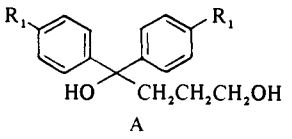
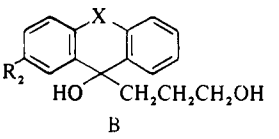
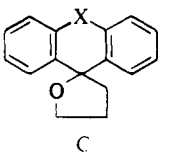
Table I. 1,1-Disubstituted 1,4-Butanediols (IV) and 2,2-Disubstituted Furans (V)



A



B

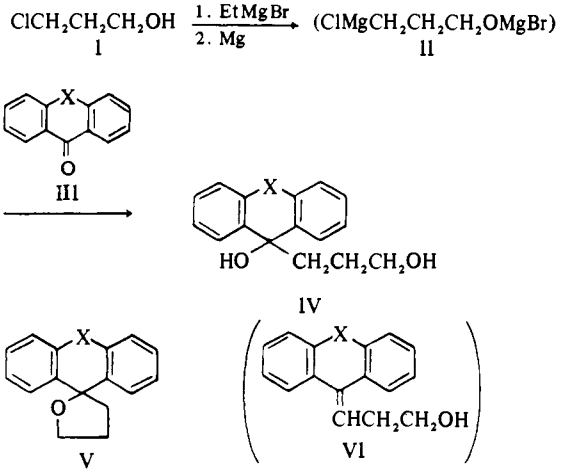


C

Type	X	R_1	R_2	Yield, %	Mp, °C[a]	Formula	Analyses[b]
A		H		q[c]	107–108[d]	$C_{16}H_{18}O_2$	
A		Cl		q	122–123	$C_{16}H_{16}Cl_2O_2$	C, H, Cl
B	CH_2CH_2		H	q	80–88[e]	$C_{18}H_{20}O_2$	
B	CH_2CH_2		CH_3	q	51–55	$C_{19}H_{22}O_2$	C, H
B	CH_2CH_2		Cl	q	Oil[f]	$C_{18}H_{19}ClO_2$	
B	$C(CH_3)_2$		H	95	138	$C_{19}H_{22}O_2$	C, H
B	S		Cl	95	Oil[g]	$C_{16}H_{15}ClO_2S$	
C	O[h]		H	q	83–84	$C_{16}H_{14}O_2$	C, H
C	O		Cl	q	104–105	$C_{16}H_{13}ClO_2$	C, H, Cl

[a]Melting points are uncorrected. [b]Analytical values represented by symbols of the elements are within ±0.4% of the theoretical values. [c]q means that the reaction proceeded almost quantitatively. [d]Reported mp 108° (ref 5). [e]Reported mp 82–86.5° (ref 2). [f]This compd was determined by the comparison of its ir and nmr spectra with those of X = CH_2CH_2 and by appropriate procedures after transformation into related 1-pyrroline (*cf.* ref 1). [g]This compd was characterized by the ir absorption at 3300 cm^{-1}, showing the presence of OH, and uv absorption; λ_{max} (95% EtOH) 270 mμ (log ε 4.23) (*cf.* ref 4). [h]Spectral data are expressed in Experimental Section.

Scheme I



the presence of a new Grignard reagent (II) as an intermediate. When this method was applied to several ketones, related diols were obtained, mostly in high yield, and they are listed in Table I. In the xanthene series, however, related diols (IV, X = O) were not stable enough to permit their recognition by techniques other than ir spectra and accordingly changed readily into the corresponding dehydration products. Their spectral data demonstrated that the dehydration products are not olefinic alcohols (VI) but the corresponding tetrahydrofurans (V). Their spectra showed no absorption characteristic of hydroxyl groups (ir) or olefinic protons (nmr). It is of interest that diols IV (X = O) exclusively afforded the corresponding furans[4] in good yield under mild conditions, in contrast to cases of IV (X = CH_2CH_2)[2] and 4,4-diphenyl-1,4-butanediol,[5] where mixtures of olefinic alcohols and furans were produced under elaborate conditions.

Experimental Section

General Procedure for Reaction of II and III. To an EtMgBr soln (prepd from 0.22 mole of EtBr, 0.20 g-atom of Mg, and 98 ml of THF) cooled in an ice bath, 0.2 mole of I was added dropwise with stirring. After the addn was complete, this mixt was stirred for 0.5 hr, and 0.20 g-atom of Mg was further added. The stirring was continued at 60° until the Mg disappeared nearly completely. To this mixt a soln contg 0.10 mole of ketone III in 73 ml of THF was added dropwise and refluxed for 3 hr with stirring. Then the reaction mixt was cooled in an ice bath and hydrolyzed with satd NH_4Cl. THF was evaporated under reduced pressure and the residue was extd with Et_2O. The Et_2O ext was dried and concd to give a crude diol IV and/or furan V.

Spectra† of spiro(tetrahydrofuran-2,9′-xanthene) (IV, X = O) showed nmr ($CDCl_3$, TMS) δ 1.8–2.4 (m, 4, CCH_2CH_2CO), 4.36 (t, 2, *J* = 7 Hz, OCH_2C), 7.0–7.7 (m, 8, aromatic protons; $\lambda_{max}^{95\% EtOH}$ 238.5 mμ (log ε 4.23), 282.5 (3.49), and 320 (3.20).

Acknowledgment. We are indebted to T. Kanaya for his technical assistance, to H. Manabe for the spectra data, and to T. Ikeda and his associates for the microanalyses.

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†Nmr spectra were determined at 60 MHz on a Varian Model A-60 spectrometer.

Synthesis and Anthelmintic Activity of Some Sulfonylbenzimidazoles

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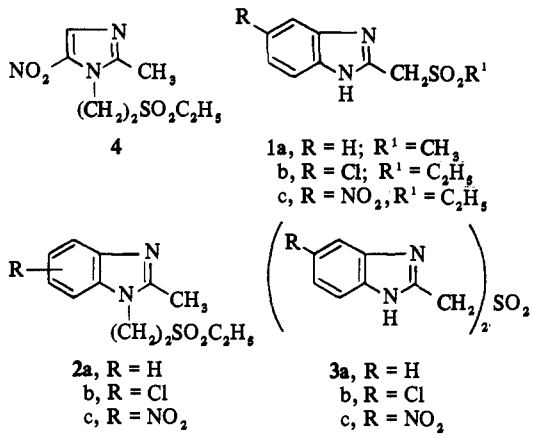
Three different types of substituted sulfonylbenzimidazoles were synthesized for evaluation of their anthelmintic activity. Whereas the 1- and 2-substituted sulfonylbenzimidazoles were derived from peracid oxidation of the corresponding sulfides, the symmetric sulfones were obtained from acid-catalyzed cyclization of *o*-phenylenediamines with sulfonyldiacetic acid. Of these, only the 2-substituted sulfonylbenzimidazoles showed marginal anthelmintic activity.

The well-documented anthelmintic activity of several

benzimidazole derivatives[1] encouraged us to synthesize the sulfonylbenzimidazoles **1**, **2**, and **3** as potential anthelmintics. The recent publication[2] describing ethyl[2-(2-methyl-5-nitro-1-imidazolyl)ethyl]sulfone [tinidazole (**4**)] as a potent antiprotozoal agent prompts us to report our findings.



4

1a, R = H; $R^1 = CH_3$
b, R = Cl; $R^1 = C_2H_5$
c, R = NO_2, $R^1 = C_2H_5$

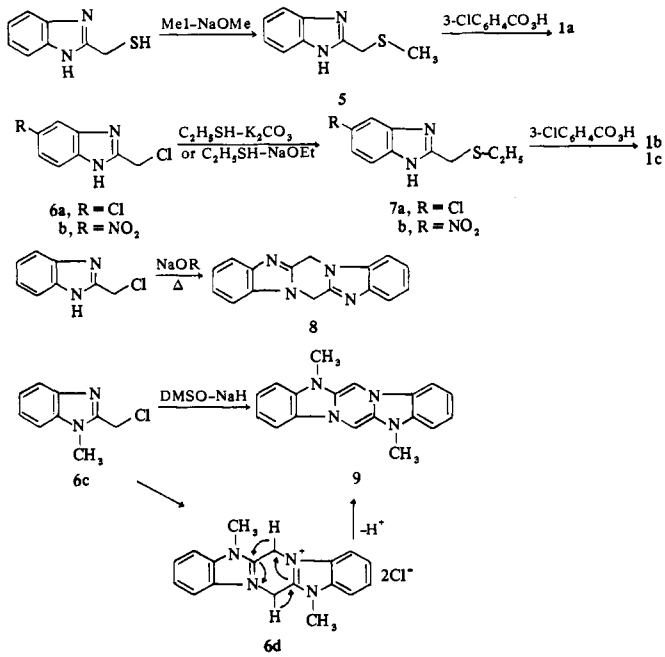
2a, R = H
b, R = Cl
c, R = NO_2

3a, R = H
b, R = Cl
c, R = NO_2

Chemistry. The synthesis of sulfonylbenzimidazoles of type **1** is outlined in Scheme I.

Alkylation of 2-benzimidazolemethanethiol with MeI-NaOMe in MeOH furnished the sulfide **5**, which upon oxidation with *m*-chloroperbenzoic acid gave **1a**. Reaction of chloromethylbenzimidazoles **6a** and **6b** with ethylmercaptan and alcoholic NaOEt, or preferably aqueous K_2CO_3 as base, led to the formation of sulfides **7a** and **7b**, respectively, which without further purification were oxidized analogously to yield the sulfonylbenzimidazoles **1b** and **1c**. The direct introduction of the sulfoxide side chain was also attempted. Since 2-chloromethylbenzimidazole is known to undergo self-condensation under basic conditions to the piperazine derivative[3] **8**, we chose to

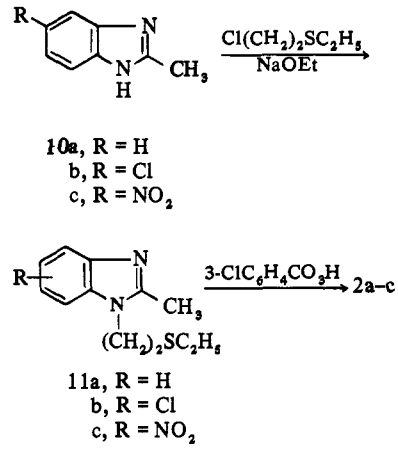
Scheme I



treat 1-methyl-2-chloromethylbenzimidazole (**6c**) with DMSO-NaH. The only solid product isolated from the dark reaction mixture showed a rather simple nmr spectrum ($CDCl_3$) devoid of the anticipated chemical shifts of a sulfoxide and revealed a 3-proton singlet at δ 3.93, a 3-proton multiplet at 7.16–7.49, a 1-proton multiplet at 7.67–8.00, and a 1-proton singlet at 8.05. Furthermore, its mass spectrum (M^+ 288) indicated it to be a halogen-free, self-condensation product of the starting material. Based on these data, we have assigned structure **9** for this product, which could arise from a double-proton abstraction of the initially formed quaternary salt, **6d**.

The synthesis of 1-substituted sulfonylbenzimidazoles **2** is depicted by Scheme II. Alkylation of 2-methylbenzimidazoles **10** with ethyl 2-chloroethyl sulfide yielded the sulfides **11**. Peracid oxidation of **11** furnised **2**. Alkylation of **10b** and **10c** was anticipated to furnish a mixture of 5 and 6 isomers of **11b** and **11c**. In the case of **10b** the mixture could be successfully separated by fractional crystn from Et_2O. Though the nmr spectrum (Table I) of the major fraction (mp 96°) differed in chemical shifts from that of the minor fraction (mp 105°), no clear-cut assignment was possible.

Scheme II

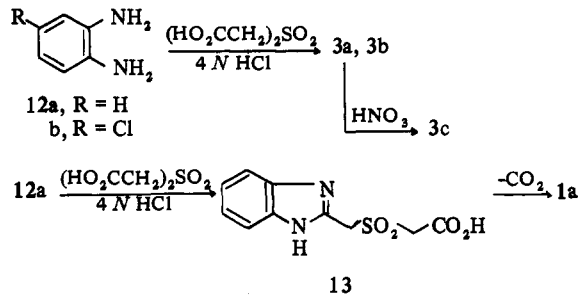


10a, R = H
b, R = Cl
c, R = NO_2

11a, R = H
b, R = Cl
c, R = NO_2

The preparation of the sulfonylbisbenzimidazoles **3** was accomplished as indicated in Scheme III. Reaction of *o*-phenylenediamines **12**, with sulfonyldiacetic acid in 4 *N* HCl yielded sulfones **3a** and **3b**. Nitration of **3a** furnished **3c**. As one would expect, the presence of the sulfonyl grouping in **3** markedly increased the acidity of the neighboring methylene hydrogens. Fifty per cent of the CH_2 signal in the nmr could be exchanged by simple addition of D_2O. Interestingly when the synthesis of **3a** was attempted, using the same quantities of reactants but 40% more 4 *N* HCl, the predominant product isolated was **1a**. This unexpected result can be explained by first postulating the formation of the sulfonylacetic acid **13** which upon decarboxylation yields **1a**.[4]

Scheme III



12a, R = H
b, R = Cl

13

Table I. Nmr[a] Data of 1-[2-(Ethylthio)ethyl]-2-methyl-5(and 6)nitrobenzimidazoles (11c)[a]

	CH_3CH_2	CH_3CH_2	2-CH_3	NCH_2CH_2S	NCH_2CH_2S	4-(or 7)	5-(or 6)	7-(or 4)
105° isomer	1.10(t)7[b]	2.51(q)7	2.65(s)	2.93(t)7	4.49(t)7	7.76(d)9	8.12(q)9;2	8.40(d)2
96° isomer	1.15(t)8	2.54(q)8	2.68(s)	2.99(t)8	4.45(t)8	7.67(d)9	8.05(q)9;2	8.56(d)2

[a]DMSO-d_6. [b]Coupling constants in hertz.

Biological Evaluation. Compounds were tested for anthelmintic activity in mice experimentally infected with *Nematospiroides dubius* and *Hymenolepis nana*. Ten female mice, 16-18 g, were infected with approximately 30 larvae of *N.dubius* and 500 embryonated *H.nana* eggs. Three weeks after infection, they were fed Rockland mouse diet containing 0.2% of the test compound for 4 days. Using the crush-plate technique, the small intestine was examined to determine the worm burden. Nontreated controls and a positive control using parbendazole as standard were run with each test. Compounds of type **1** were 34–41% active against *N.dubius*. The best compound in the series was **1c**, with 41% clearance. Compounds of type **3** were inactive and those of type **2** showed 10–25% activity against *N.dubius*. None of the compounds tested was active against *H.nana*. Parbendazole at 0.05% × 4 days gave complete clearance of *N.dubius* and *H.nana*.

Experimental Section

Melting points were determined in capillary tubes on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Proton nmr spectra were obtained on a Varian A-60 instrument. For chromatography neutral alumina (Woelm activity IV) was used. Combustion analyses were in accord with the calcd percentages within ±0.4% of theory.

2-[(Methylsulfonyl)methyl]benzimidazole (1a). A. A mixt of 20 g (0.11 mole) of 2-benzimidazolemethanethiol, 14.6 g (0.27 mole) of NaOMe, and 8 ml (0.13 mole) of MeI was dissolved in 1 l. of MeOH and refluxed for 1 hr. Upon evapn, the residue was treated with H_2O and extd with Et_2O. The combined Et_2O fractions were dried ($MgSO_4$) and evapd *in vacuo* to give a solid that was recrystd (EtOAc) to furnish 13 g of the sulfide **5**, mp 151–153°.

B. To an ice-cold, stirred soln of 5 g (28 mmoles) of **5** in 200 ml of $CHCl_3$ there was added 12 g (59 mmoles) of 85% *m*-chloroperbenzoic acid (MCPBA). The mixt was stirred for 10 min at room temp and then dild with 50 ml of H_2O, and the pH was adjusted to 8.0 with satd K_2CO_3 soln. The product was exhaustively extd with $CHCl_3$, and the combined exts were washed with H_2O until neutral. Evapn of the dried solvent ($MgSO_4$) gave the cryst sulfone **1a**. Two crystns (Et_2O) yielded 2.4 g of analytical sulfone, mp 196–198°. *Anal.* ($C_9H_{10}N_2O_2S$) C, H, N, S.

2-[(Ethylsulfonyl)methyl]-5-chlorobenzimidazole (1b). A. A soln of 8 g (46 mmoles) of **6a** in 300 ml of MeOH was added to a soln of 6.4 g (60 mmoles) of Na_2CO_3 and 3.6 g (58 mmoles) of ethyl mercaptan in 600 ml of H_2O and refluxed for 30 min. Upon cooling, the sulfide was extd with Et_2O. Evapn of the dried ext furnished 9 g of crude, oily **7a**.

B. To an ice-cold soln of 4.5 g of the crude sulfide **7a** in 50 ml of $CHCl_3$, there was added 10.6 g of MCPBA. After 30 min of stirring at room temp the mixt was worked up under conditions similar to 1a. Two crystns (Me_2CO–Et_2O) furnished 1 g of pure 1b, mp 197–199°. *Anal.* ($C_{10}H_{11}ClN_2O_2S$) C, H, N.

2-[(Ethylsulfonyl)methyl]-5-nitrobenzimidazole (1c) was prepared analogously to 1b, mp 208–210° (Me_2CO). *Anal.* ($C_{10}H_{11}N_3O_4S$) C, H, N.

5,12-Dimethyl-5*H*,12*H*-pyrazino[1,2-*a*:4,5-*a*']bisbenzimidazole (9). To 0.5 g of NaH there was added 20 ml of dry DMSO (distd from CaH_2) under N_2, and the mixt was stirred and heated to 70–75° until the H_2 evolution had ceased. After cooling, a soln of 3.5 g of 1-methyl-2-chloromethylbenzimidazole in 15 ml of DMSO was added. The reaction mixt became exothermic and the stirring was continued for 2 hr. Water was added to the sepn of a tar, which was chromatogd. Elution with $CHCl_3$ furnished a pink solid which was crystd from $CHCl_3$–Et_2O to give **9**, mp 310–312°, mass spectrum *m/e* 288 (M^+). *Anal.* ($C_{18}H_{16}N_4$) N.

1-[2-(Ethylsulfonyl)ethyl]-2-methylbenzimidazole (2a). A. To 100 ml of abs EtOH there was added cautiously 1.5 g (62 mmoles) of NaH and, a few min later, 6.6 g (50 mmoles) of 2-methylbenzimidazole and 7.4 g (59 mmoles) of ethyl 2-chloroethyl sulfide. After 2 hr of reflux, the solvent was evapd, H_2O was added, and the product was extd with Et_2O. Evapn of the solvent furnished an oil that, upon trituration with a little Et_2O, yielded 0.4 g of 2-methylbenzimidazole, which was filtered off. The filtrate was chromatogd. Elution with $CHCl_3$–MeOH (1:1) yielded, upon evapn of the solvent, 3.6 g of oily sulfide, which without further purification was used in the oxidation step below.

B. To a soln of 3.6 g of the above sulfide in 100 ml of $CHCl_3$ there was added in portions, and with external ice-bath cooling, 6.6 g of MCPBA. The mixt was stirred at room temperature for an addnl 30 min. The $CHCl_3$ layer was washed repeatedly with 10% K_2CO_3 soln. The dried organic layer, on evapn, yielded an oil. Trituration with Et_2O-petroleum ether (30–60°) furnished 0.6 g of product. The filtrate was chromatogd. Elution with $CHCl_3$–Et_2O (7:3) and later with $CHCl_3$ furnished the product, which was combined with the first crop. Crystn ($CHCl_3$–Et_2O) yielded 1.8 g of 2a, mp 99–101°. *Anal.* ($C_{12}H_{16}N_2O_2S$) C, H, N.

5(and/or 6)-Chloro-1-[2-(ethylsulfonylethyl]-2-methylbenzimidazole (2b) was prepared analogously to 2a, mp 119–120° ($CHCl_3$–Et_2O). *Anal.* ($C_{12}H_{15}ClN_2O_2S$) C, H, N.

1-[2-(Ethylthio)ethyl]-2-methyl-5(and 6)-nitrobenzimidazole (11c). Alkylation of 6.8 g (37 mmoles) of 2-methyl-5-nitrobenzimidazole with ethyl 2-chloroethyl sulfide analogously to 11b yielded, on work-up, a solid that was extd with 400 ml of hot Et_2O. The undissolved solid was filtered off to furnish, after crystn (Et_2O), 1 g of 11c, mp 105–106°. *Anal.* ($C_{12}H_{15}N_3O_2S$) C, H, N.

Concentration of the above Et_2O ext to 100 ml final vol gave 5.5 g of isomeric 11c, mp 96°. *Anal.* ($C_{12}H_{15}N_3O_2S$) C, H, N.

1-[2-(Ethylsulfonyl)ethyl]-2-methyl-5(or 6)-nitrobenzimidazole (2c). Oxidation of 4.5 g of the major isomer 11c (mp 96°) with MCPBA furnished 3.5 g of 2c, mp 151–152°. *Anal.* ($C_{12}H_{15}N_2SO_4$) C, H, N, S.

2,2'-(Sulfonyldimethylene)bisbenzimidazole (3a). A mixt of 12 g (111 mmoles) of 12a, 10 g (55 mmoles) of sulfonyldiacetic acid, and 60 ml of 4 *N* HCl was refluxed for 30 hr. On cooling, the HCl of 3a sepd. Neutralization furnished the free base, which on crystn (MeOH) gave 3.4 g of 3a, mp 295–296°. *Anal.* ($C_{16}H_{14}N_4O_2S$) C, H, N.

2,2'-(Sulfonyldimethylene)bis(5-chlorobenzimidazole) (3b). A mixt of 11.3 g (79 mmoles) of 4-chloro-*o*-phenylenediamine, 7 g (38 mmoles) of sulfonyldiacetic acid, and 60 ml of 4 *N* HCl was refluxed for 24 hr. Neutralization furnished a ppt, which was chromatogd. Elution with MeOH gave 3b which on crystn (MeOH) yielded 3 g of 3b, mp 281–283°. *Anal.* ($C_{16}H_{12}Cl_2N_4SO_2$) C, H, N.

2,2'-(Sulfonyldimethylene)bis(5-nitrobenzimidazole) (3c). A mixt of 6 g (18 mmoles) of 3a and 3.8 g (38 mmoles) of KNO_3 was slowly added to 55 ml of concd H_2SO_4 at such a rate to maintain a temp of 0–5°. After addn, the soln was stirred for 1 hr at room temp and then poured on ice. Neutralization with concd NH_3, furnished 3c, which was pptd twice from DMSO–H_2O to yield 3.7 g of 3c, mp 310°. *Anal.* ($C_{16}H_{12}N_6O_6S$) C, H, N.

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