was converted to the hydrochloride salt by ethereal HCl. Recrystallization from methanol–ether and treatment with hot hexane yielded pure **3b** (B) hydrochloride: mp 200°. [11 g, 65%, based on **2b** (B) used].

Acknowledgment. The author wishes to thank Dr. Harold Baker and his staff for the antimicrobial screening and Dr. Bruce Downey and Dr. Jon Wetzel and their staffs for the anticoccidial testing.

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Anthelmintic 1-Cinnamamido-2,4-imidazolidinediones

Robert J. Alaimo*

Chemistry Division

and Christopher J. Hatton

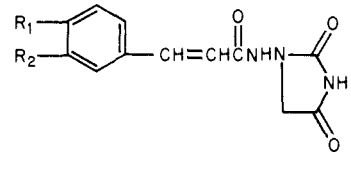
Veterinary Research Division, Norwich Pharmacal Company, Division of Morton-Norwich Products, Inc., Norwich, New York 13815. *Received July 14, 1975*

A series of 1-(substituted cinnamamido)-2,4-imidazolidinediones has been prepared from the corresponding cinnamoyl chlorides and 1-amino-2,4-imidazolidinedione hydrochloride in pyridine. These compounds possess a significant degree of anthelmintic activity against the mouse pinworm *Syphacia obvelata*. The most active compounds are those substituted with halogen or cyano groups.

A number of cinnamic acid derivatives, prepared on an exploratory basis, were screened for anthelmintic activity as a part of a continued search for new and novel anthelmintic agents.[1-3] As a result of this preliminary study, a series of substituted 1-cinnamamido-2,4-imidazolidinediones was prepared and evaluated against a number of helminth parasites. This new class of compounds possesses a significant degree of activity against the mouse pinworm *Syphacia obvelata*.

The general method for the preparation of the title compounds 1–12 involves the reaction of substituted cinnamoyl chlorides with 1-amino-2,4-imidazolidinedione hydrochloride in pyridine solution. The condensation was shown by NMR to occur on the 1-amino group rather than the 3-imido nitrogen. The NMR spectra of compounds 1–12 are consistent with the assigned structures and show two separate exchangeable proton peaks at approximately 10.4 and 11.3 ppm. The peaks are assignable to the amido N–H and the 3-imido N–H. If the condensation had occurred on the 3-imido nitrogen only a single, exchangeable peak integrating for two protons would have been observed. The cinnamoyl chlorides were prepared from the corresponding cinnamic acids by treatment with thionyl chloride. The cinnamic acids not obtained com-

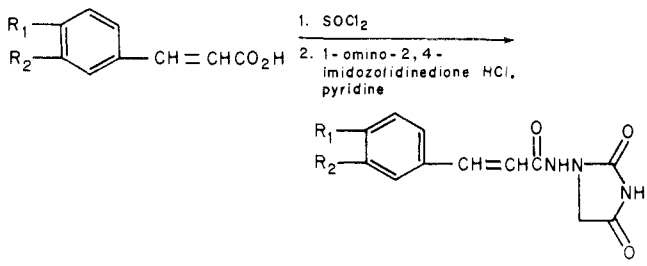
Table I. Anthelmintic 1-Cinnamamido-2,4-imidazolidinediones



No.	R_1	R_2	Mp, °C	% yield	Recrystn solvent	Formula[a]	Anthelmintic testing in vivo, *S. obvelata* % redn, dose in mg/kg 300	100	50	25	10
1	Cl	Cl	286-288	89	CH_3OH	$C_{12}H_9Cl_2N_3O_3$	100[b]	100	100	51	I[c]
2	H	H	276-278	74	CH_3OH	$C_{12}H_{11}N_3O_3$	86	75	I		
3	CH_3	Cl	271-273	38	CH_3NO_2	$C_{13}H_{12}ClN_3O_3$	99	97	100	87	34
4	Cl	H	230-235	36	CH_3OH	$C_{12}H_{10}ClN_3O_3$	100	97	52	I	
5	O—CH_2—O		258-260	81	CH_3CN	$C_{13}H_{11}N_3O_5$	100	88	I		
6	Cl	CF_3	270-273	100	CH_3NO_2	$C_{13}H_9ClF_3N_3O_3$	70	76	I		
7	F	H	241-243	62	CH_3NO_2	$C_{12}H_{10}FN_3O_3$	100	69	67	I	
8	CN	H	304-305	67	CH_3NO_2	$C_{13}H_{10}N_4O_3$	100	100	100	97	I
9	H	F	294-296	74	CH_3NO_2	$C_{12}H_{10}FN_3O_3$	100	77	I		
10	F	Cl	258-260	82	CH_3NO_2	$C_{12}H_9ClFN_3O_3$	100	100	87	I	
11	C_2H_5	Cl	231-234	55	CH_3NO_2	$C_{14}H_{14}ClN_3O_3$	100	87	I		
12	Br	CH_3	289-291	92	CH_3NO_2	$C_{13}H_{12}BrN_3O_3$	100	81	I		
Piperazine adipate							96	42	I		

[a] All compounds were analyzed for C, H, and N. Analytical results were within ±0.4% of the theoretical values. [b] All results were statistically significant at least at the 0.05 level of significance by the Mann-Whitney "U" test. [c] I, inactive at dose tested.

Scheme I



1-12

mercially were prepared by procedures described in the literature.[4,5] The synthetic procedure for the preparation of 1–12 is shown in Scheme I.

Title compounds 1–12 are shown in Table I.

Anthelmintic Testing. The compounds prepared in this work were tested against the mouse pinworm *Syphacia obvelata*.[1,2] The activity of these compounds, expressed in percent reduction in worm burden, is shown in Table I. The activity of the reference drug, piperazine adipate, is also included for comparison. Test compounds were administered perorally twice a day for 5 days. The most active compounds in reducing worm infestation are those substituted with halogen atoms (**1**, **3**, **4**, **7**, **10**) or a cyano group (**8**). However, no real structure activity trend is apparent among the cinnamamido-2,4-imidazolidinediones.

When compared to piperazine adipate for activity against *S. obvelata*, results indicate a number of compounds (**1**, **3**, **8**, and **10**) to be significantly more active, with as much as 97% reduction at 25 mg/kg (**8**).

Experimental Section

Melting points were determined in open capillary tubes using a Mel-Temp melting point apparatus and are uncorrected. The NMR spectra were obtained on a Varian A-60A instrument using tetramethylsilane as an internal standard. The aldehyde intermediates used in the preparation of compounds **3**, **6**, **10**, **11**, and **12** were prepared by a general procedure.[6] These aldehydes as well as the cinnamic acid derivatives prepared therefrom were not characterized but used directly in the subsequent reactions.

1-(3,4-Dichlorocinnamamido)-2,4-imidazolidinedione (1). 3,4-Dichlorocinnamic acid (22 g, 0.1 mol) was treated dropwise with thionyl chloride (70 ml, 1 mol). After the addition was complete, the mixture was warmed for 0.5 hr, and then the excess thionyl chloride was removed in vacuo. The residue was stirred with benzene (50 ml) and the benzene removed in vacuo. To the residue was added a suspension of 1-amido-2,4-imidazolidinedione hydrochloride (15 g, 0.1 mol) in pyridine (200 ml). The reaction mixture was heated on a steam bath for 3 hr and then treated with charcoal and filtered. The pyridine solution was poured onto ice and the precipitated product (28 g, 89%) recrystallized from methanol to give off-white crystals.

Compounds **2**–**12** in Table I were prepared in a similar manner using the appropriately substituted cinnamic acids.[4-6]

Biological Method. *S. obvelata.* The method was described previously[2] and compound effectiveness was determined as a percentage reduction in the manner described earlier.[1] The results were analyzed for their statistical significance by means of the Mann–Whitney "U" test.[7]

Acknowledgment. The authors are grateful to Mr. James Sheffer for the preparation of chemical intermediates and to Mr. Stephen Ashton and Mr. William Foote for their assistance in the biological testing. Microanalyses were performed by Mrs. Cora Jeffrey and NMR spectra were determined by Mrs. Connie Lloyd.

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Book Reviews

Annual Reports in Medicinal Chemistry. Volume 10. Edited by Richard B. Heinzelman. Academic Press, New York, N.Y. 1975. ix + 348 pp. 17 × 25.5 cm. $14.50 (soft bound).

With Volume 10 of "Annual Reports in Medicinal Chemistry" Dr. Richard Heinzelman concludes his term as Editor-in-Chief and turns this important task over to Dr. Frank Clarke. His "swan-song" has been just as successful as his previous products. The organization of the subject matter follows the established format with major sections edited by competent section editors: I, CNS Agents (Gordon); II, Pharmacodynamic Agents (Clarke); III, Chemotherapeutic Agents (Warren); IV, Metabolic Diseases and Endocrine Functions (Moreland); V, Topics in Biology (Shen); VI, Topics in Chemistry (Counsell).

There are a total of 33 topics. Interestingly, 18 of these topics in the present volume did not appear in Volume 9. Hence, medicinal chemists should not consider "Annual Reports" merely as a yearly updating process but should consult, when carrying out searches, the most recent as well as the preceding volumes.

It is hard to single out any of these excellent overviews. This reviewer found great pleasure in learning of areas in which he had little previous exposure such as "Current Concepts in Periodontal Disease" by Taichman and McArthur; "Radioimmunoassays" by Kohen et al.; and "Molecular Aspects of Membrane Function" by Baran.

In a previous review this reviewer questioned the utility of the "topics" sections vis-à-vis the methodically oriented ones. Suffice it to say that even referees can change their minds and acquire new knowledge when browsing through "Annual Reports".

This book is recommended without any reservation to all who are involved in any aspect of medicinal chemistry research.

Sterling-Winthrop Research Institute **F. C. Nachod**
Rensselaer, New York 12144

Drug Design. Volume 5. Edited by E. J. Ariens. Academic Press, New York, N.Y. 15 × 23.5 cm. xvi + 356 pp. $39.50.

The present volume in this series consists of six chapters. As the editor states in his preface they deal primarily with "the physicochemical approach to the relationship of structure and mechanism of action and the applicability of the insight gained to drug design...".

The first chapter, "Utilization of Operational Schemes for Analog Synthesis and Design", is quite short. It is essentially an