INDOLE DERIVATIVES

LII*. THE REACTION OF INDOLE WITH BENZENEDIAZONIUM CHLORIDE

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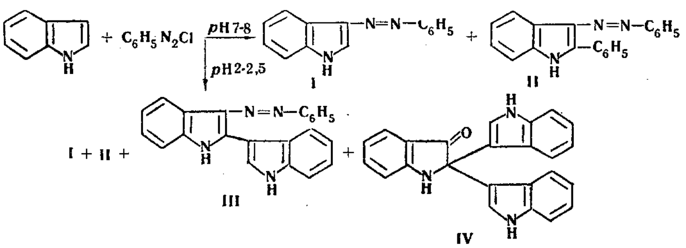
The reaction of indole with benzenediazonium chloride at pH values from 1 to 12 has been studied. The main product of the reaction at pH 6-12 is 3-phenylazoindole. The coupling reaction is accompanied by the arylation of the indole and the formation of 2-phenyl-3-phenylazoindole. The main product of the reaction at pH 1-4 is 2,2-di(indol-3'-yl)indoxyl.

The azo coupling reaction in the indole series has been studied comparatively little. It was shown in early investigations [1,2] that coupling takes place in position 3. Later, Binks and Ridd [3], studying the kinetics of the coupling of indole with diazonium salts, showed that the reaction of p-benzenediazonium salts with indole at pH 6.68 followed a first-order equation, but large deviations were found in other cases. The authors put forward the hypothesis that the latter are due to autocatalytic side reactions with the participation of the diazonium ions which do not lead to the formation of azo compounds. They were unable to isolate the byproducts, the formation of which increased at lower and higher pH values.

In order to make a more detailed study of the azo coupling reaction, we have coupled indole with benzenediazonium chloride over a wide range of pH values of the medium and at molar ratios of indole to benzenediazonium chloride of 1 : 1 and 1 : 2. It was found that when indole reacts with benzenediazonium chloride a complex mixture of substances is formed, depending on the pH.



The main reaction at pH 7-8 is 3-phenylazoindole (I) (yield 60-70 %). Compound I was characterized by by its IR, UV, and PMR spectra.

The IR spectrum of I contains, in addition to a strong narrow band at 3495 cm^{-1} (NH group) and the bands of aromatic C–C and C–H bonds (1450, 1260, and 750 cm^{-1}), strong narrow absorption bands at 1100 and 1400 cm^{-1}. The first of them is observed for all 3-substituted indoles [5]. Some remarks must be made about the absorption in the 1400 cm^{-1} region. There is information in the literature that the vibrations of the azo group are found in the 1600-1400 cm^{-1} region. In aromatic azo compounds, the absorption is shifted in the low-frequency direction. Thus, the absorption of the azo groups in azobenzenes is in the 1450 cm^{-1} region [6]; the introduction of substituents possessing a strong conjugation effect (for example, a dialkylamino group) into the para position to the azo group shifts the absorption into the 1403-1416 cm^{-1} region [6].

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*For Communication LI, see [14].

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The IR spectra of the azo compounds that we obtained with the azo group in position 3 [3-phenylazoindole, 2-phenyl-3-phenylazoindole, 2-methyl-3-phenylazoindole, 2-(indol-3-yl)-3-phenylazoindole] each have a very strong absorption band at 1400 cm^{-1}. This band is possibly due to the stretching vibrations of the azo group, and the shift into the low-frequency region as compared with azo compounds of the benzene series is due to the effect of conjugation of the azo group with the indole ring.

The UV spectrum of I shows a shift of the absorption maximum into the long-wave region (λ_{max} 362-366 nm).

Apart from I, the reaction of indole with benzenediazonium chloride gives rise to 2-phenyl-3-phenylazoindole (II) with a yield of 7-10 %. This structure was confirmed by elementary analysis and IR and UV spectroscopy. The IR spectrum of II resembles that of I, but the absorption band at 1100 cm^{-1} is absent.

For a final proof of its structure, compound II was also obtained from 2-phenylindole and benzenediazonium chloride. The IR and UV spectra of the samples obtained from the reaction products and by independent synthesis proved to be identical. The melting point of a mixture showed no depression.

The 2-phenyl-3-phenylazoindole is probably formed by the coupling of 2-phenylindole with benzenediazonium chloride, since compound I does not react with benzenediazonium chloride under the same conditions. Moreover, although we were unable to isolate 2-phenylindole, traces of it were detected chromatographically. It may be assumed that during the reaction the partial arylation of the indole takes place, after which the 2-phenylindole reacts with the diazonium cation. The amount of II increases with a rise in the pH, and also with a rise in the amount of benzenediazonium chloride.

In addition to compounds I and II we isolated another three substances in very small amounts, two of which consisted of dark yellow oils and the third of a white crystalline substance with mp 200°C and a molecular weight of 330. Their structures have not yet been determined.

The reaction of indole with benzenediazonium chloride at ph 2-2.5 leads to the formation of a more complex mixture of substances. In addition to the products formed on coupling in an alkaline medium, another two substances were isolated. One of them was a dark yellow substance with mp 162-163°C (yield 5 %). Elementary analysis and a molecular-weight determination (by the mass-spectrometric method) made it possible to assume it is a dimer of indole containing a phenylazo group. Its IR spectrum contained absorption bands of an NH group (3495 cm^{-1}) and of an aromatic system of bonds (1590, 1350, and 1260 cm^{-1}) and a band at 1400 cm^{-1}. The UV spectrum exhibited a shift of the absorption into the long-wave region (λ_{max} 420 nm) apparently due to the influence of the second indole ring.

On the basis of these facts, we assume that the compound is 2-(indol-3-yl)-3-phenylazoindole (III), which was confirmed by the independent synthesis of III from 2-(indol-3-yl)indole and benzenediazonium chloride.

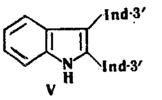
The main reaction product (yield 60-70 %) was a yellow-green crystalline substance with mp 245°C. The IR and UV spectra of this compound differed from those of the azo compounds. The IR spectrum retained the absorption band of the NH group of an indole ring (3495 cm^{-1}) but the band at 1400 cm^{-1} was absent and new bands had appeared at 3400, 3300, and 1680 cm^{-1}. The latter is characteristic for an oxo group conjugated with an aromatic ring containing an electron-donating substituent. Thus, absorption bands of a carbonyl group at 1680 cm^{-1} are observed in indoxyls, when the imino group plays the part of electron-donating substituent. The absorption bands at 3400 and 3300 cm^{-1} may be due to the vibrations of the NH group of indoxyl [7].

The UV spectrum, resembling the spectra of indoxyls [7], has a bathochromic shift (λ_{max} 400 nm), but the absorption in this region is fairly weak.

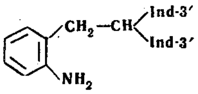
According to elementary analysis, this substance has the empirical formula $C_{24}H_{17}N_3O$ and is α, α-di(β-indoxyl)indoxyl (IV). It has been obtained previously by the oxidation of indole with peroxide compounds [8], by the nitrosation of indole, and by the reaction of α-(β-indolyl)indoxyl with indole [9]. In our case, nitrosation was excluded, since after diazotization the excess of nitrous acid was eliminated in the usual way.

The molecular weight of the compound, determined by mass spectrometry, was 363, which corresponds to 2,2-di(indol-3-yl)indoxyl. The decomposition of the molecule is accompanied by the splitting out of a CHO^+ fragment, which is characteristic for compounds containing a carbonyl group [10] and by the formation of the ion $C_6H_5NHC(Ind\text{-}3')_2$ with m/e 334. Further degradation takes place with the formation of the fragments having m/e 117, 116, and 115 which are characteristic for indole rings.

The reduction of IV with lithium aluminum hydride formed 2,3-di(indol-3'-yl)indole (V), identical with the compound described by Witkop and Patrick [8]. Thus, in the reaction of indole with benzenediazonium chloride in an acid medium the main reaction product is 2,2-di(indol-3'-yl)indoxyl (IV). The first stage of the process is probably a coupling reaction. In actual fact, when compound I was treated with indole at pH 1-2, IV was isolated, while under these conditions indole is converted into compound VI [11]. Furthermore, compound III, with a protected position 2, does not form IV under those conditions.



V



VI

We have determined the limiting values of the pH at which the reaction between indole and benzenediazonium chloride goes in one direction or the other. The reaction was followed by thin-layer chromatography on alumina. The formation of the dimeric derivative III begins at pH 5 and that of the substituted indoxyl IV at pH 4, their amounts increasing with a fall in the pH. At pH values greater than 5 only coupling products I and II are formed.

EXPERIMENTAL

The IR spectra were taken on a UR-10 instrument using CCl_4 solutions in the case of I, II, and III and mulls in paraffin oil for compounds IV and V. The UV spectra were taken of ethanolic solutions on an SF-4A instrument. The NMR spectra were taken on a JNM-4H-100 instrument with $CDCl_3$ as the solvent and TMS as the internal standard. The mass spectra were taken on an MKh-1303 instrument with the direct introduction of the samples into the ion source (30-40 eV, 100-200°C).

The prescribed pH value of the medium was monitored by means of a type 2518/5 potentiometer.

Reaction of Indole with Benzenediazonium Chloride. With stirring, 2.9 g (0.025 mole) of indole in 10 ml of ethanol was poured onto ice in a beaker for coupling. The suspension was diluted with water to 200 ml, since otherwise, when coupling was carried out in an acid medium, pronounced resinification took place. A solution of 0.025 mole of benzenediazonium chloride obtained by the diazotization of freshly distilled aniline by the usual method was added dropwise to the resulting suspension at 0-5°C over 2-3 hr. Simultaneously, a 20 % solution of sodium carbonate was added to maintain the given pH value. After the addition of the diazonium solution, the reaction mixture was stirred for 6-7 hr, and the precipitate that deposited was filtered off, washed with water, and dried.

For qualitative analysis, the reaction products were subjected to chromatography in a thin layer of Al_2O_3 (here and below, activity grade II) in the benzene-methanol (10:1) system. For quantitative separation, the reaction products were chromatographed on columns of Al_2O_3 at a ratio of sorbent to substance of 30:1.

A. Separation of 1 g of a Mixture of the Products of the Reaction of Indole with Benzenediazonium Chloride at pH 7-8. A mixture of hexane and CCl_4 (1:1) eluted a first fraction (0.05 g) containing four substances. The separation of this fraction on Al_2O_3 plates in the benzene–CCl_4 (1:1) system gave two yellow oily substances with R_f 0.87 and 0.75 and a white crystalline substance with R_f 0.9, mp 200°C, mol.wt. 330 [determined by mass spectrometry; the R_f values are given for the benzene–methanol (10:1) system].

The fourth substance is 2-phenylindole, since when it was chromatographed with an authentic sample of 2-phenylindole on Al_2O_3 plates in various systems [benzene–methanol (10:1); hexane–ether (1:1)] they had the same R_f values of 0.7, 0.19, and 0.35; on observation in ultraviolet light they had the same blue fluorescence; and on treatment with Ehrlich's reagent they gave the same violet coloration.

Further elution with CCl_4 gave 0.07 g of 2-phenyl-3-phenylazoindole (II). Benzene eluted 0.6 g of 3-phenylazoindole (I).

B. Separation of 3 g of the Mixture of Products of the Reaction of Indole with Benzenediazonium Chloride at pH 2-2.5. A mixture of hexane and CCl_4 eluted 0.03 g of a first fraction identical with that isolated in the separation of the products of the coupling reaction at pH 7-8.

TABLE 1. Characteristics of the Compounds Synthesized.

Compound	mp, °C	Solvent for crystallization	R_f*	Empirical formula	Found, %			Calculated, %			UV spectrum	
					C	H	N	C	H	N	λ_{max}	log ε
I†	134—135	CCl_4	0,46	$C_{14}H_{11}N_3$	76,0	5,1	19,0	76,0	5,0	19,0	278; 362—366	4,08 4,4
II	165—166	Petroleum ether–benzene (8 : 2)	0,67	$C_{20}H_{16}N_3$	80,6	5,3	13,9	80,8	5,1	14,1	296; 390—394	4,37 4,33
III	165,5—166	Heptane	0,38	$C_{22}H_{16}N_4$	78,4	4,9	16,8	78,6	4,8	16,7	310; 420—425	4,34 4,14
IV	245	Benzene–ethanol (6 : 2)	0,38	$C_{24}H_{17}N_3O$	79,3	4,8	11,7	79,2	4,7	11,5	262; 280—284; 400	4,21 4,23 3,58

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*Thin layer chromatography on Al_2O_3 in the benzene–methanol (10 :1) system.

† PMR spectrum of 3-phenylazoindole: δ 10.02 ppm (signal of the proton of an imino group) and doublet at δ 7.1 ppm (signal of the α-proton of an indole ring).

Carbon tetrachloride eluted 0.015 g of II, benzene 0.09 g of I, benzene–chloroform (3 :1) 0.15 g of III, and chloroform 1.8 g of IV. The reaction products isolated are characterized in Table 1.

2-Phenyl-3-phenylazoindole (II). A solution of 2.29 g (0.012 mole) of 2-phenylindole [12] in 25 ml of glacial acetic acid was added with stirring and cooling to 0°C to a solution of 10 g of NaOH in 300 ml of water. The resulting suspension was added over 2-3 hr at 0-2°C to a solution of 0.0125 mole of benzenediazonium chloride, and the mixture was stirred at the same temperature and pH 6.5-7 for 5-6 hr.

The precipitate formed was filtered off, washed with water, and dried. Weight 2.9 g, mp 166-167°C [from petroleum ether–benzene (8 : 2)], which corresponds with literature data [2].

2-(Indol-3-yl)-3-phenylazoindole (III). With stirring at a temperature of 0-1°C, a solution of benzenediazonium chloride prepared by the diazotization of 0.005 mole of aniline was brought to pH 7-7.5 by means of 20 % sodium carbonate solution, and then a solution of 1.1 g (0.005 mole) of biindolyl [13] was added dropwise over 1 hr. The reaction mixture was stirred at 0-5°C, pH 7, for 6 hr. The precipitate was worked up in the the usual way, giving 1.6 g (72.2 %) of crude product. The substance was purified chromatographically (Al_2O_3, benzene). mp 165-166°C (from heptane).

Behavior of 3-Phenylazoindole toward Benzenediazonium Chloride. A solution of 2.21 g of 3-phenylazoindole in 10 ml of ethanol was treated by the method described above with a solution of benzenediazonium chloride obtained from 0.01 mole of aniline. After the end of the reaction, 2.3 g of a crystalline substance was isolated. When it was chromatographed on plates of alumina in the benzene–methanol (10 :1) system, only the initial 3-phenylazoindole (R_f 0.46) was detected.

Reaction of 3-Phenylazoindole with Indole. A solution of 2 g of 3-phenylazoindole in 20 ml of ethanol was treated with 30 ml of water and 4 ml of conc HCl. The mixture was cooled to 0°C and 1.1 g of indole in 10 ml of ethanol was added dropwise. The dark red precipitate formed was filtered off, washed with water, and dried. Weight 2.5 g. After chromatography on alumina, 1.4 g of 3-phenylazoindole (with benzene as the eluent) and 0.6 g of a yellow-green crystalline substance with mp 245°C [from benzene–ethanol (6 : 2), obtained with chloroform as the eluent] were isolated. The IR and UV spectra of the substance with mp 245°C and of IV coincided. The melting point of a mixture of the two substances also showed no depression.

Reduction of 2,2-Di(indol-3'-yl)indoxyl (IV). With stirring in a current of dry nitrogen, 0.42 g of lithium aluminum hydride was added in small portions to 1.5 ml of absolute ether. Over 30 min, 0.8 g of IV in 56 ml of tetrahydrofuran was added to the resulting suspension. The mixture was boiled for 6 hr, after which it was cooled and 10 ml of water was added in small portions; then it was stirred for an hour and filtered. The tetrahydrofuran was distilled off in a current of nitrogen, the product was extracted with three 20-ml portions of benzene, and the combined extracts were dried with sodium sulfate and were then treated with 200 ml of petroleum ether. A pale yellow precipitate (0.7 g) of 2,3-di(indol-3'-yl)indole (V) deposited.

The substance was purified by chromatography (Al_2O_3, benzene). This gave 0.5 g of colorless crystals with mp 152-156°C (after repeated reprecipitation from benzene with petroleum ether); according to the literature [8]; 150-156°C. Found, %: C 83.3; H 5.2; N 12.3; mol. wt. 347 (mass spectrometrically). Found for $C_{24}H_{17}N_3$, %: C 83.0; H 4.9; N 12.1; mol. wt. 347.

Reaction of 2-(Indol-3-yl)-3-phenylazoindole (III) with Indole. A solution of 1.5 g of III in 20 ml of ethanol was treated with 30 ml of water and 4 ml of conc HCl.. The mixture was cooled to 0°C and then 0.6 g of indole in 5 ml of ethanol was added to it in drops and stirring was performed for 6 hr. The precipitate formed (1.8 g) was separated off, washed with water, and dried. On chromatographic separation on plates of Al_2O_3 in the benzene–methanol (10:1) system, indole with R_f 0.42, 2-(indol-3-yl)-3-phenylazoindole (III) with R_f 0.38, and the trimer VI with R_f 0.37 were detected.

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