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

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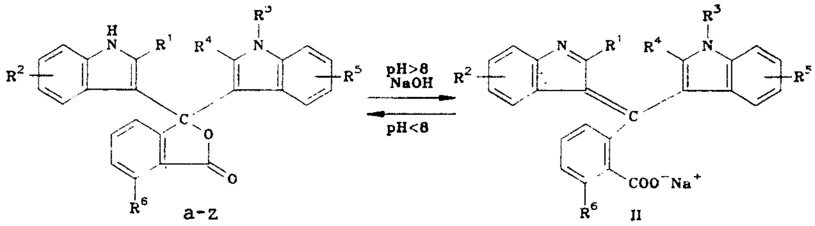
Symmetrical bis-indolylphthalides, having electron-releasing and electron-withdrawing substituents on the indole rings, were obtained from the reaction between an indole and an unsubstituted or substituted phthalic anhydride. Unsymmetrical indolylphthalides were synthesized by the condensation of 3-(o-carboxybenzoyl)indole 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.



a-z

II

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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TABLE 1. Characteristics of Bis-idolylphthalides

Compound	R^1	R^2	R^3	R^4	R^5	R^6	Empirical formula	mp, °C	Abs. max. and extinc. coeff. in a mix. of 6.4 N NaOH and ethanol (4:1)		UV spectrum (in ethanol)		pK_a	Yield, %
									λ_{max}, nm	$\varepsilon \cdot 10^4$	λ_{max}, nm	$\varepsilon \cdot 10^4$		
Ia	H	H	H	H	H	H	$C_{24}H_{16}N_2O_2$	148...150	520	2,5	280	1,5	10,7	30
Ib	H	H	H	H	H	NO_2	$C_{24}H_{15}N_3O_4$	186...187	524	2,1	287	1,3	10,3	23
Ic	COOH	H	H	COOH	H	H	$C_{26}H_{16}N_2O_6$	134...135	514	5,6	296	4,6	—	30
Id	H	7-COOH	H	H	7-COOH	H	$C_{26}H_{16}N_2O_6$	147...148	518	2,0	283	1,5	—	36
Ie	COOH	7-Cl	H	COOH	7-Cl	H	$C_{26}H_{14}Cl_2N_2O_6$	205...206	522	6,0	280	1,7	11,8	31
If	C_6H_5	H	H	C_6H_5	H	H	$C_{36}H_{24}N_2O_2$	203...204	586	2,1	296	2,3	12,2	45
Ig	C_6H_5	H	H	C_6H_5	H	NO_2	$C_{36}H_{23}N_3O_4$	210...211	582	1,9	291	2,3	8,2	25
Ih	C_6H_5	5-NO_2	H	C_6H_5	5-NO_2	H	$C_{36}H_{22}N_4O_6$	>300	620	2,8	—	—	—	19
Ii	C_6H_5	5-NO_2	H	C_6H_5	5-NO_2	NO_2	$C_{36}H_{21}N_5O_8$	205...206	618	2,3	—	—	10,8	23
Ik	H	7-NO_2	H	H	7-NO_2	H	$C_{24}H_{13}N_5O_8$	184...185	526	5,8	360	1,3	12,6	30
Iℓ	$CONHC_6H_5$	H	H	$CONHC_6H_5$	H	NO_2	$C_{38}H_{25}N_5O_6$	168...170	530	2,8	310	1,5	12,8	10
Im	CH_3	H	H	CH_3	H	H	$C_{27}H_{20}N_2O_6$	142...143	524	0,9	—	—	9,7	13
In	CH_3	5-CH_3	H	CH_3	5-CH_3	H	$C_{28}H_{24}N_2O_2$	151...152	526	0,8	—	—	9,7	48
Io	CH_3	5-CH_3	H	CH_3	5-CH_3	NO_2	$C_{28}H_{23}N_3O_4$	200...201	534	0,3	—	—	9,2	38
Ip	CH_3	5-OCH_3	H	CH_3	5-OCH_3	H	$C_{28}H_{24}N_2O_4$	159...160	520	1,9	—	—	9,7	29
Iq	CH_3	5-NO_2	H	CH_3	5-NO_2	NO_2	$C_{26}H_{17}N_5O_8$	209...210	568	2,0	328	1,6	11,8	36
Ir	H	H	H	C_6H_5	H	H	$C_{30}H_{20}N_2O_2$	284...285	542	2,1	296	1,7	13,0	36
Is	H	H	H	COOH	7-Cl	H	$C_{25}H_{15}ClN_2O_4$	185 (subl.)	522	1,5	288	1,6	10,2	63
It	H	H	H	COOH	H	H	$C_{25}H_{16}N_2O_4$	255...256	532	0,9	302	1,2	—	62
Iu	H	H	H	CH_3	H	H	$C_{25}H_{18}N_2O_4$	174...175	520	2,6	288	1,3	11,8	85
Iv	H	H	H	H	7-NO_2	H	$C_{24}H_{15}N_3O_4$	162...163	516	2,0	364	0,7	—	86
Iw	H	H	CH_3	H	H	H	$C_{25}H_{18}N_2O_2$	252...253	458	1,4	286	1,2	11,8	82
Ix	H	H	CH_3	COOH	H	H	$C_{26}H_{18}N_2O_4$	223...224	450	0,8	—	—	—	59
Iy	H	H	CH_3	H	7-NO_2	H	$C_{25}H_{17}N_3O_4$	264...265	436	1,1	—	—	12,8	86
Iz	H	H	CH_3	C_6H_5	H	H	$C_{31}H_{22}N_2O_2$	155...156	454	1,2	290	1,8	—	88

bathochromic effect in the absorption spectrum (calculations were carried out using the approximation method and parameters reported in [7 and 8]). With chlorine atoms at positions 7 and 7' and carboxyl groups at positions 2 and 2' (compound Ie) there is no hypsochromic effect. Introduction of phenylaminocarbonyl groups (Iℓ) at positions 2 and 2' causes a small (10 nm) bathochromic shift of the absorption maximum. With nitro groups at positions 5 and 7, the color deepens (compounds Ih, k, and q), whereas the strongly electron-withdrawing nitro substituents in the phthalide portion with indolylphthalide (Ib, g, and i) cause a small hypsochromic effect (∿6 nm). The introduction of methyl and, to an even greater extent, phenyl groups at positions 2 and 2' has a bathochromic effect, due to the increase in electron density at the atoms of the chromophoric system, and consequent delocalization. Moreover, as was shown earlier [9], phenyl groups at positions 2 and 2' of the indole rings, have little effect on the overall planar configuration of the dye molecule.

In the spectra of the unsymmetrical bis-indolylphthalides the following effects are observed. A carboxyl group at position 2 of the indole part of It gives a bathochromic shift of the absorption maximum (∿12 nm) in comparison with a hypsochromic displacement in the symmetrical derivatives. A chlorine atom at position 7 (Is) has almost no effect on the position of the absorption maximum, but a nitro group at position 7 of the second indole ring (Iv) causes a hypsochromic shift possibly because the strongly electron-attracting nitro group disturbs the delocalization of π-electron density in the chromophore. A phenyl group at position 2 (compound Ir), as in the symmetrical compounds, has a bathochromic effect. A methyl group on the nitrogen atom of one of the indoles produces a hypsochromic shift (62-94 nm), greater for the 3-(indolyl-3)-3-(1'-methyl-7'-nitroindolyl-3)phthalide (Iy) and smaller for the 3-(indolyl-3)-3-(1"-methylindolyl-3)phthalide (Iw). The spectral properties of such indolylphthalides in the colored state is similar to that for the unsymmetrical dyes with structure II ($R^1 = R^2 = R^6 = H$).

The acid-base characteristics (pK_a) of the bis-indolylphthalides (see Table 1) also largely depend on the nature of the substituents. Thus, the bis-indolylphthalides Ib, g and o with a nitro group in the phthalide part of the molecule are less basic than compounds Ia, f, and n without it. Introduction of a nitro group into the indole ring (compound Iq, i and k) increases the basicity of the phthalides, which also increases on introduction of a phenylaminocarbonyl group to positions 2 and 2' (Iℓ). Indolylphthalides containing carboxyl and nitro groups have pK_a values of 11-13, probably due to the formation of a hydrogen bond between the NH of the indole ring and substituents at positions 2 or 7.

EXPERIMENTAL

Absorption spectra of the indolylphthalides I were taken on an SF-10 spectrophotometer. Acid-base measurements were made by the method used for phenophthaleins and other indicator dyes [10].

Symmetrical Bis(indolyl-3)phthalides (Ia-q). A mixture of 0.01 moles of the substituted indole, 0.01 moles of phthalic anhydride and 0.003-0.350 moles of anhydrous zinc chloride was heated for 5-7 hours at 110-170°C. Water (50 ml) was added, the mixture heated under reflux for 20 minutes, and cooled. The precipitated material was filtered off, treated with 300-500 ml of 30% NaOH solution at 30-50°C, the alkaline solution filtered, and acidified with dilute (1:1) hydrochloric acid. The precipitate was filtered, washed with water to neutral reaction, dried, and dissolved in a mixture (20:1 by volume) of benzene and ethyl alcohol (300-500 ml). The solution was heated with activated charcoal, the volume reduced to 10-15 ml and to the residue was added 150-200 ml of hexane. The precipitate was filtered and recrystallized from benzene. Elemental analysis data agreed with calculated values.

Unsymmetrical Bis(indolyl-3)phthalides (Ir-z). A mixture of 2 mmoles of (indolyl-3)-benzoylbenzoic acid [5], 2 mmoles of substituted indole and 5 ml of acetic anhydride were heated for 1 hour at 120°C, 1 ml 12% p-toluensulfonic acid in acetic acid added, and after at 120° for 15 minutes, the mixture was cooled and poured into a mixture of 20 ml of water and 3 ml of ammonia. The precipitate was filtered off, washed, and dried. The unsymmetrical compounds Ir-z were purified in the same way as the symmetrical phthalides. Elemental analysis data agreed with calculated values.

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SUBSTITUTED 2-METHYL- AND 2-METHYLENEINDOLINES.

2.* NITRO- AND AMINO-SUBSTITUTED 2-METHYL- AND 2-METHYLENE-INDOLINES

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From 5- and 6-aminotetramethylindolines, 2-methyleneindolines have been synthesized; these compounds can be condensed with other heterocyclic systems. The nitration of 1,2,3,3-tetramethylindoline under different conditions was studied.

In an earlier paper we described a method of synthesizing 2-methylenindolines from an industrially available Fischer base; substituents were introduced into the benzene ring of 1,2,3,3-tetramethylindoline I and the substituted compounds then oxidized [1]. The present work deals with the syntheses of 5- and 6-amino-1,2,3,3-tetramethylindolines – starting compounds for the preparation of the 2-methylenindolines, which can be condensed with other nitrogen-containing heterocyclics.

Nitration of the indoline I using a nitrating mixture generally used for the nitration of dimethylaniline [2] gave 6-nitroindoline II in good yield. The 4,6-dinitroindoline III and 6-nitro-2-methyleneindoline IV were also isolated from the reaction mixture. The indolines II-IV were easily separated because of their different basicities. Due to the effect of the substituents, nitration of the indoline I took place only at the meta-position relative to the dialkylamino group. Under the same conditions, nitration of dimethylaniline gives up to 30% of the para-isomer [2].

It is proposed that the indolines III and IV are the products of further reaction of compound II, and that the indoline IV is formed as a result of oxidation or nitration of the tertiary carbon atom [3]. We carried out a series of experiments on the formation of the mixture of III and IV from the indoline II. Nitration in a mixture of concentrated sulfuric and nitric acids gave a complex mixture of reaction products from which only the indoline IV was separated in 25% yield.

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*For communication 1, see [1].

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