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CONVERSIONS OF 1-ARYLAMINO-3-PHENYLOXINDOLES

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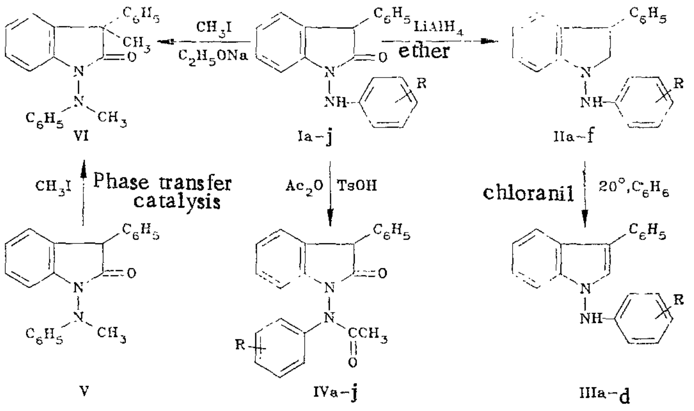
Acetylation of 1-arylamino-3-phenyloxindoles by acetic anhydride in the presence of an acidic catalyst (TsOH) gives N-acetyl derivatives; alkylation by methyl iodide in the presence of sodium ethoxide gives $C_{(3)}$- and N-dimethyl derivatives. Reduction by lithium aluminum hydride gives 1-arylamino-3-phenylindolines, which form the corresponding indoles when they are oxidized by chloranil.

The synthesis of 1-arylamino-3-phenyloxindoles was previously described in [1]. In this communication we shall consider some reactions of these compounds. The general scheme of the conversions studied is as follows:



The reduction of compounds Ia-f by lithium aluminum hydride in ether takes place with preservation of the N–N bond [2]. The reaction products are the corresponding indolines IIa-f, and their characteristics are given in Table 1. They are colorless crystalline substances, which are highly soluble in organic solvents. Owing to the presence of two enantiomeric forms of compounds IIa-f at the $C_{(3)}$ ring atom, the signal of the protons of the CH_2 group in the PMR spectra (CCl_4) is displayed in the form of two triplets at 3.63-3.85 and 4.05-4.36 ppm, and the 3-H proton also produces a triplet at 2.82-3.09 ppm. The signals of the NH group are found at 4.63-4.83 ppm. Indolines IIa-f are stable with respect to oxidation in air, except for compound IIc, which is oxidized within 24 h in an ethanolic solution (monitoring accroding to the UV spectrum). Partial oxidation is clearly attributable to the formation of a small quantity of indole IIIc during the isolation of indoline IIc (see Experimental).

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TABLE 1. 1-Arylamino-3-phenylindolines II and 1-Arylamino-3-phenylindoles III

Compound	R	mp, °C[a]	IR spectrum, cm^{-1}		UV spectrum, λ_{max}, nm (log ε)	PMR spectrum, ppm (J, Hz) in CCl_4				Found, %			Empirical formula	Calculated, %			Yield, %
			N—H	band of indole		N—H, s	3-H, t	2-CH₂, t	2-H, s	C	H	N		C	H	N	
IIa	H	122—123	3250	—	238 (4,23), 288 (4,27)	7,48	4,45 (6)	—	—	82,7	8,4	9,5	$C_{20}H_{18}N_2$	83,9	8,3	9,8	24
IIb	4-CH_3	112—113	3270	—	234 (4,37), 288 (3,99)	4,73	3,09 (9)	3,84 (8) 4,25 (8)	—	84,4	6,5	9,3	$C_{21}H_{20}N_2$	84,0	6,7	9,3	24
IIc	4-CH_3O	112—113	3300	—	244 (4,29), 300 (3,83)	4,75	3,08 (9)	3,83 (8) 4,26 (8)	—	79,6	6,5	8,8	$C_{21}H_{20}N_2O$	79,7	6,4	8,9	37
IId	4-F	97—98	3250	—	243 (4,16), 296 (4,20)	4,60	3,01 (9)	3,85 (8) 4,26 (8)	—	78,8	5,5	9,2	$C_{20}H_{17}FN_2$	78,9	5,6	9,2	24
IIe	4-Br	99—100	3270	—	252 (4,41), 292 (3,73)	4,63	2,82 (8)	3,63 (8) 4,05 (8)	—	64,4	4,9	7,4	$C_{20}H_{17}BrN_2$	65,8	4,7	7,7	40
IIf[c]	4-Cl	93—94	3275	—	252 (4,38), 294 (3,74)	4,83	3,06 (9)	3,81 (9) 4,24 (9)	—	75,0	5,3	8,6	$C_{20}H_{17}ClN_2$	74,9	5,3	8,8	30
IIIa[d]	H	138—139	3300	1550	225 (4,56), 265 (4,19), 280 (4,17)	6,16	—	—	7,73	88,5	5,8	9,7	$C_{20}H_{16}N_2$	88,7	5,7	9,9	77
IIIb	4-CH_3	116—117	3270	1555	225 (4,27), 265 (4,19), 296 (3,86)	5,80	—	—	7,73	85,0	6,0	9,3	$C_{21}H_{18}N_2$	84,5	6,1	9,4	57
IIIc	4-CH_3O	129—130	3300	1550	225,5 (4,50), 265 (4,14), 292 (4,13)	5,92	—	—	7,71	80,3	5,5	9,0	$C_{21}H_{18}N_2O$	80,2	5,8	8,9	81
IIId	4-F	125—126	3270	1545	224 (4,66), 265 (4,28), 289 (4,25)	6,23	—	—	7,73	79,3	5,2	9,3	$C_{20}H_{15}FN_2$	79,4	5,0	9,3	71

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[a] Compounds IIa-f were recrystallized from hexane, and compounds IIIa-d were recrystallizd from ethanol. [b] In DMSO.
[c] Found: Cl, 10.3%. Calculated: Cl, 11.0%. [d] mp 139-140°C [4].

TABLE 2. 1-(N-Acetyl-N-aryl)amino-3-phenyloxindoles (IVa-j)

Compound	R	mp, °C (from ethanol)	IR spectrum, cm^{-1}		PMR spectrum, ppm in CF_3COO		Found, %			Empirical formula	Calculated, %			Yield, %
			C=O	$COCH_3$	C—H	$COCH_3$	C	H	N		C	H	N	
IVa	H	153—154	1735	1690	4,23	1,74	77,5	4,9	7,8	$C_{22}H_{18}N_2O_2$	77,2	5,3	8,2	76
IVb	4-CH_3	202—203	1730	1690	4,45	1,90	78,0	5,5	8,0	$C_{23}H_{20}N_2O_2$	77,5	5,7	7,9	75
IVc	4-CH_3O	161—162	1730	1660	4,45	1,90	74,6	5,4	7,5	$C_{23}H_{20}N_2O_3$	74,2	5,4	7,5	62
IVd	4-F	190—191	1735	1695	4,48	1,90	74,0	5,1	7,9	$C_{22}H_{17}FN_2O_2$	73,3	4,8	7,8	77
IVe	4-Br	218—219	1735	1690	4,17	1,70	61,9	4,0	6,4	$C_{22}H_{17}BrN_2O_2$	62,7	4,1	6,7	79
IVf	4-Cl	217—218	1735	1695	4,17	1,74	69,8	4,3	7,4	$C_{22}H_{17}ClN_2O_2$	70,1	4,5	7,4	53
IVg	3-CH_3	142—143	1735	1685	4,43	1,90	76,9	5,3	7,7	$C_{23}H_{20}N_2O_2$	77,5	5,7	7,9	56
IVh	2-CH_3	150—151	1730	1695	4,43	1,88	77,5	5,4	7,8	$C_{23}H_{20}N_2O_2$	77,5	5,7	7,9	62
IVi	2-Br	109—110	1750	1715	4,46	1,93	63,1	4,0	6,8	$C_{22}H_{17}BrN_2O_2$	62,7	4,1	6,7	18
IVj	4-NO_2	196—197	1740	1705	4,50	1,91	68,2	4,3	10,7	$C_{22}H_{17}N_3O_4$	68,2	4,4	10,8	62

The 1-arylamino-3-phenylindolines were converted into the corresponding indoles IIIa-d (Table 1) by oxidation with chloranil after several minutes at 20°C in benzene. Indoles IIa-d were isolated by filtration through a lyer of basic aluminum oxide (50°C or more chloranil forms charge-transfer complexes with the desired products). The characteristic signal in the IR spectra of compounds IIIa-d is the band of moderate intensity at 1545-1555 cm^{-1}, which is assigned to the vibrations of the indole ring. This band is absent in the IR spectra of the original 1-arylamino-3-phenyloxindoles I and indolines II. The signal of the olefinic proton in the PMR spectra of compounds IIa-d (Table 1) is found at 7.71-7.73 ppm. In the mass spectra of compounds IIc and IIIc there are intense peaks for the molecular ions (M^+ 316 and M^+ 314, respectively). Electron impact results in the cleavage of the N—N bond in the molecular ion of IIIc with the elimination of the $NHC_6H_4OCH_3$-p group, while the remaining part of the molecule, i.e., the 3-phenylindole cation, decomposes further according to the usual scheme for phenylindoles [3] with the elimination of HCN and the formation of a fluorenyl cation (m/z 165). Indoline IIc loses two hydrogen atoms under electron impact and then decomposes in analogy to indole IIIc.

The absorption in the UV spectra of indolines IIa-f is caused primarily by the aniline residue. The UV spectra of indoles IIIa-d have three absorption maxima in the 220-300-nm region (Table 1) and are similar to the UV spectrum of the unsubstituted indole, confirming the structure of the compounds under consideration.

As a detailed study of the acetylation of compounds Ia-j showed, contratry to our earlier data [1], heating in acetic anhydride in the presence of catalytic amounts of TsOH results in the exclusive formation of 1-(N-acetyl-N-aryl)amino-3-phenyloxindoles IVa-j (Table 2). The small yield of IIi is attributed to steric hindrances (the bromine atom in the ortho position of the aryl ring). The absorption band of the carbonyl in the oxindole ring in this compound is displaced to 1750 cm^{-1}.

The PMR spectra of compounds IVa-j demonstrated the retardation of the rotation around the N—N bond, which results in the existence of compounds IVa-j in the form of mixtures of two forms with cis and trans arrangements of the phenyl group at $C_{(3)}$ and the NHAr residue relative to the plane of the oxindole ring (two TLC spots). In the PMR spectra this is manifested by splitting of the signal of the 3-H proton into two signals with a center at 4.17-4.50 ppm. Retardation of the rotation around an N—N bond was previously observed for 1-(N-benzyl-N-methylamino)-3-dialkylaminoalkyl-3-phenyloxindoles [2] and 2,3-disubstituted 1-acetaminoindoles [5], as well as for some 1,2-diacylhydrazines [6].

The alkylation of oxindole Ia by methyl iodide in the presence of sodium ethoxide takes place both at the nitrogen atom and at the $C_{(3)}$ atom of the oxindole ring, and compound VI forms with a 25% yield. Under the conditions of phase transfer catalysis with a substrate—methyl iodide—catalyst $[(CH_3)_4N^+I^-]$ ratio equal to 1:10:1 in methylene chloride with a 20% KOH solution, a mixture of the products of C and C,N alkylation forms (according to the PMR data).

Compound VI was also obtained by the alkylation of 1-(N-methyl-N-phenylamino)-3-phenyloxindole (V) under the conditions of phase transfer catalysis just described. The introduction of a substitutent into position 3 of the oxindole ring results in displacement of the absorption band of the carbonyl group in the IR spectrum from 1720 to 1735 cm^{-1}, which is characteristic of 3,3-disubstituted 1-aminooxindoles [7].

EXPERIMENTAL

The UV spectra were recorded on an SF-16 spectrometer in ethanol. The PMR spectra were recorded on a Tesla BS-487C instrument (80 MHz) for 10% solutions in CCl_4 or CF_3COOH. The mass spectra of compounds IIc and IIIc were recorded on an MKh-1303 instrument with direct introduction of the compound into the ion source at a temperature of 100°C with an ionization energy equal to 70 eV. The purity and individuality of all the compounds synthesized was monitored by TLC on Silufol in a 3:2 benzene—ether system with development by iodine vapor.

1-(N-Acetyl-N-p-nitrophenylamino)-3-phenyloxindole (IVj). A mixture of 7.65 g (50 mmole) of p-nitrophenylhydrazine and 10.3 g (125 mmole) of powdered calcined sodium acetate in 80 ml of dioxane is given an addition of 13.5 g (50 mmole) of α-chloro-α,α-diphenylacetyl chloride in 50 ml of dioxane. After 12 h, the inorganic salts are filtered out, the solvent is driven off to 40 ml, the solution is poured onto 300 g of ice, and the precipitating substance is crystallized from benzene. This gives 9.8 g of the crystal solvate of Ij with benzene, mp 96-98°C. A 2-g portion of Ij and a 50-mg portion of TsOH are heated in a water bath in 15 ml of acetic anhydride for 2 h, the acetic anhydride is distilled off in a vacuum, and the residue is treated with ether and crystallized from butanol. This gives 1.38 g (62%) of IVj, mp 196-197°C. Compounds IVa-i are obtained in a similar manner.

1-(p-Methoxyphenylamino)-3-phenylindoline (IIc) and 1-(p-Methoxy-phenylamino)-3-phenylindole (IIIc). A solution of 4.06 g (12.3 mmole) of compound Ic in 100 ml of absolute ether is given an addition of 1.5 g (37 mmole) of lithium aluminum hydride. The mixture is boiled for 8 h and decomposed by 4 ml of water, 7.5 ml of 20% NaOH, and 3 ml of water, the ethereal layer is dried by sodium sulfate, the ether is driven off, and the residue is chromatographed on silica gel (L 40/250) eluted by benzene, and crystallized after the removal of the benzene from hexane. This gives 1.43 g(37%) of IIc, mp 112-113°C. The mother solution from the crystallization step is evaporated, and the residue is crystallized from ethanol. This gives 0.3 g (8%) of indole IIIc, mp 129-130°C. Compound IIc oxidized by chloranil to IIIc with an 81% yield.

1-(p-Tolylamino)-3-phenylindole (IIIb). A solution of 200 mg of IIb in 10 ml of benzene is given an addition of a solution of 140 mg of chloranil in 18 ml of benzene. The mixture is stirred for 5 min at 20°C and filtered through a column (70 × 25 mm) with 15 g of basic Al_2O_3 (L 5/40). The product is eluted by 60 ml of benzene, and removal of the benzene leaves 113 mg (57%) of TLC-pure IIIb, mp 116-117°C (from ethanol). Indoles IIIa, c, and d are obtained in a similar manner.

1-(N-Methyl-N-phenylamino)-3-methyl-3-phenyloxindole (VI). A 0.33-g portion (1.05 mmole) of V (mp 113-114°C, obtained according to the method in [8]) is dissolved in 10 ml of methylene chloride, and 1.4 g (10 mmole) of methyl iodide and 0.2 g (1 mmole) of tetramethylammonium iodide in 10 ml of water, and 10 ml of 40% KOH are added. The mixture is shaken for 4 h, the organic layer is separated, washed with water and 10% KOH, and dried by Na_2SO_4, and the residue remaining after the removal of the solvent is crystallized from cyclohexane. This gives 0.20 g (57%) of compound VI, mp 139-140°C. IR spectrum: 1735 cm^{-1} (C=O). PMR spectrum (CCl_4): 1.79 (3H, s, $C-CH_3$), 3.31 ppm (3H, s, $N-CH_3$). Found: N, 8.5%. Calculated for $C_{22}H_{20}N_2O$: N, 8.5%.

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