A New Route to Phenazine 5,10-Dioxides and Related Compounds[1]

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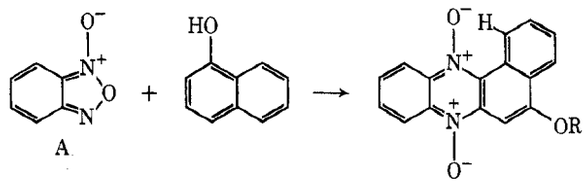
A new one-step synthetic route is described for the preparation of phenazine 5,10-dioxide derivatives and related compounds from benzofurazan 1-oxide and phenolic compounds. Mechanistic possibilities are presented.

Certain phenazine 5,10-dioxides are known to have antibacterial activity. Two of these, iodinin[2] and myxin,[3,4] are microbial metabolites. Previously, compounds of this class were prepared in low yields by a multistep synthetic route.[5] We now report a facile one-step synthesis of substituted phenazine 5,10-dioxides and some related compounds. This versatile synthesis has afforded novel compounds hitherto inaccessible by classical synthetic methods.[5]

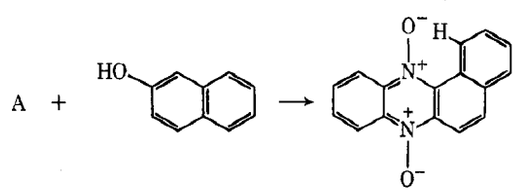
Enamines[6] and β diketones[7] react with benzofurazan 1-oxide to yield substituted quinoxaline 1,4-dioxides. It has now been found that phenolate anions react in the same sense with benzofurazan 1-oxides to afford phenazine 5,10-dioxide derivatives. Some of the successful reactions are listed in Table I. Surprisingly, the reaction of phenol with benzofurazan 1-oxide does not give the expected compound, phenazine 5,10-dioxide, but resulted in the formation of 2-phenazinol 5,10-dioxide in 5–10% yield. The same product, **1**, is obtained in better yield from the reaction of benzofurazan 1-oxide (A) with *p*-hydroquinone or *m*-methoxyphenol. In the latter case no 1-methoxyphenazine 5,10-dioxide was detected.

The presence of electron-withdrawing substituents on monohydroxybenzenes impedes the reaction, possibly due to the decreased nucleophilicity of the phenolate anions. The presence of electron-withdrawing groups on dihydroxybenzenes, however, does not affect the course of the reaction, as is shown by the reaction of carbomethoxy-*p*-hydroquinone with benzofurazan 1-oxide to furnish **13**.

The synthesis of benzo[*a*]phenazine 7,12-dioxide derivatives was achieved by allowing benzofurazan 1-oxide to react with α- and β-naphthols in the presence of base. Two compounds were obtained from α-naphthol: **14**, resulting from an initial para coupling, and **15**,[8] resulting from an initial ortho coupling. From β-naphthol, **15** was the sole product. Acetylation (acetic anhydride) and methylation (diazomethane) of **14** gave the corresponding acetoxy **16** and methoxy **17** derivative respectively. The structures were assigned



14, R = H
16, R = CCH_3 (O)
17, R = CH_3



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to the benzo[*a*]phenazine class on the basis of the large chemical shift of the hydrogens at C_1 in the nmr spectra due to the proximity of the 12-oxide. The C_1 hydrogen appears as a multiplet at δ 10.0 in **14** and at 10.65 in **15**.

The reactivities of some heterocyclic analogs of phenols toward benzofurazan 1-oxides have been examined and, in most cases, a reaction occurred affording novel heterocyclic compounds, as shown in Scheme I. Monohydroxypyridines are not nucleophilic enough to react with benzofurazan 1-oxide, but 2,3-dihydroxypyridine did react to yield the pyrido[2,3-*b*]quinoxaline **18**. 8-Hydroxyquinoline coupled with benzofurazan 1-oxide to yield the pyrido[2,3-*a*]-phenazinol **19**.

In the nmr spectrum of **19**, the C_1 hydrogen appears at δ 11.6 owing to the proximity effect of the 12-oxide. The quinolino[2,3-*a*]phenazine **20** was obtained from 1-phenazinol and benzofurazan 1-oxide. Furthermore, indole reacted with benzofurazan 1-oxide to give the indoloquinoxaline **21**; the structure of **21** was confirmed by the synthesis of this product, in poor yield, from benzofurazan 1-oxide and indoxyl acetate in alcoholic base. Reduction of **21** with sodium dithionite gave the product **22**, which was identical with an authentic sample synthesized from *o*-phenylenediamine and isatin.

Possible mechanisms for the formation of phenazine 5,10-dioxides from benzofurazan 1-oxides and phenolate anions are outlined in Scheme II. Depending on the substitution pattern on the phenolate anion, the reaction may follow one of three different pathways. If the para position of the phenolate anion is unsubstituted, the attack on the benzofurazan 1-oxide pro-

(1) Presented in part at (a) IUPAC Meeting in London, July 1968, Abstract H4, 437; (b) 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968, Medicinal Chemistry Abstract 15. Related work has been published by K. Ley, F. Seng, V. Eholzer, R. Nast, and R. Schubart, *Angew. Chem., Int. Ed. Engl.*, **8**, 596 (1969).

(2) G. R. Clemo and H. McIlwain, *J. Chem. Soc.*, 479 (1938).

(3) A. E. Peterson, D. C. Gillespie, and F. D. Cook, *Can. J. Microbiol.*, **12**, 221 (1966).

(4) M. Weigele and L. Leimgruber, *Tetrahedron Lett.*, 715 (1967).

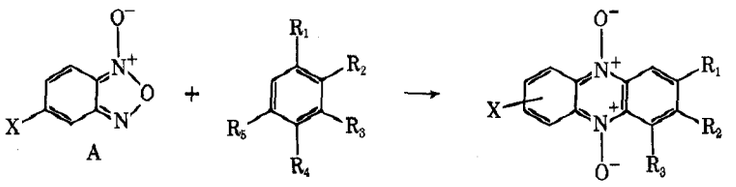
(5) Review: G. A. Swan and D. G. I. Felton, "The Chemistry of Heterocyclic Compounds," Interscience, New York, N. Y., 1957.

(6) M. J. Haddadin and C. H. Issidorides, *Tetrahedron Lett.*, 3253 (1965).

(7) C. H. Issidorides and M. J. Haddadin, *J. Org. Chem.*, **31**, 4067 (1966).

(8) I. J. Pachter and M. C. Kloetzel, *J. Amer. Chem. Soc.*, **73**, 4958 (1951).

TABLE I



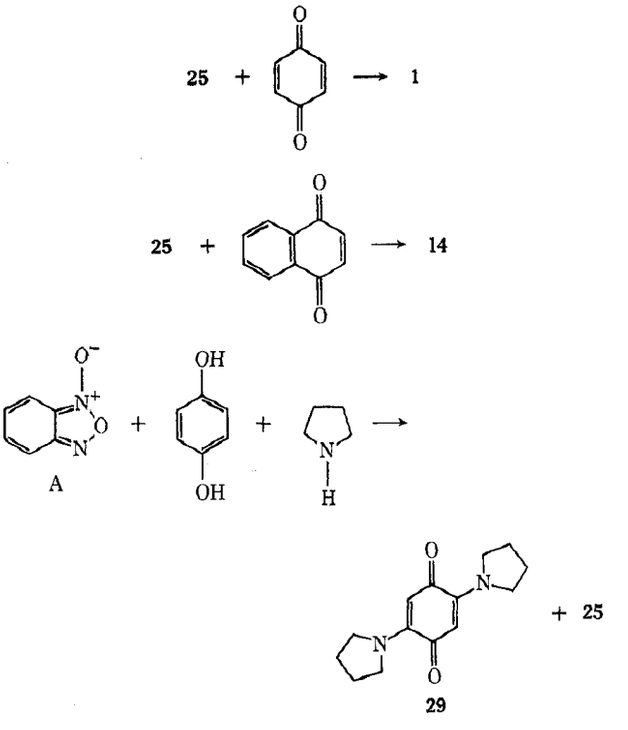
Phenazine	X	R_1	R_2	R_3	R_4	R_5	Yield, %	Method	Mp, °C	Recrystn solvent	Formula[e]
1[a]	H	OH	H	H	H	H	5–10	C	230	CF_3CO_2H–MeOH	$C_{12}H_8N_2O_3$
1	H	OH	H	H	OH	H	30	C	230	CF_3CO_2H–MeOH	$C_{12}H_8N_2O_3$
1	H	OH	H	H	H	OCH_3	15	C	230	CF_3CO_2H–MeOH	$C_{12}H_8N_2O_3$
2[b]	Cl	OH	H	H	OH	H	60	B	208	CF_3CO_2H–MeOH	$C_{12}H_7ClN_2O_3$
3[b]	OCH_3	OH	H	H	OH	H	22	B	196	CH_3CO_2H–MeOH	$C_{13}H_{10}N_2O_4$
4	H	NH_2	H	H	OH	H	56	C	215	CF_3CO_2H	$C_{12}H_9N_3O_2$
5	H	OH	OH	H	H	H	66	A + C	250	CF_3CO_2H–AcOH	$C_{12}H_8N_2O_4$
6	H	–OCH_2O–		H	OH	H	35	C	207–208	CF_3CO_2H–MeOH	$C_{13}H_8N_2O_4$
7[b]	Cl	–OCH_2O–		H	OH	H	25	C	207–208	$CHCl_3$–MeOH	$C_{13}H_7ClN_2O_4$
8[c]	H	OH	OCH_3	H	H	H	80	A + C	212–214	CF_3CO_2H–MeOH	$C_{13}H_{10}N_2O_4$
9	H	OH	CO_2H	H	OH	H	70	A	>300	CF_3CO_2H–MeOH	$C_{13}H_8N_2O_5$
10	H	OCH_3	H	H	OH	H	37	B	184	MeOH	$C_{13}H_{10}N_2O_3$
11[d]	H	OH	H	OH	H	OH	34	B	220	CF_3CO_2H–MeOH	$C_{12}H_8N_2O_4$
12	H	OH	OH	CH_3	H	H	82	A	235	CF_3CO_2H–MeOH	$C_{13}H_{10}N_2O_4$
13	H	OH	CO_2CH_3	H	OH	H	20	A	204–205	MeOH–Et_2O	$C_{14}H_{10}N_2O_5$

[a] D. L. Vivian, *J. Amer. Chem. Soc.*, **71**, 1139 (1949). [b] Position of X in the products is either at 7 or 8. [c] Product characterized as the dimethoxy derivative. [d] Product characterized as the diacetoxy derivative. [e] All compounds were analyzed for C, H, N, and Cl. The analyses were within ±0.4% of the theoretical values: Ed.

ceeds exclusively *via* pathways a or c, followed by cyclization through a Michael-type addition to the quinoidal intermediates. In pathway a, the dihydro intermediate cannot be isolated even if the reaction is conducted under an atmosphere of nitrogen; oxidation of the dihydro intermediate may be effected by benzofurazan 1-oxide, as evidenced by the isolation of benzofurazan **23** from the reaction mixture. In pathway c, elimination of an alcohol (ROH) produces the fully aromatic product. In pathway b, a substituent at the para position forces the phenolate anion to couple at the ortho position followed by cyclization and elimination of water to yield the product.

The oxidizing capacity of benzofurazan 1-oxide is illustrated in Scheme III. Thiophenol and β-thionaphthol are oxidized to the disulfides **24** and **26** respectively, while benzofurazan 1-oxide is reduced to *o*-quinonedioxime (**25**). Hydroquinones may be oxidized to quinones by benzofurazan 1-oxide as illustrated by the oxidation of 2,5-di-*tert*-butylhydroquinone to the quinone **27**. Oxidation of *o*-aminophenol with benzofurazan 1-oxide, in the presence of base, gave as one of the products the phenoxazone **28**. Other oxidizing agents, such as benzoquinone, are known to effect the same transformation.[9]

The ability of benzofurazan 1-oxide to oxidize hydroquinones to quinones may suggest alternate mechanistic possibilities for the formation of 2-phenazinol 5,10-dioxide based on an initial one- or two-electron oxidation. A radical coupling could then occur after a one-electron transfer, or, for a two-electron transfer, the resulting bisoxime **25** could then condense with the quinone. Such a condensation was observed to occur with *p*-quinone to yield **1** and with 1,4-naphthoquinone to afford **14**. Furthermore, when the reaction between benzofurazan-1-oxide and *p*-hydroquinone was catalyzed by pyrrolidine, the product was



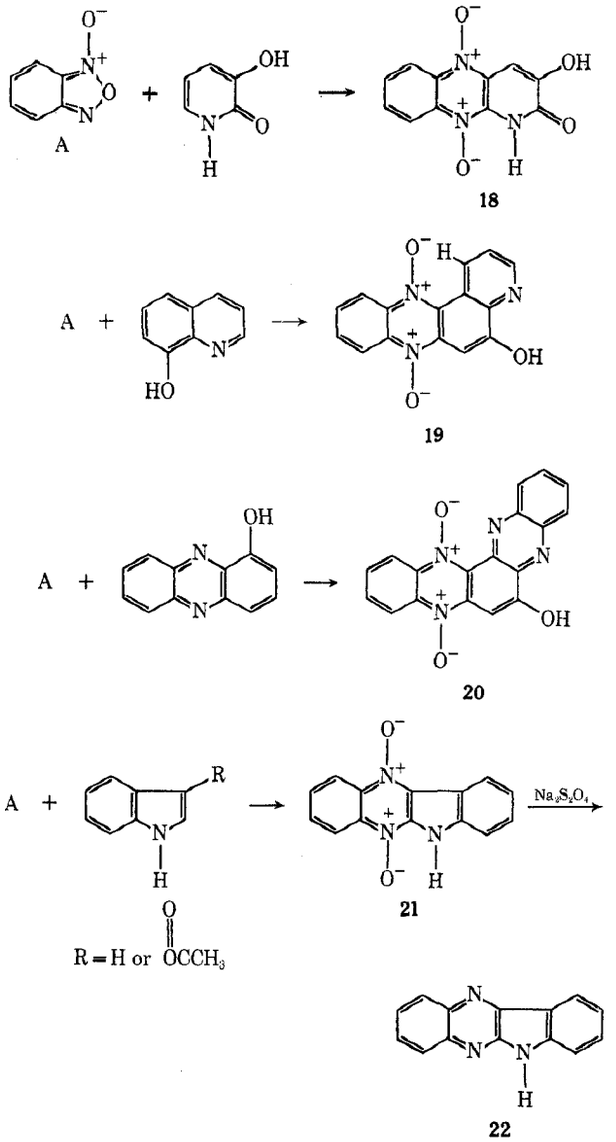
not the expected 2-phenazinol 5,10-dioxide (**1**), but the dipyrrolidinoquinone **29**. This could be the result of a reaction between pyrrolidine and either a phenolate radical anion or *p*-quinone followed by oxidations with benzofurazan 1-oxide. At present, it is not possible to choose among the mechanistic possibilities discussed above.

Experimental Section

All melting points are uncorrected and were obtained with the Buchi apparatus. The analyses were performed by the Analytical Department of Pfizer Inc., and by F. Pascher, Bonn, Germany. The phenazine 5,10-dioxides were mainly prepared

(9) A. Korczynski and S. Obarski, *Bull. Soc. Chim. Fr.*, **33**, 1823 (1923).

SCHEME I



by one of the three general methods illustrated below and the ir, uv, and nmr spectra of the reported compounds were in agreement with the assigned structures.

Method A. Methyl 3-Hydroxy-2-phenazinecarboxylate 5,10-Dioxide (13).—A solution of 5.0 g (0.029 mol) of methyl 2,5-dihydroxybenzoate and 4.0 g (0.029 mol) of benzofurazan 1-oxide in 100 ml of THF was saturated with NH_3 and the reaction mixture was stirred overnight at room temperature in a tightly stoppered flask. The following day the solution was evaporated and, after trituration with 1 *N* HCl, the residue was recrystallized from MeOH–Et_2O to give 1.5 g of a purple solid. Another recrystallization gave a dark yellow sample of **13**.

Method B. 2-Methoxyphenazine 5,10-Dioxide (10).—A solution of 6.2 g (0.048 mol) of *p*-methoxyphenol and 6.5 g (0.048 mol) of benzofurazan 1-oxide in 100 ml of 5% KOH in MeOH was allowed to stand for 3 days at room temperature and then the reaction mixture was heated to reflux overnight. The resulting slurry was filtered to give 4.5 g of a dark brown solid which decomposed at 174–184°. Recrystallization from MeOH gave a red solid, mp 184° dec (lit. 174–175°).

Method C. 2-Phenazinol 5,10-Dioxide (1).—To a solution of 12.4 g (0.1 mol) of *m*-methoxyphenol, 5.4 g (0.1 mol) of NaOMe, and 100 ml of MeOH was added a solution of 13.6 g (0.1 mol) of benzofurazan 1-oxide in 100 ml of MeOH. The reaction mixture was heated to reflux for 2 hr to yield 1.0 g of a dark purple solid (Na), mp >300°. Acidification of the filtrate yielded 2.7 g of a red solid, mp 230° dec. Recrystallization from trifluoroacetic acid–MeOH gave a red sample of **1**.

Methylation of 8.—Treatment of a slurry of 0.1 g of 2-hydroxy-3-methoxyphenazine 5,10-dioxide (**8**) in MeOH with ethereal diazomethane gave 2,3-dimethoxyphenazine 5,10-dioxide, which was recrystallized from $CHCl_3$–EtOH to give orange needles (80 mg) that melted at 222–223° with decomposition. This compound was identical with that obtained by the treatment of 2,3-dihydroxyphenazine 5,10-dioxide (**5**) with diazomethane.

Anal. Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.62; H, 4.34; N, 10.14.

Acetylation of 11.—A solution of 0.9 g of 1,3-dihydroxyphenazine 5,10-dioxide (**11**) in Ac_2O–pyridine was allowed to stand at room temperature for 12 hr, and poured onto ice–water. The precipitated solid was filtered and washed with H_2O to give 0.9 g of 1,3-diacetoxyphenazine 5,10-dioxide, which was recrystallized from MeOH to give an orange solid that melted at 135°.

Anal. Calcd for $C_{16}H_{12}N_2O_6$: C, 58.54; H, 3.68; N, 8.53. Found: C, 58.70; H, 3.83; N, 8.64.

Benzo[*a*]-phenazine 7,12-Dioxide (15) and 5-Hydroxybenzo-[*a*]phenazinol 7,12-Dioxide (14).—To a solution of 14.4 g (0.1 mol) of α-naphthol, 5.4 g (0.1 mol) of NaOMe, and 150 ml of MeOH was added a solution of 13.6 g (0.1 mol) of benzofurazan 1-oxide in 100 ml of MeOH. After stirring overnight, the resulting slurry was filtered to yield 5.2 g of **15**, mp 169–170°. Recrystallization from $CHCl_3$–MeOH gave 4.0 g of a yellowish orange solid, mp 178–178.5°.

Anal. Calcd for $C_{16}H_{10}N_2O_2$: C, 73.27; H, 3.84; N, 10.68. Found: C, 73.29; H, 3.95; N, 10.69.

The mother liquor from the reaction mixture was acidified with AcOH to yield 7.4 g of **14**, mp 230–231°. Recrystallization from trifluoroacetic acid–AcOH gave 4.65 g, mp 250–253° dec.

Anal. Calcd for $C_{16}H_{10}N_2O_3$: C, 69.06; H, 3.62; N, 10.07. Found: C, 69.20; H, 3.56; N, 10.11.

Benzo[*a*]phenazine 7,12-Dioxide (15).—To a solution of 14.4 g (0.1 mol) of β-naphthol, 5.4 g (0.1 mol) of NaOMe, and 150 ml of MeOH was added a solution of 13.6 g (0.1 mol) of benzofurazan 1-oxide in 100 ml of MeOH. A few minutes later, the slurry was filtered to give 7.6 g of a yellowish-orange solid, mp 179–180°. The mother liquor was heated to reflux for 30 min to yield an additional 5.25 g of product, mp 177–179°.

5-Acetoxybenzo[*a*]phenazine 7,12-Dioxide (16).—5-Hydroxybenzo[*a*]phenazine 7,12-dioxide (**14**, 0.15 g) was dissolved with warming in 4 ml of pyridine and 6 ml of Ac_2O and after being stirred at room temperature for 16 hr the reaction mixture was poured onto ice–water. The resulting yellow-orange solid was collected and washed with H_2O and MeOH. Recrystallization from benzene (20 ml) gave thin orange-yellow needles that melted at 204° dec.

Anal. Calcd for $C_{18}H_{12}N_2O_4$: C, 67.50; H, 3.78; N, 8.75. Found: C, 67.61; H, 3.61; N, 8.65.

5-Methoxybenzo[*a*]phenazine 7,12-Dioxide (17).—A slurry of 0.5 g of 5-hydroxybenzo[*a*]phenazine 7,12-dioxide (**14**) in MeOH was treated with etherial diazomethane and after evaporation of the solution the residue was recrystallized from $CHCl_3$–MeOH to give orange needles (300 mg) that melted at 197–198° dec.

Anal. Calcd for $C_{17}H_{12}N_2O_3$: C, 69.85; H, 4.14; N, 9.59. Found: C, 69.75; H, 4.04; N, 9.43.

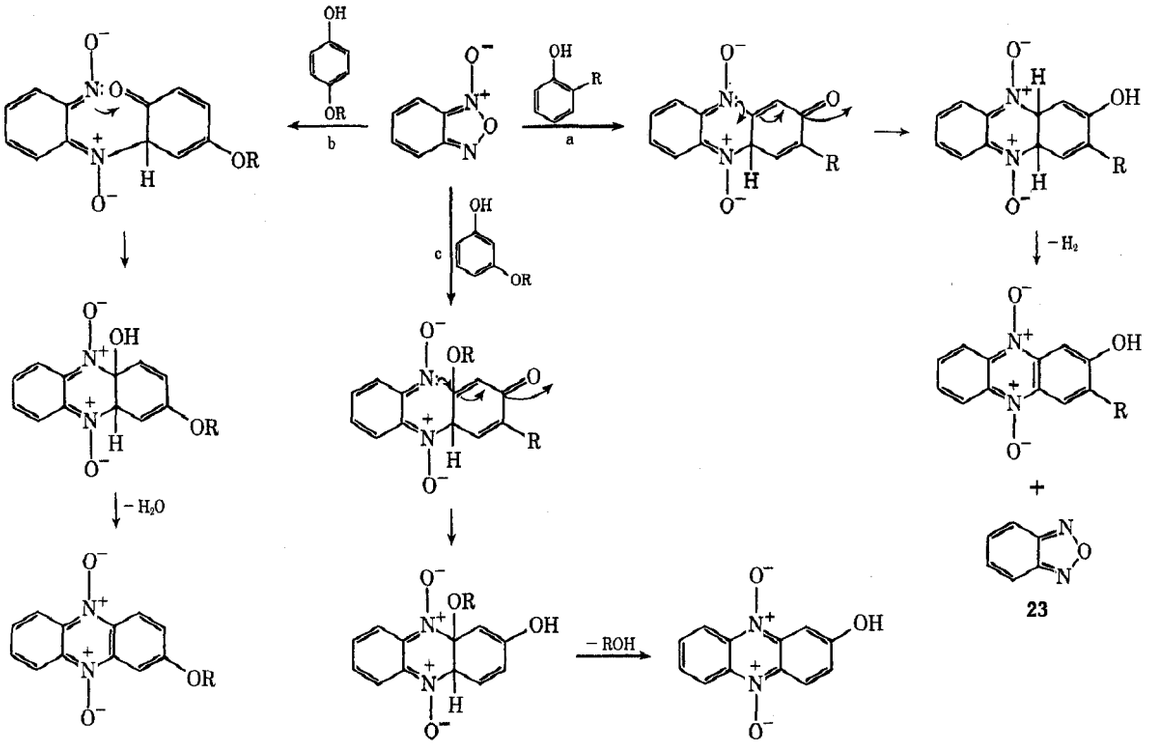
Pyrido[2,3-*b*]quinoxaline-2,3-diol 5,10-Dioxide (18).—A solution of 5.0 g (0.046 mol) of 2,3-dihydroxypyridine and 6.2 g (0.046 mol) of benzofurazan 1-oxide in 100 ml of THF was saturated with NH_3 and the flask was tightly sealed. After sitting overnight at room temperature, the reaction mixture was filtered to give 5.0 g (22%) of a brown solid which did not melt below 300°. An analytical sample was prepared by recrystallization from AcOH.

Anal. Calcd for $C_{11}H_7N_3O_4$: C, 53.88; H, 2.88; N, 17.14. Found: C, 53.84; H, 3.25; N, 16.41.

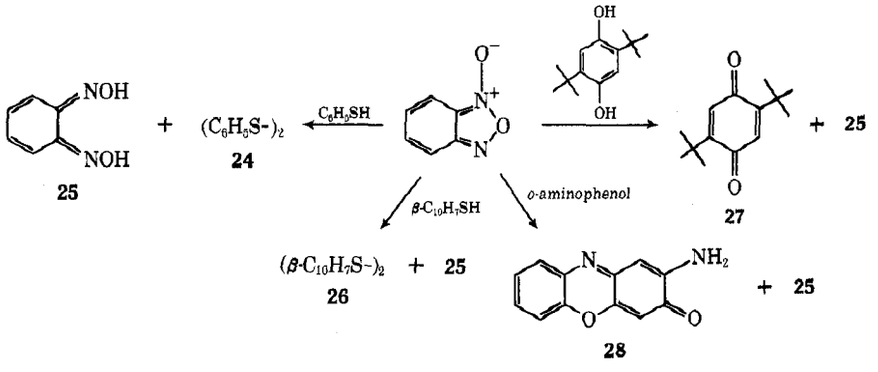
5-Pyrido[3,2-*a*]phenazinol 7,12-Dioxide (19).—To a hot solution of 14.5 g (0.1 mol) of 8-hydroxyquinoline, 5.4 g (0.1 mol) of NaOMe, and 100 ml of MeOH was added a hot solution of 13.6 g (0.1 mol) of benzofurazan 1-oxide in 150 ml of MeOH. The reaction was heated to reflux for 2.5 hr, and after cooling, filtration gave 11.4 g of a purple solid, mp >300° (sodium salt). Acidification of the filtrate with excess AcOH gave 2.1 g of an orange solid as the free phenol, mp 240–242° dec, which was recrystallized from trifluoroacetic acid–AcOH, mp 242° dec. The sodium salt may be converted to **19** by dissolving it in H_2O and acidifying the purple solution with 6 *N* HCl.

Anal. Calcd for $C_{15}H_9N_3O_3$: C, 64.51; H, 3.25; N, 15.05. Found: C, 64.48; H, 3.29; N, 14.93.

SCHEME II



SCHEME III



6-Hydroxyquinoxalino[2,3-*a*]phenazine 8,13-Dioxide (20).—To a solution of 5.0 g (0.025 mol) of 1-hydroxyphenazine and 1.35 g (0.025 mol) of NaOMe in 100 ml of MeOH was added 3.4 g (0.025 mol) of benzofurazan 1-oxide. After stirring at room temperature overnight 1.5 g (0.025 mol) of AcOH was added and the resulting slurry was filtered to give 5.0 g (60%) of a brown solid, mp >300°. Trituration of the brown solid with AcOH gave a red solid and an analytical sample was obtained by recrystallization from trifluoroacetic acid–Et_2O.

Anal. Calcd for $C_{18}H_{10}N_4O_3$: C, 65.50; H, 3.25; N, 16.98. Found: C, 65.43; H, 2.98; N, 16.78.

6*H*-Indolo[2,3-*b*]quinoxaline 5,11-Dioxide (21).—A solution of benzofurazan 1-oxide (1.4 g) and indole (1.2 g) in 5% methanolic KOH (10 ml) was heated to reflux for 2 min and allowed to stand at room temperature for 3 hr. Dilution with H_2O and acidification with dilute HCl afforded a yellow solid which was filtered and washed with H_2O and MeOH. The dried product **21** weighed 0.6 g (37% yield) and recrystallization from AcOH gave bright yellow rosettes, mp 284° dec.

6*H*-Indolo[2,3-*b*]quinoxaline (22).—To a warm solution of 6*H*-indolo[2,3-*b*]quinoxaline 5,11-dioxide (**21**, 0.1 g) in AcOH (20 ml) was added in portions a solution of $Na_2S_2O_4$ (0.5 g) in 5 ml of hot H_2O and the solution was heated to reflux for 5 min. The solution was then diluted with H_2O and the resulting yellowish solid was collected and washed with H_2O and MeOH. Recrystallization of the product from C_6H_6–MeOH gave yellow needles (100 mg), mp 296–298° (lit. 294–295°). 6*H*-Indolo[2,3-*b*]quinoxaline (**22**) prepared by the above method was identical (ir and mixture melting point) with an authentic sample synthesized from *o*-phenylenediamine and isatin.

The Reaction of Pyrocatechol and Benzofurazan 1-Oxide.—A solution of pyrocatechol (2.2 g) and benzofurazan 1-oxide (2.8 g) in 15% ethanolic potassium hydroxide (10 ml) was steam distilled to give 1.3 g of benzofurazan (**23**). Acidification of the red solution in the reaction flask with dilute HCl gave 1.6 g of 2,3-dihydroxyphenazine 5,10-dioxide (**5**).

The Reaction of Thiophenol and Benzofurazan 1-Oxide.—To a solution of 5.0 g (0.0457 mol) of thiophenol and 6.2 g (0.0457 mol) of benzofurazan 1-oxide in 50 ml of THF was added, dropwise, a solution of 2.5 g (0.0457 mol) of NaOMe in 25 ml of MeOH. After 2 hr, the solution was evaporated and H_2O was added to give a precipitate, mp 57–60° [diphenyl disulfide (**24**), mp 59–60°]. The filtrate was then acidified and concentrated to give 3.0 g (98%) of *o*-quinonedioxime (**25**) which was identified by a mixture melting point test.

The Reaction of β-Thionaphthol and Benzofurazan 1-Oxide.—To a slurry of 5.0 g (0.031 mol) of β-thionaphthol and 1.7 g (0.031 mol) of NaOMe in 50 ml of MeOH was added 4.2 g (0.031 mol) of benzofurazan 1-oxide. The slurry was stirred overnight and then filtered to give 4.5 g (90%) of a colorless solid, mp 137–139° [lit. mp 139° for 2,2′-dinaphthyl disulfide (**26**)].

The Reaction of 2,5-Di-*tert*-butylhydroquinone and Benzofurazan 1-Oxide.—A solution of 3.0 g (0.022 mol) of benzofurazan 1-oxide and 5.0 g (0.022 mol) of 2,5-di-*tert*-butylhydroqui-

none in 50 ml of THF was saturated with NH_3 and stirred overnight at room temperature. The yield of the resulting red precipitate **27**, which turned yellow on drying, was 4.5 g (98%), mp 152–153° [2,5-di-*tert*-butylquinone (**27**) mp 152.5°]. The only other product in this reaction was *o*-quinonedioxime (**25**) which was identified by tlc.

The Reaction of *o*-Aminophenol and Benzofurazan 1-Oxide.—To a solution of 5.0 g (0.045 mol) of *o*-aminophenol and 2.4 g (0.045 mol) of NaOMe in 5.0 ml of MeOH was added 6.1 g (0.045 mol) of benzofurazan 1-oxide. After stirring at room temperature for 2.5 hr, 2.7 g (0.045 mol) of AcOH was added and the resulting slurry was filtered to give 3.0 g (62%) of 2-amino-3*H*-phenoxazin-3-one (**28**) which melted after recrystallization at 254–255°.

Anal. Calcd for $C_{12}H_8N_2O_2$: C, 67.9; H, 3.78; N, 13.2. Found: C, 67.79; H, 3.85; N, 13.45.

The addition of H_2O to the filtrate resulted in the isolation of 5.0 g (82%) of *o*-quinonedioxime (**25**) which was identified by tlc and a mixture melting point test.

2-Phenozinol 5,10-Dioxide (**1**).—A solution of 0.9 g (0.0065 mol) of *o*-quinonedioxime (**25**) and 0.7 g (0.0065 mol) of *p*-quinone in 10 ml of THF after standing overnight at room temperature was filtered to give 0.5 g (34%) of a red solid which was identical in every respect with an authentic sample of 2-phenazinol 5,10-dioxide (**1**).

5-Hydroxybenzo[*a*]phenazinol 7,12-Dioxide (**14**).—A solution of 1.0 g (0.0063 mol) of 1,4-naphthoquinone and 0.88 g (0.0063 mol) of *o*-quinonedioxime (**25**) in 20 ml of THF was allowed to stand at room temperature for 1 day. Filtration gave 0.050 g (3%) of a red solid, mp 230–235°. The filtrate was allowed to sit for 2 more days and filtered again to give 0.45 g (25.6%), mp 233–235°. Finally the filtrate was allowed to stand 7 more days the solution was filtered again to give 0.7 g (40%) of a brown solid, mp 236–238°.

The three solids were combined and recrystallized from AcOH–trifluoroacetic acid to give 1.0 g of **14** (57%) which melted at 242° dec. This compound was identical in every respect with an authentic sample.

Registry No.—**1**, 303-80-0; **2**, 32839-15-9; **3**, 32839-16-0; **4**, 26390-70-5; **5**, 24890-65-1; **6**, 25629-71-4; **7**, 32846-85-8; **8**, 26390-41-0; **8** dimethoxy derivative, 32866-02-7; **9**, 25629-68-9; **10**, 303-78-6; **11**, 25629-70-3; **11** diacetate, 32861-63-5; **12**, 25629-67-8; **13**, 25629-69-0; **14**, 26390-71-6; **15**, 18636-88-9; **16**, 32861-68-0; **17**, 32861-69-1; **18**, 32861-70-4; **19**, 25629-73-6; **20**, 32861-72-6; **21**, 32861-73-7; **22**, 243-59-4; **24**, 882-33-7; **27**, 2460-77-7; **28**, 1916-59-2.

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Phenylfurazan Oxide. Chemistry

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The facile stepwise transformation of 4-phenylfurazan 2-oxide (**1**) under a variety of conditions into α-hydroxyimino-*anti*-phenylacetonitrile oxide (**2a**), α-hydroxyiminophenylacethydroxamic acid (**3**), and 3-phenyl-1,2,4-oxadiazol-5-one (**7**), as proposed in the early literature, has been confirmed. Comparison samples of compounds **3** and **7** were synthesized by independent routes. The same α-hydroxyiminophenylacethydroximoyl chloride (**6**) was obtained by the addition of hydrogen chloride to the nitrile oxide **2a**, by chlorination of *anti*-phenyl-*amphi*-glyoxime (**5**), and by reaction of α-ketophenylacethydroximoyl chloride (**9**) with hydroxylamine hydrochloride; dehydrohalogenation of this yielded the nitrile oxide isomer opposite to **2a**. 4-Phenylfurazan 2-oxide could not be methylated by methyl iodide nor by dimethyl sulfate. No reaction occurred when 4-phenylfurazan 2-oxide was irradiated with uv light. A 1:1 adduct of 4-phenylfurazan 2-oxide (or of α-hydroxyimino-*anti*-phenylacetonitrile oxide) with mesityl oxide was isolated.

4-Phenylfurazan 2-oxide (**1**) is a compound with a long history and most investigations of it preceded the arrival of instrumental techniques. In our investigation of this area of chemistry, we have shown that three isomers of phenylglyoxime, *anti*-phenyl-*amphi*-glyoxime, phenyl-*anti*-glyoxime, and phenyl-*syn*-glyoxime are present in the conventional synthesis of this precursor to phenylfurazan oxide.[1] Further, oxidation of each isomer by dinitrogen tetroxide yielded only 4-phenylfurazan 2-oxide (**1**).[2] These results contrasted with the conclusions of previous investigators who described the oxidations of only two isomers into two different phenylfurazan oxides, 3-phenylfurazan 2-oxide and 4-phenylfurazan 2-oxide.[3] In view of these discrepancies between our results and those of former researchers and considering the interesting rearrangements described for phenylfurazan oxide,[4] a reexamination of 4-phenylfurazan 2-oxide chemistry, using modern instrumentation, appeared justified.

It had been reported that phenylfurazan oxide will rearrange into α-hydroxyiminophenylacetonitrile oxide (**2**) completely in base or to the extent of 2–5% in solvents such as benzene or ether.[4,5] We have found that most handlings of 4-phenylfurazan 2-oxide result in significant or complete rearrangement into α-hydroxyimino-*anti*-phenylacetonitrile oxide (**2a**). Thus dissolution of **1** in some solvents, *e.g.*, acetone, alcohol–water, contact with alumina or treatment with a basic buffer, or heating with activated charcoal have all caused this rearrangement. This transformation was not observed when 4-phenylfurazan 2-oxide was dissolved in chloroform, *m*-xylene, or in solvents acidified with hydrogen chloride. The conversion was readily monitored by infrared spectral measurement, by observing the appearance of the strong nitrile oxide absorbance at 2288 cm^{-1} and the disappearance of the strong double bond absorbance associated with the furazan oxide ring at 1610 cm^{-1}. In the very early literature, the product from the rearrangement of phenylfurazan oxide in base was incorrectly described

(1) J. V. Burakevich, A. M. Lore, and G. P. Volpp, *J. Org. Chem.*, **36**, 1 (1971).

(2) J. V. Burakevich, A. M. Lore, and G. P. Volpp, *ibid.*, **36**, 5 (1971).

(3) For a discussion and references, see the publications cited in footnotes 1 and 2.

(4) For reviews, see J. H. Boyer in "Heterocyclic Compounds," Vol. 7, R. C. Elderfield, Ed., John Wiley & Sons, New York, N. Y., 1961, pp 499–503; L. C. Behr in "The Chemistry of Heterocyclic Compounds, Five- and Six-Membered Compounds with Nitrogen and Oxygen," A. Weissberger, Ed., Interscience Publishers, New York, N. Y., 1962, pp 287, 298.

(5) (a) G. Ponzio, *Gazz. Chim. Ital.*, **66**, 127 (1936); (b) G. Ponzio, *ibid.*, **66**, 119 (1936).