$NaHCO_3$, dried (Na_2SO_4), and evaporated. The resulting oil was distilled to give (±)-4 (32 g): bp 75–80° (0.05 mm); $n^{25}D$ 1.5254; λ max 235 nm (log ε 3.71). *Anal.* ($C_6H_7NO_2S$) C, H, N.

(+)- and (−)-1-Isopropylamino-3-(2-thiazolyloxy)-2-propanol Hydrochlorides by Synthesis. Freshly distilled CH_3SO_2Cl (1.7 ml) was added to a solution of (+)-**3a** (4.0 g) in dry C_5H_5N (15 ml) at 0°. After 10 min, the mixture was diluted with Et_2O (100 ml) and treated with solid NaOMe (15 g) for 10 min. H_2O was added and the crude epoxide was isolated by extraction with Et_2O. The residue was dissolved in C_6H_6 and this solution was washed with H_2O, 20% HOAc, saturated NaCl, saturated $NaHCO_3$, and H_2O and evaporated to dryness. A solution of the residue in isopropylamine (20 ml) was heated in a Parr screw cap bomb for 2 hr at 90°. The excess isopropylamine was evaporated under reduced pressure to yield a gum which was dissolved in 2 *N* HCl (100 ml). This solution was washed twice with CH_2Cl_2, then made alkaline with KOH, and extracted with Et_2O. The Et_2O solution was washed with H_2O, dried (Na_2SO_4), and treated with dry HCl. The precipitate was collected and recrystallized from MeOH–acetone to yield 0.6 g of (+)-hydrochloride; $[\alpha]D$ +9° (MeOH).

Treatment of (−)-**3a** in the same manner provided the (−)-hydrochloride; $[\alpha]D$ −9° (MeOH).

(2*R*)-(+)- and (2*S*)-(−)-1-Isopropylamino-3-(2-thiazolyloxy)-2-propanol Hydrochlorides (15b,c) by Chemical Resolution. (±)-**15a** (2 g) was treated with 1.3 equiv of (+)-malic acid in *i*-PrOH and allowed to crystallize. The resulting white crystalline salt was recrystallized 14 times to constant mp 132–132.5° and $[\alpha]D$ −13.8°. *Anal.* ($C_{13}H_{22}O_7N_2S$) C, H, N. Treatment of the pure salt with NH_4OH followed by extraction with CH_2Cl_2 provided the free base which upon exposure to dry HCl gave (2*S*)-(−)-**15c**: mp 112–113°; $[\alpha]D$ −15.2°.

Treatment of (±)-**15a** in the same manner with (−)-malic acid gave the malic acid salt [mp 132–132.5°; $[\alpha]D$ +15.6°. *Anal.* ($C_{13}H_{22}O_7N_2S$) C, H, N] and the hydrochloride (2*R*)-(+)-**15b** [mp 112–113°; $[\alpha]D$ +15.9°].

Pharmacological Method. The myocardial stimulant activities (*i.e.*, the myocardial contractile force and heart rate increasing effects) of 1-alkylamino-3-(2-thiazolyloxy)-2-propanols were studied in bilaterally vagotomized open chest mongrel dogs of both sexes (weight 5–20 kg), which were anesthetized intravenously with 30 mg/kg of sodium pentobarbital supplemented by 5 mg/kg/hr. Myocardial contractile force was recorded by a Walton-Brodie strain gage,[16] sutured to the right ventricle, heart rate from a cardiotachograph, and systemic blood pressure from a femoral artery.

One to six dose levels of the general β-stimulant (±)-isoproterenol hydrochloride (0.0158–1.58 μg/kg) were administered at 10-min intervals before and after each dose of test compound. Three doses of test compound (0.1–3.16 mg/kg) were usually administered. The doses of test compounds required to produce an increase in myocardial contractile force equivalent to that produced by isoproterenol (where isoproterenol = 1) appear in Table I. These were calculated by use of Finney's parallel line assay, which was modified to accept *one observation* per dose[17] and in which dose levels of isoproterenol and test compounds and the responses induced were converted to common logarithms. Compound potencies were not estimated from heart rate increases because of the variability of these increases.

Acknowledgment. We wish to thank Mrs. M. Hanks for calculating the relative stimulant potencies of the test compounds.

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Furazanobenzofuroxan, Furazanobenzothiadiazole, and Their *N*-Oxides. A New Class of Vasodilator Drugs

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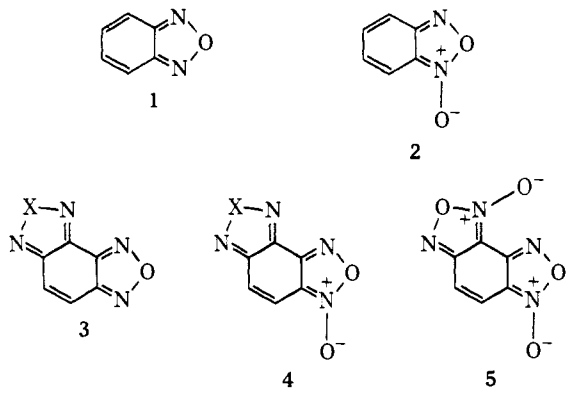
Furazanobenzofuroxan, furazanobenzothiadiazole, and their *N*-oxides have been found to be potent *in vivo* and *in vitro* vasodilators. Structure–activity relationships within this series and structural comparisons with glyceryl trinitrate (GTN) are described.

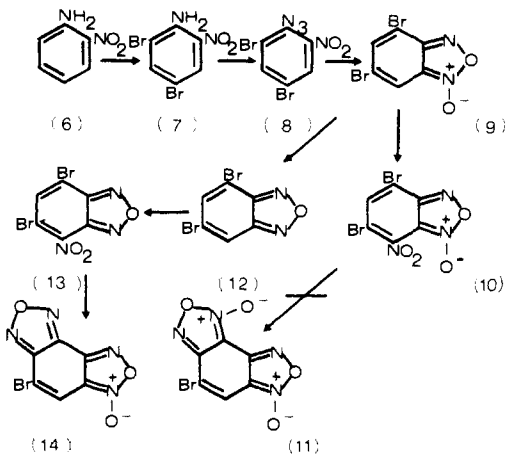
Nitrites, nitrous esters, and organic nitrates are widely used in the treatment of peripheral vascular disorders. Previous studies[1-4] of the benzoheterocyclic system benzo-2,1,3-oxadiazole, commonly known as benzofurazan (**1**), and its *N*-oxide benzofuroxan (**2**) indicated that in some instances this ring system could be considered as a cyclized form of a nitro group. With this in mind we examined a series of benzofurazans and their tricyclic derivatives **3** (X = S), **4** (X = S or O) and **5** for potential vasodilatory and hypotensive activity in the spinal cat and isolated rabbit ear artery preparations.

Chemistry. Benzofuroxan,[5] benzofurazan,[6] and 4-nitro-



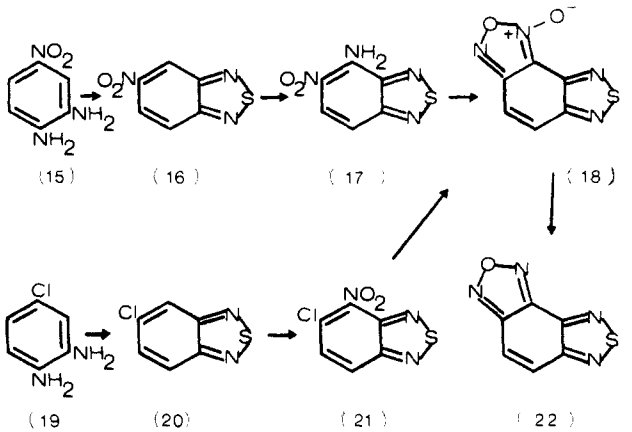
benzofurazan[7] were prepared by the published methods. The tricyclics, furazanobenzofuroxan (4, X = O), and furoxanobenzofuroxan (5) were prepared by the procedure of Boulton, Gripper-Gray, and Katritzky.[8] 6-Bromofurazanobenzofuroxan (14) was synthesized from 2-nitroaniline according to the route shown (Scheme I). Unsuccessful attempts were made to convert 5,7-dibromo-4-nitrobenzofuroxan (10) to 5-bromofuroxanobenzofuroxan (11) by replacement of the 5-Br group with N_3^- followed by pyrolysis.

Scheme I



Alkaline oxidation of 4-amino-5-nitrobenzothiadiazole[9] (17) with sodium hypochlorite afforded furoxanobenzothiadiazole† (18) in low yield (Scheme II). However, 5-chloro-4-nitrobenzothiadiazole[11] (21) was easily converted to 18 by treatment with N_3^- in DMSO at 100°. Furazanobenzothiadiazole (22) was derived from 18 by deoxygenation with $P(OEt)_3$.

Scheme II



†A preliminary report on these compounds has appeared.[10]

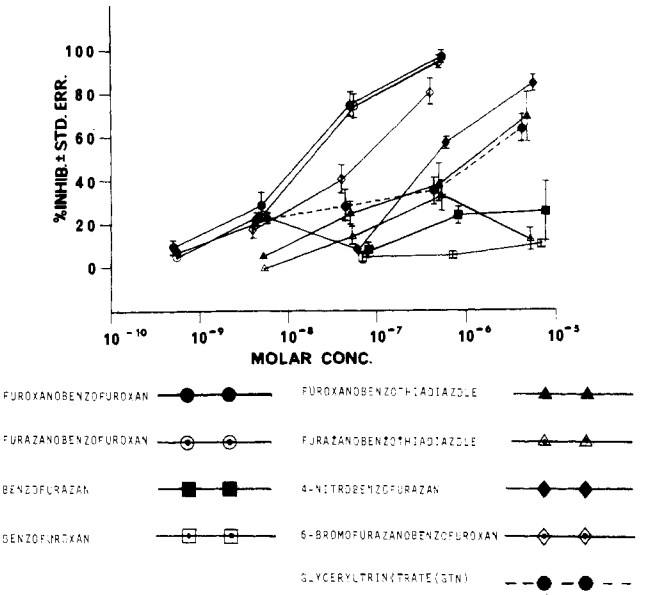


Figure 1. Inhibition of electrical stimulation in rabbit artery by drugs.

Results

The inhibitory effects of GTN, benzofurazan, benzofuroxan, 4-nitrobenzofurazan, furazanobenzofuroxan, furoxanobenzothiadiazole, furazanobenzothiadiazole, and 6-bromofurazanobenzofuroxan on the responses of the rabbit ear artery elicited by electrical stimulation are shown in Figure 1.

Furazanobenzofuroxan (4, X = O), furoxanobenzofurazan (5), and 6-bromofurazanobenzofuroxan (14) are the most active members of the group and more potent than GTN. 4-Nitrobenzofurazan has moderate activity, whereas the parent systems benzofurazan (1) and benzofuroxan (2) are relatively inactive.

Furoxanobenzothiadiazole (4, X = S) shows activity intermediate between 4-nitrobenzofurazan and benzofurazan and is similar to GTN in this regard. Removal of the *N*-oxide function from furoxanobenzothiadiazole (4, X = S) to give furazanobenzothiadiazole (3, X = S) results in a marked loss of activity. The action of 4-nitrobenzofurazan was irreversible; in contrast, the inhibitory effect of the tricyclics 3–5 was generally partially reversed within 10 min of termination of infusion through the artery.

These compounds which were active on the isolated rabbit ear artery preparation were also active as hypotensive agents in the spinal cat (Table I). Benzofurazan and benzofuroxan were inactive and 4-nitrobenzofurazan exhibited slight activity at the dose levels used. The most active compound examined, furoxanobenzofuroxan, exhibited a potent depressor effect with a rapid onset and a short (2–3 min) duration of action. A similar onset and duration was observed with the other active members of the series.

Discussion

In both the perfused rabbit ear artery preparation and spinal cat preparation furazanobenzofuroxan, furoxanobenzofuroxan, and 6-bromofurazanobenzofuroxan were more active than the bicyclic heterocycles, benzofurazan and benzofuroxan. However, the introduction of a NO_2 group into the 4 position of benzofurazan increases activity relative to the parent molecule.

The presence of additional polarized N-O groupings on

Table I. Effect of Substituted Benzofurazans on Blood Pressure of the Spinal Cat

Compound	Dose, μg/kg	Change in blood pressure, mm
Benzofurazan (1)	20	0
	200	0
Benzofuroxan (2)	20	0
	200	0
4-Nitrobenzofurazan	20	0
	200	−10
Naphthofuroxan	20	−6
	200	−50
Furazanobenzofuroxan	4	−22
(4, X = O)	25	−32
Furoxanobenzofuroxan	0.2	−20
(5)	1	−27
	5	−31
	25	−35
Glyceryl trinitrate	2	−18
(GTN)	5	−25

the benzofurazan system thus appeared to be an important factor in determining the vasodilatory action of this series. This conclusion was reinforced by the finding that the sulfur analogs, furazanobenzothiadiazole (**3**, X = S) and furoxanobenzothiadiazole (**4**, X = S), are less active than either 4-nitrobenzofurazan or furoxanobenzofuroxan.

The potent vasodilatory properties of furoxanobenzofuroxan (**5**) prompted a more thorough pharmacological investigation of this compound.‡ These studies indicated that **5** had a spectrum of pharmacological activity similar to glyceryl trinitrate (GTN).

A comparison of the planar furoxanobenzofuroxan molecule with GTN revealed some remarkable structural similarities. If the flexible GTN molecule is orientated with the nitro groups in their most extended positions as would undoubtedly result from internal polar NO_2 group repulsions and the furoxanobenzofuroxan structure superimposed, then the result is a "map" with two cationic and four anionic centers common to both molecules. The finding that **5** was more potent than GTN in the pharmacological systems used suggests that the planar or near-planar arrangement of these ionic centers is beneficial to the vasodilator activity of these compounds. The third nitro group of GTN, which at first sight does not appear necessary for binding, undoubtedly is of value in maintaining the other two nitro groups in the correct orientation relative to each other.

6-Bromofurazanobenzofuroxan was of similar potency *in vitro* (Figure 2) with furoxanobenzofuroxan (**5**) over the higher dose range suggesting that hydrophobic type bonding was possibly an unimportant factor in determining vasodilatory effects in these systems, although at concentrations less than 10^{-8} (untested) this may not be true. It is clear, therefore, that the correct orientation of positive and negative centers is the dominant factor in determining the vasodilatory effect of these compounds.

Experimental Section

Pharmacological Methods. 1. Isolated Rabbit Ear Artery. A segment of the central artery of the rabbit ear was set up as described by Gay, Rand, and Ross.[12] The preparation was perfused with a modified Krebs–Henseleit solution (NaCl 6.9, KCl 0.35, $CaCl_2$ 0.28, $MgSO_4 \cdot 7H_2O$ 0.11, KH_2PO_4 0.14, dextrose 2.0, $NaHCO_3$ 2.1 g/l.). The periarterial sympathetic nerves were stimulated by means of bipolar platinum electrodes placed around the artery using 1-msec[2] nerve pulses at a frequency of 5 Hz and supramaximal voltage. Changes in perfusion pressure were measured with a Statham pressure transducer and recorded

‡B. Everitt, P. B. Ghosh, and N. Hacket, paper in preparation.

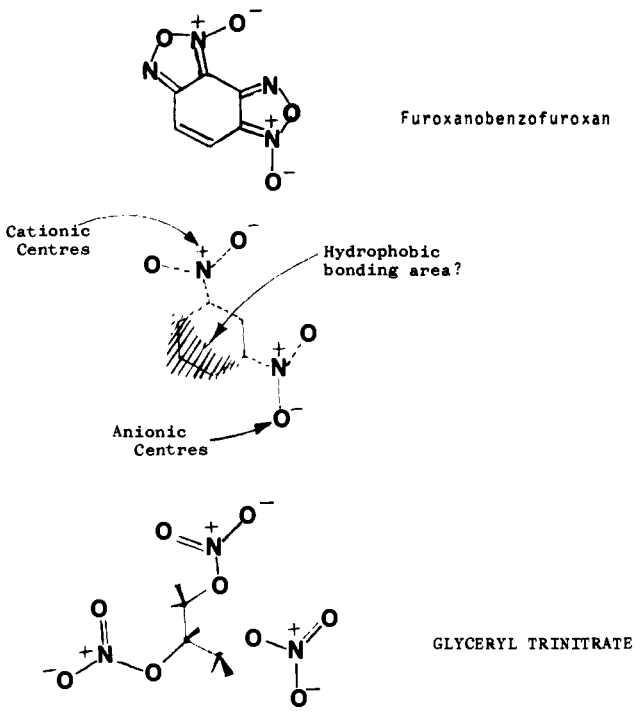


Figure 2.

on a Brush Mark 250 recorder. Bursts of stimuli were applied for 10 sec every 2 min until constant control responses were obtained. Drugs were dissolved in Krebs–Henseleit solution and infused intraluminally. Infusions were continued until three constant responses to electrical stimulation were obtained. The mean of these three responses was expressed as a percentage of the mean of the three control responses. The responses were allowed to return to normal or a constant level before the effects of a second concentration of drug were investigated.

2. Blood Pressure of the Spinal Cat. A cat weighing 2 kg was anaesthetized with Et_2O and then made spinal using the method of Burn.[13] Blood pressure was recorded from a femoral artery. Doses of each compound were administered intravenously *via* the femoral vein at two or more levels and changes in blood pressure were measured with a Statham pressure transducer and a Beckman dynograph recorder.

A concentrated (1 mg/ml) solution was prepared of each compound using 5% DMSO in water. This was diluted to the required concentration with saline or Krebs–Henseleit solution. A 5% DMSO solution did not produce an observable effect in either experimental procedure.

Stock solutions of GTN (0.1 or 1 mg/ml) in the appropriate physiological solution were prepared from an alcoholic solution (10 mg/ml in 90% ethanol) by taking a suitable aliquot and removing the ethanol with a stream of dry nitrogen.

Chemical Methods. Microanalysis was performed by the CSIRO Microanalytical Service, Melbourne.

Furoxanobenzofuroxan (5). 5-Chloro-4-nitrobenzofuroxan[8] (25.0 g, 0.116 mol) in H_2O–MeOH (1:1, 120 ml) was treated dropwise at 0° with NaN_3 (10.0 g, 0.153 mol) in H_2O (40 ml) and MeOH (80 ml) over 10 min. The solution was then allowed to attain room temperature and stirred for 16 hr.

Removal of the solvent *in vacuo* and dilution of the residue with H_2O (220 ml) precipitated the crude **5** which was collected, washed with H_2O (150 ml), and crystallized from EtOH (160 ml) to yield pure furoxanobenzofuroxan (**5**, 10.8 g, 48%) as pale yellow needles, mp 95–96° (lit.[8] mp 94–95°). Mother liquors on evaporation yielded a further 2.7 g (12%) of product.

Furazanobenzofuroxan (4, X = O). This compound was prepared according to the literature procedure,[8] mp 52–58° (lit.[8] mp 50–60°).

4,6-Dibromo-2-nitroaniline (7). *o*-Nitroaniline (Fluka Chemical Co.) was brominated in AcOH according to the procedure of Jackson and Russe,[14] mp 127–128° (lit.[14] mp 127–128°).

4,6-Dibromo-2-nitrophenyl Azide (8). 4,6-Dibromo-2-nitroaniline (**7**, 49.6 g, 0.167 mol) in AcOH (500 ml) was added with vigorous stirring to nitrosylsulfuric acid, prepared from $NaNO_2$ (15.0 g, 0.217 mol) in H_2SO_4 (200 ml, sp gr 1.84) at 0°. After 30 min of stirring at this temperature the mixture was added to crushed ice

(500 g) and added to a solution of NaN_3 (50 g, 0.77 mol) in H_2O (500 ml). The resulting pale yellow precipitate was collected, washed (H_2O), and crystallized from EtOH to afford the azide 8 (42 g, 77%) as pale yellow needles, mp 50–51° (lit.[15] mp 52–53°).

4,6-Dibromobenzofuroxan (9). The azide 8 (42 g, 0.13 mol) was refluxed in AcOH (250 ml) for 6 hr. Dilution with H_2O (750 ml) and recrystallization from EtOH (charcoal) afforded the dibromo compound 9 (24 g, 63%) as yellow plates, mp 92–93° (lit.[15] mp 92.5–93°).

5,7-Dibromo-4-nitrobenzofuroxan (10). The dibromo compound (5.88 g, 0.02 mol) in H_2SO_4 (50 ml, sp gr 1.84) at 0° was treated with stirring with HNO_3 (1.5 g, sp gr 1.5, 0.023 mol) in H_2SO_4 (10 ml). The mixture was warmed to 60° for 5 min, cooled to 20°, and allowed to stand for 30 min. Addition to crushed ice (200 g) precipitated the nitro compound 10 (4.2 g, 62%) which was recrystallized from EtOH as pale yellow plates, mp 143–145°. *Anal.* ($C_6HN_3O_4Br_2$) C, H, N.

Attempted Reaction of 4-Nitro-5,7-dibromobenzofuroxan with Sodium Azide. The dibromo compound 10 (4.0 g, 0.011 mol) in Me_2CO (45 ml) was treated at 20° with NaN_3 (1.0 g, 0.015 mol) in H_2O (6 ml) and MeOH (6 ml). The temperature rose to 50° and N_2 was evolved. After 1 hr of standing at room temperature the yellow solution was diluted with H_2O (100 ml) whereupon a brown oil deposited. Attempts to induce crystallization by the standard procedures were unsuccessful.

Repeating the above procedure at 0–5° and maintaining the temperature below 15° afforded a yellow solid which exhibited the characteristic N_3 absorption at 2160 cm^{-1}. Thermolysis of this material in refluxing AcOH gave a brown oil from which only starting material was isolated.

4,6-Dibromobenzofurazan (12). 4,6-Dibromobenzofuroxan (9, 11.84 g, 0.04 mol) in absolute EtOH (200 ml) and $P(OEt)_3$ (10.0 g, 0.06 mol) was refluxed for 3 hr. Removal of the EtOH *in vacuo* left a pale yellow oil which was shaken with H_2O (200 ml) for 30 min. The solid that separated was collected, washed with H_2O (200 ml), and crystallized from H_2O–EtOH (1:10) to yield the dibromobenzofurazan (12, 9.0 g, 81%) as pale yellow needles, mp 70–71° (lit.[15] mp 71.5–72°).

5,7-Dibromo-4-nitrobenzofurazan (13). The dibromo compound 12 (10.0 g, 0.035 mol) in H_2SO_4 (50 ml, sp gr 1.84) was treated with HNO_3 (2.5 g, 0.04 mol, sp gr 1.5) in H_2SO_4 (10 ml) at 0°. The temperature was allowed to rise to 40° and then raised to 60° for 1 hr. Addition to crushed ice (200 g) precipitated the nitro compound as a yellow solid which was recrystallized from EtOH to afford 13 (8.1 g, 70%) as yellow needles, mp 113–114°. *Anal.* ($C_6HBr_2N_3O_3$) C, H; N: calcd, 12.93; found, 12.39.

6-Bromo-4,5-furazanobenzofuroxan (14). Dibromo-4-nitrobenzoburazan (13, 3.23 g, 0.01 mol) in Me_2CO (40 ml) was treated with NaN_3 (1.0 g, 0.015 mol) in H_2O (5 ml) and MeOH (5 ml) at 0° such that the temperature did not exceed 10°. After 24 hr of standing at 0.5° the yellow solution was extracted with Et_2O. Removal of the solvent *in vacuo* afforded a yellow oil (3.0 g) which solidified on standing (mp 65–70°, N_3 stretch at 2120 cm^{-1}). Refluxing this material in AcOH for 30 min, followed by addition of ice water (50 ml) afforded a yellow precipitate which was collected, washed (H_2O), and crystallized from EtOH to yield bromofurazanobenzofuroxan (14, 1.2 g, 46%) as cream needles which sublimed at 100° (0.1 mm) as colorless needles, mp 103–104°. *Anal.* ($C_6HN_4O_3Br$) C, H, N.

5-Nitrobenzothiadiazole (16) was prepared from 4-nitro-1,2-phenylenediamine (15) as described in the literature method,[16] mp 127–128° (lit.[16] mp 128°).

4-Amino-5-nitrobenzothiadiazole (17). 5-Nitrobenzo-2,1,3-thiadiazole (20.0 g, 0.11 mol) in hot EtOH (1000 ml) was rapidly cooled with stirring to 30°. NH_2OH·HCl (40.0 g, 0.57 mol) was then added, followed by a saturated solution of KOH in EtOH (400 ml). Acidification (12 *N* HCl) and collection of the precipitate, followed by washing (H_2O, 500 ml), afforded the nitroamine 17 (20 g, 92%) as a yellow powder, mp 238–240° (lit.[9] mp 246°).

Furoxanobenzothiadiazole (18). Method A. The nitroamine 17 (1.0 g, 0.005 mol) in KOH–EtOH (10%, 750 ml) was treated with vigorous shaking at 0° with freshly prepared aqueous NaOCl solution (100 ml, 0.2 mol available Cl). Reduction of the volume of solvent *in vacuo* to *ca.* 300 ml, followed by the addition of H_2O (200 ml), precipitated a buff solid which was collected and crystallized from EtOH to yield 18 (0.2 g, 20%) as cream needles, mp 144–145°. *Anal.* ($C_6H_2N_4O_2S$) C, H, N.

5-Chlorobenzothiadiazole (20). This compound was prepared from 4-chloro-1,2-phenylenediamine (19) according to the literature procedure, mp 56–57° (lit.[17] mp 57.7°).

5-Chloro-4-nitrobenzothiadiazole (21). To stirred 5-chlorobenzothiadiazole (20, 8.5 g, 0.05 mol) in H_2O (50 ml, sp gr 1.84) at 0° was added dropwise HNO_3 (3.6 g, 0.05 mol, sp gr 1.5) in H_2SO_4 (5 ml, sp gr 1.84). After standing for 3 hr at 0°, the temperature was raised to 45° for 10 min, cooled, and added to crushed ice (200 g). Crystallization from Me_2CO–DMF (10:1) afforded the nitro derivative 21 (8.5 g, 79%) as colorless needles, mp 144–145° (lit.[11] mp 144–145°).

Furoxanobenzothiadiazole (18). Method B. 5-Chloro-4-nitrobenzothiadiazole (21, 8.0 g, 0.037 mol) in DMSO (75 ml) at 60° was treated with shaking with NaN_3 (3.0 g, 0.46 mol) in H_2O (10 ml). The temperature rose to 100° and N_2 liberation occurred. After the reaction had subsided (5 min) the temperature was raised to 125° for 3 min and the solution poured onto crushed ice (200 g). The resulting precipitate was collected and twice crystallized from Me_2CO (charcoal) to yield the tricyclic 18 (4.0 g, 55%) as buff needles, mp 144–145°. Ir spectra and analysis were identical with material prepared by method A.

Furazanobenzothiadiazole (22). Furoxanobenzothiadiazole (18, 1.0 g, 0.005 mol) was refluxed for 1 hr with $P(OEt)_3$ (20 ml). Hydrolysis of excess $P(OEt)_3$ with boiling HCl (20 ml, 2 *N*) gave, on cooling, crude 22. Crystallization from EtOH (charcoal) afforded the desoxy compounds as pale yellow plates (0.6 g, 62%), mp 130–131°. *Anal.* ($C_6H_2N_4OS$) C, H, N.

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