Studies on Antiallergy Agents. III.[1] Synthesis of 2-Anilino-1,6-dihydro-6-oxo-5-pyrimidinecarboxylic Acids and Related Compounds

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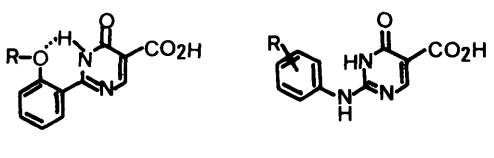
A series of 2-anilino-1,6-dihydro-6-oxo-5-pyrimidinecarboxylic acids with various substituents was synthesized and evaluated in the rat passive cutaneous anaphylaxis test for antiallergic activity. High activity by intraperitoneal and oral administrations was observed for the 3-trifluoromethyl and 2-alkoxyanilino derivatives (64, 79, 81, 82 and 85). Structure–activity relationships are discussed.

Keywords antiallergy agent; intraperitoneal activity; oral activity; 1,6-dihydro-6-oxo-5-pyrimidinecarboxylic acid; phenylguanidine; structure–activity relationship

Disodium cromoglycate (DSCG) has been shown to be effective for the prophylactic treatment of allergic disease such as bronchial asthma, and the mode of action is thought to be inhibition of the release of chemical mediators from sensitized mast cells.[2] However, DSCG is not absorbed orally to any extent and thus must be used as an insufflated powder. Extensive efforts have been made to find an orally active and more potent antiallergy agent having pharmacological properties similar to those of DSGC.[3] In particular, we are seeking orally active agents which are structurally unlike DSCG. Juby *et al.*[4] have reported that 1,6-dihydro-6-oxo-5-pyrimidinecarboxylic acids and the corresponding esters are orally effective antiallergy agents. This fact prompted us to evaluate 1,6-dihydro-2-[2-(2-methylpropoxy)phenyl]-6-oxo-5-pyrimidinecarboxylic acid (**1**), one of the most active compounds in the series, as a lead compound for the development of new antiallergy agents. In our examinations of the pharmacological and toxicological properties, compound **1** showed a 50% inhibitory dose (ID_{50}) (*p.o.*) of 1.1 mg/kg in the rat passive cutaneous anaphylaxis (PCA) test and a 50% lethal dose (LD_{50}) (i.p.) of 6.6 mg/kg in mice. It has been suggested that the high antiallergic activity of **1** is correlated with the molecular coplanarity arising from intramolecular hydrogen bonding between NH on the pyrimidine nucleus and the ethereal oxygen atom on the phenyl ring.[4] Since the effective dose for antiallergic activity of **1** is relatively close to the lethal dose, the coplanar configuration of the molecule of **1** may also contribute to the biological toxicity. Thus, in order to find a potent but less toxic drug, we designed 2-anilino-1,6-dihydro-6-oxo-5-pyrimidinecarboxylic acids (**2**), in which the phenyl ring and pyrimidine nucleus could not lie on the same plane because of the linkage *via* the nitrogen atom (Chart 1).

In the present paper, we describe the synthesis and structure–activity relationships of a new series of **2**.

Chemistry Two routes of synthesis were used for the preparation of most of the ethyl 2-anilino-1,6-dihydro-6-oxo-5-pyrimidinecarboxylates (Chart 2). In the first route, ethyl 1,6-dihydro-2-methylthio-6-oxo-5-pyrimidinecarboxylate (**3**)[5] was allowed to react with the appropriate anilines either under reflux in ethanol (method A) or neat at about 130 °C (method B) to give the esters (**4**—**7**, **9**—**14**, **16**, **17** and **19**—**42**) in good yields. As an alternative route, anilines and the *N*-methyl derivative were condensed with an excess of cyanamide in the presence of hydrochloric acid in methanol to give the phenylguanidines (**49**—**58**)[6] which were subsequently cyclized with diethyl ethoxymethylenemalonate (DEMM) to afford the esters (**8**, **15**, **18**, **43**—**48** and **104**) (method C). The synthesized esters (**4**—**48** and **104**) were converted into the desired acids (**59**—**103**, **105**) by usual hydrolysis.



1 **2**

Chart 1

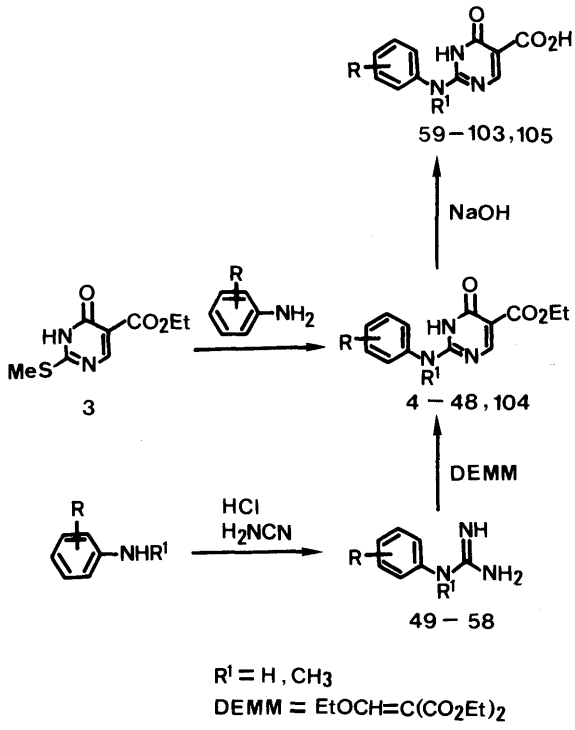
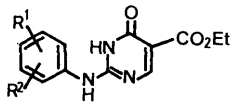


Chart 2

The synthesis of 1,6-dihydro-1-methyl-2-[2-(2-methylpropoxy)anilino]-6-oxo-5-pyrimidinecarboxylic acid (**110**) was accomplished according to the route shown in Chart 3. 2-(2-Methylpropoxy)aniline was condensed with benzo-

TABLE I. Ethyl 2-Anilino-1,6-dihydro-6-oxo-5-pyrimidinecarboxylates



Compd. No.	R^1	R^2	mp (°C)	Recrystn. solvent[a]	Method[b]	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
4	H	H	267—269	A	B	62	$C_{13}H_{13}N_3O_3$	60.23	5.05	16.21
								(59.89	5.09	15.89)
5	2-F	H	250—252	B	B	83	$C_{13}H_{12}FN_3O_3$	56.32	4.36	15.16
								(55.96	4.28	15.30)
6	4-Cl	H	296—299	B	B	98	$C_{13}H_{12}ClN_3O_3$	53.16	4.12	14.31
								(53.28	4.03	14.09)
7	4-Br	H	>300	B	B	84	$C_{13}H_{12}BrN_3O_3$	46.17	3.58	12.43
								(46.31	3.52	12.56)
8	2-Cl	6-Cl	239—242	B–C	C	77	$C_{13}H_{11}Cl_2N_3O_3$	47.58	3.38	12.81
								(47.30	3.28	12.54)
9	3-CF_3	H	229—230	B–C	B	89	$C_{14}H_{12}F_3N_3O_3$	51.38	3.70	12.84
								(51.15	3.68	12.67)
10	3-NO_2	H	226—228	B	B	60	$C_{13}H_{12}N_4O_5$	51.32	3.98	18.41
								(51.15	3.92	18.30)
11	4-$N(CH_3)_2$	H	246—248	B–C	A	91	$C_{15}H_{18}N_4O_3$	59.59	6.00	18.53
								(59.46	5.96	18.69)
12	4-$CO_2CH_2CH_3$	H	297—299	B	B	63	$C_{16}H_{17}N_3O_5$	58.00	5.17	12.68
								(58.08	5.09	12.65)
13	4-$COCH_3$	H	>300	B	B	80	$C_{15}H_{15}N_3O_4$	59.80	5.02	13.95
								(59.67	5.23	13.98)
14	2-CH_3	H	257—259	B	B	95	$C_{14}H_{15}N_3O_3$	61.53	5.53	15.38
								(61.61	5.36	15.21)
15	2-CH_2CH_3	H	226—228	B–C	C	47	$C_{15}H_{17}N_3O_3$	62.71	5.96	14.63
								(62.87	5.73	14.70)
16	4-CH_2CH_3	H	265—267	B–C	A	50	$C_{15}H_{17}N_3O_3$	62.71	5.96	14.63
								(62.52	5.88	14.79)
17	2-CH_3	3-CH_3	273—275	B–C	A	65	$C_{15}H_{17}N_3O_3$	62.71	5.96	14.63
								(62.58	5.76	14.73)
18	2-CH_3	6-CH_3	225—226	B–C	C	32	$C_{15}H_{17}N_3O_3$	62.71	5.96	14.63
								(62.80	5.74	14.46)
19	2-OH	H	289—291	B	B	56	$C_{13}H_{13}N_3O_4$	56.72	4.76	15.27
								(56.46	4.86	15.22)
20	3-OH	H	278—280	B–C	B	68	$C_{13}H_{13}N_3O_4$	56.72	4.76	15.27
								(56.68	4.59	15.31)
21	4-OH	H	>300	B–C	B	71	$C_{13}H_{13}N_3O_4$	56.72	4.76	15.27
								(56.83	4.87	15.19)
22	2-OCH_3	H	217—219	B	B	85	$C_{14}H_{15}N_3O_4$	58.13	5.23	14.53
								(58.18	5.17	14.28)
23	2-OCH_2CH_3	H	220—221	B–C	B	66	$C_{15}H_{17}N_3O_4$	59.40	5.65	13.85
								(59.19	5.66	13.64)
24	2-$O(CH_2)_2CH_3$	H	192—196	B–C	B	72	$C_{16}H_{19}N_3O_4$	60.56	6.03	13.24
								(60.73	6.12	13.40)
25	2-$OCH(CH_3)_2$	H	205—207	B	A	54	$C_{16}H_{19}N_3O_4$	60.56	6.03	13.24
								(60.36	6.05	13.18)
26	2-$O(CH_2)_3CH_3$	H	209—211	B	B	84	$C_{17}H_{21}N_3O_4$	61.62	6.39	12.68
								(61.41	6.35	12.60)
27	2-$OCH_2CH(CH_3)_2$	H	193—195[c]	B–C	B	74	$C_{17}H_{21}N_3O_4$	61.62	6.39	12.68
								(61.51	6.32	12.81)
28	2-$O(CH_2)_4CH_3$	H	170—172	B	A	67	$C_{18}H_{23}N_3O_4$	62.59	6.71	12.17
								(62.48	6.67	12.38)
29	2-$O(CH_2)_5CH_3$	H	168—170	B	A	73	$C_{19}H_{25}N_3O_4$	63.49	7.01	11.69
								(63.52	7.12	11.46)
30	2-OCH_2- 	H	165—167	B	A	68	$C_{18}H_{21}N_3O_5$	60.16	5.89	11.69
								(60.26	5.86	11.47)
31	3-OCH_3	H	233—234	B	A	73	$C_{14}H_{15}N_3O_4$	58.13	5.23	14.53
								(58.33	5.13	14.42)
32	3-OCH_2CH_3	H	221—222	B–C	B	95	$C_{15}H_{17}N_3O_4$	59.40	5.65	13.85
								(59.21	5.48	13.96)
33	3-$O(CH_2)_2CH_3$	H	184—186	B–C	A	75	$C_{16}H_{19}N_3O_4$	60.56	6.03	13.24
								(60.76	6.01	13.44)
34	3-$O(CH_2)_3CH_3$	H	181—183	B–C	A	64	$C_{17}H_{21}N_3O_4$	61.62	6.39	12.68
								(61.37	6.32	12.45)

TABLE I. (continued)

Compd. No.	R^1	R^2	mp (°C)	Recrystn. solvent[a]	Method[b]	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
35	4-OCH_3	H	277—279	B	A	73	$C_{14}H_{15}N_3O_4$	58.13	5.23	14.53
								(57.84	5.15	14.58)
36	4-OCH_2CH_3	H	263—265	B	A	71	$C_{15}H_{17}N_3O_4$	59.40	5.65	13.85
								(59.02	5.52	13.88)
37	4-$O(CH_2)_2CH_3$	H	258—260	B	A	78	$C_{16}H_{19}N_3O_4$	60.56	6.03	13.24
								(60.51	5.95	13.14)
38	4-$O(CH_2)_3CH_3$	H	238—240	B	A	57	$C_{17}H_{21}N_3O_4$	61.62	6.39	12.68
								(61.37	6.25	12.74)
39	2-$O(CH_2)_2CH_3$	5-$O(CH_2)_2CH_3$	180—182	B–D	A	41	$C_{19}H_{25}N_3O_5$	60.79	6.71	11.19
								(60.57	6.79	11.27)
40	2-$O(CH_2)_3CH_3$	5-$O(CH_2)_3CH_3$	160—162	D	A	47	$C_{21}H_{29}N_3O_5$	62.51	7.24	10.41
								(62.50	7.04	10.35)
41	3-$O(CH_2)_2CH_3$	4-$O(CH_2)_2CH_3$	145—147	B–C	A	87	$C_{19}H_{25}N_3O_5$	60.79	6.71	11.19
								(60.51	6.68	11.20)
42	3-$O(CH_2)_3CH_3$	4-$O(CH_2)_3CH_3$	144—146	B	A	75	$C_{21}H_{29}N_3O_5$	62.51	7.24	10.41
								(62.36	7.25	10.36)
43	2-SCH_3	H	154—155	B–C	C	78	$C_{14}H_{15}N_3O_3S$	55.07	4.95	13.76
								(55.09	4.88	13.71)
44	2-SCH_2CH_3	H	152—154	B–C	C	66	$C_{15}H_{17}N_3O_3S$	56.41	5.37	13.16
								(56.12	5.26	13.25)
45	2-$S(CH_2)_2CH_3$	H	133—135	D	C	54	$C_{16}H_{19}N_3O_3S$	57.64	5.74	12.60
								(57.37	5.70	12.54)
46	2-$S(CH_2)_3CH_3$	H	96—98	E–F	C	52	$C_{17}H_{21}N_3O_3S$	58.77	6.09	12.09
								(58.47	5.97	12.18)
47	2-$SCH_2CH(CH_3)_2$	H	138—140	B–C	C	70	$C_{17}H_{21}N_3O_3S$	58.77	6.09	12.09
								(58.63	6.01	12.15)
48	2-$S(CH_2)_4CH_3$	H	103—104	B–C	C	77	$C_{18}H_{23}N_3O_3S$	59.81	6.41	11.63
								(59.77	6.52	11.81)

a) A = dimethyl sulfoxide, B = *N*,*N*-dimethylformamide, C = H_2O, D = ethanol, E = isopropyl ether, F = petroleum ether. *b*) See the experimental section. *c*) After recrystallization, the compound was washed with hot water and dried.

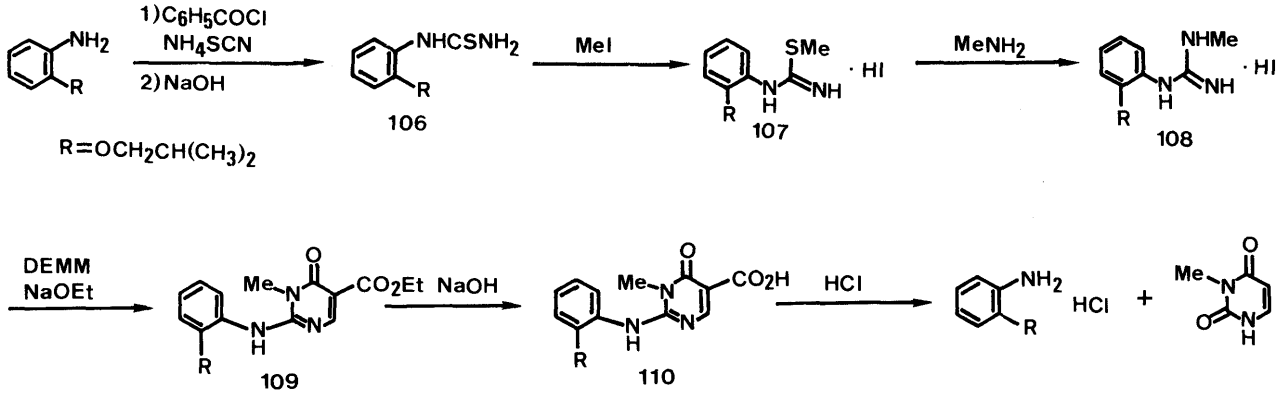


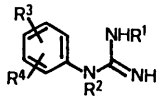
Chart 3

yl isothiocyanate prepared from ammonium thiocyanate and benzoyl chloride, followed by hydrolysis to afford the phenylthiourea (**106**).[7] This compound was converted into the phenylisothiourea hydriodide (**107**) by treatment with methyl iodide, and **107** was then reacted with an excess of methylamine to yield the phenylguanidine hydriodide (**108**). Compound **108** was cyclized with DEMM in the presence of sodium ethylate to give the ester (**109**) which was subsequently hydrolyzed to the corresponding acid (**110**). The position of the methyl group on the pyrimidine nucleus was confirmed by identification of the products by acid hydrolysis of **110**. Compound **110** was treated with 1 N hydrochloric acid to yield 3-methyl-2,4(1*H*, 3*H*)-pyrimidinedione and 2-(2-methylpropoxy)aniline hydrochloride, respectively, which were identical with authentic samples in high-performance liquid chromatographic analysis.

The synthesis of 4-methoxy-2-[2-(2-methylpropoxy)anilino]-5-pyrimidinecarboxylic acid (**113**) was performed according to the route shown in Chart 4. Ethyl 1,6-dihydro-2-[2-(2-methylpropoxy)anilino]-6-oxo-5-pyrimidinecarboxylate (**27**) was converted into the 4-chloro derivative (**111**) by a modification of the procedure described in the literature.[4] Compound **111** was treated in boiling methanol to give the 4-methoxy derivative (**112**), which was subsequently hydrolyzed to **113**.

Antiallergic Activity Male Wistar strain rats weighing 190—220 g were used. The preparation of rat anti-dinitrophenylated *Ascaris* immunogloblin E(anti-DNP-As

TABLE II. Guanidine, Thiourea and Isothiourea Derivatives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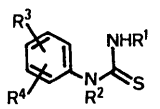
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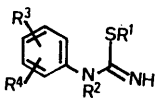
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Compd. No.	R^1	R^2	R^3	R^4	mp (°C)	Recrystn. solvent[a]	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N
49	H	H	2-Cl	6-Cl	208—212	D–E	22	$C_7H_7Cl_2N_3$	41.20	3.46	20.59
									(41.02	3.69	20.58)
50	H	H	2-CH_3	6-CH_3	263—264	D–E	35	$C_9H_{13}N_3 \cdot HCl$	54.14	7.07	21.04
									(54.33	6.96	21.31)
51	H	H	2-CH_2CH_3	H	129—131	D–E	77	$C_9H_{13}N_3$	66.23	8.03	25.74
									(66.46	8.01	25.87)
52	H	H	2-SCH_3	H	159—161	E–H	74	$C_8H_{11}N_3S$	53.01	6.12	23.18
									(53.17	6.08	23.09)
53	H	H	2-SCH_2CH_3	H	102—105	E–G	65	$C_9H_{13}N_3S$	55.35	6.71	21.52
									(55.51	6.59	21.03)
54	H	H	2-$S(CH_2)_2CH_3$	H	118—119	E–G	69	$C_{10}H_{15}N_3S$	57.38	7.22	20.08
									(57.23	7.14	19.98)
55	H	H	2-$S(CH_2)_3CH_3$	H	79—80	F–G	77	$C_{11}H_{17}N_3S$	59.16	7.67	18.81
									(59.11	7.58	18.93)
56	H	H	2-$SCH_2CH(CH_3)_2$	H	88—90	E–G	58	$C_{11}H_{17}N_3S$	59.16	7.67	18.81
									(58.94	7.57	18.97)
57	H	H	2-$S(CH_2)_4CH_3$	H	86—87	E–F	68	$C_{12}H_{19}N_3S$	60.72	8.07	17.70
									(60.70	8.25	17.43)
58	H	CH_3	2-$OCH_2CH(CH_3)_2$	H	176—177	D–E	50	$C_{12}H_{19}N_3O \cdot HCl$	55.92	7.82	16.30
									(55.76	7.77	16.14)
106	H	H	2-$OCH_2CH(CH_3)_2$	H	98—99	D–E	53	$C_{11}H_{16}N_2OS$	58.90	7.19	12.49
									(58.89	7.15	12.60)
107	CH_3	H	2-$OCH_2CH(CH_3)_2$	H	166—168	I	94	$C_{12}H_{18}N_2OS \cdot HI$	39.35	5.23	7.65
									(39.23	5.01	7.40)
108	CH_3	H	2-$OCH_2CH(CH_3)_2$	H	161—163	D–I	70	$C_{12}H_{19}N_3O \cdot HI$	41.27	5.77	12.03
									(41.11	5.57	11.79)

a) D=ethanol, E=isopropyl ether, F=petroleum ether, G=benzene, H=methanol, I=ethyl acetate.

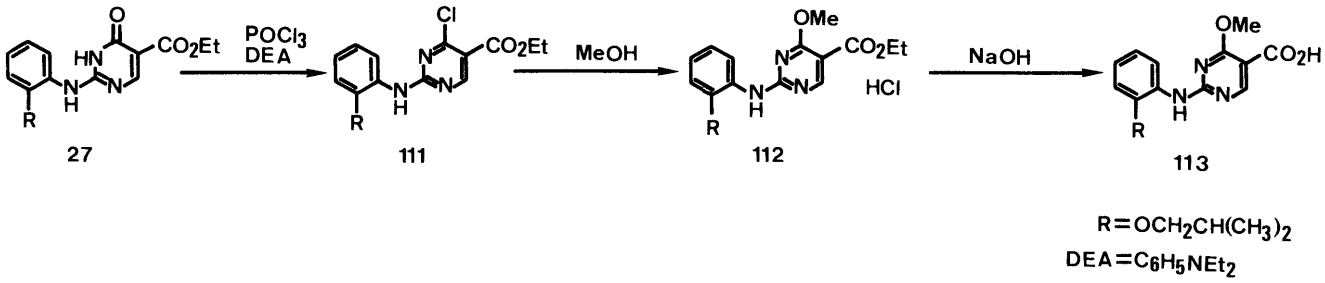


Chart 4

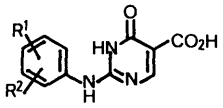
IgE) serum was performed according to the method of Tada and Okumura.[8] The anti-DNP-As IgE antibody titer of antiserum was 1 : 128 as estimated by 48 h homologous PCA in rats challenged with dinitrophenylated *Ascaris* (DNP-As). The anti-DNP-As serum (0.1 ml), which was diluted 50-fold with physiological saline, was injected intradermally at 4 sites on the shaved back of rats. After 48 h, physiological saline (1 ml) containing DNP-As (7.1 mg, 2 mg as a protein) and Evans blue (5 mg) was injected intravenously to induce on antigen–antibody reaction. The animals were sacrificed 30 min after challenge and the skins were removed for the colorimetric measurement of the blueing spots. The amount of the dye that had leaked into the PCA sites was determined as described by Katayama *et al.*[9] Test compounds suspended in 0.5% aqueous carboxymethylcellulose solution were administered intraperitoneally 30 min or orally 60 min before antigen challenge. Animals were fasted for 16 h prior to the application of antigen.

Acute Toxicity Male ddY strain mice weighing 20—25 g were used. Animals were fasted for 24 h prior to the application of test compounds. Following administration of test compounds, the animals were observed daily for 7 d, and the number of dead animals was recorded.

Results and Discussion

The obtained compounds were evaluated for antiallergic activity in the rat PCA test and the results are shown in Tables III and IV. All compounds were initially tested at the dose of 20 mg/kg by intraperitoneal administration to obtain a measure of activity and to elucidate structure–activity relationships. Initially, the effects of substituents

TABLE III. 2-Anilino-1,6-dihydro-6-oxo-5-pyrimidinecarboxylic Acids



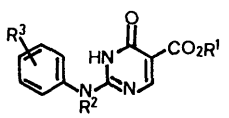
Compd. No.	R^1	R^2	mp (°C)	Recrystn. solvent[a]	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	Rat PCA test, Inhibition % 20 mg/kg, i.p.	100 mg/kg, p.o.
59	H	H	252—253	B–C	76	$C_{11}H_9N_3O_3$	57.14 (57.23)	3.92 (3.86)	18.17 (18.42)	NA	
60	2-F	H	>300	B	69	$C_{11}H_8FN_3O_3$	53.02 (52.87)	3.24 (3.31)	16.86 (16.68)	44	NA
61	4-Cl	H	257—258	B–C	98	$C_{11}H_8ClN_3O_3$	49.73 (49.87)	3.04 (2.99)	15.82 (15.69)	40	NA
62	4-Br	H	247—248	B	71	$C_{11}H_8BrN_3O_3$	42.61 (42.36)	2.60 (2.78)	13.55 (13.63)	47	NA
63	2-Cl	6-Cl	230—232	B–C	49	$C_{11}H_7Cl_2N_3O_3$	44.03 (43.96)	2.35 (2.28)	14.00 (13.77)	NA	
64	3-CF_3	H	252—254	B	68	$C_{12}H_8F_3N_3O_3$	48.17 (48.24)	2.69 (2.70)	14.04 (14.21)	75	66
65	3-NO_2	H	247—248	B–C	73	$C_{11}H_8N_4O_5$	47.83 (48.05)	2.92 (3.19)	20.28 (20.29)	37	
66	4-$N(CH_3)_2$	H	261—263	B	52	$C_{13}H_{14}N_4O_3$	56.93 (57.20)	5.14 (5.17)	20.43 (20.68)	58	NA
67	3-CO_2H	H	>300	B–C	66	$C_{12}H_9N_3O_5$	52.37 (52.31)	3.30 (3.42)	15.27 (15.09)	NA	
68	4-$COCH_3$	H	273—274	B–C	42	$C_{13}H_{11}N_3O_4$	57.14 (56.89)	4.06 (4.11)	15.38 (15.37)	86	NA
69	2-CH_3	H	232—233	B–C	89	$C_{12}H_{11}N_3O_3$	58.77 (58.93)	4.52 (4.51)	17.13 (17.11)	NA	
70	2-CH_2CH_3	H	230—231	B–C	67	$C_{13}H_{13}N_3O_3$	60.23 (60.31)	5.05 (5.03)	16.21 (16.27)	NA	
71	4-CH_2CH_3	H	248—250	B	68	$C_{13}H_{13}N_3O_3$	60.23 (60.04)	5.05 (4.91)	16.21 (16.30)	NA	
72	2-CH_3	3-CH_3	242—243	B	78	$C_{13}H_{13}N_3O_3$	60.23 (60.54)	5.05 (5.32)	16.21 (16.01)	NA	
73	2-CH_3	6-CH_3	241—242	B–C	80	$C_{13}H_{13}N_3O_3$	60.23 (59.94)	5.05 (5.10)	16.21 (16.13)	NA	
74	2-OH	H	254—256	B–C	67	$C_{11}H_9N_3O_4$	53.44 (53.52)	3.67 (3.55)	17.00 (17.00)	53	41
75	3-OH	H	234—236	B–C	54	$C_{11}H_9N_3O_4$	53.44 (53.15)	3.67 (3.69)	17.00 (16.79)	NA	
76	4-OH	H	257—259	B–C	70	$C_{11}H_9N_3O_4$	53.44 (53.35)	3.67 (3.91)	17.00 (17.06)	NA	
77	2-OCH_3	H	251—253	B	78	$C_{12}H_{11}N_3O_4$	55.17 (55.20)	4.24 (4.53)	16.09 (16.03)	61	NA
78	2-OCH_2CH_3	H	226—228	B–C	87	$C_{13}H_{13}N_3O_4$	56.72 (56.50)	4.76 (4.67)	15.27 (15.40)	55	57
79	2-$O(CH_2)_2CH_3$	H	202—204	B	62	$C_{14}H_{15}N_3O_4$	58.13 (58.04)	5.23 (5.16)	14.53 (14.42)	86	92
80	2-$OCH(CH_3)_2$	H	202—204	B	97	$C_{14}H_{15}N_3O_4$	58.13 (57.96)	5.23 (5.24)	14.53 (14.34)	100	51
81	2-$O(CH_2)_3CH_3$	H	212—214	B	73	$C_{15}H_{17}N_3O_4$	59.40 (59.25)	5.65 (5.84)	13.85 (14.00)	88	62
82	2-$OCH_2CH(CH_3)_2$	H	213—215[b]	B	57	$C_{15}H_{17}N_3O_4$	59.40 (59.57)	5.65 (5.66)	13.85 (13.78)	100	84
83	2-$O(CH_2)_4CH_3$	H	198—200	B–C	66	$C_{16}H_{19}N_3O_4$	60.56 (60.74)	6.03 (6.14)	13.24 (13.26)	73	NA
84	2-$O(CH_2)_5CH_3$	H	186—188	B–C	78	$C_{17}H_{21}N_3O_4$	61.62 (61.73)	6.39 (6.06)	12.68 (12.61)	NA	
85	2-OCH_2- 	H	220—222	B–C	60	$C_{16}H_{17}N_3O_5$	58.00 (58.12)	5.17 (5.18)	12.68 (12.49)	94	77
86	3-OCH_3	H	247—249	B	67	$C_{12}H_{11}N_3O_4$	55.17 (54.85)	4.24 (4.09)	16.09 (15.79)	NA	
87	3-OCH_2CH_3	H	219—220	B–C	88	$C_{13}H_{13}N_3O_4$	56.72 (56.52)	4.76 (4.69)	15.27 (15.24)	45	
88	3-$O(CH_2)_2CH_3$	H	186—188	B–C	83	$C_{14}H_{15}N_3O_4$	58.13 (58.18)	5.23 (5.13)	14.53 (14.25)	35	
89	3-$O(CH_2)_3CH_3$	H	183—185	B–C	80	$C_{15}H_{17}N_3O_4$	59.40 (59.71)	5.65 (5.59)	13.85 (13.52)	37	

TABLE III. (continued)

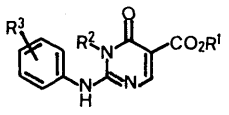
Compd. No.	R^1	R^2	mp (°C)	Recrystn. solvent[a]	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	Rat PCA test, Inhibition % 20 mg/kg, i.p.	100 mg/kg, *p.o.*
90	4-OCH_3	H	248—250	B–C	91	$C_{12}H_{11}N_3O_4$	55.17 (54.90)	4.24 (4.15)	16.09 (15.94)	NA	
91	4-OCH_2CH_3	H	250—252	B	55	$C_{13}H_{13}N_3O_4$	56.72 (56.82)	4.76 (4.63)	15.27 (15.17)	NA	
92	4-$O(CH_2)_2CH_3$	H	249—250	B	50	$C_{14}H_{15}N_3O_4$	58.13 (58.30)	5.23 (5.18)	14.53 (14.70)	NA	
93	4-$O(CH_2)_3CH_3$	H	246—248	B	49	$C_{15}H_{17}N_3O_4$	59.40 (59.52)	5.65 (5.54)	13.85 (13.70)	NA	
94	2-$O(CH_2)_2CH_3$	5-$O(CH_2)_2CH_3$	228—230	B–C	68	$C_{17}H_{21}N_3O_5$	58.78 (58.95)	6.09 (6.24)	12.10 (12.36)	46	NA
95	2-$O(CH_2)_3CH_3$	5-$O(CH_2)_3CH_3$	180—182	B–C	59	$C_{19}H_{25}N_3O_5$	60.79 (60.83)	6.71 (6.80)	11.19 (11.25)	33	
96	3-$O(CH_2)_2CH_3$	4-$O(CH_2)_2CH_3$	229—231	B–C	83	$C_{17}H_{21}N_3O_5$	58.78 (58.59)	6.09 (6.22)	12.10 (12.16)	NA	
97	3-$O(CH_2)_3CH_3$	4-$O(CH_2)_3CH_3$	226—228	B–C	77	$C_{19}H_{25}N_3O_5$	60.79 (60.84)	6.71 (6.77)	11.19 (11.08)	NA	
98	2-SCH_3	H	227—228	B–C	77	$C_{12}H_{11}N_3O_3S$	51.98 (52.08)	4.00 (3.87)	15.15 (15.00)	NA	
99	2-SCH_2CH_3	H	209—210	B–C	83	$C_{13}H_{13}N_3O_3S$	53.60 (53.47)	4.50 (4.41)	14.42 (14.30)	45	42
100	2-$S(CH_2)_2CH_3$	H	187—191	B–C	73	$C_{14}H_{15}N_3O_3S$	55.07 (54.98)	4.95 (4.87)	13.76 (13.63)	64	58
101	2-$S(CH_2)_3CH_3$	H	178—181	B–C	67	$C_{15}H_{17}N_3O_3S$	56.41 (56.64)	5.37 (5.26)	13.16 (13.16)	50	35
102	2-$SCH_2CH(CH_3)_2$	H	184—187	B–C	62	$C_{15}H_{17}N_3O_3S$	56.41 (56.51)	5.37 (5.48)	13.16 (13.29)	45	28
103	2-$S(CH_2)_4CH_3$	H	163—164	D	73	$C_{16}H_{19}N_3O_3S$	57.64 (57.48)	5.74 (5.83)	12.60 (12.48)	NA	
	DSCG									62	

a) B = *N*,*N*-dimethylformamide, C = H_2O, D = ethanol. *b*) After recrystallization, the compound was washed with hot water and dried. NA = not active.

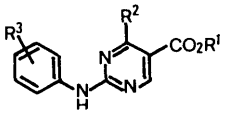
TABLE IV. Methylated 1,6-Dihydro-6-oxo-5-pyrimidinecarboxylic Acids and Related Compounds



104, 105



109, 110



111—113

Compd. No.	R^1	R^2	R^3	mp (°C)	Recrystn. solvent[a]	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	Rat PCA test, Inhibition % 20 mg/kg, i.p.
104	CH_2CH_3	CH_3	2-$OCH_2CH(CH_3)_2$	84—85	J[b]	47	$C_{18}H_{23}N_3O_4$	62.59 (62.66)	6.71 (6.75)	12.17 (12.09)	
105	H	CH_3	2-$OCH_2CH(CH_3)_2$	228—230	H	78	$C_{16}H_{19}N_3O_4$	60.56 (60.60)	6.03 (5.92)	13.24 (13.13)	NA
109	CH_2CH_3	CH_3	2-$OCH_2CH(CH_3)_2$	130—132	H	66	$C_{18}H_{23}N_3O_4$	62.59 (62.33)	6.71 (6.61)	12.17 (12.41)	
110	H	CH_3	2-$OCH_2CH(CH_3)_2$	178—179	B	57	$C_{16}H_{19}N_3O_4$	60.56 (60.23)	6.03 (5.99)	13.24 (13.34)	90
111	CH_2CH_3	Cl	2-$OCH_2CH(CH_3)_2$	93—95	F	54	$C_{17}H_{20}ClN_3O_3$	58.37 (58.62)	5.76 (5.71)	12.01 (11.78)	
112	CH_2CH_3	OCH_3	2-$OCH_2CH(CH_3)_2$	152—154	I	68	$C_{18}H_{23}N_3O_4 \cdot HCl$	56.62 (56.36)	6.33 (6.18)	11.00 (10.90)	
113	H	OCH_3	2-$OCH_2CH(CH_3)_2$	204—205	D	69	$C_{16}H_{19}N_3O_4$	60.56 (60.61)	6.03 (5.89)	13.24 (13.27)	NA

a) B = *N*,*N*-dimethylformamide, D = ethanol, F = petroleum ether, H = methanol, I = ethyl acetate, J = hexane. *b*) Compound **104** was washed with hexane. NA = not active.

attached to the anilino ring were investigated. High activity was observed for the 3-trifluoromethyl (**64**), 4-acetyl (**68**) and 2-alkoxyderivatives (**79**—**83** and **85**) with three to five carbon chains. With respect to the alkoxy derivatives, transposition of the alkoxy group from the 2-position to other positions or introduction of another medium-size

TABLE V. Antiallergic Activity and Toxicity of 2-Anilino-1,6-dihydro-6-oxo-5-pyrimidinecarboxylic Acids

Compd. No.	ID_{50} (mg/kg)		LD_{50} (mg/kg)		LD_{50} (i.p.)/ ID_{50} (*p.o.*)
	i.p.	*p.o.*	i.p.	*p.o.*	
1		1.1	6.6		6.0
64	5.8	55.0	760	>3000	13.8
79	11.0	22.2	1160	>3000	52.3
81	10.7	92.0	1230	>3000	13.4
82	4.7	39.0	780	>3000	20.0
85	4.3	70.0	860	>3000	12.3
Tranilast	40.0	110.0			

alkoxy group resulted in reduction or loss of activity, as shown for the 3- and 4-alkoxy derivatives (**86**—**93**) or 2,5- and 3,4-dialkoxy derivatives (**94**—**97**), respectively. Also, conversion of the alkoxy group into an alkylthio group led to a decrease of activity as observed for compounds **98**—**103**. Among the hydroxy derivatives (**74**—**76**), the effect of position of the substituent for activity was similar to that in the case of alkoxy derivatives. Subsequently, the *N*- or *O*-methylated compounds (**105**, **110** and **113**) were evaluated. Compounds **105** and **113** were inactive, while **110** retained the activity. This result indicates that both the free NH group of the anilino substituent and the carbonyl group on the pyrimidine nucleus are essential for activity.

For the purpose of finding orally active antiallergy agents, the compounds were further tested orally at the dose of 100 mg/kg. In this screening, the 3-trifluoromethyl and 2-alkoxy derivatives possessed significant activity, while the other compounds showed moderate potency or loss of activity, suggesting that they were poorly absorbed from the gastrointestinal tract. Table V shows ID_{50} and LD_{50} values of several compounds (**64**, **79**, **81**, **82** and **85**) selected on the basis of the above test. These compounds were more active than tranilast,[10] an orally active reference, but were less active than the lead compound **1**. On the other hand, they exhibited a marked reduction of toxicity and increase in safety margin (LD_{50} (i.p.)/ ID_{50} (*p.o.*)) in comparison with **1**. From this result, it seems likely that the coplanar configuration of **1** is correlated to both activity and toxicity. In conclusion, in an attempt to obtain more useful antiallergy agents, it was found that alteration of the configuration of **1** led to an increase in the safety margin.

Experimental

All melting points were measured on a Yanagimoto micro melting apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Nihon Bunko IRA-1 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken with a JEOL PS-100 or Bruker AC250 instrument using tetramethylsilane as an internal standard. Mass spectra (MS) were obtained with a JEOL JMS-DX300 mass spectrometer. High-performance liquid chromatography (HPLC) was performed on a Waters 6000A using a Cosmosil ODS column (particle size, 5 μm; column size, 15 cm × 4.6 mm i.d.) with methanol–5% aqueous acetic acid (55 : 45) as a mobil phase (flow rate, 1 ml/min; detector, ultraviolet (UV, 254 nm)).

Anilines Alkoxy anilines were obtained by catalytic hydrogenation of the corresponding nitro derivatives with 10% Pd on charcoal in methanol. Alkylthio anilines were prepared according to the literature.[11] *N*-Methyl-2-(2-methylpropoxy)aniline was prepared by methylation of *N*-acetyl-2-(2-methylpropoxy)aniline, followed by alkaline hydrolysis. Other anilines were obtained commercially.

Preparation of Ethyl 2-Anilino-1,6-dihydro-6-oxo-5-pyrimidinecarboxylate (4—48) (Table I) Method A. Ethyl 1,6-Dihydro-2-(2,3-dimethylanilino)-6-oxo-5-pyrimidinecarboxylate (**17**): Ethyl 1,6-dihydro-2-methylthio-6-oxo-5-pyrimidinecarboxylate (**3**) (5 g, 0.023 mol) was added to a stirred solution of 2,3-dimethylaniline(3.3 g, 0.027 mol) in ethanol (100 ml) and the mixture was heated under reflux for 15 h. After cooling, the resulting precipitate was collected by filtration, washed with ethanol and recrystallized from *N*,*N*-dimethylformamide (DMF)–H_2O to give **17** (4.3 g). IR ν_{max}^{Nujol} cm^{-1}: 3240, 3050 (NH), 1685, 1650 (C=O). MS *m/z*: 287 (M^+). ^{1}H-NMR (DMSO-d_6): 1.24 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 2.12 (3H, s, CH_3), 2.29 (3H, s, CH_3), 4.20 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 7.12—7.40 (3H, m, benzene-H), 8.37 (1H, s, pyrimidine-H), 8.40—11.00 (2H, br, 2×NH).

Compounds **11**, **16**, **25**, **28**—**31** and **33**—**42** were obtained in a manner similar to that described for the preparation of **17**.

Method B. Ethyl 2-(4-Chloroanilino)-1,6-dihydro-6-oxo-5-pyrimidinecarboxylate (**6**): A mixture of **3** (42.8 g, 0.20 mol) and 4-chloroaniline (26.8 g, 0.21 mol) was heated at 130 °C for 2 h. After cooling, the resulting solid was recrystallized from DMF to give **6** (57.4 g). IR ν_{max}^{Nujol} cm^{-1}: 3200, 3040 (NH), 1690, 1660 (C=O). MS *m/z*: 293 (M^+). ^{1}H-NMR (DMSO-d_6): 1.30 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 4.24 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 7.40 (2H, d, J=8 Hz, benzene-H), 7.70 (2H, d, J=8 Hz, benzene-H), 8.56 (1H, s, pyrimidine-H), 7.00—10.00 (2H, br, 2×NH).

Compounds **4**, **5**, **7**, **9**, **10**, **12**—**14**, **19**—**24**, **26**, **27** and **32** were obtained in a manner similar to that described for the preparation of **6**.

Method C. Ethyl 1,6-Dihydro-6-oxo-2-(2-propylthioanilino)-5-pyrimidinecarboxylate (**45**): DEMM (5.2 g, 0.024 mol) was added dropwise to a stirred solution of *N*-(2-propylthiophenyl) guanidine (**54**) (5.0 g, 0.024 mol) in ethanol (50 ml) and the mixture was heated under reflux for 4 h. After cooling, the resulting precipitate was collected by filtration, washed with ethanol and recrystallized from ethanol to give **45** (4.3 g). IR ν_{max}^{Nujol} cm^{-1}: 3220, 3160 (NH), 1720, 1660 (C=O). MS *m/z*: 333 (M^+). ^{1}H-NMR (DMSO-d_6): 0.90 (3H, t, J=7 Hz, $SCH_2CH_2C\underline{H}_3$), 1.24 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.56 (2H, m, $SCH_2C\underline{H}_2CH_3$), 2.84 (2H, t, J=7 Hz, $SC\underline{H}_2CH_2CH_3$), 4.18 (2H, q, J=7 Hz, $CO_2C\underline{H}_2CH_3$), 7.10—7.40 (2H, m, benzene-H), 7.46 (1H, dd, J_1=6 Hz, J_2=2 Hz, benzene-H), 7.82 (1H, dd, J_1=6 Hz, J_2=2 Hz, benzene-H), 8.36 (1H, s, pyrimidine-H), 8.40 −11.50 (2H, br, 2×NH).

Compounds **8**, **15**, **18**, **43**, **44** and **46**—**48** were obtained in a manner similar to that described for the preparation of **45**.

Phenylguanidines (49—58) (Table II) *N*-[2-(2-Methylpropylthio)-phenyl]guanidine (**56**): Cyanamide (10.5 g, 0.25 mol) was added to a solution of 2-(2-methylpropylthio)aniline (30 g, 0.17 mol) and 35% hydrochloric acid (17.3 ml) in methanol (100 ml). The mixture was heated overnight at 50 °C and the solvent was removed under reduced pressure. The gummy residue was dissolved in H_2O (200 ml) and the solution was adjusted to pH 14 with 10% aqueous sodium hydroxide. The resulting precipitate was collected by filtration, washed with H_2O and recrystallized from benzene–isopropyl ether to give **56** (22 g). IR ν_{max}^{Nujol} cm^{-1}: 3440, 3340, 3300, 3100, 3030 (NH, NH_2), 1620 (C=N). MS *m/z*: 223 (M^+). ^{1}H-NMR (DMSO-d_6): 0.98 (6H, d, J=7 Hz, $SCH_2CH(C\underline{H}_3)_2$), 1.82 (1H, m, $SCH_2C\underline{H}(CH_3)_2$), 2.67 (2H, d, J=7 Hz, $SC\underline{H}_2CH(CH_3)_2$), 3.00—5.50 (4H, br, 4×NH), 6.60—7.14 (4H, m, benzene-H).

Compounds **49**—**55**, **57** and **58** were obtained in a manner similar to that described for the preparation of **56**.

2-Anilino-6-oxo-5-pyrimidinecarboxylic Acids (59—103) (Table III) 1,6-Dihydro-2-(2-ethylthioanilino)-6-oxo-5-pyrimidinecarboxylic Acid (**99**): A solution of ethyl 1,6-dihydro-2-(2-ethylthioanilino)-6-oxo-5-pyrimidinecarboxylate (**44**) (2 g, 0.0063 mol) in methanol (4 ml) and 4% aqueous sodium hydroxide (20 ml) was heated at 80 °C for 2 h with stirring. The solution was cooled and acidified with 10% hydrochloric acid. The resulting precipitate was recrystallized from DMF–H_2O to give **99** (1.5 g). IR ν_{max}^{Nujol} cm^{-1}: 3250, 3060 (NH), 2600—3040 (OH), 1700, 1635 (C=O). MS *m/z*: 291 (M^+). ^{1}H-NMR (DMSO-d_6): 1.20 (3H, t, J=7 Hz, $SCH_2C\underline{H}_3$), 2.92 (2H, q, J=7 Hz, $SC\underline{H}_2CH_3$), 7.30 (2H, m, benzene-H), 7.52 (1H, dd, J_1=8 Hz, J_2=2 Hz, benzene-H), 7.84 (1H, dd, J_1=8 Hz, J_2=2 Hz, benzene-H), 8.51 (1H, s, pyrimidine-H), 9.00—12.40 (3H, br, 2×NH and CO_2H).

Compounds **59**—**98** and **100**—**103** were obtained in a manner similar to that described for the preparation of **99**.

Ethyl 1,6-Dihydro-2-[*N*-methyl-2-(2-methylpropoxy)anilino]-6-oxo-5-pyrimidinecarboxylate (104) Compound **104** was obtained by method C employed for the preparation of **45**. IR ν_{max}^{Nujol} cm^{-1}: 3335 (NH), 1720, 1685 (C=O). MS *m/z*: 345 (M^+). ^{1}H-NMR (DMSO-d_6): 0.83 (6H, d, J=7 Hz, $OCH_2CH(C\underline{H}_3)_2$), 1.23 (3H, t, J=7 Hz, $CO_2CH_2C\underline{H}_3$), 1.86 (1H, m, $OCH_2C\underline{H}(CH_3)_2$), 3.33 (3H, s, NCH_3), 3.74 (2H, d, J=7 Hz,

$OCH_2CH(CH_3)_2$), 4.15 (2H, q, $J=7$ Hz, $CO_2CH_2CH_3$), 6.99 (1H, t, $J=8$ Hz, benzene-H), 7.11 (1H, d, $J=8$ Hz, benzene-H), 7.31 (2H, m, benzene-H), 8.40 (1H, s, pyrimidine-H), 11.20 (1H, br, NH).

1,6-Dihydro-2-[*N*-methyl-2-(2-methylpropoxy)anilino]-6-oxo-5-pyrimidinecarboxylic Acid (105) Compound **104** (2.5 g, 0.0072 mol) was added to a solution of ethanol (50 ml) and 5% aqueous sodium hydroxide (50 ml) and the mixture was heated under reflux for 2 h with stirring. After cooling, the solution was acidified with 5% hydrochloric acid. The resulting precipitate was recrystallized from methanol to give **105** (1.8 g). IR ν_{max}^{Nujol} cm^{-1}: 3060 (NH), 2600—3000 (OH), 1725, 1635 (C=O). MS *m/z*: 317 (M^+). ^{1}H-NMR ($CDCl_3$): 0.91 (6H, d, $J=7$ Hz, $OCH_2CH(CH_3)_2$), 2.00 (1H, m, $OCH_2CH(CH_3)_2$), 3.49 (3H, s, NCH_3), 3.78 (2H, d, $J=7$ Hz, $OCH_2CH(CH_3)_2$), 7.08 (2H, m, benzene-H), 7.26 (1H, d, $J=6$ Hz, benzene-H), 7.46 (1H, m, benzene-H), 8.80 (1H, s, pyrimidine-H), 8.90 (1H, s, NH), 12.15 (1H, s, CO_2H).

***N*-[2-(2-Methylpropoxy)phenyl]thiourea (106)** Benzoyl chloride (56.4 g, 0.40 mol) was added dropwise to a stirred solution of ammonium thiocyanate (37 g, 0.49 mol) in acetone (100 ml). After the addition was complete, the mixture was heated under reflux for 5 min. Then 2-(2-methylpropoxy)aniline (66 g, 0.37 mol) was added dropwise to the solution at a rate such that the solution refluxed gently. After the addition, the mixture was heated under reflux for 10 min and poured into water (300 ml). The resulting precipitate was collected by filtration and heated under reflux in 10% aqueous sodium hydroxide (540 ml) for 40 min. After cooling, the solution was acidified with 10% hydrochloric acid and then adjusted to pH 10 with 28% ammonia water. The oily product was extracted with dichloromethane (400 ml), and the organic layer was washed with water and dried with Na_2SO_4. The solvent was removed under reduced pressure and the residue was recrystallized from isopropyl ether–ethanol to give **106** (44 g). IR ν_{max}^{Nujol} cm^{-1}: 3420, 3300, 3160 (NH). MS *m/z*: 224 (M^+). ^{1}H-NMR (DMSO-d_6): 0.99 (6H, d, $J=7$ Hz, $OCH_2CH(CH_3)_2$), 2.02 (1H, m, $OCH_2CH(CH_3)_2$), 3.77 (2H, d, $J=7$ Hz, $OCH_2CH(CH_3)_2$), 6.90 (1H, m, benzene-H), 7.02 (1H, d, $J=8$ Hz, benzene-H), 7.15 (1H, m, benzene-H), 7.44 (2H, br, NH_2), 7.65 (1H, d, $J=8$ Hz, benzene-H), 8.35 (1H, s, NH).

***S*-Methyl-*N*-[2-(2-methylpropoxy)phenyl]isothiourea Hydriodide (107)** A mixture of **106** (8.0 g, 0.036 mol) and methyl iodide (7.5 g, 0.053 mol) in methanol (50 ml) was heated under reflux for 3 h. The solvent was removed under reduced pressure and the residue was recrystallized from ethyl acetate to give **107** (12.4 g). IR ν_{max}^{Nujol} cm^{-1}: 3260 (NH), 2600—3200 (N^+H), 1620 (C=N). MS *m/z*: 238 ($M^+ - HI$). ^{1}H-NMR (DMSO-d_6): 0.98 (6H, d, $J=7$ Hz, $OCH_2CH(CH_3)_2$), 2.01 (1H, m, $OCH_2CH(CH_3)_2$), 2.52 (3H, s, SCH_3), 3.84 (2H, d, $J=7$ Hz, $OCH_2CH(CH_3)_2$), 7.05 (1H, m, benzene-H), 7.22 (1H, d, $J=8$ Hz, benzene-H), 7.29 (1H, d, $J=8$ Hz, benzene-H), 7.43 (1H, m, benzene-H), 9.17 (2H, br, 2 × NH), 10.90 (1H, br, N^+H).

***N*-Methyl-*N'*-[2-(2-methylpropoxy)phenyl]guanidine Hydriodide (108)** A mixture of **107** (12.5 g, 0.034 mol) and 30% methylamine in methanol (32 ml) was heated under reflux for 20 h. The solvent was removed under reduced pressure and the residue was recrystallized from ethanol–ethyl acetate to give **108** (8.3 g). IR ν_{max}^{Nujol} cm^{-1}: 3310, 3320, 3180 (NH), 2600—3100 (N^+H), 1630 (C=N). MS *m/z*: 221 ($M^+ - HI$). ^{1}H-NMR (DMSO-d_6): 0.98 (6H, d, $J=7$ Hz, $OCH_2CH(CH_3)_2$), 2.00 (1H, m, $OCH_2CH(CH_3)_2$), 2.81 (3H, s, NCH_3), 3.80 (2H, d, $J=7$ Hz, $OCH_2CH(CH_3)_2$), 7.00 (1H, m, benzene-H), 7.15 (1H, d, $J=8$ Hz, benzene-H), 7.22 (1H, d, $J=8$ Hz, benzene-H), 7.35 (1H, m, benzene-H), 7.41 (3H, br, 3 × NH), 8.88 (1H, br, N^+H).

Ethyl 1,6-Dihydro-1-methyl-2-[2-(2-methylpropoxy)anilino]-6-oxo-5-pyrimidinecarboxylate (109) DEMM (5.0 g, 0.023 mol) was added dropwise to a solution of **111** (8.0 g, 0.022 mol) in ethanol (50 ml) containing sodium ethylate (3.3 g, 0.049 mol). The mixture was heated under reflux for 1.5 h and the solvent was removed under reduced pressure. The residue was treated with 10% hydrochloric acid to give a solid. The product was collected by filtration and recrystallized from methanol to give **109** (5 g). IR ν_{max}^{Nujol} cm^{-1}: 3400 (NH), 1735, 1660 (C=O). MS *m/z*: 345 (M^+). ^{1}H-NMR (DMSO-d_6): 0.85 (6H, d, $J=7$ Hz, $OCH_2CH(CH_3)_2$), 1.22 (3H, t, $J=7$ Hz, $CO_2CH_2CH_3$), 1.91 (1H, m, $OCH_2CH(CH_3)_2$), 3.47 (3H, s, NCH_3), 3.73 (2H, d, $J=7$ Hz, $OCH_2CH(CH_3)_2$), 4.14 (2H, q, $J=7$ Hz, $CO_2CH_2CH_3$), 6.97 (1H, m, benzene-H), 7.08 (1H, d, $J=8$ Hz, benzene-H), 7.30 (2H, m, benzene-H), 8.27 (1H, s, pyrimidine-H), 9.10 (1H, s, NH).

1,6-Dihydro-1-methyl-2-[2-(2-methylpropoxy)anilino]-6-oxo-5-pyrimidinecarboxylic Acid (110) A mixture of **109** (3.0 g, 0.0087 mol) and sodium hydroxide (1.5 g, 0.038 mol) in H_2O (30 ml) was heated under reflux for 2 h. The solution was cooled and acidified with 10% hydrochloric acid with stirring. The resulting precipitate was collected and recrystallized from DMF to give **110** (1.6 g). IR ν_{max}^{Nujol} cm^{-1}: 3380 (NH), 2600—3110 (OH), 1735, 1635 (C=O). MS *m/z*: 317 (M^+). ^{1}H-NMR (DMSO-d_6): 0.83 (6H, d, $J=7$ Hz, $OCH_2CH(CH_3)_2$), 1.90 (1H, m, $OCH_2CH(CH_3)_2$), 3.57 (3H, s, NCH_3), 3.75 (2H, d, $J=7$ Hz, $OCH_2CH(CH_3)_2$), 7.00 (1H, m, benzene-H), 7.10 (1H, d, $J=8$ Hz, benzene-H), 7.31 (2H, m, benzene-H), 8.41 (1H, s, pyrimidine-H), 9.55 (1H, br s, NH), 13.00 (1H, br s, CO_2H).

Identification of the Products of Reaction of 110 with 1 N Hydrochloric Acid A solution of **110** (100 mg, 0.00032 mol) in 1 N hydrochloric acid (10 ml) and acetone (10 ml) was heated under reflux for 5 h. The solvent was removed under reduced pressure and the residue was analyzed by HPLC. Two peaks observed at t_R 1.72 and 3.25 min in the chromatogram were identical with those of authentic samples of 3-methyl-2,4(1*H*,3*H*)-pyrimidinedione and 2-(2-methylpropoxy)aniline hydrochloride, respectively.

Ethyl 4-Chloro-2-[2-(2-methylpropoxy)anilino]-5-pyrimidinecarboxylate (111) A mixture of **27** (16.6 g, 0.050 mol), phosphorus oxychloride (15.4 g, 0.10 mol) and *N*,*N*-diethylaniline (11.1 g, 0.074 mol) in acetonitrile (100 ml) was heated under reflux for 3 h. The solvent was removed under reduced pressure. The residue was treated with 10% hydrochloric acid (50 ml) and extracted with benzene. The extract was dried with Na_2SO_4 and concentrated under reduced pressure. The resulting product was recrystallized from petroleum ether to give **111** (9.5 g). IR ν_{max}^{Nujol} cm^{-1}: 3390 (NH), 1715 (C=O). MS *m/z*: 349 (M^+). ^{1}H-NMR (DMSO-d_6): 0.86 (6H, d, $J=7$ Hz, $OCH_2CH(CH_3)_2$), 1.30 (3H, t, $J=7$ Hz, $CO_2CH_2CH_3$), 1.93 (1H, m, $OCH_2CH(CH_3)_2$), 3.76 (2H, d, $J=7$ Hz, $OCH_2CH(CH_3)_2$), 4.27 (2H, q, $J=7$ Hz, $CO_2CH_2CH_3$), 6.96 (1H, m, benzene-H), 7.07 (1H, d, $J=8$ Hz, benzene-H), 7.17 (1H, m, benzene-H), 7.49 (1H, d, $J=8$ Hz, benzene-H), 8.81 (1H, s, pyrimidine-H), 9.58 (1H, s, NH).

Ethyl 4-Methoxy-2-[2-(2-methylpropoxy)anilino]-5-pyrimidinecarboxylate Hydrochloride (112) A solution of **111** (3.5 g, 0.010 mol) in methanol (50 ml) was heated under reflux for 3 h. The solvent was removed under reduced pressure and the residue was recrystallized from ethyl acetate to give **112** (2.6 g). IR ν_{max}^{Nujol} cm^{-1}: 3080 (NH), 2000—2700 (N^+H), 1715 (C=O). MS *m/z*: 345 ($M^+ - HCl$). ^{1}H-NMR (DMSO-d_6): 0.95 (6H, d, $J=7$ Hz, $OCH_2CH(CH_3)_2$), 1.29 (3H, t, $J=7$ Hz, $CO_2CH_2CH_3$), 2.05 (1H, m, $OCH_2CH(CH_3)_2$), 3.82 (2H, d, $J=7$ Hz, $OCH_2CH(CH_3)_2$), 3.97 (3H, s, OCH_3), 4.25 (2H, q, $J=7$ Hz, $CO_2CH_2CH_3$), 6.97 (1H, m, benzene-H), 7.09 (1H, d, $J=8$ Hz, benzene-H), 7.16 (1H, m, benzene-H), 7.77 (1H, br s, NH), 7.85 (1H, d, $J=8$ Hz, benzene-H), 8.78 (1H, s, pyrimidine-H), 9.70 (1H, s, N^+H).

4-Methoxy-2-[2-(2-methylpropoxy)anilino]-5-pyrimidinecarboxylic Acid (113) A mixture of **112** (2.0 g, 0.0052 mol) and NaOH (2.0 g, 0.050 mol) in methanol (30 ml) and H_2O (10 ml) was heated at 60 °C for 1 h with stirring. After cooling, the reaction mixture was adjusted to pH 4 with 10% hydrochloric acid. The precipitate was collected by filtration, washed with H_2O and recrystallized from ethanol to give **113** (1.1 g). IR ν_{max}^{Nujol} cm^{-1}: 3380 (NH), 2200—2700 (OH), 1700 (C=O). MS *m/z*: 317 (M^+). ^{1}H-NMR (DMSO-d_6): 0.95 (6H, d, $J=7$ Hz, $OCH_2CH(CH_3)_2$), 2.02 (1H, m, $OCH_2CH(CH_3)_2$), 3.80 (2H, d, $J=7$ Hz, $OCH_2CH(CH_3)_2$), 3.91 (3H, s, OCH_3), 6.90—7.10 (3H, m, benzene-H), 7.96 (1H, d, $J=8$ Hz, benzene-H), 8.60 (1H, s, NH), 8.69 (1H, s, pyrimidine-H), 12.50 (1H, br, CO_2H).

References and Notes

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