solution was extracted with water. The chloroform layer was dried ($MgSO_4$) and filtered, and the filtrate was taken to dryness in vacuo. The residue was dissolved in chloroform and filtered through a Millipore filter in vacuo, and the filtrate was evaporated in vacuo to give **17** (0.5 g) as a glass: yield 25% based on 1: UV λ_{max} ($\epsilon \times 10^{-3}$) at pH 1, decomposed; at pH 13, 257 (21.0), 287 (sh) (16.8), 294 nm (17.9); NMR δ 8.88 and 8.55 (2 s, 2 H, H_6 and H_3), 7.32 (m, 5 H, Ar), 6.77 (d, 1 H, J = 16 Hz, =C*H*Ar), 6.45 (dt, 1 H, CH=), 6.51 (d, 1 H, J = 2.6 Hz, $H_{1'}$), 4.33 (m, 4 H, SCH_2 and 5'-CH_2), 2.11, 2.07, and 1.98 (3 s, 9 H, $COCH_3$). Anal. ($C_{25}H_{26}N_4O_7S$) C, H, S.; N: calcd, 10.64; found, 10.22.

Preparation of (*E*)-4-(Cinnamylthio)-1-β-D-ribofuranosyl-1*H*-pyrazolo[3,4-*d*]pyrimidine 5'-Monophosphate Disodium Salt (18). Compound **2** was phosphorylated according to the method of Yoshikawa et al.[11] A mixture of **2** (0.5 g, 1.25 mmol) in 4 mL of triethyl phosphate was stirred and cooled in a stoppered flask (−10 °C bath). Phosphorus oxychloride (0.48 mL, 5.0 mmol) was added, and the reaction was stirred at −10 °C for 10 min, at 0 °C for 45 min, and at 0 to +5 °C for 25 min. The solution was poured onto ice, and 2 N NaOH was added until the pH value of the solution was 7. The solution was washed with chloroform and then ether. The aqueous phase was readjusted with 2 N NaOH to give a pH value of 7.58.

Traces of ether were removed in vacuo from the above neutralized solution. One-half of this solution was applied to a column containing Amberlite XAD resin (200 mL) which had been equilibrated with water. The column was washed with 3 column volumes of water to elute sodium phosphate. The nucleotide was eluted with 8 column volumes of 50% aqueous ethanol.

The remaining half of the neutalized solution was treated similarly with a 100-mL column of resin.

Both batches of nucleotide were combined and lyophilized. The lyophilized powder was dissolved in water (15 mL) and applied to a (5 × 100 cm) column containing polyacrylamide gel (P-2). The nucleotide was eluted with water. Fractions containing the nucleotide were combined and lyophilized. The powder was dissolved in 5 mL of water and precipitated by adding 50 mL of 1-propanol. This step was repeated, and the final precipitate was dried by lyophilization. The overall yield of 4-(cinnamylthio)-1-β-D-ribofuranosyl-1*H*-pyrazolo[3,4-*d*]pyrimidine 5'-monophosphate disodium salt (**18**) was 60% (0.36 g). Purity was estimated by high-performance liquid chromatography to be 99%.[21] The base/ribose/phosphate ratios were 1.00:0.96:0.97.[22] Hydrolysis by 5'-nucleotidase (EC 3.1.3.5) gave compound **2** as shown by TLC.[23]

Acknowledgment. The authors are indebted to G. Koszalka and C. Cipau for large-scale preparations of the ribonucleoside of 4-mercapto-1*H*-pyrazolo[3,4-*d*]pyrimidine, to W. Miller for the purification and characterization of **18**, to B. S. Hurlbert, R. Crouch, and A. Ragouzeos for NMR studies, and to Mrs. L. Holmes for her technical expertise in the in vitro coccidiosis studies.

Registry No. **1**, 54524-71-9; **2**, 86687-41-4; **3**, 86687-42-5; **4**, 86610-57-3; **5**, 86687-43-6; **6**, 86687-44-7; **7**, 86687-45-8; **8**, 86610-58-4; **9**, 86610-59-5; **10**, 86687-46-9; **11**, 86687-47-0; **12**, 86610-60-8; **13**, 86610-61-9; **14**, 86687-48-1; **15**, 77975-42-9; **16**, 86687-49-2; **17**, 86687-50-5; **18**, 86687-51-6; (*E*)-cinnamyl bromide, 26146-77-0; (*E*)-3-bromocinnamic acid, 14473-91-7; (*E*)-3-bromocinnamic acid chloride, 59114-87-3; (*E*)-3-bromocinnamyl alcohol, 86610-62-0; (*E*)-3-bromocinnamyl chloride, 86610-63-1; methyl (*E*)-3-hydroxycinnamate, 66417-46-7; (*E*)-3-hydroxycinnamyl alcohol, 51765-22-1; (*E*)-3-hydroxycinnamyl chloride, 86610-64-2; phenylpropargyl aldehyde, 2579-22-8; phenylpropargyl alcohol, 1504-58-1; (*Z*)-cinnamyl alcohol, 4510-34-3; (*Z*)-cinnamyl chloride, 39199-93-4; 1-(2,3,5-tri-*O*-acetyl-1-β-D-ribofuranosyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-thione, 64372-70-9.

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(23) TLC on cellulose with 1-PrOH/NH_4OH/H_2O (6:3:1, v/v): R_f of **2**, 0.97; of **18**, 0.46.

Nitrogen Bridgehead Compounds. 38.[1] New Antiallergic 4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones. 3[2]

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The weak antiallergic activity of 6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid (**4**) on the rat reaginic passive cutaneous anaphylaxis test was enhanced by the introduction of appropriate functional groups into position 9 of the pyridopyrimidine ring. The most active 9-substituted pyridopyrimidinecarboxylic acids contained an oxime, a phenylamino, or a (phenylamino)thioxomethyl group in position 9. The 9-phenylcarboxamido and 9-phenylhydrazono moieties may be regarded as bioisosteric groups in the pyridopyrimidinone series. In the series of 9-(arylamino)dihydropyridopyrimidines, the structure–activity relationship study revealed similar relationships as found for the 9-(arylhydrazono)tetrahydropyridopyrimidines. The biological activity was due to the 6*S* enantiomers. A monosubstituted arylamino moiety in position 9 was necessary for the intravenous activity. The most active compound, 9-[(3-acetylphenyl)amino]-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid (**40**) was three times as active as the reference sodium chromoglycate (DSCG) in the passive cutaneous anaphylaxis (PCA) test.

We recently described a series of 9-hydrazono-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids (**1**) with potent intravenous antiallergic activity in the rat.[2,3] The most active derivatives contain a methyl group in position 6. They are more potent than sodium

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[‡] Technical University.
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(1) Nitrogen Bridgehead Compounds. 37. Tóth, G.; Szöllösy, Á.; Almási, A.; Podányi, B. Hermecz, I.; Breining, T., Mészáros, Z. *Org. Magn. Res.*, in press.
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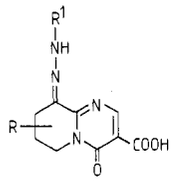
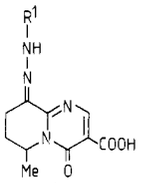
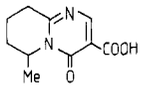


1 R=H, Me, R^1=H, Me, Ph substituted Ph, pyridyl, naphthyl.



2 R^1=Ph
3 R^1=H



4

chromoglycate (DSCG), and some of them also exhibit oral activity. The 6*S* enantiomer of 6-methyl-9-(phenylhydrazono)pyridopyrimidine-3-carboxylic acid (**2**), designated Chinoin-1045 UCB L140, was selected for detailed pharmacological investigations[4] and clinical trials. The 6-methyl-9-arylhydrazono derivatives of **1** were prepared[5] from the 6-methyltetrahydropyridopyrimidine-3-carboxylic acid **4**, which itself showed weak antiallergic–antiasthmatic activity in the rat reaginic passive cutaneous anaphylaxis (PCA) test.

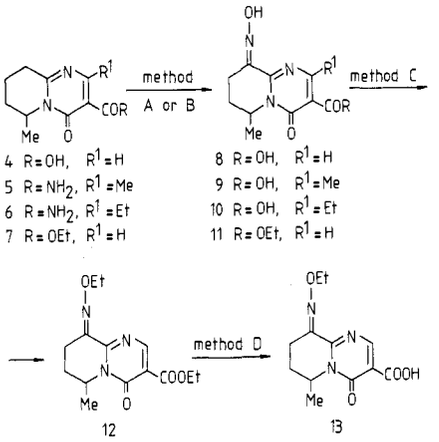
In this paper we give an account of our further studies aimed at increasing the activity of **4** by varying the substituents in position 9 of the bicyclic ring system in order to obtain compounds more potent than DSCG. Previous observations[3] suggested that the presence of the 3-carboxy and 6-methyl groups was essential for the activity. Thus, we synthesized and investigated 9-substituted 6-methylpyridopyrimidine-9-carboxylic acids.

Chemistry. For the preparation of the 9-substituted derivatives we utilized the reactivity[6] of position 9 of the 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones.

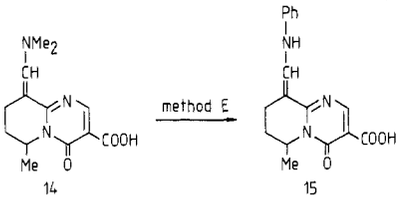
The isonitroso derivatives[7] **8–11** were prepared from the tetrahydropyridopyrimidines[2,8] **4–7** with nitrous acid in acidic medium (methods A and B). Under the conditions of method B, the 3-carboxamido group of **5** and **6** was transformed into a 3-carboxy group. From the isonitroso derivative **11**, the 9-ethoxyimino compound **12** was synthesized by ethylation with ethyl iodide (method C). The alkaline hydrolysis of **12** led to the carboxylic acid **13** (method D; see Scheme I).

The 9-(phenylamino)methylene compound[9] **15** was obtained from the 9-[(dimethylamino)methylene]pyridopyrimidine[10] **14** and aniline in acetic acid at ambient temperature (method E, Scheme II). The 9-carbamoyl 3-carboxylates **16**, **18**, and **19** were prepared as described earlier.[11,12] The alkaline hydrolysis of **16**, **18**, and **19** led

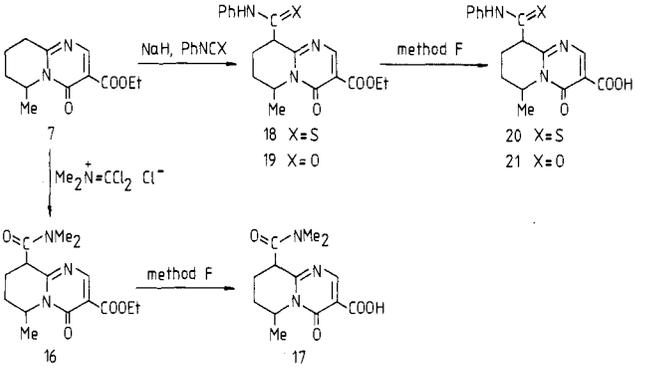
Scheme I



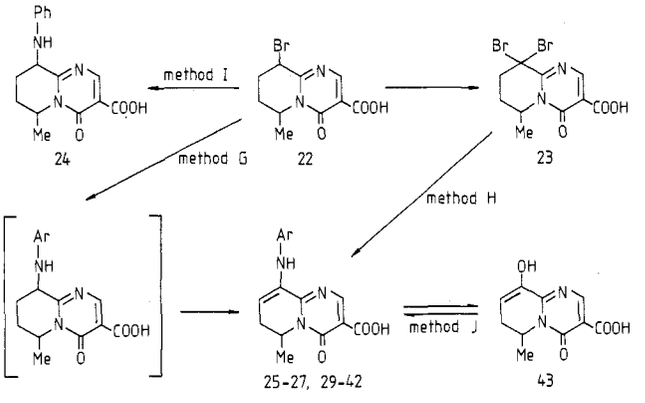
Scheme II



Scheme III



Scheme IV



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(7) Compounds **8–11** show a solvent-dependent *E–Z* geometrical isomerism around the C_9=N double bond.
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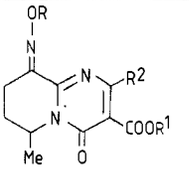
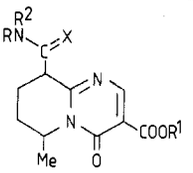
Table I. 9-Substituted 4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones



8-13

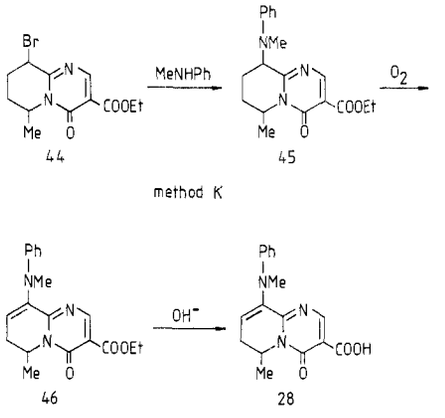


17, 19-21

compd	R	R^1	R^2	X	method	yield, %	recrystn solvent	mp, °C	formula	anal.	rat PCA: ID_{50},[a] μmol/kg iv
2					*b*						0.6
3					*c*						42.0
4					*d*						240.0
8	H	H	H		A	57	EtOH	237 dec	$C_{10}H_{11}N_3O_4$	C, H, N	19.4
9	H	H	Me		B	89	EtOH	257 dec	$C_{11}H_{13}N_3O_4$	C, H, N	>100.0
10	H	H	Et		B	94	PrOH[e]	235-236	$C_{12}H_{15}N_3O_4$	C, H, N	>100.0
11	H	Et	H		A	87	EtOH	202-203	$C_{12}H_{15}N_3O_4$	C, H, N	100.0
12	Et	Et	H		C	51	H_2O	128	$C_{14}H_{19}N_3O_4$	C, H, N	41.2
13	Et	H	H		D	89	AcOEt	149-151	$C_{12}H_{15}N_3O_4$	C, H, N	24.3
15					E	90	MeCN	262 dec	$C_{17}H_{17}N_3O_3$	C, H, N	ins[f]
17	Me	H	Me	O	F	55	dioxane	166 dec	$C_{13}H_{17}N_3O_4$	C, H, N	ins[g]
19	H	Et	Ph	O	*h*						ins[i]
20	H	H	Ph	S	F	40	EtOH	137-139 dec	$C_{17}H_{17}N_3O_3S$	C, H, N, S	9.1
21	H	H	Ph	O	F	67	dioxane	199-201	$C_{17}H_{17}N_3O_4$	C, H, N	0.56

[a] All data are considered significant at $p \leq 0.05$, as determined by Student's *t* test. [b] Racemic compound. Reference 3. [c] Reference 2. [d] Reference 8. [e] Refluxed in the solvent given. [f] Per os 10^3 μmol/kg exhibited 47% protection. [g] Per os inactive. [h] Reference 12. [i] Per os 10^3 μmol/kg exhibited 31% protection.

Scheme V



to the carboxylic acids **17**, **20**, and **21** (method F, Scheme III).

The syntheses of 9-(arylamino)pyridopyrimidine-3-carboxylic acids are shown in Schemes IV and V. 9-(Arylamino)dihydropyridopyrimidine-3-carboxylic acids were easily formed by the reaction of anilines and 9-bromo- or 9,9-dibromotetrahydropyridopyrimidine-3-carboxylic acid[13,14] **22** and **23**, respectively, at ambient temperature (methods G and H). When the starting material was the 9-bromo carboxylic acid **22**, the alkylation reaction was accompanied by oxidation. When the reaction of the 9-bromo carboxylic acid **22** and aniline was carried out under argon atmosphere, the tetrahydropyridopyrimidine-3-carboxylic acid[15] **24** was obtained (method I).

Acidic hydrolysis of the 9-(phenylamino)dihydropyridopyrimidine **25** led to the 9-hydroxy-6-methyl-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid **43**, which could be converted into 9-(arylamino)dihydropyridopyrimidine-3-carboxylic acids by the requisite aniline in ethanol under reflux (method J).

The 9-(methylphenylamino)dihydropyridopyrimidinecarboxylic acid **28** was prepared by alkaline hydrolysis of the ethyl 9-(methylphenylamino)dihydropyridopyrimidinecarboxylate **46** at 60–70 °C (method K). The ester **45** was prepared from the 9-bromo ester[8] **44** and *N*-methylaniline in methanol at reflux temperature under argon atmosphere, and the resulting 9-(methylphenylamino)tetrahydro compound **45** was oxidized by bubbling air through its solution in chloroform.

Biological Results and Discussion

The pharmacological data obtained on the new 9-substituted 6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidines in the rat PCA test[16] by the intravenous route are presented in Tables I and II.

The weak antiallergic–antiasthmatic activity observed for the 9-unsubstituted tetrahydropyridopyrimidinecarboxylic acid **4** could be enhanced by the introduction of 9-substituents.

The 9-isonitroso compound **8**, which is related to the 9-hydrazone **3** by OH for NH_2 isosteric replacement, had twice the activity of the 9-hydrazone **3** but only approximately one-tenth the activity of the reference DSCG. Transformations of **8** to **12** and **13** did not lead to a further increase in the activity. In accord with our previous observations[2] concerning the 2-alkyl-9-hydrazonopyridopyrimidinecarboxylic acids, the presence of the 2-alkyl

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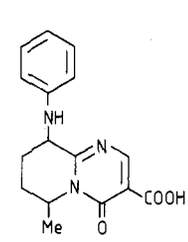
(15) 9-(Phenylamino)tetrahydropyridopyrimidine **24** shows a solvent-dependent triple tautomerism: *cis*-6,7,8,9-tetrahydro- ⇌ 1,6,7,8-tetrahydro- ⇌ *trans*-6,7,8,9-tetrahydropyridopyrimidine.
(16) The biological methods used are identical with those of ref 3.

Table II. 9-(Arylamino)-6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic Acids



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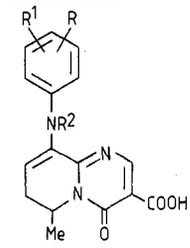


25-42

compd	R	R^1	R^2	method	yield, %	recrystn solvent	mp, °C	formula	anal.	rat PCA: ID_{50},[a] μmol/kg iv
DSCG										1.0
2[b]										0.3
24				I	46	$CHCl_3$[c]	198-199	$C_{16}H_{17}N_3O_3$	C, H, N	ins[d]
25	H	H	H	H	75	MeCN	172-173	$C_{16}H_{15}N_3O_3$	C, H, N	2.1
26[e]	H	H	H	G	75	MeCN	173-175	$C_{16}H_{15}N_3O_3$	C, H, N	1.2
27[f]	H	H	H	G	85	MeCN	170-171	$C_{16}H_{15}N_3O_3$	C, H, N	100
28	H	H	Me	K	88	MeOH	170-172	$C_{17}H_{17}N_3O_3$	C, H, N	>100
29	2'-Me	H	H	G	70	MeOH	160-163	$C_{17}H_{17}N_3O_3$	C, H, N	5.4
30	3'-Me	H	H	J	42	EtOH	148-149	$C_{17}H_{17}N_3O_3$	C, H, N	0.74
31	3'-F	H	H	J	69	MeCN	187-188	$C_{16}H_{14}N_3O_3F$	C, H, N, F	1.4
32	4'-F	H	H	J	86	EtOH[c]	200-201	$C_{16}H_{14}N_3O_3F$	C, H, N, F	8.6
33	2'-Br	H	H	J	59	MeCN	198-200	$C_{16}H_{14}N_3O_3Br$	C, H, N, Br	ins[g]
34	3'-Br	H	H	J	73	MeCN	174-175	$C_{16}H_{14}N_3O_3Br$	C, H, N, Br	10[h]
35	3'-I	H	H	H	13	$MeNO_2$	155-157	$C_{16}H_{14}N_3O_3I$	C, H, N, I	10[h]
36	4'-OH	H	H	J	86	MeCN	197-198	$C_{16}H_{15}N_3O_4$	C, H, N	2.93[i]
37	2'-COOH	H	H	J	77	EtOH[c]	232-233	$C_{17}H_{15}N_3O_5$	C, H, N	0.66
38	3'-COOH	H	H	J	38	EtOH	204-205	$C_{17}H_{15}N_3O_5$	C, H, N	0.62[j]
39	4'-COOH	H	H	J	64	EtOH[c]	230-231	$C_{17}H_{15}N_3O_5$	C, H, N	3.5[k]
40	3'-Ac	H	H	J	41	EtOH	173-174	$C_{18}H_{17}N_3O_4$	C, H, N	0.36
41	2',3'-$(CH{=}CH)_2$	H	H	J	63	EtOH	228-229	$C_{20}H_{17}N_3O_3$	C, H, N	*l*
42	3',4'-$(CH{=}CH)_2$	H	H	J	25	EtOH	187-188	$C_{20}H_{17}N_3O_3$	C, H, N	ins[m]

[a] All data are considered significant at $p \geq 0.05$, as determined by Student's *t* test. [b] Reference 3; dextrorotatory isomer with 6*S* absolute configuration. [c] Refluxed in the solvent given. [d] Per os inactive. [e] Levorotatory isomer with 6*S* absolute configuration, $[\alpha]^{20}_D$ −90° (*c* 1, $CHCl_3$). [f] Dextrorotatory isomer with 6*R* absolute configuration, $[\alpha]^{20}_D$ +92.5° (*c* 1, $CHCl_3$). [g] Per os ID_{50} = 30.7 μmol/kg. [h] Toxic at 100 μmol/kg. [i] Per os ID_{50} = 100 μmol/kg. [j] Per os ID_{50} = 92.6 μmol/kg. [k] Per os ID_{50} = 277 μmol/kg. [l] Without dose effect; ID_{50} is not extrapolable. [m] Per os ID_{50} = 30.8 μmol/kg.

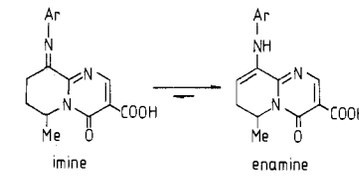
substituents in the isonitroso compounds **9** and **10** resulted in the loss of the antiallergic activity.

The 9-(phenylamino)methylene derivative **15**, which is related to the phenylhydrazone **2** by =CH for =N isosteric replacement, was not satisfactorily soluble. Following oral administration in a dose of 1 mmol/kg, **15** exhibited an inhibition of 47%.

Of the 9-amides **17** and **19–21**, the *N*-phenyl thioamide **20** and the *N*-phenyl amide **21** excelled with their significant activity. The introduction of the *N*-phenylcarboxamido group into position 9 of the pyridopyrimidine ring resulted in a more than 400-fold increase compared with the weak activity of the carboxylic acid **4**. The activity of the phenyl amide **21** surpassed that of DSCG and was equal to that of the racemic phenylhydrazone **2**. However, **21** was inactive when adminstered orally.

These results indicate that in the pyridopyrimidinone series the 9-phenylhydrazone and the 9-phenylcarboxamido moities may be regarded as bioisosteric groups. The 9-anilinotetrahydropyridopyrimidine **24** could not be investigated by intravenous administration because it is insoluble; by oral administraion it was inactive. The 9-(arylamino)dihydropyridopyrimidine-3-carboxylic acids are analogues of the 9-(arylhydrazono)tetrahydropyridopyrimidine-3-carboxylic acids **1**, differing by omission of the amino group of the hydrazone moiety. In contrast, with the 9-arylhydrazono derivatives[3], the imine (6,7,8,9-tetrahydro form) ⇌ enamine (6,7-dihydro form) tautomeric equilibrium of these compounds is shifted toward the

Scheme VI



9-(arylamino)dihydropyridopyrimidine form[17] (Scheme VI).

The 9-anilinodihydropyridopyrimidine **25** shows an activity not much lower than that of DSCG (approximately half of it).

Comparing the data on the intravenous activities of the 9-(arylamino)dihydropyridopyrimidinecarboxylic acids (Table II), we may draw conclusions that are similar to those obtained for the 9-(arylhydrazono)tetrahydropyridopyrimidinecarboxylic acids.[2,3] Thus, of the optical

(17) Compound **25**; ^1H NMR ($CDCl_3$) δ 1.45 (d, 3 H, 6-Me), 2.50 (ddd, 1 H, 7-H_{eq}, $J_{7\text{-}H_{eq},6\text{-}H} \approx 1.4$ Hz, $J_{7\text{-}H_{eq},8\text{-}H} \approx 7.3$ Hz, $^2J_{7\text{-}H_{eq},7\text{-}H_{ax}} \approx 18.4$), 2.93 (ddd, 1 H, 7-$H_{ax}$, $J_{7\text{-}H_{ax},6\text{-}H} \approx 7.0$ Hz, $J_{7\text{-}H_{ax},8\text{-}H} \approx 2.8$ Hz), 5.20 (m, 1 H, 6-H), 6.04 (ddd, 1 H, 8-H, $^4J_{6\text{-}H,8\text{-}H} \approx 1.1$), 6.90–7.65 (m, 6 H, NH + Ph), 8.87 (s, 1 H, 2-H), 13.10 (s, 1 H, OH). ^{13}C nMR ($CDCl_3$) δ 17.70 (q, 6-Me), 26.9 (t, C-7), 46.0 (d, C-6), 104.0 (d, C-8), 112.9 (s, C-3), 131.1 (s, C-9), 153.2 (s, C-9a), 158.2 (d, C-2), 163.1 (s, C-4) and 141.0 (s, C-1′), 119.8 (d, C-2′), 129.4 (d, C-3′), 122.4 (d, C-4′) of Ph; UV (EtOH) λ_{max} 323 nm (10 g ε 4.03), 261 (4.15).

antipodes **26** and **27** of the 9-phenylamino derivative **25**, the enantiomer **26** with a 6*S* absolute configuration[14] is the biologically active form, while the enantiomer **27** with a 6*R* absolute configuration is practically inactive. The inactivity of the methylphenylamino derivative **28** may be a consequence of the N,N-disubstitution and of the absence of a hydrogen-bonding amino group. The activity of compound **25** could be enhanced somewhat by the introduction of substituents onto the phenyl group.[18] Besides the 9-(*o*-carboxyphenyl)amino derivative **37**, high intravenous activities were displayed primarily by the 9-[(*m*-substituted-phenyl)amino]dihydropyridopyrimidinecarboxylic acids, i.e., the *m*-fluoro (**31**), *m*-methyl (**30**), *m*-carboxy (**38**), and *m*-acetyl (**40**) derivatives. Compounds **30**, **37**, **38**, and **40** surpass in activity the reference DSCG, and the activity of the 9-(*m*-acetylphenyl)amino derivative **40** is one order higher than that of the parent 9-phenylamino compound **25**.

Following oral administration, compounds containing a *o*-bromo (**33**), *m*-carboxy (**38**), *p*-hydroxy (**36**), or *p*-carboxy (**39**) substituent on the phenyl ring, as well as the 9-(2-naphthylamino) derivative (**42**), exhibited activity, but even the most active ones, **33** and **42**, had a far lower activity than 9-(phenylhydrazono)tetrahydropyridopyrimidinecarboxylic acid **2**.

Experimental Section

Melting points were not corrected. Combustion analyses for C, H, N, S, and halogen gave results within 0.4% of theory. The procedures for the preparation of the reported compounds, methods A–K, may be considered as general methods of preparation. Yields were not maximized. Spectra of the products (UV, Pye Unicam SP 8-200; IR, Zeiss UR 20; NMR, Brucker WP 80 DT) are in full accord with the proposed structures. Optical rotations were determined with a Zeiss polarimeter.

9-Hydroxy-6-methyl-4-oxo-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic Acid (43). 9-(Phenylamino)-6-methyl-4-oxo-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid (**25**; 10 g, 33 mmol) was stirred in a mixture of concentrated hydrochloric acid (50 mL) and water (50 mL) at ambient temperature for 2 days. The precipitated hydrochloride salt of the 9-hydroxypyridopyrimidinecarboxylic acid **43** was filtered off and added to a mixture of 5% sodium bicarbonate solution (30 mL) and chloroform (40 mL). The pH of the aqueous phase was adjusted to 2 with 5% sodium bicarbonate solution. The organic layer was separated, and the aqueous phase was extracted with chloroform (2 × 30 mL). The combined and dried (Na_2SO_4) organic phase was evaporated in vacuo, and the 9-hydroxydihydropyridopyrimidine-3-carboxylic acid **43** (2.0 g, 27%) was crystallized from ethanol, mp 163–164 °C. Anal. ($C_{10}H_{10}N_2O_4$) C, H, N.

Method A. Sodium nitrite (12 mmol, 0.83 g) in water (5 mL) was added dropwise over a period of 20 min to a stirred, chilled (0 °C) solution of 6,7,8,9-tetrahydropyridopyrimidin-4-one[8] (**4** or **7**; 10 mmol) in a mixture of water (20 mL) and concentrated hydrochloric acid (15 mL). The reaction mixture was stirred at 0 °C for 1 h and allowed to stand overnight in a refrigerator. In the preparation of **11**, the reaction mixture was neutralized with 5% sodium bicarbonate solution. The precipitated crystals (**8** or **11**) were filtered off, washed with water, dried, and crystallized.

Method B. Sodium nitrite (30 mmol, 2.37 g) in water (12 mL) was added dropwise, at 60 °C, over a period of 30 min to a solution of 2-alkyltetrahydropyridopyrimidine-3-carboxamide[2] (**5** or **6**; 15 mmol) in a mixture of water (3 mL) and concentrated sulfuric acid (9 mL). The temperature of the reaction mixture was gradually raised to 80 °C. After 10 min of stirring, the reaction mixture was poured into crushed ice (100 g), and the pH of the solution was adjusted to 1.5 with 40% sodium hydroxide solution. The precipitated acid (**9** or **10**) was filtered off, washed with water, and crystallized.

Method C. Ethyl 9-isonitrosopyridopyrimidine-3-carboxylate **11** (10 mmol, 2.66 g) and ethyl iodide (12 mmol, 1.87 g) in ethanol (50 mL) were refluxed and stirred for 1 h in the presence of potassium carbonate (10 mmol, 1.4 g). The reaction mixture was evaporated to dryness, the residue was treated with water (8 mL), and the precipitated ethoxyimino compound (**12**) was filtered off and crystallized.

Method D. 9-(Ethoxyimino)pyridopyrimidinecarboxylate (**12**; 10 mmol, 2.93 g) and potassium hydroxide (15 mmol, 0.84 g) were stirred in water (50 mL) for 3 h at ambient temperature. The pH of the reaction mixture was adjusted to 2 with 18% hydrochloric acid. The precipitated 9-(ethoxyimino)pyridopyrimidinecarboxylic acid (**13**) was filtered off and recrystallized.

Method E. A mixture of the (dimethylamino)methylene compound (**14**; 10 mmol, 2.63 g) and aniline (10 mmol, 0.93 g) was allowed to stand in glacial acetic acid (20 mL) at ambient temperature for 24 h. The solution was poured into water (100 mL), and the precipitated 9-[(phenylamino)methylene]pyridopyrimidine-3-carboxylic acid (**15**) was filtered off, washed with water, dried, and crystallized.

Method F. A mixture of the appropriate ethyl 9-(aminocarbonyl)- (**16** or **19**) or 9-(aminothiocarbonyl)pyridopyrimidine-3-carboxylate (**18**) (10 mmol) and potassium hydroxide (28.5 mmol, 1.6 g) in ethanol (20 mL) was refluxed for 20 h. After the mixture was cooled, the precipitated potassium salt was filtered off and dissolved in hot water (200 mL). The pH of the solution was adjusted to 1.5 with concentrated hydrochloric acid. The precipitated carboxylic acid **17**, **20**, or **21** was filtered off and crystallized.

Method G. A mixture of 9-bromo-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid[13,14] (**22**; 14.5 g, 50 mmol) and the requisite aniline (0.11 mol) was stirred in dimethyl sulfoxide (25 mL) in an open reaction vessel at ambient temperature for 3 days. The reaction mixture was poured into water (100 mL), and the precipitated 9-(arylamino)dihydropyridopyrimidine-3-carboxylic acid was filtered off, washed with water, dried, and crystallized.

Method H. 9,9-Dibromo-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid[13] (**23**; 18.3 g, 0.05 mol) and the requisite aniline (0.16 mol) were stirred in dimethyl sulfoxide (25 mL) at ambient temperature for 3 d ays. The reaction mixture was diluted with water (100 mL), and the precipitated 9-(arylamino)dihydropyridopyrimidine-3-carboxylic acid was filtered off, washed with water, dried, and crystallized.

Method I. A mixture of 9-bromo-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid (**22**; 2.9 g, 10 mmol) and aniline (2.79 g, 30 mmol) was stirred in dimethyl sulfoxide (5 mL) at ambient temperature for 3 days under an argon atmosphere. The reaction mixture was poured into water (20 mL), and the precipitated 9-(phenylamino)tetrahydropyridopyrimidine-3-carboxylic acid **24** was filtered off, washed with water, dried, and crystallized.

Method J. A mixture of 9-hydroxy-6-methyl-4-oxo-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acid (**43**; 1.11 g, 5 mmol) and the requisite aniline (5.5 mmol) was refluxed in ethanol for 3 h. The reaction mixture was cooled to 10 °C. The precipitated 9-(arylamino)dihydropyridopyrimidine-3-carboxylic acid was filtered off, washed with ethanol, dried, and crystallized.

Method K. Ethyl 9-bromo-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate[8] (**44**; 5 g, 16 mmol) and *N*-methylaniline (3.4 g, 32 mmol) were refluxed in ethanol (50 mL) under an argon atmosphere for 8 h. To the reaction mixture was added 5% hydrochloric acid (50 mL), and the aqueous solution was extracted with dichloromethane (3 × 25 mL). The combined and dried (Na_2SO_4) organic phase was evaporated to dryness in vacuo, and the residue was crystallized to give ethyl 9-(methylphenylamino)-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**45**; 3.0 g, 55%) mp 180–181 °C (MeCN). Anal. ($C_{19}H_{23}N_3O_3$) C, H, N. Air was bubbled through the refluxing solution of 9-(methylphenylamino)tetrahydropyridopyrimidine (**45**; 5 g, 14 mmol) in chloroform (100 mL) for 9 h. The chloroform was evaporated to dryness in vacuo, and the residue was crystallized from ethanol

(18) If the phenyl group of compound **25** contained a *o*-chloro, *o*-iodo, *o*-methoxy, *m*-nitro, *p*-methyl, *p*-chloro, *p*-bromo, *p*-methoxy, *p*-ethoxy, *p*-nitro, or *p*-phenyl substituent, of *m,p*-dichloro substituents, the resulting derivatives were insoluble, and inactive when administered orally.

to give ethyl 9-(methylphenylamino)-6-methyl-4-oxo-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (**46**; 2.9 g, 58%), mp 140–142 °C. Anal. ($C_{19}H_{21}N_3O_3$) C, H, N.

The ethyl 9-(methylphenylamino)dihydropyridopyrimidine-3-carboxylate **46** (2 g, 5.9 mmol) was stirred in 1% sodium hydroxide solution (100 mL) at 60–70 °C for 4 h. The pH of the solution was adjusted to 2 with 10% hydrochloric acid, and the precipitated 9-(methylphenylamino)dihydropyridopyrimidine-3-carboxylic acid **28** was filtered off, washed with water, dried, and crystallized.

Registry No. **2**, 70999-20-1; **3**, 70999-31-4; **4**, 32092-24-3; **5**, 70998-87-7; **6**, 86610-83-5; **7**, 32092-14-1; **8**, 86610-84-6; **9**, 86610-85-7; **10**, 86610-86-8; **11**, 64399-30-0; **12**, 86610-87-9; **13**, 86610-88-0; **14**, 71165-25-8; **15**, 71165-95-2; **16**, 86610-89-1; **17**, 86610-90-4; **18**, 82074-89-3; **19**, 86610-91-5; **20**, 86610-92-6; **21**, 86610-93-7; **22**, 70943-70-3; **23**, 77020-26-9; **24**, 71222-75-8; **25**, 70993-81-6; **26**, 71222-67-8; **27**, 77020-32-7; **28**, 77020-28-1; **29**, 71222-64-5; **30**, 86610-94-8; **31**, 86610-95-9; **32**, 86610-96-0; **33**, 86610-97-1; **34**, 77020-40-7; **35**, 86610-98-2; **36**, 86610-99-3; **37**, 86611-00-9; **38**, 86611-01-0; **39**, 77020-37-2; **40**, 86611-02-1; **41**, 77020-41-8; **42**, 86611-03-2; **43**, 70943-64-5; **44**, 38326-49-7; **45**, 71222-72-5; **46**, 71222-65-6; aniline, 62-53-3; *N*-methylaniline, 100-61-8; 2-methylaniline, 95-53-4; 3-methylaniline, 108-44-1; 3-fluoroaniline, 372-19-0; 4-fluoroaniline, 371-40-4; 2-bromoaniline, 615-36-1; 3-bromoaniline, 591-19-5; 3-iodoaniline, 626-01-7; 4-hydroxyaniline, 123-30-8; 2-aminobenzoic acid, 118-92-3; 3-aminobenzoic acid, 99-05-8; 4-aminobenzoic acid, 150-13-0; 3-acetylaniline, 99-03-6; 1-naphthylamine, 134-32-7; 2-naphthylamine, 91-59-8.

Supplementary Material Available: Yields and melting points of 12 9-(arylamino)-6-methyl-4-oxo-6,7-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic acids, which were inactive when administered orally, are collected in Table III (1 page). Ordering information is given on any current masthead page.

Antiallergic Agents. 2.[1] *N*-(1*H*-Tetrazol-5-yl)-6-phenyl-2-pyridinecarboxamides

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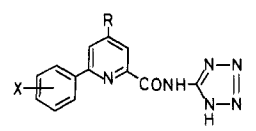
A new series of *N*-(1*H*-tetrazol-5-yl)-6-phenyl-2-pyridinecarboxamides was prepared to determine the effects of substituents on the benzene and pyridine rings on antiallergic activity in the rat passive cutaneous anaphylaxis (PCA) assay after oral administration. One member of this series, *N*-(1*H*-tetrazol-5-yl)-4-methyl-6-[4-(methylamino)-phenyl]-2-pyridinecarboxamide (**23l**), has an ED_{50} value of 0.8 mg/kg po and is 85 times more potent than disodium cromoglycate (DSCG) on intravenous administration. Further evaluation of **23l** as a clinically useful antiallergic agent is in progress.

Extensive efforts[2] have been made to find an orally active and more potent antiallergic agent possessing pharmacological properties similar to those of disodium cromoglycate (DSCG).[3]

We have previously reported that some *N*-(1*H*-tetrazol-5-yl)-6-phenyl-2-pyridinecarboxamides (1, X = H; R



1

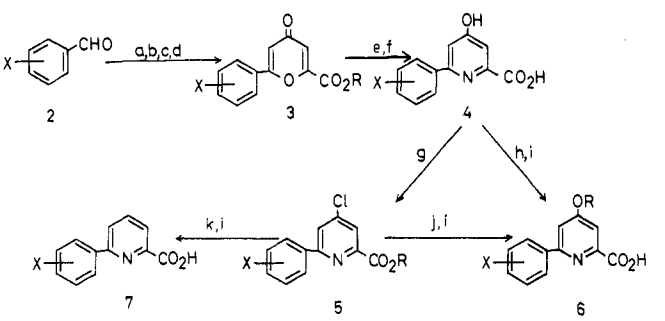
= H, OMe, Cl) displayed remarkably high potencies in the rat PCA test on oral administration.[1] Our attention was next focused on exploring this lead in an effort to enhance the activity. In this paper we describe the synthesis and antiallergic activity of this new series of *N*-tetrazolylpyridinecarboxamides represented by general structure 1, which bears various substituents on the benzene and pyridine rings.

Chemistry. Most of the *N*-(1*H*-tetrazol-5-yl)-6-phenyl-2-pyridinecarboxamides listed in table I were prepared by condensation of the corresponding carboxylic acid chloride with 5-aminotetrazole (method A).[4]

The route for the preparation of the carboxylic acids[5] (**5–7**) is illustrated in Scheme I and is analogous to that described previously.[1]

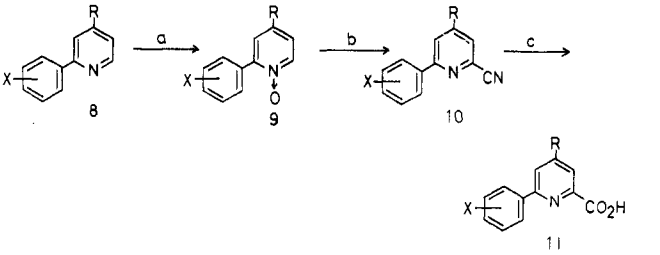
The 6-phenyl-4-alkyl-2-pyridinecarboxylic acids[5] (**11**) were synthesized from the appropriate 2-phenylpyridine

Scheme I[a]



[a] a = CH_3COCH_3, NaOH; b = $(CO_2Et)_2$/NaH; c = Br_2/CS_2; d = KOAc/ROH or DMF. e = NH_3/EtOH, 100–110 °C; f = concentrated HCl; g = (1) $POCl_3$ or $SOCl_2$, (2) MeOH. h = RX, K_2CO_3/DMF; i = KOH/MeOH; j = MeONa/MeOH; k = H_2, Pd/C.

Scheme II[a]



[a] a = 30% H_2O_2/AcOH; b = (1) Me_2SO_4; (2) = NaCN; c = concentrated HCl, reflux.

(**8**)[7] via a Reissert–Kaufman-type reaction[8] (Scheme II). The derivatives possessing amino functions on the benzene

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0022-2623/83/1826-1499$01.50/0