BISINDOLES 27.*

ELECTROPHILIC SUBSTITUTION REACTIONS OF 7,7-DICHLOROBIS(5-INDOLYL)METHANES

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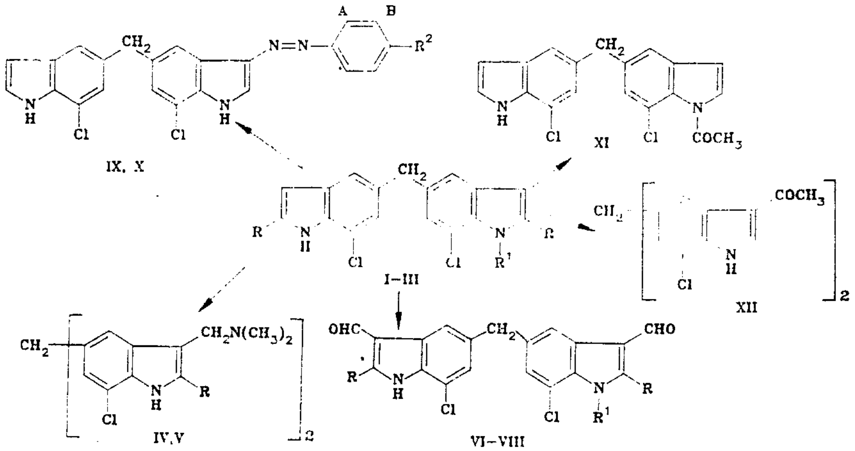
Formylation, aminomethylation and acetylation have been studied as the most characteristic electrophilic substitution reactions of 7,7'-dichlorobis(5-indolyl)methane and its diethyl ester.

We have carried out the formylation, dimethylaminomethylation, and acetylation of 7,7-dichlorobis(5-indolyl)methane (I) and its 2-carbethoxy derivative (II) which had previously been synthesized by us [1].



I, VI R=R'=H; II, VII R=COOEt, R'=H, III, VIII R=COOEt, R'=Et; IV R=H; V R=COOEt; IX R^2=NO_2, X R^2=H

Quantum chemical calculations† have shown that the bisindole I retains the character of the dispersed electron density of the indole ring [2]. The positions of greatest electron density are at 3 and 3'.

The bisindoles I, II were aminomethylated using N,N-dimethylmethyleneimmonium chloride in absolute DMF to give the disubstituted compounds IV and V whose PMR spectra showed the absence of signals for the 3- and 3'- hydrogens (Tble 1).

Formylation of the bisindole I takes place at room temperature whereas II and III (containing acceptor carbethoxyl groups) occur at 70°C. The PMR spectra of VI-VIII showed the absence of the 3-H and 3'-H protons (Table 1) and the spectrum of VIII showed evidence for three ethyl groups with three different proton spin couplings (7.33, 6.84, and 6.85 Hz).

The IR spectra of VI-VIII showed absorption bands for the NH group at 3230-3450, the aldehyde (1640-1660), and the carbethoxy carbonyl in VII, VIII (1710-1715 cm^{-1}) (Table 2).

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*For Communication 26 see [1].

†Calculations were carried out by the CNDO MO method by Dzh. A. Kereselidze at the Applied Mathematics Institute of the Tbilisi State University.

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Azo coupling of I with the diazonium salts derived from aniline and p-nitroaniline gives only the mono-substituted IX and X using aqueous-dioxane as solvent. The UV absorption maxima of IX and X are shifted from the starting indole [2] to the visible region and appear at 413 and 315 nm, respectively (Table 2). The IR spectra of IX and X show typical absorption for the N=N group at 1430 and 1440 cm^{-1} and the NMR spectra show quartet signals at 6.55 and 6.54 ppm assigned to the β-proton of the second pyrrole ring (Table 1).

Reaction of bisindole I with acetic anhydride in the presence of sodium acetate gives 1-acetyl-7,7'-dichlorobis(5-indolyl)methane (XI) or to 3,3'-diacetyl-7,7'-dichlorobis(5-indolyl)methane (XII) with $SnCl_4$ [3]. The PMR spectrum of XII shows the absence of the 3- and 3'-protons and a singlet signal for the $COCH_3$ groups at 2.45 ppm.

The mass spectra of IV, VI-IX, XI, and XII show molecular ion peaks with m/z 428, 370, 514, 542, 463, 356, and 398, respectively in agreement with the proposed structures. All of the spectra contained a triplet of peaks with ions M, [M + 2], and [M + 4] pointing to the presence of two chlorine atoms. In general terms the mass spectral pattern for the investigated compounds is the elimination of functional groups or their component parts from the pyrrole ring and the aromatic nucleus together with fission of the bonds on both sides of the carbon of the methylene group with formation of the corresponding substituted methyleneindole or indole cations. Cleavage of the indole nucleus is observed at the fundamental stages of the dissociation.

EXPERIMENTAL

Reaction monitoring, compound purity and R_f were determined using F_{254} plates. Column chromatography was carried out on 100-250 micron silica gel. IR spectra were recorded on a UR-20 instrument, UV spectra on a Specord spectrophotometer in ethanol, mass spectra on a Ribermag R10-10B, and PMR spectra on a WP-200-SY instrument using a TMS internal standard. Elemental analytical data (C, H, N, Cl) agreed with that calculated.

7,7'-Dichloro-3,3'-di(dimethylaminomethyl)bis(5-indolyl)methane (IV). Dimethylmethyleneimmonium chloride (1.5 g, 16 mmole) was added to a solution of I (0.2 g, 0.64 mmole) in DMF (20 ml), stirred at 25°C for 2 h, cooled, diluted with water, and basified to pH 10. The precipitated solid was filtered off, washed with water to pH 7 and dried. Yield 0.25 g.

7,7'-Dichloro-2,2'-dicarbethoxy-3,3'-di(dimethylaminomethyl)bis(5-indolyl)methane (V) was obtained similarly to (IV) from I (0.3 g, 0.65 mmole) in DMF (25 ml) and dimethylmethyleneimmonium chloride (3 g, 32 mmole) at 80°C. Yield 0.2 g.

7,7'-Dichloro-3,3'-diformylbis(5-indolyl)methane (VI). A solution of I (0.2 g, 0.63 mmole) in DMF (5 ml) at −5°C was added to the reagent formed from DMF (1.5 g, 20.5 mmole) and $POCl_3$ (1.2 g, 7.9 mmole). The product was heated to 80°C, stirred for 3 h, cooled, poured into ice, and basified to pH 10. The precipitated solid was filtered off, washed with water to pH 7, dried, and recrystallized from DMF. Yield 0.2 g.

7,7'-Dichloro-2,2'-dicarbethoxy-3,3'-diformylbis(5-indolyl)methane (VII) was obtained similarly to VI from II (0.3 g, 0.65 mmole). Yield 0.28 g.

1-Ethyl-7,7'-dichloro-2,2'-dicarbethoxy-3,3'-diformylbis(5-indolyl)methane (VIII) was obtained similarly to VI from III (0.28 g, 0.51 mmole). Yield 0.1 g.

7,7'-dichloro-3-p-nitrophenylazobis(5-indolyl)methane (IX). A solution of I (0.2 g, 0.65 mmole) in dioxane (20 ml) and water (10 ml) was cooled to −5°C and there was added a solution obtained by diazotization of p-nitroaniline (0.54 g, 3.9 mmole) at pH 6. The product was stirred for 3 h at 0-5°C, diluted with water, extracted with ether, and dried over $CaCl_2$. The solvent was evaporated and the residual oil purified on a column using benzene as eluent. Yield 0.02 g.

7,7-Dichloro-3-phenylazobis(5-indolyl)methane (X) was obtained similarly to IX from I (0.1 g, 0.32 mmole) and aniline (0.5 g, 0.9 mmole). Yield 0.04 g.

1-Acetyl-7,7'-dichlorobis(5-indolyl)methane (XI). A mixture of I (0.2 g, 0.63 mmole), acetic anhydride (35 ml), and sodium acetate (6 g) were stirred for 20 h at 132°C, cooled, diluted with water, extracted with ether, and dried. The ether was distilled off and the residual oil column chromatographed using benzene eluent. Yield 0.06 g.

3,3'-Diacetyl-7,7'-dichlorobis(5-indolyl)methane (XII). A solution of anhydrous stannous chloride (1.8 g, 15 mmole) in absolute benzene (5 ml) was added with stirring over 15

TABLE 1. PMR Spectra of IV-XII

Compound	Chemical shift, δ, ppm*										Spin spin coupling, Hz
	1-H, 1'-H br. s	2-H, 2'-H	3-H, 3'-H	4-H, 4'-H	6-H, 6'-H	CH$_2$ s	CHO s	CH$_2$—Et q	CH$_3$—Et t	other protons	
IV	10,27	7,27 d	—	7,61 d	7,05 d	4,15	—	—	—	3,55 (CH$_2$N, s), 2,21 (CH$_3$N, s)	$J_{12}=2,2$; $J_{46}=1,1$
V	10,58	—	—	7,83 d	7,24 d	4,18	—	4,37	1,38	3,96 (CH$_2$N, s), 2,22 (CH$_3$N, s)	$J_{46}=1,5$; $J_{CH_3CH_2}=7,3$
VI	10,64	7,94 s	—	8,32 d	7,27 d	4,16	9,91	—	—	—	$J_{46}=1,1$
VII	12,59	—	—	8,10 s	7,35 s	4,19	10,54	4,46	1,40	—	$J_{CH_3CH_3}=7,3$
VIII	12,96	—	—	8,22 d 8,11 d	7,40 d 7,35 d	4,17	10,55; 10,30	4,49 4,45	1,40 1,40	4,79 (CH$_2$—Et—N, q) 1,46 (CH$_3$—Et—N, t) $J_{CH_3CH_2—N}=6,83$ Hz)	$J_{46}=1,4$; $J_{4',6'}=1,5$; $J_{CH_3CH_2}=7,3$; $J_{(CH_3CH_2)}=6,8$
IX	10,50; 11,64	7,42 dd 8,40 s	6,55	7,32 d 8,46 d	7,14 d 7,50 d	4,23	—	—	—	8,00 (AH, d) and 8,40 ppm (BH, d, $J_{AB}=9,1$ Hz)	$J_{12}=2,6$; $J_{13}=2,2$; $J_{23}=2,9$; $J_{46}=1,5$; $J_{4'6'}=1,1$
X	10,22; 11,37	7,50 d 8,25 d	6,54 dd	7,25 d 8,42 d	7,13 d 7,50 d	4,21	—	—	—	7,40 . . . 7,82 (phenyl, m)	$J_{13}=2,0$; $J_{23}=3,1$; $J_{1'2'}=2,9$; $J_{46}=1,5$ $J_{4'6'}=0,7$
XI	11,37	7,37 dd 7,89 d	6,47 dd 6,72 d	7,41 d 7,45 d	7,07 d 7,26 d	4,08	—	—	—	2,66 (COCH$_3$, s)	$J_{12}=2,6$; $J_{13}=1,8$; $J_{23}=2,9$; $J_{2'3'}=3,6$; $J_{46}=J_{4'6'}=2,1$
XII	11,18	8,24 d	—	8,22 d	7,22 d	4,23	—	—	—	2,45 (COCH$_3$, s)	$J_{12}=3,0$; $J_{46}=1,5$

*PMR spectra of IV, V, IX, X and XII in acetone-d_6, VI-VIII, XI in DMSO-d_6.

TABLE 2. Physical Data for IV-XII

Compound	Empirical formula	R_f*	mp, °C	IR spectrum, ν, cm^{-1}**		UV spectrum, λ_{max}, nm (log ε)	Yield, %
				CO	NH		
IV	$C_{23}H_{26}Cl_2N_4$	—	122 . . . 123	—	3485	272 (4,7), 277 (4,0), 291 (4,1), 299 (3,9)	92
V	$C_{29}H_{34}Cl_2N_4O_4$	—	145 . . . 146	1710	3465	240 (4,7), 300 (4,5)	52
VI	$C_{19}H_{12}Cl_2N_2O_2$	—	300(decomp.)	1640	3245	—	85
VII	$C_{25}H_{20}Cl_2N_2O_6$	—	306 . . . 307	1655, 1715	3240	—	83
VIII	$C_{27}H_{24}Cl_2N_2O_6$	—	205 . . . 206	1660, 1710	3435	—	32
IX	$C_{23}H_{15}Cl_2N_5O_2$	0,70	249 . . . 250	—	3435	230 (4,6), 289 (4,3), 299 (4,2), 413 (4,2)	7
X	$C_{23}H_{16}Cl_2N_4$	0,62	146 . . . 148	—	3595	202 (4,5), 226 (4,4), 351 (4,7)	32
XI	$C_{19}H_{14}Cl_2N_2O$	0,37	138 . . . 140	1750	3490	233 (4,2), 245 (4,2), 292 (3,7), 301 (3,7), 312 (3,5)	22
XII	$C_{21}H_{16}Cl_2N_2O_2$	0,26	300(decomp.)	1625	3155	216 (4,7), 254 (4,6), 299 (4,4)	79

*Eluent benzene-ether, 2:1 (for IX, X), benzene (for XI), benzene-acetone 2:1 (for XII).

**IR spectra were recorded in chloroform (IV, V, VIII, X) and in vaseline mull (VI, VII, IX, XII).

min to a cooled solution of 7,7'-dichlorobis(5-indolyl)methane (0.2 g, 0.6 mmole) in absolute bezene (30 ml) and acetic anhydride (15 ml). The product was stirred for 2 h at 0-5°C, poured onto ice, and the precipitate was filtered off. Washing with water, drying and column purification using benzene-ether (2:1) as eluent gave a yield of 0.2 g.

LITERATURE CITED

1. Dzh. Zegkhugkh, D. O. Kadzhrishvili, Sh. A. Samsoniya, N. N. Suvorov, and N. Z. Kedelashvili, Khim. Geterotsikl. Soedin., No. 8, 1062 (1988).
2. M. G. Cheshmaritashvili, Sh. A. Samsoniya, L. N. Kurkovskaya, and N. N. Suvorov, Khim. Geterotsikl. Soedin., No. 1, 73 (1984).
3. G. I. Zhungietu, V. A. Budilin, and A. N. Kost, Preparative Chemistry of Indole [in Russian], Shtiintsa, Kishinev (1975), p. 116.

5-BENZOPYRIDYL-SUBSTITUTED 2-METHYL- AND 2-METHYLENEINDOLINES

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A method of synthesis of 5-(isoquinol-1-yl)- and 5-(quinol-2-yl)-1,3,3-trimethyl-2-methyleneindolines has been developed consisting of hetarylation of 1,2,3,3-tetramethylindoline with isoquinoline and quinoline in the presence of benzoyl chloride, followed by oxidation and aromatization of N-benzoyl-1,2-dihydrobenzopyridine derivatives of 1,2,3,3-tetramethylindoline formed at the first stage to 5-benzopyridyl-substituted 2-methylene-indolines.

The Fischer base – 1,3,3-trimethyl-2-methyleneindoline – is an extremely important intermediate in the synthesis of various dyes [1-3]. Of particular interest are dyes of this type in which electron-accepting substituents are present in the 5-position of the benzene ring, which, generally, cause a considerable deepening of the color, and in several cases lead to dyes with improved properties of practical use [3].

It seemed very promising to try to use the hetarylation reaction [4] to introduce benzopyridines having electron-accepting properties into the 5-position of the Fischer base. It was found that the direct hetarylation of the Fischer base leads to the introduction of the heterocyclic residue into the CH_2 group,* rather than at the 5-position of the benzene ring, similarly as salts of an N-methylacridinium cation react with the Fischer base and other enamines [6]. Therefore, to obtain 5-hetaryl-substituted 2-methyleneindolines, we used a previously developed method of synthesis of 2-methyleneindolines, consisting in the introduction of substituents into the benzene ring of 1,2,3,3-tetramethylindoline I, followed by oxidation of the compounds obtained [7]. Indoline I was hetarylated by N-benzoylisoquinolinium and quinolinium chlorides formed in situ, and also by acridine hydrochloride. The known methods of hetarylation of dialkylanilines [8-11] served as the basis for this reaction. The hetarylation reaction proceeds most readily when indoline I is reacted with isoquinoline in the presence of benzoyl chloride. A substituted indoline II is formed directly by mixing the reagents at room temperature. The reaction proceeds with a slight warming up (50...60°C) and is concluded after 1 h. Hetarylation with acridine hydrochloride proceeds fairly rapidly with the formation of indoline III. With N-benzoylquinolinium chloride formed in situ, the hetarylation proceeds, as expected, much more slowly [8]. A maximal yield of compound IV was achieved on heating the reaction mixture without a solvent for 70 h at 70...80°C.

Attempts to carry out the simultaneous dehydroaromatization of 1,2-dihydroisoquinoline and indoline fragments of compound II to the corresponding isoquinoline derivative of the Fischer base X by conventional dehydroaromatizing agents were not successful. We therefore

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*For a preliminary communication on this subject, see [15].

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