Formyl Substituted Phenazine 5,10-Dioxides

M. L. Edwards, R. E. Bambury and H. K. Kim (1a)*

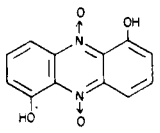
Merrell-National Laboratories (1b), Division of Richardson-Merrell Inc., Cincinnati, Ohio 45215

Received February 23, 1976

Two new formyl-substituted phenazine 5,10-dioxides were prepared, 2-formylphenazine 5,10-dioxide and 7-hydroxy-2-phenazinecarboxaldehyde 5,10-dioxide. Nitrones of these aldehydes were prepared as potential antibacterial agents but evaluation *in vitro* and *in vivo* did not disclose significant antibacterial activity.

J. Heterocyclic Chem., 13, 653 (1976).

Phenazine dioxides with antibacterial activity occur naturally [*e.g.*, Iodinin (1)], and several patents (2,3) have disclosed new antibacterial phenazine dioxides. As an



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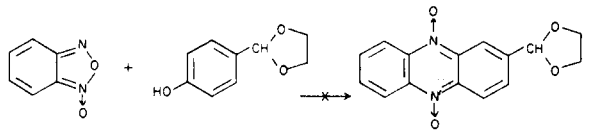
extension of our work with quinoxaline dioxides (4,5) we have prepared derivatives of formylphenazine dioxides.

We first attempted the synthesis of 2-formylphenazine 5,10-dioxide by the Beirut reaction (6,7) using benzofuroxan and the dioxolane of *p*-hydroxybenzaldehyde without success (Scheme I).

Scheme I



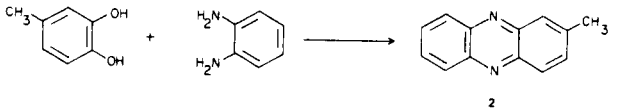
The other routes we proposed to 2-formylphenazine 5,10-dioxide would proceed through 2-methylphenazine (2). A literature survey found four methods available for the synthesis of 2-methylphenazine:

1. The condensation of 4-methyl-*o*-quinone with *o*-phenylenediamine (8).

2. The reductive cyclization of a methyl substituted *o*-nitrodiphenylamine with Pd (9), potassium hydroxide (10) or sodium borohydride/sodium ethoxide (11).

3. Synthesis of a methyl substituted tetrahydrophenazine followed by dehydrogenation to the phenazine (12a,b).

4. Condensation of a methyl substituted catechol with *o*-phenylenediamine (13).



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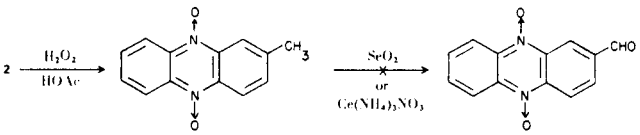
We prepared **2** by each of these methods and found the last method to be the most useful, although the yield of purified **2** was low (25%). Our first attempted route to 2-formylphenazine 5,10-dioxide from **2** was the two step sequence of Scheme II. Neither selenium dioxide nor

Scheme II



ceric ammonium nitrate oxidized the methyl group of **3** to give **4**. The longer sequence of Scheme III gave the desired aldehyde, and two nitrones of **4** were synthesized. These derivatives are tabulated in Table I.

Scheme III

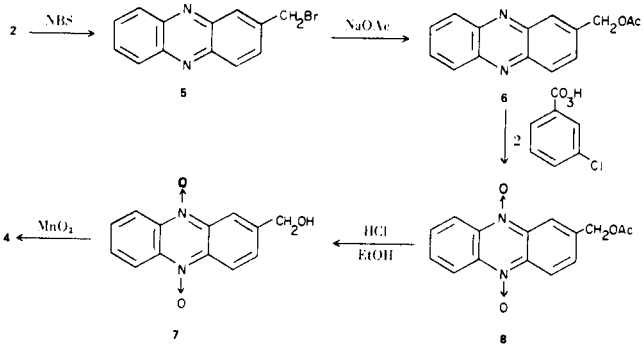
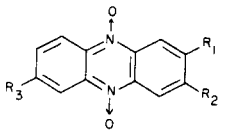


Table I

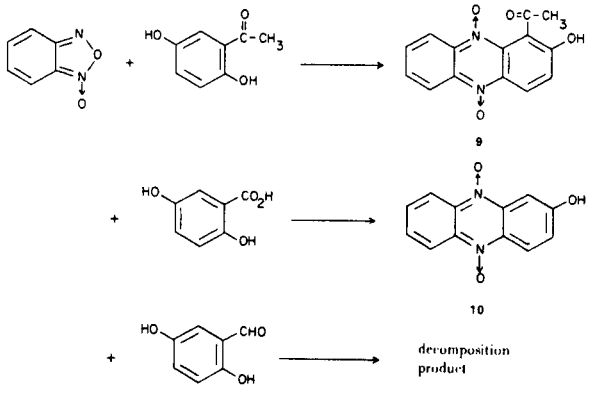
Phenazine 5,10-Dioxides



Compound No.	R_1	R_2	R_3	Yield, %	M.p., °C
3	CH_3	H	H	34	171-172
4	CHO	H	H	76	195-196
7	CH_2OAc	H	H	73	172-174
8	CH_2OH	H	H	73	180
10	OH	H	H	17	234 dec.
11	CHO	H	OH	93	221
12	$CH=N(\rightarrow O)CH_3$	H	H	60	203
13	$CH=N(\rightarrow O)CH_2CH_2OH$	H	H	30	192-193
14	$CH=N(\rightarrow O)CH_3$	H	OH	66	225
15	$CH=N(\rightarrow O)CH_2CH_2OH$	H	OH	22	203
16	$CH=NNHC(=O)NH_2$	H	OH	61	>300

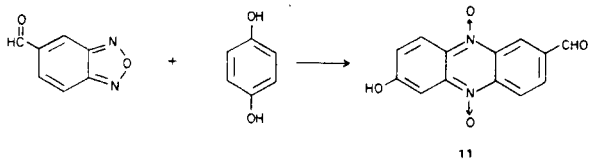
At this point we reexamined the Beirut reaction, as a one-step synthesis of a phenazine dioxide aldehyde seemed preferable to a multi-step sequence such as that outlined in Scheme III. While a substituted phenol did not react with benzofuroxan (Scheme I), substituted hydroquinones are known to give hydroxyphenazine dioxides (7). In this manner we prepared the acetylphenazine **9** and 2-hydroxyphenazine dioxide **10** (via decarboxylation during the reaction), while 2,5-dihydroxybenzaldehyde gave only decomposition products (Scheme IV).

Scheme IV



The reaction of 6-formylbenzofuroxan (14) with hydroquinone gave 7-hydroxyphenazine-2-carboxaldehyde 5,10-dioxide (**11**) in 93% yield (Scheme V). Derivatives of **11**

Scheme V



were prepared and are included in the tabulation in Table I.

In contrast to the highly active quinoxaline dioxide nitrones, the phenazine dioxides prepared did not demonstrate appreciable antibacterial activity when evaluated *in vivo* or *in vitro*.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. Ir spectra were determined in pressed potassium bromide disks. Nmr spectra were determined on a Varian spectrometer and shifts are reported in parts per million (δ) with TMS as an internal standard.

2-Methylphenazine (**2**).

A mixture of 4-methylcatechol (54 g., 0.5 mole) and *o*-phenylenediamine (50 g., 0.5 mole) was placed in two sealed tubes and the tubes were heated in a 200° oil bath for 48 hours. The dark residue was washed with hot water (600 ml.) and dried. This material, 5,10-dihydro-2-methylphenazine, was finely ground and exposed to air for a week to effect oxidization to 2-methylphenazine. The material was placed (dry) on a column of alumina and eluted with benzene to give 30 g. (29%) of yellow solid, m.p. 117° (lit. (12a) m.p. 117°).

2-Methylphenazine 5,10-Dioxide (**3**).

Compound **2** (1.5 g., 7.7 mmoles) was dissolved in acetic acid (50 ml.) and 30% hydrogen peroxide (3.5 ml. = 31 mmoles) and the mixture was heated at 65° for 48 hours, cooled and poured onto ice. The product was isolated by filtration and air dried. Recrystallization from ethyl acetate gave 0.6 g. of orange-red solid, m.p. 171-172° (lit. (16) m.p. 180°); ir: 1620, 1480, 1420, 1350, 1320, 1270, 1210, 1090, 815, 760 and 630 cm^{-1}; nmr (deuteriochloroform): δ 2.66 (S, 3H), δ 7.54-8.0 (m, 3H), δ 8.46-8.53 (m, 4H).

Phenazine-2-carboxaldehyde 5,10-Dioxide (**4**).

A mixture of **8** (22 g., 0.09 mole) and activated manganese dioxide (66 g.) in chloroform (1.3 l.) was heated at reflux for 5 hours. The mixture was filtered hot and the filter cake was washed with boiling chloroform (2 x 400 ml.). The combined filtrates were concentrated to 500 ml., chilled and filtered to give 16.4 g. of dark red solid, m.p. 195-196°, which was used without further purification. Material after recrystallization did not give a satisfactory analysis (trace of residue); ir: 1700, 1360, 1325, 1270, 1220, 1085 and 770 cm^{-1}; nmr (TFA-deuteriochloroform): δ 7.91-9.0 (m, 6H), δ 9.5-9.67 (S, b, 1H), δ 10.7 (S, 1H).

2-Bromomethylphenazine (**5**).

A mixture of **2** (30 g., 0.155 mole), *N*-bromosuccinimide (30.3 g., 0.17 mole), benzoyl peroxide (0.1 g.) and carbon tetrachloride (700 ml.) was heated at reflux with a sun lamp for 3 hours, cooled and filtered. The filter cake was washed with carbon tetrachloride until the filtrate was no longer yellow. The combined filtrates were evaporated and the residue was recrystallized from benzene to give 33 g. (75%) of yellow solid, m.p. 155-160°. A small sample was recrystallized again, m.p. 161-164°; ir: 1520, 1370, 1220 and 760 cm^{-1}; nmr (deuteriochloroform): δ 4.73 (S, 2H), δ 7.7-8.0 (m, 3H), δ 8.1-8.4 (m, 4H).

Anal. Calcd. for $C_{13}H_9BrN_2$: C, 57.17; H, 3.32; N, 10.26. Found: C, 56.93; H, 3.27; N, 10.26.

2-Acetoxymethylphenazine (**6**).

A mixture of **5** (13.9 g., 0.049 mole), sodium acetate (16.4 g., 0.2 mole) and acetic anhydride (250 ml.) was heated at reflux for 2 hours. The mixture was evaporated and the residue was washed with hot ethyl acetate until the filtrate was no longer yellow. The combined filtrates were evaporated and the yellow residue was recrystallized from ethyl acetate to give 9.5 g. (75%) of yellow solid, m.p. 125-127°; ir: 1760, 1380, 1260, 765 and 750 cm^{-1}; nmr (deuteriochloroform): δ 1.33 (S, 3H), δ 4.6 (S, 2H), δ 6.9-7.8 (m, 7H).

Anal. Calcd. for $C_{15}H_{12}N_2O_2$: C, 71.41; H, 4.80; N, 11.11. Found: C, 71.16; H, 4.96; N, 10.99.

2-Acetoxymethylphenazine 5,10-Dioxide (**7**).

A solution of **6** (23 g., 0.09 mole) and *m*-chloroperbenzoic acid (37 g., 0.18 mole) in chloroform (800 ml.) was heated at reflux for 24 hours. Another 18.5 g. (0.09 mole) of peracid was added and the solution was heated at reflux another 24 hours, cooled and filtered. The filtrate was extracted with dilute aqueous sodium bicarbonate, dried and evaporated. The red solid that remained was recrystallized from ethyl acetate to give 19 g. of red solid, m.p. 172-174°; ir: 1740, 1620, 1430, 1350, 1325, 1200, 1090, 815 and 765 cm^{-1}; nmr (TFA-deuteriochloroform): δ 1.9 (S, 3H), δ 5.19 (S, 2H), δ 7.6-7.9 (m, 3H), δ 8.2-8.5 (m, 4H).

Anal. Calcd. for $C_{15}H_{12}N_2O_4$: C, 63.37; H, 4.26; N, 9.86. Found: C, 63.10; H, 4.20; N, 9.47.

2-Hydroxymethylphenazine 5,10-Dioxide (**8**).

Two ml. of concentrated hydrochloric acid was added to a suspension of **7** (18 g., 0.063 mole) in ethanol (1.2 l.) and the mixture was stirred at reflux temperature for 7 hours, cooled and evaporated. The residue was dissolved in chloroform (1.2 l.) and the solution was extracted with dilute aqueous sodium bicarbonate, dried and evaporated to give 11 g. of red solid, m.p. 180°; ir: 3400, 1620, 1350, 1330, 1090, 820 and 765 cm^{-1}; nmr (DMSO-d_6): δ 4.82 (d, J = 4 Hz, 2H); δ 5.64 (t, J = 5 Hz, 1H, exchanges with deuterium oxide), δ 7.7-8.1 (m, 3H), δ 8.4-8.83 (m, 4H).

Anal. Calcd. for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.15; N, 11.57. Found: C, 64.42; H, 4.16; N, 11.53.

2-Hydroxyphenazine-1-yl Methyl Ketone 5,10-Dioxide (**9**).

A mixture of benzofuroxan (13.6 g., 0.1 mole) and 2,5-dihydroxyacetophenone (14.9 g., 0.09 mole) in ethanol (150 ml.) was added to a solution of sodium hydroxide (0.2 g.) in water (100 ml.). The mixture was stirred at room temperature for 18 hours, acidified and filtered. The precipitate was washed well with ethanol and dried to give 4.7 g. of orange-red solid, m.p. 180-181° (lit. (15) m.p. 173°); ir: 3120, 1720, 1620, 1600, 1560, 1420, 1340, 1280, 1190 and 1100 cm^{-1}; nmr (TFA-deuteriochloroform): δ 2.78 (S, 3H), δ 7.7-8.3 (m, 3H), δ 8.3-8.8 (m, 3H).

Anal. Calcd. for $C_{14}H_{10}N_2O_4$: C, 62.22; H, 3.73; N, 10.37. Found: C, 61.81; H, 3.73; N, 10.02.

2-Hydroxyphenazine 5,10-Dioxide (**10**).

Benzofuroxan (27.2 g., 0.2 mole) and 2,5-dihydroxybenzoic acid (30.8 g., 0.2 mole) were added to a solution of sodium hydroxide (8.4 g., 0.2 mole) in water (200 ml.). The mixture was heated at 60° for 18 hours, cooled, acidified and filtered. The solid was recrystallized from dimethylformamide to give 8.9 g. of red powder, m.p. 234° (dec.); ir: 1620, 1600, 1480, 1400, 1360, 1240, 1080, 840 and 760 cm^{-1}; nmr (TFA-deuteriochloroform): δ 7.4-8.2 (m, 4H), δ 8.3-8.6 (m, 3H).

Anal. Calcd. for $C_{12}H_3N_2O_3$: C, 63.16; H, 3.53; N, 12.28. Found: C, 62.83; H, 3.58; N, 12.45.

7-Hydroxy-2-phenazinecarboxaldehyde 5,10-Dioxide (**11**).

A mixture of 6-formylbenzofuroxan (66 g., 0.4 mole) and hydroquinone (44 g., 0.4 mole) in ethanol (500 ml.) was mixed with a solution of sodium hydroxide (0.3 g.) in water (300 ml.). The resulting mixture was stirred at room temperature for 18 hours, acidified and filtered. The precipitate was washed with ethanol and dried to give 94.4 g. of red solid, m.p. 221°; ir: 3425, 1700, 1620, 1600, 1440, 1340, 1240 and 1080 cm^{-1}; nmr (TFA-deuteriochloroform): δ 7.6-8.0 (m, 2H), δ 8.33-9.05 (m, 3H), δ 9.33-9.5 (s, b, 1H), δ 10.3 (S, 1H).

Anal. Calcd. for $C_{13}H_8N_2O_4$: C, 60.94; H, 3.15; N, 10.93. Found: C, 60.62; H, 3.25; N, 10.94.

N-Methyl-α-(2-phenazinyl)nitrone 5,10-Dioxide (**12**).

A mixture of **4** (6.7 g., 0.028 mole), methylhydroxylamine

hydrochloride (2.3 g., 0.028 mole), sodium bicarbonate (2.3 g., 0.028 mole) and ethanol (500 ml.) was stirred at room temperature for 24 hours. The solid was filtered off and washed with hot chloroform until all red color was removed. The combined ethanol and chloroform filtrates were evaporated and the residue was recrystallized from DMF to give 4.5 g. of red solid, m.p. 203°; ir: 1610, 1580, 1420, 1350, 1330, 1180, 1090, 940, 830, 790 and 770 cm^{-1}; nmr (TFA-deuteriochloroform): δ 4.33 (S, 3H), δ 8.08-8.50 (m, 3H), δ 8.58-9.08 (m, 4H), δ 9.91 (S, 1H).

Anal. Calcd. for $C_{14}H_{11}N_3O_3$: C, 62.45; H, 4.12; N, 15.61. Found: C, 62.81; H, 4.22; N, 15.70.

N-(2-Hydroxyethyl)-α-(2-phenazinyl)nitrone 5,10-Dioxide (**13**).

A mixture of **4** (10 g., 0.042 mole) hydroxyethylhydroxylamine oxalate (5.1 g., 0.021 mole), sodium bicarbonate (3.5 g., 0.042 mole) and ethanol (600 ml.) was stirred for 24 hours and filtered. The solid was washed with water and the residue was recrystallized from DMF to give 4.2 g. of red solid, m.p. 192-193°; ir: 1600, 1560, 1420, 1340, 1320, 1080 and 750 cm^{-1}; the compound was too insoluble in TFA for a spectrum to be determined.

Anal. Calcd. for $C_{15}H_{13}N_3O_4$: C, 60.20; H, 4.38; N, 14.04. Found: C, 59.93; H, 4.46; N, 14.12.

2-(7-Hydroxy-2-phenazinyl)-*N*-methylnitrone 5,10-Dioxide (**14**).

A suspension of **11** (25.6 g., 0.1 mole), *N*-methylhydroxylamine hydrochloride (8.3 g., 0.1 mole) and sodium bicarbonate (8.4 g., 0.1 mole) in ethanol (500 ml.) was stirred for 24 hours at room temperature. The mixture was filtered and the solid was washed with hot DMF, water and methanol to give 18.8 g. of red solid, m.p. 225°; ir: 3400, 1060, 1610, 1540, 1420, 1340, 1250, 1170, 1120, 1080, 955, 830 and 750 cm^{-1}; nmr (TFA-deuteriochloroform): δ 4.25 (S, 3H), δ 7.67-8.08 (m, 2H), δ 8.33 (S, 1H), δ 8.58-8.91 (m, 2H), δ 9.75 (S, 1H).

Anal. Calcd. for $C_{14}H_{11}N_3O_4$: C, 58.95; H, 3.89; N, 14.73. Found: C, 58.72; H, 4.00; N, 14.47.

α-(7-Hydroxy-2-phenazinyl)-*N*-(2-hydroxyethyl)nitrone 5,10-Dioxide (**15**).

A mixture of **11** (25.6 g., 0.1 mole), hydroxyethylhydroxylamine oxalate (12.2 g., 0.05 mole), sodium bicatbonate (8.4 g., 0.1 mole) and ethanol (500 ml.) was stirred for 24 hours and filtered. The solid was washed with DMF, water and methanol, then air dried to give 7 g. of red solid, m.p. 203°; ir: 1620, 1440, 1350, 1250, 1160, 1080, 840 and 760 cm^{-1}; nmr (TFA-deuteriochloroform): δ 4.33-5.16 (m, 4H), δ 7.6-8.0 (m, 2H), δ 8.25-8.91 (m, 4H), δ 9.91 (S, 1H).

Anal. Calcd. for $C_{15}H_{13}N_3O_5$: C, 57.14; H, 4.16; N, 13.33. Found: C, 56.97; H, 4.28; N, 13.23.

7-Hydroxy-2-phenazinecarboxaldehyde 5,10-Dioxide Semicarbazine (**16**).

A mixture of **11** (12.5 g., 0.049 mole), semicarbazide hydrochloride (5.5 g., 0.049 mole), sodium acetate (4.1 g., 0.049 mole) and ethanol (500 ml.) was heated at reflux for 2 hours and filtered. The solid was washed with DMF, water and air dried to give 9.4 g. of red solid, m.p. >300°; ir: 1710, 1620, 1580, 1420, 1350, 1240, 1080, 930, 750 cm^{-1}; nmr (TFA-deuteriochloroform): δ 7.6-8.0 (m, 2H), δ 8.3 (S, 1H), δ 8.41-9.08 (m, 4H).

Anal. Calcd. for $C_{14}H_{11}N_5O_4$: C, 53.68; H, 3.54; N, 22.36. Found: C, 53.28; H, 3.67; N, 22.22.

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