Reactivity of Primary and Secondary Amines with 2-Nitrophenazine 10-Oxide

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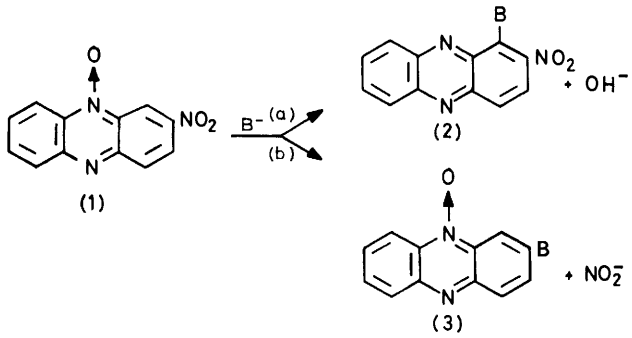
The nucleophilic substitution of primary and seondary amines on 2-nitrophenazine 10-oxide (1) was examined for homogeneous media. The formation, under the reaction conditions, of a σ anionic Meisenheimer complex was demonstrated by absorbance, conductance, and n.m.r. measurements. The photochemical reaction in the presence of primary and secondary amines caused mainly two reactions, the reduction of (1) to 2-nitrophenazine and the substitution of the nitro-group by the amino-group.

PREVIOUS research [1] established that 2-nitrophenazine 10-oxide (1) reacts with nucleophiles by one or both the pathways of Scheme 1. The compounds expected from



SCHEME 1

path (a) were isolated from all the nucleophilic reactions examined; many carbanions, conjugated bases of azoles, aliphatic primary amines, and cyanide ion reacted in this way. However, the methoxide ion reacted by path (b) and not (a). These reactions were carried out at room temperature in alcoholic suspensions or in pyridine–water.

The action between aliphatic amines and 2-nitrophenazine 10-oxide has now been examined for homogeneous media. The results obtained are here reported together with preliminary data from the photochemical reactions of the same substrates.

Good yields of 1-alkylamino-2-nitrophenazines (2; B = NHR) were obtained in dimethylformamide † solution using 3M-amine. Table 1 records the compounds and yields obtained with a series of amines and the time needed for the transformation of at least 95% of the substrate as shown by t.l.c. This measure gives a rough idea of the reaction rate with the various amines. From Table 1 it appears that the time of disappearance of (1) depends on the steric bulk of the alkyl group R. The 2-alkylaminophenazine 10-oxides (3; B = NHR), which are absent, or found only in traces when using primary amines, are formed in fair yields when secondary amines are used.

TABLE 1

Reaction between 2-nitrophenazine 10-oxide (2.8×10^{-2}M) and amines (3M) in dimethylformamide at 25°

		Yield (%) [a]			
Amine		1-Alkylamino-2-nitrophenazine (2)	2-Alkylaminophenazine 10-oxide (3)	Reaction time [b] (min)	Relative absorbance at 555 nm [c] (%)
(a)	$MeNH_2$	76	tr [d]	30	100
(b)	$EtNH_2$	72	tr [d]	75	79
(c)	Pr^nNH_2	63.5	tr [d]	100	75
(d)	Bu^nNH_2	65	tr [d]	60	55
(e)	Pr^iNH_2	47.5	tr [d]	420	20
(f)	$C_6H_{11}NH_2$	52	tr [d]	360	16
(g)	Bu^tNH_2	54		12 900	<1
(h)	Me_2NH [e]	15	21	700	35
(i)	$[CH_2]_5NH$ [e]	15	13	840	45

[a] Some phenolic by-products are also present in the reaction mixture, mostly 1-hydroxy-2-nitrophenazine. Stability tests on products (2) show that these by-products are not formed from (2) during the reaction. [b] For *ca.* 95% conversion. [c] 2-Nitrophenazine 10-oxide (1×10^{-4}M) and amine (3M): the data were tested 1 min after the mixing of the reactants. [d] Traces shown by t.l.c. (≤1%). [e] With these amines other products were also obtained: in particular, in the reaction with Me_2NH a 10% yield of 1-dimethylamino-3-nitrophenazine was obtained.

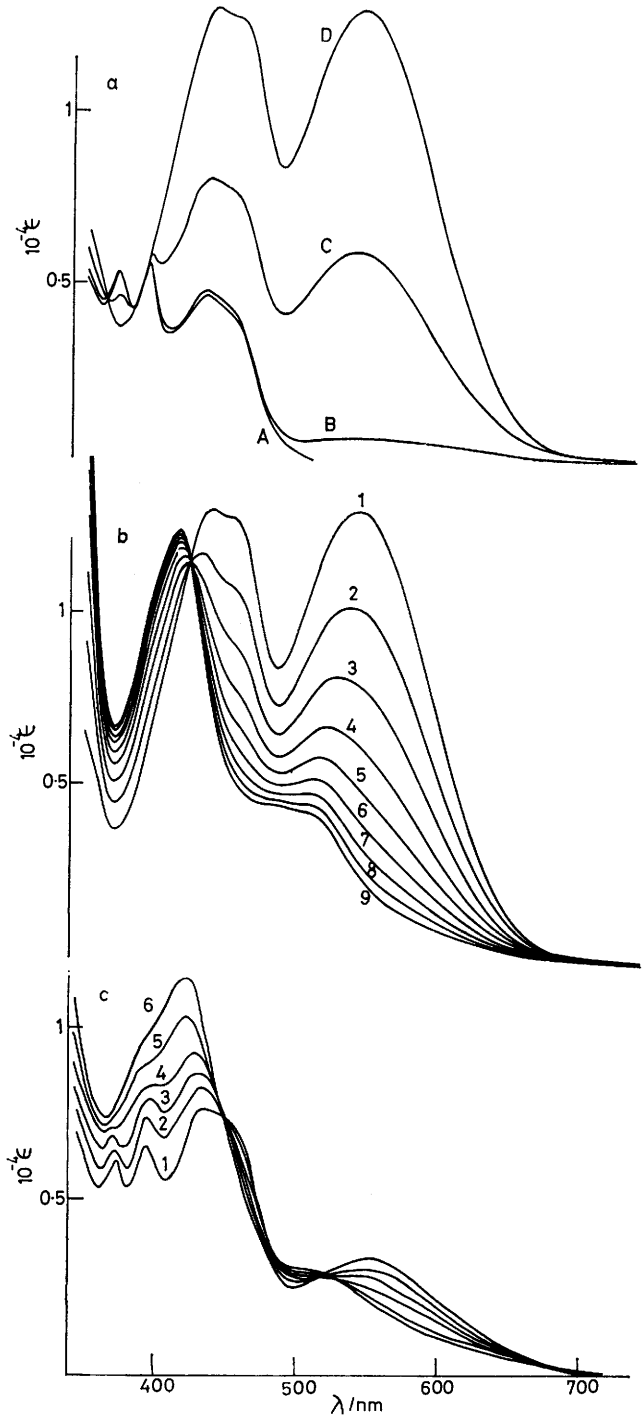
Some knowledge of the reaction mechanism between (1) and amines was obtained from the nature of the adduct which forms in less than a minute after the addition of the amine and which causes an intense red colour.‡ The greatest intensity of this colour was reached with methylamine at a concentration ≥3M. The visible spectrum, recorded a minute after the

† This solvent was chosen because of the very low solubility of (1) in other solvents.

‡ The red colour was preceded in the first few seconds after mixing by a short-lived green colour, the nature of which was not investigated.

[1] S. Pietra and M. Argentini, *Gazzetta*, 1971, **101**, 290 and references therein.

mixing of the reactants, showed a new absorption band with maximum at 555 nm (ε 1.35 × 10^4 l mol^{-1} cm^{-1})



Absorption spectra of 10^{-4}M solutions of 2-nitrophenazine 10-oxide (1) in DMF in the presence of amines: a, $MeNH_2$ A 0; B 0.1M; C 1M; D 3M; b, $MeNH_2$ 3M, 1, after 1 min; 2—9, spectra taken every 10 min; c, Pr^iNH_2 3M, 1, after 1 min; 2—6, spectra taken every 15 min

and a strong increase of the intensity of the band at 445 nm (ε 1.35 × 10^4 l mol^{-1} cm^{-1}) (Figure a, curve D). Moreover the visible bands of (1) at 372 and 392 nm disappeared and so it could be assumed that all (1) was present as a complex. With methylamine at lower concentrations, the visible absorption spectrum was between that of (1) and of the pure complex (Figure a). With the other amines at a concentration $\geqslant$3M the absorptions due to the respective complexes (maxima at 445 ± 2 and 555 ± 1 nm) were lower and the visible bands of (1) were still recognizable.

The relative intensities of the new band at 555 nm (measured 1 min after mixing) obtained with a 3M concentration of the various amines, with the absorption obtained with methylamine made equal to 100, are reported in Table 1. This value measures the approximate percentage of complex present at the beginning of the reaction. The variation in the spectrum as a function of time also proceeds in different ways depending on the concentration and type of amine. With primary amines which are not sterically hindered and sufficiently concentrated ($\geqslant$3M) the bands due to the complex change according to a first-order rate law into those of the final reaction mixture: for instance (1) (2 × 10^{-4}M) with methylamine (3M) gave k_{obs} 4.4 × 10^{-2} min^{-1} (Figure b). Using the same amines at a lower concentration, or sterically more hindered amines at both high and low concentrations, the spectrum changes into that of the final products in a more complex way, as shown in Figure c.

Tertiary amines (Me_3N) at a concentration of 3M do not form a complex as shown by the lack of the characteristic absorptions at 445 and 555 nm.

Significant information about the nature of the complex was obtained from conductance and n.m.r. measurements. The conductance measurements (Table 2) showed that the observed complex has ionic character.

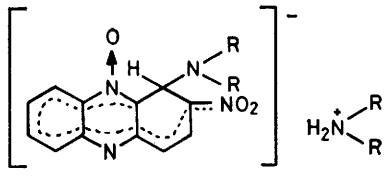
TABLE 2

Conductance (Ω^{-1} cm^{-1}) of solutions of (1) (2.8 × 10^{-2}M) with amines (4, 2, and 1M) in dimethylformamide at 25 °C

Amine	4M	2M	1M
$MeNH_2$	1.1 × 10^{-3}	4.3 × 10^{-4}	1.7 × 10^{-4}
Me_2NH	1.6 × 10^{-4}	9 × 10^{-5}	5 × 10^{-5}
Me_3N	1.5 × 10^{-5}		

Conductance of (1) (2.8 × 10^{-2}M) in dimethylformamide at 25 °C = 1.2 × 10^{-5} Ω^{-1} cm^{-1}.

The negligible variation in conductance caused by tertiary amines shows that the coloured adduct formed with primary and secondary amines are indeed complexes and not salts formed by abstraction of a proton from (1). Thus they can be regarded as σ-complexes between (1) and a molecule of amine which form an ionic species with a second molecule of amine [see formula (4)].



(4)

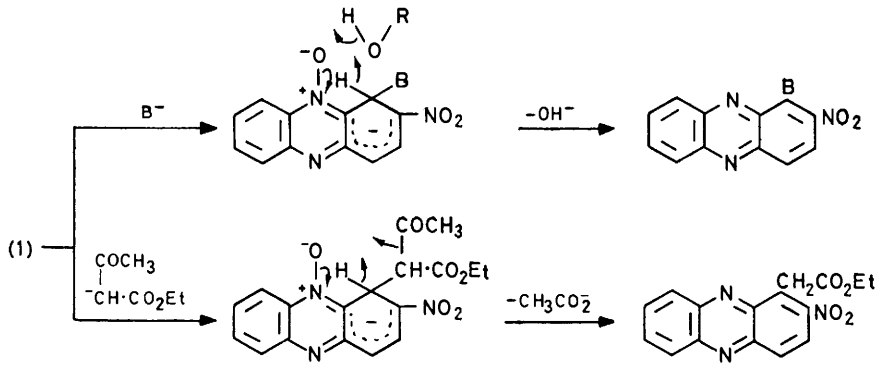
The n.m.r. data suggest that the attack of the amino-group in the complex occurs at C-1. The n.m.r. spectrum of (1) in dimethylformamide exhibits the 1-H resonance at δ 9.5 and that of the other aromatic ring protons in the range δ 8.7—8.0. When methylamine was added to the solution of (1), the proton resonance at δ 9.5 was shifted and appeared together with the aromatic protons in a crowded multiplet between δ 8.5 and 7.6. The considerable shift to high field of the resonance of 1-H is consistent with the change in the hybridization of C-1.[2] With trimethylamine (4M) there is only broadening of the signal of the hydrogen at C-1.

In summation, visible spectra, conductance, and n.m.r. measurements agree with the known characteristics of the anionic Meisenheimer complexes.[3,4]

Structure (4) also corresponds to the generally accepted σ-complex intermediate in nucleophilic aromatic substitution with amines.[5] Therefore the reaction of 2-nitrophenazine 10-oxide with amines can be considered an S_N2Ar process with the peculiarity that, in some cases, there is an accumulation of the σ-intermediate. In fact the data of Table 1 which refer to primary amines agree with that expected for an S_N2Ar reaction, the order of reactivity being $MeNH_2 > RCH_2NH_2 \gg R^1R^2CHNH_2 \gg R^1R^2R^3CNH_2$. However, on extending the examination to the data of secondary amines it can be observed that the times of disappearance of (1) are comparable to those of $R^1R^2CHNH_2$ and not lower than those of $MeNH_2$ as in the common S_N2Ar process. Furthermore it can be seen from Table 1 that in the case of primary amines there is some correlation between the times of disappearance of (1) and the absorbance at 555 nm (measured at the beginning of the reaction); a short reaction time corresponds to a high value of A_{555}. This correlation does not hold for secondary amines as the long times of disappearance of (1) are not caused by a low starting concentration of the complex which is quite high, as shown by conductance and n.m.r. data and from A_{555} measurements. To explain this difference in the behaviour of primary and secondary amines one has to consider the second step of the reaction, *i.e.* the elimination of the leaving group, which is, in the reaction we are discussing, a hydride ion.

It is known that hydride ion is a poor leaving group and its departure may be a high energy step. For this reason, if a suitable mechanism for the removal of hydride ion is lacking then nucleophilic substitution of the hydrogen atom may not occur. This being the case, Meisenheimer-type compounds may be formed.

The elimination of hydride ion can occur by means of either oxidation or autoxidation. The action of a hydride acceptor is particularly efficient if the acceptor acts intramolecularly on the reaction intermediate. This can occur either when the nucleophilic system acts as acceptor (*e.g.* direct amination of nitro-compounds by NH_2OH [6]) or when the substrate acts as acceptor.



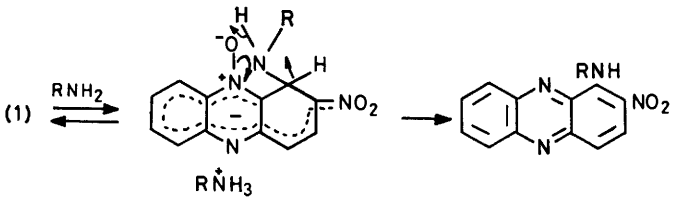
SCHEME 2

Previous research [1] has shown that the oxygen of the N ⟶ O group of nitrophenazine *N*-oxides is a highly efficient acceptor when the nucleophilic attack occurs in the *peri*-position with regard to the nitrogen of the N ⟶ O group. For instance 2-nitrophenazine 5,10-dioxide reacts quantitatively with diethyl malonate [7a] at C-1 with elimination of oxygen from position 10. 1-Nitrophenazine 5-oxide reacts with some nucleophiles [7b] at C-2 and with others at C-4. When the attack occurs at position 2, oxygen is retained but should the attack occur in position 4 oxygen is eliminated. However the hydrogen atom linked to the sp^3 carbon of the σ-complex in the *peri*-position is too far from the oxygen to allow the formation of a bond. From this we formulated the hypothesis that the σ-complex reacts with the assistance of a solvent molecule [7] or, in some cases, with the assistance of the nucleophilic part of the σ-complex.[8] The reactions in Scheme 2 are here reported as an example.

These reactions were based upon the assumption of σ-complex intermediates. The results now obtained

[2] M. J. Strauss, *Chem. Rev.*, 1970, **70**, 667.
[3] M. R. Crampton, *Adv. Phys. Org. Chem.*, ed V. Gold, Academic Press, London, 1969, vol. 7, p. 211.
[4] M. R. Crampton and V. Gold, *J. Chem. Soc.* (*B*), 1967, 23.
[5] (*a*) F. C. Bernasconi, *J. Amer. Chem. Soc.*, 1970, **92**, 129; (*b*) J. Miller, 'Aromatic Nucleophilic Substitution,' 1968, Elsevier, Amsterdam.
[6] R. Huisgen, *Annalen*, 1948, **559**, 101.
[7] S. Pietra and G. Casiraghi, *Gazzetta*, (*a*) 1967, **97**, 1826; (*b*) 1970, **100**, 138.
[8] S. Pietra, G. Casiraghi, and A. Selva, *Ann. Chim.* (*Italy*), 1968, **58**, 1387.

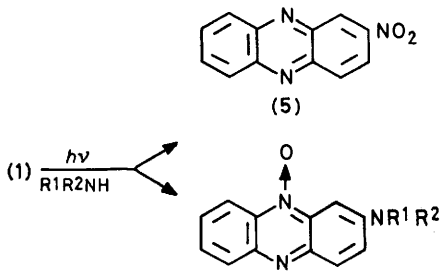
demonstrate the existence of a σ-complex and suggest that this is the intermediate of the reaction. These results support the aforesaid hypothesis of intramolecular removal of a hydride ion. The difference in behaviour between primary and secondary amines can be easily explained assuming, for primary amines, Scheme 3, in which the amine hydrogen atom is eliminated.



SCHEME 3

In the case of secondary amines, there is no hydrogen bonded to the amine nitrogen and elimination of a hydride ion is precluded. Therefore substitution in position 1 occurs to a lesser extent than with primary amines and different reactions on the substrate will occur because of the high reactivity of secondary amines, *e.g.* substitution of the nitro-group, and substitution in other positions of the ring (*e.g.* position 4, see note *e* of Table 1).

Photochemical Reactions.—The preliminary results obtained by irradiation (medium pressure mercury lamp; Pyrex filtered) of (1) in the presence of primary and secondary amines are here reported. The amines were used as 0.1M solutions in acetonitrile, methanol, and dimethylformamide with 2×10^{-3}M-(1). These experimental conditions were selected to minimize the interference of dark reactions. Irradiation at high conversion of (1) in the presence of primary amines gave many products especially when methanol and dimethylformamide were used. Most of these products have been found to be formed by further photoreaction of the amines on 2-nitrophenazine (5) which is a primary



SCHEME 4

photoproduct. For this reason, only experiments at low conversion in acetonitrile are here reported. Under these conditions there occur two main reactions, reduction to 2-nitrophenazine and the substitution of the nitro-group by the alkylamino-group (Scheme 4). Reaction (a) in Scheme 1, which leads to the formation of compounds (2), is not appreciably influenced by light.

Table 3 shows the percentage yields of compounds of

TABLE 3

Yields (%) of 2-alkylaminophenazine 10-oxides (3) from (1) with amines in CH_3CN at *ca.* 10% conversion [a]

Amine	Yield (%) of 2-alkylaminophenazine 10-oxide (3)	Reaction time (min)
$MeNH_2$	8	10
Pr^nNH_2	6	16
Pr^iNH_2	4	25
Bu^tNH_2		40
Me_2NH	4	10
$[CH_2]_5NH$	10	10

[a] The σ-complex concentration, estimated from the absorbance at 555 nm is very low (≤1%). Dark reactions under the same conditions gave only traces (t.l.c.) of (2) and (3) with the most reactive primary amines and traces of (3) with secondary amines.

type (3) formed from (1) (*ca.* 10% conversion). The amount of (3) formed depends on the nature of the amine used: this amount is at a maximum with piperidine * and falls to zero with the very hindered t-butylamine. In the case of piperidine (10^{-1}M) the quantum yields of reduction and substitution were determined in solution degassed by three or more freeze–degas–thaw cycles (Φ_{Red} 0.015; Φ_{Subst} 0.007).

Although the quantum yields are small, the photoreactions of (1) are worthy of further study because there is little information on the photoreduction of azine *N*-oxides.[9] Also photosubstitution of nitro-group in heterocyclic nitro-derivatives has received little attention [10] and 2-nitrophenazine 10-oxide offers good prospects in this respect.

EXPERIMENTAL

2-Nitrophenazine 10-oxide was prepared according to the literature method [11] and recrystallized to m.p. 204—205° (from AcOH). Pure grade amines were purified through their hydrochlorides and repeated fractionating on KOH. The purity was tested by g.l.c. on a C. Erba Fractovap 2350 instrument (Carbowax 103 column). Pure grade dimethylformamide (DMF) and freshly distilled spectroscopic grade MeCN and MeOH were used. Compounds are stated to be identical on the basis of m.p., mixed m.p., and i.r. or n.m.r. determinations.

General Procedure for Dark Reactions.—A solution of (1) and the appropriate amine (2.8×10^{-2} and 3M respectively) (15 ml) in DMF was left at 25° in a closed flask. The progress of the reaction was followed by t.l.c. (silica gel; cyclohexane–ethyl acetate 8 : 2 as eluant). The reaction was discontinued when no more starting material was detectable. The residue obtained by rapid evaporation under reduced pressure, at room temperature in an air

* In the Experimental section a high conversion preparative run with piperidine is described. In this experiment 2-piperidylphenazine 10-oxide was obtained in 45% yield.

[9] (*a*) G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.*, 1970, **70**, 321; (*b*) A. Albini, G. F. Bettinetti, and S. Pietra, *Tetrahedron Letters*, 1972, 3657.

[10] (*a*) J. Cornelisse and E. Havinga, *Chem. Rev.*, 1975, **75**, 353; (*b*) D. Dopp, *Topics Current Chem.*, 1975, **55**, 49.

[11] S. Maffei and G. F. Bettinetti, *Ann. Chim. Italy*, 1955, **45**, 1031.

stream, was treated with ethyl acetate (3 ml) and the undissolved portion (mainly phenolic by-products) was discarded. The filtrate was chromatographed on a silica gel column (Merck HR; in the ratio 1 : 500). Elution was performed with cyclohexane–ethyl acetate (8 : 2). The reaction times and yields of products (2) and (3) obtained are recorded in Table 1.

Synthesis of New 2-Alkylaminophenazine 10-Oxides (3).—Products (3a—f, h, and i) were synthesized from 2-chlorophenazine 10-oxide (1 g) in Me_2SO (15 ml) and a ten-fold excess of the appropriate amine. After the reaction, the mixture was poured into water and the solid collected. The solid was purified by passing the crude mixture through a short alumina column (benzene as eluant) and recrystallizing the product to constant m.p. from aqueous ethanol (80%). The experimental conditions, the yields, and data for characterization of the new products are recorded in Table 4.

TABLE 4

Experimental conditions and analytical data for new compounds

Compound	Reaction time (h)	Reaction temp. (°C)	Yield (%)	M.p. (°C)	Found (%) C	H	N	Formula	Required (%) C	H	N
(2h)				119—120	62.5	4.5	21.0	$C_{14}H_{12}N_4O_2$	62.7	4.5	20.9
(3a)	8	60	90	210—211	69.7	5.1	18.3	$C_{13}H_{11}N_3O$	69.3	4.9	18.7
(3b)	20	70	65	191	70.1	5.5	18.0	$C_{14}H_{13}N_3O$	70.3	5.5	17.6
(3c)	20	70	75	184	71.0	6.0	16.2	$C_{15}H_{15}N_3O$	71.1	6.0	16.6
(3d)	20	70	70	184	72.0	6.5	15.6	$C_{16}H_{17}N_3O$	72.0	6.4	15.7
(3e)	48	80	50	164—165	71.0	6.0	16.1	$C_{15}H_{15}N_3O$	71.1	6.0	16.6
(3f)	48	80	30	90—92	72.8	6.0	14.3	$C_{18}H_{19}N_3O$	73.7	6.5	14.3
(3h)	15	60	80	119—120	70.4	5.5	17.9	$C_{14}H_{13}N_3O$	70.3	5.5	17.6
(3i)	30	80	50	163—164	73.4	6.3	15.3	$C_{16}H_{15}N_3O$	73.1	6.1	15.0
1-Dimethylamino-3-nitrophenazine				179—180	62.8	4.8	20.6	$C_{14}H_{12}N_4O_2$	62.7	4.5	20.9

Measurements.—(a) *Absorbance.* Equal volumes of a solution of (1) (2×10^{-4}M) and the required amine (6M), both in DMF, were mixed at an appropriate temperature to reach 25°. The absorbance at 555 nm was recorded (1 min after the mixing) with a Baush and Lomb Spectronic and Beckman DU-2 spectrophotometers.

(b) *Conductance.* Equal volumes of a solution of (1) (5.6×10^{-2}M) and the required amine of the appropriate molarity (Table 2), both in DMF, were mixed to give a temperature of 25°. The conductance was measured 30 s after mixing with a Metroohm E 382 conductimeter equipped with an immersion cell.

(c) *N.m.r. spectra.* A solution of (1) and the required amine (9×10^{-2} and 4M respectively) was prepared by adding the appropriate amount of liquid amine to the solution of (1) in $DCON(CD_3)_2$, to give a temperature of 35°. The spectra were recorded 30 s after mixing with a Perkin-Elmer R-12 instrument, using Me_4Si as internal standard.

General Procedure for the Low Conversion Photochemical Runs.—A solution of (1) and the required amine (2×10^{-3} and 0.1M respectively) (80 ml) in MeCN, prepared by adding the appropriate amount of amine to the nitrogen-flushed solution of (1), was irradiated with a water-cooled medium pressure mercury lamp (Philips HPK equipped with a Pyrex filter) until 5—10% conversion. The solution was rapidly evaporated at reduced pressure, in an air stream, at room temperature, and the residue was chromatographed as above (dark reactions). The yields of products (3) obtained and the reaction times are reported in Table 3.

Quantum Yield Measurements.—The quantum yields were determined at 366 nm with a super high pressure mercury lamp (Osram 200 W/2 lamp; Spindler and Hoyer filter). Potassium ferrioxalate was used as actinometer.[12] The solutions of (1) (2×10^{-3}M) and piperidine (10^{-1}M) in MeCN in Pyrex test tubes were degassed by three or more freeze–degas–thaw cycles at *ca.* 10^{-3} Torr and irradiated as above. The reaction was quenched at *ca.* 10% conversion of (1).

2-Piperidylphenazine 10-Oxide: Preparative Run.—A solution of (1) (200 mg) and piperidine (4.5 ml) in MeOH (300 ml), prepared as above, was irradiated under the same conditions for 40 min. After the same work-up as above, the chromatographic separation gave 2-nitrophenazine (5 mg, 2.7%) and (3i) (104 mg, 45%).

Identification of the Products.—Products (2a—g and i) [13] and 1-hydroxy-2-nitrophenazine [14] were identified by comparison with authentic samples. The structure of (2h) was confirmed as 1-dimethylamino-2-nitrophenazine by its n.m.r. spectrum, which is characteristic of the series of compounds (2), δ 7.65 (d, *J* 11.5 Hz, 4-H). Products (3a—f, h, and i) were identified by comparison with the compounds prepared from 2-chlorophenazine 10-oxide as described previously. 1-Dimethylamino-3-nitrophenazine was identified from analytical data (Table 4) and n.m.r. δ 7.65 (d, 2-H) and 8.55 (d, *J* 2.5 Hz, 4-H).

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[6/2125 *Received*, 18*th November*, 1976]

[12] L. C. Hatchard and C. A. Parker, *Proc. Roy. Soc.*, 1956, **A253**, 318.

[13] (*a*) S. Pietra and G. Casiraghi, *Gazzetta*, 1967, **97**, 1817; (*b*) S. Pietra, G. Casiraghi, and F. Rolla, *ibid.*, 1969, **99**, 665.

[14] S. Pietra and G. Casiraghi, *Gazzetta*, 1970, **100**, 119.