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3-PHENYL-2H-1,4-BENZOXAZINE-4-OXIDES—I

SYNTHESIS AND REDUCTION†

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Abstract—The title compounds were prepared by reductive cyclisation of *o*-nitro-phenoxy-acetophenones and characterized through a cycloadduct with acrylonitrile. Reduction of the N-oxides leads to the corresponding hydroxylamines that are highly unstable and can be transformed into the corresponding nitroxides by a variety of oxidation agents, including air. Previously unknown *o*-nitro-phenoxy-acetophenones were synthesized as starting materials for cyclisation reactions.

The growth-inhibiting effect of some 1,4-benzoxazine derivatives on *Fusarium nivale* has been tested by Honkanen and Virtanen[1] who concluded, on the bases of experimental results, that the most effective in the series should be the 3,4-dihydro-4-hydroxy- 2H-1,4-benzoxazine 1 which has not yet been synthesized.

In order to provide suitable intermediates for N-hydroxy-derivatives **4a-l** we started to prepare nitrones **3a-l**, suitable to undergo appropriate reduction to N-hydroxy derivatives **4a-l**. Owing to the well known fact that condensation between an hydroxylamine and a CO group, when suitably placed on the same molecule, occurs very easily leading to cyclic nitrones,[2,3] the appropriate 2-nitrophenoxy-acetophenones **2a-l** (Table 1), were synthesized, through alkaline condensation of *o*-nitrophenols with haloketones. The reductive cyclisation of 2-nitrophenoxy-acetophenones was carried out using ammonium chloride and zinc dust and led to 3-phenyl-2H-1,4-benzoxazine-4-oxides **3a-l** with yields varying from 20 to 80% (Table 2). The reactions follow a general pathway and intermediate mixtures of hydroxylamine and of another compound, which proved to be an hydrated nitrone, were observed. These mixtures, when heated up to 50° (procedure A, Experimental), were completely transformed into compounds **3a-l** characterized by ^{1}H NMR, elemental analysis and mass spectra.

Alternatively when the mixture was maintained at room temperature (procedure B), only the hydrated form of the nitrones were obtained (as a type compound, **3a*** has been characterized and reported on Table 2), owing to oxidation of hydroxylamines during the working up.

Evidences supporting these conclusions were based on ^{1}H NMR spectra of the condensation products of **2a**.

The spectrum initially showed a singlet at 5.20 ppm corresponding to the methylene of the nitrone; a multiplet at 4.3 ppm for protons at $C_{(2)}$ and $C_{(3)}$ of the hydroxylamine; a singlet at 5.72 ppm, exchangeable with D_2O, for the N–OH proton and another singlet at 1.7, also exchangeable with D_2O. If the NMR probe was left at 36° for 30 min, bands at 4.3 and 5.72 ppm disappeared and the spectrum showed only singlets at 5.20 and 1.7 ppm. This spectrum was interpreted as due to the hydrate, for the following considerations: (i) NMR spectrum showed a one to one intensity ratio between the

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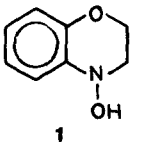

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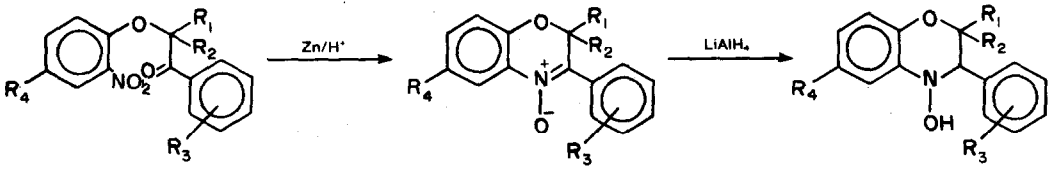


2a-l **3a-l** **4a-l**

a: $R_1 = R_2 = R_3 = R_4 = H$
a*: $a \cdot H_2O$
b: $R_1 = R_2 = R_4 = H$, $R_3 = pMe$
c: $R_1 = R_2 = R_4 = H$, $R_3 = pCl$
d: $R_1 = R_2 = R_4 = H$, $R_3 = pOMe$
e: $R_1 = R_2 = R_4 = H$, $R_3 = oOMe$
f: $R_1 = R_2 = Me$, $R_3 = R_4 = H$
g: $R_1 = R_3 = R_4 = H$, $R_2 = Me$
h: $R_1 = R_2 = R_3 = H$, $R_4 = Me$
i: $R_1 = R_3 = H$, $R_2 = R_4 = Me$
l: $R_1 = R_2 = R_4 = Me$, $R_3 = Me$

Table 1. Analytical and spectroscopic data of compound **2a-l**

Compound	Elemental analysis						I.R. (cm^{-1})a	H^1-N.M.R.[b] (p.p.m.)	M.S.: m/e	Yield %	m.p.°C
2a[8]							1685;1525,1355	5,45s(R_1=R_2=H)	257	75	118-9
2b[9]							1690;1515,1350	5,37s(R_1=R_2=H) 2,40s(R_3=Me)	271	65	120-1
2c	$C_{14}H_{10}NO_4Cl$	calc	C 57.64	H 3.45	N 4.80		1690;1515,1350	5,85s(R_1=R_2=H)	292	70	161-2
	(291.69)	found	57.80	3.53	4.70						
2d	$C_{15}H_{13}NO_5$	calc	C 62.71	H 4.56	N 4.87		1675;1515,1360	5,35s(R_1=R_2=H) 3,87s(R_3=OMe)	288	65	120-1
	(287.27)	found	62.87	4.70	4.63						
2e	$C_{15}H_{13}NO_5$	calc	C 62.71	H 4.56	N 4.87		1675;1520,1350	5,34s(R_1=R_2=H) 3,92s(R_3=o-Me)	288	63	95-6
	(287.27)	found	62.93	4.62	4.80						
2f	$C_{16}H_{15}NO_4$	calc	C 67.35	H 5.29	N 4.90		1670;1525,1350	1,75s(R_1=R_2=Me)	285	38 (DMSO) 10 (MeoH)	60-1
	(285.30)	found	67.53	5.37	4.82						
2g	$C_{15}H_{13}NO_4$	calc	C 66.41	H 4.83	N 5.16		1700;1525,1355	5,48q(R_1=H) 1,74d(R_2=Me)	271	35	70-1
	(271.27)	found	66.65	4.85	5.09						
2h	$C_{15}H_{13}NO_4$	calc	C 66.41	H 4.83	N 5.16		1695;1525,1350	5,35s(R_1=R_2=H) 2,20s(R_4=Me)	271	70	78-9
	271.27)	found	66.70	4.73	5.01						
2i	$C_{16}H_{15}NO_4$	calc	C 67.35	H 5.29	N 4.90		1690;1530,1345	5,45q(R_1=H) 1,75d(R_2=Me) 2,25s(R_4=Me)	285	43	60-1
	(285.30)	found	67.42	5.37	4.83						
2l	$C_{17}H_{17}NO_4$	calc	C 68.21	H 5.72	N 4.67		1675;1525,1355	1,73s(R_1=R_2=Me) 2,23s(R_4=Me)	299	33 (DMSO)	oil
	(299.33)	found	68.35	5.77	4.62						

a - nujol C=O, NO_2; b - $CDCl_3$, except for 1c(DMSO-d_6); c - when not indicated, solvent was methyl-ethyl-ketone.

Table 2. Analytical and spectroscopic data of compounds 3a-l

Compound	Elemental Analysis					I.R. $\nu_{N\rightarrow O}$ (+) cm^{-1}	^{1}H N.M.R. (o)	M.S.: m/e	Yield% A Proc.	m.p. °C
3a	$C_{14}H_{11}NO_2$	calc	C 74.65	H 4.92	N 6.22	1240	5.20s (R_1=R_2=H)	225	40	119-120[a]
	(225,2)	found	74.81	5.11	5.98					
3a*	$C_{14}H_{13}NO_3$	calc	C 69.11	H 5.39	N 5.76	1240	1.70s (H_2O)	243	//	110-112[a]
	(243.3)	found	69.34	5.46	5.89		5.20s (R_1=R_2=H)			
3b	$C_{15}H_{13}NO_2$	calc	C 75.30	H 5.48	N 5.85	1240	3.38s (R_3=p.Me)	239	80	115-116[b]
	(239.3)		75.19	5.36	5.98		5.25s (R_1=R_2=H)			
3c	$C_{14}H_{10}ClNO_2$	calc	C 64.75	H 3.88	N 5.39	1240	5.28s (R_1=R_2=H)	259	80	160-62[b]
	(259.7)	found	64.91	3.97	5.19					
3d	$C_{15}H_{13}NO_3$	calc	C 70.58	H 5.13	N 5.49	1240	3.84s (R_3=$POCH_3$)	255	40	102-03[c]
	(255.3)	found	70.71	5.21	5.53		5.25s (R_1=R_2=H)			
3e	$C_{15}H_{13}NO_2$	calc	C 70.58	H 5.13	N 5.49	1240	3.95s (R_3=$oOCH_3$)	255	34	65-66[b]
	(255 3)	found	70.68	5.22	5.42		4.95s (R_1=R_2=H)			
3f	$C_{16}H_{15}NO_2$	calc	C 75.87	H 5.97	N 5.53	1250	1.55s (R_1=R_2=H)	253	30	96-97[b]
	(253.3)	found	75.79	5.90	5.67		7.45s Ph			
3g(-)	$C_{15}H_{13}NO_2$	calc	C 75.30	H 5.48	N 5.85	1240	1.53d (R_2=Me)	239	20	99-100[b]
	(239.3)	found	75.45	5.56	5.72		5.65q (R_1=H)			
							11.8s (COOH)			
3h	$C_{15}H_{13}NO_2$	calc	C 75.30	H 5.48	N 5.85	1250	2.35s (R_4=Me)	239	40	106-07[b]
	(239.3)	found	75.42	5.53	5.80		5.25s (R_1=R_2=H)			
3i	$C_{16}H_{15}NO_2$	calc	C 75.87	H 5.97	N 5.53	1260	1.5d (R_2=Me)	253	35	65-66[b]
	(253.3)		75.98	5.86	5.60		2.4s (R_4=Me)			
							5.70q (R_1=H)			
3l	$C_{17}H_{17}NO_2$	calc	C 76.38	H 6.41	N 5.24	1150	1.55s (R_1=R_2=Me)	267	30	85-86[b]
	(267.3)	found	76.49	6.53	5.15		2.35s (R_4=Me)			
							7.48s Ph			

(+) = N$^+$-O$^-$ streching in Nujol; (O) = in $CDCl_3$; (−) = as oxalic acid salt. Cristallization solvent: a = MeOH/H_2O; b = light petroleum; c = Anhydrous ethyl ether.

singlets; (ii) compound $3a^+$ was isolated and elemental analysis and mass peak at 243 were in favour of the nitrone plus 1 molecule of water; (iii) this compound could be transformed into nitrone **3a** by heating as confirmed by disappearance of singlet at 1.7 ppm, and appearance of a broad and weak band at 4.3 ppm, typical of water protons.

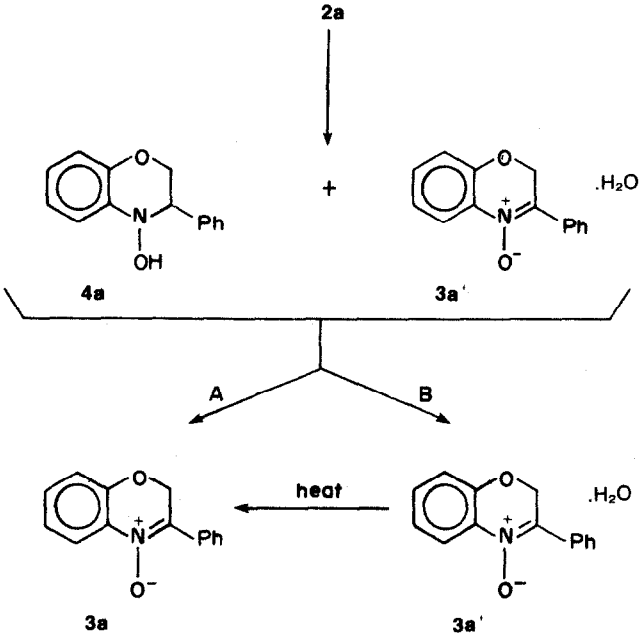
All those observations account for Scheme 1.

All the nitrones synthesized were very light sensitive and showed ESR signals due to decomposition radicals. Decomposition was also supported by the UV spectra which showed progressive decreasing bands at 350 nm and 245 nm, with a characteristic[4] ϵ in the range of 1.5×10^4.

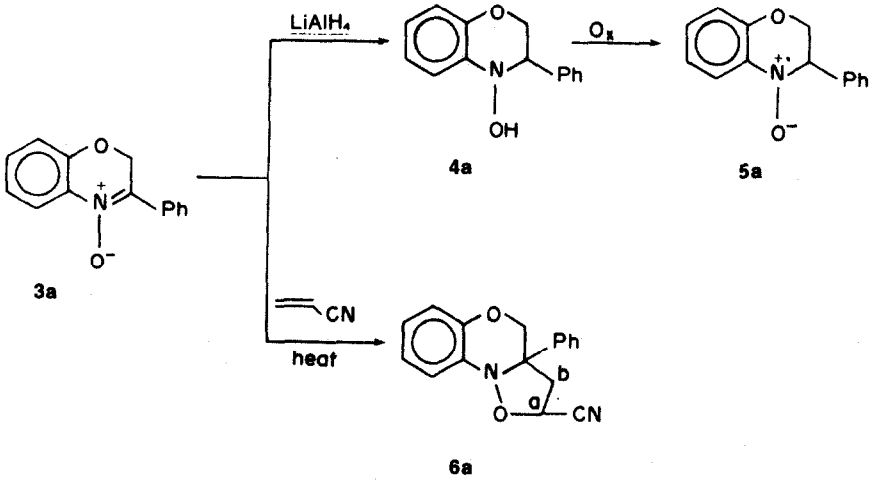
Upon treatment with lithium aluminum hydride **3a** yielded the corresponding hydroxyilamine **4a** (Scheme 2) which being unstable was transformed into the nitroxide **5a** showing the characteristic spectrum of Fig. 1 in particular the value of 7.40 gauss (evidence[5] for one α-hydrogen) in agreement with the parent hydroxylamine structure. The radical was not stable and its spectrum changed rapidly to one (Fig. 2) consisting of a triplet of triplets due to (1) $a^N = 10.50$ g and (2) $a^H = 3.00$ g. Probably all the N-oxides of the series would undergo photochemical decomposition in presence of oxygen resulting in this spectrum, as more detailed studies on benzoxazine-nitroxides demonstrate.[6]

Nitrone **3a** was also characterized by means of 1,3-cycloaddition with acrylonitrile[7] which produced only one regioisomer, corresponding to **6a** by NMR assignment.

Finally this work clearly demonstrated that in spite of the possibility of obtaining the desired N-hydroxy-derivatives **4a-l**, these cannot be used for biological purposes, because of their instability.



Scheme 1.



Scheme 2.

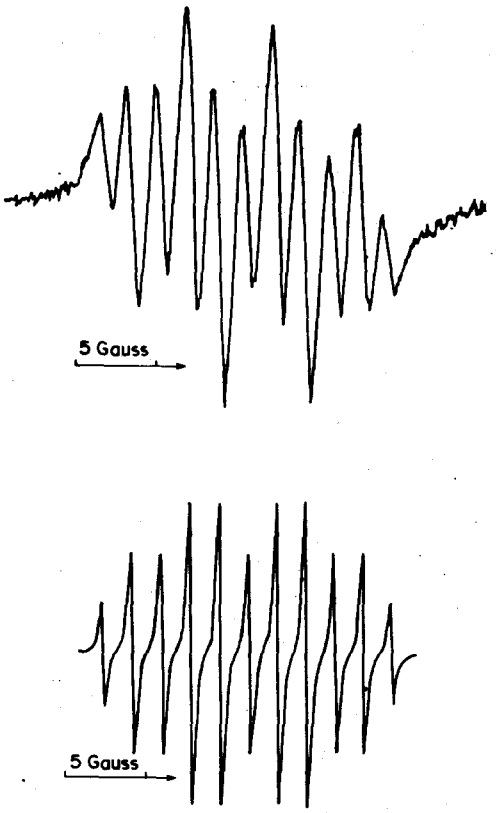


Fig. 1. Top. Experimental ESR first derivative spectrum of nitroxide **5a** in dioxane solution. (1)a^N = 11.10 G; (1)a^H = 7.40 G; (2)a^H = 3.70 G. Bottom simulated ESR spectrum of **5a**.

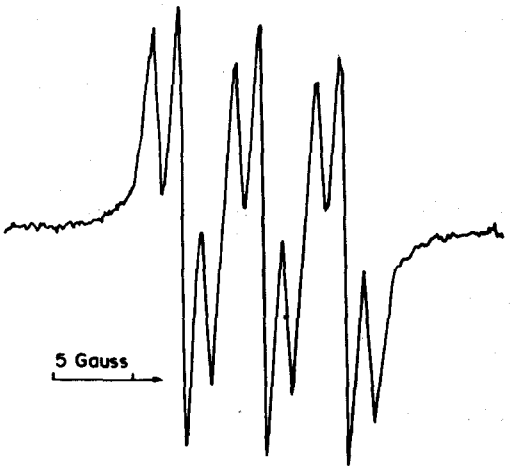


Fig. 2. ESR first derivative spectrum corresponding to the final decomposition stage of nitrones **3a-l**.

EXPERIMENTAL

IR spectra were recorded as mull (Nujol) on a Perkin–Elmer 257 apparatus. UV spectra were recorded on a Perkin–Elmer 402 spectrophotometer. NMR spectra were recorded on a Perkin–Elmer R-12B 60 MHZ apparatus using TMS as internal standard. ESR spectra were performed with a JEOL-1X ESR spectrometer. Mass spectra were obtained from a Varian-Mat 111 apparatus.

General method for preparation of ω-(o-nitrophenoxy-) acetophenones (**2a-l**). Potassium *o*-nitrophenate (1 mM) in presence of the appropriate bromoketone (1 mM) was refluxed in 30 ml of stated solvent (see Table 1) for 6 hr. The soln was then concentrated under vacuum to approximately 20 ml, diluted with water and extracted with benzene. The extract was twice washed with 10% $NaHCO_3$ aq, dried over Na_2SO_4 and concentrated. Compounds **2a-l** were then crystallized from EtOH.

General method for reduction of ω(o-nitrophenoxy) acetophenones to 3-Ph-2H-1,4-*benzoxazine-N-oxides* (**3a–1**). *Procedure A.* Zn dust (1 g) was added in small portions to a stirred suspension of the keto compound (1 g) dissolved in 80 ml EtOH and 20 ml H_2O containing ammonium chloride (1 g), under N_2 at 0–10°. After 2 hr Zn was filtered off and the soln heated at 70° for 2 additional hr, diluted with water and extracted with $CHCl_3$. The extract was dried over Na_2SO_4 and concentrated under vacuum. The resulting nitrones were cyrstallized from the appropriate solvent (Table 2). *Procedure B.* The reaction was carried out as in procedure A, but the heating omitted. The soln, separated from Zn, was then diluted with water and the separated solid **3a***, purified by crystallisation from EtOH–water.

Reduction of nitrone **3a** *with lithium aluminium hydride.* An anhydrous ethereal soln of nitrone (1 mM) was refluxed with LAH (2 mM) for 2 hr. The excess LAH was carefully destroyed with water and the suspension extracted with ether; the ethereal soln was dried over Na_2SO_4 and solvent removed under vacuum. The yellow oil obtained was characterized as the N-hydroxy-derivative **4a** on the basis of IR and NMR spectra [3-Ph-2H-3,4-dihydro-1,4-benzoxazine N-hydroxy, IR 3400 cm^{-1} (OH broad); 1240 cm^{-1} (NO strech), ^1H NMR ($CDCl_3$): δ = 7.40 (*s*, 3H), 5.72 (s, 1H), 4.3 (m, 3H)]. The corresponding nitroxide radical was obtained by direct oxidation in the ESR spectrometer cavity.

Cycloaddition of nitrone **3a** *with acrylonitrile.* The nitrone (0.5 mM) and the acrylonitrile (1 mM) were dissolved in benzene (20 ml) and the soln refluxed for 2 hr. After concentration under vacuum, the residue was crystallized from petroleum-ether and characterized as **6a** m.p. 164–66° (from petroleum-ether), MS: *m/e* 278; IR (Nujol): 2245 cm^{-1} (CH weak); 1260 cm^{-1} (N–O strech); ^1H NMR ($CDCl_3$): δ = 4.83 (t, $1H_a$, J = 6 c/s), δ = 4.4–4.0 (9, 2H, AB system J_{AB} = 12 c/s), δ = 2.97 (d, $2H_b$, J = 6 c/s).

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