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Imidazo[4,5-*f*]quinolines. 4. Synthesis and Anthelmintic Activity of a Series of Imidazo[4,5-*f*]quinolin-9-ols[1]

Robert J. Alaimo,* Claude F. Spencer, James B. Sheffer, Ronald J. Storrin, Christopher J. Hatton,[2] and Robert E. Kohls

Scientific Affairs Department, Norwich-Eaton Pharmaceuticals, Division of Morton-Norwich Products, Inc., Norwich, New York 13815. *Received October 17, 1977*

A series of 2-arylimidazo[4,5-*f*]quinolin-9-ols has been prepared by a multistep procedure from various 5-aminobenzimidazoles. These compounds possess a significant degree of anthelmintic activity against the mouse tapeworm *Hymenolepis nana*. The most active compound is the 2-(2-furyl) analogue. Additional anthelmintic testing is reported for this compound.

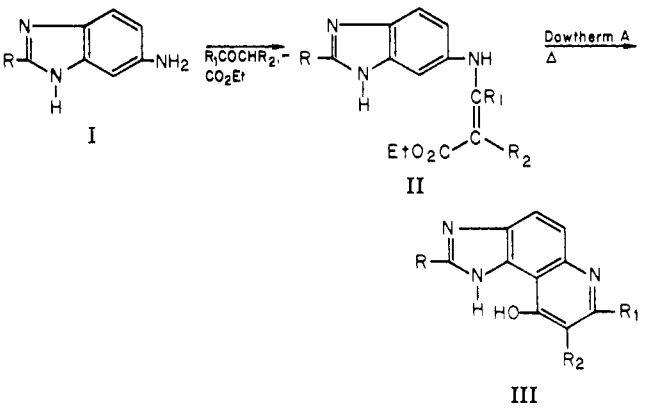
The first paper in this series reported the synthesis of a number of imidazo[4,5-*f*]quinolin-9-ols.[3] As a result of the anthelmintic activity shown by one of these compounds, **7** (Table I), a number of analogues were prepared and tested for anthelmintic activity. This paper reports the synthesis and preliminary anthelmintic evaluation of these new analogues[4] and an improved synthesis and further evaluation of one of them (**1**, furodazole).

Chemistry. The imidazo[4,5-*f*]quinolin-9-ols III (Table I) were prepared (Scheme I) by the condensation of a 5-amino-2-substituted benzimidazole I with the appropriate β-keto ester, followed by thermal cyclization of the resultant benzimidazolylacrylate II in boiling Dowtherm A. The 5-amino-2-substituted benzimidazoles I required for compounds **2–7** were prepared (Scheme II) from 2,4-dinitroaniline. Acylation with the appropriate acid chloride, followed by catalytic hydrogenation and acid-catalyzed cyclization of the intermediate 2,4-dinitrobenzanilides IV, gave the amino compounds I. The 5-aminobenzimidazole I required for compound **1** was prepared from the 5-nitro derivative[5] by catalytic hydrogenation. Intermediates II and IV were isolated but not purified prior to reaction. The 5-amino-2-substituted benzimidazoles I generally were used without isolation.

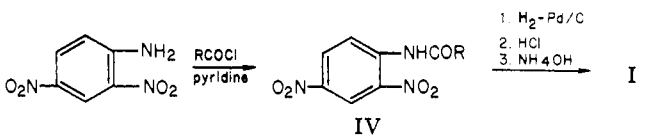
As a result of significant activity shown by **1** (see the biological section), a large quantity of this material was needed for additional anthelmintic evaluation. The preparation of **1** (Scheme I) from the aminobenzimidazole I was well adapted for large-scale synthesis. The preparation of this aminobenzimidazole, however, could not be scaled up conveniently, and alternate syntheses were investigated. The Weidenhagen synthesis of this intermediate[5] had several disadvantages. Two steps are involved (Scheme III): the preparation and isolation of the copper salt **8** and treatment of **8** with hydrogen sulfide to give **9**. Furthermore, the use of hydrogen sulfide on a large scale could create serious environmental problems with waste disposal and odor. In addition, the presence of residual amounts of sulfur in the product caused difficulties in the subsequent reduction step to the amine.

A second synthetic sequence for the preparation of **9** involved the reaction of 2-furancarbonyl chloride with 1,2-diamino-4-nitrobenzene in the classic Phillips synthesis (Scheme IV).[6] Although it has been reported that this sequence is impractical for this type of compound,[5] we were

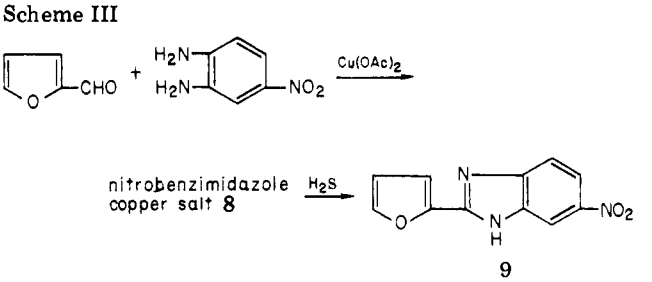
Scheme I



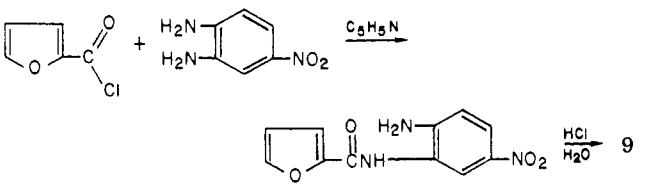
Scheme II



Scheme III



Scheme IV



able to produce **9** in high yield.[4] This sequence, although better adapted to scale-up than the Weidenhagen syn-

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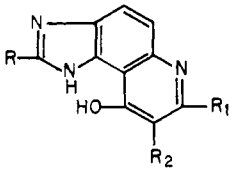
Table I



III

No.	R	R_1	R_2	Mp, °C	Recrystn solvent	Formula[a]	% yield[b] overall	Anthelmintic testing in vivo, *H. nana*, dose in mg/kg,[c] % redn						
								300	100	50	25	10	5	2.5
1	2-Furyl	Me	H	280-282	$MeNO_2$	$C_{15}H_{11}N_3O_2 \cdot 0.25H_2O$	37	100	100	100	100	75	57	35
2	4-Me-Ph	Me	H	280-281	$MeNO_2$	$C_{18}H_{15}N_3O \cdot 0.25H_2O$	57	70	I[d]					
3	Ph	Cyclopentano		369-375	DMF	$C_{19}H_{15}N_3O$	41	100	100	41	I			
4	Ph	Me	Me	328-338	DMF	$C_{18}H_{15}N_3O \cdot 0.5H_2O$	43	100	100	94	I			
5	Ph	Ph	H	304-307	DMF-H_2O	$C_{22}H_{15}N_3O$	49	100	100	82	I			
6	2-Cl-Ph	Me	H	366-367	DMF	$C_{17}H_{15}ClN_3O$	48	100	100	75	I			
7[e]	Ph	Me	H					100	93	94	77	I		
Bunamidine								Toxic	100	59	30	I		

[a] All compounds were analyzed for C, H, and N. Analytical results were within ±0.4% of the theoretical values. [b] Percent overall yield from commercially available starting materials. [c] All results were statistically significant at least at the 0.05 level of significance by the Mann-Whitney "U" test. [d] I, inactive at dose tested. [e] See ref 3.

Table II. Activity against *Taenia crassiceps*

	Dose, mg/kg	No. of worms recovered at necropsy
Unmedicated	0	4
Control	0	1
	0	9
Furadazole (1)	100	0
	100	0
	100	0
Bunamidine	44	0
(200-mg tablets)	48	1
	52	0
Niclosamide	160	0
(500-mg tablets)	153	0
	171	0

thesis, was not considered practical due to the additional time and more expensive chemical requirements.

An investigation of the Weidenhagen synthesis was undertaken to see if it could be adequately modified for our purposes. A more suitable nonmetal oxidizing agent was sought, since the use of cupric acetate and hydrogen sulfide was the primary drawback to the original synthesis. After numerous other oxidants were tried with little or no success, benzoquinone was selected and proved to be well suited for the synthesis of **9**.

By the use of this procedure, **9** could be prepared in high yield directly from 2-furancarboxaldehyde and 1,2-diamino-4-nitrobenzene in one step even on a pilot plant scale without complications. The use of benzoquinone as an oxidant in the preparation of other benzimidazoles has shown equal utility, although the full scope of this process has not been investigated.[7]

Anthelmintic Testing. The compounds were tested as previously described[8] against the mouse tapeworm *Hymenolepis nana*. Their activity, along with that of the reference drug bunamidine, is expressed in percent reduction in worm burden in Table II.[9] The results were analyzed for their statistical significance by means of the Mann-Whitney "U" test.[10]

The most active compounds in reducing worm infestation are **1**, **4**, and **7**. These all are unsubstituted 2-aryl derivatives. Addition of a methyl group at position 8 (**4**) or a 7,8-cyclopentano group (**3**) results in a decrease in activity when compared to **7**, which is unsubstituted at position 8. The 2-furyl analogue **1** is the most active overall.

When compared to bunamidine for activity against *H. nana*, the results indicate **1** to be significantly more active. These results prompted further evaluation of **1**, which has the U.S. adopted name "furodazole".

Secondary evaluation was performed against *Taenia pisiformis* and *Taenia crassiceps* in the dog, *Syphacia obvelata* in the mouse, and *Moniezia* sp. in sheep. Furodazole (**1**) provided complete clearance of *T. pisiformis* in beagle dogs with single oral doses ranging from 50 to 150 mg/kg of body weight. No drug-related emesis or other untoward clinical signs were observed in dogs treated with **1**.

Using a recently isolated strain of *T. crassiceps*, **1** was screened against this tapeworm in dogs. Complete clearance was accomplished with a single dose of **1** at 100 mg/kg. Comparison of **1**, bunamidine, and niclosamide against *T. crassiceps* is shown in Table II. This is the first reported example of compound screening against this parasite, and results indicate that *T. crassiceps* could be of value as a secondary tapeworm screening model.

Evaluation of **1** against the mouse pinworm *S. obvelata* resulted in complete clearance of this parasite at 50 mg/kg. A 68% reduction in worm burden at 10 mg/kg was also noted.

Preliminary testing of **1** against *Moniezia* sp. in sheep indicated that it has high activity. Complete clearance was accomplished when infected sheep were administered **1** as a drench at 50 mg/kg.

Experimental Section

Melting points were determined in open capillary tubes using a Mel-Temp melting point apparatus and are uncorrected.

7-Methyl-2-(*p*-tolyl)-1*H*-imidazo[4,5-*f*]quinolin-9-ol Tetartohydrate (2). A. 2′,4′-Dinitro-4-methylbenzanilide.[11] *p*-Methylbenzoyl chloride (62 g, 0.4 mol) was added dropwise to a stirred mixture of 2,4-dinitroaniline (73 g, 0.4 mol) in pyridine (400 mL). The temperature was maintained below 50 °C. After the addition was complete the reaction was heated under reflux for 3 h. The hot reaction mixture was poured into ice water and the precipitated product collected by filtration and washed with water (115 g, 95%).

B. 5-Amino-2-(*p*-tolyl)benzimidazole.[12] A mixture of 2′,4′-dinitro-4-methylbenzanilide (57 g, 0.19 mol) in EtOH (1000 mL) was catalytically hydrogenated over 5% Pd/C catalyst (40 psi of initial pressure). After the reduction was complete, the catalyst was filtered and the solvent removed in vacuo. The residue was boiled for 3 h in a mixture of concentrated HCl (30 mL) and H_2O (1000 mL), then chilled, diluted with H_2O (3000

mL), and made basic with concentrated NH_4OH. The precipitated product weighed 36 g (85%).

C. Ethyl 3-[5-(2-*p*-Tolyl)benzimidazolylamino]crotonate. A stirred mixture of 5-amino-2-(*p*-tolyl)benzimidazole (36 g, 0.16 mol), ethyl acetoacetate (24 g, 0.16 mol), anhydrous $CaSO_4$ (30 g), and HOAc (5 mL) in anhydrous EtOH (400 mL) was heated under reflux for 12 h. The $CaSO_4$ was filtered and the solvent removed in vacuo to provide a red oily residue which was used directly in part D.

D. 2. The residue from part C was poured into boiling Dowtherm A (800 mL) and the heating continued for 1 h. After cooling, the product was removed by filtration, washed with hexane, and dried to provide 33 g (70%). Recrystallization from CH_3NO_2 gave an analytical sample.

The remaining compounds in Table I were prepared in a similar manner using the appropriate β-keto esters.

2-(2-Furyl)-5-nitrobenzimidazole (9). A mixture of 1,2-diamino-4-nitrobenzene (31 g, 0.2 mol) and 2-furancarboxaldehyde (25 g, 0.26 mol) in 2-propanol was treated with *p*-benzoquinone (24 g, 0.22 mol). The reaction mixture was heated under reflux for 2 h. The reaction solution was diluted with water to precipitate the product. After drying, the crude product weighed 46 g (100%). Recrystallization from nitromethane provided an analytical sample which melted at 228–229 °C. Anal. Calcd for $C_{11}H_7N_3O_3$: C, 57.64; H, 3.08; N, 18.34. Found: C, 57.55; H, 3.04; N, 18.53.

3-[[2-(2-Furyl)-2-benzimidazolyl]amino]crotonate. A solution of 2-(2-furyl)-5-nitrobenzimidazole (66 g, 0.29 mol) (**9**) in 2-propanol (500 mL) was subjected to catalytic hydrogenation at 40 psi of initial pressure over Raney nickel catalyst. After the hydrogen uptake was complete, the catalyst was removed and the filtrate refluxed for 8 h with ethyl acetoacetate (38 g, 0.29 mol), anhydrous $CaSO_4$ (100 g), and HOAc (20 mL). The $CaSO_4$ was removed and the filtrate concentrated in vacuo to give 66 g (74%) of product. Recrystallization from nitromethane gave analytical material which melted at 177–178 °C. Anal. Calcd for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.48; H, 5.47; N, 13.47.

2-(2-Furyl)-7-methyl-1*H*-imidazo[4,5-*f*]quinolin-9-ol (1). Dowtherm A (500 mL) was preheated to 230 °C and to it was added 3-[[2-(2-furyl)-5-benzimidazolyl]amino]crotonate (38.5 g, 0.1 mol) in small portions. After the addition was complete, the reaction mixture was maintained at 230 °C for 15 min and then poured into a beaker and allowed to cool.

The precipitated product was filtered and washed thoroughly with hexane to give 20 g (74%). Recrystallization from nitromethane gave analytical material which melted at 280–282 °C. Anal. Calcd for $C_{15}H_{11}N_3O_2 \cdot 0.25H_2O$: C, 66.78; H, 4.30; N, 15.58. Found: C, 66.56; H, 4.43; N, 15.40.

Biological Method. Primary Evaluation of 1–7. *H. nana.* This test procedure and the reference standard have been described in an earlier publication.[8]

Secondary Evaluation of 1. *T. pisiformis.* Screening tests were conducted against *T. pisiformis* in beagle dogs ranging in age from puppies to animals 2–3 years old. All of the dogs were raised at the Norwich-Eaton Pharmaceuticals Animal Research Center at North Norwich, N.Y., and none had been exposed to *T. pisiformis.*

The tapeworms were introduced into the dogs in the form of cysts collected from the cottontail rabbit. Cysts (10–20) were administered to each animal. Following exposure, the dogs were maintained in individual cages until each animal was diagnosed as being infected with tapeworms (about 6 weeks).

Drugs were administered orally in gelatin capsules in a single dose, in some dogs after overnight fasting and in others after a light feeding. Generally three to five dogs were used at each drug level.

Total fecal eliminations were collected for 96 h after treatment and washed through a series of fine mesh screens to 200 mesh in order that all worms and/or segments could be collected. Following the 96-h period, the treated dogs were maintained in their individual cages for a 10-day observation period to allow any scolices in the animal to regenerate some strobila and thereby be easier to find.

After the 10-day period the dogs were euthanized. The intestines were removed and slit open and their contents were washed through the fine mesh screens. The material retained was placed in formalin. This material was examined minutely to detect and remove any strobila or scolices. Examination was conducted with a large magnifying lens over a dish on a black surface into which a small quantity of the material was added. The intestine itself was scraped and this material was also washed through the screens and closely examined after preserving in formalin. The presence of scolices during these examinations would indicate inactivity of the test drug at that dose level.

T. crassiceps. A newly isolated strain of *T. crassiceps* was made available by Dr. R. S. Freeman of the University of Toronto. Young beagle dogs were infected with cysts removed from mice, 40 cysts per dog, administered perorally in gelatin capsules. Thirty-seven days later the dogs were treated with the drug in gelatin capsules, three dogs in each test.

Nine days after drug treatment the dogs were sacrificed and the intestines examined for scolices as described in the *T. pisiformis* method.

Moniezia **sp.** Naturally infected sheep were used in this procedure. The drug was administered as a drench prepared by mixing it with water and sonifying it to a creamy consistency. Three days after dosing the sheep were sacrificed and the intestines examined as described for the dogs.

S. obvelata. This method was described previously.[8]

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