Photochemical Reactions of Primary Amines on Nitrophenazines

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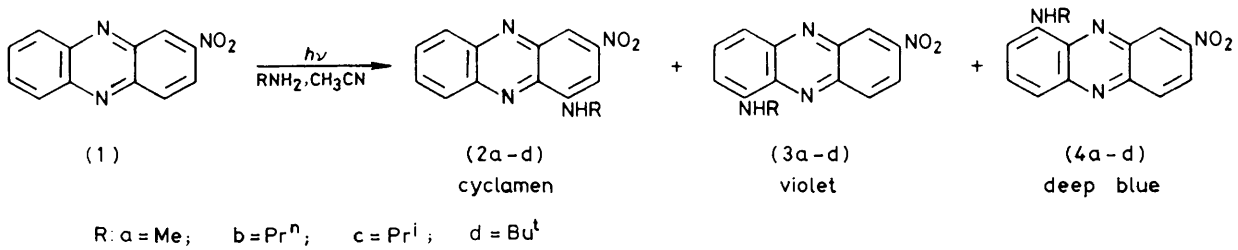
The photochemical nucleophilic substitution reactions of some primary amines on 2-nitrophenazine produce good yields of 6- and 9-alkylamino-2-nitrophenazines with minor amounts of 4-alkylamino-2-nitrophenazine. Irradiation of 1-nitrophenazine yields 6- and 9-alkylamino-1-nitrophenazines in addition to other products which are formed thermally. The regioselectivity of this reaction is discussed and compared with the orientation rules of Havinga and Cornelisse. An addition–elimination mechanism is proposed.

PHOTOCHEMICAL reactions of aromatic nitro-derivatives in the presence of nucleophiles have been studied extensively. Reduction, or in some cases substitution, of the nitro-group, substitution of other groups and even substitution of hydrogen atoms are observed. The pattern of the substitution often differs from that observed in ground-state reactions.[1] However, nucleophilic photosubstitution on aromatic nitro-compounds without other substituents which are good leaving groups is generally inefficient and usually requires a high concentration of the nucleophile.

required to yield *o*- and *p*-nitroanilines. 4-Nitropyridine 1-oxide[4] is an example of the photosubstitution of a nitro-group by amines. A similar photosubstitution on 2-nitrophenazine 10-oxide[5] was also described recently as a minor process with reduction of the N→O group predominating.

Here we wish to discuss the photoreactions of mononitrophenazines and aliphatic primary amines. These reactions are also interesting from a synthetic point of view.

In all cases tested, three types of substitution products



SCHEME 1

TABLE 1

Reaction between 2-nitrophenazine (1) (2.10^{-3}M) and amines in MeCN at 20 °C

Amine		Molarity	Reaction time [a] (min)	% Yield [b,c] 4-Alkylamino-2-nitrophenazine (2)-type compounds	6-Alkylamino-2-nitrophenazine (3)-type compounds	9-alkylamino-2-nitrophenazine (4)-type compounds
Me	(a)	0.5	15	3	31	17
Pr^n	(b)	0.5	30	4	24	14
Pr^i	(c)	0.5	50	4	27	12
Bu^t	(d)	0.5	80	4	44	13
Pr^n	(b)	0.05	170	4	54	20

[a] For ca. 70% conversion. [b] % Yield based on converted (1). [c] % Yield and reaction times were not significantly varied by purging the solutions by N_2 stream for 10 min.

Only a few examples of photoamination of mononitro-derivatives have been described. Irradiation of 1-nitronaphthalene[2] in ammonia–methanol gives 1-aminonaphthalene in poor yield (*ca.* 10%). This reaction was considered by the authors of reference 2 to be a real substitution rather than a reduction of the nitro-group. While nitroanisoles[1a] are easily photoaminated with both ammonia and amines, nitrobenzene[3] only reacts under drastic conditions: irradiation in liquid ammonia is

were obtained by irradiation of solutions of 2-nitrophenazine (1) in acetonitrile with a Pyrex-filtered medium-pressure mercury lamp in the presence of primary amines. All products were shown by elemental analysis to be isomeric monoalkylamino-nitrophenazines.† The products obtained are shown in Scheme 1 by the formulae (2a—d), (3a—d), and (4a—d). The corresponding tautomeric imino-forms can justifiably be excluded, as suggested by the literature data.[6]

† For clarity, the positions in which the substitutions occur are numbered maintaining the nitro-group in position 2.

[1] (*a*) J. Cornelisse and E. Havinga, *Chem. Rev.*, 1975, **75**, 353; (*b*) J. Cornelisse, *Pure Appl. Chem.*, 1975, **41**, 433; (*c*) E. Havinga and J. Cornelisse, *Pure Appl. Chem.*, 1976, **47**, 1.

[2] P. A. T. M. Brand and J. Cornelisse, unpublished results cited in ref. 1*a*.

[3] A. van Vliet, M. E. Kronenberg, J. Cornelisse, and E. Havinga, *Tetrahedron*, 1970, **26**, 1061 and references therein.

[4] R. M. Johnson and C. W. Rees, *J. Chem. Soc.* (B), 1967, 15.

[5] G. Minoli, A. Albini, G. F. Bettinetti, and S. Pietra, *J.C.S. Perkin II*, 1977, 1661.

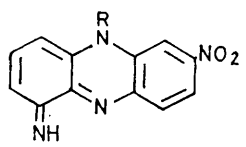
[6] J. Elguero, C. Marzin, A. R. Katrizky, and P. Linda, 'The Tautomerism of Heterocycles', Academic Press, New York, 1976, p. 170—179.

Table 1 reports the yields of photoproducts obtained with the amines considered and the time needed for the conversion of *ca.* 70% of (1). This gives a rough idea of the relative quantum yields of the reactions of (1) with the various amines.

Each set of compounds is characterized by absorption maxima at *ca.* 550, 560, and 590 nm. The bands in the region 1 600—1 500 cm^{-1} are also characteristic of each set of products. The spectral data of the photoproducts are reported in Tables 2 and 3. Compounds (2a—d) were identified as 4-alkylamino-2-nitrophenazines by examining their n.m.r. spectra in which the signals of H-1 and H-3 are recognizable (typical *meta* coupling constants). The internal charge-transfer bands in the spectrum of (3)-type and (4)-type compounds are shifted towards the red with respect to compounds of type (2). This means that the electron-withdrawing group and the electron-releasing group are further away from each other. The structure of 6-(or 9-)alkylamino-2-nitrophenazine might be proposed for these compounds on the basis of their n.m.r. spectra. However, the position of the alkylamino-group in the two sets of compounds could not be assigned since the n.m.r. spectra are almost identical. This ambiguity was solved by means of a chemical identification. The dealkylation of t-butylaminophenazine derivatives by concentrated sulphuric acid [7] was used. By this method 6-amino-2-nitrophenazine (5) was obtained from (3d), and (5) was hydrogenated to give 1,7-diaminophenazine (6). The latter was identical to a sample prepared from 1,7-dinitrophenazine according to the method of Otomasu [8] (Scheme 2). Therefore, the alkylamino-group is in position 6 in the (3)-type products and, consequently, in position 9 in products of type (4). N.m.r. and u.v. spectra of (5) are very similar to those of (3) and (4) (Tables 2 and 3). Thus, products (3) and (4) are actually alkylamino-nitrophenazines and not imino-derivatives with the alkylamino-group on a heterocyclic nitrogen atom [*e.g.* formula (7) in the case of compounds (3)]. Compounds such as (7) would be formed if a mechanism involving opening and closure of the heterocyclic ring [an S_N (ANRORC)-type mechanism] [9] were operative.

In practice, the thermal reaction of the amines on (1) (which yields 1-alkylamino-2-nitrophenazine) [10] does not take place at all under the irradiation conditions described here, as was checked by parallel experiments in the dark.

1-Nitrophenazine (8) is also photoaminated by irradiation in the presence of amines in low concentration, but the reaction is less efficient. Thus, (8) reacts photochemically with methylamine and n-propylamine to yield the monosubstituted products (9) and (10), in addition to appreciable amounts of other products



(7)

which are formed by thermal reactions. 4-Alkylamino-1-nitrophenazines (11) was the most abundant of these (Scheme 3, Table 4). The exclusive thermal formation of these products was proved by parallel experiments in

TABLE 2

Spectroscopic characteristics of compounds (2)—(5)

2-Nitrophenazine derivatives		$\lambda_{max.}$/nm (log ε) [a]	ν/cm^{-1} [b]
4-MeNH	(2a) [c]	548 (3.46)	1 592s, 1 560s
6-MeNH	(3a) [c]	560 (3.38)	1 555vs, 1 540m
9-MeNH	(4a) [c]	592 (3.36)	1 570s, 1 545s
6-NH_2	(5)	558 (3.33)	1 592s, 1 535s

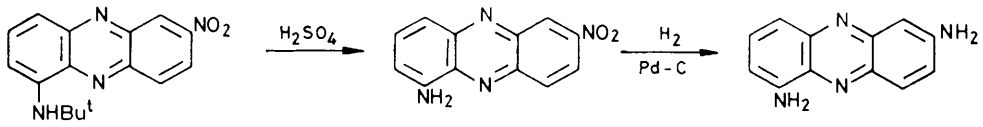
[a] In ethanol 95%. [b] In Nujol. [c] The other compounds of each set show almost identical characteristics.

TABLE 3

N.m.r. spectral data on compounds (2)—(5) [a,b]

2-Nitrophenazine derivatives	Chemical shift (δ) H-1	H-3	H-4	H-6	H-7	H-8	H-9
4-MeNH (2a) [c,d]	8.27(d)	7.28(d)	← 8.25—7.70(m) →				
6-MeNH (3a) [c,e]	9.10(d)	8.60(q)	8.28(d)		6.68(q)	7.75(q)	7.45(q)
9-MeNH (4a) [c]	9.02(d)	8.50(q)	8.20(d)	7.38(q)	7.75(q)	6.58(q)	
6-NH_2 (5)	9.05(d)	8.50(q)	8.35(d)		6.35(q)	7.70(q)	7.45(q)

[a] In $CDCl_3$. [b] Coupling constants in Hz; d = doublet, q = quartet, m = multiplet. [c] The other compounds of each set show almost identical characteristics. [d] $J_{1,3}$ = 2 Hz. [e] $J_{1,3} = J_{7,9}$ = 2 Hz; $J_{3,4} = J_{8,9}$ = 9 Hz; $J_{7,8}$ = 8 Hz; analogous values for compounds (4).

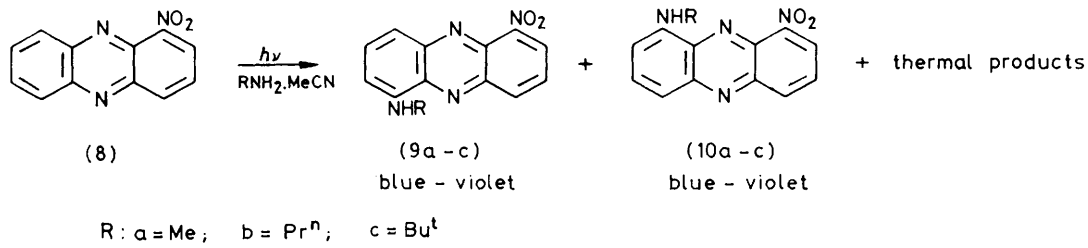


(3d) (5) (6)

SCHEME 2

[7] S. Pietra, G. Casiraghi, and F. Rolla, *Gazzetta*, 1969, **99**, 665.
[8] H. Otomasu, *Chem. Pharm. Bull.*, 1958, **6**, 77.
[9] A. P. Kroan, H. C. van der Plas, *Rec. Trav. chim.*, 1973, **92**, 1020 and references therein.
[10] S. Pietra and G. Casiraghi, *Gazzetta*, 1967, **97**, 1826.

the dark and by photochemical reactions at lower amine concentration. In fact, by irradiation (5 h) in the presence of 0.05M-methylamine, 16% of (8) is converted and products of type (9) and (10) are still formed (yield 20 and 15%, respectively) while (11) and the other thermal products are only formed to a minimal extent. With t-butylamine the photochemical reaction is very slow and products of type (9) and (10) are only formed in low yields (see Table 4). Compounds of type (9) and (10) are blue–violet coloured. The visible absorption maximum is at 578 nm for both, and also the 1 600—1 500 cm^{-1} region of the i.r. spectrum is practically identical for both types of compounds. However, the two types can be distinguished as the C–H bending bands in the 900—700 cm^{-1} region are different and are almost superimposable within each set (see Table 5).



SCHEME 3

TABLE 4

Reaction between 1-nitrophenazine (8) (2.10^{-3}M) and amines in MeCN at 20 °C [a]

Amine		Molarity	Reaction time (h)	% Yield [b]: 6-alkylamino-1-nitro phenazine (9)-type compounds	9-alkylamino-1-nitro phenazine (10)-type compounds	4-alkylamino-1-nitro phenazine (11)-type compounds
Me	(a)	0.5	2 [c]	12	8	27
Pr^n	(b)	0.5	7 [c]	27	15	20
Bu^t	(c)	0.5	7 [c]	2	2	2
Me	(a)	0.05	5 [d]	20	15	2

[a] Owing to the instability of (9)- and (10)-type products by irradiation in the presence of air, the runs were performed on solutions purged by nitrogen flushing. [b] % Yield on converted (8). [c] For *ca.* 70% conversion. [d] For *ca.* 15% conversion

TABLE 5

Spectroscopic characteristics of compounds (9)—(11)

1-Nitrophenazine derivatives		λ_{max}/nm (log ε) [a]	ν/cm^{-1} [b]
6-MeNH	(9a) [c]	578 (3.40)	1 560m, 1 525vs, 890s, 830s, 755s
9-MeNH	(10a) [c]	578 (3.40)	1 565m, 1 525vs, 800s, 745s
4-MeNH	(11a) [c]	511 (3.86)	1 563s, 1 540s.

[a] In ethanol 95%. [b] In Nujol. [c] The other compounds of each set show almost identical characteristics.

U.v. and n.m.r. spectra of these compounds show that photosubstitution has occurred on the α position of the benzene ring not bearing the nitro-group. As in the previous case the uncertainty between position 6 and position 9 remains (Tables 5 and 6). Since only small amounts of t-butylamino-derivatives were at our disposal, the identification was obtained by a different chemical approach. Thus, (9b) was transformed into 1,6-diacetoxyphenazine (14) *via* catalytic hydrogenation to the diamine-derivative (12) and subsequent hydrolysis of this compound to the dioxy-derivative (13) in phosphoric acid (see Scheme 4). The acetylated products (14) was shown to be identical with an authentic sample prepared from 1,6-dinitrophenazine according to the method of Otomasu.[8]

The results reported here show that the photochemical reactivity of nitrophenazine is the reverse of their thermal reactivity. Firstly, (1), which is thermally the less reactive of the two substrates, is photochemically the most reactive. Secondly, the photoamination takes place at positions 6 and 9 in both substrates—and also at position 4 in the case of (1), though to a far lesser extent—while thermally position 1 for (1) and mainly position 4 for (8) are attacked. The regioselectivity in these photochemical reactions can be understood in terms of the rule of the preferential ' α ' reactivity found by Havinga and Cornelisse [1] to hold for several aromatic compounds. However, the photochemical behaviour of nitrophenazines is different from that of homocyclic aromatic compounds, in that an H atom and not the nitro-group is substituted; moreover, the substitution occurs almost exclusively in the ring not bearing the nitro-group. Furthermore, in the case of (1) position 6 is more reactive towards photosubstitution than position 9. This phenomenon is reminiscent of the ' extended *meta* activation ' rule [11] which holds in the case of photosubstitution on some methoxy-nitronaphthalenes, in that the position not ' thermally activated ' is photochemically more reactive.

The photosubstitution of an H atom by an amine in such mild conditions is an unusual example in the field

[11] G. M. J. Bejersbergen van Henegouwen and E. Havinga, *Rec. Trav. chim.*, 1970, **89**, 907.

of nucleophilic photosubstitution. Such an easy reaction could presumably be due to the possibility of a mechanism *via* addition and subsequent rearomatisation offered by the heterocyclic ring (Scheme 5). A necessary step for this reaction is an oxidation which can be accomplished by dissolved oxygen and/or other molecules of nitrophenazine.

Finally, it is to be noted that no photoamination is observed if phenazine is irradiated under the conditions described here for nitrophenazines. Phenazine was reported to give 1-hydroxyphenazine or its ethers or esters by irradiation in water, alcohols, and carboxylic acids under strongly acidic conditions.[12,13] Thus, the presence of the electron-withdrawing groups appears to be the critical factor for photoamination on the phenazine ring.

TABLE 6

N.m.r. spectral data of compounds (9)—(11) [a,b]

1-Nitrophenazine derivatives		Chemical shift (δ) H-2	H-3	H-4	H-6	H-7	H-8	H-9
6-MeNH	(9a) [c,d]	8.45(d)	8.00(t)	8.45(d)		6.70(d)	7.88(t)	7.33(d)
9-MeNH	(10a) [c]	8.45(d)	8.00(t)	8.45(d)	7.33(d)	7.88(t)	6.70(d)	
4-MeNH	(11a) [c,e]	8.52(d)	6.30(d)		← 8.30—7.70(m) →			

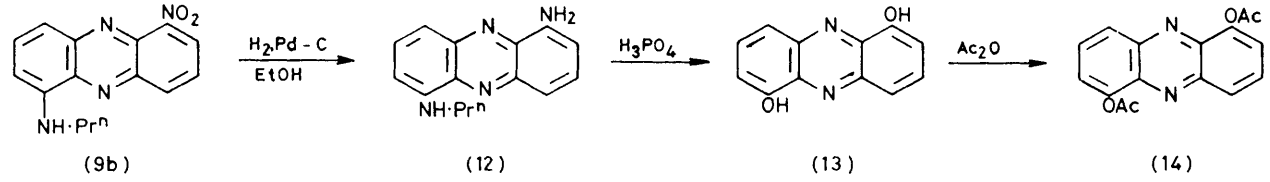
[a] In $CDCl_3$. [b] Coupling constants in Hz; d = doublet, t = triplet, q = quartet, m = multiplet. [c] The other compounds of each set show almost identical characteristics. [d] $J_{2,4} = 2$ Hz; $J_{2,3} = J_{3,4} = 9$ Hz; $J_{7,8} = J_{8,9} = 8$ Hz; analogous values for compounds (10). [e] $J_{2,3} = 2$ Hz.

EXPERIMENTAL

U.v. and visible spectra were recorded on a Perkin-Elmer 200 spectrophotometer, i.r. spectra on a Perkin-Elmer 257 spectrophotometer, and n.m.r. spectra on a Perkin-Elmer R-12 instrument, using $SiMe_4$ as internal standard. Mass determinations were obtained on a Du Pont 492 B mass spectrometer. M.p.s are uncorrected. Analytical data of the new compounds are reported in Table 7.

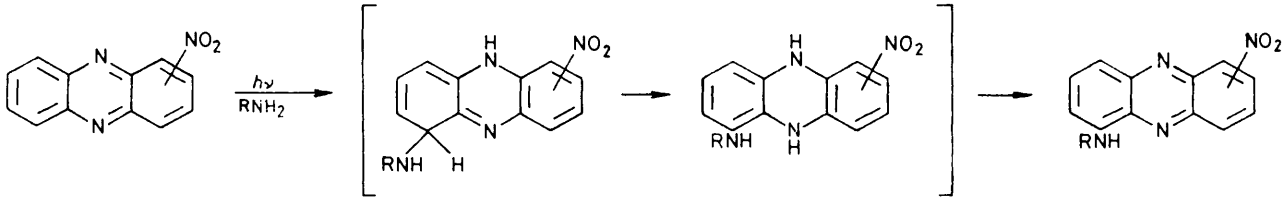
Materials.—Methylamine, n-propylamine, isopropylamine, and t-butylamine (C. Erba and Schuchardt pure grade reagents) were further purified by two recrystallisations of their hydrochlorides and repeated fractional distillation from KOH. Acetonitrile (C. Erba, pure grade solvent) was used after distillation. 1-Nitrophenazine was prepared according to a literature method,[14] purified by passage through an alumina column (toluene as eluant) and recrystallized, m.p. 193—194 °C (from nitroethane, lit.,[14] 195 °C). 2-Nitrophenazine was prepared by heating 2-nitrophenazine 10-oxide (5 g) under reflux with PCl_3 (30 ml) for 30 h and work-up of the reaction mixture in the usual manner. The crude product was purified as above and recrystallized from nitroethane to m.p. 225—226 °C (yield 4 g).

General Procedure.—To a solution of (1) or (8), degassed by nitrogen purging if required, the desired amine was added to reach the required molarity. The resulting solution was irradiated by a medium-pressure, water-cooled, mercury lamp (Hanau TQ 150) through a Pyrex filter. The irradiated sample was evaporated at reduced pressure at room temperature. Some toluene was added in order to avoid an increase of the amine concentration during the evaporation of the solvent. A first rough separation of the reaction products was performed on a silica-gel column using cyclohexane–ethyl acetate (8 : 2) as eluant, while the separation of compounds (2), (3), and (4) was achieved on a silica-gel column using benzene–nitroethane (95 : 5) as eluant.



(9b) (12) (13) (14)

SCHEME 4



SCHEME 5

6-Amino-2-nitrophenazine (5).—Compound (3d) (50 mg) was dissolved in conc. H_2SO_4 (1 ml), and the light green

[12] A. Albini, G. F. Bettinetti, M. De Bernardi, and S. Pietra, *Gazzetta*, 1970, **100**, 700.

[13] (*a*) S. Wake, H. Inoue, Y. Otsuji, and E. Imoto, *Tetrahedron Letters*, 1970, 2415; (*b*) S. Wake, Y. Otsuji, and E. Imoto, *Bull. Chem. Soc. Japan*, 1974, **47**, 1251.

[14] S. Pietra and G. Casiraghi, *Gazzetta*, 1970, **100**, 138.

solution was heated at 50 °C for 90 min before being poured onto ice (10 g). The deep violet–grey precipitate was washed with 10% aqueous $NaHCO_3$ and water, and then recrystallised from nitroethane to give compound (5) (42 mg) as lustrous violet needles, m.p. 264—266 °C.

1,7-*Diaminophenazine* (6).—Compound (5) (35 mg) was hydrogenated at room temperature in ethanol (30 ml) in the presence of Pd on charcoal. After 2 h the solution was colourless. Removal of the solvent and recrystallisation from methanol gave (6) (30 mg) as orange needles, m.p. 221 °C (lit.,[15] 223°). This product was identical, according to its i.r. spectrum, m.p. and mixed m.p., with an authentic sample prepared according to the procedure of Otomasu.[8]

1-*Amino*-6-*n*-*propylaminophenazine* (12).—Compound (10b) (30 mg) was hydrogenated at room temperature in ethanol (30 ml) in the presence of Pd on charcoal. After 45 min the solution was colourless. Removal of the solvent and recrystallisation from aqueous ethanol gave (12) (26 mg) as red needles, m.p. 158—160 °C.

1,6-*Diacetoxyphenazine* (14).—Compound (12) (25 mg) was heated under reflux in 35% aqueous H_3PO_4 (5 ml) for 24 h. The solution was neutralized with dilute ammonia, extracted with $CHCl_3$, and the solvent removed. The crude product was chromatographed on a silica-gel column, using cyclohexane–ethyl acetate (8 : 2) as eluant; the dihydroxy-derivative (13) (12 mg) was directly acetylated with Ac_2O and pyridine at room temperature. After 16 h the solution was poured into water and extracted with $CHCl_3$. Removal of the solvent and recrystallisation from ethanol gave (15) (8 mg) as light yellow crystals, m.p. 233—235 °C. This product was identical, according to its i.r. spectrum, m.p., and mixed m.p. with an authentical sample prepared according to the procedure of Otomasu.[8]

TABLE 7

Analytical data for new compounds [a]

			Found (%)				Required (%)		
2-Nitrophenazine derivatives		M.p. (°C)	C	H	N	Formula	C	H	N
4-MeNH	(2a)	172—173 [b]		M^+ 254.0806		$C_{13}H_{10}N_4O_2$		M^+ 254.0804	
6-MeNH	(3a)	227—228 [b]	61.3	4.3	22.1		61.4	4.0	22.0
9-MeNH	(4a)	218—220 [b]		M^+ 254.0807					
4-Pr^{n}NH	(2b)	117—119 [b]	64.1	5.1	19.5	$C_{15}H_{14}N_4O_2$	63.8	5.0	19.9
6-Pr^{n}NH	(3b)	162—163 [b]	63.8	5.2	19.6				
9-Pr^{n}NH	(4b)	159—160 [b]	63.6	4.9	19.4				
4-Pr^{i}NH	(2c)	168—169 [b]	63.5	5.2	20.2				
6-Pr^{i}NH	(3c)	193—194 [b]	63.4	5.2	19.8				
9-Pr^{i}NH	(4c)	190—191 [b]		M^+282.1117				M^+ 282.1117	
4-Bu^{t}NH	(2d)	167—168 [b]		M^+ 296.1273		$C_{16}H_{16}N_4O_2$		M^+ 296.1273	
6-Bu^{t}NH	(3d)	200—202 [b]	64.5	5.7	18.6		64.9	5.4	18.9
9-Bu^{t}NH	(4d)	208—210 [b]		M^+ 296.1276					
6-NH_2	(5)	264—266 [c]	59.7	3.9	22.8	$C_{12}H_8N_4O_2$	60.0	3.4	23.3
1-Nitrophenazine derivatives									
6-MeNH	(9a)	214—216 [b]	61.3	4.0	22.2	$C_{13}H_{10}N_4O_2$	61.4	4.0	22.0
9-MeNH	(10a)	196—198 [b]	61.7	3.8	22.1				
6-Pr^{n}NH	(9b)	137—138 [b]	63.3	5.0	20.3	$C_{15}H_{14}N_4O_2$	63.8	5.0	19.9
9-Pr^{n}NH	(10b)	131—132 [b]		M^+ 282.1120				M^+ 282.1117	
4-Pr^{n}NH	(11b)	188—190 [b]	63.4	5.0	19.5				
6-Bu^{t}NH	(9c)	106—107 [b]		M^+ 296.1279		$C_{16}H_{16}N_4O_2$		M^+ 296.1273	
9-Bu^{t}NH	(10c)	105—106 [b]		M^+ 296.1276					
2-Amino-6-*n*-propylamino-phenazine	(12)	158—160 [d]		M^+ 252.1372		$C_{15}H_{16}N_4$		M^+ 252.1375	

[a] Compounds (11a) and (11c) have been already described.[14] [b] From ethanol 95%. [c] From nitroethane. [d] From 80% aqueous ethanol.

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[7/1130 *Received*, 28*th June*, 1977]

[15] S. Maffei and H. Aymon, *Gazzetta*, 1954, **84**, 667.