INDOLE DERIVATIVES.
135.* 5-[2-(4-METHOXYPHENYL)ETHENYL]INDOLINES AND INDOLES

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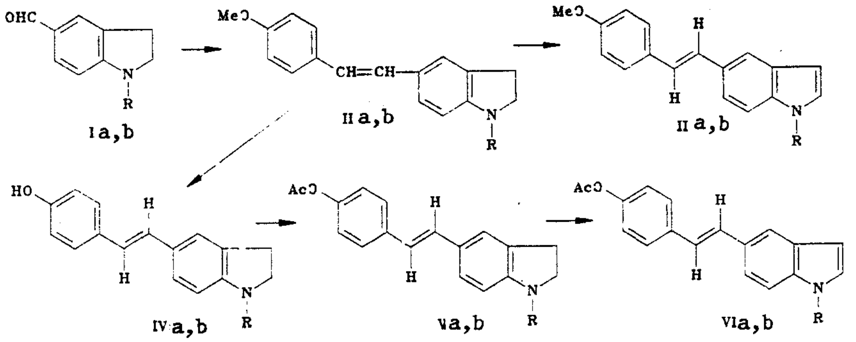
5-[2-(4-Methoxyphenyl)ethenyl]indolines were obtained from 5-formyl-1-methyl- or 5-formyl-1-benzylindolines by the Witting reaction with 4-methoxybenzylidenetriphenylphosphorane. Their dehydrogenation led to the formation of the corresponding compounds of the indole series. The corresponding hydroxy compounds were obtained by demethylation of the methoxyindole with boron tribromide and were converted into the acetoxy derivatives of indoline and indole.

While continuing work [2] on the synthesis of the heterocyclic analogs of diarylethylenes, we realized the synthesis of 4-methoxy- and 4-acetoxyphenyl-substituted compounds of the 5-(2-phenylethenyl)indoline and indole series. The Grignard and Wittig reactions were used as methods for construction of the ethylene bridge between the phenyl and indole parts of the molecule.

The olefin (IIa) was obtained in the form of the pure trans isomer by the condensation of the aldehyde (Ia) with 4-methoxybenzylmagnesium chloride followed by dehydration. Here anisaldehyde was reduced with sodium borohydride according to the familiar scheme to 4-methoxybenzyl alcohol [3], which was converted with hydrogen chloride into the chloride [4] and then with an excess of magnesium into the Grignard reagent [5]. However, in spite of the high stereospecificity, the method does not give satisfactory yields of the olefin (IIa) and is complicated in preparative respects on account of the side reactions which occur during the production of the Grignard reagent.



I-VI a $R=CH_3$; b $R=CH_2C_6H_5$

For the Wittig condensation the corresponding phosphonium salt [6], which gives 4-methoxybenzylidenetriphenylphosphorane with butyllithium [7], was obtained from triphenylphosphine hydrobromide with 4-methoxybenzyl alcohol. With aldehydes of the indoline series (Ia, b) this phosphorane forms the olefins (IIa, b) as mixtures of the cis and trans isomers.

According to the PMR data, the ratio of the isomers amounts to ∿1:1. The trans isomer is easily separated by crystallization (yield 34%). The configuration of the double bond in

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*For communication 134, see [1].

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TABLE 1. The Characteristics of the Synthesized Compounds

Compound	Molecular formula	mp, °C*	PMR spectrum, ppm				
			CH_2 of benzyl	CH_3, s	2H	3H	CH=CH**
IIa	$C_{18}H_{19}NO$	205,5...7,0	—	2,87 ($N-CH_3$); 3,93	3,04 t	3,43 t	7,06; 7,12
IIb	$C_{24}H_{23}NO$	127,0...8,5	4,29 s	3,85	3,00 t	3,35 t	6,83; 6,92
IIIa	$C_{18}H_{17}NO$	204,5...6,0	—	3,83 ($N-CH_3$); 3,86	7,06 d	6,50	7,05; 7,15
IIIb	$C_{24}H_{21}NO$	141,5...3,0	5,31 s	3,84 s	7,09 d	6,55 q	6,98; 7,09
Va	$C_{19}H_{19}NO_2$	118,5...20,0	—	2,30; 2,78 ($N-CH_3$)	2,97 t	3,35 t	6,86; 6,98
Vb	$C_{25}H_{23}NO_2$	131,5...3,0	4,29 s	2,28	3,00 t	3,39 t	6,84; 6,95
VIa	$C_{19}H_{17}NO_2$	175,0...6,5	—	2,30; 2,78 ($N-CH_3$)	7,10 d	6,50	7,08; 7,22
VIb	$C_{25}H_{21}NO_2$	169,5...70,5	5,31 s	2,30	7,12 d	6,55 q	7,04; 7,20

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*All the compounds were recrystallized from ethanol.

**For compounds (IIa, b, IIIa, b, Va, b, VIa, b) J = 16 Hz.

the trans isomers (IIa, b) was confirmed by the observation of the signals for the olefinic protons with the characteristic spin–spin coupling constant (J = 16 Hz) in the PMR spectra. The oily cis isomers of (IIa, b) were not isolated in the pure form.

In spite of the absence of stereospecificity, the Wittig synthesis of compounds (IIa, b) is more convenient in preparative respects than the synthesis with the Grignard reagent. Of particular interest in preparative respects is the Wittig condensation under the conditions of phase-transfer catalysis [9], which makes it possible to avoid the use of anhydrous solvents and organometallic compounds as bases. However, during the condensation of the aldehyde (Ib) with 4-methoxybenzyltriphenylphosphonium bromide under the conditions of phase-transfer catalysis the yield of the trans isomer (IIb) was less than 20%, in spite of the long reaction time and the excess of the phosphonium salt.

The dehydrogenation of compounds (IIa, b) with active manganese dioxide [10] by the method in [2] led to the corresponding derivatives of indole (IIIa, b), the trans configuration of which was established by PMR by analogy with the foregoing. Attempts at the demethylation of (IIa, b) with HBr [11] and $(CH_3)_3I$ [12] did not lead to the corresponding phenols. For this reason the methyl group was removed by means of boron tribromide according to the method in [13]. The formation of the phenols (IVa, b) was confirmed by the appearance of a band corresponding to the stretching vibrations of the OH group (3280 and 3220 cm^{-1} respectively) in the IR spectrum. The trans configuration of (IVa, b) was confirmed by the PMR data (J = 16 Hz).

The acetylation of the phenols (IVa, b) with acetic anhydride gave the corresponding derivatives of indoline (Va, b). During dehydrogenation with active manganese dioxide [2] compounds of the indole series (VIa, b) were isolated.

EXPERIMENTAL

The PMR spectra were obtained on a Bruker M-250 spectrometer at 250.13 MHz in deuterochloroform, acetone-d_6, and methanol-d_4. The mass spectra were recorded on a Varian MAT-112 spectrometer at 70 eV (direct injection), and the M^+ values for all the compounds agreed with the calculated molecular masses. The reactions and the purities of the compounds were monitored by TLC on Silufol UV-254 plates. The obtained compounds were purified by filtration of the benzene solution through a layer of silica gel L140/100.

The characteristics of the synthesized compounds are given in Table 1.

1-Methyl-5-[trans-2-(4-methoxyphenyl)ethenyl]indoline (IIa). To a solution of 4-methoxybenzylmagnesium chloride [obtained by the slow addition (2 h) of a solution of 6.7 ml (49.2 mmole) of 4-methoxybenzyl chloride in 50 ml of anhydrous ether to 5.98 g (246.2 mmole) of magnesium in 300 ml of ether and filtration of the excess of magnesium] we added dropwise with stirring at 0°C a solution of 5 g (31 mmole) of 1-methyl-5-formylindoline (Ia) in 35 ml of anhydrous THF. The mixture was stirred at 0°C for 15 min and at 20°C for 15 min and cooled at 10°C. A solution of 50 g of ammonium chloride in 150 ml of water was added. The organic layer was separated, and the product was extracted from the aqueous layer with chloroform (2 × 50 ml). The combined extract was washed with water and dried, and the solvent was evaporated. To the residue (~9.5 g) we added 7.2 g of sulfosalicylic acid and 120 ml of benzene. The mixture was boiled with a Dean–Stark tube, 150 ml of a 2% solution of sodium carbonate was added, and the mixture was heated and stirred until the precipitate had dissolved. The organic layer was separated, and the aqueous layer was extracted with chloroform (2 × 50 ml). The combined extract was dried, the solvent was evaporated, the residue was dissolved in benzene, the solution was filtered through silica gel, and 1.8 g (22%) of (IIa) was obtained.

1-Benzyl-5-[trans-2-(4-methoxyphenyl)ethenyl]indoline (IIb). To 30 ml of freshly distilled THF at −10°C in a stream of argon we added 55 ml of a 1.0 N solution of n-butyllithium in anhydrous petroleum ether. A 10.7-g sample (23.1 mmole) of 4-methoxybenzyltriphenylphosphonium bromide was added in portions with stirring and cooling. The formation of the ylide was monitored from the appearance of a red-brown color in the reaction mass. The mixture was stirred for a further 1 h, and a solution of 5 g (21 mmole) of 1-benzyl-5-formylindoline (Ib) in 35 ml of THF was added dropwise at −10°C. After 2 h the mixture was poured into water and ice, the organic layer was separated, and the product was extracted with ether (3 × 50 ml). The combined extract was dried, the solvent was evaporated, benzene was added, and the product was passed through silica gel. After crystallization we obtained 2.42 g (34%) of (IIb).

Compound (IIa) was obtained similarly.

1-Benzyl-5-[trans-2-(4-methoxyphenyl)ethenyl]indole (IIIb). To a solution of 0.8 g (2.3 mmole) of (IIb) in 15 ml of benzene, while stirring at room temperature, we added 3 g of active manganese dioxide in portions. The mixture was stirred for 3 h, filtered, and washed with benzene and chloroform. The combined filtrate was dried, the solvent was evaporated, and after purification we obtained 0.49 g (62%) of (IIIb).

Compound (IIIa) was obtained similarly.

1-Methyl-5-[trans-2-(4-acetoxyphenyl)ethenyl]indoline (Va). To a solution of 1.2 g (4.5 mmole) of (IIa) in 40 ml of anhydrous distilled methylene chloride, while cooling, we added dropwise with stirring a solution of 0.62 ml (6.8 mmole) of boron tribromide in 4 ml of methylene chloride. The mixture was stirred for 1 h and poured into water. The precipitated phenyl was filtered off and washed with ethyl acetate, and 0.75 g of the phenol (IVa) was obtained. The product was extracted from the aqueous layer with chloroform (2 × 50 ml). The extract was washed with water, dried, and evaporated, and a further 0.2 g of the phenol (IVa) was obtained. The total yield was 84%. A 0.95-g sample of the indoline (IVa) in 2 ml of pyridine was boiled with 1.05 ml (11.4 mmole) of acetic anhydride for 30 min. The mixture was cooled, poured into 100 ml of water and ice, extracted with ether, and washed with dilute hydrochloric acid, a saturated solution of sodium bicarbonate, and water. The extract was dried and evaporated, and after purification and recrystallization we obtained 0.85 g (86%) of (Va).

Compound (Vb) was obtained similarly.

1-Methyl-5-[trans-2-(4-acetoxyphenyl)ethenyl]indole (VIa) and 1-Benzyl-5-[trans-2-(4-acetoxyphenyl)ethenyl]indole (VIb). Compounds (VIa, b) were obtained from compounds (Va, b) similarly to (IIIa, b).

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BIS(INDOLYL-3-)PHTHALIDES AND THEIR SPECTRAL PROPERTIES

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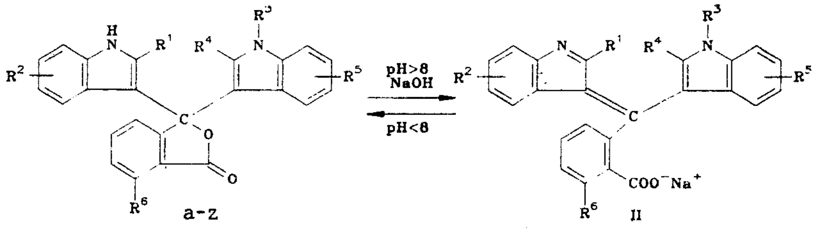
Symmetrical bis-indolylphthalides, having electron-releasing and electron-withdrawing substituents on the indole rings, were obtained from the reaction between an indole and an unsubstituted or substituted phthalic anhydride. Unsymmetrical indolylphthalides were synthesized by the condensation of 3-(o-carboxybenzoyl)indole with a substituted indole. A relationship was found to exist between the nature of the substituent, and the spectral and acid-base properties of the compounds.

The indolylphthalides I, like phenolphthalein, are sensitive to changes in pH [1-3]. In alkaline solution, the lactone ring is opened to give a carbonyl compound which is converted to the colored salt of an acid with the quinoid structure II. In this work, symmetrical and unsymmetrical indolylphthalides I have been synthesized and their spectral properties have been studied.



The symmetrical indolylphthalides I were obtained by heating an indole derivatives with phthalic anhydride in the presence of zinc chloride [4]. The symmetrical compounds I were synthesized via the intermediate compound 3-(o-carboxybenzoyl)indole, by condensation with substituted indoles in acetic anhydride in the presence of acetic and p-toluenesulfonic acids [6]; 3-(o-carboxybenxoyl)indole was obtained by the reaction of indolylmagnesium iodide with phthalic anhydride [5].

Spectra of the colored form of both symmetrical and unsymmetrical indolylphthalides in a 4:1 mixture of 6.4 N sodium hydroxide and ethyl alcohol were obtained, as well as UV spectral data for the compounds in ethyl alcohol solution, and pK_a values corresponding to the pH at which 50% of the indolylphthalide (as for phenolphthalein) is converted to the colored form (see Table 1).

As can be seen from the Table 1, in alkaline solution, the unsubstituted 3,3-bis(indolyl-3)phthalide Ia has an absorption maximum at 520 nm. A carboxyl group at position 2 of the indole rings (Ic) causes a small hypsochromic shift of the absorption maximum, but a carboxyl group at position 7 (Id) has very little effect on the color. This is probably due to steric hindrance in the molecule of the dye: the electron density at the atoms making up the chromophoric system is decreased, but it is more uniformly distributed, which should result in a

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