

inoculation with a loopful of culture from the slant, the seeded broths were incubated at  $37 \pm 1^\circ\text{C}$  for 24 h. The twofold serial dilution technique<sup>11</sup> was applied. A set of tubes containing only inoculated broth was kept as control. After incubation for 24 h, the last tube with no growth of the microorganism was taken to represent the minimum inhibitory concentration (MIC, expressed in  $\mu\text{g/mL}$ ). A compound inhibiting the growth of the microbe in a concentration of  $25 \mu\text{g/mL}$  was considered active.

**Antifungal Assay.** All the fungi were maintained on Sabouraud's agar slants.<sup>10</sup> Testing was done in Sabouraud's broth. Loopfuls of the fungal cultures (*C. albicans* and *C. neoformans*) from slants were inoculated into broth and the respective inoculated broths were used for testing after incubation for 24 h at  $28 \pm 1^\circ\text{C}$ . In the case of the other three strains, small pieces of mycelia were introduced into conical flasks containing 50 mL of broth. The flasks were then incubated with shaking for 24–48 h and the clear broths were taken out of the flasks. The compounds were tested by the serial dilution method as in case of antibacterial testing. A compound, which inhibited the growth of the fungus at  $25 \mu\text{g/mL}$  concentration, was considered to be active.

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## References and Notes

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## Imidazo[4,5-*f*]quinolines. 2. A Series of 9-(Substituted amino)imidazo[4,5-*f*]quinolines as Antitapeworm Agents<sup>1,2</sup>

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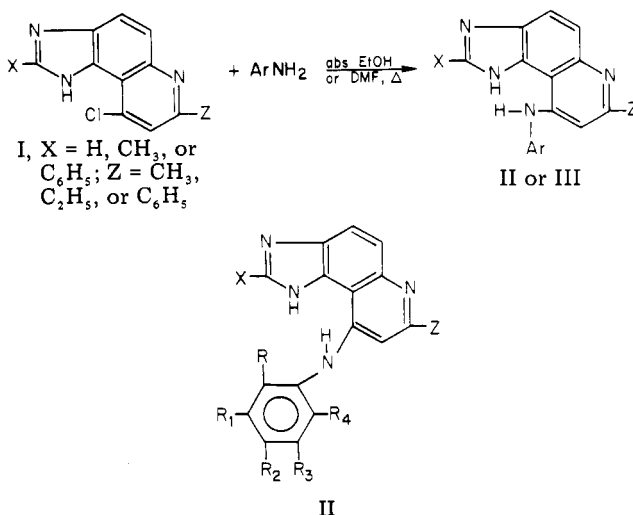
A number of 9-(substituted amino)imidazo[4,5-*f*]quinolines have been prepared and tested for anthelmintic activity in mice. All of these compounds are active in varying degrees against the tapeworm *Hymenolepis nana*.

Our success with a series of alkyl 6,7-dialkoxy-4-hydroxy-3-quinolinecarboxylates as anticoccidial agents<sup>3</sup> led us to consider the corresponding 6,7-diamino compounds. As a logical extension of this idea into an unexplored area, a number of imidazo[4,5-*f*]quinolin-9-ols were prepared.<sup>1</sup> Some of these were converted into 9-substituted amino analogues. During the biological evaluation of these latter compounds they were found to possess activity against the tapeworm *Hymenolepis nana* in mice. Since we felt there is a need for a better antitapeworm drug, a more extensive program was undertaken to study the effect of certain structural changes on the anthelmintic action of this type of imidazo[4,5-*f*]quinoline.

**Chemistry.** All of the compounds in Tables I and II were prepared by treating the appropriate 9-chloroimidazo[4,5-*f*]quinoline (I) with the prerequisite amine in refluxing EtOH or DMF (see Scheme I). The intermediates I were prepared by the method of Spencer et al.<sup>1</sup> Whenever possible, the required amine was purchased. However, in several cases it was necessary to reduce the appropriate nitro compound catalytically to the aniline which was then allowed to react directly with I. The physical properties of compounds II and III are reported in Tables I and II.

**Antitapeworm Activity.** The compounds prepared in this work were tested against the tapeworm *H. nana* in the

Scheme I



mouse. The percent reduction in worm burden for each is shown in Tables I and II. Structure-activity trends are difficult to correlate but a few generalizations can be made. Of the eight most active compounds—those that show activity at a dose level of  $25 \text{ mg/kg}$ —all have substituted

Table I. 9-(Substituted anilino)imidazo[4,5-*f*]quinolines II (See Scheme I)

No.	X	Z	R	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	Mp, °C
1	H	CH <sub>3</sub>	H	H	H	H	H	368-370
2	H	CH <sub>3</sub>	H	H	CH <sub>3</sub>	H	H	>400
3	H	CH <sub>3</sub>	H	H	CH(CH <sub>3</sub> ) <sub>2</sub>	H	H	248-254
4	H	CH <sub>3</sub>	H	H	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	H	H	303-306
5	H	C <sub>6</sub> H <sub>5</sub>	H	H	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	H	H	324-326
6	H	CH <sub>3</sub>	H	H	<i>s</i> -C <sub>4</sub> H <sub>9</sub>	H	H	228-233
7	H	CH <sub>3</sub>	H	H	C <sub>6</sub> H <sub>5</sub>	H	H	343 dec
8	H	CH <sub>3</sub>	C <sub>6</sub> H <sub>5</sub>	H	H	H	H	270-272
9	H	CH <sub>3</sub>	2,3-Benzo		H	H	H	358-360
10	H	CH <sub>3</sub>	H	3,4-Benzo		H	H	384-386
11	H	CH <sub>3</sub>	Cl	H	H	CH <sub>3</sub>	H	336-338
12	H	CH <sub>3</sub>	H	Cl	C <sub>2</sub> H <sub>5</sub>	H	H	284-287
13	H	CH <sub>3</sub>	H	Cl	<i>n</i> -C <sub>4</sub> H <sub>9</sub>	H	H	272-274
14	H	CH <sub>3</sub>	H	Cl	CH <sub>3</sub>	H	H	368 dec
15	H	CH <sub>3</sub>	CH <sub>3</sub>	H	Cl	H	H	199-206
16	H	CH <sub>3</sub>	CH <sub>3</sub>	Cl	H	H	H	340 dec
17	H	CH <sub>3</sub>	H	CF <sub>3</sub>	H	H	H	300 dec
18	H	CH <sub>3</sub>	H	CF <sub>3</sub>	Cl	H	H	298 dec
19	H	CH <sub>3</sub>	H	NO <sub>2</sub>	CH <sub>3</sub>	H	H	344-345
20	H	CH <sub>3</sub>	H	H	Br	H	H	343 dec
21	H	CH <sub>3</sub>	H	H	I	H	H	313-315
22	H	CH <sub>3</sub>	H	Cl	Cl	H	H	Nondescrip
23	H	CH <sub>3</sub>	H	Cl	F	H	H	371 dec
24	H	CH <sub>3</sub>	H	H	N(CH <sub>3</sub> ) <sub>2</sub>	H	H	215-217
25	H	CH <sub>3</sub>	H	N(CH <sub>3</sub> ) <sub>2</sub>	H	H	H	313-317
26	H	CH <sub>3</sub>	H	H	N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	H	H	299-300
27	H	CH <sub>3</sub>	H	H	<i>c</i> -NC <sub>5</sub> H <sub>10</sub>	H	H	328 dec
28	H	CH <sub>3</sub>	H	H	<i>c</i> -N(CH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> N-CH <sub>3</sub>	H	H	311-314
29	H	CH <sub>3</sub>	H	Cl	N(CH <sub>3</sub> ) <sub>2</sub>	H	H	338-340
30	H	CH <sub>3</sub>	H	Cl	<i>c</i> -NC <sub>4</sub> H <sub>8</sub>	H	H	318-320
31	H	CH <sub>3</sub>	H	Cl	<i>c</i> -NC <sub>5</sub> H <sub>10</sub>	H	H	265-272
32	H	CH <sub>3</sub>	H	Cl	<i>c</i> -N(CH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> N-CH <sub>3</sub>	H	H	265-272
33	H	CH <sub>3</sub>	H	Cl	<i>c</i> -N(CH <sub>2</sub> CH <sub>2</sub> ) <sub>2</sub> N-CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	226-234
34	H	CH <sub>3</sub>	H	H	OCH <sub>3</sub>	H	H	300-305
35	H	CH <sub>3</sub>	H	OCH <sub>3</sub>	H	H	H	316-317
36	H	CH <sub>3</sub>	OCH <sub>3</sub>	H	H	H	H	291-293
37	CH <sub>3</sub>	CH <sub>3</sub>	H	H	OCH <sub>3</sub>	H	H	315-317
38	H	C <sub>2</sub> H <sub>5</sub>	H	H	OCH <sub>3</sub>	H	H	308-310
39	C <sub>6</sub> H <sub>5</sub>	CH <sub>3</sub>	H	H	OCH <sub>3</sub>	H	H	258-274
40	H	C <sub>6</sub> H <sub>5</sub>	H	H	OCH <sub>3</sub>	H	H	294 dec
41	H	CH <sub>3</sub>	H	H	OC <sub>2</sub> H <sub>5</sub>	H	H	330-331
42	H	CH <sub>3</sub>	H	H	O(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	H	H	317-318
43	H	CH <sub>3</sub>	H	H	OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	H	H	305-307
44	H	CH <sub>3</sub>	H	H	OC <sub>6</sub> H <sub>5</sub>	H	H	336-338
45	H	CH <sub>3</sub>	OCH <sub>3</sub>	H	Cl	H	H	295-297
46	H	CH <sub>3</sub>	H	Cl	OC <sub>2</sub> H <sub>5</sub>	H	H	308-311
47	H	CH <sub>3</sub>	H	H	SCH <sub>3</sub>	H	H	318-321
48	H	CH <sub>3</sub>	H	SCH <sub>3</sub>	H	H	H	313-315
49	H	CH <sub>3</sub>	SCH <sub>3</sub>	H	H	H	H	295-296
50	H	CH <sub>3</sub>	H	H	OCH <sub>2</sub> CH <sub>2</sub> N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	H	H	205 dec
51	H	CH <sub>3</sub>	H	OCH <sub>2</sub> O		H	H	384-388
52	H	CH <sub>3</sub>	H	OCH <sub>3</sub>	OCH <sub>3</sub>	H	H	278-280
53	H	CH <sub>3</sub>	H	OC <sub>2</sub> H <sub>5</sub>	OC <sub>2</sub> H <sub>5</sub>	H	H	279-280
54	H	CH <sub>3</sub>	H	OCH(CH <sub>3</sub> ) <sub>2</sub>	OCH(CH <sub>3</sub> ) <sub>2</sub>	H	H	278-279
55	H	CH <sub>3</sub>	H	<i>n</i> -OC <sub>4</sub> H <sub>9</sub>	<i>n</i> -OC <sub>4</sub> H <sub>9</sub>	H	H	252-254
56	H	CH <sub>3</sub>	H	<i>i</i> -OC <sub>4</sub> H <sub>9</sub>	<i>i</i> -OC <sub>4</sub> H <sub>9</sub>	H	H	273-277
57	H	CH <sub>3</sub>	H	<i>n</i> -OC <sub>5</sub> H <sub>11</sub>	<i>n</i> -OC <sub>5</sub> H <sub>11</sub>	H	H	244-246
58	H	CH <sub>3</sub>	H	<i>i</i> -OC <sub>5</sub> H <sub>11</sub>	<i>i</i> -OC <sub>5</sub> H <sub>11</sub>	H	H	265-266
59	H	CH <sub>3</sub>	H	<i>s</i> -OC <sub>5</sub> H <sub>11</sub>	<i>s</i> -OC <sub>5</sub> H <sub>11</sub>	H	H	249-252
60	H	CH <sub>3</sub>	OCH <sub>3</sub>	H	H	OCH <sub>3</sub>	H	255-258
61	H	CH <sub>3</sub>	OC <sub>2</sub> H <sub>5</sub>	H	H	OC <sub>2</sub> H <sub>5</sub>	H	273-275
62	H	CH <sub>3</sub>	OC <sub>2</sub> H <sub>5</sub>	H	H	OCH <sub>3</sub>	H	260-273
63	H	CH <sub>3</sub>	OCH <sub>3</sub>	H	H	OC <sub>2</sub> H <sub>5</sub>	H	273-276
64	H	CH <sub>3</sub>	OCH <sub>3</sub>	H	Cl	OCH <sub>3</sub>	H	277-279
65	H	CH <sub>3</sub>	OC <sub>2</sub> H <sub>5</sub>	H	Cl	OC <sub>2</sub> H <sub>5</sub>	H	190-194, 280-282
66	H	CH <sub>3</sub>	OCH <sub>3</sub>	H	OCH <sub>3</sub>	Cl	H	>400
67	H	CH <sub>3</sub>	<i>n</i> -OC <sub>4</sub> H <sub>9</sub>	H	Cl	<i>n</i> -OC <sub>4</sub> H <sub>9</sub>	H	240-243
68	H	CH <sub>3</sub>	H	OCH <sub>3</sub>	OCH <sub>3</sub>	OCH <sub>3</sub>	H	288-289
69	H	CH <sub>3</sub>	OC <sub>2</sub> H <sub>5</sub>	H	OC <sub>2</sub> H <sub>5</sub>	OC <sub>2</sub> H <sub>5</sub>	H	168-170
70	H	CH <sub>3</sub>	H	H	COCH <sub>3</sub>	H	H	336-338
71	H	CH <sub>3</sub>	H	COCH <sub>3</sub>	H	H	H	225-228
72	H	CH <sub>3</sub>	H	H	COC <sub>2</sub> H <sub>5</sub>	H	H	328-330
73	H	CH <sub>3</sub>	H	H	COC <sub>3</sub> H <sub>7</sub>	H	H	205-235
74	H	CH <sub>3</sub>	H	H	N=NC <sub>6</sub> H <sub>5</sub>	H	H	339 dec

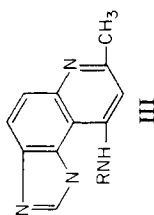
Bunamidine

<sup>a</sup> I = inactive. <sup>b</sup> mg/kg b.i.d.

Yield, %	Recrystn solvent	Emp formula	% redn, <i>H. nana</i> in mice				
			300 <sup>b</sup>	100 <sup>b</sup>	50 <sup>b</sup>	25 <sup>b</sup>	10 <sup>b</sup>
40	EtOH	C <sub>17</sub> H <sub>14</sub> N <sub>4</sub> ·HCl		40			
47	DMF	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> ·HCl	100	I <sup>a</sup>			
75	<i>i</i> -PrOH	C <sub>20</sub> H <sub>20</sub> N <sub>4</sub> ·HCl·0.5H <sub>2</sub> O		100	53	I	
100	MeNO <sub>2</sub>	C <sub>21</sub> H <sub>22</sub> N <sub>4</sub> ·HCl	100	I			
93	MeOH-Et <sub>2</sub> O	C <sub>26</sub> H <sub>24</sub> N <sub>4</sub> ·HCl	69	I			
98	MeOH-Et <sub>2</sub> O	C <sub>21</sub> H <sub>22</sub> N <sub>4</sub> ·HCl·0.25H <sub>2</sub> O		100	I		
65	MeOH-Et <sub>2</sub> O	C <sub>23</sub> H <sub>18</sub> N <sub>4</sub> ·HCl·0.25H <sub>2</sub> O		100	94	I	
59	MeOH-Et <sub>2</sub> O	C <sub>23</sub> H <sub>18</sub> N <sub>4</sub> ·HCl·0.25H <sub>2</sub> O	100	I			
76	MeOH	C <sub>21</sub> H <sub>16</sub> N <sub>4</sub> ·HCl·0.25H <sub>2</sub> O		100	I		
94	MeOH	C <sub>21</sub> H <sub>16</sub> N <sub>4</sub> ·HCl		72	I		
55	MeOH	C <sub>18</sub> H <sub>15</sub> ClN <sub>4</sub> ·HCl	98	I			
80	<i>i</i> -PrOH	C <sub>19</sub> H <sub>17</sub> ClN <sub>4</sub> ·HCl		100	93	I	
67	<i>i</i> -PrOH	C <sub>21</sub> H <sub>21</sub> ClN <sub>4</sub> ·HCl·0.5H <sub>2</sub> O		100	100	65	
98	MeOH-Et <sub>2</sub> O	C <sub>18</sub> H <sub>15</sub> ClN <sub>4</sub> ·HCl		94	90	I	
61	EtOH	C <sub>18</sub> H <sub>15</sub> ClN <sub>4</sub> ·HCl		100	I		
37	MeOH-Et <sub>2</sub> O	C <sub>18</sub> H <sub>15</sub> ClN <sub>4</sub> ·HCl·H <sub>2</sub> O		100	94	I	
66	EtOH	C <sub>18</sub> H <sub>13</sub> F <sub>3</sub> N <sub>4</sub> ·HCl·0.5H <sub>2</sub> O	100	I			
64	MeOH	C <sub>18</sub> H <sub>12</sub> ClF <sub>3</sub> N <sub>4</sub> ·HCl·0.75H <sub>2</sub> O		84	87	I	
100	MeOH	C <sub>18</sub> H <sub>15</sub> N <sub>5</sub> O <sub>2</sub> ·HCl	83	I			
81	MeOH	C <sub>17</sub> H <sub>13</sub> BrN <sub>4</sub> ·HCl		61	I		
98	EtOH	C <sub>17</sub> H <sub>13</sub> IN <sub>4</sub> ·HCl		84	I		
17	MeOH	C <sub>17</sub> H <sub>12</sub> Cl <sub>2</sub> N <sub>4</sub> ·HCl·0.5H <sub>2</sub> O		65	I		
69	MeOH	C <sub>17</sub> H <sub>12</sub> ClFN <sub>4</sub> ·HCl		82	I		
42	MeOH	C <sub>19</sub> H <sub>19</sub> N <sub>5</sub> ·HCl·1.5H <sub>2</sub> O		100	I		
64	MeOH	C <sub>19</sub> H <sub>19</sub> N <sub>5</sub> ·HCl		100	87	I	
92	MeOH	C <sub>21</sub> H <sub>23</sub> N <sub>4</sub> ·HCl		79	I		
100	MeOH	C <sub>21</sub> H <sub>23</sub> N <sub>5</sub> ·HCl		64	62	I	
92	MeOH	C <sub>22</sub> H <sub>24</sub> N <sub>5</sub> ·HCl·1.75H <sub>2</sub> O	80	I			
25	EtOH	C <sub>19</sub> H <sub>18</sub> ClN <sub>5</sub> ·HCl		71	I		
66	MeOH-Et <sub>2</sub> O	C <sub>21</sub> H <sub>20</sub> ClN <sub>5</sub> ·HCl·0.5H <sub>2</sub> O		100	46	I	
98	MeOH-Et <sub>2</sub> O	C <sub>22</sub> H <sub>22</sub> ClN <sub>5</sub> ·HCl·0.25H <sub>2</sub> O		100	80	I	
11	MeOH-Et <sub>2</sub> O	C <sub>22</sub> H <sub>23</sub> ClN <sub>6</sub> ·2HCl·3.5H <sub>2</sub> O	100	I			
60	DMF	C <sub>28</sub> H <sub>27</sub> ClN <sub>6</sub> ·HCl		100	100	77	I
73	EtOH-Et <sub>2</sub> O	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> O·HCl·0.5H <sub>2</sub> O		64	I		
69	MeOH	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> O·HCl		73	I		
93	MeOH	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> O·HCl		66	I		
96	MeOH	C <sub>19</sub> H <sub>18</sub> N <sub>4</sub> O·HCl	100	I			
63	EtOH	C <sub>19</sub> H <sub>18</sub> N <sub>4</sub> O·HCl		46	I		
68	EtOH	C <sub>24</sub> H <sub>20</sub> N <sub>4</sub> O·HCl·0.5H <sub>2</sub> O		94	I		
48	DMF	C <sub>23</sub> H <sub>18</sub> N <sub>4</sub> O·HCl		66	I		
36	EtOH	C <sub>19</sub> H <sub>18</sub> N <sub>4</sub> O·HCl		100	I		
57	EtOH	C <sub>21</sub> H <sub>22</sub> N <sub>4</sub> O·HCl	100	I			
100	EtOH	C <sub>24</sub> H <sub>20</sub> N <sub>4</sub> O·HCl·0.25H <sub>2</sub> O		81	64		
87	MeOH	C <sub>23</sub> H <sub>18</sub> N <sub>4</sub> O·HCl		100	66	I	
77	DMF	C <sub>18</sub> H <sub>15</sub> N <sub>4</sub> O·HCl		52	I		
92	MeOH	C <sub>19</sub> H <sub>17</sub> N <sub>4</sub> O·HCl		100	50	I	
60	MeOH	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> S·HCl·H <sub>2</sub> O		100	62		
81	MeOH	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> S·HCl		100	I		
100	EtOH	C <sub>18</sub> H <sub>16</sub> N <sub>4</sub> S·HCl·0.5H <sub>2</sub> O	93	I			
64	EtOH-HCl-Et <sub>2</sub> O	C <sub>23</sub> H <sub>27</sub> N <sub>5</sub> O·3HCl·H <sub>2</sub> O	100	I			
75	MeOH	C <sub>18</sub> H <sub>14</sub> N <sub>4</sub> O <sub>2</sub> ·HCl	100	I			
67	MeOH	C <sub>19</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub> ·HCl		73	I		
100	MeOH	C <sub>21</sub> H <sub>22</sub> N <sub>4</sub> O <sub>2</sub> ·HCl		100	84	I	
72	EtOH-Et <sub>2</sub> O	C <sub>23</sub> H <sub>26</sub> N <sub>4</sub> O <sub>2</sub> ·HCl		100	94	I	
48	MeOH	C <sub>25</sub> H <sub>30</sub> N <sub>4</sub> O <sub>2</sub> ·HCl		100	95	I	
48	EtOH	C <sub>25</sub> H <sub>30</sub> N <sub>4</sub> O <sub>2</sub> ·HCl		100	78	77	I
100	MeOH	C <sub>27</sub> H <sub>34</sub> N <sub>4</sub> O <sub>2</sub> ·HCl·0.25H <sub>2</sub> O		63	I		
61	EtOH	C <sub>27</sub> H <sub>34</sub> N <sub>4</sub> O <sub>2</sub> ·HCl·0.25H <sub>2</sub> O		100	100	67	I
52	MeNO <sub>2</sub>	C <sub>27</sub> H <sub>34</sub> N <sub>4</sub> O <sub>2</sub> ·HCl		100	100	92	I
41	MeOH	C <sub>19</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub> ·HCl·0.5H <sub>2</sub> O		100	I		
72	MeOH	C <sub>21</sub> H <sub>22</sub> N <sub>4</sub> O <sub>2</sub> ·HCl		100	100	I	
33	EtOH	C <sub>20</sub> H <sub>20</sub> N <sub>4</sub> O <sub>2</sub> ·HCl·H <sub>2</sub> O		100	76	I	
63	MeOH	C <sub>20</sub> H <sub>20</sub> N <sub>4</sub> O <sub>2</sub> ·HCl		100	89	I	
63	MeOH	C <sub>19</sub> H <sub>17</sub> ClN <sub>4</sub> O <sub>2</sub> ·HCl		100	72	100	I
81	MeOH	C <sub>21</sub> H <sub>21</sub> ClN <sub>4</sub> O <sub>2</sub> ·HCl		100	100	I	
17	MeOH	C <sub>19</sub> H <sub>17</sub> ClN <sub>4</sub> O <sub>2</sub> ·HCl·H <sub>2</sub> O		85	82	I	
82	MeOH	C <sub>25</sub> H <sub>29</sub> ClN <sub>4</sub> O <sub>2</sub> ·HCl		100	84	74	I
44	MeOH	C <sub>20</sub> H <sub>20</sub> N <sub>4</sub> O <sub>3</sub> ·HCl		70	I		
41	EtOH	C <sub>23</sub> H <sub>26</sub> N <sub>4</sub> O <sub>3</sub> ·HCl·1.5H <sub>2</sub> O		89	80	I	
73	MeOH	C <sub>19</sub> H <sub>16</sub> N <sub>4</sub> O·HCl		100	100	56	I
82	MeOH	C <sub>19</sub> H <sub>16</sub> N <sub>4</sub> O·HCl·0.5H <sub>2</sub> O		96	I		
93	MeOH	C <sub>20</sub> H <sub>18</sub> N <sub>4</sub> O·HCl		75	78	I	
61	MeOH	C <sub>21</sub> H <sub>20</sub> N <sub>4</sub> O·HCl·0.5H <sub>2</sub> O	100	I			
85	MeOH	C <sub>23</sub> H <sub>18</sub> N <sub>6</sub> ·HCl	100	I			
				100	59	30	I

Table II. 9-(Substituted amino)imidazo[4,5-f]quinolines

No.	R	Mp, °C	Yield, %	Recrystn solvent	Emp formula	% retn, <i>H. nana</i> in mice			
						300 <sup>a</sup>	100 <sup>a</sup>	50 <sup>a</sup>	25 <sup>a</sup>
75	CH <sub>2</sub> -C <sub>6</sub> H <sub>4</sub> -p-OCH <sub>3</sub>	250-255 dec	98	MeOH-Et <sub>2</sub> O	C <sub>19</sub> H <sub>14</sub> N <sub>4</sub> O·HCl·0.75H <sub>2</sub> O	60	I <sup>b</sup>		
76	C <sub>6</sub> H <sub>11</sub>	174-178	54	EtOH-Et <sub>2</sub> O	C <sub>17</sub> H <sub>20</sub> N <sub>4</sub> ·HCl·H <sub>2</sub> O	81	I		
77	3-C <sub>5</sub> H <sub>3</sub> N-6-OCH <sub>3</sub>	268-271	98	EtOH	C <sub>17</sub> H <sub>15</sub> N <sub>5</sub> O		100	94	I
78	3-C <sub>5</sub> H <sub>3</sub> N-6-c-(CH <sub>2</sub> CH <sub>3</sub> ) <sub>2</sub> N-CH <sub>3</sub>	256-259	51	MeOH	C <sub>21</sub> H <sub>23</sub> N <sub>7</sub> ·2.5HCl·H <sub>2</sub> O	64	I		
79	3-C <sub>5</sub> H <sub>3</sub> N-6-c-NC <sub>5</sub> H <sub>10</sub>	354-358	35	EtOH-Et <sub>2</sub> O	C <sub>21</sub> H <sub>22</sub> N <sub>7</sub> ·HCl·0.25H <sub>2</sub> O	100	I		



III

<sup>a</sup> mg/kg b.i.d. <sup>b</sup> I = inactive.

anilino groups at position 9. Five of these have two alkoxy substituents (56, 58, 59, 64, and 67); two also have a chlorine atom. Of the remaining three, one has a butyl group and chlorine atom (13), one has chlorine and a 4-benzyl-1-piperazino group (33), and the other has a lone acetyl group (70).

In the dialkoxy compounds tested the position of the groups is unimportant, but branched chains are better than straight chains (i.e., isobutoxy is more active than *n*-butoxy; isoamyloxy and *sec*-amyloxy are better than *n*-amyloxy).

In some cases the presence of a chlorine atom enhances activity (13 vs. 4, 14 vs. 2, 64 vs. 60); in others there is little or no effect (65 vs. 61, 45 vs. 36).

All of the eight compounds cited above showed a higher degree of activity against *H. nana* than the standard drug, bunamidine,<sup>4</sup> which is included in Table I for comparison. Further evaluation of these compounds awaits more extensive investigation.

Screening of the compounds prepared in this work against other helminths revealed only minor activity.

### Experimental Section

Melting points were determined in open capillary tubes using a Mel-Temp melting point apparatus and are uncorrected. The analyses for all compounds were determined for C, H, and N and were within ±0.4% of the calculated values. Some of the compounds were extremely difficult to dry. For all those reported as hydrates, the presence of water was indicated by the appearance of droplets in the upper portions of capillaries during melting point determinations. In several cases differential thermal analysis also showed elimination of water at elevated temperatures. IR and NMR spectra are consistent with assigned structures in all cases. The physical constants for all of the 9-(substituted anilino)-imidazo[4,5-f]quinolines are reported in Table I and for the rest of the 9-(substituted amino)imidazo[4,5-f]quinolines in Table II. Unless otherwise specified, the necessary amines were purchased. The following nitro compounds were prepared by literature procedures: 3-chloro-4-ethoxynitrobenzene,<sup>5</sup> 3,4-diisopropoxynitrobenzene,<sup>3</sup> 3,4-dibutoxynitrobenzene,<sup>3</sup> 3,4-diisobutoxynitrobenzene,<sup>3</sup> 3,4-diamyloxynitrobenzene,<sup>3</sup> 3,4-diisoamyloxynitrobenzene,<sup>3</sup> di-*sec*-amyloxynitrobenzene,<sup>3</sup> 5-ethoxy-3-methoxynitrobenzene,<sup>6</sup> 2-ethoxy-5-methoxynitrobenzene,<sup>6</sup> 2,4,5-triethoxynitrobenzene,<sup>7</sup> 4-(2-diethylaminoethoxy)nitrobenzene,<sup>8</sup> 4-piperidinonitrobenzene,<sup>9</sup> 4-(4-methylpiperazino)nitrobenzene,<sup>10</sup> 3-chloro-4-dimethylaminonitrobenzene,<sup>11</sup> 3-chloro-4-(4-methylpiperazino)nitrobenzene,<sup>10</sup> and 3-chloro-4-ethylnitrobenzene.<sup>12</sup> Two intermediates, 4-*sec*-butylnitrobenzene and 4-chloro-2,5-dibutoxynitrobenzene, were purchased. The physical properties of the final products are listed in Tables I and II.

**5-Nitro-2-piperidinopyridine.** A mixture of 2-chloro-5-nitropyridine (23.7 g, 0.15 mol) and absolute EtOH (100 mL) was placed in a 500-mL, three-neck flask fitted with a stirrer, thermometer, condenser, and addition funnel. The mixture was stirred while a solution of piperidine (25.5 g, 0.3 mol) in absolute EtOH (200 mL) was added. The reaction mixture was stirred at reflux for 3 h. The resulting solution was treated with charcoal and filtered hot. The filtrate was chilled and the crystals were collected to yield 24.6 g (79%) of product, mp 74-79 °C. A small portion (2.0 g) was recrystallized from absolute EtOH to yield 0.8 g of yellow crystals, mp 74-76 °C. Anal. (C<sub>10</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>).

In a similar manner, 2-(*N*-methylpiperazino)-5-nitropyridine was prepared from 2-chloro-5-nitropyridine and *N*-methylpiperazine: mp 95-97 °C after recrystallization from aqueous EtOH. Anal. (C<sub>10</sub>H<sub>14</sub>N<sub>4</sub>O<sub>2</sub>).

**3-Chloro-4-pyrrolidinonitrobenzene.** A mixture of 3,4-dichloronitrobenzene (38.4 g, 0.2 mol) and pyrrolidine (28.4 g, 0.4 mol) was heated at 100-115 °C in a 250-mL glass-lined pressure bottle for 9 h. The reaction mixture was removed, ground in a mortar with H<sub>2</sub>O (ca. 250 mL), and filtered. The dark brownish yellow solid was dissolved in boiling absolute EtOH (450 mL) and filtered while hot. The chilled filtrate was filtered to yield 36.0 g (80%) of dark yellow crystals, mp 87-92 °C. An analytical sample was prepared by recrystallization from absolute EtOH: mp 89-92 °C. Anal. (C<sub>10</sub>H<sub>11</sub>ClN<sub>2</sub>O<sub>2</sub>).

**3-Chloro-4-piperidinonitrobenzene.** A 250-mL, three-neck flask fitted with a stirrer, condenser, and thermometer was charged with 3,4-dichloronitrobenzene (19.2 g, 0.1 mol) and piperidine (17.0 g, 0.2 mol). The mixture was stirred for 3.5 h at 95 °C. The reaction mixture was diluted with water (ca. 200 mL) and stirring was continued as the mixture cooled. The solid was collected and recrystallized from absolute EtOH (70 mL) to yield 15.8 g (66%) of yellow crystals, mp 36–41 °C. An analytical sample was prepared by a second recrystallization from absolute EtOH: mp 39–42 °C. Anal. ( $C_{11}H_{13}ClN_2O_2$ ).

**4-(4-Benzylpiperazino)-3-chloronitrobenzene.** To a 500-mL, three-neck flask fitted with a stirrer, condenser, and thermometer was added 3,4-dichloronitrobenzene (19.2 g, 0.1 mol), 1-benzylpiperazine (35.2 g, 0.2 mol), and DMF (200 mL). The mixture was stirred for 2.5 h while heating at reflux. The reaction mixture was diluted with  $H_2O$  (500 mL) and extracted with  $Et_2O$ . The organic layer was separated and dried over anhydrous  $MgSO_4$ . The drying agent was removed and the filtrate evaporated to dryness in vacuo. The residue was recrystallized from absolute EtOH to yield 22.5 g (68%) of product melting at 92–95 °C. An analytical sample was prepared by recrystallization from absolute EtOH to give yellow crystals, mp 93–95 °C. Anal. ( $C_{17}H_{18}ClN_3O_2$ ).

The experimental procedures described below are typical for the preparation of the compounds listed in Tables I and II.

**A. From the Aniline.** 9-(4-*n*-Butylanilino)-7-methylimidazo[4,5-*f*]quinoline Hydrochloride (4). A mixture of 9-chloro-7-methylimidazo[4,5-*f*]quinoline (I, R = H;  $R_1 = CH_3$ )<sup>1</sup> (21.7 g, 0.1 mol) and 4-*n*-butylaniline (14.9 g, 0.1 mol) in absolute EtOH (200 mL) was stirred at reflux overnight. The reaction solution was concentrated to dryness in vacuo. The residue was dried at 100 °C to yield crude 4 (36.5 g), mp 296–303 °C dec.

**B. From the Nitro Compound.** 9-(4-*n*-Butyl-3-chloro-anilino)-7-methylimidazo[4,5-*f*]quinoline Hydrochloride Hemihydrate (13). A 500-mL reduction bottle was charged with 2-chloro-4-nitro-*n*-butylbenzene (prepared from 4-nitrobutylbenzene by the method of Kövendi and Kircz)<sup>12</sup> (24.0 g, 0.11 mol) and DMF (200 mL). The mixture was shaken in an atmosphere of hydrogen together with Raney active nickel catalyst No. 28 in water (1 teaspoon). After the hydrogen uptake had ceased (85% of theory), the catalyst was removed by filtration. The filtrate was placed in a 500-mL, three-neck flask fitted with a stirrer, condenser, and thermometer. To the solution was added 9-chloro-7-methylimidazo[4,5-*f*]quinoline (I, R = H;  $R_1 = CH_3$ )<sup>1</sup> (21.7 g, 0.1 mol) and DMF (100 mL). The mixture was stirred overnight at 110 °C. The solution was chilled and filtered. The crystals were dried at 60 °C to yield 26.9 g of crude 13.

**Biological Method.** The taeniocidal activity was determined by the use of *H. nana* as described previously by Culbertson<sup>13</sup> using modified techniques of Steward<sup>14</sup> and Standen.<sup>15</sup> In ad-

dition, on the 13th day of infection, to the end of testing, the mice were given hydrocortisone (USP-microfine, Merck & Co., Inc., Rahway, N.J.) at the rate of 25 mg/L in their drinking water to prevent natural worm elimination. Medication was administered twice a day for 3 days (days 18–20 inclusive of the infection) to groups of five mice. Necropsy was performed on infection day 22 and worm counts were made by pressing the small intestine between glass plates and scanning at 7× magnification.

Compound effectiveness was determined as a percentage reduction in the manner described previously.<sup>16</sup>

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## Synthesis of Medroxyprogesterone Bromoacetate for Affinity Labeling

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Medroxyprogesterone bromoacetate (17 $\alpha$ -hydroxy-6 $\alpha$ -methyl-4-pregnene-3,20-dione 17-bromoacetate) was synthesized by reaction of 17 $\alpha$ -hydroxy-6 $\alpha$ -methyl-4-pregnene-3,20-dione with bromoacetic acid-trifluoroacetic anhydride followed by treatment of the intermediate with dilute ethanolic HBr. The product forms conjugates with L-cysteine, L-histidine, and L-methionine and inactivates 20 $\beta$ -hydroxy steroid dehydrogenase (E.C. 1.1.1.53.) from *Streptomyces hydrogenans* in a time-dependent and irreversible manner. The title compound possesses a long-acting progestational effect in day 9 pregnant bilaterally ovariectomized rats. The affinity labeling analogue of the oral contraceptive medroxyprogesterone acetate is proposed for use in reproductive biological experiments.

Previous reports from this laboratory described the synthesis of 16 $\alpha$ -bromoacetoxypregesterone<sup>1</sup> and 19-nortestosterone bromoacetate<sup>2</sup> which are affinity-labeling steroids<sup>3</sup> that terminate pregnancy in rats by apparently interfering with uterine progesterone uptake.<sup>2,4</sup> In order

to further explore the effect that the bromoacetoxy reagent group has on the biological activity of progesterone analogues we attempted the synthesis of medroxyprogesterone bromoacetate (2, Scheme 1), a brominated analogue of the powerful progestin.<sup>5</sup> Attempts to synthesize 2 by