# 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 $\alpha^4$-norpyridoxol and its derivatives as the weak vitamin $B_6$ 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.

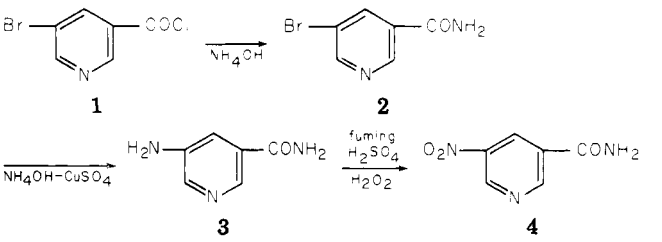
In order to elucidate the structure–activity relationship of this type of compounds, a series of 5-nitronicotinamide was prepared.

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).

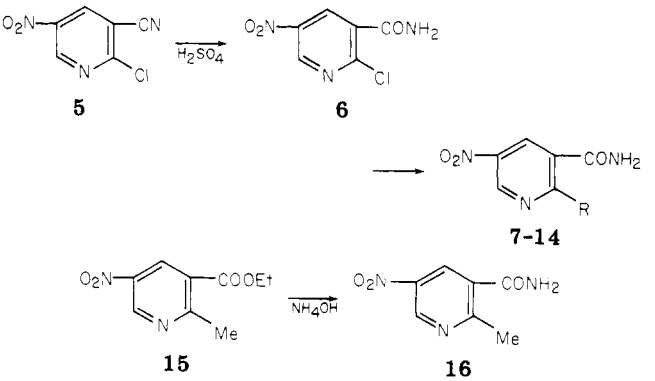
Piskov et al.[5] reported that 2-methyl-5-nitronicotinamide (16) could be obtained from 2-methyl-5-nitronicotinic acid (26) only by the mixed anhydride method and compound 16 was inactive against *E. tenella* and *E. necatrix*. However, this compound could be prepared from the nicotinate 15 also by treatment 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.

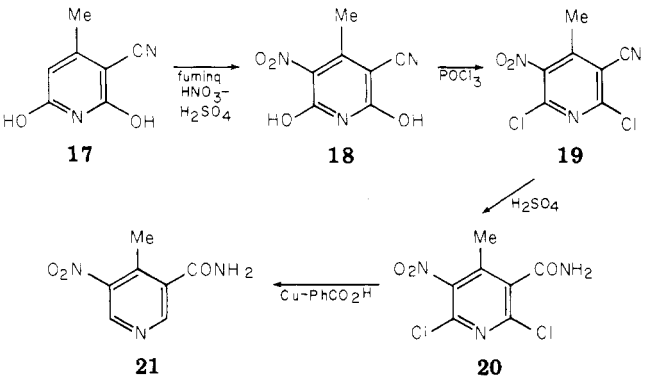
**Scheme I**




**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 procedure[7] with Cu powder in molten benzoic acid, 2,6-dichloro-4-methyl-5-nitronicotinamide (20), obtained by

Scheme IV

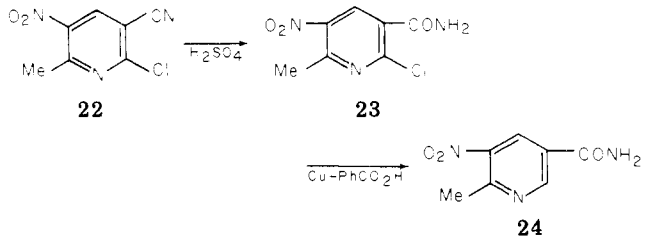
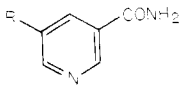


Table I. Anticoccidial Activity of 

| No. | R | ACI[a] |
|---|---|---|
| 2 | Br | 60 |
| 3 | $NH_2$ | 66 |
| 4 | $NO_2$ | 198 |

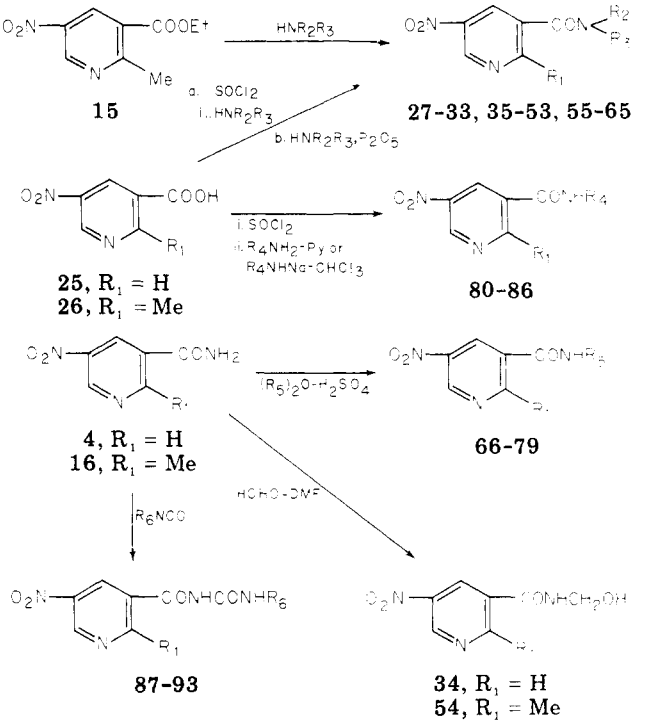
[a] ACI = percent survival + percent relative weight gain − lesion score − oocyst score. Values are at 0.015% drug in feed.

heating **19** with $H_2SO_4$, 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 $H_2SO_4$, 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 $SOCl_2$ 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 $SOCl_2$, 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 $P_2O_5$ or the reaction of ethyl 2-methyl-5-nitronicotinate (**15**) with the corresponding amine. Several *N*-aromatic or heterocyclic acyl

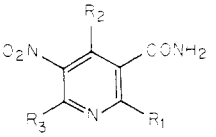
Scheme V



$R_1$ = H or Me; $R_2$ = H, alkyl, or allyl; $R_3$ = H, OH, alkyl, allyl, cyclohexyl, phenyl, benzyl, pyridyl, or pyridylmethyl; $R_4$ = aromatic or heterocyclic acyl; $R_5$ = alkanoyl or alkenoyl; $R_6$ = alkyl, cyclohexyl, or phenyl

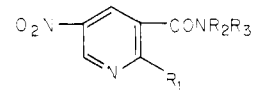
5-nitronicotinamides were prepared from 5-nitronicotinoyl or 2-methyl-5-nitronicotinoyl chloride and an appropriate amide in pyridine, applying the method of Thompson[8] for the preparation of the diacylamides. *N*-Alkanoyl or *N*-alkenoyl analogues were conveniently obtained from 5-nitronicotinamide (**4**) or 2-methyl-5-nitronicotinamide (**16**) and an acid anhydride containing a trace of $H_2SO_4$. 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-*n*-hexane | | $C_6H_4ClN_3O_3$ | 79 |
| 7 | OMe | H | H | A | 223-225 | MeOH | 63.0 | $C_7H_7N_3O_4$ | 142 |
| 8 | OEt | H | H | A | 178-179 | EtOAc-*n*-hexane | 57.5 | $C_8H_9N_3O_4$ | 147 |
| 9 | OPr | H | H | A | 169-170 | EtOAc-*n*-hexane | 68.6 | $C_9H_{11}N_3O_4$ | 130 |
| 10 | $OCH_2Ph$ | H | H | A | 155-157 | EtOAc-*n*-hexane | 48.2 | $C_{13}H_{11}N_3O_4$ | 118 |
| 11 | OPh | H | H | A | 190-192 | EtOAc-*n*-hexane | 54.7 | $C_{12}H_9N_3O_4$ | 76 |
| 12 | NHEt | H | H | B | 210-212 | EtOAc | 80.8 | $C_8H_{10}N_4O_3$ | 135 |
| 13[e] | $N(Et)_2$ | H | H | B | ~185 | EtOAc | 61.0 | $C_{10}H_{14}N_4O_3$ | 132 |
| 14 | $NHCH_2Ph$ | H | H | B | 180-183 | EtOH | 36.7 | $C_{13}H_{12}N_4O_3$ | 111 |
| 16 | Me | H | H | | 190-191 | EtOH | 34.8 | $C_7H_7N_3O_3$ | 198 |
| 21 | H | Me | H | | 146-147 | EtOAc-*n*-hexane | | $C_7H_7N_3O_3$ | 170 |
| 24 | H | H | Me | | 181-182 | EtOH | | $C_7H_7N_3O_3$ | 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. | $R_1$ | $R_2$ | $R_3$ | Method[a] | Mp, °C | Recrystn solvent | Yield, %[b] | Formula[c] | ACI[d] |
|---|---|---|---|---|---|---|---|---|---|
| 27 | H | H | Me | C | 180-181 | $H_2O$ | 85.9 | $C_7H_7N_3O_3$ | 197 |
| 28 | H | H | Et | C | 167 | EtOH-$H_2O$ | 67.0 | $C_8H_9N_3O_3$ | 195 |
| 29 | H | H | $CH_2CH=CH_2$ | D | 104-105 | EtOAc-*n*-hexane | 58.7 | $C_9H_9N_3O_3$ | 169 |
| 30 | H | H | *n*-Bu | C | 101-102 | EtOH-$H_2O$ | 46.2 | $C_{10}H_{13}N_3O_3$ | 139 |
| 31 | H | Me | Me | C | 109-110 | $H_2O$ | 31.0 | $C_8H_9N_3O_3$ | 183 |
| 32 | H | Me | Et | D | 65 | EtOAc-*n*-hexane | 45.5 | $C_9H_{11}N_3O_3$ | 179 |
| 33 | H | H | OH | C | 184-185 | EtOH-*n*-hexane | 17.4 | $C_6H_5N_3O_4$ | 187 |
| 34 | H | H | $CH_2OH$ | E | 145-146 | EtOH | 30.6 | $C_7H_7N_3O_4$ | 180 |
| 35 | H | H | $CH_2CH_2OH$ | C | 108-109 | EtOH-$H_2O$ | 28.9 | $C_8H_9N_3O_4$ | 154 |
| 36 | H | H | $CH_2CH_2OEt$ | D | 95 | EtOAc-*n*-hexane | 24.8 | $C_{10}H_{13}N_3O_4$ | 101 |
| 37 | H | H | $C_6H_{11}$ | C | 180 | EtOH-$H_2O$ | 88.2 | $C_{12}H_{15}N_3O_3$ | 90 |
| 38 | H | H | Ph-*p*-$NO_2$ | C | 190 | EtOAc-*n*-hexane | 27.8 | $C_{12}H_8N_4O_5$ | 77 |
| 39 | H | H | Ph-*p*-Cl | C | 195-197 | EtOH-*n*-hexane | 21.2 | $C_{12}H_8ClN_3O_3$ | 114 |
| 40 | H | H | $CH_2$Ph-*p*-Cl | C | 162-164 | EtOH-$H_2O$ | 36.4 | $C_{13}H_{10}ClN_3O_3$ | 96 |
| 41 | H | H | Ph-*p*-OMe | C | 135-136 | EtOAc-*n*-hexane | 31.0 | $C_{13}H_{11}N_3O_4$ | 101 |
| 42 | H | H | $CH_2$Ph-*p*-OMe | C | 144-145 | EtOH-$H_2O$ | 36.9 | $C_{14}H_{13}N_3O_4$ | 58 |
| 43 | H | H | $C_5H_4N$ | C | 263-265 | EtOH-$H_2O$ | 34.1 | $C_{11}H_8N_4O_3$ | 71 |
| 44 | H | H | 4-$CH_2C_6H_4N$ | C | 69-70 | EtOH-*n*-hexane | 17.1 | $C_{12}H_{10}N_4O_3$ | 69 |
| 45 | H | H | 2,4-$Me_2$-$C_5H_2N$ | C | 174-176 | EtOAc-*n*-hexane | 44.4 | $C_{13}H_{12}N_4O_3$ | 65 |
| 46 | Me | H | Me | J | 159-160 | EtOAc-*n*-hexane | 24.5 | $C_8H_9N_3O_3$ | 191 |
| 47 | Me | H | Et | J | 152-153 | EtOAc-*n*-hexane | 15.4 | $C_9H_{11}N_3O_3$ | 195 |
| 48 | Me | H | Pr | J | 111-112 | EtOAc-*n*-hexane | 74.5 | $C_{10}H_{13}N_3O_3$ | 124 |
| 49 | Me | H | $CH_2CH=CH_2$ | J | 120-122 | EtOAc-*n*-hexane | 19.8 | $C_{10}H_{11}N_3O_3$ | 150 |
| 50 | Me | H | *n*-$C_4H_9$ | J | 98-99 | EtOAc-*n*-hexane | 75.0 | $C_{11}H_{15}N_3O_3$ | 161 |
| 51 | Me | H | *i*-$C_4H_9$ | J | 167-169 | EtOAc-*n*-hexane | 62.2 | $C_{11}H_{15}N_3O_3$ | 154 |
| 52 | Me | H | *n*-$C_8H_{17}$ | J | 82-83 | EtOAc-*n*-hexane | 50 2 | $C_{15}H_{23}N_3O_3$ | 115 |
| 53 | Me | H | OH | C | 164-166 dec | EtOH-*n*-hexane | 10.3 | $C_7H_7N_3O_4$ | 182 |
| 54 | Me | H | $CH_2OH$ | E | 149-151 | MeOH | 24.5 | $C_8H_9N_3O_4$ | 161 |
| 55 | Me | H | $CH_2CH_2OH$ | J | 143-145 | EtOAc-*n*-hexane | 29.7 | $C_9H_{11}N_3O_4$ | 163 |
| 56 | Me | H | $CH_2CH_2OEt$ | C | 99-100 | EtOAc-*n* hexane | 25.4 | $C_{11}H_{15}N_3O_4$ | 159 |
| 57 | Me | H | $CH_2CH_2CH_2OMe$ | J | 66-66.5 | EtOAc-*n*-hexane | 83.3 | $C_{11}H_{15}N_3O_4$ | 115 |
| 58 | Me | H | $C_6H_{11}$ | J | 176-177 | EtOAc-*n*-hexane | 9.5 | $C_{13}H_{17}N_3O_3$ | 99 |
| 59 | Me | Et | Et | D | Oil | | 59.6 | $C_{11}H_{15}N_3O_3$ | 193 |
| 60 | Me | Me | Et | D | 61-62 | EtOAc-*n*-hexane | 38.2 | $C_{10}H_{13}N_3O_3$ | 183 |
| 61 | Me | Pr | Pr | D | Oil | | 29.8 | $C_{13}H_{19}N_3O_3$ | 102 |
| 62 | Me | $CH_2CH=CH_2$ | $CH_2CH=CH_2$ | D | Oil | | 66.7 | $C_{13}H_{15}N_3O_3$ | 72 |
| 63 | Me | H | $CH_2$Ph | D | 167-168 | EtOAc-*n*-hexane | 52.0 | $C_{14}H_{13}N_3O_3$ | 125 |
| 64 | Me | H | Ph-*o*-Me | D | 203 | MeOH | 31.4 | $C_{14}H_{13}N_3O_3$ | 109 |
| 65 | Me | Me | Ph | D | 105 | EtOAc-*n*-hexane | 32.8 | $C_{14}H_{13}N_3O_3$ | 120 |
| 66 | H | H | COMe | F | 162-163 | EtOAc-*n*-hexane | 42.1 | $C_8H_7N_3O_4$ | 176 |
| 67 | H | H | $COC_4H_9$ | F | 116-118 | EtOAc-*n*-hexane | 41.8 | $C_{11}H_{13}N_3O_4$ | 172 |
| 68 | H | H | $COC_7H_{15}$ | F | 108-109 | EtOAc-*n*-hexane | 34.2 | $C_{14}H_{19}N_3O_4$ | 189 |
| 69 | H | H | COCH=CHMe | F | 175-177 | EtOAc-*n*-hexane | 25.6 | $C_{10}H_9N_3O_4$ | 175 |
| 70 | Me | H | COMe | F | 200-201 | EtOAc | 33.9 | $C_9H_9N_3O_4$ | 196 |
| 71 | Me | Et | COMe | F | 90-91 | EtOAc-*n*-hexane | 43.7 | $C_{11}H_{13}N_3O_4$ | 108 |
| 72 | Me | H | $COCH_2Cl$ | F | 155-156 | EtOAc | 15.0 | $C_9H_8N_3O_4Cl$ | 164 |
| 73 | Me | H | COEt | F | 171-173 | EtOAc-*n*-hexane | 51.2 | $C_{10}H_{11}N_3O_4$ | 197 |
| 74 | Me | H | $COC_4H_9$ | F | 162-163 | EtOAc-*n* hexane | 40.6 | $C_{12}H_{15}N_3O_4$ | 189 |
| 75 | Me | H | $COC_7H_{15}$ | F | 125-126 | EtOAc-*n*-hexane | 43.7 | $C_{15}H_{21}N_3O_4$ | 189 |
| 76 | Me | H | $COC_{17}H_{35}$ | F | 108-110 | EtOAc-isopropyl ether | 11 2 | $C_{25}H_{41}N_3O_4$ | 178 |
| 77 | Me | H | COCH=CHMe | F | 146-148 | EtOAc-*n*-hexane | 41.3 | $C_{11}H_{11}N_3O_4$ | 193 |
| 78 | Me | H | $COCH(Me)_2$ | F | 185-187 | EtOAc-isopropyl ether | 24.0 | $C_{11}H_{13}N_3O_4$ | 191 |
| 79 | Me | H | $COCMe_3$ | F | 138-139 | EtOAc-isopropyl ether | 21.2 | $C_{12}H_{15}N_3O_4$ | 190 |
| 80 | H | H | COPh | H | 176-177 | EtOAc-*n*-hexane | 5.9 | $C_{13}H_9N_3O_4$ | 178 |
| 81 | H | H | COPh-*p*-OMe | G | 146-147 | EtOAc-*n*-hexane | 7.2 | $C_{14}H_{11}N_3O_5$ | 195 |
| 82 | H | H | COPh-*p*-Me | G | 172-174 | EtOAc-*n*-hexane | 6.9 | $C_{14}H_{11}N_3O_4$ | 196 |
| 83 | H | H | 2-$COC_4H_3S$ | H | 187 | EtOAc | 5.2 | $C_{11}H_7N_3O_4S$ | 166 |
| 84 | H | H | 3-$COC_5H_4N$ | G | 164-166 | EtOAc | 4.6 | $C_{12}H_8N_4O_4$ | 154 |
| 85 | H | H | 3-CO-5-$NO_2$-$C_5H_3N$ | G | 191-193 | EtOH | 4.1 | $C_{12}H_7N_5O_6$ | 198 |
| 86 | Me | H | COPh | H | 155-157 | EtOAc-*n*-hexane | 5.1 | $C_{14}H_{11}N_3O_4$ | 190 |
| 87 | H | H | CONHEt | I | 215-216 | EtOAc-*n*-hexane | 50.8 | $C_9H_{10}N_4O_4$ | 50 |
| 88 | Me | H | CONHEt | I | 164-166 | EtOAc-*n*-hexane | 41.3 | $C_{10}H_{12}N_4O_4$ | 176 |
| 89 | Me | H | $CONHC_4H_9$ | I | 111-112 | EtOAc-*n*-hexane | 43.2 | $C_{12}H_{16}N_4O_4$ | 127 |
| 90 | Me | H | CONHPh | I | 131-132 | EtOAc-*n*-hexane | 20.2 | $C_{14}H_{12}N_4O_4$ | 90 |
| 91 | Me | H | $CONHCH(Me)_2$ | I | 154-156 | EtOAc-*n*-hexane | 13.7 | $C_{11}H_{14}N_4O_4$ | 166 |
| 92 | Me | H | $CONHC(Me)_3$ | I | 172-173 | EtOAc-*n*-hexane | 28.8 | $C_{12}H_{16}N_4O_4$ | 100 |
| 93 | Me | H | $CONHC_6H_{11}$ | I | 181-182 | EtOAc-*n*-hexane | 72.4 | $C_{14}H_{18}N_4O_4$ | 78 |
| 94 | 1-(4-Amino-2-*n*-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 ±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 $Br_2$ (1.96 g, 12 mmol) was heated at 160–170 °C for 10 h. The reaction mixture was treated with 28% $NH_4OH$ 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. ($C_6H_5BrN_2O$) 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 $CuSO_4 \cdot 5H_2O$ (0.2 g, 0.8 mmol) in 28% $NH_4OH$ (4 ml) was heated at 175–180 °C in a sealed tube for 20 h. To the cooled reaction mixture, an aqueous solution of $Na_2S$ 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. ($C_6H_8ClN_3O$) C, H, Cl, N. A solution of **3** in a mixed solution of fuming $H_2SO_4$ (40 ml) and 30% $H_2O_2$ (20 ml) was stirred at 15–18 °C for 96 h, diluted with $H_2O$, neutralized with $NH_4OH$, and extracted with EtOAc. The extract was dried over $Na_2SO_4$ 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. ($C_6H_5N_3O_3$) C, H, N.

**2-Chloro-5-nitronicotinamide (6).** A solution of the cyanopyridine **5** (3.9 g, 21 mmol) in concentrated $H_2SO_4$ (10 ml) was stirred at 60 °C for 1 h, poured onto ice, and neutralized with $NaHCO_3$ 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. ($C_6H_4ClN_3O_3$) 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 $H_2O$ (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. ($C_7H_7N_3O_4$) 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 $EtNH_2$ (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. ($C_8H_{10}N_4O_3$) C, H, N.

**2-Methyl-5-nitronicotinamide (16).** A suspension of the nicotinate **15** (1.0 g, 4.7 mmol) and 28% $NH_4OH$ (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. ($C_7H_7N_3O_3$) 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 $H_2SO_4$ (40 ml) was added dropwise under cooling fuming $HNO_3$ (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 $H_2O$ and neutralized with $NaHCO_3$ to give a yellow product, which was recrystallized from aqueous MeOH to afford 10.7 g (43.2%) of **18**, mp >300 °C. Anal. ($C_7H_5N_3O_4 \cdot 3H_2O$) 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 $POCl_3$ (40 ml) was heated at 180 °C for 6 h in a sealed tube. The reaction mixture was added carefully to ice–$H_2O$, neutralized with $NaHCO_3$, and extracted with $Et_2O$ and EtOAc. The extract was dried over $MgSO_4$. 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. ($C_7H_3Cl_2N_3O_2$) 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 $H_2SO_4$ (1.5 ml) was heated at 100 °C for 1 h, cooled, poured onto ice, neutralized with $NaHCO_3$, and extracted with EtOAc. The extract was dried over $MgSO_4$, 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. ($C_7H_5Cl_2N_3O_3$) 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 $Na_2CO_3$. The extract was washed with $H_2O$ and dried over $MgSO_4$ 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. ($C_7H_7N_3O_3$) C, H, N.

**2-Chloro-6-methyl-5-nitronicotinamide (23).** A solution of **22** (1.7 g, 8.6 mmol) in concentrated $H_2SO_4$ (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. ($C_7H_6ClN_3O_3$) 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 $Na_2CO_3$ solution and water, and dried over $Na_2SO_4$. 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*-**Toluoyl**)-**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-thiophenecarboxamide 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. ($C_6H_{10}N_4O_4$) 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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