An analytical sample was prepared by washing with hot EtOH, hot H_2O, and hot acetone.

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Products from Furans. 1. Synthesis and Anticoccidial and Antimicrobial Activity of 5-Amino-5,6-dihydro-6-methoxy-2-methyl-2-(4'-biphenylyl)-2*H*-pyran-3(4*H*)-ones and Related Compounds

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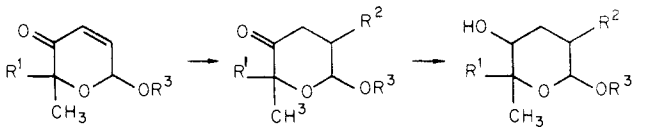
A Michael type addition of an amine to 6-methoxy-2-methyl-2-(4'-biphenylyl)-2*H*-pyran-3(6*H*)-one (1) dissolved in ether, benzene, or THF gave 5-amino derivatives of 5,6-dihydro-6-methoxy-2-methyl-2-(4'-biphenylyl)-2*H*-pyran-3(4*H*)-one (**2**). These by subsequent reduction with $LiAlH_4$ were converted to 5-amino derivatives of 6-methoxy-2-methyl-2-(4'-biphenylyl)tetrahydro-2*H*-pyran-3-ol (**3**). Both isomers A and B of 1 (in regard to the methoxy group at C_6) were used for the synthesis of **2** and **3**. The in vitro antimicrobial activity of the amine adducts **2** was of the same order of magnitude as the starting material. Amine adducts in general, however, were by far more active as coccidiostats than the starting material and retained their activities when they were reduced. 5,6-Dihydro-6-methoxy-2-methyl-2-(4'-biphenylyl)-5-(dimethylamino)-2*H*-pyran-3(4*H*)-one hydrochloride (A) and 5,6-dihydro-6-methoxy-2-methyl-2-(4'-biphenylyl)-5-(dimethylamino)-2*H*-pyran-3(4*H*)-one hydrochloride (B), prepared from isomer A and B of 1, respectively, were the most active as coccidiostats. These compounds when administered orally to chickens 1 day prior to infection at a concentration 0.05% in their diet gave them total protection against *Eimeria tenella*.

The conversion of furans to pyran derivatives had previously been reported[1,2] when Lefebvre announced his synthesis of 6-hydroxy-2*H*-pyran-3(6*H*)-ones 1 by oxidation of 2-furanmethanol.[3] His procedure has been extensively used for the syntheses of compounds for biological screening.[4] However, the versatile 6-hydroxy-2*H*-pyran-3(6*H*)-ones 1 may be used as starting material for the synthesis of a variety of products.[5] In this note the synthesis of 5-amino-5,6-dihydro-6-methoxy-2-methyl-2-(4'-biphenylyl)-2*H*-pyran-3(4*H*)-ones **2** and 5-amino-6-methoxy-2-methyl-2-(4'-biphenylyl)tetrahydro-2*H*-pyran-3-ols **3** will be reported and the biological properties of the prepared compounds will be discussed.

Synthesis. The synthesis of the reported compounds is illustrated in Scheme I. A Michael type addition of amine to 6-methoxy-2-methyl-2-(4'-biphenylyl)-2*H*-pyran-3(6*H*)-one (1) gave 5-amino-5,6-dihydro-6-methoxy-2-methyl-2-(4'-biphenylyl)-2*H*-pyran-3(4*H*)-one derivatives **2** and these, by a subsequent reduction, yielded

Scheme I



1 2 3

5-amino-6-methoxy-2-methyl-2-(4'-biphenylyl)tetrahydro-2*H*-pyran-3-ols.

Biology. 1. Methods. Methods used in the biological evaluation of these compounds were the same as those used for 6-hydroxy-2*H*-pyran-3(6*H*)-ones.[4]

(a) Antibacterial Screening. The antibacterial properties of the compounds were tested in vitro by halving dilutions in nutrient broth (Difco). The following gram-positive organisms were used: *Staphylococcus pyogenes* S (penicillin-sensitive), *Staphylococcus pyogenes* R (penicillin-resistant), and *Streptococcus faecalis*. The gram-negative organisms were *Salmonella pullorum*, *Pseudomonas aeruginosa*, *Escherichia coli* No. 198, *Aerobacter aerogenes*, *Proteus vulgaris*, *Klebsiella pneumoniae*, and *Serretia marcescens*. The results are ex-

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pressed in Table I as the minimum concentration of the compound which inhibits growth after 24 hr of incubation at 37°.

(b) Antifungal Screening. The antifungal properties of the compounds were tested in vitro by halving dilutions in Sabouraud broth. The following test organisms were used: *Candida albicans*, *Microsporum gypseum*, and *Trichophyton granulosum*. Table I shows the minimum concentration of the compound which inhibited growth after 5 days of incubation at 37° for *C. albicans* and 10 days at 28° for the two other organisms. In these two tests, compounds that inhibit growth at a concentration greater than 32 μg/ml are designated as being inactive (–).

(c) Anticoccidial Screening. The anticoccidial properties were tested against *Eimeria tenella* and *Eimeria acervulina* in experimental coccidiosis in chickens. In each test, the particular compound was administered orally 1 day prior to infection at a concentration of 0.05% of the diet. The efficacy was evaluated after 6 days on the basis of survival and weight gains. In Table I the compounds are designated as inactive (–) when survival and weight gains are equal to or poorer than the nonmedicated infected controls, slightly active (+) when there is improved weight gains but little improvement in mortality, active (++) when there is moderate improvement in both parameters, and very active (+++) when weight gains and survival are equal to that of the noninfected controls.

2. Results. It may be concluded from Table I that the antimicrobial activity of amine adducts in vitro was of the same order of magnitude as the starting material. These data suggest the possibility that such activity may be due to a retro-Michael reaction. When amine adducts were reduced to more stable hydroxy derivatives they were found to be inactive as antimicrobials. Amine adducts in general, however, were by far more active than their starting materials as coccidiostats. Three general observations may be drawn from Table I concerning this type of activity. First, the smaller the amine substituent, the better the anticoccidial activity. Thus, amine adducts of dimethylamine on the two isomeric 6-methoxy-2-methyl-2-(4'-biphenylyl)-2*H*-3(6*H*)-ones were the most active. Second, amine adducts retained their anticoccidial activity when they were reduced. Third, compounds **2a** (A) and **2b** (B), when compared with the most active 6-hydroxy-2*H*-pyran-3(6*H*)-one derivatives[4] **1c,d**, were found to possess equal, if not better, activity.

Conclusion

Contrary to what was believed,[4] biological evaluation of amine adducts **2** and their reduction products **3** (Table I) indicates that the requirement for coccidiostatic activity is not necessarily linked to the 2*H*-pyran-3(6*H*)-one structure. It may be interesting to note that two out of the few prepared compounds, **2a** (A) and **2b** (B), were found to be at least equally active if not better than the best 6-hydroxy-2*H*-pyran-3(6*H*)-one derivatives prepared by others[4] in great numbers.

Experimental Section

The technique used to prepare the amine adducts **2** was varied according to the nature of the amine used. Thus, gaseous amines were bubbled through a benzene or ether solution of 6-methoxy-2-methyl-2-(4'-biphenylyl)-2*H*-pyran-3(6*H*)-one **1**, while liquid amines were simply added, preferably to an ether solution of **1**. It was found that amines, when available in a water solution, could be used as such. In this case, tetrahydrofuran was used as a solvent for the reaction and yields were lower than those by the previous technique. An example is given for each of these different methods, labeled A, B, C, and D. Amine adducts were reduced by $LiAlH_4$. Melting points were determined in a Thomas-Hoover apparatus and are uncorrected. Compounds were analyzed for C, H, N, and where applicable for Cl. Results are within ±0.3% of the theoretical values. Spectral features, ir, uv, and NMR, were in agreement with the proposed structures.

Starting Materials. Isomer A and isomer B of 6-methoxy-2-methyl-2-(4'-biphenylyl)-2*H*-pyran-3(6*H*)-one (**1**) were used as starting materials. Although the synthesis and biological properties of these isomers are known their relative configuration has not been reported.[4] Achmatowicz and his coworkers[2] have assumed a half-chair conformation with an equatorial R^1 group for similar insomeric products and have confirmed this assumption by NMR. They have named their compounds as glycosides and therefore have reported the coupling constants $J_{5,6}$ and $J_{4,6}$ as $J_{1,2}$ (vicinal) and $J_{1,3}$ (allylic), respectively. These workers have found that the magnitudes of these coupling constants are small and that the magnitude of $J_{1,3}$ is characteristic for each isomer having the smallest value in the α-glycosidic configuration. Considering the magnitudes of these coupling constants for isomer A, $J_{1,2}$ = 1.5 Hz and $J_{1,3}$ = 1.5 Hz, and for isomer B, $J_{1,2}$ = 2.5 Hz and $J_{1,3}$ = 1 Hz (NMR data supplied by R. Laliberte and G. Medawar, Ayerst Laboratories), one concludes that isomer A corresponds rather to a β-anomer while isomer B to an α-anomer. However, in this report we are comparing the biological properties of the prepared compounds with those of the starting materials. Therefore we prefer to maintain the original names of the starting materials by which their biological activities have been reported. In order to distinguish the products derived from isomer A from those of isomer B a letter A and B is added, respectively, after the name of each prepared compound.

5,6-Dihydro-6-methoxy-2-methyl-2-(4'-biphenylyl)-5-(dimethylamino)-2*H*-pyran-3(4*H*)-one Hydrochloride A [2a (A)]. Method A. Dimethylamine was passed through a solution of **1a** (A) (10 g) in benzene (200 ml) for 30 min. The reaction mixture was transferred to a hood and the excess dimethylamine allowed to evaporate overnight. The reaction mixture was further concentrated under reduced pressure to a syrup which upon treatment with ethereal HCl yielded the amine hydrochloride **2a** (A). Trituration with acetone and washing with hot ether–acetone and boiling *n*-hexane gave analytically pure material: mp 161–162° (10 g, 80%).

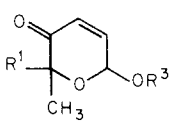
5,6-Dihydro-6-methoxy-2-methyl-2-(4'-biphenylyl)-5-(methylamino)-2*H*-pyran-3(4*H*)-one Hydrochloride B [2c (B)]. Method B. Monomethylamine was passed through a solution of **1b** (B) (5 g) in ether (200 ml) for 1 hr. The reaction mixture was allowed to evaporate at room temperature, then concentrated under reduced pressure, and taken up in ethereal HCl, which yielded the crude amine hydrochloride **2c** (B). Further treatment with acetone–ether and boiling *n*-hexane as before in **2a** (A) yielded 5.6 g (91%) of analytically pure material: mp 168–172° dec.

Method C. Monomethylamine (4–5 ml of 40% solution) was added to a solution of **1b** (B) (3 g) in tetrahydrofuran (10–20 ml) and the reaction mixture was stirred. After 30–35 min TLC (ether–hexane, 1:1) showed that the reaction was complete. The mixture was then evaporated under reduced pressure. The residue was treated as before (method B) yielding **2c** (B) (2.6 g, 82.4%).

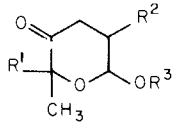
5,6-Dihydro-6-methoxy-2-methyl-2-(4'-biphenylyl)-5-(4'-methyl-1'-piperazinyl)-2*H*-pyran-3(4*H*)-one Hydrochloride B [2d (B)]. Method D. *N*-Methylpiperazine (12 ml) was added to a solution of **1b** (B) (5.9 g) in ether (250 ml) and gently refluxed for 2 hr. The reaction mixture was washed with water, dried, and evaporated under reduced pressure. The amine adduct was crystallized as a free base from *n*-hexane, mp 117–119°, and characterized. The mother liquors of the crystallization were combined with the crystalline material and evaporated under reduced pressure. The free base was converted to the maleate salt by a saturated maleic acid solution in acetone (12.4 g quantitative). Treatment with hot acetone (twice) afforded **2d** (B), analytically pure maleate (11 g, 88%) melting at 160–163°.

6-Methoxy-2-methyl-2-(4'-biphenylyl)-5-(dimethylamino)tetrahydro-2*H*-pyran-3-ol Hydrochloride B [3b (B)]. To a stirred solution of crude **2b** (B), prepared from 13 g of **1b** (B), in ether–THF (1:1) $LiAlH_4$ (1 g) was added portionwise. The reduction was followed by TLC (30% MeOH in $CHCl_3$) and when completed, water was added (4.2 ml), and the mixture was stirred for some time, filtered through Celite, dried, and evaporated under reduced pressure. The crude product obtained in this manner

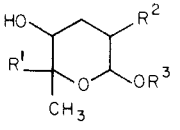
Table I. 5,6-Dihydro-6-methoxy-2-methyl-2-(4'-biphenylyl)-2*H*-pyran-3(4*H*)-one and 6-Methoxy-2-methyl-2-(4'-biphenylyl)tetrahydro-2*H*-pyran-3-ol Amino Derivatives. Structure and Activity



1



2



3

Compd no.[a]	R^{3b}	R^2	Formula	Yield, %	Mp, °C	Solvents[f]	Antimicrobial act. (in vitro), MIC values in μg/ml: Antibact[g] g +	*C. albicans*	*M. gypseum*	*T. granulosum*	Anticoccidial act.: *E. tenella*	*E. acervulina*
1a (A)	CH_3						6.2	32	2	1	+	ND[j]
1b (B)	CH_3						6.2	16	2	8	–	ND
1c	$CONHCH_3$						–[i]	250	1.6	1.6	+++	–
1d[c]	$CON(CH_3)_2$						6.2	50	8	6.2	+++	+
2a (A)	CH_3	$N(CH_3)_2$	$C_{21}H_{25}NO_3 \cdot HCl$	80	161–162	A-M, E, H	3.2	16	4	8	+++	++
2b (B)	CH_3	$N(CH_3)_2$	$C_{21}H_{25}NO_3 \cdot HCl$	80	160–162	A-M, E, H	6.2	16	8	8	+++	+
2c (B)	CH_3	$NHCH_3$	$C_{20}H_{23}NO_3 \cdot HCl$	91	168–172 dec	A-E, H	0.8	ND	ND	ND	+++	–
2d (B)	CH_3	c-$N(CH_2CH_2)_2N$-*p*-CH_3	$C_{24}H_{30}N_2O_3 \cdot 2Mal$[e]	88	160–163	A	6.2	ND	3.2	1.6	–	+
2e (B)	CH_3	c-$N(CH_2CH_2)_2O$	$C_{23}H_{27}NO_4$	75	128–129	H	3.2	–	3.2	16	+	–
3a (A)	CH_3	$N(CH_3)_2$	$C_{21}H_{27}NO_3 \cdot HCl$	65[d]	200	M-E, H	–	–	–	–	++	+
3b (B)	CH_3	$N(CH_3)_2$	$C_{21}H_{27}NO_3 \cdot HCl$	65[d]	177–178	M-E, H	–	–	–	–	+++	+
3c (B)	CH_3	$NHCH_3$	$C_{20}H_{25}NO_3 \cdot HCl$	68[d]	221	M-E, H	–	–	–	–	–	–
3d (B)	CH_3	c-$N(CH_2CH_2)_2N$-*p*-CH_3	$C_{24}H_{32}N_2O_3 \cdot 2Mal$[e]	71[d]	169–171	A, E, H	–	–	–	–	+	–
3e (B)	CH_3	c-$N(CH_2CH_2)_2O$	$C_{23}H_{29}NO_4 \cdot HCl$	68[d]	188.5–189 dec	E, H	–	–	–	–	–	–
Methyl benzoquate[h]											+++	ND

[a] The capital letter A or B in parentheses indicates the isomerism at C_6 (ether A or B).[4] [b] R' = 4-biphenylyl. [c] The most active 2*H*-pyran-3(6*H*)-one derivative.[4] [d] Total yield in two steps. [e] Maleic acid. [f] A = acetone, M = methanol, E = ether, H = *n*-hexane. [g] The antibacterial activities were of the same order of magnitude as the starting material for the test gram-positive bacteria used. All compounds were inactive against gram-negative bacteria. [h] Against *Eimeria tenella* at a concentration 0.002%. [i] – indicates that compounds exhibit MIC > 32 μg/ml and that they are considered inactive. [j] Not determined.

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

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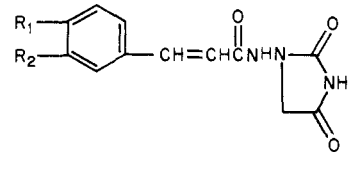
A series of 1-(substituted cinnamamido)-2,4-imidazolidinediones has been prepared from the corresponding cinnamoyl chlorides and 1-amino-2,4-imidazolidinedione hydrochloride in pyridine. These compounds possess a significant degree of anthelmintic activity against the mouse pinworm *Syphacia obvelata*.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