acid–base (0.1 M HCl, concentrated K_2CO_3) extraction was then done to remove nonbasic substances. The base extracts were dried over anhydrous sodium sulfate, and the volume was reduced to 0.1 mL under a stream of nitrogen. This solution was analyzed by GC–MS on 2% Dexyl (160 °C for 1 min, then increasing 3.5 °C/min).

Electron-impact mass spectra (EIMS) were obtained by gas chromatography–mass spectrometry (GC–MS) on an AEI MS-12 mass spectrometer which is interfaced to a PDP 8/I computer using the DS-30 software. An Infotronics 2400 gas chromatograph using helium as the carrier gas is interfaced to the mass spectrometer via a Biemann–Watson molecular separator. Mass spectra were taken with an 8-kV accelerating voltage, a trap current of 500 μA, an electron beam energy of 70 eV, a source temperature of 200 °C, and a resolving power of 1200.

SIR analyses were obtained with the above GC–MS system modified for analog SIR operation with 4-channel output to a Rikadenki KA-42 four-pen recorder.[10]

Control Experiments. Several control incubations were done for the nicotine studies using exactly the reagents and procedures described above, except that the liver preparation was heated for 10 min on a steam cone before the cofactors and substrate were added.

References and Notes

(1) A part of this work has been reported in a preliminary form: T.-L. Nguyen, L. D. Gruenke, and N. Castagnoli, Jr., *J. Med. Chem.*, 19, 1168 (1976).

(2) B. Testa and P. Jenner, in "Drug Metabolism—Chemical and Biochemical Aspects", Marcel Dekker, New York, 1976, p 82.

(3) (a) H. A. Dugger, R. A. Coombs, H. J. Schwarz, B. H. Migdalof, and B. A. Orwig, *Drug Metab. Dispos.*, 4, 262 (1976); (b) M. A. Schwartz and S. J. Kolis, *J. Pharmacol. Exp. Ther.*, 180, 180 (1972).

(4) J. W. Gorrod and P. Jenner, *Assays Toxicol.*, 6, 829 (1975).

(5) H. B. Hucker, J. R. Gillette, and B. B. Brodie, *J. Pharmacol. Exp. Ther.*, 129, 94 (1960).

(6) (a) P. Murphy, *J. Biol. Chem.*, 248, 2797 (1973). (b) The stereochemical assignments of the 5′-substituted nicotine derivatives have not been established.

(7) (a) E. Sanders, J. DeBardeleben, and T. Osdene, *J. Org. Chem.*, 40, 2848 (1975); (b) Y. Hubert-Brierre, D. Herlem, and F. Khuong-Huu, *Tetrahedron*, 31, 3049 (1975).

(8) (a) J. Gal, L. D. Gruenke, and Neal Castagnoli, Jr., *J. Med. Chem.*, 18, 683 (1975); (b) E. Dagne, L. Gruenke, and N. Castagnoli, Jr., *J. Med. Chem.*, 17, 1330 (1974); (c) W. Sadee, W. Garland, N. Castagnoli, Jr., *J. Med. Chem.*, 14, 643 (1971).

(9) S. D. Nelson, G. D. Breck, W. F. Trager, *J. Med. Chem.*, 16, 1106 (1973).

(10) L. D. Gruenke, presented at the 24th Annual Conference on Mass Spectrometry and Allied Topics, San Diego, Calif., 1976.

(11) T.-L. Nguyen and N. Castagnoli, Jr., *J. Labelled Compd. Radiopharm.*, 14, 919 (1978).

Antiallergy Agents. 1. 1,6-Dihydro-6-oxo-2-phenylpyrimidine-5-carboxylic Acids and Esters

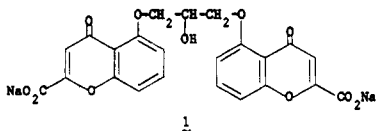
Peter F. Juby,* Thomas W. Hudyma, Myron Brown, John M. Essery, and Richard A. Partyka

Research Division, Bristol Laboratories, Division of Bristol-Myers Company, Syracuse, New York 13201.

Received August 17, 1978

The synthesis of some 1,6-dihydro-6-oxo-2-phenylpyrimidine-5-carboxylic acids and esters with potent oral and intravenous antiallergic activity against passive cutaneous anaphylaxis in the rat is described. Requirements for high activity include a free NH group in the pyrimidinone nucleus and a small to medium size ortho alkoxy or alkenyloxy group on the phenyl ring. It is suggested that in the case of the highly active compounds hydrogen bonding occurs between a nitrogen of the pyrimidine ring and the ethereal oxygen. The nature of this bonding and its possible contribution to an optimum configuration for the molecules is discussed.

The introduction in 1968 of the mediator release inhibitor disodium cromoglycate (DSCG, 1) provided an important new and safe method for the prophylactic and adjunctive treatment of allergic disease such as bronchial asthma. DSCG (1), however, is not absorbed orally to any

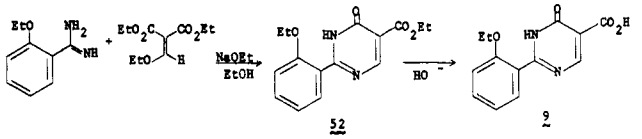


1

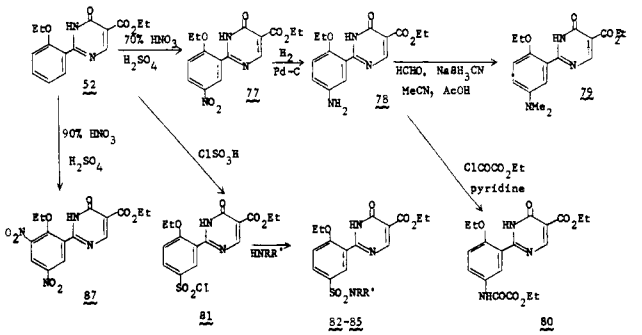
significant extent, and for the treatment of asthma must be inhaled as a powder.[1] Extensive efforts have already been made to find an orally effective alternative.[2]

In this paper we describe the synthesis and structure–activity relationships of some 1,6-dihydro-6-oxo-2-phenylpyrimidine-5-carboxylic acids and esters (Tables I and II), some of which show potent antiallergic activity by both oral and intravenous routes of administration.[3] Just as we were completing our work some related, although considerably less potent, pyrimidine-5-carboxylic acid antiallergy agents were disclosed.[4] 2-Phenylpyrimidine-5-carboxylic acids and esters with antiinflammatory, antipyretic, and analgetic activity have also been reported.[5]

Scheme I



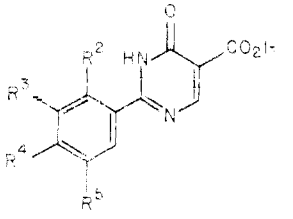
Scheme II



Chemistry. Most of the monosubstituted and some of the disubstituted acids and esters in Tables I and II were

0022-2623/79/1822-0263$01.00/0

Table I. 1,6-Dihydro-6-oxo-2-phenylpyrimidine-5-carboxylic Acids



no.	R^2	R^3	R^4	R^5	formula[a]	mp, °C[b]	crystn solvent[c]	yield, %	PCA[d] ID_{50}, mg/kg po
2	H	H	H	H	$C_{11}H_8N_2O_3$	280-281[e]	A	78	50
3	F	H	H	H	$C_{11}H_7FN_2O_3$	265-266	B	71	5
4	Cl	H	H	H	$C_{11}H_7ClN_2O_3$	201-203	B	51	5
5	NO_2	H	H	H	$C_{11}H_7N_3O_5 \cdot H_2O$	196-198	C-D	83	>50
6	NH_2	H	H	H	$C_{11}H_9N_3O_3$	257-258	A	56	50
7	HO	H	H	H	$C_{11}H_8N_2O_4$	272-274	E	57	>5
8	MeO	H	H	H	$C_{12}H_{10}N_2O_4$	242-244	A	77	10
9	EtO	H	H	H	$C_{13}H_{12}N_2O_4$	186-188	B	67	0.5[f]
10	*n*-PrO	H	H	H	$C_{14}H_{14}N_2O_4$	205.5-207.5	E	97	0.9
11	*i*-PrO	H	H	H	$C_{14}H_{14}N_2O_4$	193-195	F	99	0.8
12	*n*-BuO	H	H	H	$C_{15}H_{16}N_2O_4$	165-166	E	97	0.5
13	*i*-BuO	H	H	H	$C_{15}H_{16}N_2O_4$	206-207	A	60	0.5
14	*s*-BuO	H	H	H	$C_{15}H_{16}N_2O_4$	142-144	G-D	99	0.5
15	$n\text{-}C_5H_{11}O$	H	H	H	$C_{16}H_{18}N_2O_4$	145.5-147.5	E	82	3
16	$CH_2{=}CHCH_2O$	H	H	H	$C_{14}H_{12}N_2O_4$	192-194	E	99	0.5
17	c-$PrCH_2O$	H	H	H	$C_{15}H_{14}N_2O_4$	219-220	E	98	0.1
18	$PhCH_2O$	H	H	H	$C_{18}H_{14}N_2O_4$	227.5-228.5	H	96	5
19	MeS	H	H	H	$C_{12}H_{10}N_2O_3S$	203-205	E	90	>20
20	EtS	H	H	H	$C_{13}H_{12}N_2O_3S$	167-169	B	71	25
21	MeS(O)	H	H	H	$C_{12}H_{10}N_2O_4S$	197-199	I	104	>5
22	H	CF_3	H	H	$C_{12}H_7F_3N_2O_3$	239-241	J	78	33
23	H	MeO	H	H	$C_{12}H_{10}N_2O_4$	258-260	B	74	10
24	H	EtO	H	H	$C_{13}H_{12}N_2O_4$	251-253	A	77	5
25	H	H	Cl	H	$C_{11}H_7ClN_2O_3$[g]	297	A	82	5
26	H	H	CF_3	H	$C_{12}H_7F_3N_2O_3$	268-270	I	93	>5
27	H	H	MeO	H	$C_{12}H_{10}N_2O_4$	277-278[h]	A	100	>5
28	HO	$CH_2{=}CHCH_2$	H	H	$C_{14}H_{12}N_2O_4$	246.5-249.5	A	97	>0.5
29	$-OCH(CH_3)CH_2-$		H	H	$C_{14}H_{12}N_2O_4$	218-220	E	31	5
30	MeO	H	MeO	H	$C_{13}H_{12}N_2O_5$	260-261.5	A	100	5
31	MeO	H	H	MeO	$C_{13}H_{12}N_2O_5$	268-270	J	89	1.0
32	EtO	H	H	Cl	$C_{13}H_{11}ClN_2O_4$	234.5-237	J	81	0.5
33	EtO	H	H	MeO	$C_{14}H_{14}N_2O_5$	176-178	B	48	0.2
34	EtO	H	H	CO_2H	$C_{14}H_{12}N_2O_6$	283-285	A	92	25
35	EtO	H	H	NO_2	$C_{13}H_{11}N_3O_6$	220-222	B	52	25
36	EtO	H	H	NH_2	$C_{13}H_{13}N_3O_4$	276	B	39	1.2
37	EtO	H	H	NMe_2	$C_{15}H_{17}N_3O_4$	195-198	K-D	29	0.3
38	EtO	H	H	$NHCOCO_2Et$	$C_{17}H_{17}N_3O_7$	271-271.5	J	44	25
39	EtO	H	H	SO_2Cl	$C_{13}H_{11}ClN_2O_6S$[i]	195			j
40	EtO	H	H	SO_2NH_2	$C_{13}H_{13}N_3O_6S$	256-258	J	63	>50
41	EtO	H	H	SO_2NMe_2	$C_{15}H_{17}N_3O_6S$	212-215	C	70	>50
42	EtO	H	H	SO_2NEt_2	$C_{17}H_{21}N_3O_6S$	169-172	C	63	40
43	EtO	H	H	$SO_2N(Me)$-*i*-Pr	$C_{17}H_{21}N_3O_6S$	193-195	C	69	>10
44	*n*-PrO	H	H	MeO	$C_{14}H_{16}N_2O_5$	178-180	B	49	0.3

[a] All compounds were analyzed for C, H, and N and, where appropriate, Cl. All results are within ±0.4% of the theoretical values, except where noted. [b] Most of the acids melted with decomposition. [c] A = $MeOCH_2CH_2OH$, B = MeCN, C = 2-PrOH, D = *n*-hexane, E = EtOH, F = MeOH, G = dioxane, H = AcOH, I = 95% EtOH, J = $MeNO_2$, K = C_6H_6, L = cyclohexane, M = H_2O. [d] In this test, DSCG had ID_{50} values of 0.3 mg/kg iv and >>30 mg/kg po. All data are considered significant at $p \leq 0.05$ as determined by Student's *t* test. [e] S. Ruhemann, *Ber. Dtsch. Chem. Ges.*, 30, 821 (1897), gives mp 214 °C. [f] ID_{50} = 0.07 mg/kg iv. [g] Cl: calcd, 14.15; found, 13.69. [h] P. C. Mitter and N. Palit, *Q. J. Indian Chem. Soc.*, 2, 61 (1925). [i] Crude material, used without characterization. [j] Not tested.

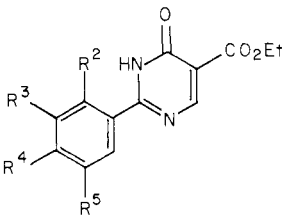
prepared by condensation of the appropriate benzamidine with diethyl ethoxymethylenemalonate followed by base-catalyzed hydrolysis of the intermediate ester. The route is illustrated with the *o*-ethoxyphenyl acid **9** and ester **52** in Scheme I and is analogous to an earlier synthesis of the *p*-methylphenyl analogues by Mitter and Bardhan.[6]

Other disubstituted esters were obtained directly from the *o*-ethoxyphenyl ester **52** as outlined in Scheme II.

The *o*-(allyloxy)phenyl acid **16** and ester **59** both underwent the Claisen rearrangement to give the 3-allyl-2-hydroxyphenyl acid **28** and ester **70**, respectively (Scheme III). Treatment of **70** with hydrogen bromide in acetic acid followed by an aqueous workup gave a mixture of the dihydrofuran acid **29** and ester **71**.

The *o*-aminophenyl ester **49** was obtained by reduction of the *o*-nitrophenyl ester **48**. Hydrogenolysis of the *o*-(benzyloxy)phenyl ester **61** gave the corresponding *o*-hydroxyphenyl compound **50**. The *o*-methylthio acid **19** was oxidized with sodium metaperiodate to give the sulfoxide **21**.

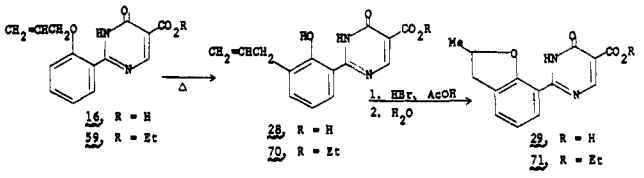
Table II. Ethyl 1,6-Dihydro-6-oxo-2-phenylpyrimidine-5-carboxylates



no.	R^2	R^3	R^4	R^5	formula[a]	mp, °C	crystn solvent[c]	yield, %	PCA[d] ID_{50}, mg/kg po
45	H	H	H	H	$C_{13}H_{12}N_2O_3$	220-221[e]	E	85	>20
46	F	H	H	H	$C_{13}H_{11}FN_2O_3$	151-153	B	33	>10
47	Cl	H	H	H	$C_{13}H_{11}ClN_2O_3$	139-141	B	12	5
48	NO_2	H	H	H	$C_{13}H_{11}N_3O_5$	175-177	B	20	*j*
49	NH_2	H	H	H	$C_{13}H_{13}N_3O_3$[k]	228-230	B	56	*j*
50	HO	H	H	H	$C_{13}H_{12}N_2O_4$	234-235	A	86	5
51	MeO	H	H	H	$C_{14}H_{14}N_2O_4$	148-150	B	72	10
52	EtO	H	H	H	$C_{15}H_{16}N_2O_4$	147-150	B	75	2
53	*n*-PrO	H	H	H	$C_{16}H_{18}N_2O_4$	112-113	L	96	5
54	*i*-PrO	H	H	H	$C_{16}H_{18}N_2O_4$	128-130	L	85	2
55	*n*-BuO	H	H	H	$C_{17}H_{20}N_2O_4$	123-125	E	82	0.5
56	*i*-BuO	H	H	H	$C_{17}H_{20}N_2O_4$	92-93	E-M	85	3
57	*s*-BuO	H	H	H	$C_{17}H_{20}N_2O_4$	134-136	L	77	0.5
58	n-$C_5H_{11}O$	H	H	H	$C_{18}H_{22}N_2O_4$	121.5-122.5	L	79	2
59	CH_2=CHCH$_2$O	H	H	H	$C_{16}H_{16}N_2O_4$	118.5-120.5	L	89	0.5
60	c-PrCH$_2$O	H	H	H	$C_{17}H_{18}N_2O_4$	104-105	L	93	0.3
61	PhCH$_2$O	H	H	H	$C_{20}H_{18}N_2O_4$	156.5-157.5	E	41	>5
62	MeS	H	H	H	$C_{14}H_{14}N_2O_3S$	155-156	K	92	>25
63	EtS	H	H	H	$C_{15}H_{16}N_2O_3S$	117-120	B	67	>5
64	H	CF_3	H	H	$C_{14}H_{11}F_3N_2O_3$	151-152	L	27	50
65	H	MeO	H	H	$C_{14}H_{14}N_2O_4$	169-170	B	79	10
66	H	EtO	H	H	$C_{15}H_{16}N_2O_4$	156.5-158	E	79	50
67	H	H	Cl	H	$C_{13}H_{11}ClN_2O_3$	245-247	A	80	>30
68	H	H	CF_3	H	$C_{14}H_{11}F_3N_2O_3$	225-226.5	I	92	>5
69	H	H	MeO	H	$C_{14}H_{14}N_2O_4$	230-232[h]	E	91	30
70	HO	CH_2=CHCH$_2$	H	H	$C_{16}H_{16}N_2O_4$[l]	186-191	A	67	*j*
71	-OCH(CH$_3$)CH$_2$-		H	H	$C_{16}H_{16}N_2O_4$	158-159	K-D	27	5
72	MeO	H	MeO	H	$C_{15}H_{16}N_2O_5$	190-192	I	76	5
73	MeO	H	H	MeO	$C_{15}H_{16}N_2O_5$	149-150	B	72	5
74	EtO	H	H	Cl	$C_{15}H_{15}ClN_2O_4$	209-212	B	68	0.5
75	EtO	H	H	MeO	$C_{16}H_{18}N_2O_5$	149-152	B	64	0.3
76	EtO	H	H	CO_2Et	$C_{18}H_{20}N_2O_6$	180-181.5	E	76	1
77	EtO	H	H	NO_2	$C_{15}H_{15}N_3O_6$	222-224	B	55	5
78	EtO	H	H	NH_2	$C_{15}H_{17}N_3O_4 \cdot H_2O$	107-110	E-M	31	0.5
79	EtO	H	H	NMe_2	$C_{17}H_{21}N_3O_4$[m]				*j*
80	EtO	H	H	NHCOCO$_2$Et	$C_{19}H_{21}N_3O_7$	192-193	B	49	5
81	EtO	H	H	SO_2Cl	$C_{15}H_{15}ClN_2O_6S$	172-173	B	52	*j*
82	EtO	H	H	SO_2NH_2	$C_{15}H_{17}N_3O_6S$	262-264	J	49	50
83	EtO	H	H	SO_2NMe_2	$C_{17}H_{21}N_3O_6S$	200-201	C	51	50
84	EtO	H	H	SO_2NEt_2	$C_{19}H_{25}N_3O_6S$	190-193	C	7	10
85	EtO	H	H	$SO_2N(Me)$-*i*-Pr	$C_{19}H_{25}N_3O_6S$	180-184	C	69	>10
86	*n*-PrO	H	H	MeO	$C_{17}H_{20}N_2O_5$	124-126	B	47	0.7
87	EtO	NO_2	H	NO_2	$C_{15}H_{14}N_4O_8$	130-133	C	32	>50

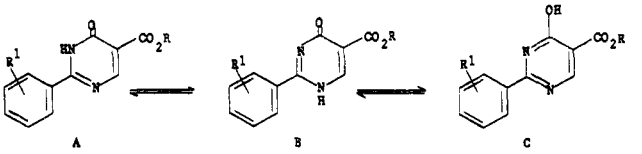
[a,c,d,e,h,i,j] See footnotes to Table I. [k] C, H only. [l] Not analyzed. [m] An oil, used crude without characterization.

Scheme III



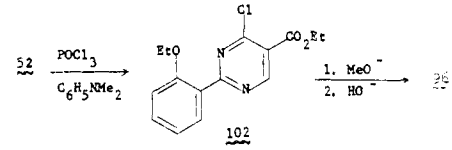
All but one of the required benzamidines were prepared by standard procedures, as indicated under the Experimental Section. *o*-Nitrobenzamidine could only be obtained by treatment of *o*-nitrobenzonitrile with urea and aluminum chloride.[7]

We have shown the final acid and ester products as 1,6-dihydro-6-oxo-2-phenylpyrimidines, A, although two



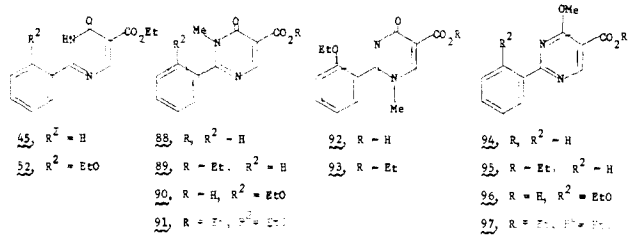
additional tautomeric forms, B and C, are possible. Judging by the two strong IR absorption bands which are observed for each compound in the regions of 1690–1760 (acid or ester C=O) and 1610–1680 cm^{-1}, both acids and

Scheme IV



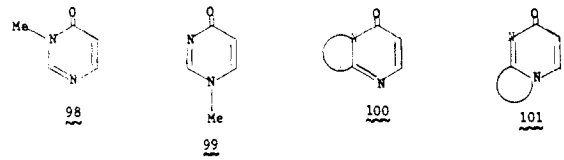
esters exist predominantly in an amide form in the solid state.

It is well documented that the products from alkylation of pyrimidinones possessing a free NH group depend greatly upon the reagents and conditions used.[8] Treatment of the thallium(I) salt of **52** with iodomethane in DMF gave



almost exclusively the N-methylated products **91** and **93**, with **91** predominating.[9] Methylation of the sodium salt of **45** with iodomethane in DMF gave a mixture of **89** and **95** in a ratio of about 3:5. Treatment of **52** with diazomethane in methylene chloride gave predominantly **91** and **97** in equal proportions.

Structural assignments for the alkylated products are based on spectral data. The IR spectra of **89** and **91** have bands at 1671 and 1672 cm^{-1}, respectively (amide C=O, KBr). The IR spectrum (KBr) of **93** shows a strong band at 1640 cm^{-1} (amide C=O). By comparison, the IR spectra (KBr) of the model lactams **98** and **99** show C=O

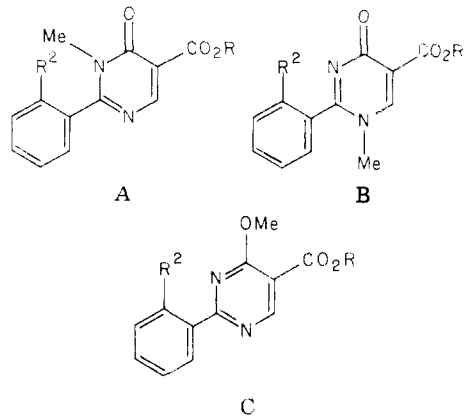


stretching bands at 1675 and 1653 cm^{-1}, respectively.[10] The O-methylated products **95**–**97** are characterized by the lack of amide C=O stretching bands in the IR and the presence of typical OMe (4.2–4.25 ppm) and ring proton (9.1–9.3 ppm) bands in the NMR spectra. All N-methylated products have typical NMe bands (3.43–3.55 ppm) in their NMR spectra, but the single ring proton bands of the $\alpha\beta,\gamma\delta$-unsaturated pyrimidinones **89** (8.70 ppm) and **91** (8.72 ppm) fall at about 0.5-ppm downfield from the corresponding band of the $\alpha\beta:\alpha'\beta'$-unsaturated pyrimidinone **93** (8.2 ppm). Furthermore, the UV spectrum of **89** exhibits three bands characteristic of compounds with the chromophore **100** in which the ratio of $\epsilon_c/\epsilon_b > 1$.[11] Compound **93** has a three-band UV spectrum characteristic of compounds with the chromophore **101** in which the ratio of $\epsilon_c/\epsilon_b < 1$.[11]

The esters **89**, **91**, **93**, and **95** were converted to the corresponding acids **88**, **90**, **92**, and **94**, respectively, by base-catalyzed hydrolysis. In addition, the *o*-methyl acid **96** was obtained as outlined in Scheme IV.

Finally, the UV spectra of the secondary amides **9** and **52** closely resemble the spectrum of **91**, suggesting that, at least in aqueous ethanol, **9** and **52** exist predominantly in the tautomeric form A. Form A is probably a preferred form in solution for the remaining acids and esters in Tables I and II, since other workers have also shown the predominance in solution of the 1,6-dihydro-6-oxopyrimidine form of 4-hydroxypyrimidine.[10]

Table III. N- and O-Methylated Pyrimidinones



no.	class	R	R^2	PCA[d] ID_{50}, mg/kg po
88	A	H	H	50
89	A	Et	H	>5
90	A	H	EtO	>50
91	A	Et	EtO	>40
92	B	H	EtO	>40
93	B	Et	EtO	*n*
94	C	H	H	>10
95	C	Et	H	>5
96	C	H	EtO	>5

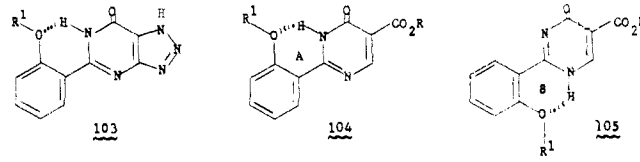
[d] See footnotes to Table I. [n] ID_{50} > 1 mg/kg iv. Compound not tested po.

Structure–Activity Relationships. Both acids and esters were tested for antiallergy activity in the passive cutaneous anaphylaxis (PCA) model in the rat, and in each case the dose of compound required to inhibit the response by 50% (ID_{50}) was determined. The results are listed in Tables I–III.

Although only oral data were obtained for most compounds, compound **9** was found to be approximately four times more potent than DSCG when both were administered intravenously.

With respect to oral activity, several generalizations and trends can be observed. (1) A free NH (or OH) group in the pyrimidine nucleus appears to be important for high activity. All the N- or O-methylated compounds in Table III show relatively weak activity. (2) The carboxylic acids tend to be more active than the corresponding esters. (3) Highest activity is observed for compounds where the phenyl ring is substituted with an alkoxy or alkenyloxy group in an ortho position. Considerably less activity is observed with other ortho substituents, including alkylthio. (4) Among the ortho monosubstituted ether compounds, activity peaks with two to four carbon atoms. (5) Some potentiation of the activity of the ortho monosubstituted ether compounds is observed with electron-releasing groups at position 5 of the phenyl ring.

The necessity for a free NH group and an alkoxy or alkenyloxy group in the ortho position of the phenyl ring for optimum activity is analogous to the findings of Broughton et al. in a series of antiallergic 2-phenyl-8-azapurinones, **103**.[12] The May and Baker group postu-



lated that biological activity is increased by hydrogen bonding between the 1 position of the azapurine system and the oxygen of a suitable *o*-ether group on the phenyl ring. They interpreted the relationship to mean that coplanarity of the phenyl substitutent with the azapurinone nucleus is a requirement for high antiallergy activity.

It is possible that similar factors are in operation in the case of the 2-phenylpyrimidinones and that optimum activity is seen for those compounds where the essentially planar configuration of the molecule is stabilized, as shown in **104**. Only acids (**104**, R = H) and esters (**104**, R = Et) which have an *o*-alkoxy or *o*-alkenyloxy group on the phenyl ring ring show a sharp NH stretching band around 3220 cm^{-1} (KBr) in their IR spectra, which can be ascribed to intramolecular hydrogen bonding. All other acids and esters show broad NH bands, often with poorly defined maxima. The electronic nature of the ortho substituent which is required for optimum activity supports a hydrogen-bond hypothesis,[13] as does the relative inactivity of the *N*-methyl-*o*-ethoxy compounds **90** and **91** and the *o*-alkylthio acids **19** and **20**. The ability of oxygen at position 2 to hydrogen bond is presumably reinforced by electron-releasing groups at position 5 of the phenyl ring.

Two additional possibilities, however, should also be considered. First, there may be a contribution from the alternative coplanar bonded form **105** to in vivo activity, in spite of in vitro spectral evidence (see Chemistry section). Second, perhaps the function of the hydrogen bonding in either **104** or **105** is to generate a new ring A or B, respectively, with the hydrocarbon substituent R^1 oriented for optimum biological activity. Similar possibilities also apply to the azapurinones.

The analogy between the 1,6-dihydro-6-oxo-2-phenylpyrimidine-5-carboxylic acid and 2-phenyl-8-azapurinone antiallergy agents draws closer if one considers the acidic nature[14] of the triazolo ring proton of **103** and the fact that the carboxylic acids generally show higher biological activity than the corresponding esters, which may require in vivo hydrolysis.

In summary, we have described a series of 1,6-dihydro-6-oxo-2-phenylpyrimidine-5-carboxylic acids and esters with potent oral and intravenous antiallergic activity in the rat. Requirements for high activity include a free NH group in the pyrimidinone nucleus and a small to medium size *o*-alkoxy or *o*-alkenyloxy group on the phenyl ring. Although we have postulated hydrogen bonding between a nitrogen of the pyrimidine ring and the ethereal oxygen, the exact nature of this bonding and its contribution to an optimum biological configuration for the molecules remains unclear. We will attempt to clarify this matter in subsequent papers.

Experimental Section

Biological Methods. A modified version of the rat PCA screen as described by Ovary[15] was used. Male Sprague–Dawley rats were used with an interval of 24 h between sensitization and challenge. Where possible, acidic test compounds were solubilized with aqueous $NaHCO_3$; other compounds were suspended in an aqueous sodium citrate solution containing Tween 40/sodium carboxymethylcellulose. Test compounds were administered iv or po 1 or 10 min (optimum times), respectively, prior to antigen challenge. DSCG, solubilized in saline, was administered iv at the time of challenge and po arbitrarily 30 min prior to challenge.

Chemical Methods. IR and NMR spectra were obtained for all compounds and were consistent with assigned structures. IR spectra were recorded on either Beckman IR 9 or IR 4240 spectrophotometers. ^1H NMR spectra were obtained using a Perkin-Elmer R12B 60-MHz spectrometer. Chemical shifts (δ) in parts per million were measured downfield from Me_4Si. UV spectra were recorded on a Beckman Model Acta III spectrophotometer. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical values. Melting points are uncorrected.

Benzamidines. The majority of the benzamidines are known compounds and were prepared by methods previously summarized.[12,16] Reference 16 is a particularly useful compilation. Most of the benzamidines were subjected to minimal purification.

2-Ethoxy-5-chlorobenzamidine hydrochloride [mp 227 °C dec. Anal. ($C_9H_{11}ClN_2O$·HCl) C, H, N], 2-ethoxy-5-methoxybenzamidine hydrochloride (mp 166–167 °C), 5-methoxy-2-propoxybenzamidine hydrochloride (crude oil), 2-(cyclopropylmethoxy)benzamidine hydrochloride (mp 166–171 °C), and 5-carbomethoxy-2-ethoxybenzamidine (mp 133–135 °C) were prepared by treatment of the corresponding crude benzimidates with ethanolic NH_3. The benzimidates, in turn, were obtained by O-alkylation of the corresponding benzamides with triethyloxonium fluoroborate or methyl fluorosulfonate. To avoid S-alkylation, 2-(methylthio)benzamidine hydrochloride[16] and 2-(ethylthio)benzamidine hydrochloride [mp 296–297 °C. Anal. ($C_9H_{12}N_2S$·HCl) Cl] were prepared by Raney nickel catalyzed hydrogenolysis, in EtOH, of the corresponding benzamidoximes. The latter were prepared by the addition of hydroxylamine to the corresponding benzonitriles. *o*-Nitrobenzamidine was obtained by treatment of *o*-nitrobenzonitrile with urea and $AlCl_3$.[7]

Ethyl 1,6-Dihydro-6-oxo-2-phenylpyrimidine-5-carboxylates (Table II, 45–47, 51–69, 72–76, and 86). The above esters were prepared in a manner similar to that described for the preparation of ethyl 1,6-dihydro-6-oxo-2-(2-ethoxyphenyl)pyrimidine-5-carboxylate (**52**), as follows.

A solution of diethyl ethoxymethylenemalonate (9.7 g, 0.045 mol) in EtOH (20 mL) was added dropwise during 5 min to a cooled (ice–water), stirred mixture of 2-ethoxybenzamidine (7.4 g, 0.045 mol) in EtOH (60 mL) containing NaOEt (prepared from 1.04 g of Na, 0.045 g-atom). The stirred mixture was heated under reflux for 2.25 h and then poured into 500 mL of ice–water. The mixture was acidified with 6 N HCl to provide **52** (10.2 g), mp 144–149 °C. Recrystallization from CH_3CN gave the analytical sample: UV λ_{max} (95% EtOH) 205 nm (ϵ 17 800), 228 (ϵ 10 700), 261 (shoulder, ϵ 6440), 331 (ϵ 13 700).

Highest yields were usually obtained with NaOEt, but this base could be replaced by either K_2CO_3 or NaOH or even omitted. K_2CO_3 was found to be necessary in the preparation of the *o*-nitrophenyl ester **48** because decomposition of the intermediate *o*-nitrobenzamidine occurred with the use of NaOEt. An additional equivalent of NaOEt was used for benzamidines in the salt form. Ester interchange occurred in the preparation of **76** from 5-carbomethoxy-2-ethoxybenzamidine.

1,6-Dihydro-6-oxo-2-phenylpyrimidine-5-carboxylic Acids (Table I, 2–20, 22–27, 30–36, and 44). The above acids were prepared from the corresponding esters by saponification with dilute NaOH in a manner similar to that described for the preparation of 1,6-dihydro-6-oxo-2-(2-ethoxyphenyl)pyrimidine-5-carboxylic acid (**9**), as follows. A mixture of **52** (2.0 g, 6.9 mmol) and 20 mL of 1 N NaOH was heated under reflux for 10 min. The solution was cooled and acidified with 6 N HCl to precipitate **9** (1.8 g) as a colorless paste, mp 168–184 °C. Recrystallization from CH_3CN gave the analytical sample (1.2 g): UV λ_{max} (95% EtOH) 208 nm (ϵ 15600), 228 (ϵ 10200), 263 (ϵ 7710), 323 (ϵ 9780).

Ethyl 1,6-Dihydro-6-oxo-2-(2-ethoxy-5-nitrophenyl)pyrimidine-5-carboxylate (77). Compound **52** (1.0 g, 3.46 mmol) was added over a 20-min period to a cooled (ice–water), stirred mixture of 70% HNO_3 (1.7 mL, *d* 1.42, 26.6 mmol) and 96% H_2SO_4 (2 mL, *d* 1.84). The mixture was stirred at room temperature for 19 h. The solution was poured into ice–water (300 mL). The precipitate was recrystallized from CH_3CN to give **77** (0.64 g, 55%): mp 222–224 °C; NMR ($CDCl_3$) δ 7.22 (d, 1 H, J = 9 Hz), 8.4 (dd, 1 H, J = 3 and 9 Hz), 8.85 (s, 1 H, pyrimidine H-4), 9.35 (d, 1 H, J = 3 Hz).

Ethyl 1,6-Dihydro-6-oxo-2-(2-ethoxy-3,5-dinitrophenyl)pyrimidine-5-carboxylate (87). Compound **52** (5.0 g, 17.3 mmol) was added slowly to a cooled (ice–water), stirred mixture of 90% HNO_3 (12 mL, *d* 1.5, 0.26 mol) and 96% H_2SO_4 (15 mL, *d* 1.84). The mixture was stirred at room temperature for 1 h, rapidly heated to 50 °C, and immediately poured onto crushed ice. The precipitate was collected and recrystallized from 2-PrOH to give **87** (2.1 g, 32%). mp 130–133 °C.

Ethyl 1,6-Dihydro-6-oxo-2-(5-amino-2-ethoxyphenyl)pyrimidine-5-carboxylate (78). A mixture of **77** (0.42 g, 1.26 mmol) and 10% Pd/C (70 mg) in EtOH (200 mL) was shaken with hydrogen at a pressure of about 50 psi until uptake of hydrogen ceased. The mixture was filtered, the filtrate was reduced to dryness, and the residue was recrystallized from water followed by aqueous EtOH to give **78** (0.12 g, 31%), mp 107–110 °C.

Ethyl 1,6-Dihydro-6-oxo-2-(5-ethoxalylamido-2-ethoxyphenyl)pyrimidine-5-carboxylate (80). Ethyloxalyl chloride (0.18 g, 1.32 mmol) was added dropwise over a period of 5 min to a cooled (ice-water), stirred solution of **78** (0.40 g, 1.32 mmol) and pyridine (0.21 g, 2.64 mmol) in CH_2Cl_2 (6 mL). The mixture was stirred at room temperature for 40 min and then concentrated. The residue was triturated with water (15 mL) for 40 min. The solid was collected and recrystallized from CH_3CN to give **80** (0.26 g, 49%), mp 192–193 °C.

1,6-Dihydro-6-oxo-2-(5-ethoxalylamido-2-ethoxyphenyl)pyrimidine-5-carboxylic Acid (38). Compound **38** was prepared from 1,6-dihydro-6-oxo-2-(5-amino-2-ethoxyphenyl)-pyrimidine-5-carboxylic acid (**36**) and ethyloxalyl chloride in a manner similar to that described for **80**.

Ethyl 1,6-Dihydro-6-oxo-2-(5-chlorosulfonyl-2-ethoxyphenyl)pyrimidine-5-carboxylate (81). Compound **52** (4.0 g, 13.84 mmol) was added slowly to cold (−10 °C) chlorosulfonic acid (28 mL). The solution was allowed to stand at −5 °C for 64 h and then poured onto ice. The precipitate was collected, washed with ice-water, and dried to give **81** (2.8 g, 52%), mp 165–168 °C. Recrystallization from CH_3CN gave an analytical sample: mp 172–173 °C dec; NMR (Me_2SO-d_6) δ 7.18 (d, 1 H, J = 9 Hz), 7.8 (dd, 1 H, J = 3 and 9 Hz), 8.08 (d, 1 H, J = 3 Hz), 8.65 (s, 1 H, pyrimidine H-4).

Ethyl 1,6-Dihydro-6-oxo-2-(2-ethoxy-5-sulfamoylphenyl)pyrimidine-5-carboxylate (82). Compound **81** (0.6 g, 1.55 mmol) was added slowly to a cooled (ice-water) solution of concentrated NH_4OH (0.54 mL) in EtOH (15 mL). The mixture was stirred at room temperature for 19 h and then heated on a steam bath for 10 min. The mixture was concentrated, treated with water (20 mL), and acidified with 6 N HCl. The precipitate was recrystallized from CH_3NO_2 to give **82** (0.28 g, 49%), mp 262–264 °C.

Ethyl 1,6-dihydro-6-oxo-2-[2-ethoxy-5-(*N*,*N*-dimethylsulfamoyl)phenyl]pyrimidine-5-carboxylate (83), ethyl 1,6-dihydro-6-oxo-2-[2-ethoxy-5-(*N*,*N*-diethylsulfamoyl)-phenyl]pyrimidine-5-carboxylate (84), and ethyl 1,6-dihydro-6-oxo-2-[2-ethoxy-5-(*N*-isopropyl-*N*-methylsulfamoyl)phenyl]pyrimidine-5-carboxylate (85) were all prepared from **81** and the appropriate dialkylamine in a manner similar to that described for the preparation of **82**.

1,6-Dihydro-6-oxo-2-(5-chlorosulfonyl-2-ethoxyphenyl)-pyrimidine-5-carboxylic Acid (39). Compound **9** (4.0 g, 15.2 mmol) was added slowly to cold (−5 °C) chlorosulfonic acid (28 mL). The solution was allowed to stand at 8 °C for 136 h and then poured onto ice. The precipitate was collected and dried to give crude **39** (3.9 g), mp 195 °C dec.

1,6-Dihydro-6-oxo-2-(2-ethoxy-5-sulfamoylphenyl)pyrimidine-5-carboxylic acid (40), 1,6-dihydro-6-oxo-2-[2-ethoxy-5-(*N*,*N*-dimethylsulfamoyl)phenyl]pyrimidine-5-carboxylic acid (41), 1,6-dihydro-6-oxo-2-[2-ethoxy-5-(*N*,*N*-diethylsulfamoyl)phenyl]pyrimidine-5-carboxylic acid (42), and 1,6-dihydro-6-oxo-2-[2-ethoxy-5-(*N*-isopropyl-*N*-methylsulfamoyl)phenyl]pyrimidine-5-carboxylic acid (43) were prepared by reaction of **39** with either NH_4OH or the appropriate dialkylamine in a manner similar to that described for the preparation of **82**.

1,6-Dihydro-6-oxo-2-[5-(dimethylamino)-2-ethoxyphenyl]pyrimidine-5-carboxylic Acid (37). A solution (1.9 mL) of 37% formaldehyde (23.8 mmol) in water followed by $NaBH_3CN$ (0.45 g, 7.15 mmol) were added to a stirred solution of **78** (0.72 g, 2.38 mmol) in CH_3CN (14 mL). Glacial AcOH (0.24 mL) was then added over a period of 1 min. The mixture was stirred at room temperature for 2 h. Additional glacial AcOH (0.24 mL) was added and stirring continued for 0.5 h. The mixture was treated with Et_2O (35 mL). The organic layer was washed with 10% aqueous $NaHCO_3$ (3 × 10 mL) followed by brine (30 mL) and dried (Na_2SO_4). The solvent was removed, and a solution of the residue in CH_3CN/Et_2O (containing ester **79**) was extracted with 1 N NaOH (3 × 20 mL). The extract was acidified with glacial AcOH to pH 6. The precipitate was collected and recrystallized from CH_3CN to give **37** (0.21 g, 29%), mp 187–196 °C. Recrystallization from C_6H_6/*n*-hexane gave analytical material, mp 195–198 °C.

1,6-Dihydro-6-oxo-2-(3-allyl-2-hydroxyphenyl)pyrimidine-5-carboxylic Acid (28). 1,6-Dihydro-6-oxo-2-[2-(allyloxy)phenyl]pyrimidine-5-carboxylic acid (**16**, 900 mg) was heated at an oil bath temperature of 200–210 °C for about 3 min. The resulting yellow solid (870 mg), mp 240–243 °C, was crystallized from 2-methoxyethanol to provide the analytical sample.

Ethyl 1,6-Dihydro-6-oxo-2-(3-allyl-2-hydroxyphenyl)pyrimidine-5-carboxylate (70). Ethyl 1,6-dihydro-6-oxo-2-[2-(allyloxy)phenyl]pyrimidine-5-carboxylate (**59**, 4.8 g) was heated at an oil bath temperature of 225 °C for 5 min. The resulting solid was recrystallized from 2-methoxyethanol to provide yellow crystals (3.2 g) of crude **70**, mp 186–191 °C.

(±)-Ethyl 1,6-Dihydro-6-oxo-2-(2,3-dihydro-2-methylbenzofur-7-yl)pyrimidine-5-carboxylate (71) and (±)-1,6-Dihydro-6-oxo-2-(2,3-dihydro-2-methylbenzofur-7-yl)pyrimidine-5-carboxylic Acid (29). HBr was bubbled into a solution of **70** (2.41 g, 8.03 mmol) in AcOH (40 mL). The stirred mixture was then refluxed for 1.5 h with additional saturation with HBr every 20 min. The mixture was concentrated to dryness and partitioned between AcOEt/toluene and aqueous $NaHCO_3$. The organic layer was washed (water and brine), dried (Na_2SO_4), and concentrated to dryness. The resulting froth was crystallized from C_6H_6/*n*-hexane to afford **71** (660 mg), mp 151–162 °C. Crude **71** was suspended in CH_3NO_2, and the insoluble material was removed. The CH_3NO_2 filtrate was concentrated and the residue recrystallized twice from C_6H_6/*n*-hexane to provide pure **71** (380 mg). The $NaHCO_3$ layer was filtered and the filtrate acidified with AcOH/HCl to precipitate crude **29**, mp 205–209 °C. Crystallization from AcOH provided the analytical sample (670 mg).

Ethyl 1,6-Dihydro-6-oxo-2-(2-aminophenyl)pyrimidine-5-carboxylate (49). A mixture of ethyl 1,6-dihydro-6-oxo-2-(2-nitrophenyl)pyrimidine-5-carboxylate (**48**, 0.91 g, 3.14 mmol) and 10% Pd/C (0.34 g) in EtOH (200 mL) was shaken with hydrogen at a pressure of 50 psi until hydrogen uptake ceased. The mixture was filtered, the filtrate was concentrated, and the residue was recrystallized from CH_3CN to give **49** (0.455 g, 56%), mp 228–230 °C dec.

Ethyl 1,6-Dihydro-6-oxo-2-(2-hydroxyphenyl)pyrimidine-5-carboxylate (50). A mixture of ethyl 1,6-dihydro-6-oxo-2-[2-(benzyloxy)phenyl]pyrimidine-5-carboxylate (**61**, 3.5 g, 0.01 mol) in EtOH (200 mL) containing 10% Pd/C (0.5 g) was shaken with hydrogen at an initial pressure of 50 psi for 7 min (reduction ceased). The mixture was filtered and the collected solid was stirred with warm 5% aqueous $NaHCO_3$ (80 mL). The mixture was filtered and the filtrate was acidified with AcOH to precipitate **50** (2.24 g), mp 227–230 °C.

1,6-Dihydro-6-oxo-2-[2-(methylsulfinyl)phenyl]pyrimidine-5-carboxylic Acid (21). A solution of $NaIO_4$ (1.63 g, 7.63 mmol) in water (30 mL) was added to a stirred mixture of 1,6-dihydro-6-oxo-2-[2-(methylthio)phenyl]pyrimidine-5-carboxylic acid (**19**, 2.0 g, 7.63 mmol) in 23 mL of 0.335 N NaOH (7.7 mmol). Stirring was continued for 18 h at 25 °C. Acidification with 1 N HCl precipitated **21** (2.2 g), mp 202–203.5 °C. Crystallization from 95% EtOH provided buff crystals of the analytical sample.

Ethyl 1,6-Dihydro-1-methyl-6-oxo-2-phenylpyrimidine-5-carboxylate (89) and Ethyl 4-Methoxy-2-phenylpyrimidine-5-carboxylate (95). A mixture of ethyl 1,6-dihydro-6-oxo-2-phenylpyrimidine-5-carboxylate (**45**, 10.0 g, 0.0409 mol) and NaH (1.8 g of a 57% dispersion in mineral oil, 0.0429 mol of NaH) in DMF (100 mL) was heated with stirring for 20 min with an oil bath maintained at 55 °C. The solution was cooled to room temperature and iodomethane (6.8 g, 0.0479 mol) added. The mixture was stirred at room temperature for 2 h and then heated for 3.5 h with an oil bath maintained at 35 °C. The solvent was removed under reduced pressure, and the residue was triturated with ice-cold 3% aqueous AcOH (150 mL). The mixture was filtered, and the collected solid (9.8 g) was exhaustively extracted with boiling *n*-pentane. The residue A and the extract B were worked up separately.

Residue A (3.3 g) was exhaustively extracted with *n*-hexane. This extract was concentrated and cooled to yield a crystalline solid (2.8 g, 27%), mp 127–129 °C. Recrystallization from *n*-hexane gave **89**: mp 129–131 °C; IR (KBr) ν_{max} 1671 (amide C=O), 1740 cm^{-1} (ester C=O); NMR ($CDCl_3$) δ 3.55 (s, 3 H, NMe), 8.7 (s, 1 H, pyrimidine H-4); UV λ_{max} (95% EtOH) 203 nm (ϵ 20000), 233 (ϵ 8120), 312 (ϵ 10800). Anal. ($C_{14}H_{14}N_2O_3$) C, H, N.

Extract B was concentrated and cooled to yield a crystalline solid (5.3 g, 50%), mp 46–48 °C. Two recrystallizations from *n*-pentane gave **95**: mp 51–52 °C; IR (KBr) ν_{max} 1730 cm^{-1} (ester C=O); NMR ($CDCl_3$) δ 4.22 (s, 3 H, OMe), 9.1 (s, 1 H, pyrimidine H-6). Anal. ($C_{14}H_{14}N_2O_3$) C, H, N.

1,6-Dihydro-1-methyl-6-oxo-2-phenylpyrimidine-5-carboxylic Acid (88). A mixture of **89** (1.8 g, 6.97 mmol), 1 N NaOH (7 mL), and EtOH (5 mL) was heated under reflux for 15 min. The solution was evaporated to dryness, and a solution of the residue in water (20 mL) was acidified with concentrated HCl. The precipitate was collected and recrystallized from EtOH to give **88** (0.62 g, 39%), mp 193–195 °C. Anal. ($C_{12}H_{10}N_2O_3$) C, H, N.

4-Methoxy-2-phenylpyrimidine-5-carboxylic Acid (94). Compound **94**, mp 214–215 °C, after recrystallization from EtOH, was prepared in 87% yield by hydrolysis of ester **95** under conditions similar to those described for the preparation of **88** above. Anal. ($C_{12}H_{10}N_2O_3$) C, H, N.

Ethyl 1,6-Dihydro-1-methyl-6-oxo-2-(2-ethoxyphenyl)-pyrimidine-5-carboxylate (91) and Ethyl 1,4-Dihydro-1-methyl-4-oxo-2-(2-ethoxyphenyl)pyrimidine-5-carboxylate (93). A solution of **52** (5.77 g, 0.02 mol) in DMF (65 mL) at room temperature was treated with thallium(I) ethoxide (5.0 g, 0.02 mol) followed by iodomethane (2.84 g, 0.02 mol). The mixture was stirred at room temperature for 2 h and then stored at 5 °C for 15.5 h. The mixture was filtered and the filtrate concentrated. The partially solid residue was washed with a small volume of cyclohexane and then recrystallized from EtOH to give **91** (4.0 g, 66%). mp 136.5–139 °C. Recrystallization from EtOH gave analytical material: mp 138.5–140 °C; IR (KBr) ν_{max} 1672 (amide C=O), 1740 cm^{-1} (ester C=O); NMR ($CDCl_3$) δ 3.43 (s, 3 H, NMe), 8.72 (s, 1 H, pyrimidine H-4); UV λ_{max} (95% EtOH) 205 nm (ϵ 16200), 217 (ϵ 13200), 312 (ϵ 10800). Anal. ($C_{16}H_{18}N_2O_4$) C, H, N.

From the mother liquors of the product with mp 136.5–139 °C was obtained, by fractional crystallization, **93** (450 mg, 7%), mp 124–129 °C. Compound **93** was purified by chromatography on silicic acid with toluene/acetone (4:1, changing to 1:1) followed by recrystallization from AcOEt to give analytical material: mp 127.5–128 °C; IR (KBr) ν_{max} 1632 (amide C=O), 1733 cm^{-1} (ester C=O); NMR ($CDCl_3$) δ 3.5 (s, 3 H, NMe), 8.2 (s, 1 H, pyrimidine H-6); UV λ_{max} (95% EtOH) 204 nm (ϵ 19800), 241 (ϵ 17300), 286 (ϵ 9050). Anal. ($C_{16}H_{18}N_2O_4$) C, H, N.

1,6-Dihydro-1-methyl-6-oxo-2-(2-ethoxyphenyl)pyrimidine-5-carboxylic Acid (90). Compound **90**, mp 121–122.5 °C, after recrystallization from aqueous EtOH, was prepared in 83% yield by hydrolysis of ester **91** under conditions similar to those described for the preparation of **88** above. Anal. ($C_{14}H_{14}N_2O_4$) C, H, N.

1,4-Dihydro-1-methyl-4-oxo-2-(2-ethoxyphenyl)pyrimidine-5-carboxylic Acid (92). Compound **92**, mp 203–204 °C, after recrystallization from EtOH, was prepared by hydrolysis of **93** in 64% yield in a manner similar to that described for the preparation of **88**. Anal. ($C_{14}H_{14}N_2O_4$) C, H, N.

Methylation of Ethyl 1,6-Dihydro-6-oxo-2-(2-ethoxyphenyl)pyrimidine-5-carboxylate (52) with Diazomethane. A mixture of **52** (1.0 g, 3.47 mmol) in Et_2O (10 mL), CH_2Cl_2 (30 mL), and MeOH (0.25 mL) was treated with an excess of CH_2N_2 in Et_2O and then allowed to stand over ice for 16 h. The mixture was filtered and the filtrate concentrated to leave a mixture of **91** and ethyl 4-methoxy-2-(2-ethoxyphenyl)pyrimidine-5-carboxylate (**97**) as a pale yellow oil: IR ($CHCl_3$) ν_{max} 1675 (amide C=O), 1710, 1735 cm^{-1} (ester carbonyl); NMR ($CDCl_3$) δ 3.45 (s, NMe), 4.2 (s, OMe), 8.72 (s, **91** pyrimidine H-4), 9.1 (s, **97** pyrimidine H-6). The NMR spectrum indicated equal proportions of **91** and **97**.

Ethyl 4-Chloro-2-(2-ethoxyphenyl)pyrimidine-5-carboxylate (102). A mixture of **52** (2.0 g, 6.9 mmol), *N,N*-dimethylaniline (0.84 g, 6.9 mmol), and $POCl_3$ (20 mL, 0.21 mol) was heated under reflux for 50 min. The excess $POCl_3$ was removed under reduced pressure. The residue was treated with ice–water followed by aqueous Na_2CO_3 until the pH remained at about 8. The aqueous supernatant was decanted from the gummy solid. The latter was triturated with 1 N HCl to give a solid, which was washed with water, dried, and recrystallized from cyclohexane to give **102** (1.7 g, 80%), mp 64–65 °C. Anal. ($C_{15}H_{15}ClN_2O_3$) C, H, N; Cl: calcd, 11.56; found, 10.96.

2-(2-Ethoxyphenyl)-4-methoxypyrimidine-5-carboxylic Acid (96). Compound **102** (1.1 g, 3.6 mmol) was added to an ice-cool solution of Na (0.1 g, 4.3 g-atoms) in MeOH (5 mL), and the mixture was stirred at room temperature for 35 min. The mixture was concentrated and the residue treated with 10% aqueous AcOH (10 mL). The aqueous layer was decanted from the gum. The gum was partitioned between water and Et_2O. The ether layer was washed with water followed by brine, dried (Na_2SO_4), and flashed to dryness. A mixture of the residual gum, 1 N NaOH (3.6 mL), and EtOH (3.6 mL) was heated under reflux for 10 min. The solution was concentrated, and the residue was treated with water (10 mL). The solution was acidified with 10% HCl to precipitate **96** (0.8 g, 84%), mp 145–148 °C. The product was recrystallized twice from C_6H_6 to give analytical material: mp 149–151 °C; IR (KBr) ν_{max} 1718 cm^{-1} (carboxyl C=O); NMR ($CDCl_3$) δ 4.25 (s, 3 H, OMe), 9.3 (s, 1 H, pyrimidine H-6). Anal. ($C_{14}H_{14}N_2O_4$) C, H, N.

Acknowledgment. We thank Dr. Paul Siminoff and Mr. Fred Reed for kindly providing us with all the rat PCA data and the Analytical Department for their services.

References and Notes

(1) R. N. Brogden, T. M. Speight, and G. S. Avery, *Drugs*, **7**, 164–296 (1974).
(2) (a) R. E. Giles and D. J. Herzig, *Annu. Rep. Med. Chem.*, **10**, 80 (1975); (b) A. L. Oronsky and J. F. Wasley, *ibid.*, 11, 51 (1976); (c) A. L. Oronsky and J. F. Wasley, *ibid.*, **12**, 70 (1977).
(3) Some of these compounds have been described by P. F. Juby and R. A. Partyka, U.S. Patent 4031093 (1977).
(4) W. E. Barth, U.S. Patent 3883653 (1975).
(5) T. Y. Shen, G. L. Walford, and B. E. Witzel, U.S. Patent 3660403 (1972).
(6) P. C. Mitter and J. C. Bardhan, *J. Chem. Soc.*, **123**, 2179 (1923).
(7) W. F. Short and M. W. Partridge, U.S. Patent 2450386 (1948).
(8) (a) D. J. Brown in "The Pyrimidines", Interscience, New York, N.Y., 1962, p 359; (b) D. J. Brown in "The Pyrimidines, Supplement I", Wiley-Interscience, New York, N.Y., 1970, p 270.
(9) According to E. C. Taylor and A. McKillop, *Acc. Chem. Res.*, **3**, 338 (1970), alkylation of thallium(I) salts of heterocyclic amides takes place exclusively on nitrogen.
(10) D. J. Brown, E. Hoerger, and S. F. Mason, *J. Chem. Soc.*, 211 (1955).
(11) C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. VanAllan, *J. Org. Chem.*, **24**, 779 (1959).
(12) B. J. Broughton, P. Chaplen, P. Knowles, E. Lunt, S. M. Marshall, D. L. Pain, and K. R. H. Wooldridge, *J. Med. Chem.*, **18**, 1117 (1975).
(13) G. C. Pimentel and A. L. McClellan in "The Hydrogen Bond", W. H. Freeman, San Francisco, Calif., 1960.
(14) Y. Hirata, I. Teshima, and T. Goto, *Nagoya Sangyô Kagaku Kenkyûjo Kenkyû Hôkoku*, **No. 9**, 80 (1956); *Chem. Abstr.*, **51**, 8516 (1957).
(15) Z. Ovary in "Immunological Methods", J. F. Ackroyd, Ed., F. A. Davis, Philadelphia, Pa., 1964, pp 259–283.
(16) B. J. Broughton, B. J. Large, S. M. Marshall, D. L. Pain, and K. R. H. Wooldridge, U.S. Patent 3819631 (1974).