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SYNTHESIS AND SPECTROSCOPIC CHARACTERISTICS OF 2,3'-BIINDOLYLS AND 2,2'-INDOLYLPYRROLES

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Abstract - A general and selective method has been achieved to synthesize 2,3'-biindolyls and 2,2'-indolylpyrroles through an acid catalyzed reaction of 3-bromoindoles with indoles or pyrroles. I.R., ^{1}H-NMR, ^{13}C-NMR and MS data of the dimers are also reported.

Dimeric indoles are relatively difficult to synthesize and only few compounds have been reported fully characterized. A recent synthesis of simple 2,2'-biindolyls by coupling 2-haloindoles in presence of copper has been reported[1], and analogous substituted biindolyls have been obtained from 2-alkoxy-3-hydroxyindolines in the presence of Lewis acids[2]. No general convenient method, however, is known for the synthesis of 2,3'-biindolyls, although simple dimers have been obtained by treating indole with Se at 310°C[3], or by bromination with dioxane perbromide[4], or by refluxing oxindoles and indoles in the presence of $POCl_3$[5].

Our recent studies on selective halogenation of indoles provide a high yield route to 3-bromoindoles[6], which were capable of reaction with indoles to give 2,3'-dimers in good yields[7]. In this paper we report in detail the new synthesis of 2,3'-biindolyls and 2,2'-indolylpyrroles, together with their main spectroscopic characteristics.

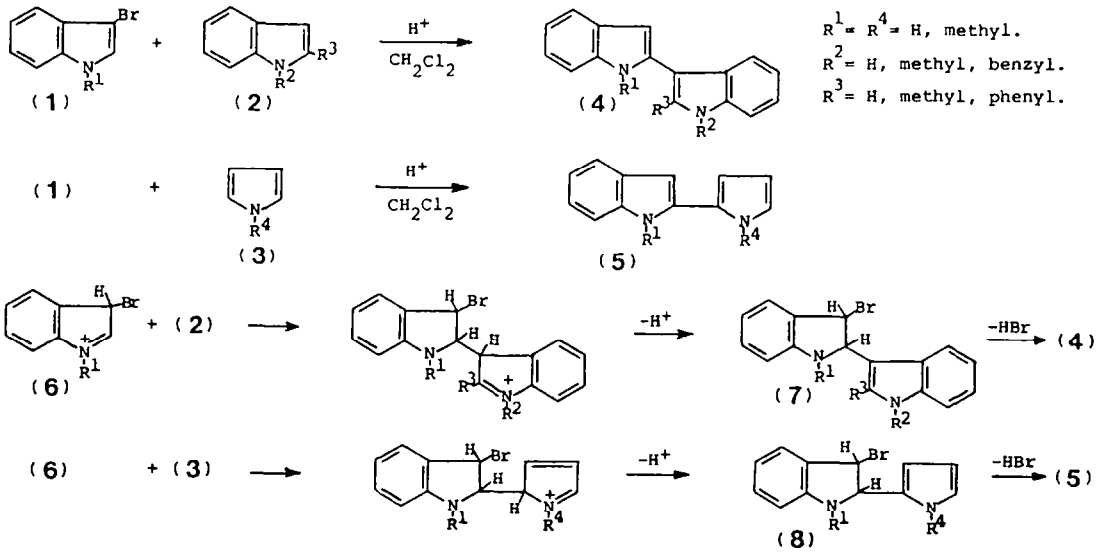
RESULTS AND DISCUSSION

The reaction of 3-bromoindoles (**1**) with indoles (**2**) or pyrroles (**3**) to give dimeric derivatives (**4,5**) was carried out at room temperature in dry chlorinated solvents, by mixing equimolecular amounts of the reagents in presence of protic or Lewis acids.

We think that the protic acid (CF_3COOH, HCl or HBr) produces a bromoindolinium cation (**6**), that behaves as an electrophilic species, reacting with indoles (pyrroles) to give indoline dimeric intermediates (**7,8**), which rearomatize by the loss of HBr to the corresponding stable dimers (**4,5**) (Scheme 1). The same behaviour is shown by the 3-bromoindole in the presence of Lewis acids ($TiCl_4$,$SnCl_4$). The catalytic activity of the latter could be due to the direct interaction with indoles or to the action of trace amounts of protic acid derived from a partial hydrolysis of the chloride.

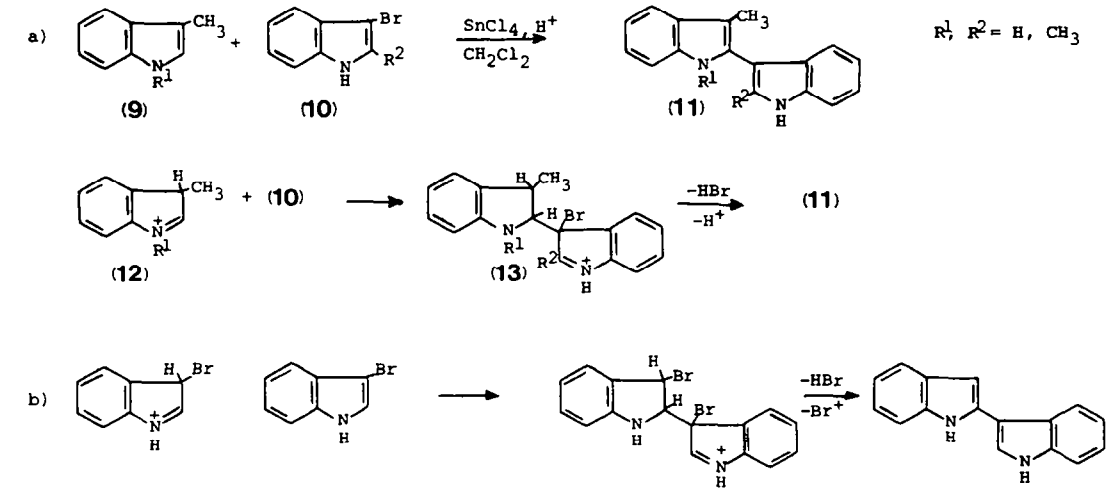
The best yields have been obtained using trifluoroacetic acid, although in some cases comparable high yields have been reached using the Lewis acids (N-alkylindole dimers). The main by-products were studied in detail in the case of the reaction with indole. The indoline dimer (2-(3-indolyl)-2,3-dihydroindole)[8], and the two open trimers (2-(3-indolyl)-3-(2-indolyl)indole[7] and 2-(3-indolyl)-3-(3-indolyl)indole[5], were identified. The dimer is probably derived from the reaction of the indolinium cation with indole[9], the trimers from a further reaction of the dimeric product. Secondary products from pyrroles were 2,5-disubstituted derivatives, which amount could be decreased by working with a small excess of the pyrrole.

Scheme 1.



Another aspect of the reactivity of the 3-bromoindoles is their selective reaction with 3-alkylindoles in the presence of protic or Lewis acids, to give the substituted 2,3-biindolyls. The mechanism of the reaction is proposed in the Scheme 2a and implies a preferential protonation of the more basic 3-methylindole (**9**) to give the electrophilic species (**12**), that attacks the 3-bromoindole (**10**) and originates a charged dimeric intermediate (**13**), which loses HBr and H^+ evolving to the more stable unsaturated dimer (**11**). Good yields of dimer were obtained working with $SnCl_4$ and with trifluoroacetic acid. The susceptibility of the 3-bromoindole to undergo an electrophilic attack is also indicated by its decomposition in the solid state, promoted by acids. In this reaction the 2,3'-biindolyl is the main product while linear and cyclic trimers, tetramers and other products coming from reactions of oxidation and bromination are the by-products. Dimerization of 3-bromoindole probably follows the mechanism proposed for the condensation of 3-bromoindole with indole, with release in the last step of a bromomium ion instead of a proton (Scheme 2b). Oxindoles and monobromobiindolyls have also been observed in the reaction mixture. In this connection it is well known that indolenine species such as BNPS-skatole (2-(2-nitrophenylsulphenyl)-3-methyl-3-bromoindolenine) are used as reagents for cleaving tryptophanyl peptides[10], and that oxidative halogenation of 3-substituted indoles leads to oxindoles[10,11].

Scheme 2.



The main spectroscopic characteristics of 2,3'-biindolyls and of 2,2'-indolylpyrroles synthesized are reported in the Table 1. The ν_{NH} stretching was in the range usually shown by simple indoles (3360-3430 cm^{-1})[12]; the ^{1}H-NMR signals were as expected[13]. We assigned the ^{1}H-chemical shifts of the 2,3'-biindolyl (1) and of the 2,2'-indolylpyrrole (6) by homonuclear double resonance experiments.

In Figure 1 we report the ^{1}H spectrum of 2,3'-indolylpyrrole (1). The protons of the 2-substituted ring were assigned on account of the fact that Hb, Hc, Hd and He signals were modified upon irradiation of the proton Hf. The selective irradiation of protons was also used to assign the chemical shifts to the ^{13}C spectra of compounds (1) and (6), that well agree with known shifts of indole and pyrrole carbons[14]. The ^{13}C chemical shifts of the dimers (2-5) and (7-12) reported in the Table were attributed by comparison with the spectra of (1) and (6). Quaternary carbon lines were assigned only to carbons a (1-7), carbon b (10-12) and carbons b' (1-12); shifts reported in brackets are ascribed to quaternary carbons, although they were not specifically assigned so far. The lines of o and m carbons of compounds 3 and 5 were easily recognized by their higher intensities. The ^{13}C spectrum of the compound 8 lacks a quaternary carbon, probably covered by another singlet line.

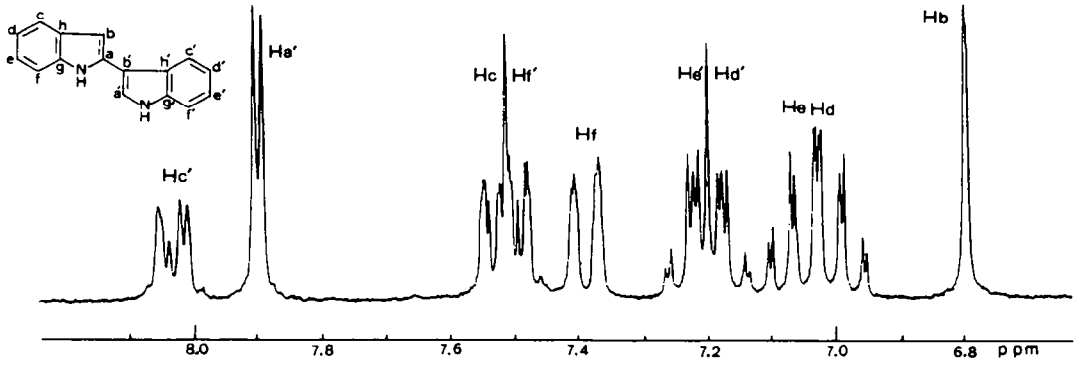


Figure 1. Partial 200 MHz ^{1}H NMR spectrum of 2,3'-biindolyl (1) in DMSO-d_6 at 25°C.

EXPERIMENTAL SECTION

I.R. spectra were recorded with a Perkin Elmer 298 instrument as KBr disks. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian XL-100 instrument at a frequency of 100 and 25.2 MHz respectively. ^{1}H- and ^{13}C-NMR spectra of the compounds (1) and (6) were also recorded on a Brucker CXP-200 instrument at 200 and 50.4 MHz, using TMS as internal standard. Mass spectra were obtained on a Varian Mat CH-5 single focus spectrometer at 250°C and 70 eV. Purification of products was made by liquid column chromatography (Kieselgel 60 Merck for preparative plates) using a low overpressure during the elution (0.5-1.0 Atm), and detecting with U.V. and Ehrlich reagent. M.ps were determined on a "Buchi" apparatus and are uncorrected.

General procedure for the preparation of the 2,3'-biindolyls (1-5, 8-9) and the 2,2'-indolylpyrroles (6-7).

The 3-bromoindole and the 3-bromo-N-methylindole were prepared from indoles and bromine in DMF[6], and stored in solution (ethyl acetate).

The sample of 3-bromoindole (1 mmol) in ethyl acetate was evaporated to dryness, dissolved in CH_2Cl_2 (10 ml) previously distilled and dried on $CaCl_2$. Then indole (pyrrole) (1 mmol) was added, followed by trifluoroacetic acid (0.03 ml). The mixture was kept under stirring at room temperature for 20 minutes. The solution was then made basic with few drops of aqueous ammonia and

evaporated to dryness. The residue was dissolved in ethyl acetate, the solution was concentrated, adsorbed on silica gel (5 ml) and fractionated by column chromatography (1.5 x 30 cm), eluting with a mixture of hexane and ethyl acetate (8/2, v/v). The dimers (1-3, 6,7) were further purified by sublimation at 0.1 mm Hg at 150-200°C; the other products were crystallized from a mixture of hexane and ethyl acetate. The analytical data are reported in Table 1.

Synthesis of the 2,3'-skatolylindoles (10-12)

a) With $SnCl_4$. Skatole (N-methylskatole) (1 mmol) was dissolved in 10 ml of dry CH_2Cl_2, then $SnCl_4$ (1 mmol) was added dropwise, under stirring, at room temperature. To this, a CH_2Cl_2 solution of the 3-bromoindole (2-CH_3-3-bromoindole) (5 ml, 1 mmol) was added. The reaction mixture was kept at room temperature for 10 minutes, then made basic with aqueous ammonia, mixed with ethyl acetate (40 ml), dried on sodium sulphate, and fractionated through a silica gel column, as already reported for compounds (1-9).

b) With trifluoroacetic acid. Skatole (N-methylskatole) (1 mmol) was dissolved in 10 ml of dry CH_2Cl_2 and treated with trifluoroacetic acid (0.2 mmol). To this, a CH_2Cl_2 solution of the 3-bromoindole (5 ml, 1 mmol) was dropped, then the mixture was stirred at room temperature for 1 hour. At the end aqueous ammonia was added and the products were recovered as previously described.

Synthesis of the 2,3'-biindolyl (1) through the 3-bromoindole dimerization, promoted by acids.

An ethyl acetate solution containing 1.0 g of 3-bromoindole was evaporated to dryness and put in contact for few seconds with HCl vapours. In few minutes the 3-bromoindole decomposed with release of HBr vapours. The brown-green residue was treated with aqueous ammonia, dissolved into ethyl acetate, dried and fractionated on silica gel as previously described. The 2,3'-biindolyl was then recovered (0.45 g), together with some secondary products such as isomer biindolyls (M^+ = 232), open and cyclic trimeric products (M^+ = 347 and M^+ = 345)[1], hydroxindoles (M^+ = 149) and probably 3-bromo-2,3'-biindolyl (M^+ = 310-312). Tetramers have also been detected (M^+ = 462).

Acknowledgements

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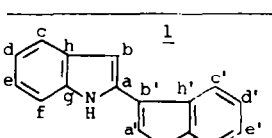
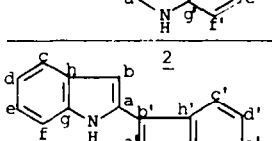
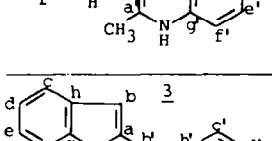
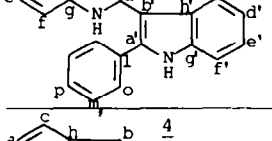
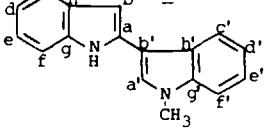
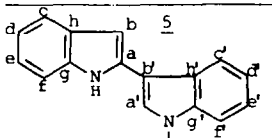
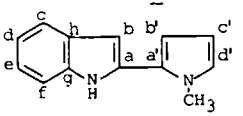
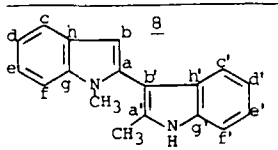
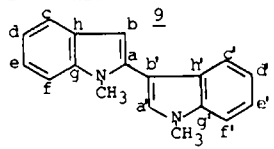
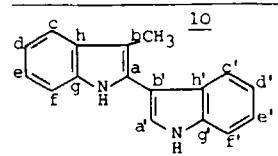
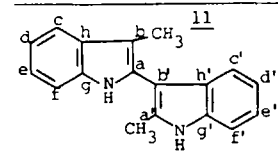
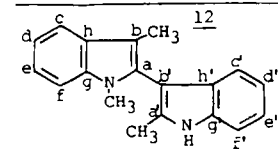
Table 1. Analytical data for the 2,3'-Biindolyls(1-5, 8-12) and the 2,2'-Indolylpyrroles(6,7).

Compound N°	M.p. °C	Yield[a] %	I.R.(KBr) ν_{NH} (cm^{-1})	^{1}H-NMR (DMSO-d_6, $CDCl_3$) δ, ppm (TMS ref.)	Proton decoupled ^{13}C-NMR (DMSO-d_6) (TMS ref.)	Mass spectra m/e(% rel. int.)
 1	203[b] 205	85	3380	DMSO-d_6: 6.79(Hb, d J=2Hz), 6.98 (Hd), 7.06(He), 7,18(Hd'), 7.22 (He'), 7.38(Hf), 7.49(Hf'), 7.53 (Hc), 7.90(Ha'), 8.03(Hc'), 11.23(NH), 11.42(N'H).	b = 96.8 c =118.9 a'=122.8 b'=108.4 c'=119.4 a =124.5 f =110.3 d'=119.7 h,h',g,g'(129.0, f'=111.7 e =120.2 133.8, 135.8, 136.5) d =118.7 e'=121.6	M$^+$= 232(100) 204(23) 176(5) 116(26) 102(17)
 2	155-156	92	3400	$CDCl_3$: 2.56(3H,s,CH_3); 6.50(1H, Hb, d J=2Hz); 6.80-7.80(m, 8H arom, NH); 8.0(1H, NH, broad).	b = 98.7 c =118.6 a =126.7 b'=104.9 c'=118.7 CH_3(a')=12.7 f =110.5 d'=119.0 h,h',g,g',a'(128.7, f'=110.7 e =119.7 133.4, 133.5, 134.9, d =118.3 e'=120.5 136.2)	M$^+$= 246(100) 231(41) 217(12) 204(9) 123(15)
 3	212-214	82	3400	$CDCl_3$/DMSO-d_6(1/1): 6.50(1H,Hb, d J=2Hz); 6.70-7.90(m, 13H arom); 9.20(1H, NH, broad); 10.50(1H, NH, broad).	b =100.5 c =119.0 a =127.4 a',h,h',g, b'=105.3 c'=119.0 o =127.4 g',1(128.4, f =110.9 d'=119.5 p =127.5 132.0, 132.3 f'=111.2 e =120.1 m =128.2 134.9, 135.8 d =118.6 e'=121.9 136.3)	M$^+$= 308(100) 153(26) 105(8)
 4	142-144	70	3400	DMSO-d_6: 3.80(3H,s,CH_3); 6.76 (1H, Hb, d J=2Hz); 6.80-8.20 (m, 9H arom); 11.22(1H, NH, broad).	b = 96.9 c =118.9 a =124.8 b'=107.5 c'=119.6 a'=126.9 f =109.6 d'=119.8 N'-CH_3= 32.5 f'=110.3 e =120.2 h,h',g,g'(129.0, 133.5, d =118.7 e'=121.7 135.9, 136.9)	M$^+$= 246(100) 231(41) 204(34) 123(69) 102(29)
 5	158-160	65	3420	DMSO-d_6: 5.42(2H,s,-CH_2-); 6.80 (1H, Hb, d J=2Hz); 6.90-8.20(m, 14 H arom); 11.30(1H,NH,broad).	b = 97.1 c'=119.8 o =126.8 b'=108.3 d'=119.8 m =128.3 f =110.8 e =120.2 p =126.2 f'=110.8 e'=121.7 N'-CH_2= 49.2 d =118.6 a =125.1 h,h',g,g',1(128.9, 133.2, c =118.9 a'=127.2 135.9, 136.3, 137.5)	M$^+$= 322(45) 203(4) 91(100) 78(8)
 6	216-218	83	3430	DMSO-d_6: 6.16(Hc'), 6.60(Hb'), 6.63(Hb), 6.89(Hd'), 6.97(Hd), 7.05(He), 7.35(Hf), 7.48(Hc), 11.16(NH), 11.28(N'H).	b = 95.1 c =119.1 a',h,g(128.7, 132.4, c'=108.6 e =120.3 136.0) f =110.5 d =118.9 d'=118.8 a =124.9 b'=105.6	M$^+$= 182(100) 154(37) 127(12) 91(10) 78(8)

[a] Isolated yield, based on starting indoles(pyrroles); reaction carried out in presence of trifluoroacetic acid. [b] Lit[3]: 203.5-205.

Table 1. (continue)

 7	91-92	76	3420	$CDCl_3$: 3.67(3H,s,CH_3); 6.16(1H, Hc', dd, Jc'b'=4Hz, Jc'd'=2.5Hz); 6.30(1H,Hb', dd, Jb'd'=1.5Hz);6.43 (1H,Hb,d J=2Hz);6.66(1H,Hb' dist.t) 7.0-7.7(m, 4H arom);7.85(1H,NH).	b = 97.8 c'=108.2 f =110.5 d =118.8 b'=107.1	c =119.3 e =120.7 d'=124.5 a =125.6 N-CH_3= 35.4	a',h,g(128.5, 130.6, 135.9	M^+= 196(100) 181(12) 168(11) 154(8)
 8	194-196	86	3360	DMSO-d_6: 2.45(3H,s,C-CH_3); 3.55 (3H,s,N-CH_3);6.46(1H,Hb,d J=2Hz); 6.90-7.70(m, 8H arom); 11.4(1H, NH,broad).	b =101.3 b'=103.5 f =109.5 f'=110.8 d =118.0	c =119.0 c'=119.3 d'=119.3 e =119.8 e'=120.6	CH_3(a')=12.1 N-CH_3=30.5 a,a',h,h',g,g'(127.9, 128.0, 135.1, 135.1, 137.3)	M^+= 260(100) 245(41) 217(13) 130(64) 122(49),109(27)
 9	135[c] 137	73	----	$CDCl_3$: 3.43(6H,s,2CH_3); 6.38(1H,s, Hb); 6.68(1H,s,Ha'); 6.70-7.70(m, 8H arom).	b =100.0 b'=105.7 f =109.4 f'=109.8 d =119.8	c =119.2 c'=119.2 d'=119.7 e =120.3 e'=121.6	a'=128.8 N-CH_3=30.7 N'-CH_3=32.4 a,h,h',g,g'(126.6, 127.8, 134.7, 136.5, 137.4)	M^+= 260(100) 245(16) 217(15) 130(45)
 10	154-156	64	3390	DMSO-d_6: 2.40(3H,s,CH_3);6.80-7.90 (m, 9H arom);10.85(1H,NH,broad); 11.40(1H,NH,broad).	b =105.0 b'=107.7 f =110.5 f'=111.5 d =117.3	c =118.0 c'=119.1 d'=119.7 e =120.0 e'=121.3	a'=124.4 CH_3(b)=9.7 a,h,h'g,g'(125.6, 129.2, 129.9, 135.8, 135.9)	M^+= 246(100) 217(29) 130(20) 123(40) 117(24),109(24)
 11	d	91	3400	DMSO-d_6: 2.24(3H,s,CH_3(b)); 2.45 (3H,s,CH_3(a')); 6.80-7.70(m, 8H arom); 10.86(1H,NH,broad);11.27 (1H,NH,broad).	b =104.5 b'=106.4 f =110.5 f'=110.5 d =117.5	c =117.8 c'=118.5 d'=118.8 e =120.1 e'=120.4	CH_3(a')=12.5 CH_3(b)=9.8 a,a',h,h',g,g'(127.8, 129.0, 129.5, 133.9, 135.2, 136.1)	M^+= 260(100) 243(27)
 12	226-228	73	3380	DMSO-d_6:2.13(3H,s,CH_3(b));2.34 (3H,s,CH_3(a'));3.49(3H,s,N-CH_3); 6.90-7.60(m, 8H arom);11.40(1H, NH,broad).	b =102.3 b'=107.8 f =109.1 f'=110.7 d =117.7	c =118.0 c'=118.1 d'=119.1 e =120.4 e'=120.4	CH_3(a')=12.2 CH_3(b)=9.5 CH_3-N =30.2 a,a',h,h',g,g'(128.1, 128.2, 131.6, 135.3, 135.3, 136.8)	M^+= 274(100) 257(28) 137(47) 129(74)

[c]Lit[1]: 137-138. [d]The product retains solvent.