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Notes

Pyridine Isosteres of the β-Adrenergic Antagonists, 2-(*p*-Nitrophenyl)-1-isopropylamino-2-ethanol and 3-(*p*-Nitrophenoxy)-1-isopropylamino-2-propanol†

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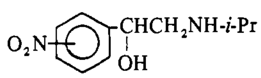
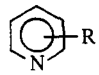
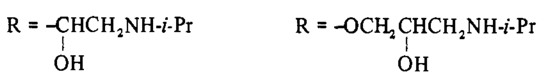
Structure-activity relationships (SAR) of cardiac β-adrenergic agonists and antagonists are of great current interest and are becoming clearer with newer understanding of the mode of action of adrenergic drugs.[1] Yet the structural criteria for agonism and antagonism are still elusive. As part of a general SAR program, the nitrobenzene ring of known β-antagonists[2] was replaced with the isosteric pyridine ring to ascertain whether these compounds would be bioisosteric as is often the case with this transformation.[3]



1a, ortho isomer
1b, meta isomer
1c, para isomer (INPEA)

The pyridine compounds selected were the following types





2a, α isomer
2b, β isomer
2c, γ isomer

3a, α isomer
3b, β isomer
3c, γ isomer

as these are the side chains known to confer β-adrenergic receptor antagonism to many aromatic ring systems.[4]

Chemistry. The syntheses of the three isomeric pyridyl isopropylaminoethanols from the known ω-bromo ketones followed the sequence shown in Scheme I. This is essentially the method of Friz[5] who prepared the 4-pyridyl isomer. The intermediate bromohydrins are unstable in alkaline solution forming deep colored products, presumably from condensation reactions. Decomposition was prevented by rapid conversion to the HCl salts. The alternate sequence involving reaction of the bromo ketone with isopropylamine, followed by $NaBH_4$ reduction, was not as satisfactory. The properties of the amino alcohols prepared are listed in Table I.

The synthetic approaches to the 2,3- and 4-pyridyl analogs of the 3-(nitrophenoxy)-1-isopropylamino-2-propanols were quite different and it was possible to prepare only the 4 isomer. From the reaction of 3-pyridol with epichlorohydrin, followed by excess i-$PrNH_2$, the expected pyridyl ether was not isolated but 1,3-diisopropylamino-2-propanol (see Experimental Section) and some unreacted 3-pyridol were. Recently Howe, *et al.*,[6] reported that reaction of the sodium salt of 3-pyridol with 1-chloro-3-(*N*-benzyl-*N*-isopropylamino)-2-propanol gave the betaine (**7**).

Scheme I

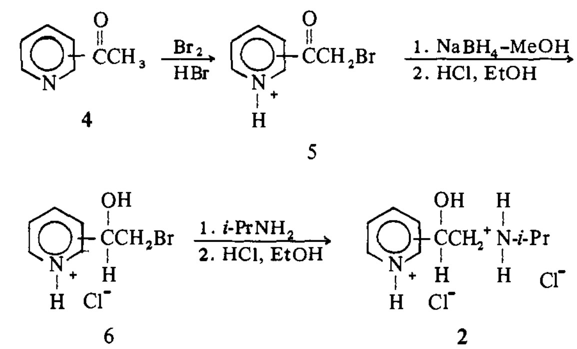
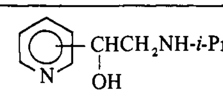
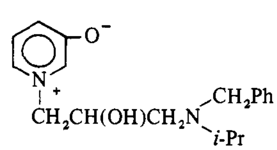


Table I



Compd	% yield (base)	Recrystn solvent (2HCl)	Mp, °C dec (2HCl)	Formula
2a	37	*i*-PrOH	153–156	$C_{10}H_{18}N_2OCl_2$[a]
2b	46	EtOH	162–164	
2c	73	EtOH-Et_2O	182–183[b]	

[a]*Anal.* C, H; H: calcd, 7.16; found, 7.63. [b]Lit.[5] 186° dec.



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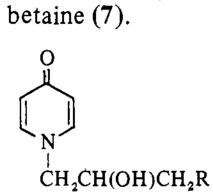

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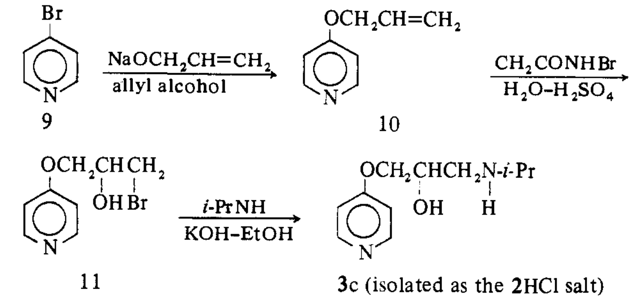
A similar reaction sequence involving 4-hydroxypyridine and epichlorohydrin followed by isopropylamine led only to N-substitution, giving 4-pyridone compounds of general structure **8**. Reaction of 4-hydroxypyridine with epichlorohydrin and Ag_2CO_3 in acetone also gave only ketone products in accord with the reported reaction of alkyl halides with the silver salt of 4-pyridol.[7] A successful synthesis of the 4-pyridyl analog is outlined in Scheme II.

For the addition of HOBr to the known 4-allyloxy ether,[8]

†Presented in part at the ASPET-Division of Medicinal Chemistry of the American Chemical Society Meeting, Burlington, Vt., Aug 22-26, 1971.

Scheme II



only the reaction of *N*-bromoacetamide in dilute sulfuric acid gave an adequate yield. Since it was known that the bromohydrin was a mixture of isomers, it was treated with isopropylamine in the presence of KOH to form the epoxide which would be expected to give a single amino alcohol. While ir and nmr spectra (see Experimental Section) do not completely eliminate the alternate structure it is felt that these data along with the large literature experience with such epoxides are indicative of the structure as written (3c).

The synthesis of the 2-pyridyl analog (3a) by the same route was abandoned because of the very low yields in the first step.

2-(*p*-Nitrophenyl)-1-isopropylamino-2-ethanol (INPEA) and its 2 and 3 isomers[2] were a gift from Dr. Pitambar Somani of this department.

Pharmacology. Methods. The change in chronotropic action of isolated spontaneously beating atria from young adult, pigmented guinea pigs was used to evaluate β-adrenergic activity. The technique was that described by the Edinburgh pharmacology staff.[9] Basal diastolic force was set at 1.0 g, and action was recorded *via* a Grass FT03c force transducer on a Grass polygraph. Data for dose-response curves were obtained by cumulative additions[10] at 3-min intervals. When propranolol was used to characterize β-receptor agonists it was allowed to be in contact with the atria for approximately 45 min before addition of the agonist under study.

Results

As can be seen in Table II all of the isopropylaminoethanols except 4-INPEA displayed agonist action.

Villa, *et al.*,[11] reported no agonist action on guinea pig atria for 2- and 4-INPEA and "low" agonism for the 3 isomer. The difference between our results and theirs can probably be attributed to the particular strain and/or age of the animals used, for we have noted that atria from older guinea pigs are significantly less responsive to β-agonists while atria from albino animals may show qualitatively different effects from those shown by atria of pigmented animals.[12]

Typical dose-response curves and their shift by propranolol are shown in Figure 1a-c.

Table II

Compd	Approx ia	Approx pD_2 [a]	Autoinhibition
1a	0.5	5.1	Yes
2a	0.6	4.9	Slight
1b	0.3	5.3	Yes
2b	0.6	5.8	No
1c			
2c	0.3	4.9	Yes

[a] Average of two dose-response runs.

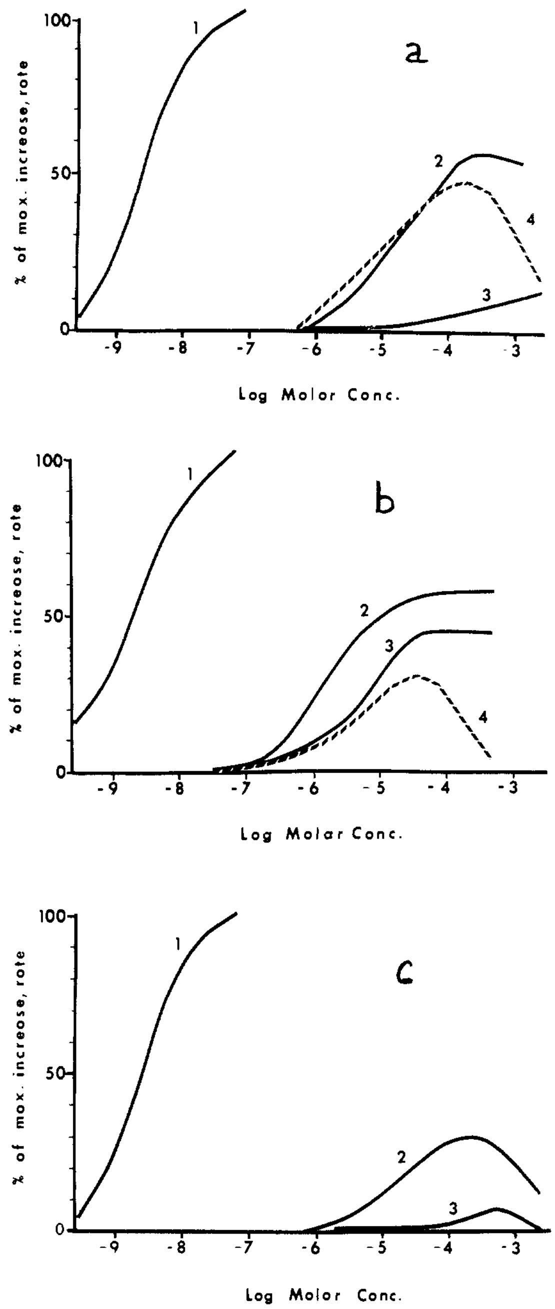


Figure 1. Cumulative log dose-response curves for the three pairs of isopropylaminoethanol isomers (pyridine and *p*-nitrobenzene) as β-agonists on guinea pig atria. In each set the curve 3 indicates a propranolol bath concn of 10^{-7} *M*. In Figure 1a-c curve 1 represents isoproterenol; curve 2 (a) **2a**, (b) **2b**, (c) **2c**; curve 3, propranolol plus (a) **2a**, (b) **2b**, (c) **2c**; and curve 4, (a) **1a**, (b) **1b**, and (c) unlabeled. In 1c the curve for 1c would be on the abscissa (intrinsic activity = 0).

While the 2- and 3-substituted isomer sets have some pharmacological resemblance the compounds are not identical in action and the 4-substituted pair differs markedly. It was anticipated that 2c would be a potent antagonist with essentially no agonist action; that it behaves as both a partial agonist and partial antagonist is seen from Figure 2.

To determine if the pyridine compounds are acting at the β-receptor the action of propranolol was studied. Tests with 10^{-7} *M* propranolol showed a significant shift of the dose-response curves to the right (Figure 1). However, the curves are not shifted parallelly and intrinsic activity was diminished by the propranolol making it impossible to calculate

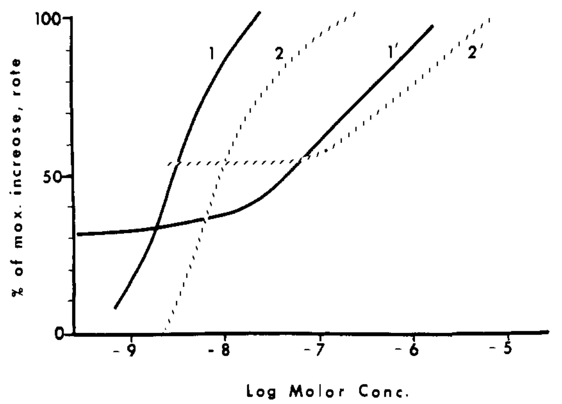


Figure 2. Cumulative log dose–response curves for **2b** and **2c** as antagonists to isproterenol. The pyridine compounds were each present in the bath in a concn of 10^{-3} *M* and 20 min was allowed before the isoproterenol dose–response curve was rerun. Curve 1 and 2 represent isoproterenol; curve 1′, **2c** plus isoproterenol; and curve 2′, **2b** plus isoproterenol.

pA_2 values. It does appear probable that these compounds act at the β-receptor based on this result.

The 4-pyridine ether derivative (**3c**) was a pure antagonist (ia = 0) with a pA_2 = 7.0 *vs.* isoproterenol (from 6 dose–response runs). Thus it was 10 times as potent as its *p*-nitrophenoxy isostere (**1c**)[13] (pA_2 = 6.0). It appears that the basic nitrogen of the pyridine ring does not interfere with the antagonist action and is therefore not a site of attachment (on or near the receptor).

Experimental Section

Melting points were taken in a Thomas-Hoover capillary melting point apparatus and are corrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. The analyses of C, H, N were within 0.4% of the theoretical values. Ir spectra were recorded on a Perkin-Elmer 700 spectrophotometer and nmr spectra were run on a Varian A-60 or T-60. Tlc was done on Eastman silica gel 6060 sheets. Evaporation *iv* means removal of solvent *in vacuo* on a rotary evaporator.

4-ω-Bromoacetylpyridine Hydrobromide (5). The reaction involving Br–HBr and 4-acetylpyridine was run according to Friz:[5] yield 77%; mp 195–197° dec (lit.[5] mp 200–205° dec). Crystn of 4-ω-bromoacetylpyridine·HBr from MeOH–Et_2O produced white needles: mp 198–202°. From spectral data this was probably the dimethyl ketal derivative: ν_{max}^{Nujol} 1160, 1105, 1075, 1025 (COCOC); 1455, 1425 cm^{-1} (CH_3). It could be hydrolyzed to the bromo ketone by heating with HOAc at 72° for 15 hr.

1-[4-Pyridyl]-2-bromoethanol Hydrochloride (6). This was prepared by $NaBH_4$ redn of the bromo ketone according to Friz.[5] The product was isolated as its HCl salt (31%) and recrystd from EtOH–Et_2O: mp 115.5–117.7° (lit.[5] 140–142°). Our product was probably a hydrate or alcoholate: ν_{max}^{Nujol} 3310 (OH), 2570 (C=N^+H), 1085 cm^{-1} (secondary OH).

1-(4-Pyridyl)-2-isopropylaminoethanol Dihydrochloride (2c). The procedure of Friz[5] was followed. The bromohydrin·HCl (**6**) was allowed to react with excess *i*-$PrNH_2$ at room temp for 26.5 hr. After work-up, the crude free base was distd in a bulb-to-bulb apparatus [bp 140–170° (bath temp) (0.11 mm), 73%] and converted to its 2-HCl salt in EtOH. *Note*: Incomplete saturation of the ethanolic soln with HCl gave the monohydrochloride monohydrate: mp 99.5–102.8°. It was recrystd from either EtOH–Et_2O or *i*-PrOH–Me_2CO. *Anal.* ($C_{10}H_{20}N_2O_2Cl$) C, H, N.

4-Allyloxypyridine (10). This compd was prepared from 4-bromopyridine (**9**) and sodium allyloxide in allyl alcohol by the procedure of Moffett.[8] Distn of the crude free base gave two main fractions: (1) 90–98° (10 mm); (2) 98–103° (10 mm) [lit.[8] bp 104° (11 mm)]. The ir spectra of these two fractions were identical.

1-Isopropylamino-3-(4-pyridyloxy)-2-propranol Dihydrochloride (3c). To 4-allyloxypyridine (**10**) (0.5000 g, 0.0037 mole) in H_2O (2 ml) was added, with stirring, *N*-bromoacetamide (0.5519 g, 0.004 mole). A white gum formed. Then 1 *N* H_2SO_4 (4 ml) was added, and the temp rose to 35°. After a few minutes, the pH was lowered from 4 to 1 by addn of more 1 *N* H_2SO_4 (4 ml) (total concn of H_2SO_4, 0.0048 mole). This was stirred for 0.5 hr, then heated to 45° during 0.5 hr, and the stirring continued for another 0.5 hr with heat removed. The colorless soln was stirred with $NaHSO_3$ (0.417 g, 0.004 mole), neutralized carefully with $NaHCO_3$, satd with K_2CO_3, and extd with Et_2O followed by CH_2Cl_2. The combined organic ext was dried (Na_2SO_4, K_2CO_3) and evapd *iv*, leaving a pale yellow viscous oil (0.7573 g). This crude bromohydrin intermediate showed two spots on tlc [$CHCl_3$–MeOH (10:1)] R_f 0.17 (major), 0.32 (minor). 4-Allyloxypyridine gave a single spot at R_f 0.58: ν_{max}^{film} 3150 (broad, OH), 1030 cm^{-1} (OH).

The crude bromohydrin (**11**) (0.7473 g, 0.00322 mole) in 95% EtOH (5 ml) was stirred and mixed with *i*-$PrNH_2$ (1.10 ml, 0.013 mole). Then a soln of KOH (0.1807 g, 0.00322 mole) in 95% EtOH (5 ml) was added, followed by 95% EtOH (2 ml). A white ppt formed, and the mixt was heated at 50° for 5 hr. Another 1.1 ml of *i*-$PrNH_2$ was added after 2 hr. The soln was evapd *iv* to dryness, and the residue dissolved in H_2O and extd with CH_2Cl_2. After drying (K_2CO_3), the organic ext was evapd *iv*, leaving a pale yellow oil (0.5605 g); 0.5322 g of this oily base was disoslved in Me_2CO, cooled to 0°, and slowly satd with HCl. A white gum formed which was dissolved by addn of a small volume of abs EtOH. The resulting yellow soln was concd *iv* to one-third volume and put in the freezer. After 55 days, white crystals were filtered and dried (0.320 g). Concn of the filtrate produced more product (0.046 g) (total yield 40%). Recrystn ($EtOH–Et_2O$) gave white hygroscopic crystals: mp 171–174°; ν_{max}^{Nujol} 3245 (OH), 2700 ($R_2N^+H_2$), 2460 sh (C=N^+H), 1640, 1610, 1510, 1320, 1205, 1150 (COC), 1030 (OH), 835 cm^{-1}; τ (D_2O) 1.23 (d, 2 H, *J* = 8 Hz, pyr 2.6 H), 2.30 (d, 2 H, *J* = 8 Hz, pyr 3.5 H), 5.38 (broad s, 3 H, CH_2, CH), 6.37 (m, 3 H, CH_2, CH), 8.52 (d, 6 H, CH_3). *Anal.* ($C_{11}H_{20}N_2O_2Cl_2$) C, H, N.

1,2-Diisopropylamino-2-propanol Dihydrochloride. A soln of NaOEt (0.0538 mole), 3-hydroxypyridine (5.000 g, 0.0525 mole), and epichlorohydrin (4.5 ml, 0.058 mole) in abs EtOH (45 ml) was stirred at room temp for 45 min. The pptd NaCl was filtd through Super-Cel, and the brown filtrate (50 ml) was cooled to 5–10° and slowly mixed with *i*-$PrNH_2$ (18 ml, 0.210 mole). The mixture was stirred at room temp for 21 hr. After the usual work-up, a dark brown oil (3.673 g) was obtained. Its HCl salt was prepd in Me_2CO–MeOH: white crystals (1.1384 g); mp 263–264°; recrystd from *i*-PrOH, then EtOH, mp 266.5–268.3°; ν_{max}^{Nujol} 3310 (OH), 2750 ($R_2N^+H_2$), 1100 cm^{-1} (secondary OH); τ (D_2O) 5.77 (m, 1 H, HCOH), 6.63 (m, 6 H, CH_2, CH), 8.64 (d, 12 H, *J* = 3 Hz, CH_3). *Anal.* ($C_9H_{24}N_2OCl_2$) C, H, N.

A control reaction between epichlorohydrin (1 equiv) and *i*-$PrNH_2$ (3 equiv) at room temp did not give the above product. After acidification with HCl the only product obtained was white crystals of *i*-$PrNH_2$·HCl: mp 139–140.5° (lit. mp from 139.5 to 155°[14]).

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p-Dimethylaminobenzonitrile. A Chemically Simple Coccidiostat

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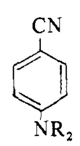
p-Dimethylaminobenzonitrile (**1**) possesses an unexpected degree of anticoccidial activity for so simple a chemical. For example, **1** at 0.025% in the diet prevented mortality and nearly controlled blood loss in feces of chicks infected with a virulent strain of *Eimeria tenella.* Per cent fecal score was 86.4 and weight gain was 82.5% that of noninfected, nonmedicated controls. The same infection caused 70% mortality in infected, nonmedicated controls.

p-Dimethylaminobenzonitrile (**1**) resembles *p*-aminobenzonic acid (PABA) chemically. In protozoa, PABA is a precursor for the biosynthesis of folates. The inhibition of this synthesis by PABA antagonist sulfonamides leads to cellular damage since these organisms are almost completely unable to utilize exogenous folates. In the organism the utilization of folic acid is inhibited by dihydrofolate reductase inhibitors such as certain diaminopyrimidines and related compounds. Synergistic combinations of a dihydrofolate reductase inhibitor and a PABA antagonist have provided reliable therapy for several protozoal diseases and are used in the prophylaxis of coccidiosis.[1-8] The chemical resemblance of **1** to PABA prompted us to attempt to potentiate the activity of **1** by combining with it a folic acid antagonist.



1, R = CH_3
8, R = H
9, R = C_2H_5

Two folic acid antagonists, both of which are known to potentiate coccidiostatic sulfonamides, were found to be effective: 2,4-diamino-5-(4,5-dimethoxy-2-methylbenzyl)-pyrimidine (**2**)[4,8] and 2,4-diamino-5-(4-chlorophenyl)-6-ethylpyrimidine (**3**).[2,5-7] Chicks fed prophylactically a combination of **1** (0.025%) and **2** (0.0075%) and infected with *Eimeria tenella* performed as well as noninfected, nonmedicated controls; there was no mortality, weight gain was equivalent and no blood was detected in feces. The combination of **1** (0.025%) and **3** (0.004%) protected the chicks nearly as well; there was no mortality, weight gain was 84.6% that of controls and only a trace of blood was detected in the feces. Three other folic acid antagonists did not do as well although optimum doses may not have been found for these combinations: 4,6-diamino-1-(*p*-chlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine·HCl (**4**), 4,6-diamino-1-(3,4-dichlorophenyl)-1,2-dihydro-2,2-dimethyl-*s*-triazine·HCl (**5**),[7] and 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine (**6**).[9] Although no mortality was observed with these combinations, weight gain was poorer or blood loss was more severe. Compound **5** is reported to have coccidiostatic activity[7] but did not control mortality in this test. Compound 4 (cycloguanil) and **6** (trimethoprim) are best known for their antimalarial[10] and antibacterial[9] activity, respectively, and do not have significant coccidiostatic activity at these levels. In combination with **1**, compounds **4**, **5**, and **6** did not significantly improve the activity of **1** alone.

Table I. Activity of *p*-Aminobenzonitriles and Combinations with Folate Antagonists against *Eimeria tenella* in Chicks

Compd	% diet	Compd	% diet	% gain	% FS	% survival
1	0.05			44.7	82.5	100.0
1	0.025			82.5	86.4	100.0
1	0.0125			42.3	35.3	100.0
1	0.0125	2	0.0075	102.4	100.0	100.0
1	0.0125	3	0.004	84.6	98.4	100.0
1	0.025	3 7	0.004 0.025	89.0	95.4	100.0
1	0.025	4	0.005	69.7	54.4	100.0
1	0.025	5	0.0025	85.1	85.4	100.0
1	0.025	6	0.0075	60.3	47.7	100.0
8	0.0125			35.8	33.2	90.0
8	0.0125	3	0.004	80.8	90.7	100.0
9	0.025			49.0	48.7	100.0
9	0.025	2	0.0075	80.2	77.4	100.0
9	0.025	3	0.004	71.6	56.9	100.0
9	0.025	6	0.0075	73.2	48.3	100.0
2	0.0075			60.2	20.8	90.0
3	0.004			25.3	24.7	66.7
5	0.0025			39.7	37.4	90.0
Infected, nonmedicated				46.6	15.4	30.0
Noninfected, nonmedicated				100.0	100.0	100.0

The addition of PABA 7 at 0.025% in the diet did not adversely affect the coccidiostatic activity of a combination of **1** (0.025%) and 3 (0.004%).

A combination of **1** and **2** was also tested against a strain of *E. tenella* which was resistant[11] to the coccidiostat amprolium [1-(2-propyl-4-amino-5-pyrimidylmethyl)-2-methylpyridinium chloride hydrochloride]. Using the same experimental method (14 birds per group), a mixture of **1** (0.025%) and **2** (0.0075%) prevented mortality. Birds receiving amprolium (Amprol Plus, 0.0125%) suffered 29% mortality. Infected, nonmedicated controls suffered 50% mortality.

p-Aminobenzonitrile (**8**) also demonstrated anticoccidial activity and a combination of **8** (0.0125%) and **3** (0.004%) appeared synergistic. Compound **9** at 0.025% in the diet also controlled mortality and may be potentiated by diaminopyridines **2**, **3**, and **6**.

Experimental Section

Cockerel broiler chicks, 16 days old, were weighed individually and separated into weight-balanced groups. Replicate groups of 10 birds were used for each experiment. Data reported are mean values for the 2 groups. Medicated diets were fed 48 hr prior to infection with 200,000 oocysts and continued for 7 days. Individual weights were recorded and mean weight gains relative to noninfected, nonmedicated controls were calculated.

Percentage fecal score (% FS, the relative area of the pan under the cage free of hemorrhagic fecal droppings) was calcd using a grid system and proportionately adjusted for mortality.

Benzonitriles **1**, **8**, and **9** are well known.[12-14] They are commercially available and were purified before use. We are indebted to Hoffmann-LaRoche for a sample of **2** and to Burroughs-Wellcome & Company for samples of **3** and **6**. Compd **4** is a well-known antimalarial.[10] Compd **5** was prepared according to a literature procedure,[15] mp 226-227°. *Anal.* ($C_{11}H_{13}Cl_2N_5$·HCl) C, H, Cl, N.