BISINDOLES.

31.* SYNTHESIS OF NEW DERIVATIVES OF 2,5′- AND 3,5′-BIS-1H-INDOLES

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Using p-aminoacetophenone as starting material, new derivatives of 2,5′- and 3,5′-bis-1H-indoles containing amino, nitro, acetyl, and ester groups have been prepared.

We have previously reported [2, 3] on the development of a general method for the preparative synthesis of unsymmetrical bisindoles coupled by atoms of the pyrrole and benzene ring — 2,5′- and 3,5′-bis-1H-indoles.

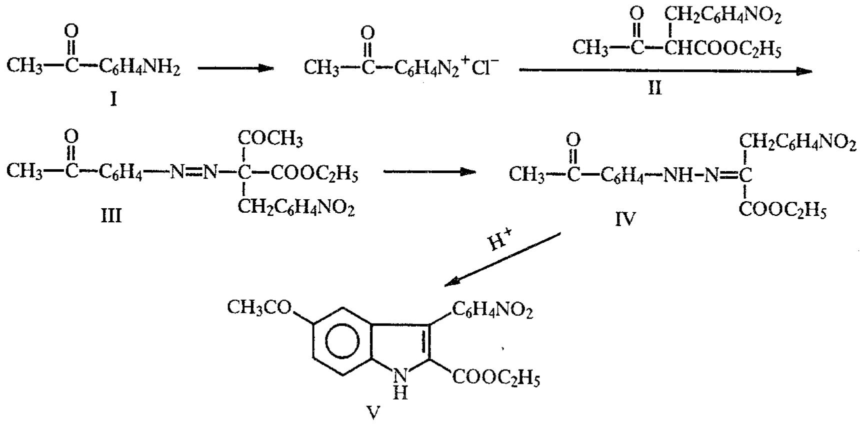
Derivatives of 2,5′-bis-1H-indole and 3,5′-bis-1H-indole were prepared from a single key compound — 2-ethoxy-3-p-nitrophenyl-5-acetylindole (V) which has been prepared previously [4].

The general scheme for the conversion includes two successive stages of the Emil Fischer indolization. Azo-coupling of p-acetylphenyldiazonium chloride (II) with α-p-nitrobenzylacetoacetic ester proceeds smoothly at pH 6, the azoester III precipitating from the reaction mixture in the form of stable yellow crystals which are used in other reactions without further purification.

Hydrolysis of the azoester III was carried out in 1:1 water—dioxane. The hydrazone IV is formed largely as one geometrical isomer in 96% yield.

The best yield of 2-ethoxycarbonyl-3-p-nitrophenyl-5-acetylindole (V) (70% after purification on a column) was achieved by cyclization of the hydrazone IV in polyphosphoric acid.

The nitro group of compound V was reduced in Fe/H_2O in boiling toluene and of compound X by diimide over Raney nickel in ethanol with the formation of amines VI and XI respectively.



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*For Communication 30, see [1].

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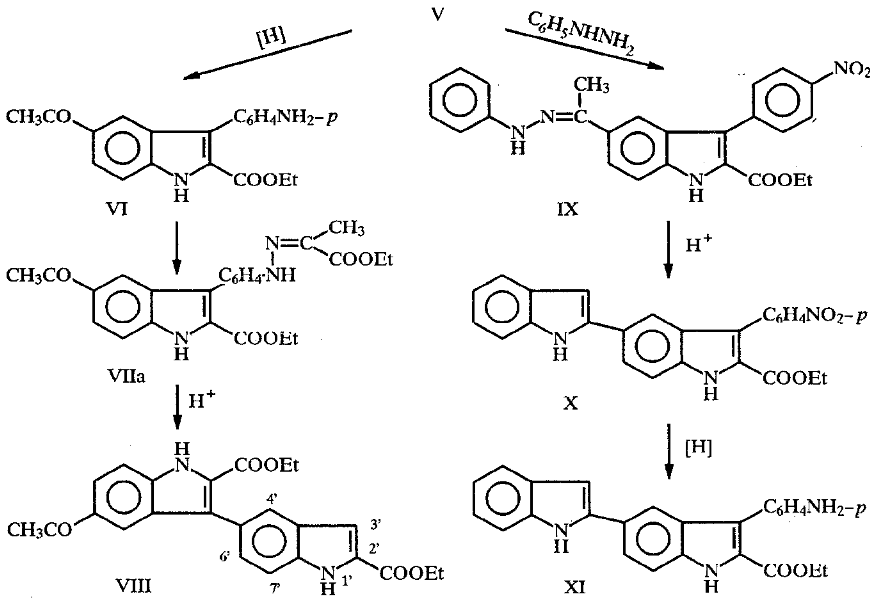
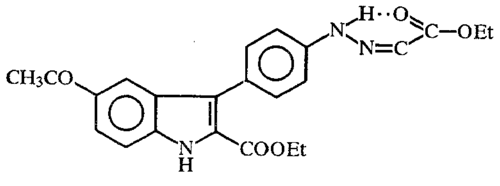


In the preparation of the hydrazone VIIa by the Japp—Klingemann reaction from the amine VI and α-methylacetoacetic ester a mixture of several compounds is formed from which it is possible to separate the anti-isomer VIIa.



VII

The hydrazone IX was prepared in alcohol solution with the addition of a few drops of glacial acetic acid.

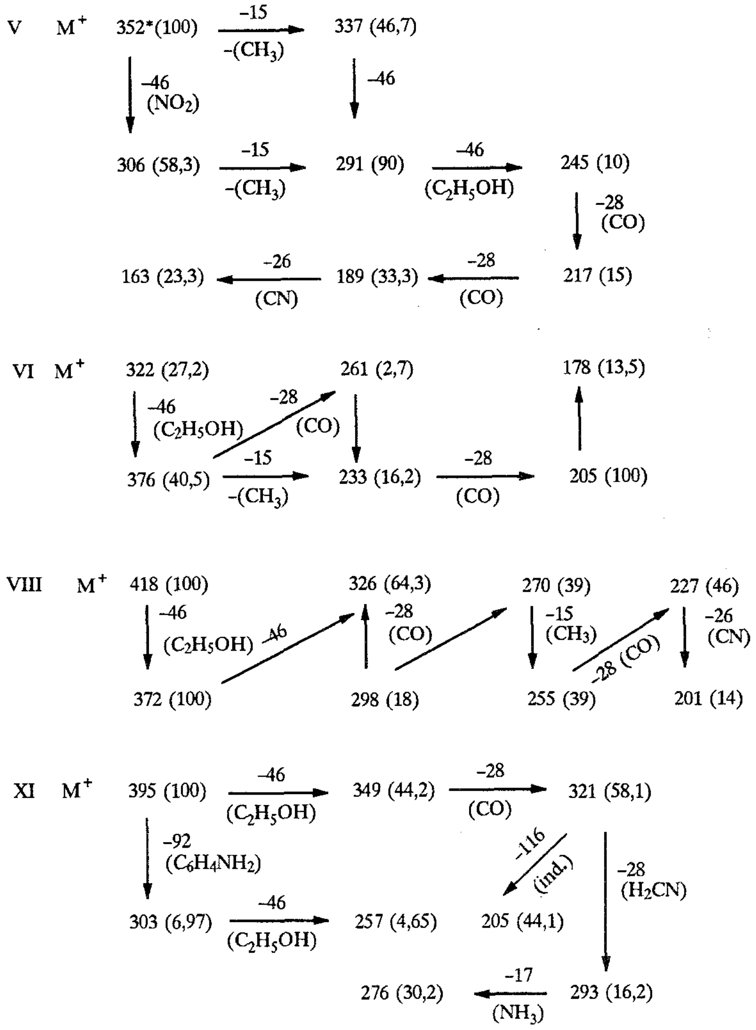
In the PMR spectra of hydrazones IV, VIIa, and IX (in $CDCl_3$) signals for the protons of the hydrazone NH group were recorded in the region of 8.33, 9.43, and 9.17 ppm respectively (Table 1), which points unequivocally to the anti-orientation of the substituents in compounds IV and VIIa. When the syn-isomer is formed, strong intramolecular hydrogen bonding can occur (for example, in the isomer VIIb); in such a case there is marked deshielding of the specified proton and its signal shifts downfield [5-7].

Indolization of the hydrazones VII and IX takes place in various systems, but the highest yields of bisindoles VIII and X (26 and 40% respectively) were attained in polyphosphoric acid.

In the IR spectra of all the compounds there were absorption bands for ester carbonyl at 1690-1720 cm^{-1}; in the case of compounds III-VIII there were bands in the 1660-1680 cm^{-1} region which we assigned to the carbonyl of the acetyl group. The characteristic vibrations of the NO_2 group of compounds IV, V, IX, and X appeared in the form of two bands in the 1350 and 1550 cm^{-1} regions, of the amino group of compounds VI and XI as broad bands in the 3330-3460 cm^{-1} region, and of the indole NH as narrow, more intense bands in the 3200-3460 cm^{-1} region (Table 2).

The molecular weights of compounds III-XI, determined by mass spectrometry, corresponded to the calculated values of compounds III-VIII there were bands in the 1660-1680 cm^{-1} region which we assigned to the carbonyl of the acetyl group. (Table 2) and the dissociative ionization could be represented in the manner shown in the scheme at the bottom of the previous page.

It can be seen from the scheme that the breakdown of the molecular ion is not inconsistent with the proposed structure. For example, fragmentation of the bisindole VIII proceeds via successive splitting off of the two ester groups, then acetyl and HCN. The aniline group in compounds VI and XI seems quite stable to electron bombardment. For example, in the breakdown of compound VI separation of NH_3 or NH_2 is not observed either from the molecular or from the fragmentation ions, and in compound XI breakdown takes place after splitting off of the ester group and one of the pyrrole rings. Splitting off of the NO_2 group in compounds V and X takes place at an early stage of the decomposition of the molecular ion.



*Values of m/z are given with (in brackets) the intensity relative to the maximum ion current.

EXPERIMENTAL

The progress of the reactions and the individuality of the compounds prepared was monitored by TLC on Silufol UV-254 plates. Silica gel with particle size 100-250 μm was used for column chromatography. Infrared spectra were recorded on a UR-20 instrument as mulls in mineral oil and UV spectra on a Specord spectrophotometer in ethanol. A WP-200 SY spectrometer was used to record PMR spectra with TMS as internal standard and mass spectra were obtained on a Ribermag R 10-10B spectrometer with ionization energy 70 eV.

The results of elemental analysis of the compounds prepared were in agreement with those calculated.

α-p-Nitrobenzylacetoacetic ester (II) was prepared by the method given in [4].

p-(2-Ethoxycarbonyl-5-acetylindol-3-yl)phenylhydrazone of the Ethyl Ester of Pyruvic Acid (VIIa). To a mixture of 1 g (3 mmoles) of 2-ethoxycarbonyl-3-(p-aminophenyl)-5-acetylindole (VI) in 70 ml water and 10 ml conc. HCl was added, with stirring, a solution of 0.21 g (3 mmoles) $NaNO_2$ in 5 ml water, keeping the temperature below 0°C. After 30 min, when the diazotization was complete, sodium acetate was added to the reaction mixture to give pH 6 and the mixture quickly poured into a solution of 0.43 g (3 mmoles) of α-methylacetoacetic ester and 0.17 g (3 mmoles) KOH in 50 ml ethanol and 15 ml water (it was necessary to maintain the pH strictly at 6). The reaction mixture was stirred at the same temperature for 4 h and the crystals which separated were filtered off, washed with water, and dried. Purification was effected on a column with 1:1 benzene—ether. Yield 0.43 g (33%).

2,2′-Diethylcarbonyl-5-acetyl-3,5′-bis-1H-indole (VIII). A mixture of 4.35 g (10 mmoles) of hydrazone VIIa and 35 g of polyphosphoric acid was slowly warmed to 80°C and stirred for 15 min. It was then cooled and poured into ice water

TABLE 1. PMR Spectra of Compounds III-XI

Compound	Chemical shift, δ, ppm
III*	1,16 (3H, t, J = 7, $CH_2C\underline{H}_3$); 4,21 (2H,q , $C\underline{H}_2CH_3$); 2,23& 2,65 (6H, 2 , CH_3CO); 3,59 & 3,72 (2H,d , J_{gem} = 13,89, CH_2); 7,79 (2H, d , J_{12} = 8,40, 1-H); 8,15 (2H, e, 2-H); 7,42 (2H, d, J_{34} = 8,80, 3-H); 8,12 (2H,d , 4-H)
IV	1,40 (3H, t, J = 7,25, $CH_2C\underline{H}_3$); 4,36 (2H,q , $C\underline{H}_2CH_3$); 2,54 (3H,s , CH_3CO); 4,14 (2H, s, CH_2); 8,33 (1H, s, NH); 7,89 (2H, e, J_{12} = 8,54, 1-H); 7,18 (2H,d., 2-H); 7,39 (2H, d, J_{34} = 8,54, 3-H); 8,15 (2H, d, 4-H)
V	12,55 (1H,s , 1-H); 8,16 (1H, d, J_{46} = 1,1, 4-H); 7,36 (1H,dd., J_{67} = 8,77, 6-H); 7,61 (1H,e., 7-H); 7,85 (2H, d, J_{ab} = 8,35, a-H); 8,35 (2H,d., 6-H); 2,58 (3H,s , CH_3CO); 1,2 (3H, t, J = 6,35, $CH_2C\underline{H}_3$); 4,27 (2H, q, $C\underline{H}_2CH_3$)
VI	12,04 (1H, c, 1-H); 8,17 (1H, d, J_{46} = 1,45, 4-H); 7,86 (1H, д.д, J_{67} = 8,77, 6-H); 7,52 (1H,d , 7-H); 7,22 (2H, d, J_{ab} = 8,40, a-H); 6,67 (2H,d , 6-H); 5,40 (2H, s. NH_2); 2,56 (3H, s, CH_3CO); 1,23 (3H, t, J = 7,31, $CH_2C\underline{H}_3$); 4,25 (2H, q, $C\underline{H}_2CH_3$)
VIIa**	8,26 (1H, d, J_{46} = 1,40, 4-H); 8,05 (1H, d.d., J_{67} = 8,70, 6-H); 7,52 (1H, d., 7-H); 7,70 (2H, d, J_{ab} = 8,40, a-H); 7,90 (2H, d, 6-H); 4,31 (2H, q, J = 7,3, $C\underline{H}_2CH_3$); 4,35 (2H, q , $C\underline{H}_2CH_3$); 1,28 (3H, т, $CH_2C\underline{H}_3$); 1,32 (3H, t, $CH_2C\underline{H}_3$); 2,41 (3H, s , CH_3CO); 1,71 (3H, s, $CH_3C{=}N$); 9,43 (1H, s, NH)
VIII	11,30 (1H,s, 1-H); 11,09 (1H, s, 1′-H); 7,29 (1H, dd , J_{13} = 2,2; J_{37} = 1,0; 3′-H); 8,33 (1H, d., J_{46} = 1,47; 4-H); 7,94 (1H, d, 4′-H); 8,00 (1H, dd , J_{67} = 8,77; 6-H); 7,55 (1H, dd , 6′-H); 7,67 (1H, dd., 7-H); 7,65 (1H, dd., 7′-H); 2,56 (3H,s , CH_3CO); 4,39 (2H, q, J = 6,95; $C\underline{H}_2CH_3$); 1,40 (3H, t, $CH_2C\underline{H}_3$); 1,19 (3H, t, $CH_2C\underline{H}_3$)
IX	12,25 (1H, s, 1-H); 7,72 (1H, d., J_{46} = 1,82; 4-H); 8,05 (1H, dd ., J_{67} = 8,77; 6-H); 7,55 (1H, d, 7-H); 7,86 (2H, d, J_{ab} = 8,77, a-H); 8,34 (2H, d, 6-H); 7,22 (5H, b-H-, d-, d. H); 4,26 (2H, q, J = 7,31, $C\underline{H}_2CH_3$); 1,21 (3H, t, $CH_2C\underline{H}_3$); 2,26 (3H, s., $CH_3C{=}N$); 9,17 (1H, s , N—NH)
X	11,45 (1H, s , 1-H); 12,34 (1H, c, 1′-H); 6,83 (1H,br,s , 3-H); 7,49 (1H, d , J_{46} = =1,46; 4-H); 8,00 (1H, d., $J_{4'6'}$ = 1,46; 4′-H); 7,05 (2H, m, J_{45} = J_{56} = J_{67} = 8,70; 5-H, 6-H); 7,87 (1H, dd , 5′-H); 7,36 (1H, d., 7-H); 7,62 (1H, d , 7′-H); 7,87 (2H, d., J_{ab} =8,78, a-H); 8,37 (2H, d, 6-H); 4,27 (2H,q., J = 7,31, $C\underline{H}_2CH_3$); 1,22 (3H, t, $CH_2C\underline{H}_3$)
XI	11,49 (1H, s, 1-H); 11,77 (1H, s, 1′-H); 6,75 (1H, br.s, 3-H); 7,52 (1H, d , J_{46} = =1,46, 4-H); 7,97 (1H, d, 4′-H); 6,99 (2H, м, J_{45} = J_{56} =J_{67} = 8,77, 5-H, 6-H); 7,80 (1H, dd., 6′-H); 7,34 (1H, d, 7-H); 7,48 (1H, d, 7′-H); 7,25 (2H, J_{ab} = 8,40, a-H); 6,69 (2H, d, 6-H); 4,25 (2H, q, $C\underline{H}_2CH_3$); 1,24 (3H, t, $CH_2C\underline{H}_3$); 5,29 (2H, s, NH_2)

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*Spectra of compounds III, V, VI, X, XI run in DMSO-D_6, IV, VIIa, IX in $CDCl_3$, VIII in acetone-D_6.

**Because of NH → ND exchange, the 1-H signal was absent.

and the precipitate separated, washed with water, and dried. The yield of crude indole was 4 g (95%). It was purified on a column with 2:1 benzene—ether to give 1.1 g (26%).

Phenylhydrazine of 2-Ethoxycarbonyl-3-(p-nitrophenyl)-5-acetylindole (IX). To a solution of compound V in 25 ml ethanol was added 5 ml phenylhydrazine and 0.5 ml glacial acetic acid. This was stirred at 50°C for 2 h and then poured into 300 ml ice water and the precipitate filtered off, washed with water, and dried to yield 1.8 g hydrazone IX.

2′-Ethoxycarbonyl-3′-(p-nitrophenyl-2,5′-bis-1H-indole (X). A mixture of 1.8 g (4 mmoles) of hydrazone IX and 15 g of polyphosphoric acid was slowly warmed to 80°C and stirred for 30 min. It was then cooled, poured into ice water and the precipitate filtered off, washed with water, and dried. Yield 0.9 g (53%) bisindole X. This was purified on a column using 2:1 hexane—ether to yield 0.7 g.

2′-Ethoxycarbonyl-3′-(p-aminophenyl)-2,5-bis-1H-indole (XI). To a suspension of 0.4 g (1 mmole) bisindole X in 30 ml ethanol and 0.3 g skeletal nickel was added, dropwise at bp over 1 h, 10 ml hydrazine hydrate. This was held at bp for

TABLE 2. Physicochemical Characteristics of Compounds III-XI

Compound	Empirical formula	mp, °C	M^+	R_f	IR spectrum, ν, cm^{-1}								UV spectrum, λ_{max} nm (lg ε)	Yield, %
					N=N	C=N	C=O	C=O ester	NH	NH indole	NO_2	NH_2		
III	$C_{21}H_{21}N_3O_6$	120...121	411	0,5*	1640	—	1700	1740	—	—	—	—	241 (3,9), 280 (4,0), 363 (4,5)	78
IV	$C_{19}H_{19}N_3O_5$	151...152	369	0,3*	—	1620	1670	1710	3330	—	1360...1530	—	203 (4,4), 216 (4,2), 281 (4,5)	95
V	$C_{19}H_{16}N_2O_5$	245...246	352	0,53*	—	—	1680	1720	3200	—	1370...1530	—	200 (4,4), 266 (4,8), 327 (4,37)	70
VI	$C_{19}H_{18}N_2O_3$	226...227	322	0,43*2	—	—	1700	—	3300	—	—	3455	202 (4,9), 266 (4,97)	84
VIIa	$C_{24}H_{25}N_3O_5$	191...192	435	0,16*	—	1620	1680	1730	3200...3400	—	—	—	202 (3,3), 208 (2,5), 271 (3,7), 331 (2,6)	33
VIII	$C_{24}H_{22}N_2O_5$	150...152	418	0,27*2	—	—	1620	1660	—	3250...3260	—	—	206 (4,3), 276 (4,9)	26
IX	$C_{25}H_{22}N_4O_4$	247...248	442	0,6*3	—	1620	—	1700...1710	3390	3350	1365...1530	—	201 (4,5), 261 (4,1)	81
X	$C_{25}H_{19}N_3O_4$	232...233	425	0,31*3	—	—	—	1720	—	3460...3470	1360...1550	—	206 (4,4), 258 (4,6), 273 (4,5)	40
XI	$C_{25}H_{21}N_3O_2$	205...205	395	0,26*4	—	—	—	1700	—	3300...3350	—	3450	203 (4,6), 250 (4,5), 260 (4,5)	44

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*1:1 benzene—ether.

*2 2:3 benzene—ether.

*3 2:1 CCl_4—ether.

*4 2:1 hexane—ether.

a further hour and the solution filtered hot. The filtrate was cooled and evaporated to a volume of 5 ml. The crystals which formed were filtered off and dried to give 0.27 g (68%) bisindole XI. This was purified on a column using 2:1 CCl_4—ether. Yield 0.18 g.

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