

Oxidation and Photochemical Reactions of 3-Phenyl-2*H*-1,4-Benzoxazines

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3-Phenyl-2*H*-1,4-benzoxazines 4-oxides are light sensitive compounds, irradiation leads to 3-phenyl-2*H*-1,4-benzoxazines and to their 3-oxidized derivatives, whenever possible. Intermediate oxaziridines are formed during the photolysis and transformed into stable nitroxide radicals. The structure of these radicals was confirmed through peracid oxidation of 3-phenyl-2*H*-1,4-benzoxazines and 3-phenyl-3,4-dihydro-2*H*-1,4-benzoxazines. A reaction mechanism is proposed on the basis of experimental observations.

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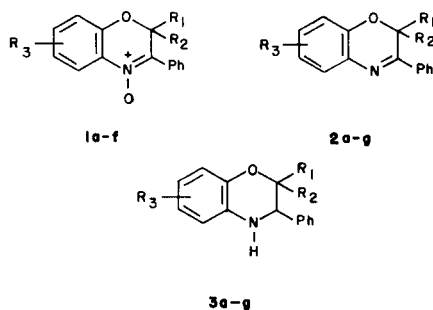
In the course of work (1) concerning the preparation of 3-phenyl-2*H*-1,4-benzoxazine-4-oxides **1a-f** it has been observed that all the compounds synthesized were light sensitive leading to reaction mixtures that show esr signals. In the work we demonstrated that the decomposition reaction leads to some different products, the nature of which has been recognized through hplc chromatography and esr spectroscopy. Peracid oxidation of 3-phenyl-2*H*-1,4-benzoxazines **2a-g** and 3-phenyl-2*H*-3,4-dihydro-1,4-benzoxazines **3a-g** was also performed. In addition to the ones already known (2), compounds **2g** and **3g** were prepared. Photochemical reactions of acyclic nitrones were extensively studied (3). Rearrangement to amides *via* unstable oxaziridines was the normal route of the decomposition, photolysis of  $\alpha$ -acylnitrones gave diacylamines (4,5).

Long lived radicals were detected (6) during the uv irradiation of a series of diarylnitrones and recognized as *N*-benzoylnitroxides. Photochemical reactions of cyclic

nitrones, instead, were episodically studied. Thus 7-chloro-4,5-epoxy-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine was formed when 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide was irradiated (7); oxaziridino-[2,3-*a*]pyrrolidines were the products of the photolysis of -pyrroline 1 oxides (8-12). The nature of the substituent in position 2 seems to effect the reaction, thus 2-unsubstituted 1-pyrroline 1-oxides formed oxaziridine readily, whilst 2-substituted isomers have been reported not to give oxaziridines (9). Meanwhile 2,5,5-trimethyl-1-pyrroline 1-oxide formed the oxaziridine on irradiation (10).

Oxaziridino[2,3-*a*]pyrrolidines were shown to rearrange to the corresponding 2-pyrrolidones either thermally or photolytically (8,9,11). Ring expansion to 2-phenyl-4-phenylimino-4*H*-3,1-benzoxazine was observed during the photolysis of 2-phenyl-3-phenylimino-3*H*-indole-1-oxide (13). An intermediate oxaziridine was proposed. Photocatalyzed ring expansions in heteroaromatic *N*-oxides are well documented (14). It seems generally accepted that the oxaziridines are the primary products of the photolytic transformation on cyclic nitrones (15,16). The nitrones have also been reported to act as radical traps for short lived radicals. In this case radicals add to the  $\alpha$ -carbon atom, giving stable nitroxide. In addition to the many examples on open nitrones (17-19) it was shown that 2-phenylisatogen and 1-oxy-2-phenyl-3-phenylimino-3*H*-indoles (20), that can be considered as cyclic nitrones, were easily transformed into stable indole nitroxides by reactions with aryl, alkyl and peroxyalkyl radicals.

Photolysis of nitrones **1a-f** appears less univocal than that of the examples previously reported, even if the first step of the process does consist in the isomerization of the nitron into the oxaziridine following the general rule (see latter for discussion). In all cases one can observe, on irradiation the fast disappearance (about 5-10 minutes) of band at 350 nm ( $\epsilon \approx 18,000$ ) that is characteristic of the nitron group (21). Two samples **1a** and **1e** were chosen and the photolysis followed by hplc.



- a**, R<sub>1</sub> = R<sub>2</sub> = R<sub>3</sub> = H  
**b**, R<sub>1</sub> = R<sub>2</sub> = H, R<sub>3</sub> = Me  
**c**, R<sub>1</sub> = R<sub>3</sub> = H, R<sub>2</sub> = Me  
**d**, R<sub>1</sub> = H, R<sub>2</sub> = Me, R<sub>3</sub> = 6-Me  
**e**, R<sub>1</sub> = R<sub>2</sub> = Me, R<sub>3</sub> = H  
**f**, R<sub>1</sub> = R<sub>2</sub> = Me, R<sub>3</sub> = 6-Me  
**g**, R<sub>1</sub> = R<sub>2</sub> = Me, R<sub>3</sub> = 7-Me

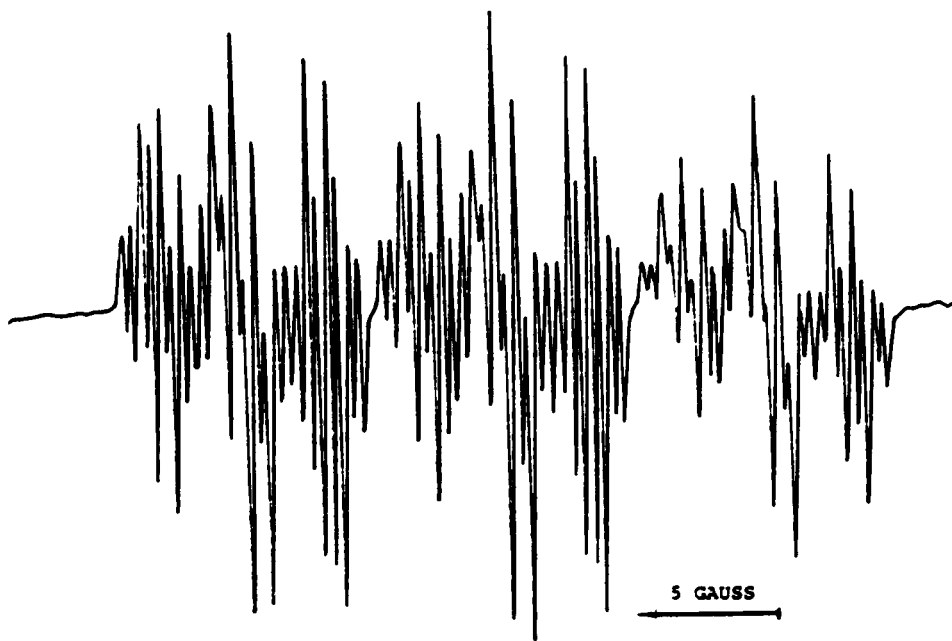
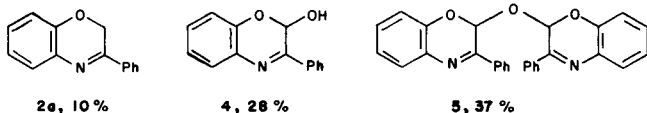
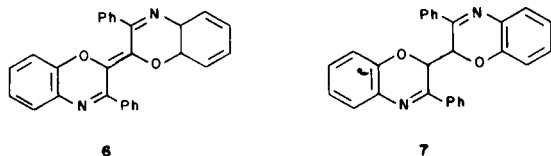


Figure 1. The esr spectra of compound **1a** after irradiation.

In the first example 2-hydroxy-3-phenyl-2*H*-1,4-benzoxazine (**4**) and compounds **5**, together with some 3-phenyl-2*H*-1,4-benzoxazine (**2**) were the reaction products. Small amounts of unidentified compounds were also present. The total yield on transformation products, calculated on the starting nitron, was 75%. Compounds **4** and **5** were already obtained (22) during the oxidation of **2a**.



No trace of compounds **6** and **7** was detected that were obtained when the oxidation of **2a** was performed in the absence of oxygen.



Photolysis of 2,2-dimethyl-3-phenyl-2*H*-1,4-benzoxazine 4-oxide (**1e**) leads only to the benzoxazine **2e**.

Because of the formation of a unique end product, this case appears simple enough to recognize the formation of the intermediate oxaziridine **1e**. If one compared the ir spectrum of the photolysed nitron in deuteriochloroform after 10 minutes of irradiation with the ir spectra of nitron **1e** and of benzoxazine **2e**, the existence of the ox-

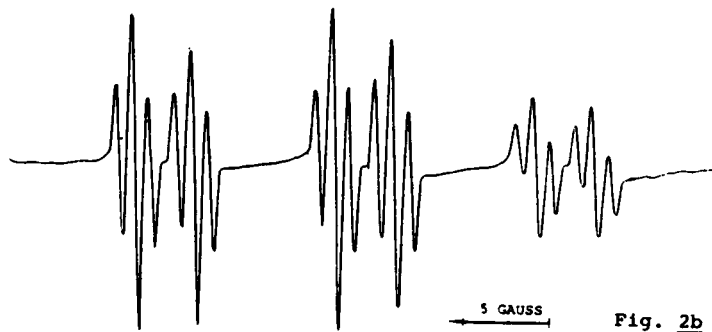
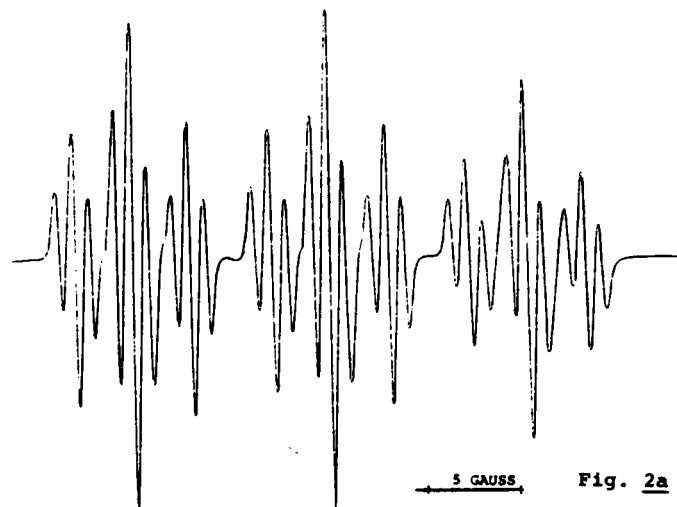
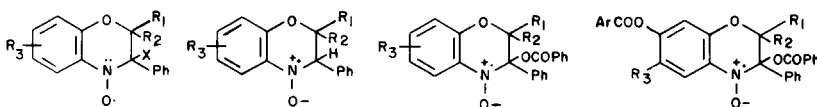


Figure 2. The esr spectra due to oxidation of compound **2e** by means of *m*-chloroperbenzoic acid: a) signal attributed to nitroxide **13e**, b) signal attributed to radical **15e**.

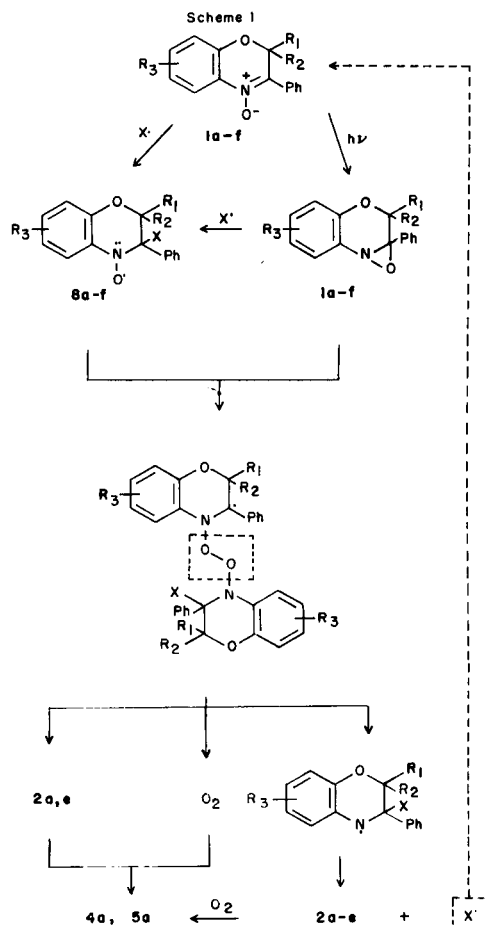
Table  
HFSC for Radicals **8**, **12**, **13** and **15**.

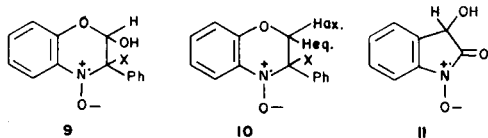


	<sup>a</sup> N	<sup>a</sup> H <i>o,p</i>	<sup>a</sup> H <i>m</i>	<sup>a</sup> H <i>c-2</i>	<sup>a</sup> N	<sup>a</sup> H <i>o,p</i>	<sup>a</sup> H <i>m</i>	<sup>a</sup> H <i>c-3</i>	<sup>a</sup> H <i>c-2</i>	<sup>a</sup> N	<sup>a</sup> H <i>o,p</i>	<sup>a</sup> H <i>m</i>	<sup>a</sup> H <i>c-2</i>	<sup>a</sup> N	<sup>a</sup> H <i>o</i>	<sup>a</sup> H <i>m</i>	<sup>a</sup> H <i>c-2</i>
a	10.50	3.20	0.85	0.85 0.40	11.10	3.70		7.40		10.50	3.20	0.85	0.85 0.40	10.75	3.00	0.84	0.84 0.38
b	10.50	3.25	0.80 (4H)	0.80 0.40	11.10	3.70		7.40		10.60	3.35	0.83 (4H)	0.83 0.37	10.60	3.30	0.83 (4H)	0.83 0.35
c	10.35				10.50	3.10	0.80	6.70	0.79	10.56	3.13						
d	10.75	3.25	0.76 (4H)	0.40	10.55	3.00	0.76 (4H)	6.64	0.76	10.56	3.06						
e	10.70	3.20	0.90		10.60	3.00	0.88	6.00		10.50	3.10	0.90		10.90	3.25	0.90	
f	10.70	3.05	0.88 (4H)		10.50	3.00	0.83 (4H)	6.00						10.85	3.20	0.90 (4H)	
g					11.10	3.19 (4H)		6.25		11.00	3.05 (4H)	0.85					

aziridine **1e** seems well enough supported. All three spectra show a strong band at  $1615\text{ cm}^{-1}$ , that persists unchanged during the full process. A band at  $1570\text{ cm}^{-1}$  is present only in **1e** and **2e** (C=N stretching) and another one at  $1070\text{ cm}^{-1}$  (N→O stretching) is present only in **1e**. Instead bands at  $1095$  and  $1280\text{ cm}^{-1}$  are present in **1e** but not in **1b** and **2e**. These new bands can be attributed to the C–N–O ring. An esr analysis of the reaction mixture of all the nitrones **1a-f** shows that intermediate radicals are involved in the photolytic process. As a matter of fact photolysis of an anhydrous solution of nitrones for 15–30 minutes lead to radicals (Fig. 1, Table 1) showing a  $a^N$  in the range of 11 gauss and  $a^H$  for different protons in the range of 3 and 1 gauss respectively. The relatively high value of the nitrogen coupling constant is in favour (24–27) of a  $sp^3$  hybridized C–3 carbon atom, while the hydrogen splitting constants must be attributed to the benzo-protons, as the comparative analysis of the various substituted nitrones shows and which is confirmed in the literature (24–29). Structure **8a-f** is reasonable for such radicals. They can be originated by reaction of some unstable radical (oxygen itself or a product of decomposition of the intermediate oxaziridine) formed during the photolysis of the nitrones. The following reaction scheme can account for all the observations made and the products obtained (Scheme 1).

Radicals **8a-f** need further discussion on the base of the experimental results. The esr spectra of radicals originated by nitrones **1a-b** ( $R_1 = R_2 = H$ ) show the ex-



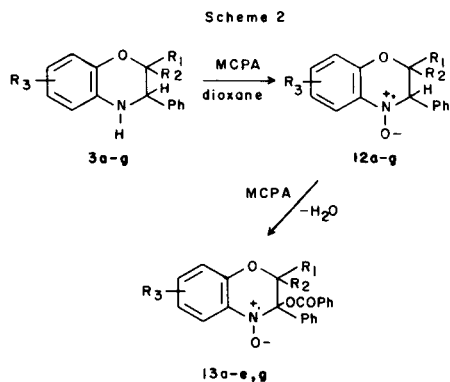


istence of two different hydrogens at the C-2 position characterized by  $a^H$  of about 0.8 and 0.4 gauss, respectively. Two different structures **9** and **10** could be assumed.

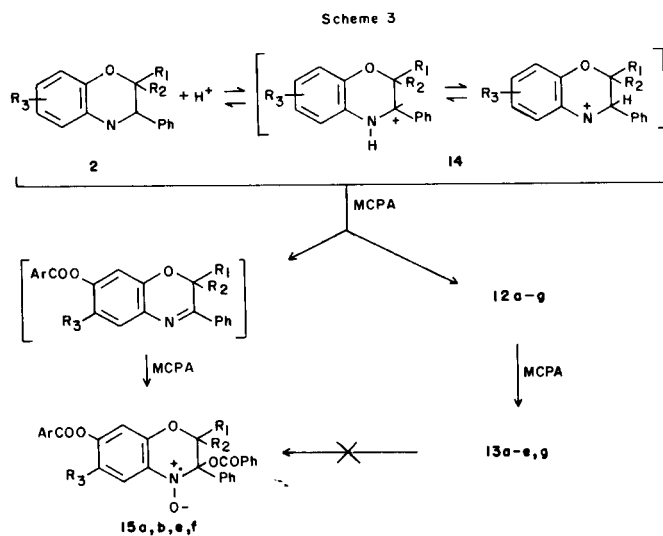
A value of 0.4 gauss for the OH hydrogen in position 2 seems to high. No hydrogen hfsc was found (**29**) in radical **11** for the hydroxyl hydrogen; an  $a^H = 0.75$  gauss was instead observed for the benzylic hydrogen. The existence of two different methylene hydrogens at the C-2 carbon (structure **10**) can be substantiated on the base of steric and resonance considerations.

In the starting nitrones as in the corresponding benzoxazines, the methylene is out of plane and the two hydrogens, that are respectively axial and equatorial, can easily interconvert without affecting the conjugation of the  $\pi$  electrons of the  $>C=N$  or of  $>C=N-O$  group with the benzo ring. The nmr spectra of both nitrones and benzoxazines show a singlet at about 5 ppm attributed to the methylene group, that in the case of nitroxides shift at 3.8 ppm, the region of the methylene hydrogens in the corresponding hydroxylamines (**1**) and 3-phenyl-2H-3,4-dihydro-1,4-benzoxazines (**2**).

In order to confirm the structure of radicals **8**, 3-phenyl-3,4-dihydro-2H-1,4-benzoxazines were oxidized by means of *m*-chloroperbenzoic acid. Radicals **12a-g** (**1**) (Table 1) were obtained immediately. The signals, showing an  $a^H$  in the range of 6–7.4 gauss due to a hydrogen at the C-3 carbon, are identical to that observed in the oxidation of 3-phenyl-4-hydroxy-2H-3,4-dihydro-1,4-benzoxazine (**1**). Aryloxylation at C-3 progressively changes radicals **12** into **13a-e,g** (Table 1) that show signals identical to that of radicals **8**. In that way the structure of radicals **8** was confirmed. However a question still remains if these radicals arise by oxidation of 3-phenyl-2H-1,4-benzoxazines formed during the photolysis of nitrones, rather than being intermediates in that process, as indicated in the reaction scheme.



Oxidation of benzoxazines **2** by means of *m*-chloroperbenzoic acid in dioxane solution leads to an interesting series of different signals that change during time. The first signal observed in all cases in the one corresponding to radicals **12**. It progressively evolves to that of radicals **13**, in the same way as the oxidation of dihydrobenzoxazines with *m*-chloroperbenzoic acid. Only a small fraction of the 2H-benzoxazines however follows this route, as the very weak esr signals that were observed demonstrate. At longer times new and stronger signals appear, that must be attributed to radicals **15** (Fig. 2, Table 1) bearing one more aryloxy group at C-7 of the benzo ring. Formation of radicals **15** and **12-13** must follow different routes: MCPA initially protonates the benzoxazines **2** leading to an equilibrium between the benzoxazine itself and its protonated form **14**. Oxidation by MCPA on **14** is responsible for the formation of radicals **12-13**. At the same time the reacting system undergoes aryloxylation at C-7. No substitution at C-5 was observed nor occurred when position 7 is substituted by a methyl group (*i.e.*, **2g**) (Scheme 3).



The system reacts further with *m*-chloroperbenzoic acid to give stable radicals **15a,b;e,f**. The lack of reactivity of C-5 toward *m*-chloroperbenzoic acid is apparently in contrast with the results of aryloxylation of the indolinone nitroxide radicals and of their amine precursors (**30**) where the benzo carbon atom in the *ortho* position with respect to the nitroxide group was mainly of interest. The difference observed must be attributed to the different reacting substrate. In the case of indolinones the aryloxylation is directed on the nitroxide radicals, while in the present case it is directed on the benzoxazines. The different reactivity of the two type of radicals is confirmed by the fact that nitroxide **12a-g** and **13a-g** are not transformed into the corresponding 7-aryloxylylated radicals, as it is

demonstrated by the fact that reaction of *m*-chloroperbenzoic acid on 3-phenyl-3,4-dihydro-2H-1,4-benzoxazines **3a-f** does not lead to radicals of type **15**.

## EXPERIMENTAL

The ir spectra of the pure compounds were recorded as nujol mulls on a Perkin-Elmer 257 apparatus while the photodecomposition of nitrones **1a-f** was followed on a FT, IR-IBM, IR 98 spectrophotometer, by irradiating a deuteriochloroform solution of the sample with a 4 watt uv lamp, in the sample compartment. The nmr spectra were recorded on a Perkin-Elmer R-12B,60 MHz apparatus using TMS as the internal standard. The esr spectra were performed with a JEOL-1X esr spectrometer. Mass spectra were obtained from a Varian Mat III apparatus.

### Chemicals.

3-Phenyl-2H-1,4-benzoxazines-4-oxides (**1a-f**), 3-phenyl-2H-1,4-benzoxazines (**2a-f**) and 3-phenyl-2H-1,4-dihydrobenzoxazines (**3a-f**) are known compounds (1,2).

### 2,2,7-Trimethyl-3-phenyl-2H-1,4-benzoxazines (**2g**).

The compounds were obtained following the general method previously reported (2). It was obtained as a crude oil that was subjected to column chromatography on silica gel using 1:4 benzene/cyclohexane as eluent, yield 70%; nmr (carbon tetrachloride):  $\delta$  1.55 (s, 6H, R1 = R2 = Me), 2.30 (s, 3H, 7Me); ir (nujol): 1620  $\text{cm}^{-1}$  (m), 1570  $\text{cm}^{-1}$  (w); ms: m/e = 251 (M<sup>+</sup>).

Anal. Calcd. for C<sub>17</sub>H<sub>17</sub>NO: C, 81.27; H, 6.77. Found: C, 81.35; H, 6.70.

### 2,2,7-Trimethyl-3-phenyl-2H-3,4-dihydro-1,4-benzoxazine (**3g**).

This compound was obtained as a crude oil following the general route previously described (2). It was purified by column chromatography on silica gel using 1:4 benzene/cyclohexane as eluent, yield 88%; nmr (carbon tetrachloride):  $\delta$  1.15 (s, 3H),  $\delta$  1.27 (s, 3H),  $\delta$  2.24 (s, 3H), 7.35 (s, 5H), 4.10 (br, s, 1H); ir (nujol): 3350  $\text{cm}^{-1}$  (s); ms: m/e = 253.

Anal. Calcd. for C<sub>17</sub>H<sub>19</sub>NO: C, 80.63; H, 7.51. Found: C, 80.70; H, 7.60.

Compounds **4**, **5**, **6** and **7** have been obtained as authentic samples from G. Prota which is kindly acknowledged.

### Photolysis of Compounds **1a**, **1c**.

Solution of compounds **1a** and **1c** (10<sup>-2</sup> M) in dioxane were submitted to uv irradiation (4 watt lamp) from a few minutes to one hour. The solutions were then examined via hplc using a Perkin Elmer Sil A column at the following operative conditions: flow 1.0  $\text{cm}^3/\text{minute}$ ; solvent, heptane/chloroform 90:10; temperature, 23° C; uv detector 257 nm.

The esr signals have been obtained directly in the spectrometer cavity either by oxidation with *m*-chloroperbenzoic acid or by photolysis with a 4 watt uv lamp.

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## REFERENCES AND NOTES

- (1) P. Battistoni, P. Bruni and G. Fava, *Tetrahedron*, **35**, 1771 (1979).
- (2) P. Battistoni, P. Bruni and G. Fava, *Synthesis*, 220 (1979).
- (3) G. G. Spence, E. C. Taylor and O. Buchart, *Chem. Rev.* **70**, 236 (1970).
- (4) F. Kröhnke, *Ann. Chem.*, **604**, 203 (1957).
- (5) A. Padwa, *J. Am. Chem. Soc.*, **87**, 4365 (1965).
- (6) A. L. Bluhm and J. Veinstein, *ibid.*, **92**, 1444 (1970).
- (7) L. H. Sternbach, B. A. Keochlin and E. Reeder, *J. Org. Chem.*, **27**, 4671 (1962).
- (8) L. S. Kaminsky and M. Lamchen, *J. Chem. Soc., C*, 2295 (1966).
- (9) R. Bonnett, V. M. Clark, and A. Todd, *J. Chem. Soc.*, 2102 (1959).
- (10) L. S. Kaminsky and M. Lamchen, *Chem. Commun.*, 130 (1965).
- (11) L. S. Kaminsky and M. Lamchen, *J. Chem. Soc., C*, 2128 (1967).
- (12) J. B. Bapat and D. St. C. Black, *Chem. Commun.*, 73, (1967).
- (13) M. Colonna and M. Poloni, *Ann. Chim.*, **63**, 287 (1973).
- (14) A. R. Katrizky and J. M. Lagowsky, "Heterocyclic Chemistry", Academic press, New York, p 195, 1971.
- (15) A. Padua, *Chem. Rev.*, **77**, 37 (1977).
- (16) B. Bigot, D. Roux, A. Sevin and A. Devaquet, *J. Am. Chem. Soc.*, **101**, 2560 (1979).
- (17) M. Iwamura and N. Inamoto, *Bull. Chem. Soc. Japan*, **40**, 702, (1967); *ibid.*, **43**, 860 (1970).
- (18) L. K. Dyal and K. M. Pausaker, *J. Chem. Soc.*, 18 (1961).
- (19) E. G. Janzen and B. J. Blackburn, *J. Am. Chem. Soc.*, **90**, 5909 (1968); *ibid.*, **91**, 3108, 4481 (1969).
- (20) M. Colonna, L. Greci and L. Marchetti, *Gazz. Chim. Ital.*, **109**, 29 (1979).
- (21) K. Shinzawa and I. Tanaka, *J. Phys. Chem.*, **68**, 1205 (1964).
- (22) F. Chioccare, E. Poniglinone, G. Prota and R. H. Thomson, *Tetrahedron*, **32**, 2033 (1976).
- (23) H. Shindo and B. Umezawa, *chem. Pharm. Bull.*, **10**, 492 (1962).
- (24) P. Bruni and M. Colonna, *Tetrahedron*, **29**, 2425 (1973).
- (25) C. Berti, M. Colonna, L. Greci and L. Marchetti, *ibid.*, **31**, 1745 (1975).
- (26) C. Berti, M. Colonna and L. Greci, *ibid.*, **32**, 2147 (1976).
- (27) L. Marchetti, L. Greci and M. Poloni, *Gazz. Chim. Ital.*, **107**, 7 (1977).
- (28) L. Lunazzi, G. F. Pedulli, G. Maccagnani and A. Mangini, *J. Chim. Soc., B*, 1072 (1967).
- (29) G. A. Russell, C. L. Myers, P. Bruni, F. A. Neugebauer and R. Blankespoor, *J. Am. Chem. Soc.*, **92**, 2762 (1970).
- (30) C. Berti, M. Colonna, L. Greci and L. Marchetti, *Tetrahedron*, **33**, 2321 (1977).