Synthesis and properties of 2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-5-nitroindazole

L. Y. Ukhin,[a] G. I. Orlova,[a] S. V. Lindeman,[b] V. N. Khrustalyov,[b] Yu. T. Struchkov,[b] and A. I. Prokof'ev [b]*

[a] *Institute of Physical and Organic Chemistry, Rostov State University, 344771 Rostov-on-Don, Russian Federation. Fax: +7 (863) 228 5667*

[b] *A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 117813 Moscow, Russian Federation. Fax: +7 (095) 135 5085*

N-(2-Azido-5-nitrobenzylidene)-3,5-di-*tert*-butyl-4-hydroxyaniline (**3a**) and N-(2-azido-5-nitrobenzilidene)aniline (**3b**), when heated in dimethylformamide yielded 2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-5-nitroindazole (**4a**) and 2-phenyl-5-nitroindazole (**4b**), respectively. The structure of **4b** was confirmed by X-ray analysis. A stable phenoxyl radical was shown to originate from the oxidation of **4a** with lead (IV) dioxide.

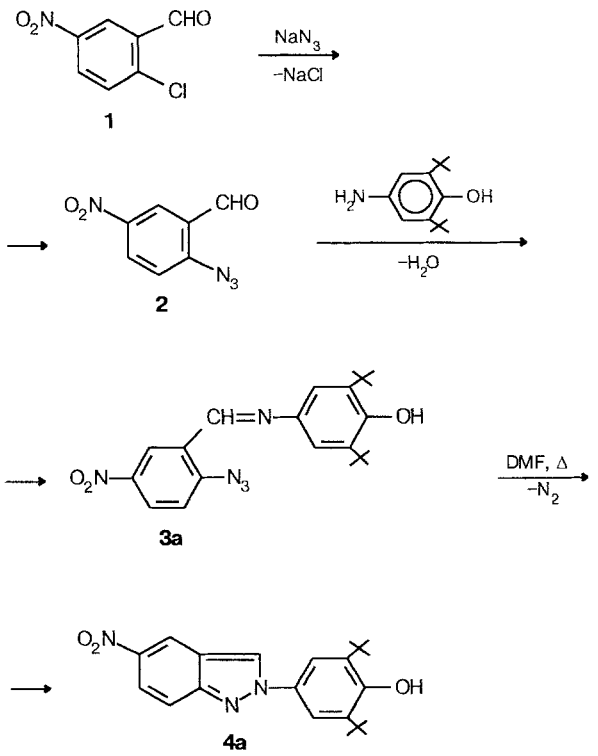
Key words: azide, azomethine, indazole, sterically hindered phenol, antioxidant, phenoxyl radical.

The search for new effective antioxidants is one of the acute problems of modern organic chemistry. Sterically hindered phenols are the substances that are most often used as antioxidants. This is primarily due to a complex of properties inherent in them such as high antioxidant activity, low toxicity, and the possibility of modulating the former over a wide range by changing the substituents in position 4 (see Refs. 1, 2).

The aim of the present work is to synthesize antioxidants that combine in their molecules the substructures of a sterically hindered phenol and indazole. We found no information on such compounds in literature. A known technique[3] of thermal decomposition of 2-azidobenzylidene amines to 1,2-dichloro- or to 1,2,4-trichlorobenzene, leading to 2-substituted indazoles, was chosen for the synthesis.

2-Chloro-5-nitrobenzaldehyde (**1**) was used to prepare the azido aldehyde (**2**), which was condensed with 3,5-di-*tert*-butyl-4-hydroxyaniline (DBHA). Dimethylformamide (DMF) was used as the solvent; the intermediate azomethine **3a** was not isolated (Scheme 1). As we had discovered that a similar reaction involving *N*-(2-azido-5-nitrobenzilidene) methylamine gave 1-methyl-5-nitroindazole (see Ref. 4, m.p. 127 °C), and not 2-methyl-5-nitroindazole (see Ref. 4, m.p. 163 °C), that is, insertion of nitrene in the N—CH_3 bond rather than its addition to the azomethine nitrogen, we were led to consider the probability of structure **4a** for the product obtained by heating **2** and DBHA in DMF (presumably *via* **3a**).

Therefore, we decided to perform an X-ray study of aryl-substituted indazole. As the quality of the crystals of **4a** prevented using them for this purpose, we synthesized its phenyl analog, **4b**, from **2** and aniline. The



Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 6, pp. 1095—1097, June, 1994.

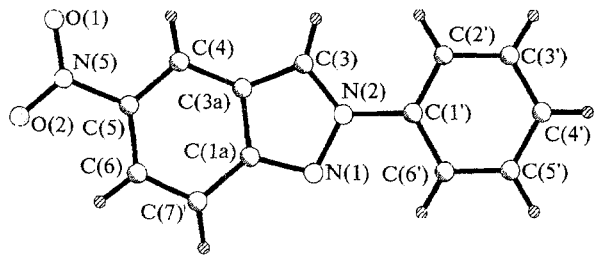


Fig. 1. A general view of molecule **4b**.

X-ray analysis of the latter has confirmed that the aryl substituent, as was expected, is in position 2 of the indazole ring, *i.e.*, the compound is 2-phenyl-5-nitroindazole.

A general view of molecule **4b** is given in Fig. 1. Molecule **4b** is practically planar (the dihedral angles between the planes of the nitro and phenyl substituents and the indazole system are 4.5(8) and 2.5(8)°, respectively, in spite of the very short intramolecular distance between the hydrogen atoms, H(3)...H(2') (2.2(2) Å). Within the limits of the fairly high experimental error (due to the low quality of crystals), the bond lengths and angles have normal values.

Table 1. Coordinates of non-hydrogen atoms ($\times 10^4$) in the structure of **4b**

Atom	*x*	*y*	*z*
N(1)	4732(9)	7289(16)	734(4)
N(2)	4791(9)	5477(16)	1159(4)
C(3)	3804(11)	3696(19)	1002(4)
C(4)	1829(10)	3239(21)	28(5)
C(5)	1358(11)	4518(24)	−509(5)
C(6)	1992(12)	6692(23)	−665(5)
C(7)	3119(11)	7746(22)	−281(5)
C(1a)	3623(10)	6545(18)	277(5)
C(3a)	3014(10)	4309(20)	435(5)
N(5)	117(10)	3484(23)	−933(5)
O(1)	−389(10)	1487(20)	−826(4)
O(2)	−365(9)	4651(19)	−1394(4)
C(1')	5911(11)	5615(23)	1708(5)
C(2')	5978(12)	3813(24)	2143(5)
C(3')	7077(14)	3970(24)	2658(5)
C(4')	8024(13)	5883(26)	2727(5)
C(5')	7919(12)	7684(24)	2298(5)
C(6')	6857(13)	7559(24)	1775(5)

Table 2. Coordinates of hydrogen atoms ($\times 10^3$) in the structure of **4b**

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
H(3a)	367	228	124	H(4a)	137	174	11
H(6a)	161	746	−105	H(7a)	358	923	−38
H(2'a)	528	250	209	H(3'a)	718	273	297
H(4'a)	878	599	308	H(5'a)	859	903	236
H(6'a)	678	879	146				

When **4a** was oxidized with PbO_2 in a benzene solution at room temperature (under a vacuum) the corresponding phenoxy radical (**5**) was recorded by the ESR technique. The hyperfine structure of the ESR spectrum fully corresponded to the molecular structure of monodehydro-**4a**. The observed six lines with an approximate ratio (1 : 4 : 7 : 7 : 4 : 1) were in a good agreement with the interaction of one uncoupled electron with the *meta*-positioned protons of the phenoxy rings, *para*-positioned nitrogen nucleus, and the proton of the pyrazole ring, $a_H^{meta} = a_H^{CH} = a_N^{para} = 1.65$ e, $g_{iso} = 2.0043$).

Experimental

IR spectra were recorded on a Specord IR-75 instrument in Vaseline oil. ^{1}H NMR spectra were taken on a Varian LX-300 spectrophotometer. The ESR spectrum of **5** was taken on a Varian E-12A instrument.

2-azido-5-nitrobenzaldehyde (2). 0.96 g (0.005 mol) of 2-chloro-5-nitrobenzaldehyde (**1**) was dissolved, with heating, in ethanol (15 mL). A solution of sodium azide (0.65 g, 0.01 mol) in water (2 mL) was added, while stirring. The mixture was boiled for 30 min, cooled, and diluted with 50 mL of water. The precipitate was collected by filtration and recrystallized from hexane. Yellowish light-sensitive crystals were obtained. Yield 0.45 g (49 %), m.p. 89—95 °C. Found (%): C, 44.10; H, 2.45; N, 28.80. $C_7H_4N_4O_3$. Calculated (%): C, 43.75; H, 2.08; N, 29.17. IR, ν/cm^{-1}: 2127, 2094 (N_3), 1694, 1681 (C=O), 1521, 1350 (NO_2).

2-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-5-nitroindazole (4a). 2-Azido-5-nitrobenzaldehyde **2** (0.03 g, 0.0015 mol) and DBHA (0.33 g, 0.0015 mol)[5*] in dimethylformamide (3 mL) were boiled for 20 min. Then the mixture was cooled and succesively diluted with isopropanol (10 mL) and water. The dark product that precipitated with water was collected by filtration and recrystallized from *i*-PrOH on an ice bath to give pinkish-grey crystals. Yield 0.3 g (53 %), m.p. 210—212 °C. Found (%): C, 68.81; H, 7.20; N, 11.11. $C_{21}H_{25}N_3O_3$. Calculated (%): C, 68.66; H, 6.81; N, 11.44. IR, ν/cm^{-1}: 3573(OH), 1621, 1594, 1567 (arom. and heterocycl. rings), 1500, 1333 (NO_2). ^{1}H NMR ($CDCl_3$), δ: 1.50 (s, 18 H, *t*-C_4H_9); 5.47 (s, 1 H, OH); 7.63 (s, 2 H, arom. protons of the hydroxyphenyl ring); 7.82 (sd, 1 H, C(7)—H of the indazole); 8.12 (d. d, 1 H, C(6)—H of the indazole); 8.76 (d, 1 H, C(4)—H of the indazole).

5-Phenyl-5-nitroindazole (4b). 2-Azido-5-nitrobenzaldehyde (0.5 g, 0.0026 mol), DMF (3 mL), and aniline (0.5 mL, 0.0054 mol) were boiled for 1 h. Then the mixture was cooled. 10 mL of isopropanol was added to the copiously

* 3,5-Di-*tert*-butyl-4-hydroxyaniline (DBHA) is extremely unstable in air. Immediately after synthesis, it was converted to its perchlorate (which is stable under ordinary conditions) by adding an excess of the 50-70% $HClO_4$ solution to the solution of hydroxyaniline in the alcohol-ether mixture. Immediately before synthesizing **4a**, the calculated amount of the perchlorate (DBHA · $HClO_4$) was treated in ethanol with a concentrated aqueous solution of NH_4OH; the precipitated hydroxyaniline was filtered off, washed with water on the filter, dissolved in DMF (without drying), and used immediately in the reaction .

Table 3. Bond lengths (d) in the structure of **4b**

Bond	d/ Å	Bond	d/ Å	Bond	d/ Å
N(1)—N(2)	1.37(1)	C(5)—C(6)	1.40(2)	C(1′)—C(2′)	1.37(2)
N(1)—C(1a)	1.37(1)	C(5)—N(5)	1.46(1)	C(1′)—C(6′)	1.37(2)
N(2)—C(3)	1.34(1)	C(6)—C(7)	1.35(1)	C(2′)—C(3′)	1.39(2)
N(2)—C(1′)	1.45(1)	C(7)—C(1a)	1.41(1)	C(3′)—C(4′)	1.36(2)
C(3)—C(3a)	1.38(1)	C(1a)—C(3a)	1.42(2)	C(4′)—C(5′)	1.36(2)
C(4)—C(5)	1.38(2)	N(5)—O(1)	1.23(2)	C(5′)—C(6′)	1.38(2)
C(4)—C(3a)	1.42(1)	N(5)—O(2)	1.22(1)		

Table 4. Bond angles (ω) in the structure of **4b**

Angle	ω/deg	Angle	ω/deg
N(2)—N(1)—C(1a)	103.0(8)	C(3)—C(3a)—C(4)	134.7(10)
N(1)—N(2)—C(3)	114.3(7)	C(3)—C(3a)—C(1a)	105.5(8)
N(1)—N(2)—C(1′)	118.5(8)	C(4)—C(3a)—C(1a)	119.8(9)
C(3)—N(2)—C(1′)	127.2(9)	C(5)—N(5)—O(1)	120.2(10)
N(2)—C(3)—C(3a)	106.5(9)	C(5)—N(5)—O(2)	117.5(11)
C(5)—C(4)—C(3a)	115.3(10)	O(1)—N(5)—O(2)	122.3(10)
C(4)—C(5)—C(6)	124.4(9)	N(2)—C(1′)—C(2′)	119.2(10)
C(4)—C(5)—N(5)	116.6(11)	N(2)—C(1′)—C(6′)	118.5(10)
C(6)—C(5)—N(5)	119.0(9)	C(2′)—C(1′)—C(6′)	122.4(9)
C(5)—C(6)—C(7)	121.2(10)	C(1′)—C(2′)—C(3′)	117.9(11)
C(6)—C(7)—C(1a)	116.8(11)	C(2′)—C(3′)—C(4′)	120.1(12)
N(1)—C(1a)—C(7)	126.7(9)	C(3′)—C(4′)—C(5′)	121.2(10)
N(1)—C(1a)—C(3a)	110.8(8)	C(4′)—C(5′)—C(6′)	120.1(12)
C(7)—C(1a)—C(3)a	122.5(9)	C(1′)—C(6′)—C(5′)	118.3(11)

precipitating crystalline substance, and after cooling with ice, the precipitate was filtered off and washed with cool isopropanol and hexane. Beige-colored crystals were obtained. Yield 0.52 g (84%), m.p. 196—198 °C (from *i*-PrOH—CH_3CN, 1 : 5). Found (%): C, 65.46; H, 3.78; N, 17.99. $C_{13}H_9N_3O_2$. Calculated (%): C, 65.27; H, 3.76; N, 17.57. IR, ν/cm^{-1}: 1627, 1594, 1567 (arom. and heterocycl. rings), 1501, 1341 (NO_2), 747, 681 (monosubst. benzene ring). ^{1}H NMR ($CDCl_3$), δ: 7.44—7.60 (m, 3 H, protons of the phenyl ring); 7.83 (d, 1 H, C(7)—H of indazole); 7.88—7.92 (m, 2 H, protons of phenyl ring); 8.12 (d. d, 1 H, C(6)—H of indazole); 8.67 (c, 1 H, C(3)—H of indazole); 8.77 (d 1 H, C(4)—H of indazole).

X-ray analysis of 4b. Monoclinic crystals, space group $P2_1/c$, for T = 20 °C: a = 9.025(2), b = 5.549(1), c = 21.878(6) Å, β = 98.47(2)°, V = 1083.7(0.8) Å^3, Z = 4, $C_{13}H_9N_3O_2$, M = 239.23, d_{calc} = 1.446 g cm^{-3}, μ(Mo-$K\alpha$) = 0.96 cm^{-1}.

The unit cell dimensions and intensity data were obtained on an automatic four-circle Siemens P3/PC diffractometer (T = −20 °C, λMo-$K\alpha$, graphite monochromator, θ/2θ-scan technique, θ_{max} = 28 °).

The structure was solved by direct methods (the MULTAN program) and refined by the full-matrix least-squares technique in an anisotropic approximation for the non-hydrogen atoms. The positions of the hydrogen atoms were calculated after each least-squares bit cycle and their contribution to F_{calc} was allowed for with the fixed U_{iso}=0.04 Å^2. The final divergence factor R = 0.094, R_w = 0.113 from 856 independent reflections.

All the calculations were done on an IBM PC/AT-286 personal computer using the SHELXTL package of programs. The atomic coordinates are given in Tables 1 and 2, and the geometric parameters of the molecule are given in Tables 3 and 4.

References

1. V. V. Ershov, G. A. Nikiforov, and A. A. Volod'kin, *Prostranstvenno zatrudnennye fenoly* [*Sterically Hindered Phenols*], Khimiya, Moscow, 1972 (in Russian).
2. V. A. Roginskii, *Fenol'nye antioksidanty* [*Phenolic Antioxidants*], Nauka, Moscow, 1988 (in Russian).
3. L. Krbechek and H. Takimoto, *J. Org. Chem.*, 1964, **29**, 1150.
4. Ch. A. Jaffari and A. J. Nunn, *J. Chem. Soc. Perkin Trans.*, 1973, 2371.
5. G. A. Nikiforov and V. V. Ershov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1964, 1335 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1964, 1244 (Engl. Transl.)].

Received December 7, 1993