BENZINDOLES. 18.* SOME ELECTROPHILIC SUBSTITUTION REACTIONS INVOLVING THE HYDROGEN ATOMS IN 4,5,6,7-DIBENZINDOLE

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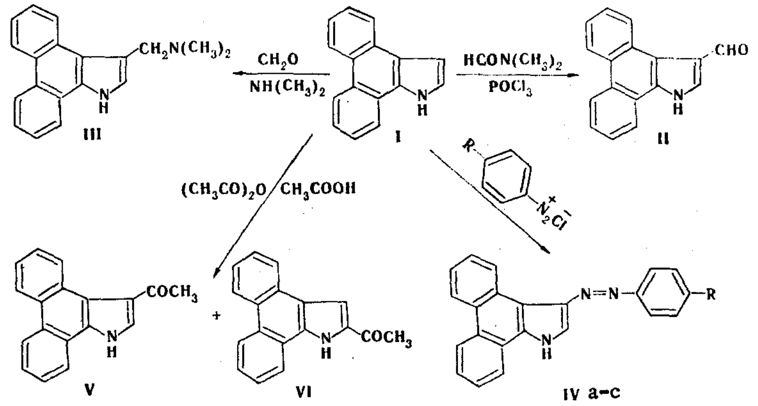
The principal electrophilic substitution reactions involving the hydrogen atom of 4,5,6,7-dibenzindole – the Vilsmeier reaction, the Mannich reaction, diazo coupling, and acylation – were studied, and a qualitative comparison of its reactivities with indole and 4,5- and 6,7-benzindoles was made. It was established that 4,5,6,7-dibenzindole has the most clearly expressed electron-donor properties. The structures of the synthesized compounds were proved by data from the IR, UV, PMR, and mass spectra.

The aim of the present communication was to study the electrophilic substitution reactions of the hydrogen atoms in the previously obtained 4,5,6,7-dibenzindole (I) [2] and to make a qualitative comparison of its reactivity with the reactivities of indole and 4,5- and 6,7-benzindoles.



IV a R=H; b R=Cl; c R=NO_2

3-Formyl-4,5,6,7-dibenzindole (II) was obtained by the reaction of dimethylformamide (DMF) and phosphorus oxychloride with I. The reaction proceeds quantitatively.

The PMR spectrum contains the characteristic signal of a formyl proton at weak field (9.94 ppm) and the signal of a proton attached to a nitrogen atom (13.02 ppm). The double-resonance method made it possible to determine the chemical shift of the 2-H proton (8.36 ppm). Replacement of the 3-H proton by a CHO group gives rise to a shift to weak field of the 4-H proton. The position of the 11-H signal changes only slightly. The low-field multiplet corresponds to the 4-H proton and the higher-field multiplet corresponds to the 11-H proton.

The C=O bond is in a transoid orientation with respect to the aromatic system of C_2-C_3 bonds; this is confirmed by the pronounced shift of the 4-H proton to weak field (s 8.27 to 9.66 ppm) because of marked deshielding of the 4-H proton due to the formyl group.

The aminomethylation of dibenzindole was carried out by the action of formaldehyde and an aqueous solution of dimethylamine. The Mannich reaction, like the Vilsmeier reaction, proceeds quantitatively.

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*See [1] for communication 17.

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The PMR spectrum of III confirms that the dimethylaminomethyl group replaces the hydrogen atom attached to the 3-C atom of the pyrrole ring. The signal of the 1-H proton is observed at weak field (11.89 ppm), but the signal of the 3-H proton is absent. Signals in the strong-field region with chemical shifts of 3.75 and 2.24 ppm, which should be assigned to the CH_2 and CH_3 groups, respectively, appear simultaneously.

For the investigation of diazo coupling we selected benzenediazonium and p-chloro- and p-nitrobenzenediazonium chlorides as the diazo components. Because of the low solubility of dibenzindole in water, diazo coupling was carried out in an aqueous dioxane solution at pH 5-6. Over this pH range diazo coupling in the indole series proceeds without substantial complication by side processes [3-5].

Neither 4,5- nor 6,7-benzindole [6] underwent coupling with benzenediazonium chloride, whereas 4,5,6,7-dibenzindole undergoes coupling with all three diazo components.

The IR spectra of IV contain narrow intense absorption bands at 1110 and 1395 cm^{-1}, in addition to an intense absorption band of an NH group (3450-3460 cm^{-1}) and absorption bands of aromatic C–C and C–H bonds (1460, 1260, and 760 cm^{-1}).

The first of the above bands is observed in the spectra of 3-substituted indoles [7]. According to the data in [8], vibrations of an azo group are noted at 1400-1600 cm^{-1}. In the case of aromatic azo compounds the absorption frequency is shifted to the low-frequency region. Thus the absorption of the azo groups of azobenzenes lies at 1450 cm^{-1}.

The IR spectra of the compounds that we obtained contain an intense band at 1395 cm^{-1}. This band is evidently due to the stretching vibrations of an azo group, while the shift to the low-frequency region as compared with azo compounds of the benzene series is explained by the effect of conjugation of the azo group with the dibenzindole ring.

The UV spectra of the azo compounds contain intense absorption maxima in the long-wave region (445, 415, and 482 nm, respectively, for IVa,b,c).

The PMR spectra of IV confirm that coupling takes place in the 3 position of the pyrrole ring. Signals of protons attached to a nitrogen atom are observed at weak field, but signals of protons bonded to the β-carbon atoms of the pyrrole ring are absent. The assignment of the protons of the benzene ring was hindered by their overlapping with the signals of the protons of the phenanthrene ring.

The acetylation of dibenzindole with acetic anhydride differs from the acetylation of indole [10] and benzindoles [11]. As a result of the reaction, we isolated two absolutely different (with respect to the R_f values) products with different melting points. The absorption band at 1630 cm^{-1} that is characteristic for the C=O bond is retained in the IR spectra (mineral oil suspensions) for one of them. The spectrum of the other product contains a narrow intense absorption band at 1645 cm^{-1}, which is evidently due to the stretching vibrations of a C=O group, and an intense band of a free N–H bond at 3300 cm^{-1}. The molecular weights of the two products according to mass spectrometry are 259 and correspond to monoacetyldibenzindoles.

With allowance for the results of elementary analysis, it may be assumed that these compounds are isomers. This was confirmed by their PMR spectra.

The PMR spectrum of one of them is very similar to the spectrum of 3-formyldibenzindole. It contains the characteristic signal of the 1-H proton attached to a nitrogen atom in the low-field region of the spectrum (12.69 ppm), a signal of the protons of a CH_3 group (2.60 ppm), and a signal of a 2-H proton (8.36 ppm), which are revealed by double resonance. This proves that the acetyl group is in the 3 position. Replacement of the 3-H proton of the $COCH_3$ group should give rise to a shift of the signal of the 4-H proton to weak field. The position of the signal of the 11-H proton should not undergo any significant change. The following assignment is therefore logical: the lowest-field multiplet corresponds to the 4-H proton, and the highest-field multiplet corresponds to the 11-H proton. The orientation of the C=O group is the same as for the aldehyde. The pronounced deshielding of the 4-H proton also indicates that the substituent is in the 3 position.

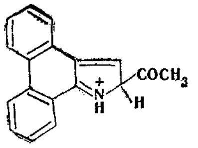
The PMR spectrum of the other compound contains a singlet of the 1-H proton in the low-field region of the spectrum (12.48 ppm), a triplet of the protons of the CH_3 group (2.54 ppm), and a signal of a proton with a chemical shift of 7.95 ppm. The location of this signal in the highest-field region of the spectrum as compared with other protons of dibenzindole makes it possible, on the basis of literature analogies with indole [12] and angular benzindoles [13], to assign it to the 3-H proton. Thus this compound is 2-acetyl-4,5,6,7-dibenzindole (VI), and it is obtained in 19% yield.

The principal reaction product is 2-acetyl-4,5,6,7-dibenzindole (V) (42%). 1,3-Diacetylindole is formed under the same conditions in the acylation of indole. The observed hindrance to acylation at the nitrogen atom in the case of dibenzindole is evidently due to the steric hindrance created by the closeness of the benzene ring fused in the 6 and 7 positions. Steric hindrance in the case of acetylation at the nitrogen atom has been noted for 6,7-benzindole [11].

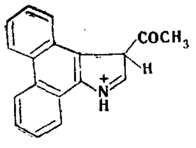
The formation of VI in the acetylation of dibenzindole, which does not have analogies in either the indole series or in the angular benzindole series, could have been the result of migration of the acetyl group from the 3 position to the 2 position during the reaction.

There are data [14] that confirm the rearrangement of 2-acetylindole to 3-acetylindole. However, heating a genuine sample of 3-acetyl-4,5,6,7-dibenzindole with acetic anhydride for 30 h (under the conditions for the acetylation of I) showed that the starting compound remains unchanged. Compound V consequently does not undergo rearrangement to VI under the reaction conditions.

The formation of VI can evidently be explained by the sufficient stability of cation VII, which is formed by attack by the electrophilic agent in the 2 position of the dibenzindole ring, in which the conjugated diphenyl grouping is retained.



VII



VIII

Although it is lower than in the case of cation VIII (hence the high yield of the 3-acetyl derivative), the thermodynamic stability of cation VII, because of retention of the aromatic diphenyl system, is sufficiently high, and the difference in their stabilities is considerably less than in the case of the corresponding cations of both indole itself and angular benzindoles; this also specifies acetylation in the 2 and 3 positions of I.

On the basis of the investigated electrophilic substitution reactions and the data obtained from a comparison of the donor properties of indole, angular benzindoles, and dibenzindole, in the formation of complexes by means of hydrogen bonds with certain acceptors [2] one should assume that dibenzindole has more clearly expressed electron-donor properties.

EXPERIMENTAL

The UV spectra of solutions of the compound in ethanol were recorded with a Specord UV-vis spectrophotometer. The IR spectra were recorded with a UR-20 spectrometer. The mass spectrum was recorded with an MKh-1303 spectrometer with introduction of the samples into the ion source at a cathode emission current of 1.5 mA, an accelerating voltage of 50 eV, and a temperature of 100 deg C. The PMR spectra of solutions of the compounds in DMSO were recorded with a JNM-MH-100 spectrometer with tetramethylsilane as the internal standard. The course of the reactions and the purity of the compounds were monitored on Silufol UV-254 plates. Activity II aluminum oxide was used.

3-Formyl-4,5,6,7-dibenzindole (II). A 0.2-ml (2 mmole) sample of $POCl_3$ was added dropwise with stirring to 0.62 ml (8 mmole) of cooled (to −5 deg C) freshly distilled dimethylformamide (DMF), and the resulting complex was stirred at room temperature for 1 h. It was then cooled to −5 C, and a solution of 0.43 g (2 mmole) of dibenzindole in 1.2 ml (150 mmole) of DMF was added dropwise. The mixture was maintained at 35-40°C for 45 min, after which it was poured over ice (20 g). A 10% solution of NaOH was added dropwise to the solution to pH 7, and the mixture was stirred at room temperature for 1 h. The precipitate was removed by filtration, washed with water, and dried to give 0.48 g (85%) of product with mp 245-246°C (from aqueous alcohol). IR spectrum (in mineral oil): 735-770 (benzene ring CH), 1640 (C=O), and 3120 cm^{-1} (NH). UV spectrum, λ_{max}(log ε): 205 (4.39), 247 (4.53), 255 (4.58), 262 (4.62), 272 (4.48), 320 (3.71), 336 (3.47), 352 nm (3.26). PMR spectrum, δ: 13.02 (s, 1-H), 9.94 (s, CHO), 8.36 (d, 2-H), 9.40 (m, 4-H), 8.40 (m, 11-H), 8.68 (m, 7-H, 8-H), and 7.57 ppm (m, 5-H, 6-H, 9-H, 10-H). Found: C 83.4; H 4.6; N 5.6%. $C_{17}H_{11}NO$. Calculated: C 83.3; H 4.5; N 5.7%.

3-Dimethylaminomethyl-4,5,6,7-dibenzindole (III). A previously prepared mixture of 0.4 g (9 mmole) of a 33% aqueous solution of dimethylamine, 6 ml (0.104 mole) of glacial acetic acid, and 0.23 g (8 mmole) of 40% formalin was added with cooling (to 0 C) to 0.43 g (2 mmole) of I, and the clear reaction mixture was stirred at room temperature for 3 h. Water (5 ml) was added, and the mixture was filtered. A 10% solution of NaOH was added dropwise to the filtrate with stirring to pH 9, and the resulting precipitate was removed by filtration, washed with water, and dried with potassium hydroxide to give 0.52 g (96%) of a product with mp 204-205°C (from alcohol). IR spectrum (in $CHCl_3$): 735-770 (benzene ring CH), 1360 (C−N<), and 3490 cm^{-1} (NH). UV spectrum, λ_{max}(log ε): 207 (4.40), 253 (4.67), 261 (4.84), 292 (4.27), 313 nm (3.88). PMR spectrum, δ: 11.89 (s, 1-H), 3.75 (m, CH_2), 2.24 (s, CH_3), 8.36 (d, 2-H), 8.87 (m, 4-H), 8.41 (m, 11-H), 8.67 (m, 7-H, 8-H), and 7.58 ppm (m, 5-H, 6-H, 9-H, 10-H). Found: C 83.4; H 6.7; N 10.4%. $C_{19}H_{18}N_2$. Calculated: C 83.2; H 6.6; N 10.2%.

3-Phenylazo-4,5,6,7-dibenzindole (IVa). A solution of 2 mmole of benzenediazonium chloride was added at 0 C to a solution of 0.43 g (2 mmole) of I in 30 ml of dioxane and 20 ml of water while maintaining the pH at 5-6 by the addition of sodium acetate, after which the mixture was stirred for 3 h. The azo compound was extracted with ether, and the ether solution was washed with 10% NaOH solution and with water to neutrality, dried with $CaCl_2$, and evaporated to dryness. The IVa was purified by chromatography [Al_2O_3, ether−hexane (1 : 1)] to give 0.33 g (56%) of a product with mp 207-208 C. IR spectrum (in KBr): 735-770 (benzene ring CH), 1395 (N=N), and 3460 cm^{-1} (NH). UV spectrum, λ_{max}(log ε): 203 (4.50), 247 (4.59), 255 (4.54), 275 (4.41), 345 (3.86), 445 nm (4.47). PMR spectrum, δ: 12.79 (s, 1-H), 8.37 (m, 2-H), 8.87 (m, 4-H), 8.40 (m, 11-H), 8.67 (m, 7-H, 8-H), and 7.56 ppm (m, 5-H, 6-H, 9-H, 10-H). Found: C 82.4; H 4.9; N 13.1%. $C_{22}H_{15}N_3$. Calculated: C 82.2; H 4.7; N 13.1%.

3-(4'-Chlorophenylazo)-4,5,6,7-dibenzindole (IVb). This compound, with mp 245-246°C (from benzene), was similarly obtained in 68% yield by the reaction of I with a solution of p-chlorobenzenediazonium chloride. IR spectrum ($CHCl_3$): 735-770 (benzene ring CH), 1395 (N=N), and 3460 cm^{-1} (NH). UV spectrum, λ_{max}(log ε): 203 (4.44), 247 (4.54) 257 (4.51), 268 (4.37), 276 (4.38), 347 (3.77), 415 nm (4.47). PMR spectrum, δ: 12.78 (s, 1-H), 8.36 (m, 2-H), 8.85 (m, 4-H), 8.41 (m, 11-H), 8.67 (m, 7-H, 8-H), and 7.57 ppm (m, 5-H, 6-H, 9-H, 10-H). Found: C 74.1; H 4.1; Cl 10.0; N 12.1%. $C_{22}H_{14}ClN_3$. Calculated: C 74.3; H 3.9; Cl 9.8; N 11.8%.

3-(4'-Nitrophenylazo)-4,5,6,7-dibenzindole (IVc). This compound, with mp 302-303°C, was similarly obtained in 96% yield by the reaction of I with a solution of p-nitrobenzenediazonium chloride. IR spectrum (in mineral oil): 735-770 (benzene ring CH), 1395 (N=N), and 3450 cm^{-1} (NH). UV spectrum, λ_{max}(log ε): 203 (4.44), 246 (4.52), 258 (4.48), 277 (4.31), 482 nm (4.49). PMR spectrum, δ: 13.10 (s, 1-H), 8.56 (m, 2-H), 9.01 (m, 4-H), 8.62 (m, 11-H), 8.83 (m, 7-H, 8-H), and 7.78 ppm (m, 5-H, 6-H, 9-H, 10-H). Found: C 72.2; H 4.0; N 15.5%. $C_{22}H_{14}N_4O_2$. Calculated: C 72.1; H 3.8; N 15.3%.

3-Acetyl-4,5,6,7-dibenzindole (V) and 2-acetyl-4,5,6,7-dibenzindole (VI). A mixture of 0.5 g (2 mmole) of I, 5 ml (530 mmole) of freshly distilled acetic anhydride, and 0.5 ml (870 mmole) of acetic acid was refluxed for 30 h, and the mixture was poured into water. The aqueous mixture was extracted with ethyl acetate, and the extract was washed with $NaHCO_3$ solution and water. It was then concentrated to 10 ml, and the concentrate was passed through a column filled with Al_2O_3 (elution with ether), as a result of which three substances were isolated. The first substance, with R_f 0.91, was 50 mg (10% based on the amount used for the reaction) of unchanged I. The second substance, with R_f 0.63, was 97 mg (19%) of VI with mp 278-279°C. IR spectrum (in mineral oil): 735-770 (benzene ring CH), 1650 (C=O), and 3250 cm^{-1} (NH). UV spectrum, λ_{max} (log ε): 201 (4.34), 247 (4.54), 259 (4.66), 266 (4.71), 275 (4.39), 334 (4.22), 347nm (4.13). PMR spectrum, δ: 12.48 (s, 1-H), 2.54 (m, CH_3), 7.95 (m, 3-H), 8.24 (m, 4-H), 8.72 (m, 7-H, 8-H, 11-H), and 7.58 ppm (m, 5-H, 6-H, 9-H, 10-H). Found: C 83.4; H 5.2; N 5.2%. $C_{18}H_{13}NO$. Calculated: C 83.4; H 5.0; N 5.4%.

The third substance, with R_f 0.24, was 0.21 g (41%) of V with mp 269-270°C. IR spectrum (in mineral oil): 735-770 (benzene ring CH), 1630 (C=O), and 3250 cm^{-1} (NH). UV spectrum, λ_{max}(log ε): 204 (4.41), 262 (4.70), 289 (3.99), 311 nm (3.49). PMR spectrum, δ: 12.79 (s, 1-H), 2.60 (s, CH_3), 8.36 (d, 2-H), 9.70 (m, 4-H), 8.41 (m, 11-H), 8.67 (m, 7-H, 8-H), and 7.56 ppm (m, 5-H, 6-H, 9-H, 10-H). Found: C 83.4; H 5.1; N 5.3%. $C_{18}H_{13}NO$. Calculated: C 83.4; H 5.0; N 5.4%.

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REACTION OF 2-METHYLENE-3-OXOQUINUCLIDINE WITH INDOLES

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2-(3-Indolylmethyl)- and 2-(phenyl-3-indolylmethyl)-3-oxoquinuclidines were obtained by the reaction of 2-methylene-3-oxoquinuclidine with indole and 2-phenylindole, respectively. Their reduction by the Kishner method and with sodium borohydride was studied. The structures of the products were confirmed by means of their PMR spectra, and the configurations of two diastereomeric 2-(3-indolylmethyl)-3-hydroxyquinuclidines were established.

The reaction of 2-methylene-3-oxoquinuclidine (I) with various nucleophilic reagents (water, alcohol, phenols and naphthols), which makes it possible to synthesize a number of previously unknown 2-substituted 3-oxoquinuclidines, was described in previous communications [1, 2]. The transformations of the synthesized compounds, particularly the formation of diquinuclidine derivatives and polycyclic quinuclidine compounds, have been studied.

In a continuation of these investigations and in order to synthesize 2-indolylquinuclidines we studied the reaction of I with indoles. A number of compounds of the indoloquinuclidine class have been described in the literature. This is primarily true of the alkaloid cinchonamine and its derivatives, obtained by partial [3] or total synthesis [4, 5], and alkaloids of the aimaline, sarpagine, and quinamine group. Some synthetic representatives of this group of substances are also known [6–8].

We have shown that indole does not react with I without a catalyst. The electrophilic addition of unsaturated ketone I to indole and 2-phenylindole proceeds readily in the presence of both basic (sodium ethoxide) and acidic (acetic acid) catalysts and leads to 2-(3-indolylmethyl)- and 2-(2-phenyl-3-indolylmethyl)-3-oxoquinuclidines (II, III). It should be noted that whereas the use of sodium ethoxide makes it possible to obtain II and III in ~60% yields, II is formed in quantitative yield in the case of an acidic catalyst. In this case, when acetic acid is present, the increase in the electrophilicity of the olefinic bond in unsaturated ketone I due to the acceptor properties of the positively charged nitrogen atom of the quinuclidine ring is of substantial significance. In contrast to the literature data [9], the addition of acetic anhydride leads to a decrease in the yield of II. 1-Methyl-2-phenylindole does not react with unsaturated ketone I either in the presence of alkalis

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