Direct Amination. Part 2.[1] Reaction of 2-Phenylindole with Primary Aromatic Amines. A Chemical and Electrochemical Investigation

Corrado Berti,[a] Lucedio Greci,*[,a] Romano Andruzzi,[b] and Antonio Trazza[b]
[a] *Istituto Chimico della Facoltà di Ingegneria dell'Università, Viale Risorgimento, 2-40136 Bologna, Italy*
[b] *Dipartimento di Ingegneria Chimica, Università 'La Sapienza,' and Centro di Studio per la Elettrochimica e la Chimica Fisica delle Interfasi del C.N.R., Via del Castro Laurenziano, 7-00161 Roma, Italy*

The reaction of 2-phenylindole with primary aromatic amines to form 2-phenyl-3-arylimino-3*H*-indoles, in the presence of *N*-chlorobenzotriazole, *N*-chloroisatin or lead tetra-acetate, were also investigated by anodic oxidation. The chemical and electrochemical results suggest a mechanism involving an intermediate nitrenium ion, whose formation was demonstrated by an independent route. The reaction of 1-hydroxy-2-phenylindole with *p*-anisidine to form 2-phenyl-3-*p*-methoxyphenylimino-3*H*-indole 1-oxide, previously studied under anodic oxidation is here described in the presence of *N*-chlorobenzotriazole.

There are no examples in the literature[2] of direct arylamination using primary aromatic amines. Recently, however, we described the anodic arylamination of 1-hydroxy-2-phenylindole with primary aromatic amines to form 2-phenyl-3-arylimino-3*H*-indole 1-oxides,[1] the reaction being interpreted as occurring *via* a mechanism involving attack by the amino radical cation on the C-3 of the indole nucleus. In this paper we describe the reaction between 1-hydroxy-2-phenylindole and *p*-anisidine with *N*-chlorobenzotriazole (NCBT), and the reaction of 2-phenylindole with primary aromatic amines, either by anodic oxidation or in the presence of NCBT, *N*-chloroisatin (NCI), or lead tetra-acetate (LTA). The combined results of the parallel chemical and electrochemical investigations suggest that the isolated arylimino compounds are formed *via* a mechanism involving nitrenium ions.

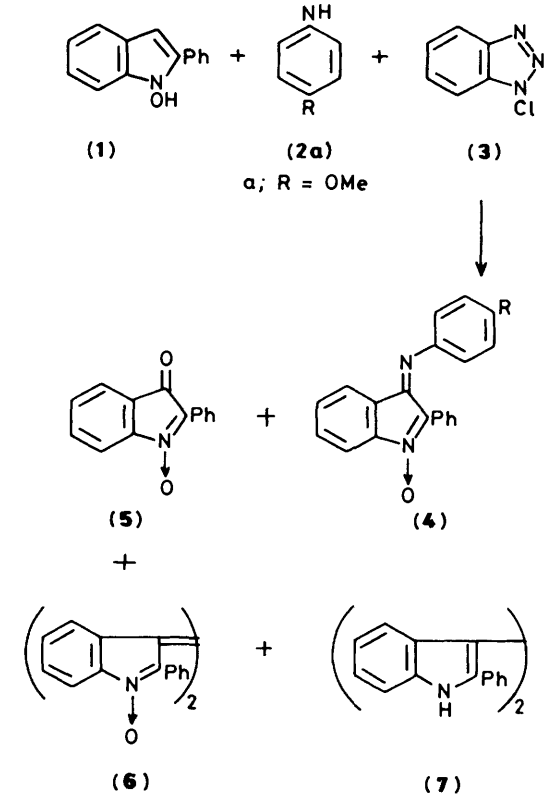
Results and Discussion

1-Hydroxy-2-phenylindole (**1**) and *p*-anisidine (**2a**) treated at room temperature with NCBT (**3**) in a 1:2:2 molar ratio, respectively, gave the *p*-methoxyphenylimino 1-oxide[3] (**4**), the bisnitrone[4] (**6**) the phenylisatogen[5] (**5**), and the bisindole[6] (**7**). All compounds were identified by comparison with authentic samples, compounds (**5**)—(**7**) having been reported as the products of the reaction 1-hydroxy-2-phenylindole with NCBT.[7] 2-Phenylindole (**8**) and primary aromatic amines (**2**) with NCBT, NCI, or LTA in a 1:2:4 molar ratio, respectively, yielded 3-arylimino-3*H*-indoles (**9**) (see Table 1). Several of the isolated products were identified by comparison with authentic samples.[3]

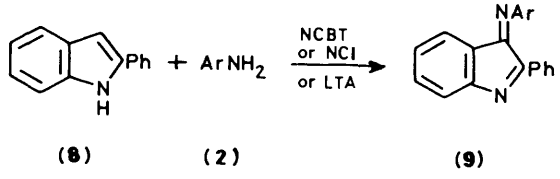
The new 3-arylimino derivatives (**9b'**), (**9c**), and (**9g**—**i**) were identified on the basis of their analytical data and by comparison of these (Table 2) with those of the 3-arylimino-3*H*-indoles obtained by an independent synthesis.[3] The ^{1}H n.m.r. spectra of all new compounds showed a multiplet at *ca.* δ 8.5, which is due to two aromatic hydrogens of the phenyl group at C-2; this signal is typical of 2-phenyl-3*H*-indoles.[8]

The reactions of 1-hydroxy-2-phenylindole (**1**) with aromatic amines (**2**) to form 3-arylimino *N*-oxides (**4**) carried out by anodic oxidation have been interpreted as proceeding *via* the intermediate formation of amino radical cations.[1] As 1-hydroxy-2-phenylindole (**1**) also reacts with *p*-anisidine in the presence of NCBT to form the corresponding arylimino *N*-oxide (**4**; R = OMe) (this paper), the reaction could be interpreted in the same way owing to the high oxidation power of NCBT[9] on the amine.

The reaction under conditions of anodic oxidation of 2-phenylindole (**8**) with primary aromatic amines (**2**) to form 3-arylimino-3*H*-indole (**9**) occurs when the electrolysis potential is neither lower nor higher than the oxidation potential of 2-phenylindole (**8**) [$E_{\frac{1}{2}}$ 0.75 V *vs.* Ag–$AgClO_4$ (0.1M in acetonitrile)]. Since the same reaction also takes place in



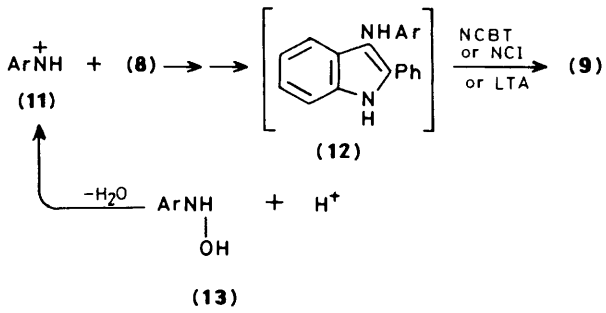
Scheme 1.



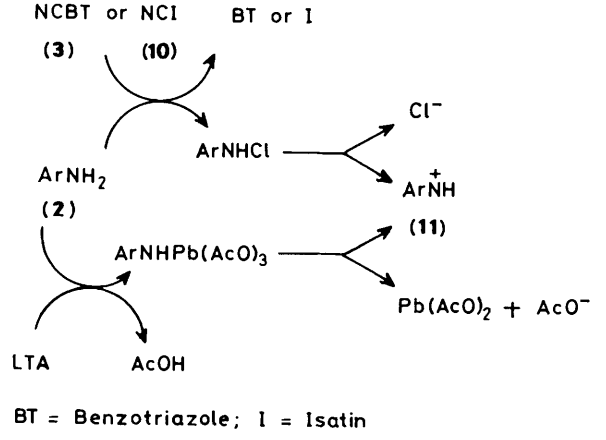
Scheme 2.

the presence of NCBT, NCI, or LTA, it seems likely that a nitrenium ion rather than an amino radical cation is involved as an intermediate. This is suggested by the fact that the nitrenium ion (**11**) formed by treatment of the phenylhydroxylamine with acid (see Experimental section) in the presence of 2-phenylindole (**8**) or 1-hydroxy-2-phenylindole (**1**) forms 2-phenyl-3-phenylimino-3*H*-indole (**9d**) (Scheme 3) or the corresponding 1-oxide (**4**; R = H), respectively. The oxidation of the postulated intermediate (**12**) to give (**9**) is brought about by the excess of NCBT (see below), NCI[10] or LTA,[11] or to the action of PbO_2 in the reaction with PhN(H)OH (Scheme 3).

The above reported mechanistic evidence is in agreement with the literature reports. In fact, a nitrenium ion (Scheme 4) has also been proposed as an intermediate in the reaction between amines and chlorinating agents.[12] On the other hand,



Scheme 3.



Scheme 4.

the formation of *N*-chloroamines in the reaction medium may be explained by the high chlorinating power of NCBT[13] and NCI.[14] In the case of LTA, the nitrenium ion (**11**) could be formed in the decomposition of the intermediate $ArNHPb(AcO)_3$,[15] as proposed for many of the reactions of LTA with aromatic nitrogen compounds.

As to the efficacy of the reagent used, we can deduce from

Table 1. Synthesis of 2-phenyl-3-(arylimino)-3*H*-indoles (**9a**—i)

2-Phenyl-indole	Amine	Reagent[a]	Products (%)[b]	Total yield[c] (%)
(**8**)	**a**; Ar = C_6H_4OMe-*p*	NCBT	(**9a**)	50
(**8**)	**a**; Ar = C_6H_4OMe-*p*	NCI	(**9a**)	45
(**8**)	**b**; Ar = C_6H_4Me-*p*	NCBT	(**9b**) (50), (**9b′**)[d] (50)	78
(**8**)	**c**; Ar = C_6H_4Me-*o*	NCBT	(**9c**) (90), (**9h**) (10)	60
(**8**)	**c**; Ar = C_6H_4Me-*o*	LTA	(**9c**)	15
(**8**)	**d**; Ar = Ph	NCBT	(**9d**) (63), (**9e**) (37)	90
(**8**)	**e**; Ar = C_6H_4Cl-*p*	NCBT	(**9e**)	50
(**8**)	**f**; Ar = C_6H_4Br-*p*	NCBT	(**9f**)	41
(**8**)	**g**; Ar = C_6H_3OMe-*p*-NO_2-*o*	NCBT	(**9g**)	76
(**8**)	**h**; Ar = C_6H_3Cl-3-OMe-2	LTA	(**9h**)	20
(**8**)	**i**; Ar = $C_6H_2Me_3$-2,4,6	NCBT	(**9i**)	43
(**8**)	**i**; Ar = $C_6H_2Me_3$-2,4,6	NCI	(**9i**)	40

[a] NCBT = *N*-chlorobenzotriazole, NCI = *N*-chloroisatin, LTA = lead tetra-acetate; [b] Percentage of arylimino derivatives in the total yield; [c] Yield of isolated arylimino derivatives; [d] (**9b′**) Ar = C_6H_3Cl-2-Me-4

Table 2. Analytical and spectroscopic data of compounds (**9b′**), (**9c**), and (**9g**—i)

Compd.[a]	M.p. (°C)	Formula	Found (%) (Calc.) C	H	N	$\nu_{max.}$ (cm^{-1})[b]	δ_H
(**9b′**)	118[d]	$C_{21}H_{15}ClN_2$	76.15 (76.24)	4.65 (4.57)	8.40 (8.47)	1 655, 1 615, 1 597, 1 538	2.45 (3 H, s, Me), 6.5—7.58 (10 H, m, ArH), 8.4—8.53 (2 H, m, ArH)
(**9c**)	84[e]	$C_{21}H_{16}N_2$	85.25 (85.10)	5.35 (5.44)	9.40 (9.45)	1 650, 1 618, 1 600, 1 535	2.18 (3 H, s, Me), 6.54 (1 H, d, ArH), 6.78—7.0 (2 H, m, ArH), 7.14—7.6 (11 H, m, ArH), 8.4—8.6 (2 H, m, ArH)
(**9g**)	193[d]	$C_{21}H_{15}N_3O_3$	71.0 (70.50)	4.32 (4.24)	11.82 (11.79)	1 640, 1 610, 1 595, 1 565, 1 528	3.96 (3 H, s, Me), 6.54—7.82 (10 H, m, ArH), 8.30—8.5 (2 H, m, ArH)
(**9h**)	125[d]	$C_{21}H_{15}ClN_2$	76.30 (76.24)	4.45 (4.57)	8.50 (8.47)	1 655, 1 610, 1 595, 1 540	2.16 (3 H, s, Me), 6.54—7.64 (10 H, m, ArH), 8.4—8.54 (2 H, m, ArH)
(**9i**)	135[d]	$C_{23}H_{20}N_2$	85.24 (85.15)	6.35 (6.21)	8.51 (8.64)	1 648, 1 612, 1 597, 1 540	2.0 (6 H, s, 2 Me), 2.38 (3 H, s, Me), 6.4—7.66 (9 H, m, ArH), 8.5—8.66 (2 H, m, ArH)

[a] All compounds gave the expected molecular ion peak in the mass spectrum. [b] Nujol. [c] $CDCl_3$. [d] From ethanol. [e] From n-hexane.

Table 1 that the best yields were obtained with NCBT, even though this reagent also forms chlorinated products such as (**9b'**), (**9h**), and (**9e**). On the basis of the experimental results, it is difficult to know whether the chlorination takes place on the starting amine or on the intermediate, the 3-arylaminoindole (**12**); however, an independent experiment carried out between the 3-anilinoindole (**12**; Ar = Ph) and NCBT yielded a mixture of compounds (**9d**) and (**9e**) (see Experimental section). The NCI reaction does not involve chlorination and works as well as NCBT when the amines shows a low oxidation potential. The LTA reaction generally gave products (**9**) in lower yield than that with NCBT.

Conclusions.—The reactions described here can be considered as an alternative method to that reported in the literature for the synthesis of compounds (**4**) and (**9**) using commercial aromatic amines instead of nitrosobenzenes.[3] On the basis of the experimental results it is difficult to distinguish which species (amino radical cation or nitrenium ion) is involved in the reaction, even though, in the case of 2-phenylindole (**8**), the electrochemical investigation excludes the possibility that the reaction takes place *via* the intermediate formation of an amino radical cation.

Experimental

M.p.s are uncorrected. I.r. spectra were recorded on a 257 Perkin-Elmer spectrophotometer. ^{1}H N.m.r. spectra were recorded on a Varian XL-100 spectrometer using Me_4Si as an internal standard. Mass spectra were recorded on a Varian 112-S apparatus. Liquid chromatography was performed on a Perkin-Elmer series 2 chromatograph with column C 18 (10 μm), using 75% MeOH–H_2O as the eluant, temperature 60 °C, flow 1.0 and the u.v. detector at 254 nm. The electrochemical experiments were carried out with an Amel Electrochemolab equipped with a potentiostat-galvanostat (Mod. 562), function generator (Mod. 567), interface unit (Mod. 563), and recorder (Mod. 862/D).

2-Phenylindole and the aromatic amines used were commercial products. 1-Hydroxy-2-phenylindole,[16] phenylhydroxylamine,[17] NCBT,[18] and NCI[14] were prepared as described in the literature.

Reaction of 1-*Hydroxy*-2-*phenylindole* (**1**) *with* p-*Anisidine* (**2a**) *and NCBT.*—NCBT (**3**) (10 mmol) in CH_2Cl_2 (30 ml) was added dropwise to a solution of 1-hydroxy-2-phenylindole (**1**) and *p*-anisidine (**2a**) (5 and 10 mmol, respectively in 70 ml of CH_2Cl_2), with stirring at room temperature. The solution immediately became orange. After 1 h the precipitated benzotriazole hydrochloride was filtered off. The filtrate was evaporated to dryness and the residue taken up in benzene and chromatographed on a column of silica gel eluting with benzene. The bisindole (**7**),[6] phenylisatogen (**5**),[5] 3-*p*-methoxyphenylimino-2-phenyl-3*H*-indole 1-oxide (**4**),[3] and the bisnitrone (**6**)[4] were isolated in 10, 10, 54, and 13% yields, respectively. All products were identified by comparison with authentic samples.

Reactions of 2-*Phenylindole* (**8**) *with Aromatic Primary Amines* (**2**) *and NCBT or NCI.*—The reactions were carried out as described above, starting with 2-phenylindole (1 mmol), the amine (2 mmol), and NCBT or NCI (4 mmol). After 1 h the benzotriazole hydrochloride or isatin was filtered off. The filtrate was washed with 10% aqueous $NaHCO_3$ (50 ml). The organic layer was separated, dried (Na_2SO_4), and evaporated to dryness. The residue, taken up in benzene, was chromatographed on a column of silica gel eluting with benzene. The reddish orange fraction gave compounds (**9**). In the case of NCBT, for which chlorinated imino derivatives were also formed in some cases, the chlorinated to unchlorinated derivative ratio was determined by h.p.l.c. The yields are reported in Table 1. All compounds were identified by comparison with authentic samples or from their analytical and spectroscopic data (Table 2).

Reactions of 2-*Phenylindole* (**8**) *with Aromatic Primary Amines* (**2**) *and LTA.*—LTA (4 mmol) was added to a stirred solution of 2-phenylindole (**8**) and the amine (**2**) (2 and 4 mmol, respectively) in benzene (20 ml) during 20 min at room temperature. After 10 min the insoluble salts were filtered off and the filtrate was chromatographed on a column of silica gel eluting with benzene. The arylimino derivatives (**9**) were obtained from the reddish orange fraction. The yields are reported in Table 1.

Anodic Oxidations.—Controlled-potential anodic oxidations of 2-phenylindole (**8**)–primary aromatic amines (**2**) mixtures were carried out in acetonitrile with tetrabutylammonium perchlorate as the supporting electrolyte, using a cylindrical electrolytic cell equipped with a working electrode of platinum gauze and a reference electrode of Ag–0.1M-$AgClO_4$ in acetonitrile. The procedure was the same as that described for the direct amination of 1-hydroxy-2-phenylindole (**1**).[1] In a typical run, 2-phenylindole (**8**) (0.5 mmol) was dissolved in a 0.1M solution of tetrabutylammonium perchlorate in acetonitrile and the amine (**2**) (1.0 mmol) was added. The resulting solution was deaerated with nitrogen and then oxidized at a controlled potential *ca.* 50 mV more positive than the oxidation potential ($E_{\frac{1}{2}}$) of the amine used. The electrolysis usually involved more than two electrons per molecule of amine. Moreover, the residual current was always higher than the background current, indicating that there were other species oxidized at the electrode present in the solution. The reaction solution checked by t.l.c. did not contain the expected 3-arylimino-3*H*-indole (**9**), not even when the reaction was carried out at an oxidation potential higher than that of 2-phenylindole (**8**) ($E_{\frac{1}{2}}$ 0.75 V). The products obtained from the oxidation of the amines were not identified.

Reaction of 2-*Phenylindole* (**8**) *with Phenylhydroxylamine* (**13**) *and Trifluoroacetic Acid.*—Phenylhydroxylamine (**13**) (2 mmol) in CH_2Cl_2 (10 ml) was added dropwise to a stirred solution of 2-phenylindole (**8**) (1 mmol) in CH_2Cl_2 (20 ml) and CF_3CO_2H (0.3 ml) at room temperature. The formation of the intermediate 3-arylaminoindole (**12**; Ar = Ph) was observed by t.l.c. in time. After 5 h the reaction mixture was treated with PbO_2 (1 g) and stirred for a further 30 min. The insoluble salts were filtered off and the filtrate evaporated to dryness. The residue, chromatographed by preparative t.l.c. eluting with benzene, gave the starting 2-phenylindole and compound (**9d**) in 35% yield.

Reaction of 1-*Hydroxy*-2-*phenylindole* (**1**) *with Phenylhydroxylamine* (**13**) *and Hydrogen Iodide.*—Phenylhydroxylamine (**13**) (2 mmol) in MeCN (10 ml) was added dropwise to a stirred solution of 1-hydroxy-2-phenylindole (**1**) (1 mmol) in MeCN (40 ml) and 57% aqueous HI (2 ml), at room temperature. After 15 min the reaction mixture was poured into 5% aqueous $NaHCO_3$ and extracted with benzene. The benzene layer was separated, dried (Na_2SO_4), and evaporated to dryness. The residue was chromatographed on a column of silica gel eluting with benzene. From the orange-yellow fraction compound (**4**; R = H)[3] was obtained in 70% yield.

Reaction of 3-*Phenylaminoindole* (**12**; Ar = Ph) *with NCBT.*—NCBT (2 mmol) in CH_2Cl_2 (20 ml) was added dropwise to a stirred solution of the 3-anilinoindole (**12**; Ar = Ph) (1 mmol) in CH_2Cl_2 (20 ml), at room temperature. The solution became red immediately. After 1 h the benzotriazole hydrochloride was

filtered off and the filtrate was treated with 10% aqueous $NaHCO_3$ (50 ml). The organic layer was separated, dried (Na_2SO_4) and examined by h.p.l.c. The starting material had been completely converted into compounds (**9d**) and (**9e**), and their percentage yields were 80 and 20%, respectively.

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