(2.7 g, 0.024 mol), and triethylamine (1.4 mL) in dry anisole (20 mL) was added a solution of $TiCl_4$ (1.75 mL) in anisole (5 mL). The mixture was stirred under N_2 at 140 °C for 3 h and then worked up as in method A to give 0.9 g (44%), mp 110 °C (cyclohexane).

Physical Methods. ^1H NMR spectra were recorded at 60 and 360 MHz on Varian A-60A and Bruker WH 360 spectrometers using $CDCl_3$ (99.8%) as solvent. ^{13}C NMR spectra were recorded at 20.0 MHz on a FT-80A spectrometer using $CDCl_3$ as the solvent for the spectra at ambient temperature and C_5D_5N for some of the variable-temperature work. All chemical shifts were referred to Me_4Si at δ 0.00. ^1H nuclear Overhauser effects were measured by integrating both coupled and homonuclear proton-decoupled spectra.

pK_a values were calculated by potentiometric titration of the piperazine distal nitrogen of the hydrochloride salts with 1.0 N NaOH in 60% dimethylformamide/water at 21 °C.

X-ray Crystallographic Studies. The X-ray crystal structures of compounds **2** monohydrate, **4**, and **8** have been determined. The crystal data for these compounds are given in Table IV (see paragraph at the end of paper concerning Supplementary Material). The intensity data were collected on an automated four-angle X-ray diffractometer using monochromatic copper radiation. The structures were solved using the direct-methods program, MULTAN, and they were refined by the least-squares method to R factors of 0.055, 0.060, and 0.052, respectively. In the final refinement of each structure, all non-hydrogen atoms were included with anisotropic temperature factors, and all hydrogen atoms were included at assumed positions with isotropic temperature factors. The atomic coordinates for the non-hydrogen atoms are given in Table V (Supplementary Material), and the structures are shown in Figures 2-4. (The crystallographic numbering of atoms is cited in the relevant part of discussion.)

Pharmacology. Dopaminergic Receptor Binding ([^{3}H]-Spiroperidol). The assay was carried out in the striatum of the rat brain using the method described previously.[26]

Muscarinic Cholinergic Receptor Binding ([^{3}H]QNB). The method used was based on that described by Yamamura and Snyder.[27]

Male, Lilly Wistar rats (250-350 g), fed and watered ad libitum, were killed by cervical dislocation, the brains were rapidly removed, and the cerebellum was discarded. As each brain was dissected out, it was rapidly homogenized in 10 vol of ice-cold sucrose (0.32 M) in a Teflon/glass homogenizer (0.05-0.10 mm clearance, 25 strokes by hand). The homogenates were combined and rehomogenized in the same Teflon/glass homogenizer (25 strokes by hand). The combined homogenate was centrifuged at 1500g for 5 min at 0-4 °C, and the supernatant was used for the assay. After determination of the protein concentration,[28] the tissue was divided into 5-mL aliquots, which were stored at -50 °C for up to 3 months.

For each binding assay the tissue preparation was diluted in Krebs-Hensleit buffer, pH 7.4 (118.5 mM NaCl, 4.75 mM KCl, 2.52 mM $CaCl_2$, 1.17 mM KH_2PO_4, 1.18 mM $MgSO_4 \cdot 7H_2O$, and 2.5 mM $NaHCO_3$, gassed with 5% CO_2 in oxygen at 37 °C) to a concentration of 0.44 mg/mL. Incubations were carried out in 2.0 mL of Krebs-Hensleit buffer, pH 7.4, containing 0.5 mg of protein, 0.75 nM *dl*-[^{3}H]QNB, and varying concentrations of test compound. After incubation for 25 min at 37 °C in an atmosphere of 5% CO_2 in oxygen, the reaction was stopped by rapid centrifugation at 8000g for 45 min. The supernatant was aspirated off, the tissue pellet was digested in 1 mL of Soluene-350, and the radioactivity was determined. In every experiment, each concentration of test compound was assayed in quadruplicate.

Physostigmine Lethality. The method used was essentially that described by Collier et al.[7] Groups of 10 CFW mice (19-26 g) were dosed with the test compound, dissolved in distilled water or suspended in 0.5% carboxymethylcellulose, 1 h (0.5 h for hyoscine) prior to the administration of physostigmine (1 mg/kg ip). Mice were scored for tremor or death at 10, 20, and 60 min after the administration of physostigmine. The following scoring system was used: dead at 10 min reading (4), dead at subsequent reading (3), marked tremor (2), slight tremor (1), no effect (0). The results are expressed as the percent reduction in group score from the appropriate control group. The significance levels (Student's t test) refer to the difference in mean score between the treated and control groups.

Acknowledgment. We thank Dr. Douglas Dorman for obtaining the 360-MHz ^1H NMR spectra of compounds **2** and **4**, David Smith for computer analyses of the X-ray structures, Fiona Crutchley for measuring the pK_a of clozapine, and Joy Howard and Margaret Baverstock for their technical assistance.

Supplementary Material Available: Crystal data and atomic coordinates for compounds **2**, 4, and **8** (2 pages). Ordering information is given on any current masthead page.

Nitrogen Bridgehead Compounds. 18.[1] New Antiallergic 4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones. 1

István Hermecz,*[†] Tibor Breining,[†] Zoltán Mészáros,[†] Agnes Horváth,[†] Lelle Vasvári-Debreczy,[†] Franz Dessy,[‡] Christine DeVos,[‡] and Ludovic Rodriguez[‡]

Chinoin Pharmaceutical and Chemical Works, H-1325 Budapest, Hungary, and UCB Pharmaceutical Sector, B-1060 Brussels, Belgium. *Received September 23, 1981*

A new type of antiallergic agent, 9-hydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones, was synthesized and evaluated for inhibitory effects in the rat reagenic passive cutaneous anaphylaxis (PCA) screen. Several racemic 6-methyl derivatives were found to be more potent than disodium chromoglycate intravenously and some were also active orally. Structure-activity relationships are discussed. High stereospecificity was observed in the 6-methyl series between the enantiomers with 6*S* and 6*R* absolute configuration, the former being more active. Compound **17**, (+)-6(*S*)-methyl-9-(phenylhydrazono)-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid [Chinoin-1045; UCB L140], has an ED_{50} value of 1.0 μmol/kg po and is now under clinical investigation.

The discovery of the mediator release inhibitor disodium chromoglycate 1 (DSCG) has provided a new approach to the therapy of bronchial asthma in man.[2]

In the past 10 years, since the introduction of DSCG for the treatment of asthma and allergic diseases,[3] there have

[†] Chinoin Pharmaceutical and Chemical Works.
[‡] UCP Pharmaceutical Sector.

(1) Part 17. G. Tóth, C. De La Gruz, I. Bitter, I. Hermecz, B. Pete, and Z. Mészáros, *J. Heterocycl. Chem.*, to be published.
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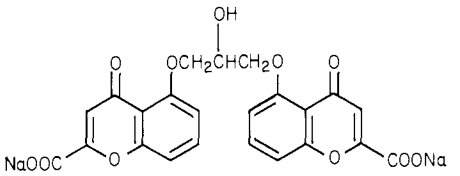

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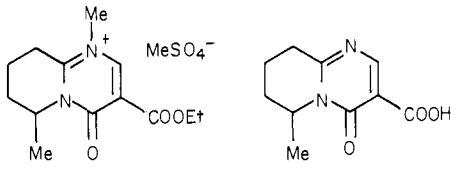


2 3

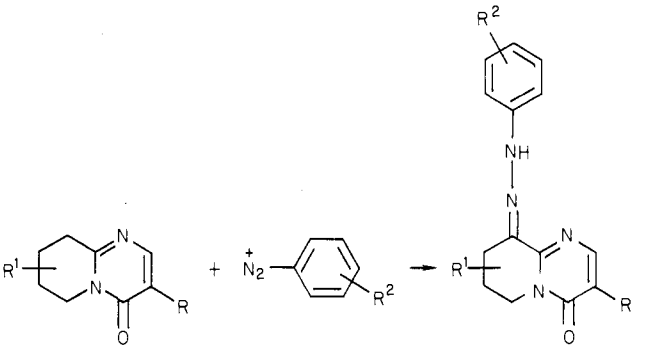
been intensive efforts in numerous laboratories to find orally active DSCG-like antiallergic agents.[4]

During the clinical investigation of the analgetic pyridopyrimidine (**2**, rimazolium),[5] a favorable side effect of the compound on the respiratory system was observed.[6] Furthermore, on the basis of structural similarities to known antiallergic agents,[4] we thought that some specific derivatives of rimazolium, e.g., compound **3**, would perhaps have useful antiallergic properties. Preparation and pharmacological evaluation of compound **3** indicated a weak passive cutaneous anaphylaxis (PCA) activity [ID_{50} of 240 μmol/kg iv], which we have been able to enhance by introducing various functional groups into the 9-position of the pyridopyrimidine system. We now report the preparation and pharmacological evaluation of some 9-(phenylhydrazono)-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]-pyrimidin-4-ones.

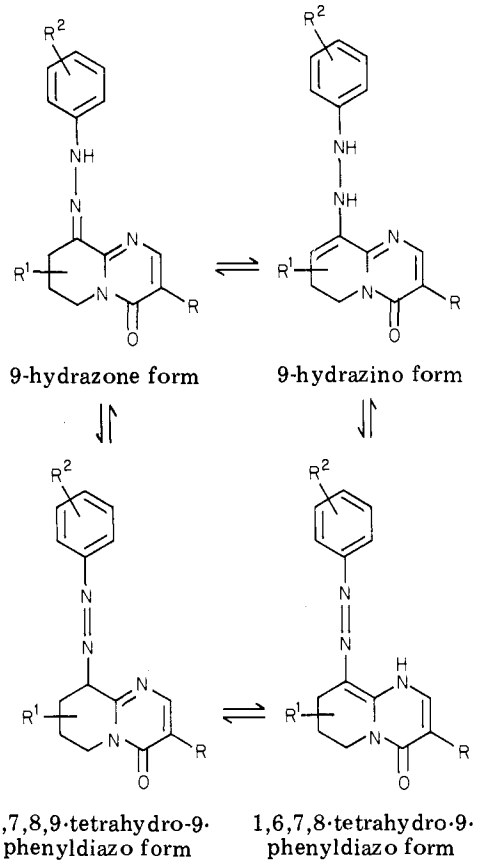
Chemistry. 6,7,8,9-Tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones[7] contain a reactive methylene group in position 9 that reacts easily with electrophilic reagents.[8] The 9-(phenylhydrazono) derivatives were thus synthesized from tetrahydropyridopyrimidines by reaction with phenyldiazonium chlorides (see Table I and Scheme I). The 3-carboxamide (**12**) and 3-carbohydrazide (**13**) were prepared from the 3-ester (**8**) with ammonmia and hydrazine hydrate, respectively.

For the structure of the products, four tautomers can be considered, but the phenylhydrazone form[9] (see Scheme II) predominates as shown by the ^1H NMR spectra: For example, in the spectra of compounds **4–18** and **20–69** (R^1 = Me), five protons can be observed in the aliphatic region, in addition to the doublet of the methyl group. This fact excludes the 6,7,8,9-tetrahydro-9-phenyldiazo form (which would contain six aliphatic ring protons), as well as the 9-hydrazino form (containing three aliphatic ring protons). The C(2) H appears as a singlet, indicative of the 9-hydrazone form. In the 1,6,7,8-tetrahydro-9-phenyldiazo tautomer, the C(2) H would be expected as a doublet,[8a,c] and the phenyl protons should also give characteristic signals,[10] different from ours.

Scheme I



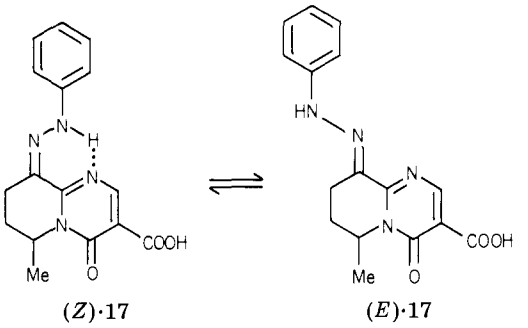
Scheme II



9-hydrazone form 9-hydrazino form

6,7,8,9-tetrahydro-9-phenyldiazo form 1,6,7,8-tetrahydro-9-phenyldiazo form

Scheme III



(*Z*)-17 (*E*)-17

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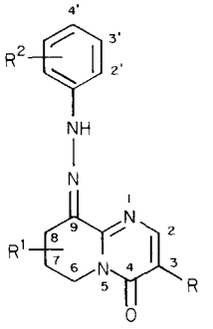
Table 1. 9-(Phenylhydrazono-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones



compd	R	R^1	R^2	yield, %	mp, °C	recrystn solvent	formula	rat PCA: ID_{50}, μmol/kg iv	rat PCA: ID_{50}, μmol/kg po	inhibn of hist release: EC_{50}, μmol/L
DSCG								1.0	inactive	
3								240		
4	H	6-Me	H	52	163-165	MeOH	$C_{15}H_{16}N_4O$		>100	
5	H	6-Me	2′-COOH	27	223-224	MeOH	$C_{16}H_{16}N_4O_3 \cdot H_2O$	>100	>100	100
6	H	6-Me	3′-COOH	58	260-262	MeOH[a]	$C_{16}H_{16}N_4O_3$	>100	>100	655
7	H	6-Me	4′-COOH	52	230	MeOH	$C_{16}H_{16}N_4O_3 \cdot MeOH \cdot 0.5H_2O$	>100	>100	450
8	COOEt	6-Me	H	64	137-138	EtOH	$C_{18}H_{20}N_4O_3$		>1000	
					82-83	EtOH	$C_{18}H_{20}N_4O_3 \cdot EtOH$			
9	COOEt	6-Me	2′-COOH	44	230	MeOH	$C_{19}H_{20}N_4O_5$	10-100[b]		100
10	COOEt	6-Me	3′-COOH	40	179-180	MeOH	$C_{19}H_{20}N_4O_5 \cdot H_2O$	~100		740
11	COOEt	6-Me	4′-COOH	18	230	MeOH	$C_{19}H_{20}N_4O_5$	~100		66
12[c]	$CONH_2$	6-Me	H	62	248-249	$MeNO_2$	$C_{16}H_{17}N_5O_2$		>1000	
13[d]	$CONHNH_2$	6-Me	H	83	205-206	EtOH	$C_{16}H_{18}N_6O_2$		>1000	
14	CN	6-Me	H	75	233-234	MeCOMe	$C_{16}H_{17}N_5O_2 \cdot H_2O$		>1000	
15	CH_2COOH	6-Me	H	63	207	*e*	$C_{17}H_{18}N_4O_3$	100		430
16	COOH	6-Me	H	75	267-268	DMF	$C_{16}H_{16}N_4O_3$	0.6	1.2	2.2
17[f,h]	COOH	6-Me	H	60	255-256	DMF	$C_{16}H_{16}N_4O_3$	0.3	1.0	0.6
18[g,i]	COOH	6-Me	H	65	258-259	DMF	$C_{15}H_{14}N_4O_3$	54.8	>100	8
19	COOH	H	H	75	267-268	MeOH	$C_{15}H_{14}N_4O_3$	31.6	>100	2.9
20	COOH	7-Me	H	65	260-262	MeOH[a]	$C_{16}H_{16}N_4O_3$	5.7	>320	13
21	COOH	8-Me	H	52	230-232	MeCOMe	$C_{16}H_{16}N_4O_3$	32.0	>320	5.4
22	COOH	6-Me	2′-F	65	216-217	MeOH[a]	$C_{16}H_{15}N_4O_3F$	5.0	>1000	1.2
23	COOH	6-Me	4′-F	90	260-261	MeOH[a]	$C_{16}H_{15}N_4O_3F$	12.2	>1000	1.2
24	COOH	6-Me	2′-Cl	23	260-262	DMF	$C_{16}H_{15}N_4O_3Cl$		>1000	
25	COOH	6-Me	3′-Cl	65	263-265	AcOH	$C_{16}H_{15}N_4O_3Cl$	0.6	>100	311
26	COOH	6-Me	4′-Cl	67	262-264	MeOH[a]	$C_{16}H_{15}N_4O_3Cl$	0.5	>100	16.6
27	COOH	6-Me	2′-Br	47	265-267	MeOH[a]	$C_{16}H_{15}N_4O_3Br$		>320	
28	COOH	6-Me	3′-Br	56	260-262	AcOH	$C_{16}H_{15}N_4O_3Br$	0.4	>320	6.7
29	COOH	6-Me	4′-Br	55	250-252	MeOH[a]	$C_{16}H_{15}N_4O_3Br$	0.8	>100	2
30	COOH	6-Me	2′-I	59	246-248	AcOH	$C_{16}H_{15}N_4O_3I$		>1000	
31	COOH	6-Me	3′-I	23	258-260	AcOH	$C_{16}H_{15}N_4O_3I$		>1000	
32	COOH	6-Me	4′-I	71	245-246	EtOH[a]	$C_{16}H_{15}N_4O_3I$		>1000	
33	COOH	6-Me	2′-OH	44	252-254	DMF	$C_{16}H_{16}N_4O_4$	0.26	>100	208
34	COOH	6-Me	4′-OH	70	243-245	AcOH	$C_{16}H_{16}N_4O_4$	1.7	>100	1.3
35[f,j]	COOH	6-Me	4′-OH	65	220-222	AcOH	$C_{16}H_{16}N_4O_4$	~0.14[b]	>100	15.6
36[g,k]	COOH	6-Me	4′-OH	72	214-215	AcOH	$C_{16}H_{16}N_4O_4$	110.5	>100	26.2
37	COOH	6-Me	2′-OMe	96	216-218	AcOH	$C_{17}H_{18}N_4O_4 \cdot 1.5H_2O$		>1000	
38	COOH	6-Me	4′-OMe	92	212-214	$MeNO_2$	$C_{17}H_{18}N_4O_4$	0.8	7.6	128

39	COOH	6-Me	2′-OEt	65	226–227	$MeNO_2$	$C_{18}H_{20}N_4O_4$		>1000	
40	COOH	6-Me	3′-OEt	48	212–213	$MeNO_2$	$C_{18}H_{20}N_4O_4$	0.2	>100	4.7
41	COOH	6-Me	4′-OEt	50	218–219	MeOH	$C_{18}N_{20}N_4O_4$	1.6	>100	17.6
42[f,l]	COOH	6-Me	4′-OEt	51	208–209	DMF	$C_{18}H_{20}N_4O_4$	0.2	>100	1.0
43[g,m]	COOH	6-Me	4′-OEt	60	213–214	DMF	$C_{18}H_{20}N_4O_4$	100.0	>100	19.2
44	COOH	6-Me	2′-Me	77	221–223	MeOH	$C_{17}H_{18}N_4O_3$		>1000	
45	COOH	6-Me	3′-Me	88	242–243	MeOH	$C_{17}H_{18}N_4O_3$	0.4	72.5	72.9
46	COOH	6-Me	4′-Me	85	242–244	AcOH	$C_{17}H_{18}N_4O_3$	1.3	>1000	0.28
47	COOH	6-Me	2′-CF_3	80	270–271	AcOH	$C_{17}H_{15}N_4O_3F_3$		>1000	
48	COOH	6-Me	3′-CF_3	93	273–274	MeOH[a]	$C_{17}H_{15}N_4O_3F_3$		>1000	
49	COOH	6-Me	4′-CF_3	76	238–240	MeOH[a]	$C_{17}H_{15}N_4O_3F_3$	38.6	>1000	0.28
50	COOH	6-Me	2′-NO_2	66	270–274	MeOH[a]	$C_{16}H_{15}N_5O_5$		>1000	
51	COOH	6-Me	3′-NO_2	67	268–270	DMF–AcOH	$C_{16}H_{15}N_5O_5$	0.5	>100	
52	COOH	6-Me	4′-NO_2	56	262–264	MeOH[a]	$C_{16}H_{15}N_5O_5$	0.8	>320	8.9
53	COOH	6-Me	2′-COMe	54	255–256	$MeNO_2$	$C_{18}H_{18}N_4O_4$		>1000	
54	COOH	6-Me	3′-COMe	37	238–240	AcOH	$C_{18}H_{18}N_4O_4$		>1000	
55	COOH	6-Me	4′-COMe	72	240–242	AcOH	$C_{18}H_{18}N_4O_4$	9.5	>100	8.1
56	COOH	6-Me	2′-COOH	51	276–277	MeOH[a]	$C_{17}H_{16}N_4O_5$	0.48	>100	1300
57[f,n]	COOH	6-Me	2′-COOH	51	261–262	MeOH[a]	$C_{17}H_{16}N_4O_5$	0.5	>100	569
58[g,o]	COOH	6-Me	2′-COOH	46	260–261	MeOH[a]	$C_{17}H_{16}N_4O_5$	37.1	>100	1100
59	COOH	6-Me	3′-COOH	51	262–265	MeOH[a]	$C_{17}H_{16}N_4O_5 \cdot 1.5H_2O$	26.6	>100	10
60	COOH	6-Me	4′-COOH	84	290–291	MeOH[a]	$C_{17}H_{16}N_4O_5$	7.6		1000
61	COOH	6-Me	4′-Et	73	208–210	MeOH[a]	$C_{18}H_{20}N_4O_3$		>1000	
62	COOH	6-Me	4′-*i*-Pr	81	227–228	MeCN	$C_{19}H_{22}N_4O_3$	2.4	>100	1.2
63	COOH	6-Me	4′-Bu	49	205–207	MeOH	$C_{20}H_{24}N_4O_3$	7.8	~100[b]	0.7
64	COOH	6-Me	4′-Ph	28	160–162	AcOH	$C_{22}H_{20}N_4O_3 \cdot 2.5H_2O$	1.1	>100	4.4
65	COOH	6-Me	3′-COOEt	92	230–232	MeOH	$C_{19}H_{20}N_4O_5$		>100	
66	COOH	6-Me	4′-c-Pr	88	215–217	AcOH	$C_{19}H_{20}N_4O_3$	41.1	100	~1.0[b]
67	COOH	6-Me	4′-CH_2COOH	62	250–252 dec	*e*	$C_{18}H_{18}N_4O_5$	60.9	>100	3.4
68	COOH	6-Me	4′-$CONHCH_2$	48	260	EtOH[a]	$C_{19}H_{19}N_5O_6$	9.6	>100	100
69	COOH	6-Me	2′-CH_2CH_2OH	59	210–212	EtOH[a]	$C_{18}H_{20}N_4O_4 \cdot EtOH$	10.8	>100	330

[a] Refluxed in the solvent given. [b] Flat slope. [c] Prepared by method B. [d] Prepared by method C. [e] Dissolved in 5% HCl and precipitated with 5% NaOH. [f] Dextrorotatory isomer with 6*S* absolute configuration. [g] Levorotatory isomer, with 6*R* absolute configuration. [h] $[\alpha]^{20}_D$ +407.5° (*c* 2, MeOH). [i] $[\alpha]^{20}_D$ −407° (*c* 2, DMF). [j] $[\alpha]^{20}_D$ +310° (*c* 0.5, DMF). [k] $[\alpha]^{20}_D$ −308° (*c* 0.5, DMF). [l] $[\alpha]^{20}_D$ +350° (*c* 0.5, DMF). [m] $[\alpha]^{20}_D$ −345° (*c* 0.1, DMF). [n] $[\alpha]^{20}_D$ +222.5° (*c* 1, DMF). [o] $[\alpha]^{20}_D$ −247.5° (*c* 1, DMF).

The phenylhydrazone group shows a solvent-dependent Z–E isomerization (see Scheme III). The chemical shift of the NH proton of the phenylhydrazone group ranges between 10 and 12 ppm for the E isomers, while it is around 14 ppm for the Z isomers. The ratio of the E and Z isomers can be estimated by the intensity of the NH signals. For example, the ^{1}H NMR spectrum of a freshly prepared solution of the hydrazone **17** in $CDCl_3$ shows only the Z isomer, whereas in Me_2SO-d_6 only the E isomer can be detected. This also indicates a low free energy of activation (ΔG^+ <15 kcal/mol) for the interconversion between the E and Z geometric isomers.

Biological Results and Structure–Activity Relationship

The hydrazones were examined for their ability to inhibit the rat PCA reaction and histamine release from sensitized rat mast cells in vitro, as described under Experimental Section.

The PCA active compounds were found among the derivatives containing a carboxylic group in position 3 of the pyridopyrimidine ring (see Table I). Derivatives **5–7** bearing the carboxy group only on the phenyl ring or those having an ester (**8**), carboxamide (**12**), carbohydrazide (**13**), or nitrile group (**14**) in position 3 were inactive. The slight activity of compounds **9–11** may be due to the partial enzymatic transformation of the 3-ester group to the carboxylic group. Separation of the 3-carboxylic group and the pyridopyrimidine ring by a methyl group (**15**) decreased the activity to less than a hundredth that of compound (**16**).

The most potent carboxylic acids contained a methyl group in position 6 of the pyridopyrimidine. Absence of the methyl group (**19**) or chaning its position to 7 (**20**) or 8 (**21**) also resulted in a decrease in effectiveness. The methyl-substituted derivatives in Table I are the first reported examples of PCA active compounds that contain an asymmetric center. With the 6-methyl substituted derivatives **16**, **34**, **41**, and **56**, we also synthesized and investigated the enantiomers (**17** and **18**, **35** and **36**, **42** and **43**, **57** and **58**, respectively). An essential difference was found between the PCA activities of the enantiomers, and the one with the 6S absolute configuration[11] was always responsible for the action. Enantiomers with the 6R absolute configuratrion were practically inactive[12] in the PCA test.

There is not such a substantial difference between the inhibitory effects of the enantiomers on histamine release (see Table I).

The difference in rank order of potency between the results of the PCA and histamine release tests may be the consequence of two phenomena. First, the difference may derive from the different biochemical mechanisms of the two tests. The stereospecificity and potency of the PCA activity would suggest a highly specific interaction between the compound and unidentified receptor(s),[13] which is perhaps not required for action in the histamine release test. Secondly, the difference may partly arise due to the binding of the compound to plasma proteins in the in vivo test. Such a measurement has been carried out for compound **17**, with the result that 85 to 90% of the compound is bound to plasma proteins.

Introduction of a substituent into the phenyl ring decreased the solubility. Compounds containing m-chloro (**25**), m-bromo (**28**), m-ethoxy (**40**), m-methyl (**45**), m-nitro (**51**), p-chloro (**26**), o-carboxy (**56**), and o-hydroxy (**28**) substituents on the phenyl ring exhibited the same or slightly greater activity than compound **16**, but the oral activity of these derivatives decreased or disappeared, perhaps due to poor absorption from the gastrointestinal tract.

The p-hydroxy compounds (**34** and **35**), identified as the main metabolites[14] of **16** and **17**, were inactive by the oral route but active when administered iv.

Compound **17**, designated as Chinoin-1045 (UCB L140), was selected for further pharmacological[15] and clinical investigations.

Experimental Section

Melting points were not corrected. Combustion analyses for C, H, N, and halogen gave results within 0.4% of theory. The procedures for the preparation of the reported compounds, methods A–C, may be considered as general methods for preparation. Yields were not maximized. Spectra of the products (UV, Pye Unicam SP 8-200; IR, Zeiss UR 20; ^{1}H and ^{13}C NMR, JEOL FX-100 Models) are in full accord with the proposed structures. Optical rotations were determined by use of a Zeiss polarimeter.

6-Methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-nitrile. 6-Methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide[17a] (2.07 g, 10 mmol) in $POCl_3$ (2.7 mL) was heated at 98–100 °C for 1 h in the presence of PPA (Fluka, 0.1 g). At the end of the reaction period, the mixture was treated at 80–100 °C with propanol (6 mL) and then poured onto 7% $NaHCO_3$ solution (75 mL). The aqueous phase was decolorized with active charcoal and filtered, and the filtrate was extracted with $CHCl_3$ (3 × 15 mL). The $CHCl_3$ phase was dried (Na_2SO_4) and evaporated. Recrystallization of the residue from water yielded the title compound (1.12 g, 46%), mp 108–111 °C. Anal. ($C_{10}H_{11}N_3O$) C, H, N.

Method A. Diazonium Coupling. Phenyldiazonium chlorides were prepared by the usual procedure[16] from aromatic amines (10 mmol) in 1:1 diluted hydrochloric acid (5 mL) at 0 °C with a solution of sodium nitrite (10 mmol) in water (5 mL). To a solution of the phenyldiazonium chloride and sodium acetate (6 g) was added dropwise at 0 °C a solution of the requisite 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-4-one[17] (10 mmol) in water (5 mL). The carboxylic acid **3** was used as its sodium salt. The mixture was kept at room temperature for 1 day. The resulting crystalline product was filtered off, washed with water, dried, and recrystallized (see Table I). The tendency of the 9-hydrazonopyridopyrimidine to form stable complexes with solvents is reflected in some of the elemental analyses:

Z–E isomeric ratio of compound **17** in $CDCl_3$, 100:0; ^{1}H NMR δ 1.44 (d, 3 H, 6-Me), 1.90–2.25 (m, 2 H, 7-CH_2), 2.87–3.15 (m, 2 H, 8-H_2), 4.95–5.35 (m, 1 H, 6-H), 7.0–7.6 (m, 5 H, Ph), 9.00 (s, 1 H, 2-H), 13.10 (broad, 1 H, OH), 14.27 (broad, 1 H, NH); UV ($CHCl_3$) λ_{max} 453 nm (ϵ 22 900), 303 (5970); isomeric ratio in Me_2SO-d_6, 0:100; ^{1}H NMR δ 1.29 (d, 3 H, 6-Me), 1.75–2.25 (m, 2 H, 7-H_2), 2.50–3.00 (m, 2 H, 8-H_2), 4.90–5.35 (m, 1 H, 6-H), 6.8–7.6 (m, 5 H, Ph), 8.75 (s, 1 H, 2-H), 10.48 (broad, 1 H, NH),

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(11) I. Hermecz, M. Kajtár, P. Surján, K. Simon, T. Breining, G. Horváth, G. Tóth, and Z. Mészáros, unpublished results.
(12) The levorotatory isomer **18** showed about 180 times less iv PCA activity than the dextrorotatory isomer **17**. This activity can be produced by less than 1% of **17** as an impurity in **18**.
(13) R. E. C. Altounyan, *Clin. Allergy*, **10**, 481 (1980).
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(16) A. I. Vogel, "Practical Organic Chemistry", Longman Group Ltd., London, 1974, pp 590–619.
(17) (a) Z. Mészáros, J. Knoll, P. Szentmiklósi, Á. Dávid, G. Horváth, and I. Hermecz, *Arzneim. Forsch.*, **22**, 815 (1972). (b) Z. Mészáros, J. Knoll, J. Hermecz, L. Vasvári-Debreczy, and Á. Horváth, DOS 2 414 751; *Chem. Abstr.*, **82**, 4299 (1975). (c) E. Fogassy, M. Ács, and I. Hermecz, *Period. Polytech., Chem. Eng.*, **20**, 263 (1976); *Chem. Abstr.*, 87, 84 930 (1977).

13.25 (broad, 1 H, OH); ^{13}C NMR (Me_2SO-d_6) δ 16.9 (q, 6-Me), 19.8 (t, C-8), 23.6 (t, C-7), 46.6 (d, C-6), 109.8 (s, C-3), 131.5 (s, C-9), 156.9 (s, C-9a), 158.4 (d, C-2), 162.3 (s, C-4) and 144.1 (s, C-1′), 114.2 (d, C-2′), 129.3 (d, C-3′), 122.3 (d, C-4′) of Ph: UV (Me_2SO) λ_{max} 416 nm (ε 30 650), 294 (5150).

Method B. 6-Methyl-9-(phenylhydrazono)-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (12). To a solution of 9-(phenylhydrazono)pyridopyrimidine 8 (10 mmol) in ethanol (25 mL) was added concentrated aqueous ammonium hydroxide (30 mL). After 1 day the precipitated carboxamide (12) was filtered off, dried, and recrystallized.

Method C. 6-Methyl-9-(phenylhydrazono)-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carbohydrazide (13). A mixture of 9-(phenylhydrazono)pyridopyrimidine 8 (10 mmol) and 3 mL of hydrazine hydrate (98%) was refluxed in ethanol (25 mL) for 2 h. The clear reaction mixture was cooled to 10 °C. The precipitated hydrazide (13) was filtered off and dried.

Passive Cutaneous Anaphylaxis (PCA) Test. Adult female Sprague–Dawley rats (~200 g, five rats per group) were sensitized at two sites with an intradermal injection (0.05 mL) of rat serum containing reaginic antibodies to chicken ovalbumin. After a 48-h latent period, the animals were challenged with 20 mg/kg of chicken ovalbumin, together with 124 mg/kg of Evans blue. Thirty minutes later, the rats were sacrificed and skinned. The area of the dermal bluing that occurred at the sites of sensitization was measured (~100 mm^2 spot in the control rats), and the results were used for calculation of the drug-induced percent inhibition of this effect. For iv administration, the test compounds (32; 3.2 and 0.32 μmol/kg) were injected at the same time as the antigen challenge. When given po, the compounds were administered 15 min prior to the challenge. At least three doses and five animals for each dose (i.e., 10 spots) were used for obtaining a dose–inhibition relationship. The dose that inhibited the PCA by 50% (ID_{50}) was determined from a dose–response regression curve for each compound.

In Vitro Histamine Release. Adult female Sprague–Dawley rats (~200 g) were passively sensitized with an intravenous injection of an antiserum rich in IgE directed against *Nippostrongylus brasiliensis*. After 24 h, the rats were decapitated and injected intraperitoneally with 10 mL of the antigen is the buffered solution (containing Tris, 3.75 g; NaCl, 6.95 g; KCl, 0.37 g; $CaCl_2 \cdot 2H_2O$, 0.09 g; $MgCl_2 \cdot 6H_2O$, 0.23 g; HCl to adjust pH to 7.4 in a volume of 1 L). The animals were abdominally massaged for 5 min. The peritoneal fluid was recovered by gentle aspiration using a polypropylene syringe and brought to a final volume of 20 mL with the buffered solution. Aliquots of 0.8 mL of the fluid were placed into 2-mL plastic tubes, and the test compound was added (0.1 mL) just before *Nippostrongylus* extract (0.1 mL). The tubes were incubated for 30 min at 37 °C and centrifugated at 150*g* at 4 °C. The supernatant was mixed with an equal volume of 0.8 N $HClO_4$, and the cell pellet was reconstituted with 0.4 N $HClO_4$ (1 mL). Histamine was assayed fluorometrically. Percent inhibition was determined by comparison with histamine release in the absence of drug, after correction for the spontaneous release values. The statistical significance of the results was determined by the Student's *t* test ($p \leq 0.05$).

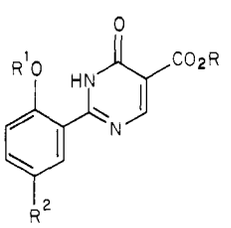
Antiallergy Agents. 2. 2-Phenyl-5-(1*H*-tetrazol-5-yl)pyrimidin-4(3*H*)-ones

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 February 25, 1982

Some 2-(2-alkoxyphenyl)- and 2-[2-(alkenyloxy)phenyl]-5-(1*H*-tetrazol-5-yl)pyrimidin-4(3*H*)-ones were prepared and found to be about 5–10 times more potent than the corresponding pyrimidine-5-carboxylic acids when tested orally against passive cutaneous anaphylaxis in the rat. Structure–activity relationships within the two series are similar. 2-(2-*n*-Propoxyphenyl)-5-(1*H*-tetrazol-5-yl)pyrimidin-4(3*H*)-one is in clinical trial for the prophylactic treatment of asthma.

We recently described a series of 1,6-dihydro-6-oxo-2-phenylpyrimidine-5-carboxylic acids and esters 1 with

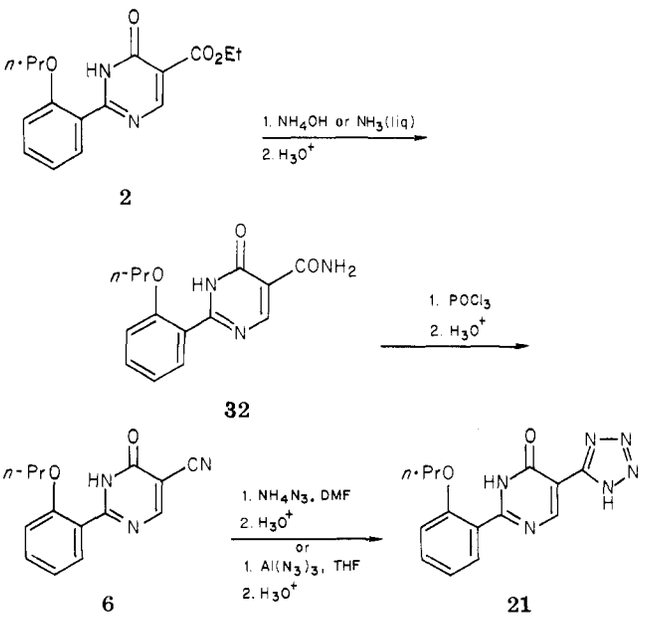


1, R = H, Et; R^1 = C_1–C_5 lower alkyl, allyl; R^2 = MeO, Cl, NH_2, NMe_2

potent oral and intravenous antiallergic activity in the rat.[1] The compounds had been prepared as part of a program designed to produce an orally effective alternative to disodium cromoglycate (DSCG), which for the prophylactic treatment of asthma is inhaled as a powder. In this paper we describe the synthesis and properties of a related series of 2-phenyl-5-(1*H*-tetrazol-5-yl)pyrimidin-4(3*H*)-ones (Table I), some of which show even more potent antiallergic activity in the rat.[2]

Chemistry. Many of the 2-phenyl-5-(1*H*-tetrazol-5-yl)pyrimidin-4(3*H*)-ones listed in Table I were synthesized

Scheme I



from the corresponding ethyl 1,6-dihydro-6-oxo-2-phenylpyrimidine-5-carboxylates[1] (1, R = Et) by standard procedures. The route is illustrated with the 2-*n*-propoxyphenyl analogue **6** in Scheme I. Choice of either

(1) P. F. Juby, T. W. Hudyma, M. Brown, J. M. Essery, and R. A. Partyka, *J. Med Chem.*, **22**, 263 (1979).
(2) P. F. Juby and R. A. Partyka, U.S. Patent 4 082 751 (1978).

0022-2623/82/1825-1145$01.25/0