3′-dibenzylidenebis(5-indolyl)sulfone (V).

The IR spectrum of compound V shows no absorption bands in the 3490-3100 cm^{-1} region but there is a carbonyl absorption band shifted by 30 cm^{-1} to higher frequency in comparison with the initial ester II. Apparently, the presence of an NH group in compound II results in its association on account of the formation of intermolecular hydrogen bonds; this is not possible in compound V because of the absence of an NH group.

Compound V is a highly reactive compound. In air, it rapidly absorbs water.

The presence of a mobile halogen of benzhydryl type in compound III is responsible for its ability to react to react with different bisphenols and diamines. Thus, reaction of the dibromide III with diaminodiphenyl oxide in DMF in the presence of triethylamine with molar ratio 1:1:2 at 80°C yielded a polyamine VI with reduced viscosity 0.3 dl/g.

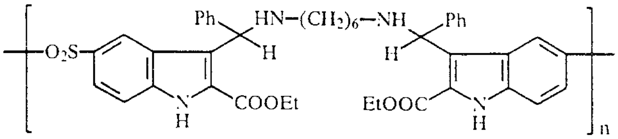


VI

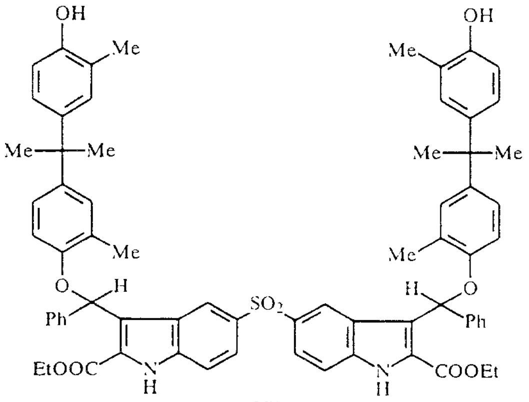
Thus, for the first time polyamines with indole fragments in the chain have been prepared in which the bonding of the indole fragments takes place via the β-position.

Reaction of dibromide III with hexamethylenediamine 2,2′-bis(3-methyl-4-hydroxyphenyl)propane gave the oligomer VII with reduced viscosity 0.04 dl/g and bis[2-ethoxycarbonyl-3-α-(p-hydroxy-m-methylphenylisopropyl-o-methylphenoxy)-benzyl-5-indolyl]sulfone (VIII).

The existence of p-hydroxyphenyl groups as the terminal groups of compound VIII is supported by its ability to dissolve in aqueous NaOH. In the IR spectrum of compound VIII a broad absorption band is observed in the 3500-3200 cm^{-1} region which appears to be an overlap of the bands for hydroxyl and indole NH with one another. Elemental analysis data also confirm the proposed elemental composition of compound VIII.



VII

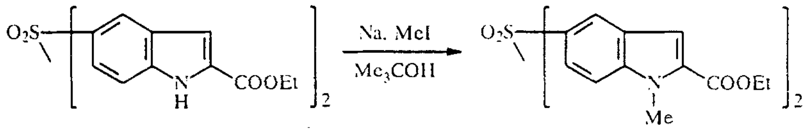


VIII

In the PMR spectra of compounds VI and VII broad signals are observed for the protons which is characteristic for macromolecular compounds. Thus, the signals at 11.9 and 5.92 ppm are assigned respectively to NH and methyl protons. Proton signals for the CH_2 and CH_3 groups appear at 4.34; 4.37 and 1.26; 1.31 ppm, respectively. Signals at 8.33 and 8.62 ppm are assigned to 4-H protons, the remaining aromatic protons giving signals in the 7.12-7.62 ppm region. Signals for the NH (amine) protons are absent from the spectrum on account of the high exchange rate of NH $\rightleftarrows$ ND. In the spectrum of compound VII proton signals for the $(CH_2)_6$ group are observed at 3.0; 1.16 ppm.

From the work of [6-8] it follows that the reaction of 2-ethoxycarbonylindoles with aromatic aldehydes on heating in acid media proceeds with the formation of di(2-ethoxycarbonyl-3-indolyl)phenylmethanes and that N-methylated indoles enter readily into this condensation.

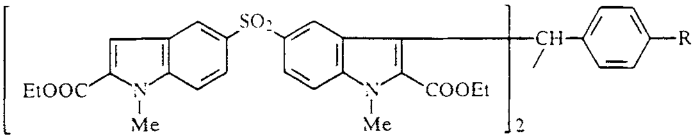
The synthesis of 2,2′-diethoxycarbonyl-bis(N-methyl-5-indolyl)sulfone (IX) takes place according to the scheme:



II IX

In the IR spectrum of compound IX, in contrast to the sulfone II starting material, the NH absorption band is absent; in the UV spectrum of compound IX bands are observed at 246 (br) (4.62), 260 (4.70), 305 (4.36), and 314 (br) nm (4.31).

It has been established that acid condensation of compound IX with p-methoxybenzaldehyde and with benzaldehyde takes place mainly with the formation of p-methoxyphenyl-di-3-[1-methyl-2-ethoxycarbonyl-5-(1-methyl-2-ethoxycarbonyl-5-indolylsulfonyl)indolyl]methane (X) and its phenyl analog XI, respectively:



X, XI

X R = OMe, XI R = H

Both the small nucleophilicity of the β-position of the initial diester and steric hindrance could be reasons for the restricted chain growth. However, on reacting compound IX with formaldehyde in a mixture of CH_3COOH and 1% HCl no polymer formation is observed. Thus, the principal reason for this process is the inductive effect of the SO_2 group which reduces the activity of the β-position of the indole ring of the diester IX.

EXPERIMENTAL

The progress of the reactions was monitored, and the purity of the compounds and their R_f values determined, on Silufol UV-254 TLC plates. IR spectra were run on a UR-20 instrument as KBr disks and UV spectra on a Specord spectrophotometer in tetrahydrofuran. A Varian CFT-20 instrument was used to obtain PMR spectra at a working frequency of 80 MHz in DMSO solution with TMS as internal standard.

Elemental analysis data were in agreement with the calculated.

The purity of the original reactants and solvents was checked by known methods; their physicochemical constants were in agreement with literature data.

2,2′-Diethoxycarbonyl-3,3′-dibromobenzyl-bis(5-indolyl)sulfone (III, $C_{36}H_{30}N_2Br_2O_6S$). To 4.4 g (10 mmole) sulfone (II) was added 2.12 g (20 mmole) benzaldehyde and 10 ml acetic acid saturated with hydrogen bromide. This was heated at bp 10 min until al the initial material had dissolved; the sulfone was precipitated on cooling and was filtered off, washed with acetic acid and then with the minimum amount of ether and dried. Yield 0.62 g (80%), mp 255-256°C (with evolution of HBr). IR spectrum (cm^{-1}): 3380 (NH), 1730, 1720 (C=O). UV spectrum (λ_{max} nm ($\log \varepsilon$)): 222 (4.59), 256 (4.61), 310 (4.33). PMR spectrum: 10.4 (NH, br.s), 8.21 (4H, br.s), 7.58 (CH, s), 7.5-7.2 (Ar), 4.36 (CH_2, q), 1.36 (CH_3, t), $J_{CH_2CH_3}$ = 7.1 Hz.

Polymer (IV, $C_{29}H_{24}N_2O_5$) Based on 2,2′-Diethoxycarbonyl-bis(5-indolyl) Oxide and Benzaldehyde. This was prepared under conditions analogous to those for the preparation of the dibromide III using 3.32 g (10 mmole) 2,2′-diethoxycarbonyl-bis(5-indolyl) oxide (I). The polymer was precipitated by petroleum ether. Yield 1.7 g (35%), decomp. 400°C, η_{red} 0.11 dl/g (0.5% in DMF, 25°C). IR spectrum (cm^{-1}): 3400 (NH), 1720, 1710 (C=O).

2,2′-Diethoxycarbonyl-3,3′-dibenzylidene-bis(5-indolyl)sulfone (V, $C_{36}H_{28}N_2O_6S$). An excess of triethylamine was added to a suspension of 9.77 g (1 mmole) sulfone III in benzene. The precipitated triethylamine hydrobromide was filtered off. Sulfone V was precipitated from the filtrate with petroleum ether in the form of yellow crystals which were filtered off, washed with ether and dried in vacuum. Yield 0.2 g (25%), decomp. 125-126°C. IR spectrum (cm^{-1}): 1720 (C=O), 1600 (Ar).

Method for the Preparation of Polyamines. To a solution of 1 mmole dibromide III and 1 mmole diamine in DMF was added 2 mmole triethylamine (the concentration of the reactants was 0.6 mole/liter), and the mixture stirred 4 h at 80°C. The polymer was precipitated with water, washed, and dried. In this way were prepared:

Polyamine (VI, $C_{48}H_{40}N_4O_7S$) Based on Dibromide III and Diaminodiphenyl Oxide. Yield 86%. η_{red} 0.3 dl/g (0.5% in DMF, 25°C). IR spectrum (cm^{-1}): 3450-3230, 1480(NH), 1720 (C=O). PMR spectrum (ppm): 11.9 (1H, br.s), 8.33 (4H, s), 7.6 (6H, s), 7.5-7.2 (Ar), 6.58 (Ph–O–Ph, s), 5.92 (CH, s), 4.34 (CH_2, q), 1.26 (CH_3, t).

Oligomer (VII, $C_{42}H_{44}N_4O_6S$) Based on Dibromide III and Hexamethylenediamine. Yield 89%, decomp. 248-250°C. η_{red} 0.04 dl/g (0.5% in DMF, 25°C). IR spectrum (cm^{-1}): 3300, 3200, 1480 (NH), 1730 (C=O). UV spectrum (λ_{max} nm (log ε)): 222 (4.43), 263 (4.68), 309 (4.38). PMR spectrum (ppm): 11.9 (1H, br.s), 8.62 (4H, br.s), 7.6-7.1 (Ar), 5.92 (CH, s), 4.37 (CH_2–Et, br.s), 1.31 (CH_2–Et, br.s), 3.0, 1.16 ($-N(CH_2)_6-$, br.s) (ND ⇄ NH).

Bis[2-ethoxycarbonyl-3-α-(p-hydroxy-m-methylphenoxy)benzyl-5-indolyl]sulfone (VIII, $C_{70}H_{68}N_2O_{10}S$). This was prepared in a similar manner to polyamine VI from 1 mmole dibromide III and 1 mmole bis-3-methyl-4-hydroxyphenylpropane. Yield 80%, decomp. 149-150°C. IR spectrum (cm^{-1}): 3500-3200 (OH, NH), 1720 (C=O), 1280 (–C–O). UV spectrum (λ_{max} nm (log ε)): 222 (4.87), 232 (4.88), 260 (4.84), 309 (4.55).

2,2′-Diethoxycarbonyl-bis(N-methyl-5-indolyl)sulfone (IX, $C_{24}H_{24}N_2O_6S$). Sodium metal (0.14 g (6 mmole)) was dissolved in 50 ml **tert-butanol** at bp and 1.32 g (3 mmole) sulfone II added. After 50 min, 0.73 g (0.12 mmole) CH_3I was added and boiling continued for 5 h. The reaction mixture was poured into water, and the precipitate filtered off and recrystallized from 50% aqueous methanol. Yield 0.7 g (50%), mp 155-156°C. IR spectrum (cm^{-1}): 1720 (C=O). UV spectrum (λ_{max} nm (log ε)): 246 (br) (4.62), 260 (4.70), 305 (4.36), 314 (br) (4.31).

p-Methoxyphenyl-di-3-[1-methyl-2-ethoxycarbonyl-5-(1-methyl-2-ethoxycarbonyl-5-indolylsulfonyl)indolyl]-methane (X, $C_{56}H_{54}N_4O_{13}S_2$). This was prepared in a similar manner to dibromide III from 0.47 g (1 mmole) 2,2′-diethoxycarbonyl-bis(N-methyl-5-indolyl)sulfone (IX) and 0.27 g (2 mmole) p-methoxybenzaldehyde. Yield 0.32 g (30%), decomp. 150-152°C. IR spectrum (cm^{-1}): 1730 (C=O). UV spectrum (λ_{max} nm (log ε)): 223 (4.83), 263 (4.96), 294 (br) (4.55), 307 (4.59).

Phenyldi-3-[1-methyl-2-ethoxycarbonyl-5-(1-methyl-2-ethoxycarbonyl-5-indolylsulfonyl)indolyl]methane (IX, $C_{55}H_{52}N_4O_{12}S_2$). This was prepared in a similar manner to the dibromide III from 0.47 g (1 mmole) 2,2′-diethoxycarbonyl-bis(N-methyl-5-indolyl)sulfone (IX) and 0.21 g (2 mmole) benzaldehyde. Yield 0.36 g (35%), mp 209-210°C. IR spectrum (cm^{-1}): 1725 (C=O). UV spectrum (λ_{max} nm (log ε)): 222 (4.82), 259 (4.81), 265 br (4.79), 309 (4.15).

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