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Synthesis of Indole Derivatives Attached to Poly(ethylene Oxides)

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ABSTRACT

N-Benzyl 5-, 6-, and 7-bromoindolines were converted to the respective organosodium derivatives and used as initiators for the anionic polymerization of ethylene oxide. The resulting indoline derivatives attached to polyethylene oxide were dehydrogenated to the indole derivatives, which in turn were converted through suitable reactions to the tryptamine and indole acetic acid derivatives.

Many indole derivatives have important biological activities. Indoleacetic acid is a plant growth hormone [1-3], while tryptamine and especially its 5-hydroxy derivative (serotonin) [4-8] possess a variety of pharmacological actions. It seemed interesting to modify such biologically active compounds by attaching them to polymers, which may affect their solubility, partition coefficients between

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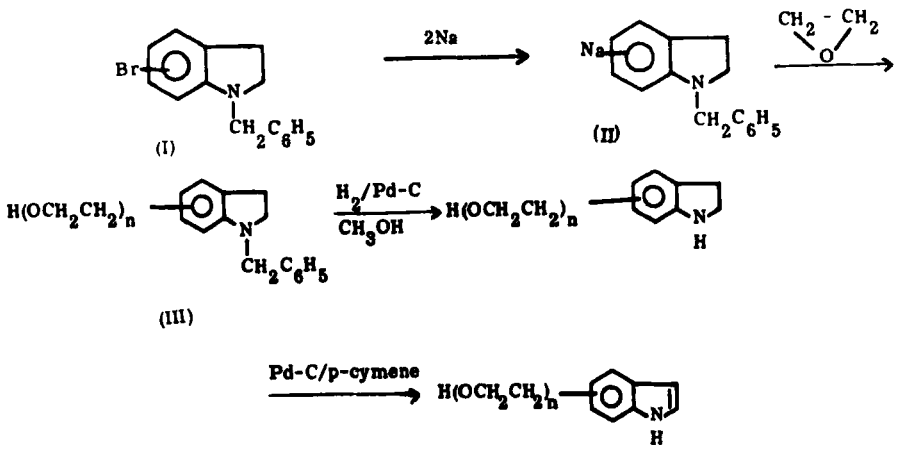
hydrophilic and lipophylic phases in the body, and penetration into biological membranes, factors which are very important in determining the biological activities of the compounds.

We attached the indole derivatives to poly(ethylene oxides), since the latter are nontoxic [9-11] and are soluble in both aqueous and organic solvents. Since the position on the indole moiety to which the substituent is attached is of significant importance in determining the extent and type of biological activity of the indole derivative, synthetic methods were developed for attaching the polyethylene oxides to positions 5, 6, and 7 of the indole derivatives.

Indoline was used as starting material for the synthesis of the polymeric indole derivatives. It was converted to the N-benzyl-protected 5-, 6-, and 7-bromindolines. The 5-bromo derivative was obtained by direct bromination of N-benzylindoline [12], while the other two derivatives were prepared by benzylation of the respective bromoindolines with benzyl chloride in the presence of sodium bicarbonate.

The reaction scheme (1) shows the route by which polyethylene oxide was attached to positions 5, 6, and 7 of the indole derivatives.

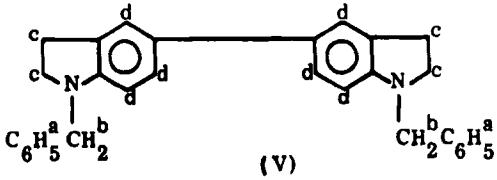


(1)

The N-benzyl bromo derivative (I) was metallated by reaction with sodium in benzene. The resulting organosodium derivative (II) was used as initiator for the anionic polymerization of ethylene oxide. The resulting indoline derivative attached to poly(ethylene oxide) (III) was catalytically hydrogenated at room temperature and low pressure

to remove the N-benzyl group, and then aromatized to the indole derivative (IV) by heating with Pd-C (10%) in cymene or β-methylnaphthalene at 170-180° C. The aromatization was completed in about 4 hr. In lower-boiling solvents, such as xylene, the reaction was very slow. The end of the aromatization was easily detected by the disappearance of the multiplet in the nmr at δ = 2.75-3.40, belonging to the two methylene groups in the five-membered ring and the appearance of two signals belonging to the H_α (α to the nitrogen) and H_β in the indole. Both resonate as doublets H_α at δ = 6.8 and $H_{\beta'}$ upfield at δ = 6.35.

In the metallation reaction with sodium, mentioned above, a Wurtz coupling reaction occurs to a minor extent (4-10%) depending on the reaction conditions leading, in the case of the 5-bromoderivative to the formation of the solid dimeric compound, N,N'-dibenzyl-5,5'-biindolinyl (V). Its structure was elucidated from elemental analysis and the NMR spectrum, which shows the protons at position c as a multiplet at δ = 3.0, those at b as singlets at δ = 4.10, and those at d as multiplets at δ = 6.25-7.08.



(V)

Since the anionic polymerization of ethylene oxide in aprotic solvents is a living one [13], it was possible to control the $\overline{DP}$ of the attached polyethylene oxides by controlling the {monomer}/{initiator} ratio. The organosodium derivative (II) was insoluble in benzene, and the polymerization required relatively long reaction times [14] for obtaining high conversions. Table 1 shows the influence of reaction time on $\overline{DP}$.

The molecular weights were determined by two methods, both of them based on NMR. In the first method, the peak area of the poly(ethylene oxide) residue was compared with that of the benzyl hydrogens. The second method was based on the work of Page and Bressler [15]. Their technique involved taking advantage of the complex formed between pyridine and –OH groups in the presence of traces of dry HCl, to shift the resonance of the terminal $-CH_2OH$ groups from that of the internal $-CH_2O-$ groups (235 and 222 cps,

TABLE 1. N-Benzyl-5[β-(polyethylene oxide)ethyl] indolines: Effect of Reaction Conditions on $\overline{DP}_n$ of the Poly(ethylene Oxide)[a]

[Ethylene oxide] / [N-benzyl-5-bromoindoline]	Reaction time (hr)	$\overline{DP}_n$ [b]
5	24	0.75
10	24	1.75
15	24	2.50
20	24	4.70
2	24	0.50
2	140	1.25
8	140	6.60

[a]N-Benzyl-5-bromoindoline in benzene was metallated by sodium and reacted with ethylene oxide as described.

[b]Determined from NMR on a Varian HA 100D instrument.

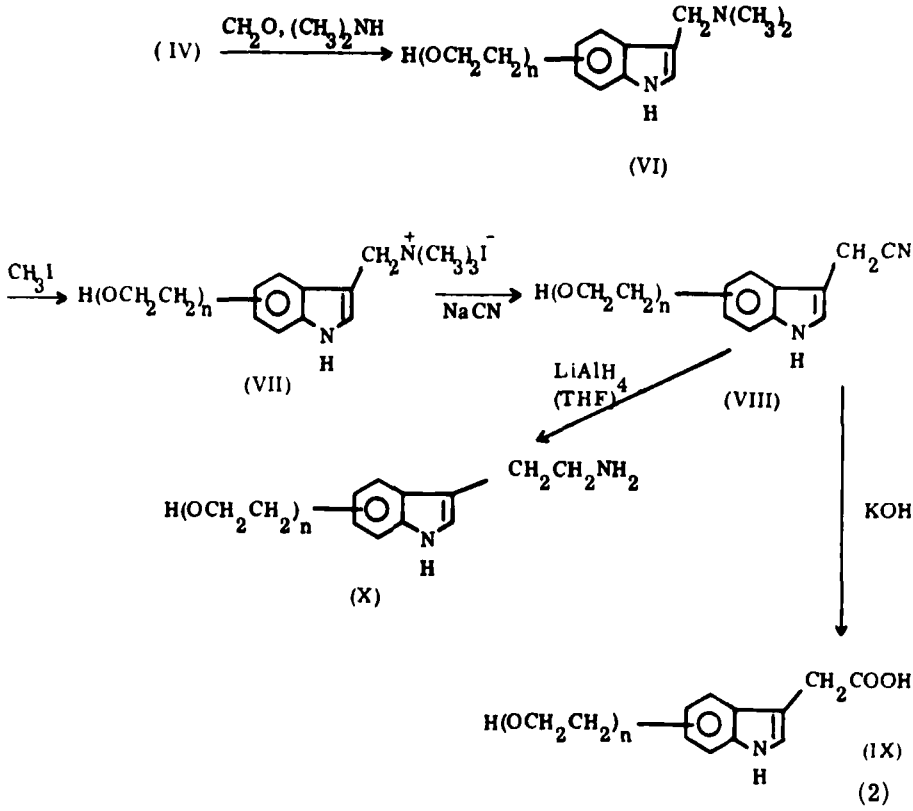
respectively). The $\overline{DP}$ of the polyethylene oxide attached to the indole can thus be determined from the ratio of these peak areas.

From IV, two biologically important derivatives, those of indole acetic acid and of tryptamine, were prepared according to scheme (2).

The indole derivative IV gave a smooth Mannich reaction on heating with formaldehyde and dimethylamine in dioxane-acetic acid to give the gramine derivative VI which showed a sharp singlet at $\delta = 2.2$ [$-N(CH_3)_2$]. The gramine (VI) was methylated and converted to the quaternary ammonium derivative (VII), which in turn, on nucleophilic substitution by CN^- gave the nitrile (VIII). The hydrolysis of the nitrile to the indole acetic acid derivative (IX) went smoothly on heating with KOH in diethylene glycol-water. In ethanol as solvent, no significant hydrolysis occurred. The nitrile was reduced by lithium aluminum hydride in THF to the tryptamine derivative X.

EXPERIMENTAL

NMR spectra were taken on a Varian T-60 instrument, IR spectra on a 257-Perkin-Elmer instrument, and UV spectra on Unicam SP-800



spectrophotometer. TLC was carried out on silica gel plates (Merck, PF254) or aluminum oxide G (Merck). Dry tetrahydrofuran was distilled from sodium benzophenone. N-Benzyl-5-bromoindoline [14], 6-bromoindoline [16], and 7-bromoindoline [16] were prepared according to the literature.

Since the preparation of the various polymeric derivatives starting with the 5-, 6-, and 7-bromoindolines was carried out under the same conditions, detailed procedures will be given for only the 5 isomer.

N-Benzyl-6-bromoindoline

Benzyl chloride (5.08 g, 0.04 mole) was added dropwise with stirring during 90 min to a mixture of 6-bromoindoline (7.92 g, 0.04 mole),

sodium bicarbonate (4.2 g, 0.05 mole), and water (10 ml) heated on a water bath at 90-95° C. Heating was continued for another 3.5 hr, the mixture was cooled, and extracted with ether. The ethereal extract was dried ($MgSO_4$) and distilled in vacuo; the product passed at 184-6° C/0.6 Torr; yield 4.96 g (86%).

NMR ($CDCl_3$): δ3.0 (m, 4, CH_2CH_2N), 4.10 (s,2, $\underline{CH_2C_6H_5}$), 7.15 (s,5, C_6H_5). ANAL. Calcd for $C_{15}H_{14}NBr$: C, 62.51%; H, 4.90%; N, 4.86%. Found: C, 62.27%; H, 4.96%; N, 5.00%.

N-Benzyl-7-bromoindoline

N-Benzyl-7-bromoindoline was prepared in 81% yield, as described for the 6-bromo isomer; bp 171° C/0.6 Torr. ANAL. Calcd for $C_{15}H_{14}NBr$: C, 62.51%; H, 4.90%; N, 4.86%. Found: C, 62.72%; H, 5.06%; N, 4.85%.

N-Benzyl-5-[β-(polyethylene oxide)ethyl]indoline (III)

N-Benzyl 5-bromoindoline (I) (8.6 g, 0.03 mole) was dissolved under nitrogen in dry benzene (80 ml), and sodium dispersion (0.08 mole) was added. The exothermic reaction was maintained below 40° C, and the mixture was stirred for 2 hr. Ethylene oxide was bubbled in at room temperature with stirring or added as a benzene solution. After the required time (Table 1), cold water (30 ml) was cautiously added with cooling. The mixture was stirred for 30 min at room temperature, extracted four times with benzene, washed with water, dried ($CaCl_2$), and evaporated. [When the $\overline{DP}$ of the poly(ethylene oxide) was > 2, the successive extractions lowered significantly the yield because of greater solubility of the product in water]. The oily residue was extracted with petroleum ether (40-60° C). The insoluble solid was recrystallized from CCl_4-methanol (mp 150-152° C) and was identified as V. The petroleum ether extract was evaporated and the polymeric product was purified by TLC on silica gel (chloroform-methanol-acetic acid, 75:20:2.5), to give a colorless oil, yield 20-70% (depending on the $\overline{DP}_n$).

IR (neat): 1100 cm^{-1} (CH_2OCH_2). NMR ($CDCl_3$): δ = 8.08 (m,4, CH_2CH_2N), 4.12 (s,2, $\underline{NCH_2}$ C_6H_5),3.50 (s,8, CH_2OCH_2) 7.14 (s,5, C_6H_5), 6.60 (m, 3, $\overline{C_6H_3}$).

ANAL. Calcd for $C_{19}H_{23}NO_2$ (n = 2): C, 76.74%, H, 7.80%; N, 4.71%. Found: C, 76.38%; H, 7.91%; N, 4.53%.

5-[β-(Polyethylene oxide)ethyl]indoline

N-Benzyl 5-[β-(polyethylene oxide)ethyl]indoline (III) (14.9 g, 0.05 mole) in absolute methanol (50 ml) was hydrogenated in the presence of 10% Pd/C (1 g) at 40 psi at room temperature. After the theoretical amount of hydrogen was absorbed (1-1.5 hr), the catalyst was filtered and the solvent was evaporated to give an oily product, which was purified by TLC on alumina (chloroform); yield 6.2 g (60%).

IR (neat): 1105 cm^{-1} (CH_2OCH_2). NMR ($CDCl_3$): δ = 3.10 (m,4, CH_2CH_2N), 3.50 (s,8, CH_2OCH_2).

ANAL. Calcd for $C_{12}H_{17}NO_2$ (n = 2); C, 69.54%; H, 8.27%; N, 6.76%. Found: C, 69.20%; H, 8.50%; N, 6.71%.

5-[β-(Polyethylene oxide)ethyl] indole (IV)

5-[β-(Polyethylene oxide)ethyl]indoline (4.15g, 0.02 mole) was heated under reflux for 4 hr in p-cymene (or β-methylnaphthalene) (60 ml) at 170-180°C with 10% Pd-C (0.5 g). The solution was filtered while still hot, and the solvent was carefully distilled under reduced pressure. The remaining yellow oily product was purified by TLC on alumina (chloroform), yield 3.31 g (81%).

NMR ($CDCl_3$): δ = 3.52 (s,8, CH_2OCH_2), 6.39 (t,1, Ph–CH=), 7.01 (m,3, C_6H_3). UV_{max} (EtOH): 220 nm (2.16×10^4), 274 nm (6.4×10^3), 279 nm (5.21×10^3).

ANAL. Calcd for $C_{12}H_{15}NO_2$ (n = 2): C, 70.22%; H, 7.37%; N, 6.82%. Found: C, 70.00%; H, 7.22%; N, 6.50%.

5-[β-(Polyethylene oxide)ethyl]gramine (VI)

To a solution of acetic acid (20 ml) and dioxane (20 ml), 37% formaldehyde solution (1.6 g, 0.02 mole), and 28% dimethylamine solution (3.2 g, 0.02 mole) were added. The mixture was cooled to 0°C, and 5-[β-(polyethyleneoxide)ethyl]indole (4.1 g, 0.02 mole) in dioxane (20 ml) was added dropwise. The solution was left overnight at room temperature, diluted with water to 300 ml, filtered, and made strongly basic with sodium hydroxide. The mixture was kept at 0°C for 4 hr for quantitative separation of the oily product, which was extracted with chloroform, dried, evaporated and purified by TLC on alumina (benzene-ethanol 5:1); yield 79%.

NMR ($CDCl_3$): δ = 3.34 (s,8, CH_2OCH_2), 2.18 [s,6, $N(CH_3)_2$], 6.88 (m,3, C_6H_3). UV_{max} (EtOH): 221 nm (3.34×10^4), 282 nm (7.4×10^3), 2.88 nm (6.8×10^3).

ANAL. Calcd for $C_{15}H_{22}NO_2$ (n = 2): C, 72.58%; H, 8.87%; N, 5.64%. Found: C, 72.35%; H, 8.50%; N, 5.42%.

5-[β-(Polyethylene oxide)ethyl]gramine methiodide (VII)

To a solution of 5-[β-(polyethylene oxide)ethyl]gramine (VI) (1.25 g, 0.005 mole) in benzene (60 ml), methyl iodide (4 ml, 0.064 mole) in benzene (10 ml) was added dropwise with vigorous stirring at room temperature. The stirring was continued for 2 hr, and the methiodide was filtered and air-dried, mp 57-61°C.

ANAL. Calcd for $C_{16}H_{25}IN_2O_2$ (n = 2): C, 47.52%; H, 6.19%; N, 6.93%; I, 31.44%. Found: C, 47.20%; H, 6.01%; N, 6.60%; I, 31.20%.

5-[β-(Polyethylene oxide)ethyl]indole-3-acetonitrile (VIII)

To a solution of 5-[β-(polyethylene oxide)ethyl]gramine methiodide (VI) (1.95 g, 0.005 mole) in ethanol-water (1:1) (100 ml), sodium cyanide (3.0 g, 0.06 mole) was added. The solution was heated with stirring on a steam bath at 80-90°C for 2 hr. The mixture was cooled, water (100 ml) was added, and the mixture was extracted by chloroform. The organic phase was washed with water, dried ($MgSO_4$), and evaporated to give an oily product which was purified by TLC on alumina (benzene-ethanol 5:1 or 9:1); yield 0.93 g (96%).

IR (neat): 2220 cm^{-1} (CN). NMR ($CDCl_3$): δ = 3.6 (s,2, CH_2CN). UV_{max} (ethanol): 234 nm (4.5×10^4), 286 nm (7.9×10^3).

ANAL. Calcd for $C_{14}H_{16}N_2O_2$ (n = 2): C, 68.83%; H, 6.60%; N, 11.47%. Found: C, 68.45%; H, 6.42%; N, 11.10%.

5-[β-(Polyethylene oxide)ethyl]-3-indole acetic acid (IX)

To a solution of 5-[β-(polyethylene oxide)ethyl]indole-3-acetonitrile (VIII) (1.22 g, 0.005 mole) in diethylene glycol (15 ml) a

solution of KOH (4.5 g) in water (10 ml) was added. The solution was heated at 160°C for 16 hr, cooled, diluted to 100 ml with water, filtered, acidified with 5% HCl solution to pH1 and extracted three times with chloroform. The organic layer was extracted with 4% NaOH, and the aqueous solution was acidified with dilute HCl, extracted with chloroform, dried and evaporated. The remaining brown-yellow oil was purified by TLC on alumina (benzene-ethanol 5:1); yield, 0.53 g (40%).

IR (neat): 1715 cm^{-1} (COOH). NMR ($CDCl_3$): δ = 3.30 (m,8, CH_2OCH_2), 3.61 (s,2, = C–CH_2), 7.02 (m,3, C_6H_3). UV_{max} (ethanol): 241 nm (5.01×10^4), 2.92 nm (7.91×10^3)

ANAL. Calcd for $C_{14}H_{17}NO_4$ (n = 2): C, 63.87%; H, 6.51%; N, 5.32%. Found: C, 63.95%; H, 6.40%; N, 5.07%.

5-[β-(Polyethylene oxide)ethyl]tryptamine (X)

To a solution of 5-[β-(polyethylene oxide)ethyl]indole-3-acetonitrile (VIII) (0.85 g, 0.0035 mole) in dry THF (80 ml) under nitrogen, $LiAlH_4$ (2.0 g, 0.053 mole) was added. The mixture was heated under reflux with stirring for 16 hr. To the cold mixture, aqueous ammonium chloride solution was added, the mixture extracted with methylene chloride, dried, and evaporated to give an oily product which was purified by TLC on silica gel (chloroform-96% acetic acid, 95:5, or i-PrOH-25% NH_3-H_2O, 100:5:10); yield, 0.55 g (63%).

IR (neat): 3360 cm^{-1} (NH_2). NMR ($CDCl_3$); δ = 3.35 (m,8, CH_2OCH_2); 2.90 (m,4, CH_2CH_2N). UV_{max} (ethanol): 240 nm (3.61×10^4), 281 nm (6.01×10^3)

ANAL. Calcd for $C_{14}H_{20}N_2O_2$ (n = 2): C, 67.72%; H, 8.12%; N, 11.28%. Found: C, 67.50%; H, 8.35%; N, 11.40%.

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