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Condensation Polymers Containing Indole Derivatives

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ABSTRACT

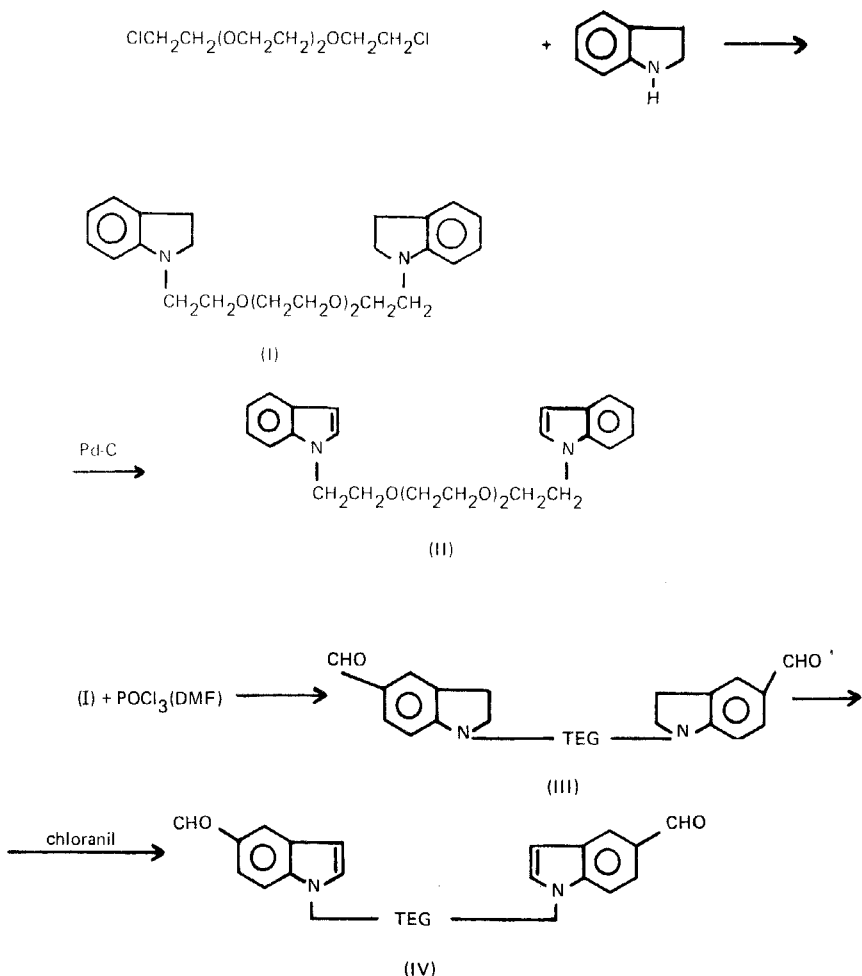
Indole-containing bifunctional monomers (diacids, dialcohols, and dialdehydes) were synthesized by using as the basic nucleus two indoles attached by a tetraethylene glycol chain. These monomers were used for the preparation of polyesters, polyamides, and polyazomethines.

As part of a program to investigate the effect of the attachment of biologically active compounds to polymers [1-4], we have synthesized condensation polymers containing indole derivatives. Many indole derivatives have important biological activities, e. g., indoleacetic acid is a plant growth hormone, while tryptamine derivatives possess a variety of pharmacological activities.

Bifunctional indole derivatives were prepared by attaching two indole derivatives by a short-chain poly(ethylene oxide) (tetraethylene glycol) through the nitrogen. Tetraethylene glycol was converted by thionyl chloride to β, β' -di-(β -chloroethoxy)diethyl ether which was reacted with indoline to yield the bisindoline derivative (I). I was dehydrogenized on heating in β -methylnaphthalene in the presence of 10% Pd/C to give the corresponding indole derivative (II). Reacting

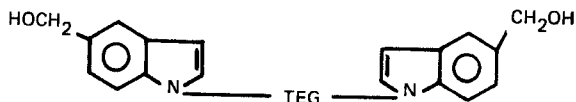
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the diindoline derivative (I) with $\text{POCl}_3(\text{DMF})$ [5] gave the dialdehyde III. Aromatization of III with chloranil in boiling xylene yielded the corresponding diindole derivative IV in 40% yield:

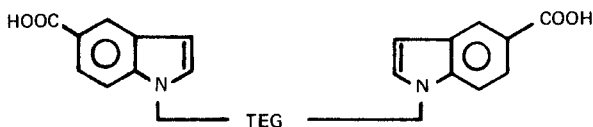


where TEG represents $\text{CH}_2\text{CH}_2\text{O}(\text{CH}_2\text{CH}_2\text{O})_2\text{CH}_2\text{CH}_2$. Aromatization with Pd/C could not be carried out, since it leads to simultaneous decarbonylation [6]. On the other hand, dehydrogenation cannot be performed before formylation, since formylation will preferentially proceed to position 3 and not 5. The dialcohol derivative (V) was prepared by either reduction with LiAlH_4 of the dialdehyde IV or

preferentially by reduction of the indoline derivative III and aromatization of the dialcohol by Pd/C in boiling xylene, which gives a better yield than aromatization with chloranil.



The diacid VI was prepared by oxidation of the dialdehyde IV. Mild oxidation with Ag_2O under basic conditions [7] was not effective, and the oxidation was carried out by potassium permanganate in acetone-water [8].

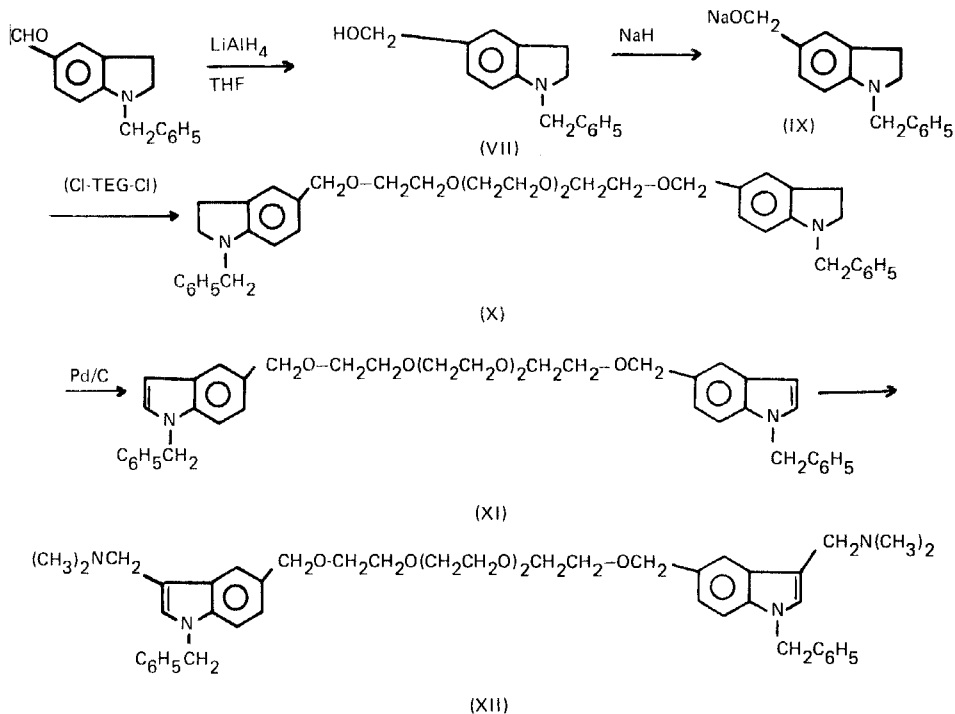


Other bifunctional indole intermediates, having two indole groups connected together at the 5,5' position by a tetraethylene glycol chain were prepared starting with 5-formyl-N-benzylindoline (VII).

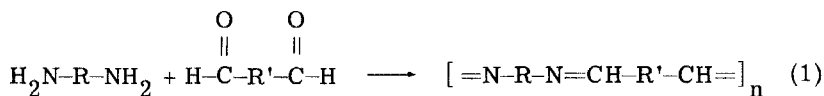
5-Formyl N-benzylindoline (VII) [1] was reduced by LiAlH_4 to 5-(hydroxymethyl)-N-benzylindoline (VIII) which was converted to X by reaction of the alkoxide derivative IX with β,β' -di(β -chloroethoxy)-diethyl ether. X was dehydrogenized on heating in p-cymene with 10% Pd/C to give the corresponding indole derivative XI which was converted to the corresponding digramine derivative XII on heating with formaldehyde and dimethylamine (Mannich reaction).

Preparation of polyesters from the diacids or the dialcohols was carried out by heating equimolar amounts of the diacid and dialcohol first at atmospheric pressure and then under vacuo. Similarly, polyamides were prepared by heating the diacids with diamines. Besides the indole containing difunctional derivatives, adipic acid and hexamethylene diamine were used as starting materials for the condensation polymerization.

The dialdehyde IV, was utilized as starting material for the preparation of azomethines.



The reaction between a dialdehyde and diamine to yield a poly-schiff base (poly-Schiff base) [Eq. (1)] usually yields polymers having a low degree of polymerization [9, 10].



Marvel and Bonsignore [11] reacted *o*-phenylenediamine and methylene bis(5-salicylaldehyde) in a water-ethyl acetate emulsion in the presence of sulfuric acid as catalyst. A polymer was obtained in 92% yield having $\eta_{\text{inh}} = 0.23$. However in our case, reacting the dialdehyde (VIII) with *p*-phenylenediamine or hexamethylenediamine in a chloroform-water emulsion in the presence of poly(vinyl alcohol) as emulsifier and a drop of concentrated sulfuric acid did not yield to significant polymerization, and the starting material was isolated. Reaction in boiling ethanol [12] or dimethylformamide [13] did not yield satisfactory yields, and the polymerization was finally carried out in bulk [14] by heating equimolar amounts of the reactants. Polymers having melting points above 300°C were obtained. The

polymer with p-phenylenediamine dissolves slowly in chloroform and had $[\eta] = 0.16$ dl/g, probably due to a low degree of polymerization. Both NMR and IR of the polymers show the azomethine structure.

Thermal gravimetric analysis of the polyazomethine obtained from p-phenylene diamine carried out under nitrogen and heating rate ($6^\circ/\text{min}$) showed the polymer to be stable up to 250°C , losing 45% of its weight between 250 and 450°C .

EXPERIMENTAL

NMR spectra were taken on Varian T60 and IR on Perkin-Elmer 457 instruments.

β, β' -Di(β -chloroethoxy)diethyl ether was prepared according to Pederson [15].

β, β' -Di-[β -(N,N' diindoline)ethoxy] diethyl Ether (I)

I was prepared in analogy with the preparation of N-benzylindoline [16] by reaction of 1 mole β, β' -di(β -chloroethoxy)diethyl ether with 2 mole indoline. At the end of the reaction, excess reactants were distilled off in vacuo, and the residue was steam-distilled. The fraction that remained was taken up in ether, dried (Na_2SO_4), and the ether was distilled off. The product was purified by chromatography on a silica gel column by using CCl_4 as eluent and then by preparative thin layer chromatography (TLC) on aluminum oxide G (Merck) with the use of chloroform; yield 71%.

NMR (CDCl_3) showed $\delta = 3.48$ (s, 16, CH_2OCH_2); 3.0(m, 4, $\text{CH}_2\text{CH}_2\text{N}$); 6.9(m, 4, C_6H_4).

IR (neat) showed a band at 1125 cm^{-1} (CH_2OCH_2). The ultraviolet spectrum in EtOH showed maxima at 257 ($\epsilon = 1.86 \times 10^4$) and 306 nm ($\epsilon = 4.2 \times 10^3$).

ANAL. Calcd. for $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_3$: C, 72.70%; H, 8.13%; N, 7.06%. Found: C, 72.74%; H, 8.10%; N, 7.21%.

β, β' -Di-[β -(N,N'-diindoline-5,5' diformyl)ethoxy]-diethyl Ether (III).

The formylation with POCl_3 and DMF was carried out as described before [1]. The oily product was extracted with chloroform, which was dried and distilled off. The residue was purified by TLC on aluminum oxide by using chloroform or benzene-ethanol (9:1); yield 63%.

NMR (CDCl_3) showed $\delta = 2.80$ (m, 8, $\text{CH}_2\text{CH}_2\text{N}$), 3.48 (m, 16, $\text{CH}_2\text{CH}_2\text{O}$); 9.60 (s, 2, CHO).

The IR spectrum (neat) showed bands at 1670 cm^{-1} (CHO) and 1100 cm^{-1} (CH_2OCH_2). The ultraviolet spectrum in (EtOH) showed maxima at ($\epsilon = 1.72 \times 10^4$) and 357 nm (4.95×10^4).

ANAL. Calcd for $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}$: C, 69.01%; H, 7.13%; N, 6.19%. Found: C, 68.84%; H, 7.01%; N, 6.14%.

β, β' -Di-[β -(N,N'-diindolyl-5,5'-diformyl)ethoxy]-diethyl Ether (IV)

III (2.26 g, 0.005 mole) was dissolved in xylene (25 ml), chloranil (1.35 g, 0.0055 mole) was added, and the solution was heated under reflux for 16 hr. The mixture was filtered, washed with dilute NaOH, water, 15% HCl, and water, and dried over MgSO_4 . The solvent was distilled off in vacuo, and the residual oil was purified on TLC on silica gel (Merck, PF 254) by using chloroform-96% acetic acid (95:5); yield, 0.9 g (40%).

The NMR (CDCl_3) showed $\delta = 6.40$ (d, 2, Ph-CH=).

The IR spectrum (neat) showed bands at 1665 (CHO) and 1100 cm^{-1} (CH_2OCH_2). The ultraviolet spectrum in EtOH showed a maximum at 254 nm ($\epsilon = 6.07 \times 10^3$).

ANAL. Calcd for $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_5$: C, 69.63%; H, 6.29%; N, 6.25%. Found: C, 69.57%; H, 6.20%; N, 6.01%.

β, β' -Di-[β -N,N'-Diindolyl-5,5'-hydroxymethyl)-ethoxy]-diethyl ether (V)

The dialdehyde (IV) was reduced by LiAlH_4 in THF as described for VIII. A yellowish oil was obtained in 90% yield.

NMR (CDCl_3) showed $\delta = 3.0$ (m, 8, $\text{CH}_2\text{CH}_2\text{N}$); 3.5 (d, 16, CH_2OCH_2); 4.35 (s, 4, OCH_2).

The IR spectrum (neat) showed bands at 3440 cm^{-1} (OH) and 1100 cm^{-1} (CH_2OCH_2). The ultraviolet spectrum (EtOH) showed a maximum at 239 nm ($\epsilon = 2.41 \times 10^3$).

ANAL. Calcd for $\text{C}_{26}\text{H}_{32}\text{N}_2\text{O}_5$: C, 69.0%; H, 7.1%; N, 6.2%. Found: C, 67.0%; H, 7.4%; N, 6.4%.

β, β' -Di-[β -(N,N'-diindolyl-5,5' dicarboxy)ethoxy]-diethyl Ether (VI)

To a solution of dialdehyde (IV) (0.56 g, 1.25×10^{-3} mole) in acetone (4 ml) a solution of potassium permanganate (0.395 g, 2.5×10^{-3} mole) in water (1.5 ml) and acetone (10 ml) was added with stirring at room temperature. The mixture was stirred for 3 hr, filtered, the acetone was evaporated, and the aqueous solution was concentrated to half its volume and acidified to pH 1. The diacid separated as an oil which was taken up in chloroform and extracted by dilute NaOH.

The solution was acidified to pH 1, the acid taken up in chloroform, and recovered on evaporation of the chloroform. The diacid was purified by TLC on silica gel by using chloroform-96% acetic acid (95:5); yield, 0.29 g (49%).

The IR spectrum (neat) showed a band at 1680 cm^{-1} (COOH). The ultraviolet spectrum (EtOH) showed maxima at 245 nm ($\delta = 1.96 \times 10^4$) and 285 nm (4.68×10^3).

ANAL. Calcd for $\text{C}_{26}\text{H}_{28}\text{N}_2\text{O}_7$: C, 64.99%; H, 5.87%; N, 5.83%. Found: C, 64.70%; H, 5.81%; N, 5.63%.

5-(Hydroxymethyl)-N-benzylindoline (VIII)

5-Formyl-N-benzylindoline (VII) [1] (2.37 g, 0.01 mole) was dissolved in dry THF (50 ml), and LiAlH_4 (0.46 g, 0.012 mole) was added in small portions during cooling in ice water. The mixture was stirred for 30 min at room temperature and heated under reflux for 1 hr. Excess water was added dropwise while cooling in ice and the mixture was extracted with chloroform. The chloroform extract was washed with water, dried over MgSO_4 and evaporated. The residue crystallized on cooling and was recrystallized from heptane; yield, 2.15 g (90%); mp 72°C .

The NMR (CDCl_3) showed $\delta = 2.18$ (-OH); 4.0 (s, 2, OCH_2); 4.3 (s, 2, NCH_2).

The IR spectrum (Nujol) showed a band at 3400 cm^{-1} (-OH). The ultraviolet spectrum (EtOH) showed maxima at 265 ($\epsilon = 1.03 \times 10^4$) and 304 nm ($\epsilon = 2.06 \times 10^3$).

ANAL. Calcd for $\text{C}_{16}\text{H}_{17}\text{NO}$: C, 80.30%; H, 7.16%; N, 5.85%. Found: C, 79.97%; H, 7.01%; N, 5.57%.

Indoline Derivative (X)

5-(Hydroxymethyl)-N-benzyl indoline (VIII) (0.478 g, 0.002 mole) in xylene (3 ml) was stirred for 10 min with sodium hydride (0.048 g, 0.002 mole) (55% dispersion in paraffin), and β, β' -di(β -chloroethoxy)-diethyl ether (0.231 g, 0.001 mole) in xylene (1 ml) was added, and the mixture was heated under reflux for 16 hr. The mixture was filtered and evaporated in vacuo. The residual oil was purified by TLC on aluminum oxide by using chloroform; yield, 0.42 g (65%).

The IR spectrum (neat) showed a band at 1090 cm^{-1} (CH_2OCH_2); no OH peak. NMR (CDCl_3) showed δ , 3.58 (m, 16, $-\text{CH}_2\text{OCH}_2$); 4.15 (s, 4, OCH_2); 4.32 (s, 4, NCH_2).

The ultraviolet spectrum (EtOH) showed maxima at 265 nm ($\epsilon = 3.38 \times 10^4$) and 300 nm ($\epsilon = 8.65 \times 10^{-3}$).

ANAL. Calcd for $\text{C}_{40}\text{H}_{48}\text{N}_2\text{O}$: C, 75.44%; H, 7.60%; N, 4.40%. Found: C, 75.20%; H, 7.30%; N, 4.17%.

Indole Derivative (XI)

X (0.64 g, 0.001 mole) was dissolved in *p*-cymene (10 ml) and heated under reflux with 10% Pd/C (0.05 g) for 40 hr. The solvent was evaporated in vacuo, and the residue purified on TLC on aluminum oxide by using benzene-ethanol (9:1) or chloroform; yield 0.58 g (92%).

NMR (CDCl₃) showed $\delta = 6.30$ (d, 2, Ph-CH=), no CH₂CH₂N peaks.

The IR spectrum showed a band at 1090 cm⁻¹ (CH₂OCH₂). The ultraviolet spectrum (EtOH) showed maxima at 216 nm ($\epsilon = 1.95 \times 10^4$) and 272 nm ($\epsilon = 5.7 \times 10^3$).

ANAL. Calcd for C₄₀H₄₄N₂O : C, 75.92%; H, 7.01%; N, 4.43%.
Found: C, 75.54%; H, 7.20%; N, 4.27%.

Digramine Derivative (XII)

The Mannich reaction on XI was carried out by reacting the compound with formaldehyde and dimethylamine as described before [2]. The product was purified by TLC on aluminum oxide by using benzene-ethanol (5:1); yield, 60%.

NMR (CDCl₃) showed $\delta = 2.16$ (s, 12, N(CH₃)₂); 3.50 (m, 16, CH₂OCH₂); 5.0 (s, 4, NCH₂);

The IR spectrum (neat) showed a band at 1090 cm⁻¹ (CH₂OCH₂). The ultraviolet spectrum (EtOH) showed maxima at 221 nm ($\epsilon = 3.9 \times 10^4$) and 277 nm (6.61×10^3).

ANAL. Calcd for C₄₆H₅₈N₄O₅ : C, 74.00%; H, 7.78%; N, 7.51%.
Found: C, 73.82%; H, 7.55%; N, 7.40%.

Polyesters

Equimolar amounts of the indole dialcohol (V) and adipic acid or the indole diacid (VI) were heated for 8 hr under nitrogen at 190°C at atmospheric pressure and then for 16 hr in vacuo (0.5 Torr). The polymers were dissolved in dichloromethane and washed with ethanol and chloroform, mp > 300°C.

The IR spectrum (Nujol) showed absorption bands at 1700-1730 cm⁻¹ (OCO).

Polyamide from VI and 1,6-hexamethylene diamine

Equimolar amounts of the indole diacid (VI) and 1,6-hexamethylenediamine were heated under nitrogen in an oil bath at 190°C for 8 hr, and then for 16 hr under vacuo. The polymer was allowed to stand overnight under dichloromethane and then washed with ethanol and chloroform, mp > 300°C.

Poly-Schiff Base from IV and 1,6-Hexamethylene-diamine

Equimolar quantities of the dialdehyde (IV) and 1,6-hexamethylene-diamine were heated under nitrogen in an oil bath at 100°C for 1 hr. The polymer was insoluble, mp > 300°C.

The IR spectrum (Nujol) showed a band at 1510 cm⁻¹ (C=N).

ANAL. Calcd for C₃₂H₄₀N₄O₃: C, 72.70%; H, 7.63%; N, 10.60%. Found: C, 72.41%; H, 7.61%; N, 10.45%.

Poly-Schiff Base from IV and p-Phenylenediamine

The reaction was carried out as before, the product was purified by solution in CHCl₃ and precipitation with petrol ether; mp > 300°C; [η] = 0.16 dl/g in chloroform at 30°C.

The NMR spectrum was not sharp, but the integration ratios were according to the structure of the polymer.

The IR spectrum (Nujol) showed a band at 1510 cm⁻¹ (C=N).

ANAL. Calcd for C₃₂H₃₂N₄O₃: N, 10.8%. Found: N, 11.6%.

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