

Studies on Anticoccidial Agents. 10. Synthesis and Anticoccidial Activity of 5-Nitronicotinamide and Its Analogues

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5-Nitronicotinamide (1) was prepared from 5-bromonicotinoyl chloride by treatment with ammonia and then oxidation with fuming H_2SO_4 and 30% H_2O_2 . 2-Chloro-, 2-alkoxy-, 2-benzyloxy-, 2-phenoxy-, 2-alkylamino-, and 2-benzylamino-5-nitronicotinamides were also prepared via 2-chloro-3-cyano-5-nitropyridine. 2-Methyl-5-nitronicotinamide (2) was obtained from ethyl 2-methyl-5-nitronicotinate by treatment with ammonia; the 4-methyl analogue 3 was from 3-cyano-2,6-dihydroxy-4-methylpyridine by nitration, chlorination, and dechlorination, and the 6-methyl analogue 4 was prepared by transforming 2-chloro-3-cyano-6-methyl-5-nitropyridine to the corresponding amide, followed by dechlorination. Of these compounds, the 5-nitronicotinamide, the 2-methyl and 4-methyl but not the 6-methyl, analogue showed significant anticoccidial activity against *Eimeria tenella*. N-Substituted analogues of 5-nitronicotinamide and 2-methyl-5-nitronicotinamide were prepared in a conventional manner and optimal anticoccidial activity was attained with their lower N-alkyl analogues, N-alkanoyl and -alkenoyl analogues, and N-aromatic acyl analogues together with these parent compounds.

Antagonists of vitamins offer the basis for the design of anticoccidial agents. In the preceding papers,¹ we reported that α^4 -norpyridoxol and its derivatives as the weak vitamin B₆ antagonists showed coccidiostatic activity against *Eimeria acervulina*. On the other hand, Ball et al.² reported that 6-aminonicotinamide was a potent nicotinamide antagonist and was active against *E. tenella*, as well as being toxic to chickens.

In a continuing search for new anticoccidial agents, some 5-substituted nicotinamides were screened for coccidiostatic activity in chickens. 5-Nitronicotinamide showed significant activity against *E. tenella*, but not 5-amino- and 5-bromonicotinamide. The new coccidiostat, 5-nitronicotinamide, has no antinicotinamide activity for *Lactobacillus arabinosus*. Therefore, the anticoccidial activity of the nicotinamide derivatives is not necessarily proportional to their antinicotinamide activity.

Nakadate et al.³ reported the synthesis of 5-nitronicotinamide from ethyl nicotinate N-oxide. This paper provides another route to the 5-nitro derivative 4 as shown in Scheme I. Reaction of 5-bromonicotinoyl chloride (1) with ammonia gave 5-bromonicotinamide (2), which was treated with ammonia in the presence of cupric sulfate and oxidized with fuming H_2SO_4 and 30% H_2O_2 to give the 5-nitro derivative 4.

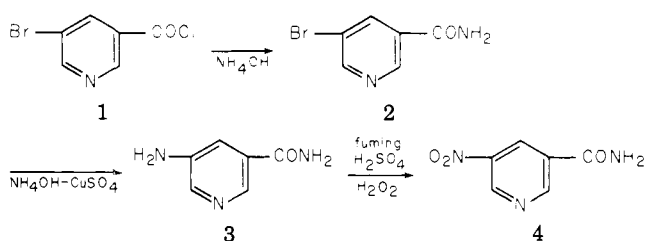
In order to elucidate the structure-activity relationship of this type of compounds, a series of 5-nitronicotinamide was prepared.

Firstly, the analogues of 5-nitronicotinamide were synthesized wherein the hydrogen atom at position 2 is replaced by a chlorine, alkoxy, benzyloxy, phenoxy, substituted amino, or methyl group. The 2-substituted derivatives 7-14 were prepared via 2-chloro-3-cyano-5-nitropyridine (5), which had been prepared by Fanta et al.,⁴ the cyanopyridine derivative 5 was heated at 90 °C with H_2SO_4 to afford 2-chloro-5-nitronicotinamide (6), which was converted to the 2-substituted 5-nitronicotinamides 7-14 by treatment with sodium alkoxides, benzyl oxide, phenoxide, or amines (Scheme II).

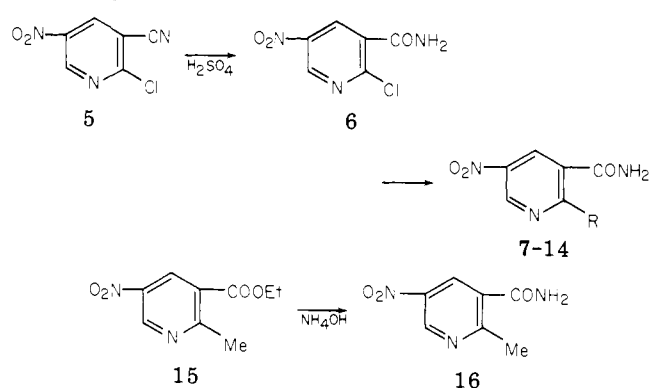
Piskov et al.⁵ reported that 2-methyl-5-nitronicotinamide (16) could be obtained from 2-methyl-5-nitronicotinic acid (26) only by the mixed anhydride method and compound 16 was inactive against *E. tenella* and *E. necatrix*. However, this compound could be prepared from the nicotinate 15 also by treatment with aqueous ammonia and was found to have truly marked coccidiostatic activity.

Secondly, the analogues of 5-nitronicotinamide modified at the 4 or 6 position, 4-methyl-5-nitronicotinamide (21) and 6-methyl-5-nitronicotinamide (24), as two isomers of 16 were also prepared as shown in Schemes III and IV.

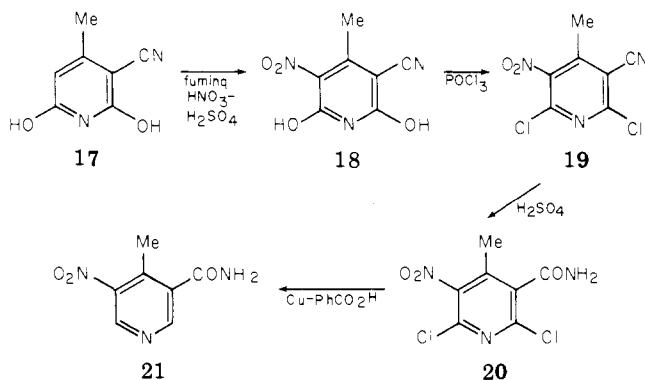
Scheme I



Scheme II



Scheme III



3-Cyano-2,6-dihydroxy-4-methylpyridine (17)⁶ was nitrated with fuming HNO_3 and H_2SO_4 at 15 °C to the dihydroxynitropyridine 18. The conversion of the dihydroxypyridine 18 to the corresponding dichloropyridine 19 was accomplished by heating with POCl_3 in a sealed tube, resulting in a poor yield. Applying the dechlorination procedure⁷ with Cu powder in molten benzoic acid, 2,6-dichloro-4-methyl-5-nitronicotinamide (20), obtained by

Scheme IV

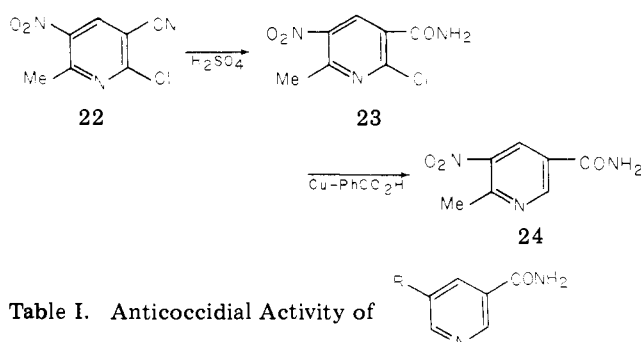


Table I. Anticoccidial Activity of

No.	R	ACI ^a
2	Br	60
3	NH ₂	66
4	NO ₂	198

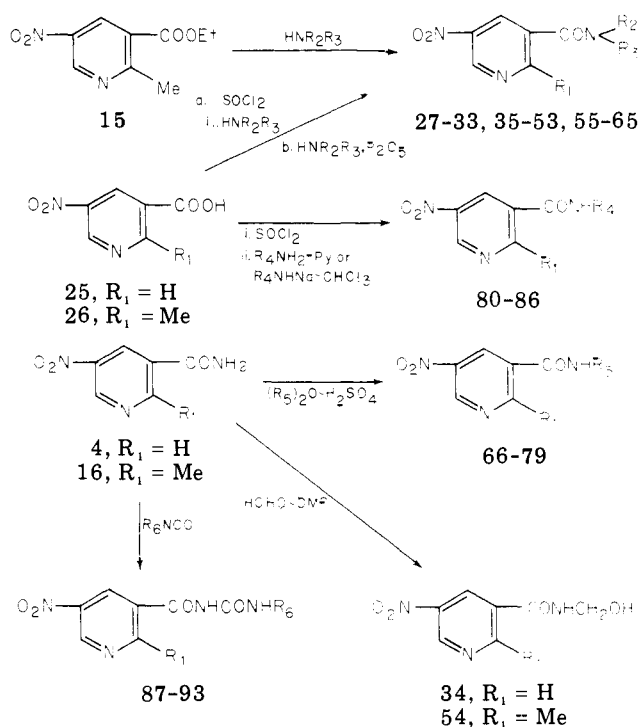
^a ACI = percent survival + percent relative weight gain - lesion score - oocyst score. Values are at 0.015% drug in feed.

heating 19 with H₂SO₄, was converted to 4-methyl-5-nitronicotinamide (21).

6-Methyl-5-nitronicotinamide (24) was prepared by transforming 2-chloro-3-cyano-6-methyl-5-nitropyridine (22) to the chloronitronicotinamide 23 with H₂SO₄, followed by dechlorination.

Finally, a number of the N-substituted analogues of 5-nitronicotinamide (4) and 2-methyl-5-nitronicotinamide (16), modified at the amide side chain, were prepared in a conventional manner as shown in Scheme V, wherein one or two hydrogen atoms of the carboxamide were replaced by one or two alkyl, an alkenyl, benzyl, phenyl, hydroxy, acyl, or carbamoyl group. Such N-alkyl, N-alkenyl, N-benzyl, N-phenyl, or N-hydroxy derivatives were easily prepared by chlorination of 5-nitronicotinic acid (25) with SOCl₂ and treatment with the corresponding amine, whereas the chlorination of 2-methyl-5-nitronicotinic acid (26) was accomplished only by treatment with equimolecular amounts of SOCl₂, because the methyl group is reactive toward this reagent. A better preparation of N-alkyl-, N-alkenyl-, N-benzyl-, or N-phenyl-2-methyl-5-nitronicotinamides involved the reaction of the acid 26 with the amine in the presence of P₂O₅ or the reaction of ethyl 2-methyl-5-nitronicotinate (15) with the corresponding amine. Several N-aromatic or heterocyclic acyl

Scheme V



R₁ = H or Me; R₂ = H, alkyl, or allyl; R₃ = H, OH, alkyl, allyl, cyclohexyl, phenyl, benzyl, pyridyl, or pyridylmethyl; R₄ = aromatic or heterocyclic acyl; R₅ = alkanoyl or alkenoyl; R₆ = alkyl, cyclohexyl, or phenyl

5-nitronicotinamides were prepared from 5-nitronicotinoyl or 2-methyl-5-nitronicotinoyl chloride and an appropriate amide in pyridine, applying the method of Thompson⁸ for the preparation of the diacylamides. N-Alkanoyl or N-alkenoyl analogues were conveniently obtained from 5-nitronicotinamide (4) or 2-methyl-5-nitronicotinamide (16) and an acid anhydride containing a trace of H₂SO₄. Treatment of the amides 4 and 16 with HCHO in DMF at 100 °C gave N-hydroxymethyl derivatives 34 and 54, while heating the amides 4 and 16 with the corresponding isocyanate led to the N-carbamoyl analogues 87-93.

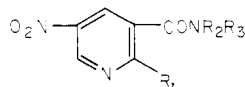
Biological Results. The compounds listed in Tables I-III were tested for *E. tenella* using the 1-(4-amino-2-n-propyl-5-pyrimidinylmethyl)-2-picolinium chloride hydrochloride (Amprolium) resistant strain by the pro-

Table II. Physical Properties and Anticoccidial Activity of

No.	R ₁	R ₂	R ₃	Method ^a	Mp, °C	Recrystn solvent	Yield, % ^b	Formula ^c	ACI ^d
6	Cl	H	H		181-183	EtOAc- <i>n</i> -hexane		C ₆ H ₄ ClN ₃ O ₃	79
7	OMe	H	H	A	223-225	MeOH	63.0	C ₇ H ₅ N ₃ O ₄	142
8	OEt	H	H	A	178-179	EtOAc- <i>n</i> -hexane	57.5	C ₈ H ₇ N ₃ O ₄	147
9	OPr	H	H	A	169-170	EtOAc- <i>n</i> -hexane	68.6	C ₉ H ₉ N ₃ O ₄	130
10	OCH ₂ Ph	H	H	A	155-157	EtOAc- <i>n</i> -hexane	48.2	C ₁₃ H ₁₁ N ₃ O ₄	118
11	OPh	H	H	A	190-192	EtOAc- <i>n</i> -hexane	54.7	C ₁₂ H ₉ N ₃ O ₄	76
12	NHEt	H	H	B	210-212	EtOAc	80.8	C ₈ H ₁₀ N ₄ O ₃	135
13 ^e	N(Et) ₂	H	H	B	~185	EtOAc	61.0	C ₁₀ H ₁₄ N ₄ O ₃	132
14	NHCH ₂ Ph	H	H	B	180-183	EtOH	36.7	C ₁₃ H ₁₂ N ₄ O ₃	111
16	Me	H	H		190-191	EtOH	34.8	C ₇ H ₇ N ₃ O ₃	198
21	H	Me	H		146-147	EtOAc- <i>n</i> -hexane		C ₇ H ₇ N ₃ O ₃	170
24	H	H	Me		181-182	EtOH		C ₇ H ₇ N ₃ O ₃	124

^a The letters relate to the general procedure given in the Experimental Section. ^b The yield of the analytically pure compounds isolated is given. ^c The compounds were analyzed for C, H, N, and, where present, Cl. Analytical results are within 0.3% of the theoretical values unless otherwise stated. ^d See footnote a in Table I. ^e The compound is hygroscopic. C: calcd, 50.42, found, 49.96. N: calcd, 23.52, found, 22.98.

Table III. Physical Properties and Anticoccidial Activity of



No.	R ₁	R ₂	R ₃	Meth- od ^a	Mp, °C	Recrystn solvent	Yield, % ^b	Formula ^c	ACI ^d
27	H	H	Me	C	180-181	H ₂ O	85.9	C ₇ H ₉ N ₃ O ₃	197
28	H	H	Et	C	167	EtOH-H ₂ O	67.0	C ₈ H ₉ N ₃ O ₃	195
29	H	H	CH ₂ CH=CH ₂	D	104-105	EtOAc- <i>n</i> -hexane	58.7	C ₉ H ₉ N ₃ O ₃	169
30	H	H	<i>n</i> -Bu	C	101-102	EtOH-H ₂ O	46.2	C ₁₀ H ₁₃ N ₃ O ₃	139
31	H	Me	Me	C	109-110	H ₂ O	31.0	C ₈ H ₉ N ₃ O ₃	183
32	H	Me	Et	D	65	EtOAc- <i>n</i> -hexane	45.5	C ₉ H ₁₁ N ₃ O ₃	179
33	H	H	OH	C	184-185	EtOH- <i>n</i> -hexane	17.4	C ₆ H ₇ N ₃ O ₄	187
34	H	H	CH ₂ OH	E	145-146	EtOH	30.6	C ₇ H ₉ N ₃ O ₄	180
35	H	H	CH ₂ CH ₂ OH	C	108-109	EtOH-H ₂ O	28.9	C ₈ H ₉ N ₃ O ₄	154
36	H	H	CH ₂ CH ₂ OEt	D	95	EtOAc- <i>n</i> -hexane	24.8	C ₁₀ H ₁₃ N ₃ O ₄	101
37	H	H	C ₆ H ₁₁	C	180	EtOH-H ₂ O	88.2	C ₁₂ H ₁₅ N ₃ O ₃	90
38	H	H	Ph- <i>p</i> -NO ₂	C	190	EtOAc- <i>n</i> -hexane	27.8	C ₁₂ H ₈ N ₃ O ₅	77
39	H	H	Ph- <i>p</i> -Cl	C	195-197	EtOH- <i>n</i> -hexane	21.2	C ₁₂ H ₈ ClN ₃ O ₃	114
40	H	H	CH ₂ Ph- <i>p</i> -Cl	C	162-164	EtOH-H ₂ O	36.4	C ₁₃ H ₁₀ ClN ₃ O ₃	96
41	H	H	Ph- <i>p</i> -OMe	C	135-136	EtOAc- <i>n</i> -hexane	31.0	C ₁₃ H ₁₁ N ₃ O ₄	101
42	H	H	CH ₂ Ph- <i>p</i> -OMe	C	144-145	EtOH-H ₂ O	36.9	C ₁₄ H ₁₃ N ₃ O ₄	58
43	H	H	C ₆ H ₅ N	C	263-265	EtOH-H ₂ O	34.1	C ₁₁ H ₈ N ₃ O ₃	71
44	H	H	4-CH ₂ C ₆ H ₄ N	C	69-70	EtOH- <i>n</i> -hexane	17.1	C ₁₂ H ₁₀ N ₃ O ₃	69
45	H	H	2,4-Me ₂ -C ₆ H ₃ N	C	174-176	EtOAc- <i>n</i> -hexane	44.4	C ₁₃ H ₁₂ N ₃ O ₃	65
46	Me	H	Me	J	159-160	EtOAc- <i>n</i> -hexane	24.5	C ₈ H ₉ N ₃ O ₃	191
47	Me	H	Et	J	152-153	EtOAc- <i>n</i> -hexane	15.4	C ₉ H ₁₁ N ₃ O ₃	195
48	Me	H	Pr	J	111-112	EtOAc- <i>n</i> -hexane	74.5	C ₁₀ H ₁₃ N ₃ O ₃	124
49	Me	H	CH ₂ CH=CH ₂	J	120-122	EtOAc- <i>n</i> -hexane	19.8	C ₁₀ H ₁₁ N ₃ O ₃	150
50	Me	H	<i>n</i> -C ₄ H ₉	J	98-99	EtOAc- <i>n</i> -hexane	75.0	C ₁₁ H ₁₅ N ₃ O ₃	161
51	Me	H	<i>i</i> -C ₄ H ₉	J	167-169	EtOAc- <i>n</i> -hexane	62.2	C ₁₁ H ₁₅ N ₃ O ₃	154
52	Me	H	<i>n</i> -C ₈ H ₁₇	J	82-83	EtOAc- <i>n</i> -hexane	50.2	C ₁₅ H ₂₃ N ₃ O ₃	115
53	Me	H	OH	C	164-166	EtOH- <i>n</i> -hexane	10.3	C ₇ H ₇ N ₃ O ₄	182
54	Me	H	CH ₂ OH	E	149-151	MeOH	24.5	C ₈ H ₉ N ₃ O ₄	161
55	Me	H	CH ₂ CH ₂ OH	J	143-145	EtOAc- <i>n</i> -hexane	29.7	C ₉ H ₁₁ N ₃ O ₄	163
56	Me	H	CH ₂ CH ₂ OEt	C	99-100	EtOAc- <i>n</i> -hexane	25.4	C ₁₁ H ₁₅ N ₃ O ₄	159
57	Me	H	CH ₂ CH ₂ CH ₂ OMe	J	66-66.5	EtOAc- <i>n</i> -hexane	83.3	C ₁₁ H ₁₅ N ₃ O ₄	115
58	Me	H	C ₆ H ₁₁	J	176-177	EtOAc- <i>n</i> -hexane	9.5	C ₁₃ H ₁₇ N ₃ O ₃	99
59	Me	Et	Et	D	Oil		59.6	C ₁₁ H ₁₅ N ₃ O ₃	193
60	Me	Me	Et	D	61-62	EtOAc- <i>n</i> -hexane	38.2	C ₁₀ H ₁₃ N ₃ O ₃	183
61	Me	Pr	Pr	D	Oil		29.8	C ₁₃ H ₁₉ N ₃ O ₃	102
62	Me	CH ₂ CH=CH ₂	CH ₂ CH=CH ₂	D	Oil		66.7	C ₁₃ H ₁₅ N ₃ O ₃	72
63	Me	H	CH ₂ Ph	D	167-168	EtOAc- <i>n</i> -hexane	52.0	C ₁₄ H ₁₃ N ₃ O ₃	125
64	Me	H	Ph- <i>o</i> -Me	D	203	MeOH	31.4	C ₁₄ H ₁₃ N ₃ O ₃	109
65	Me	Me	Ph	D	105	EtOAc- <i>n</i> -hexane	32.8	C ₁₄ H ₁₃ N ₃ O ₃	120
66	H	H	COMe	F	162-163	EtOAc- <i>n</i> -hexane	42.1	C ₈ H ₉ N ₃ O ₄	176
67	H	H	COC ₄ H ₉	F	116-118	EtOAc- <i>n</i> -hexane	41.8	C ₁₁ H ₁₃ N ₃ O ₄	172
68	H	H	COC ₆ H ₁₃	F	108-109	EtOAc- <i>n</i> -hexane	34.2	C ₁₄ H ₁₉ N ₃ O ₄	189
69	H	H	COCH=CHMe	F	175-177	EtOAc- <i>n</i> -hexane	25.6	C ₁₀ H ₉ N ₃ O ₄	175
70	Me	H	COMe	F	200-201	EtOAc	33.9	C ₉ H ₉ N ₃ O ₄	196
71	Me	Et	COMe	F	90-91	EtOAc- <i>n</i> -hexane	43.7	C ₁₁ H ₁₃ N ₃ O ₄	108
72	Me	H	COCH ₂ Cl	F	155-156	EtOAc	15.0	C ₉ H ₉ N ₃ O ₄ Cl	164
73	Me	H	COEt	F	171-173	EtOAc- <i>n</i> -hexane	51.2	C ₁₀ H ₁₁ N ₃ O ₄	197
74	Me	H	COC ₄ H ₉	F	162-163	EtOAc- <i>n</i> -hexane	40.6	C ₁₂ H ₁₅ N ₃ O ₄	189
75	Me	H	COC ₆ H ₁₃	F	125-126	EtOAc- <i>n</i> -hexane	43.7	C ₁₅ H ₂₁ N ₃ O ₄	189
76	Me	H	COC ₁₇ H ₃₅	F	108-110	EtOAc-isopropyl ether	11.2	C ₂₅ H ₄₁ N ₃ O ₄	178
77	Me	H	COCH=CHMe	F	146-148	EtOAc- <i>n</i> -hexane	41.3	C ₁₁ H ₁₁ N ₃ O ₄	193
78	Me	H	COCH(Me) ₂	F	185-187	EtOAc-isopropyl ether	24.0	C ₁₁ H ₁₃ N ₃ O ₄	191
79	Me	H	COCMe ₃	F	138-139	EtOAc-isopropyl ether	21.2	C ₁₂ H ₁₅ N ₃ O ₄	190
80	H	H	COPh	H	176-177	EtOAc- <i>n</i> -hexane	5.9	C ₁₃ H ₉ N ₃ O ₄	178
81	H	H	COPh- <i>p</i> -OMe	G	146-147	EtOAc- <i>n</i> -hexane	7.2	C ₁₄ H ₁₁ N ₃ O ₅	195
82	H	H	COPh- <i>p</i> -Me	G	172-174	EtOAc- <i>n</i> -hexane	6.9	C ₁₄ H ₁₁ N ₃ O ₄	196
83	H	H	2-COC ₄ H ₉ S	H	187	EtOAc	5.2	C ₁₁ H ₉ N ₃ O ₄ S	166
84	H	H	3-COC ₅ H ₄ N	G	164-166	EtOAc	4.6	C ₁₂ H ₈ N ₃ O ₄	154
85	H	H	3-CO-5-NO ₂ -C ₆ H ₃ N	G	191-193	EtOH	4.1	C ₁₂ H ₇ N ₃ O ₆	198
86	Me	H	COPh	H	155-157	EtOAc- <i>n</i> -hexane	5.1	C ₁₄ H ₁₁ N ₃ O ₄	190
87	H	H	CONHEt	I	215-216	EtOAc- <i>n</i> -hexane	50.8	C ₉ H ₁₀ N ₃ O ₄	50
88	Me	H	CONHEt	I	164-166	EtOAc- <i>n</i> -hexane	41.3	C ₁₀ H ₁₂ N ₃ O ₄	176
89	Me	H	CONHC ₄ H ₉	I	111-112	EtOAc- <i>n</i> -hexane	43.2	C ₁₂ H ₁₆ N ₃ O ₄	127
90	Me	H	CONHPh	I	131-132	EtOAc- <i>n</i> -hexane	20.2	C ₁₄ H ₁₂ N ₃ O ₄	90
91	Me	H	CONHCH(Me) ₂	I	154-156	EtOAc- <i>n</i> -hexane	13.7	C ₁₁ H ₁₄ N ₃ O ₄	166
92	Me	H	CONHC(Me) ₃	I	172-173	EtOAc- <i>n</i> -hexane	28.8	C ₁₂ H ₁₆ N ₃ O ₄	100
93	Me	H	CONHC ₆ H ₁₁	I	181-182	EtOAc- <i>n</i> -hexane	72.4	C ₁₄ H ₁₈ N ₃ O ₄	78
94	1-(4-Amino-2- <i>n</i> -propyl-5-pyrimidinylmethyl)-2-picolinium chloride hydrochloride								98
95	2-Methyl-3,5-dinitrobenzamide								195

^{a-c} See footnotes in Table II. ^d See footnote a in Table I.

cedure described in the preceding paper.^{1a} The criteria of anticoccidial activity were survival, weight gain, lesion score, and oocyst output and these were combined into the anticoccidial index (ACI) by the Cuckler method.⁹ The ACI above 180 was determined as an excellent coccidiostatic effect, 180–160 as a marked, 160–140 as a moderate, 140–120 as a slight, and below 120 as an inactive one. Of 5-nitronicotinamides modified at the 2 position, compounds 6 and 9–14 substituted with a chlorine, ethylamine, diethylamine, benzylamine, propoxy, phenoxy, or benzyloxy group have no significant activity, but 2-methoxy or 2-ethoxy analogues 7 and 8 showed some activity and the 2-methyl analogue 16 proved to be as active as the parent compound 4. The isomer of 2-methyl-5-nitronicotinamide (16), 4-methyl-5-nitronicotinamide (21), showed also marked protective action in the coccidiosis of chickens, but another isomer, 6-methyl-5-nitronicotinamide (24), was almost inactive. This suggests that any further study of the structure–activity relationship should focus on the *N*-substituents of 4 and 16. The activities of a series of *N*-substituted derivatives of 4 and 16 against *E. tenella* are given in Table III. *N*-Monoalkyl and *N*-dialkyl derivatives with the methyl or ethyl moiety were almost as active as the parent compounds (4 and 16), and the compounds with a longer chain alkyl substituent were less active. Furthermore, unsaturation in the alkyl group (29 and 49) and introduction of a hydroxy (34, 35, 54, and 55) or an alkoxy function (36, 56 and 57) lead to a decrease in activity, although *N*-hydroxy derivatives (33 and 53) show excellent anticoccidial activity. *N*-Phenyl, *N*-benzyl, *N*-(4-pyridyl), *N*-(2-pyridyl) or *N*-(4-pyridyl)methyl analogues 38–45 and 63–65 lack activity, and a similar reduction of the activity was observed in the *N*-acyl analogue of the *N*-monoalkyl derivative 71, but *N*-acylation of 5-nitronicotinamide (4) and 2-methyl-5-nitronicotinamide (16) maintains significant activity. A less beneficial effect was noted with *N*-carbamoyl analogues 87–93. Thus, optimal anticoccidial activity was attained with (1) 5-nitronicotinamide; (2) 2-methyl-5-nitronicotinamide, (3) their lower *N*-alkyl analogues, (4) their *N*-alkanoyl or alkenoyl analogues, and (5) their *N*-aromatic acyl analogues.

Experimental Section

Melting points are uncorrected. IR and NMR were determined on a Perkin-Elmer 221 and a Varian A-60, respectively. Spectral data were consistent with the assigned structures. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within $\pm 0.3\%$ of the theoretical values. The typical experimental procedures are described.

5-Bromonicotinamide (2). A mixture of nicotinoyl chloride hydrochloride (1.6 g, 9 mmol) and Br₂ (1.96 g, 12 mmol) was heated at 160–170 °C for 10 h. The reaction mixture was treated with 28% NH₄OH under cooling to give a crystalline product, which was recrystallized from aqueous EtOH to give 1.44 g (80%) of the analytical sample, mp 141–142 °C. Anal. (C₆H₅BrN₂O) C, H, Br, N.

5-Aminonicotinamide (3) and 5-Nitronicotinamide (4). A mixture of the bromo compound 2 (2.0 g, 9.9 mmol) and CuSO₄·5H₂O (0.2 g, 0.8 mmol) in 28% NH₄OH (4 ml) was heated at 175–180 °C in a sealed tube for 20 h. To the cooled reaction mixture, an aqueous solution of Na₂S was added dropwise until precipitation of CuS ceased and the solution was filtered. The filtrate was concentrated to dryness to give crude 5-aminonicotinamide (3), which was partly recrystallized from MeOH containing HCl to afford the analytical sample, 3·HCl, mp 246–247 °C dec. Anal. (C₆H₅ClN₃O) C, H, Cl, N. A solution of 3 in a mixed solution of fuming H₂SO₄ (40 ml) and 30% H₂O₂ (20 ml) was stirred at 15–18 °C for 96 h, diluted with H₂O, neutralized with NH₄OH, and extracted with EtOAc. The extract was dried over Na₂SO₄ and the solvent was removed to give a crystalline solid. Recrystallization from EtOAc gave 0.35 g (21.0%) of

compound 4, mp 180–182 °C. Anal. (C₆H₅N₃O₃) C, H, N.

2-Chloro-5-nitronicotinamide (6). A solution of the cyanopyridine 5 (3.9 g, 21 mmol) in concentrated H₂SO₄ (10 ml) was stirred at 60 °C for 1 h, poured onto ice, and neutralized with NaHCO₃ to give a crystalline product. Recrystallization from EtOAc-*n*-hexane yielded 3.3 g (77.5%) of the analytical sample, mp 181–183 °C. Anal. (C₆H₄ClN₃O₃) C, H, Cl, N.

2-Methoxy-5-nitronicotinamide (7). Method A. A solution of the chloropyridine 6 (1.0 g, 4.9 mmol) in MeOH (50 ml) was added dropwise at –10 °C to a solution of NaOMe, prepared from Na (0.11 g) and MeOH (10 ml). The solution was stirred at room temperature for 1 h, diluted with H₂O (10 ml), and cooled to –5 °C. A yellow precipitate formed which was collected and recrystallized from MeOH to afford 0.6 g (63.0%) of the analytical sample as yellow needles, mp 223–225 °C. Anal. (C₇H₇N₃O₄) C, H, N.

2-Ethylamino-5-nitronicotinamide (12). Method B. A mixture of the chloropyridine 6 (0.7 g, 3.4 mmol) and 70% aqueous EtNH₂ (6 ml) was stirred at room temperature for 1 h to give a yellow crystalline product. Recrystallization from EtOAc yielded 0.59 g (80.8%) of 12 as yellow needles, mp 210–212 °C. Anal. (C₈H₁₀N₄O₃) C, H, N.

2-Methyl-5-nitronicotinamide (16). A suspension of the nicotinate 15 (1.0 g, 4.7 mmol) and 28% NH₄OH (20 ml) was stirred at room temperature for 2 days. The crystalline product was separated, decolorized, and recrystallized from EtOH to yield 0.3 g (34.8%) of 16, mp 189–191 °C. Anal. (C₇H₇N₃O₃) C, H, N.

3-Cyano-2,6-dihydroxy-4-methyl-5-nitropyridine (18). To a solution of the pyridine 17 (15.0 g, 99 mmol) in concentrated H₂SO₄ (40 ml) was added dropwise under cooling fuming HNO₃ (20 ml) to give a yellow crystalline product. After stirring at 15 °C for 1 h, the mixture was poured onto ice and the crystalline solid was separated by filtration. The product was dissolved in hot H₂O and neutralized with NaHCO₃ to give a yellow product, which was recrystallized from aqueous MeOH to afford 10.7 g (43.2%) of 18, mp >300 °C. Anal. (C₇H₅N₃O₄·3H₂O) C, H, N.

3-Cyano-2,6-dichloro-4-methyl-5-nitropyridine (19). A solution of the nitropyridone 18 (13.0 g, 66 mmol) in POCl₃ (40 ml) was heated at 180 °C for 6 h in a sealed tube. The reaction mixture was added carefully to ice–H₂O, neutralized with NaHCO₃, and extracted with Et₂O and EtOAc. The extract was dried over MgSO₄. After removal of the solvent, the residue was purified by silica-gel chromatography and recrystallization from EtOAc-*n*-hexane to give 0.6 g (5.0%) of 19, mp 107–108 °C. Anal. (C₇H₃Cl₂N₃O₂) C, H, Cl, N.

2,6-Dichloro-4-methyl-5-nitronicotinamide (20). A solution of the cyanopyridine 19 (0.50 g, 2.2 mmol) in concentrated H₂SO₄ (1.5 ml) was heated at 100 °C for 1 h, cooled, poured onto ice, neutralized with NaHCO₃, and extracted with EtOAc. The extract was dried over MgSO₄, the solvent was removed, and the crystalline residue was recrystallized from EtOAc-*n*-hexane to give 0.38 g (70.4%) of 20, mp 167–168 °C. Anal. (C₇H₅Cl₂N₃O₃) C, H, Cl, N.

4-Methyl-5-nitronicotinamide (21). Powdered Cu (1.0 g, 15 mmol) was added portionwise at 155–160 °C to a mixture of the dichloropyridine 20 (0.30 g, 1.2 mmol) and benzoic acid (1.0 g, 8.2 mmol). The mixture was stirred at the same temperature for 5 min, cooled, and then shaken with EtOAc and aqueous Na₂CO₃. The extract was washed with H₂O and dried over MgSO₄ and the solvent was evaporated to give a semisolid, which was purified by silica-gel chromatography and recrystallization from EtOAc-*n*-hexane to afford 0.062 g (28.7%) of 21, mp 146–147 °C. Anal. (C₇H₇N₃O₃) C, H, N.

2-Chloro-6-methyl-5-nitronicotinamide (23). A solution of 22 (1.7 g, 8.6 mmol) in concentrated H₂SO₄ (4 ml) was stirred at 60 °C for 1 h, poured onto ice, and neutralized to give a crystalline product, which was collected and recrystallized from EtOAc-*n*-hexane to give 1.3 g (70.3%) of 23, mp 195–196 °C. Anal. (C₇H₆ClN₃O₃) C, H, Cl, N.

6-Methyl-5-nitronicotinamide (24). Copper powder (4.5 g, 70 mmol) was added portionwise to a stirred mixture of the chloro compound 23 (3.0 g, 13.9 mmol) and benzoic acid (5.4 g, 44 mmol) at 150 °C. After stirring was continued for 3 min, the mixture was diluted with EtOAc, washed with aqueous Na₂CO₃ solution and water, and dried over Na₂SO₄. The crystalline residue, after

removal of the solvent, was purified by silica-gel chromatography and recrystallization from EtOH to give 0.4 g (15.7%) of 23, mp 181–182 °C. Anal. ($C_7H_7N_3O_3$) C, H, N.

N-Methyl-5-nitronicotinamide (27). Method C. A mixture of 5-nitronicotinic acid (25, 0.84 g, 5 mmol) and $SOCl_2$ (40 ml) was refluxed for 4 h. After removal of the excess $SOCl_2$, the residual oil was diluted with anhydrous ether and the ethereal solution was dropwise added to 20% aqueous $MeNH_2$ (5 ml) under cooling to give a crystalline product (0.89 g). Recrystallization from H_2O afforded the analytical sample, mp 180–181 °C. Anal. ($C_7H_7N_3O_3$) C, H, N.

N-Allyl-5-nitronicotinamide (29). Method D. To a stirred mixture of 5-nitronicotinic acid (25, 0.84 g, 5 mmol) and allylamine (5 ml, 66.5 mmol) in $CHCl_3$ (50 ml), P_2O_5 (10 g) was added portionwise. The mixture was refluxed for 2 h, and the organic layer was separated, washed with aqueous $NaHCO_3$ and water, and dried over $MgSO_4$. The residual oil after removal of the solvent solidified gradually. Recrystallization from EtOAc-*n*-hexane gave the analytical sample (0.61 g), mp 104–105 °C. Anal. ($C_9H_9N_3O_3$) C, H, N.

N-Hydroxymethyl-5-nitronicotinamide (34). Method E. A solution of 5-nitronicotinamide (4, 1.0 g, 6 mmol) in DMF (3 ml) containing 37% $HCHO$ (2 ml, 24.6 mmol) was stirred at 100 °C for 2 h, cooled, poured into ice-water, and extracted with EtOAc. The extract was washed with H_2O and dried over $MgSO_4$ and the solvent was evaporated in vacuo to leave a solid, which was chromatographed over silica gel to give a crystalline product. Recrystallization from EtOH yielded 0.6 g (50.9%) of 34, mp 145–146 °C. Anal. ($C_7H_7N_3O_4$) C, H, N.

N-Octanoyl-5-nitronicotinamide (68). Method F. A mixture of the amide 4 (1.0 g, 6 mmol), octanoic anhydride (3.0 g, 11 mmol), and a trace of concentrated H_2SO_4 was stirred at 115 °C for 7.5 h, diluted with ice-water, made alkaline with dilute $NaHCO_3$, and extracted with EtOAc. The extract was washed with H_2O and dried and the solvent was evaporated to give an oily residue, which was purified by silica-gel chromatography and the oil obtained was crystallized from *n*-hexane. Recrystallization from EtOAc-*n*-hexane gave 0.6 g (34.3%) of the analytical sample, mp 108–109 °C. Anal. ($C_{14}H_{19}H_3O_4$) C, H, N.

N-(*p*-Toluoxy)-5-nitronicotinamide (82). Method G. A mixture of the acid 25 (1.5 g, 8.9 mmol) and $SOCl_2$ (50 ml) was refluxed for 4 h. After removal of the excess reagent, the residual acid chloride was dissolved in pyridine (5 ml) under cooling (–10 °C) and to this solution *p*-toluamide (1.35 g, 10 mmol) was added. The mixture was stirred at room temperature for 16 h and diluted with EtOH and the solvent was removed in vacuo to give a brown oil which was chromatographed over silica gel and the crystalline residue after evaporation of the solvent was recrystallized from EtOAc-*n*-hexane to yield 0.175 g (6.9%) of the analytical sample, mp 172–174 °C. Anal. ($C_{14}N_{11}N_3O_4$) C, H, N.

N-(2-Thenoyl)-5-nitronicotinamide (83). Method H. A mixture of the acid 25 (1.5 g, 8.9 mmol) and $SOCl_2$ (30 ml) was refluxed for 3 h. Excess $SOCl_2$ was distilled off to give oily 5-nitronicotinoyl chloride. The acid chloride thus obtained was dissolved in $CHCl_3$ (30 ml) and to this solution was added portionwise the sodium salt of 2-thiophenecarboxamide (1.5 g, 12 mmol), prepared by heating a solution of 2-thiophene-

carboxamide in dioxane with 50% NaH suspended in a mineral oil. The mixture was stirred at room temperature for 16 h. After separation of the $NaCl$ precipitate, the solution was concentrated and chromatographed over silica gel eluting with benzene-EtOAc (1:1). The crystalline residue after evaporation of the solvent was recrystallized from EtOAc to give the analytical sample (0.13 g, 5.2%), mp 187 °C. Anal. ($C_{11}H_7N_3O_4S$) C, H, N, S.

3-(4-Ethylallophanoyl)-5-nitropyridine (87). Method I. A suspension of the amide 4 (0.8 g, 4.8 mmol) and $EtNCO$ (1.4 g, 19 mmol) in toluene (40 ml) was refluxed for 18 h. After the solvent was removed, the crystalline residue was chromatographed over silica gel to give the starting material (0.41 g) recovered and the product (0.4 g). Recrystallization from EtOAc-*n*-hexane gave 0.3 g (50.8%) of the analytical sample, mp 215–216 °C. Anal. ($C_8H_{10}N_4O_4$) C, H, N.

N-(3-Methoxypropyl)-2-methyl-5-nitronicotinamide (57). Method J. A mixture of ethyl 2-methyl-5-nitronicotinate (15, 1.0 g, 4.8 mmol) and 3-methoxypropylamine (5 ml 48.7 mmol) was stirred at room temperature for 8 h. The reaction mixture was concentrated to dryness in vacuo and chromatographed over silica gel to give a crystalline residue. Recrystallization from EtOAc-*n*-hexane afforded 1.0 g (83.3%) of the analytical sample, mp 66–66.5 °C. Anal. ($C_{11}H_{15}N_3O_4$) C, H, N.

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