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BISINDOLES

33.* SYNTHESIS OF WATER-SOLUBLE POLYMERS HAVING INDOLE FRAGMENT IN THE POLYMER CHAIN

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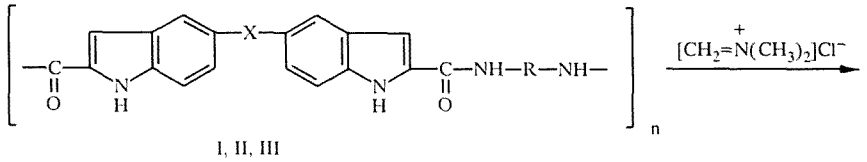
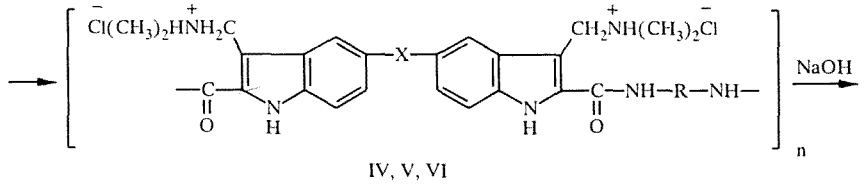
Dimethylaminomethylation of polyamides and polyethers based on the di-acid chloride of 2,2-dihydroxy-carbonylbis(5-indolyl)oxide, and -sulfone, hexamethylenediamine, 4,4'-diaminodiphenyloxide, and 2,2-di(4-hydroxy-3-chlorophenyl)propane has yielded gramine analogs which were converted into the corresponding water-soluble polyhydrochlorides; the preparation of sodium salts of several polyamides and polyamines containing indole fragments in the polymer chain is also described.

Derivatives of bis(5-indolyl)oxide and -sulfone which have been prepared previously possess curate-like, nicotine-like properties and display fungicidal activity [2, 3].

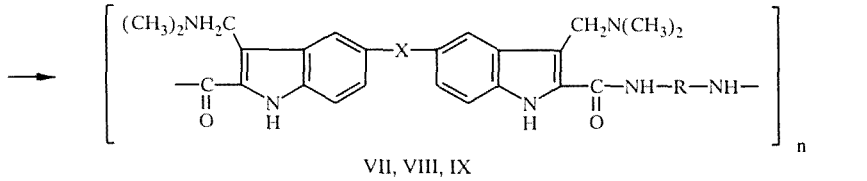
With the object of prolonging the effect of this action we have prepared polymeric analogs of these biologically active compounds.



I, II, III

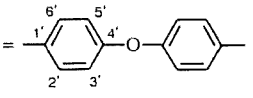


IV, V, VI



VII, VIII, IX

I, IV, VII X = O, R = $-(CH_2)_6-$; II, V, VIII X = SO_2, R = $-(CH_2)_6-$;

III, VI, IX X = O, R = 

*For Communication 32, see [1].

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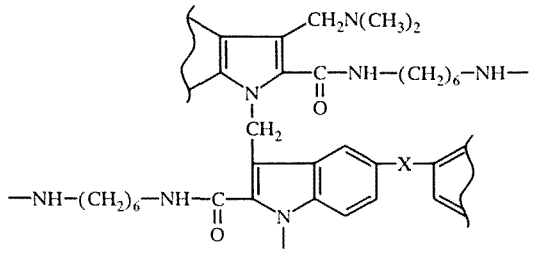
Preparation of polymeric analogs of gramine was effected by dimethylaminomethylation of polyamides, I, II, and II according to the scheme above.

The reactions were carried out in dry DMF with a ten times excess of Mannich reagent $[CH_2 = N^+(CH_3)_2]Cl$. In addition to the listed polygramines VII, VIII, and IX we also isolated byproducts X and XI in yields of 25 and 16% respectively.

The formation of compounds X and XI is evidently associated with condensation [4] of the polygramines VII and VIII.



X, XI

X X = O; XI X = SO_2

The infrared spectra of compounds X and XI provide evidence in favor of the proposed structure; in contrast to the spectra of VII and VIII, there are no absorption bands characteristic of the indole NH.

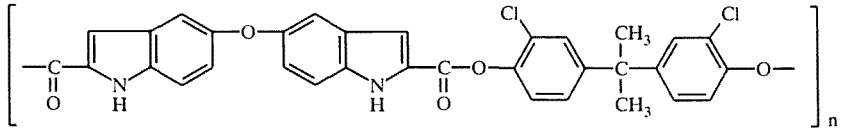
In the IR spectra of polymers VII-XI, there are characteristic bands in the regions 3260-3200 (amide NH), 1680-1620 (C=O), 1590-1550 (amide-II), and for polymers VII-IX bands corresponding to indole NH at 3440, 3420, and 3300 cm^{-1} respectively.

Polymers X and XI differ from VII and VIII in being insoluble; this results from the spatial structure of the latter.

The PMR spectra of compounds VII and VIII differ from those of the starting materials I and II in that signals for the protons of the pyrrole ring are absent whereas there are signals for methyl groups at 2.15 and 2.24 ppm, and for the methylene protons of the aminomethyl groups at 3.77 and 1.2-3.5 ppm respectively (Table 1).

Evidence for the proposed structure of the polygramine IX is provided by the PMR spectrum in which there are board bands for the protons of the NH group at 13.0 with amide NH in the form of a singled at 11.5 ppm. A broad band at 7.26 was assigned to the 4H proton and a doublet at 6.97 and 7.44 ppm with $J_{67} = 9.2$ Hz to the 6H and 7H protons. Singled signals at 3.74 and 2.33 ppm were assigned to the protons of the $N-CH_2$ and $N-CH_3$ groups. Doublets at 7.6 and 7.0 ppm with $J_{2',3'} = J_{5',6'} = 8$ Hz were assigned respectively to the 2′, 6′ and 3′, 5′ protons (Table 1).

Attempts to prepare a polygramine based on polyether XII, which was itself prepared by polycondensation of the di-acid chloride of 2,2′-dihydroxycarbonyl-bis(5-indolyl)oxide and 2,3-di-(4-hydroxy-3-chlorophenyl)propane [5] under conditions similar to those used for the preparation of polygramins VII, VII, and IX did not give the expected results; in this case we obtained the polygramine XIII:



XIII

In the PMR spectrum of compound XIII, in addition to singled signals at 4.16 and 2.64 ppm assigned to CH_2-N and $N(CH_3)_2$, signals were observed for NH group protons at 11.7 and 11.2 ppm and for the remaining protons in the range 7.4 to 6.72 ppm (Table 1). The existence of two signals for the NH group protons indicates that the molecule is unsymmetrical, probably resulting from the presence of free β-protons of the pyrrole ring.

The reduced viscosity of polygramines VII, VIII, IX, and XIII varied in the range 0.2 to 0.3 dl/g.

With the object of preparing water−soluble forms of polygramines VII, VIII, IX, and XIII they were converted into the corresponding polyhydrochlorides IV, V, VI, and XIV.

The IR spectra of polyhydrochlorides IV, V, VI, and XIV differed from those of polygramines VII, VIII, IX, and XIII in showing an absorption band for the NH≡ group at 2720-2470 cm^{-1}

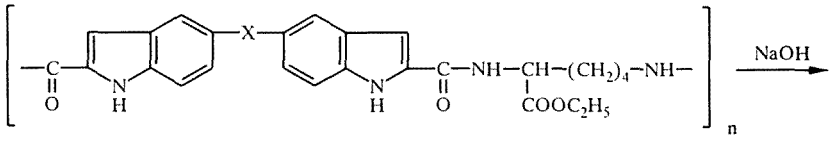
TABLE 1. PMR Spectra of Polymers I, II, VII, VIII, IX, and XIII in DMSO-d_6

Compound	Chemical shift, δ, ppm									
	1H	2H	3H	4H	6H	7H	$(CH_2)_6$	N—CH_2	N—CH_3	Coupling constant, J, Hz
I	11,55 br.s.	8,46 br.s,	7,00 s	7,11 s	6,92 d	7,41 d	1,35, 1,53, 3,27	—	—	J_{67}=8,8
II	10,25 br.s.	8,40 br.s,	7,05 s	8,26 c	7,79 d	7,65 d	1,38, 1,57, 3,27	—	—	J_{67}=8,8
VII	11,2 br.s	10,10 br.s	—	7,30 d	6,85 d.d	7,35 d	1,2...3,5		2,15 s	J_{46}~2,0 J_{67}=8,0
VIII	—*	10,22 br.s	—	8,35 d	7,65 d	7,53 d	1,40, 1,55, 3,31	3,77 s	2,24 s	J_{67}=8,0
IX*[2]	13,0 br.s.	11,5 s	—	7,26 br.s	7,97 d	7,44 d	—	3,74 s	2,33 s	J_{67}=9,2 $J_{2'3'}J_{5'6'}$= =8,8
XIII*[3]	11,7 br.s 11,2 br.s	—	—	Ar 7,44...6,72			—	4,16 s	2,64 s	—

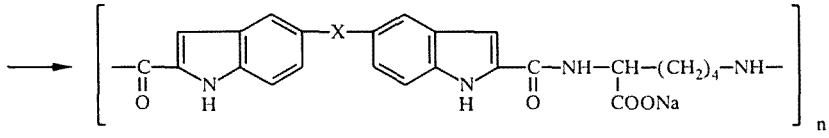
*1H proton signal absent on account of rapid NH ⇄ ND exchange.

2*For compound IX 2′-H = 6′-H and 3′-H = 5′-H signals shown at 7.65 ppm (d) and 7.00 ppm (d) respectively.

3*For compound XIII C−CH_3 signal shown at 1.53 ppm (s).



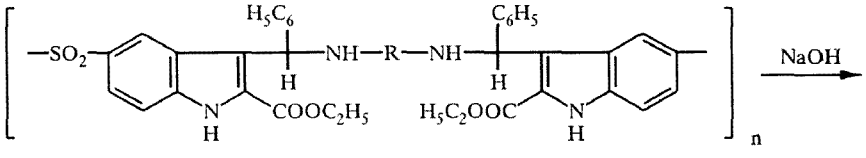
XV, XVI



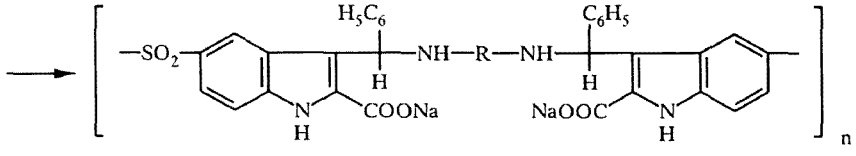
XVII, XVIII

XV, XVII X = O; XVI, XVIII X = SO_2

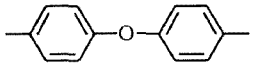
Water-soluble forms of the bisindole-containing polyamides XVII and XVIII and polyamines XXI and XXII were obtained by saponification of polyamides XV and XVI and polyamines XIX and XX, which we prepared previously, using the method of [6, 7].



XIX, XX



XXI, XXII

XIX, XXI R =  ; XX, XXII R = $-(CH_2)_6-$

The IR spectra of polyamides XVII and XVIII showed absorption bands as follows: 1590 and 1610 cm^{-1} comparatively weak bands at 1400 cm^{-1} ($-COO^-$), bands in the region of 3400-3250 cm^{-1} (NH), at 1650 and 1630 cm^{-1} (amide-I) and at 1535 and 1550 cm^{-1} (amide-II) respectively; in the IR spectra of polyamides XXI and XXII there were bands at 1610, 1600, and 1400 cm^{-1}, characteristic for the carboxylate anion, and at 3420 and 3230 cm^{-1}, assigned to the NH groups.

EXPERIMENTAL

Infrared spectra were run on a UR-20 instrument in KBr, and PMR spectra on a Varian CFT-20 in DMSO at a working frequency of 80 MHz with TMS as internal standard.

Purification of the starting materials and solvents was carried out by standard methods; their physical constants corresponded to literature data.

Reduced viscosities were determined for solution of concentration 0.5 g/100 ml at 25°C in DMF.

The PMR spectra of compounds, I, II, VII-IX, and XIII are detailed in Table 1.

Polyamides I-III (General Method). To a solution of the diamine in HMPA was added, with stirring, the di-acid chloride of 2,2′-dihydrocarbonylbis(5-indolyl)oxide or -sulfone. The molar ratio of the reactants was 1:1 and the concentration 0.3 M. The reaction mixture was stirred for 6 h at 80°C. The polymer was precipitated with water, filtered off, and extracted with methanol. Diamines used were hexamethylenediamine (I, II) and 4,4′-diaminodiphenyloxide (III). When aliphatic diamines were used, the calculated quantity of triethylamine was added.

Polygramine VII. To a solution of 0.41 g (1 mmole) polyamide I in 10 ml dry DMF was added, in portions, 0.94 g (10 mmole) $[(CH_3)_2N^+=CH_2]Cl$ and the mixture stirred 2 h at room temperature and then 3 h at 60-70°C. It was the poured into 20 ml ice–water and the pH adjusted to 10. The precipitate was filtered off, washed with water to pH 7 and dried in vacuum over KOH. Yield 0.46 g (87%), η_{red} 0.3 dl/g. IR spectrum (cm^{-1}): 3440, 3260 (NH), 1680 (C=O), 1510 (amide-II).

Polygramine VIII was prepared in a similar way to VII from 0.46 g (1 mmole) polyamide II, heated 5 h at 70-80°C. Yield 0.48 g (83%), η_{red} 0.29 dl/g. IR spectrum (cm^{-1}): 3420, 3240 (NH), 1160 (C=O), 1540 (amide-II).

Polygrmaine IX was prepared in a similar way to VII from 0.5 g (1 mmole) polyamide III, heated 5 h at 70-80°C. Yield 0.52 g (85%). IR spectrum (cm^{-1}): 3420, 3300 (NH), 1670 (C=O), 1550 (amide-II).

Polygramine XIII was prepared in a similar way to VII from 0.59 g (1 mmole) polyether XII, heated 6 h at 70-80°C. Yield 0.56 g (86%), η_{red} 0.2 dl/g. IR spectrum (cm^{-1}): 3420 (NH), 1720 (C=O).

Polyhydrochloride IV-VI and XIV Based on Polygramines VII-IX and XIII. To a solution of 1 mmole polygramine in 30 ml THG was added, dropwise with stirring, a saturated solution of HCl in THF until the solution was acid. After 30 min, 50 ml dry ether was added and the precipitate filtered off, washed with ether and dried in vacuum.

Polyhydrochloride IV. Yield 0.43 g (71%). IR spectrum (cm^{-1}): 3430, 3280 (NH), 2720 (N^+H), 1630 (C=O), 1580 (amide-II).

Polyhydrochloride V. Yield 0.41 g (63%). IR spectrum (cm^{-1}): 3400, 3270 (NH), 3720 (N^+H), 1660 (C=O), 1540 (amide-II).

Polyhydrochloride VI. Yield 0.44 g (64%). IR spectrum (cm^{-1}): 3420, 3300 (NH), 2690 (N^+H), 1660 (C=O), 1550 (amide-II).

Polyhydrochloride XVI. Yield 0.38 g (42%). IR spectrum (cm^{-1}): 3420 (NH), 2720 (N^+H), 1710 (C=O).

Sodium Salt XVII of Polyamide XV, Prepared from the Di-acid Chloride of 2,2′-Dihydroxycarbonylbis(5-indolyl)oxide and the Ethyl Ester of N,N′-Di(trimethylsilyl)lysine. To a solution of 0.47 g (1 mmole) polyamide XV in 7 ml dry DMSO was added an alcohol solution of 0.05 g (1.5 mmole) NaOH. The mixture was stirred 3 h at room temperature and the heated 5 h at 50°C. The reaction mixture was poured into a three times excess of isopropanol and the precipitated solid filtered off, washed with isopropanol and with ether and dried in vacuum. Yield 0.45 g (88%). IR spectrum (cm^{-1}): 3450-3300 (NH), 1650 (C=O), 1590, 1400 (COO^-), 1535 (amide-II).

Sodium Salt XVIII of Polyamide XVI was prepared in a similar manner to XVII from 0.52 g (1 mmole) polyamide XVI. Yield 0.49 g (95%). IR spectrum (cm^{-1}): 3400-3250 (NH), 1625 (C=O), 1610, 1400 (COO^-), 1550 (amide-II).

Sodium Salt XXI of Polyamide XIX was prepared in a similar manner to XVII from 0.82 g (1 mmole) polyamide XIX, heating for 2 h at 80°C. Yield 0.52 g (65%). IR spectrum (cm^{-1}): 3420-3300, 3250 (br), 1430 (NH), 1610, 1410 (COO^-), 1520 (Ar).

Sodium Salt XXII of Polyamide XX was prepared in a similar manner to XVII from 0.82 g (1 mmole) polyamide XX, heating 3 h at 80°C. Yield 0.41 g (57%). IR spectrum (cm^{-1}): 3400, 3240, 1480 (NH), 1600, 1410 (COO^-), 1560 (Ar).

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