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Studies on Anticoccidial Agents. 11. Synthesis and Anticoccidial Activity of Nitropyridinecarboxamides and Derivatives

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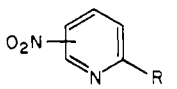
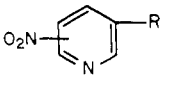
Of the nine nitropyridinecarboxamides, which are isomers of 5-nitronicotinamide, a potent anticoccidial agent, 2-nitropyridine-3-, -4-, -5-, or -6-carboxamides and 3-nitropyridine-4- or -6-carboxamides were prepared from the corresponding acids via the esters or the acid chlorides. 3-Nitropyridine-2-carboxamide was obtained from 2-methyl-3-nitropyridine by oxidation with SeO_2, oximation, dehydration with Ac_2O, and hydrolysis with H_2SO_4. 4-Nitropyridine-2-carboxamide was prepared from 2-cyano-4-nitropyridine by hydrolysis, and the 3-carboxamide analogue was obtained from 4-amino-3-cyanopyridine by oxidation with H_2O_2 and fuming H_2SO_4. Of these compounds 2-nitro- and 3-nitro- but not 4-nitropyridinecarboxamides were found to be active against *Eimeria tenella*. N-Substituted analogues of 2-nitro- and 3-nitropyridinecarboxamides were also prepared in a conventional manner and optimal anticoccidial activity was attained with 2-nitroisonicotinamide and its N-alkanoyl, N-aromatic, and N-heterocyclic acyl derivatives.

In the previous paper[1] we demonstrated that 5-nitronicotinamide and its derivatives possessed very potent anticoccidial activity. The present study was performed to determine whether a similar potency would be noted for the other nine isomeric nitropyridinecarboxamides and their derivatives. These compounds fall into three classes depending upon whether the carboxamide group is in the 2, 3, or 4 position in the pyridine ring. The first type with the carboxamide group in the 2 position consists of four isomers with the nitro group in the 3, 4, 5, and 6 positions, respectively. Schmidt-Thome et al.[2] have obtained 5-nitropyridine-2-carboxamide (**1a**) by treatment of 2-bromo-5-nitropyridine with cuprous cyanide, followed by hydrolysis. We obtained the amide **1a** by treatment of 5-nitropyridine-2-carboxylic acid (**1b**)[3] with $SOCl_2$ and then with ammonia. Similar transformations have been effected in the synthesis of the 6-nitro compound **2a** starting from 6-nitropyridine-2-carboxylic acid (**2b**).[3] 3-Nitropyridine-2-carboxamide (**3g**) had been previously prepared by Berrie et al.[4] using a somewhat tedious procedure. We have prepared this compound from 2-methyl-3-nitropyridine. Brown[3] has reported the preparation of 3-nitropyridine-2-carboxylic acid (**3c**) by the oxidation of **3a** with $KMnO_4$, but under the same oxidation conditions we isolated the acid **3c** in only 3.7% yield along with 3-nitropyridine (**3b**) and the starting material. Therefore, the synthesis of 3-nitropyridine-2-carboxamide (**3g**) was achieved in an indirect manner: oxidation of **3a** with SeO_2, oximation, dehydration with Ac_2O, and hydrolysis with H_2SO_4. 4-Nitropyridine-2-carboxamide (**4b**) was easily obtained from 2-cyano-4-nitropyridine (**4a**)[5] with H_2SO_4.



1a, R = $CONH_2$, 5-NO_2
b, R = COOH, 5-NO_2
2a, R = $CONH_2$, 6-NO_2
b, R = COOH, 6-NO_2
3a, R = Me, 3-NO_2
b, R = H, 3-NO_2
c, R = COOH, 3-NO_2
3d, R = CHO, 3-NO_2
e, R = CH=NOH, 3-NO_2
f, R = CN, 3-NO_2
g, R = $CONH_2$, 3-NO_2
4a, R = CN, 4-NO_2
b, R = $CONH_2$, 4-NO_2

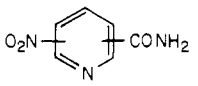
The second class consists of the four isomers containing the carboxamide group in the 3 position and the nitro group in either the 2, 4, 5, or 6 position; one of these has already been reported in the previous paper[1] as a potent coccidiostat. 2-Nitronicotinamide (**5c**) and 6-nitronicotinamide (**6c**) were prepared from the corresponding acids **5a** and **6c** by esterification and ammonolysis. The synthesis of 4-nitronicotinamide (**7**) was accomplished by oxidation of 4-amino-3-cyanopyridine[6] with persulfuric acid.



5a, R = COOH, 2-NO_2
b, R = COOMe, 2-NO_2
c, R = $CONH_2$, 2-NO_2
6a, R = COOH, 6-NO_2
b, R = COOMe, 6-NO_2
c, R = $CONH_2$, 6-NO_2
7, R = $CONH_2$, 4-NO_2

The compounds in the last type of nitropyridinecarboxamide are 2-nitro- and 3-nitroisonicotinamides. These two isomers were prepared by the action of am-

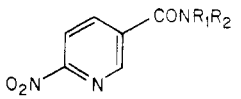
Table I. Anticoccidial Activity of Nitropyridinecarboxamides



No.	Position of $CONH_2$	Position of NO_2	Concn of drug in feed, %	ACI[a]
1a	2	5	0.015	165
2a	2	6	0.015	164
3g	2	3	0.015	132
4b	2	4	0.015	105
5c	3	2	0.015	135
6c	3	6	0.007	122
7	3	4	0.015	92
8b	4	2	0.015	195
			0.007	193
9b	4	3	0.015	165
5-Nitronicotinamide			0.015	198
			0.007	195
1-(4-Amino-2-*n*-propyl-5-pyrimidinylmethyl)-2-picolinium chloride hydrochloride			0.015	98
2-Methyl-3,5-dinitrobenzamide			0.015	195

[a] ACI = percent survival + percent relative weight gain − lesion score − oocyst score.

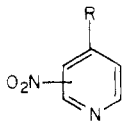
Table II. Physical Properties and Anticoccidial Activity of



No.	R_1	R_2	Method[a]	Yield, %[b]	Mp, °C	Recrystn solvent	Formula[c]	ACI[d]
10	H	OH	A	38.4	158-160 dec	EtOH-H_2O	$C_6H_5N_3O_4$	131
11	Et	Et	A	48.0	84-85	EtOAc-hexane	$C_{10}H_{13}N_3O_3$	124
12	H	COMe	C	55.5	175-177 dec	EtOAc-hexane	$C_8H_7N_3O_4$	127
13	H	COPh-*p*-Me	E	10.8	182-184	EtOAc-hexane	$C_{14}H_{11}N_3O_4$	128
14	H	COPh-*p*-Cl	D	20.4	180-182	EtOAc-hexane	$C_{13}H_8ClN_3O_4$	126

[a] The letter refers 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. [d] See footnote *a* in Table I. Values are at 0.007% in feed.

monia on the corresponding nitroisonicotinoyl chlorides, which were readily obtained by treatment of the 2- and 3-nitroisonicotinic acids[3] with $SOCl_2$, respectively.

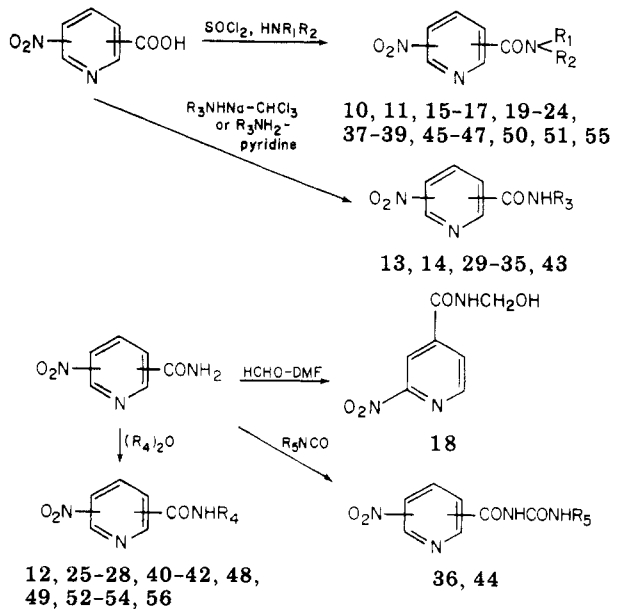


8a, R = COOH, 2-NO_2 9a, R = COOH, 3-NO_2
b, R = $CONH_2$, 2-NO_2 b, R = $CONH_2$, 3-NO_2

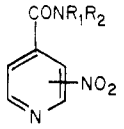
In order to examine the effect of changes in the amide side chain on anticoccidial activity, some N-substituted derivatives were prepared as shown in Scheme I. *N*-Alkyl, *N*-alkenyl, and *N*-hydroxyl derivatives were obtained from the corresponding pyridinecarboxylic acids by treatment with $SOCl_2$ and then with the amine. *N*-Alkanoyl and *N*-alkenoyl analogues were prepared from the corresponding amides and acid anhydride containing a trace of H_2SO_4, whereas N-aromatic and N-heterocyclic acylamides were made from the pyridinecarboxylic acid chlorides with an appropriate amide in pyridine or with the sodium salt of an amide in $CHCl_3$. Reaction of the amides with HCHO in DMF produced *N*-hydroxymethyl derivatives, while heating of the amides with the corresponding isocyanate led to the *N*-carbamoyl analogues.

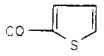
Biological Results. The compounds listed in Tables I–IV were tested for *Eimeria tenella* using the 1-(4-amino-2-*n*-propyl-5-pyrimidinylmethyl)-2-picolinium chloride hydrochloride (amprolium) resistant strain by the procedure described in the preceding paper.[7] For an ACI above 180, the coccidiostatic effect was determined as excellent, 180–160 as marked, 160–140 as moderate,

Scheme I[a]

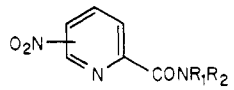


[a] R_1 = H, alkyl, or allyl; R_2 = OH, alkyl, alkoxyalkyl, or hydroxyalkyl; R_3 = aromatic or heterocyclic acyl; R_4 = alkanoyl or alkenoyl; R_5 = alkyl. The numbers correspond to those of the respective compounds in Tables I–IV.

Table III. Physical Properties and Anticoccidial Activity of 

No.	Position of NO_2	R_1	R_2	Method[a]	Yield, %[b]	Mp, °C	Recrystn solvent	Formula[c]	ACI[d]
15	2	H	Me	A	84.5	131-133	EtOAc-hexane	$C_7H_7N_3O_3$	170
16	2	H	Et	A	85.1	65-67	EtOAc-hexane	$C_8H_9N_3O_3$	170
17	2	H	C_3H_7	A	58.1	90-91	EtOAc-hexane	$C_9H_{11}N_3O_3$	135
18	2	H	CH_2OH	B	63.8	128-130	EtOAc	$C_7H_7N_3O_4$	186
19	2	H	$(CH_2)_2OH$	A	32.5	141-143	EtOH-ether	$C_8H_9N_3O_4$	135
20	2	H	$(CH_2)_2OEt$	A	67.0	64-65	EtOAc-hexane	$C_{10}H_{13}N_3O_4$	118
21	2	H	$CH_2CH=CH_2$	A	84.7	97-98	EtOAc-hexane	$C_9H_9N_3O_3$	145
22	2	Me	Me	A	96.6	131-132	EtOAc-hexane	$C_8H_9N_3O_3$	167
23	2	Me	Et	A	85.0	84-86	EtOAc-hexane	$C_9H_{11}N_3O_3$	170
24	2	Et	Et	A	53.7	54-55	EtOAc	$C_{10}H_{13}N_3O_3$	170
25	2	H	COMe	C	60.5	181-183	EtOAc	$C_8H_7N_3O_4$	190
26	2	H	$COCHMe_2$	C	80.7	153-155	EtOAc-hexane	$C_{10}H_{11}N_3O_4$	192
27	2	H	$COCH=CHCH_3$	C	77.9	152-153	EtOAc-hexane	$C_{10}H_9N_3O_4$	150
28	2	H	COC_7H_{15}	C	84.4	108-110	EtOAc-hexane	$C_{14}H_{19}N_3O_4$	197
29	2	H		D	18.4	164-165	EtOAc-hexane	$C_{11}H_7N_3O_4S$	194
30	2	H	COPh	E	11.8	169-171	EtOAc-hexane	$C_{13}H_9N_3O_4$	191
31	2	H	COPh-*p*-Cl	D	18.0	180-181	EtOAc-hexane	$C_{13}H_8ClN_3O_4$	197
32	2	H	COPh-*p*-OMe	D	15.4	174-176	EtOAc-hexane	$C_{14}H_{11}N_3O_5$	195
33	2	H	COPh-*o*-Me	D	17.6	191-192	EtOAc-hexane	$C_{14}H_{11}N_3O_4$	190
34	2	H	COPh-*m*-Me	E	18.6	147-148	EtOAc-hexane	$C_{14}H_{11}N_3O_4$	199
35	2	H	COPh-*p*-Me	E	9.1	194-196 dec	EtOAc-hexane	$C_{14}H_{11}N_3O_4$	199
36	2	H	CONHEt	F	13.2	196-198	EtOAc-hexane	$C_9H_{10}N_4O_4$	143
37	3	H	Me	A	61.9	157-158	EtOAc-hexane	$C_7H_7N_3O_3$	180
38	3	H	$CH_2CH=CH_2$	A	81.9	91-92	EtOAc-pet. ether	$C_9H_9N_3O_3$	182
39	3	Me	Me	A	62.0	111	EtOAc-pet. ether	$C_8H_9N_3O_3$	181
40	3	H	COMe	C	87.2	175-176	EtOAc	$C_8H_7N_3O_4$	186
41	3	H	COC_5H_{11}	C	72.5	144-147	EtOH-EtOAc	$C_{12}H_{15}N_3O_4 \cdot HCl$	170
42	3	H	$COCH=CHMe$	C	30.0	150-152	EtOAc-hexane	$C_{10}H_9N_3O_4$	177
43	3	H	COPh	D	29.6	142-143	EtOAc-hexane	$C_{13}H_9N_3O_4$	187
44	3	H	CONHEt	F	70.4	129-130	EtOAc-hexane	$C_9H_{10}N_4O_4$	180

[a-c] See corresponding footnotes in Table II. [d] See footnote *a* in Table I. Values are at 0.015% in feed.

Table IV. Physical Properties and Anticoccidial Activity of 

No.	Position of NO_2	R_1	R_2	Method[a]	Yield, %[b]	Mp, °C	Recrystn solvent	Formula[c]	ACI[d]
45	3	H	Et	A	8.0[e]	88-89	EtOAc-hexane	$C_8H_9N_3O_3$	152
46	3	H	$CH_2CH=CH_2$	A	18.2[e]	87-88	EtOAc-hexane	$C_9H_9N_3O_3$	165
47	3	Me	Me	A	18.9[e]	Oil		$C_8H_9N_3O_3$	185
48	3	H	$COCH=CHMe$	C	51.4	161-163	EtOAc-hexane	$C_{10}H_9N_3O_4$	156
49	3	H	COC_7H_{15}	C	62.5	63-64	EtOAc-hexane	$C_{14}H_{19}N_3O_4$	143
50	5	H	Me	A	94.4	158-160	EtOAc	$C_7H_7N_3O_3$	170
51	5	Me	Me	A	58.6	116-117	EtOH-hexane	$C_8H_9N_3O_3$	167
52	5	H	COMe	C	62.9	150-152	EtOAc-hexane	$C_8H_7N_3O_4$	182
53	5	H	COEt	C	55.5	94-96	EtOAc-hexane	$C_9H_9N_3O_4$	176
54	5	H	COC_7H_{15}	C	69.0	73-74	EtOAc-hexane	$C_{14}H_{19}N_3O_4$	176
55	6	H	Me	A	70.0	126-127	EtOAc-hexane	$C_7H_7N_3O_3$	130
56	6	H	COMe	C	79.9	130-131	EtOAc-hexane	$C_8H_7N_3O_4$	122

[a-c] See corresponding footnotes in Table II. [d] See footnote *a* in Table I. Values are at 0.015% in feed. [e] The yield from 2-methyl-3-nitropyridine is given, because pure 3-nitropyridine-2-carboxylic acid was not isolated.

140–120 as slight, and below 120 as inactive.

From the biological data in Table I it is apparent that the 2-, 3-, 5-, and 6-nitro-, but not the 4-nitro-, pyridinecarboxamides are active and the anticoccidial activity of 2-nitroisonicotinamide (**8b**) is equal to those of 5-nitronicotinamide and 2-methyl-3,5-dinitrobenzamide. N-Alkylation (**15–24**) of **8b** led to a slight decrease in activity, but *N*-acyl derivatives **25–35** were found to possess an activity equal to that of the parent compound. Marked anticoccidial activity was also demonstrated for 3-nitroisonicotinamide (**9b**). N-Methylation (**37, 39**), N-allylation (**38**), and N-acylation (**40–43**) of this amide **9b** contribute to its activity. Less effective results were seen for 6-nitronicotinamide (**6c**) and its *N*-acyl derivatives **12–14**, and the activity of 3-nitropyridine-2-carboxamide (**3g**) was increased by alkylation (**45, 47**) or acylation (**48, 49**) of the amide moiety. Both methylation (**55**) and acetylation (**56**) of the amide in 6-nitropyridine-2-carboxamide (**2a**) led to

a decrease in activity, while methylation (**50**, **51**) and acylation (**52**–**54**) of 5-nitropyridine-2-carboxamide (**1a**) effected the same or a slight increase in activity.

Thus, it is noteworthy that N-substitution of the amide moiety in the nitropyridinecarboxamides affects their activity differently. Among the compounds herein, optimal anticoccidial activity was obtained in 2-nitroisonicotinamide and its N-alkanoyl, N-aromatic, and N-heterocyclic acyl derivatives.

Experimental Section

Melting points are uncorrected. IR and NMR spectra 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. Typical experimental procedures are described.

5-Nitropyridine-2-carboxamide (1a). A mixture of the acid **1b** (0.54 g, 3.2 mmol) and $SOCl_2$ (5.5 mL, 74 mmol) was refluxed for 30 min. After removal of the excess $SOCl_2$, the yellow crystalline residue was stirred with 28% ammonia (4 mL) for 4 h and the product was separated and recrystallized from EtOH–Et_2O to give 0.21 g (39.1%) of **1a**, mp 247 °C (lit.[2] mp 246–247 °C). Anal. ($C_6H_5N_3O_3$) C, H, N.

6-Nitropyridine-2-carboxamide (2a). This compound was prepared from **2b** in 48.5% yield, mp 189–190 °C, as described for **1a**. Anal. ($C_6H_5N_3O_3$) C, H, N.

3-Nitropyridine-2-carboxamide (3g). (A). The nitropicoline **3a** (3.0 g, 21.7 mmol) was oxidized with $KMnO_4$ (6.5 g, 41 mmol) as previously described.[3] The starting material (1.88 g, 62.7%) was recovered from benzene extract. The acid **3c** (0.11 g, 3.7%), mp 104–105 °C (lit.[3] mp 105 °C), and 3-nitropyridine (**3b**, 0.24 g), mp 38–40 °C (lit.[8] mp 38–40 °C), were isolated from the aqueous layer.

(B). A solution of **3a** (2.37 g, 17 mmol) in dioxane (12 mL) was added dropwise at 50 °C to a solution of SeO_2 (2.25 g, 20.5 mmol) in dioxane (12 mL) and H_2O (1.2 mL). The mixture was refluxed for 3 h and after separation of the Se, the filtrate was concentrated to dryness to yield an oil. Chromatography using silica gel and recrystallization from EtOAc–hexane gave **3d** (1.03 g, 39.5%), mp 61–63 °C. Anal. ($C_6H_4N_2O_3$) C, H, N.

To a solution of NH_2OH in 90% EtOH (10 mL), prepared from NH_2OH·HCl (0.36 g, 5.1 mmol) and NaOAc (0.42 g, 5.1 mmol), was added portionwise a solution of **3d** (0.68 g, 4.5 mmol). The mixture was stirred at 70 °C for 3 h and cooled to give a crystalline product, which was recrystallized from EtOAc to produce **3e** (0.61 g, 81.3%), mp 172–173 °C dec. Anal. ($C_6H_5N_3O_3$) C, H, N.

A mixture of **3e** (0.6 g, 3.6 mmol) and Ac_2O (6.5 ml) was refluxed for 3.5 h, diluted with H_2O, made alkaline with Na_2CO_3, and extracted with EtOAc. The crystalline residue after removal of the solvent was recrystallized from EtOAc–hexane to give **3f** (0.45 g, 81.8%), mp 77–78 °C (lit.[4] mp 78 °C). Anal. ($C_6H_3N_3O_2$) C, H, N.

A solution of **3f** (0.4 g, 2.6 mmol) in concentrated H_2SO_4 (0.8 mL) was stirred at 80 °C for 1 h, diluted with ice–H_2O, made alkaline, and extracted with EtOAc. The extract was worked up as usual and the crystalline product was recrystallized from EtOH to give **3g** (0.35 g, 81.4%), mp 210–211 °C (lit.[4] mp 211 °C). Anal. ($C_6H_5N_3O_3$) C, H, N.

4-Nitropyridine-2-carboxamide (4b). A solution of **4a** (0.6 g, 4 mmol) in concentrated H_2SO_4 (1 mL) was stirred at 90 °C for 1.5 h and worked up as usual. Recrystallization from EtOAc–hexane gave **4b** (0.38 g, 56.7%), mp 162–164 °C. Anal. ($C_6H_5N_3O_3$) C, H, N.

2-Nitronicotinamide (5c). A solution of **5a** (0.8 g, 4.7 mmol) in absolute Et_2O (350 mL) was methylated with CH_2N_2 at room temperature and after excess reagent was decomposed with AcOH, the mixture was made alkaline with $NaHCO_3$ and extracted with EtOAc. **5b** (0.56 g, 64.6%) was obtained as an oil from the extract. Anal. ($C_7H_6N_2O_4$) C, H, N.

A solution of **5b** (0.54 g, 2.9 mmol) in MeOH (3 mL) was stirred with concentrated NH_4OH (2 mL) at room temperature for 1 h. After removal of the solvent, the residual crystalline product was recrystallized from EtOH to give **5c** (0.21 g, 42.9%), mp 193–195 °C. Anal. ($C_6H_5N_3O_3$) C, H, N.

6-Nitronicotinamide (6c). By a method similar to that described for **5c**, **6a** (0.4 g, 2.3 mmol) was converted to the ester **6b** (0.1 g, 23.3%), mp 135–138 °C. Anal. ($C_7H_6N_2O_4$) C, H, N. Treatment of **6b** (0.15 g, 0.82 mmol) with NH_4OH (2 mL) afforded **6c** (0.12 g, 87.6%), mp 189–190 °C on recrystallization from EtOH. Anal. ($C_6H_5N_3O_3$) C, H, N.

4-Nitronicotinamide (7). 4-Aminonicotinamide (0.5 g, 3.6 mmol) was added portionwise to a mixed solvent of fuming H_2SO_4 (10 mL) and 30% H_2O_2 (5 mL) and the mixture was stirred at room temperature for 30 h, poured into ice–H_2O, neutralized with $NaHCO_3$, and extracted with EtOAc. The residue after removal of the solvent was chromatographed using silica gel to give an unidentified substance (0.35 g), mp 116–117 °C, and **7** (0.16 g, 26.2%), mp 158–159 °C dec, on recrystallization from MeOH–Et_2O. Anal. ($C_6H_3N_3O_2$) C, H, N.

2-Nitroisonicotinamide (8b). This compound was prepared from **8a** by a similar method described for **1a** in 78% yield, mp 173 °C dec. Anal. ($C_6H_5N_3O_3$) C, H, N.

***N,N*-Dimethyl-2-nitroisonicotinamide (22). Method A.** A mixture of **8a** (0.91 g, 5.4 mmol) and $SOCl_2$ (9 mL) was refluxed for 1 h and the excess $SOCl_2$ was removed to leave an oily residue (0.84 g). This acid chloride was dissolved in $CHCl_3$ (10 mL) and to this solution was added under cooling 40% aqueous Me_2NH solution (8 mL) to give a crystalline product, which was extracted with $CHCl_3$. The residue after removal of the solvent was purified by silica gel chromatography and recrystallization from EtOAc–hexane to afford **22** (0.85 g, 80.5%), mp 131–132 °C. Anal. ($C_8H_9N_3O_3$) C, H, N.

***N*-Hydroxymethyl-2-nitroisonicotinamide (18). Method B.** A solution of **8b** (0.8 g, 4.8 mmol) in DMF (2 mL) containing 37% HCHO (2 mL) was stirred at 110 °C for 2 h, cooled, diluted with ice–H_2O, and extracted with EtOAc. The extract was washed with H_2O and dried and the solvent was removed to give a crystalline product, which was recrystallized from EtOAc to give **18** (0.6 g, 63.8%), mp 128–130 °C. Anal. ($C_7H_7N_3O_4$) C, H, N.

***N*-Octanoyl-2-nitroisonicotinamide (28). Method C.** A mixture of the amide **8b** (0.8 g, 4.8 mmol), octanoic anhydride (24 mL), and 2 drops of concentrated H_2SO_4 was stirred at room temperature for 16 h, diluted with H_2O, made alkaline with $NaHCO_3$, and extracted with EtOAc. The extract was washed with H_2O and dried and the solvent was removed leaving a residue which was purified by silica gel chromatography and recrystallization from EtOAc–hexane to give **28** (1.36 g, 97.1%), mp 108–110 °C. Anal. ($C_{14}H_{19}N_3O_4$) C, H, N.

***N*-(*p*-Chlorobenzoyl)-2-nitroisonicotinamide (31). Method D.** To a solution of the acid chloride (0.80 g, 4.3 mmol) in $CHCl_3$ (15 mL), prepared as described above, was added portionwise the sodium salt (0.8 g, 4.5 mmol) of *p*-chlorobenzamide in dioxane with 50% NaH suspended in a mineral oil. The mixture was stirred at room temperature for 1 h, poured into ice–H_2O, and extracted with $CHCl_3$. The extract was washed with H_2O and dried and the solvent was removed to give a yellow crystalline product, which was purified by silica gel chromatography and recrystallization from EtOAc–hexane to give **31** (0.17 g, 18.0%), mp 179–181 °C. Anal. ($C_{13}H_8ClN_3O_4$) C, H, Cl, N.

***N*-(*p*-Toluoyl)-2-nitroisonicotinamide (35). Method E.** 2-Nitroisonicotinoyl chloride (1.8 g, 9.7 mmol) prepared as above was dissolved in pyridine (5 mL) at −10 °C and to this solution *p*-toluamide (1.5 g, 11.1 mmol) was added portionwise. The mixture was stirred at room temperature for 1 h and diluted with EtOH and the solvent was removed in vacuo to give a brown solid, which was extracted with EtOAc. Insoluble product (0.81 g, 49.7%) was the acid **8a**. The extract was dried, concentrated, and chromatographed using silica gel and recrystallized from EtOAc–hexane to give **35** (0.25 g, 9.1%), mp 194–196 °C dec. Anal. ($C_{14}H_{11}N_3O_4$) C, H, N.

4-(4-Ethylallophanoyl)-2-nitropyridine (36). Method F. A suspension of **8b** (0.84 g, 5.0 mmol) and EtNCO (0.75 g, 9.6 mmol) in toluene (30 mL) was refluxed for 6 h, and after separation of the insoluble starting material (0.40 g, 47.6%) the solvent was removed to leave an oil, which was chromatographed using silica gel to give **8b** (0.20 g, 23.8%) and **36** (0.15 g, 12.6%), mp 196–198 °C, on recrystallization from EtOAc–hexane. Anal. ($C_9H_{10}N_4O_4$) C, H, N.

3-Nitroisonicotinamide (9b). This compound was prepared from **9a** by a similar method described for **1a** in 50% yield, mp

159–160 °C, on recrystallization from EtOAc–petroleum ether. Anal. ($C_6H_5N_3O_3$) C, H, N.

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3-Aminotetrahydrocarbazoles as a New Series of Central Nervous System Agents

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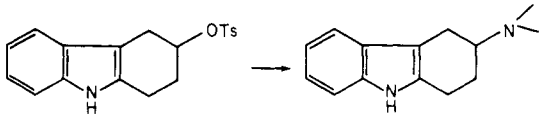
3-Dimethylamino-1,2,3,4-tetrahydrocarbazole, a structurally modified tryptamine, prevented amphetamine-induced stereotyped behavior in rats and prevented reserpine-induced ptosis in mice. Further study of this compound and a number of substituted derivatives indicated that either imipramine-like or chlorpromazine-like profiles were obtainable by changing substituents and their positions.

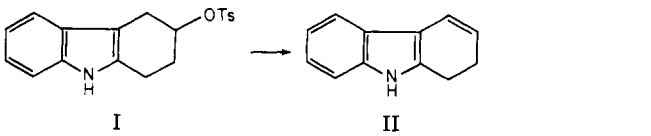
Our work began with the premise that 3-aminotetrahydrocarbazoles might have central nervous system activity paralleling the tryptamine types. The basic nitrogen present in these compounds is fixed neither "up" as in lysergic acid nor "down" as in reserpine.[1] Our first compound, 3-dimethylamino-1,2,3,4-tetrahydrocarbazole, was interesting because it prevented reserpine-induced ptosis in mice and amphetamine-induced stereotyped behavior in rats. Additional work suggests that the compound exhibited imipramine-like effects on cortical evoked potentials in cats and antidepressant activity in man.[2] We elaborated on the series and found that some of the members exhibited only imipramine-like activity, whereas others exhibited only chlorpromazine-like activity.

Synthesis. 3-Substituted amino-1,2,3,4-tetrahydrocarbazoles have been prepared by the usual Fischer cyclization. In order to prepare a number of N-substituted derivatives for a study of the effect of varying the side chain, the initial synthetic approach involved displacement of the 3-tosyloxy group with a base. This enabled us to

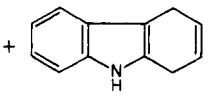
method A



prepare a variety of N-substituted 3-aminotetrahydrocarbazoles; the compounds thus prepared are included in Table I. This method suffers from the drawback that elimination in varying amounts also occurs in both possible directions. Compound II was presumed to be formed since



I II



III

Table I. Comparison of Profiles of Activity of 3-Dimethylaminotetrahydrocarbazoles with Chlorpromazine and Imipramine

	Prevention of reserpine-induced ptosis, mg/kg ip	Prevention of *d*-amphetamine stereotyped behavior in rats, mg/kg po
3-Dimethylamino-tetrahydrocarbazole (3)	Active at 10, 30, 50	Active, ED_{50} = 10.3 (7.9–13.9)
3-Dimethylamino-5-methyltetrahydro-carbazole (60)	Active at 10, 30, 50	Inactive at 32
3-Dimethylamino-6,8-difluorotetrahydro-carbazole (48)	Inactive at 30, 50	Active, ED_{50} = 1.4 (0.8–2.4)
Chlorpromazine	Inactive at 1, 10, 30, 50	Active, ED_{50} = 8.6 (5.6–13.3)
Imipramine	Active at 10, 30, 50	Inactive at 32

during isolation of these side products, highly colored oils finally result in a stable crystalline mixture on which a mass spectrum shows mass ions for both carbazole (*m/e* 167) and dihydrocarbazole (*m/e* 169). The NMR spectrum shows four allylic hydrogens and two ethylenic hydrogens and an excess of aromatic hydrogens approximating 20% of carbazole in the mixture. The UV spectrum of the mixture run against a blank containing 20% carbazole is similar to 2,3-dimethylindole, indicating that the predominant component in the mixture is III. Evidently any II which is formed is oxidized to carbazole during the work-up giving a mixture of 80% III and 20% carbazole, indicating that elimination of the tosyloxy group leads preferentially to III.

It became apparent that **3** (Table II) was the most interesting CNS compound in the series and this compound was studied in great detail. For reasons outlined below, in our continuing synthetic work the basic ketone used was generally 4-dimethylaminocyclohexanone (IV)[3]