0.38 g (34% yield) of product **9c**, mp 141–143 °C.

Compounds **9a,b** were prepared by method E. Compound **8a** was synthesized with a concentrated ammonium hydroxide solution instead of methylamine in the above procedure.

3-[(Methylsulfonyl)methyl]quinoxaline 1-Oxide (8e). Method F. 2-Acetyl-3-[(methylsulfonyl)methyl]quinoxaline 1-oxide (0.50 g, 18 mmol) was added to methylamine–water (40%, 20 mL). The reaction mixture was heated under reflux for 5 min, and the mixture turned purple. While the mixture was cooled to room temperature, a solid formed, which was collected by suction filtration. The solid was washed with water and dried to afford 0.34 g (80%) of **8e**, mp 196–197 °C.[16]

This method was used to prepare **9d**.

2-(Methylsulfonyl)-3-[(methylsulfonyl)methyl]quinoxaline 1-Oxide (8f). Method G. 2-(Methylthio)-3-[(methylthio)methyl]quinoxaline 1-oxide (0.46 g, 1.8 mmol) was dissolved in methylene chloride (30 mL) and 85% *m*-chloroperbenzoic acid (1.57 g, 7.8 mmol) was added. The reaction mixture was allowed to stir at room temperature overnight. The reaction was worked up in the same manner as described above for **7a**, which gave 0.51 g (89%) of **8f**, mp 197–200 °C.

2-Acetyl-3-[(methylsulfonyl)methyl]quinoxaline (17a). Method H. 2-Acetyl-3-[(methylsulfonyl)methyl]quinoxaline 1-oxide (0.61 g, 2.2 mmol) was suspended in 1-propanol (10 mL) containing trimethyl phosphate (0.56 g, 4.8 mmol).[6] The reaction mixture was heated under reflux for 4 h. While the solution was cooled to room temperature, crystals formed. The solid was collected by suction filtration and washed with ether to afford 0.39 g (69%) of **17a**, mp 191–194 °C.

Compounds **11a–d** and **17b** were prepared by method H. Quinoxaline 1,4-dioxide precursors were synthesized by procedures similar to those described previously.[3,8]

2-[(Methylthio)methyl]quinoxaline-3-carboxylic Acid 1-Oxide (12). Method I. Methyl 2-[(methylthio)methyl]-quinoxaline-3-carboxylate 1-oxide (2.00 g, 7.6 mmol) was treated with 1 N sodium hydroxide solution (30 mL) for 2 h at room temperature. The reaction mixture was neutralized with 1 N hydrochloric acid solution, and the resulting solid was collected by suction filtration, washed with water, and dried to afford 1.22 g (77%) of **12**, mp 144–145 °C.

2-[(Methylthio)methyl]quinoxaline 1-Oxide (13). Method J. A solution of 2-[(methylthio)methyl]quinoxaline-3-carboxylic acid 1-oxide (1.00 g, 4.0 mmol) in toluene (20 mL) was heated under reflux for 1 h. The reaction mixture was cooled to room temperature and evaporated, leaving an amber oil. The oil was crystallized from benzene–hexane to yield 0.67 g (81%) of **13**, mp 74–75 °C.

Acknowledgment. We are indebted to Drs. Leonard J. Czuba and Richard C. Koch for helpful discussions regarding this work. We thank Richard James, Donald Soucy, Eleanor Shoop, and Jan Watrous for their technical assistance.

Registry No. **3a**, 61522-57-4; **3b**, 61528-76-5; **3c**, 85976-66-5; **4a**, 85957-66-0; **4b**, 85957-67-1; **4c**, 85957-68-2; **4d**, 85957-69-3; **5a**, 85957-70-6; **5b**, 85976-67-6; **5c**, 85957-71-7; **5d**, 85957-72-8; **5e**, 85957-73-9; **5f**, 85957-74-0; **5g**, 85957-75-1; **5h**, 85957-76-2; **6a**, 85957-77-3; **6b**, 85957-78-4; **7a**, 85957-79-5; **7b**, 85957-80-8; **7c**, 85957-81-9; **7d**, 85957-82-0; **7e**, 85957-83-1; **7f**, 85957-84-2; **7g**, 85957-85-3; **7h**, 85957-86-4; **8a**, 85957-87-5; **8b**, 85957-88-6; **8c**, 85957-89-7; **8d**, 85957-90-0; **8e**, 85957-91-1; **8f**, 85957-92-2; **9a**, 85957-93-3; **9b**, 85957-94-4; **9c**, 85957-95-5; **9d**, 85957-96-6; **10a**, 85957-97-7; **10b**, 85957-98-8; **10c**, 56944-42-4; **10d**, 34930-76-2; **11a**, 85957-99-9; **11b**, 85958-00-5; **11c**, 85958-01-6; **11d**, 85958-02-7; **12**, 85958-03-8; **13**, 85958-04-9; **14**, 85958-05-0; **15**, 85958-06-1; **17a**, 85958-07-2; **17b**, 85958-08-3; 3-methyl-2-(methylthio)quinoxaline 1,4-dioxide, 39576-50-6; methyl mercaptan, 74-93-1; 2-mercaptoethanol, 60-24-2; sodium methylsulfinate, 20277-69-4.

(16) This deacylation procedure described herein was an outgrowth of a serendipitous result obtained with some substituted 2-acetylquinoxaline 1,4-dioxides and methylamine–water. It is assumed that deacylation is facilitated by the electron-withdrawing *N*-oxide functionality on the quinoxaline ring.

Nitrogen Bridgehead Compounds. 33.[1] New Antiallergic 4*H*-Pyrido[1,2-*a*]pyrimidin-4-ones. 2.

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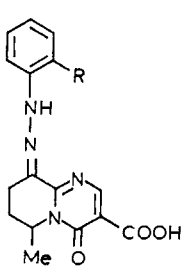
Chinoin Pharmaceutical and Chemical Works, Ltd., H-1325 Budapest, Hungary, and UCB Pharmaceutical Sector B-1060, Brussels, Belgium. *Received October 26, 1982*

A series of 9-hydrazono-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones was prepared. The compounds were evaluated in the rat passive cutaneous anaphylaxis test for antiallergic activity. Structure–activity relationship studies revealed that the presence of a monosubstituted hydrazone moiety in position 9 and an unsubstituted 2-position are necessary for the intravenous activity.

We recently reported[2] the synthesis and pharmacological investigation of antiallergic 9-(phenylhydrazono)-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones of type **1** on rat reaginic passive cutaneous anaphylaxis (PCA). Structure–activity relationship studies revealed that the presence of a carboxy group in the 3-position was necessary for activity, the most potent derivatives bore a methyl group in the 6-position, and the biological effect was due to the 6-*S* enantiomers. The substituents on the phenyl group caused subtle differences in the potency: meta



1 R = H

2 R = COOH

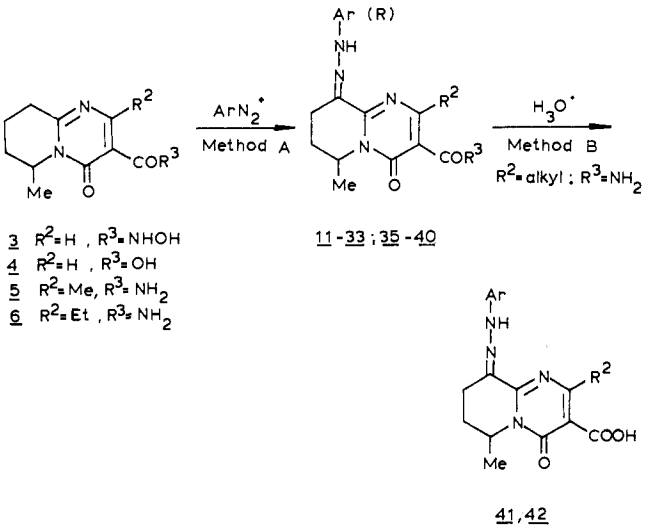
substituents and a hydroxy or carboxy group in the ortho position (compound **2**) slightly enhanced the activity observed following intravenous injection. The orally active 6-*S* enantiomer of **1** was selected for further development.[3]

(1) Part 32. Hermecz, I.; Kajtár, M.; Surján, P. R.; Breining, T.; Simon, K.; Horváth, G.; Tóth, G.; Mészáros, Z. *J. Chem. Soc. Perkin Trans. 2*, in press.

(2) Hermecz, I.; Breining, T.; Meszáros, Z.; Horváth, A.; Vasvári-Debreczy, L.; Dessy, F.; DeVos, C.; Rodriquez, L. *J. Med. Chem.* **1982** *25*, 1140.

0022-2623/83/1826-1126$01.50/0

Scheme I



3 R^2=H , R^3=NHOH
4 R^2=H , R^3=OH
5 R^2=Me, R^3=NH_2
6 R^2=Et , R^3=NH_2

11-33 ; 35-40

41,42

Detailed pharmacological studies, including cross-tachyphylaxis testing, indicate that compounds of type 1 have a disodium cromoglycate (DSCG) like mechanism of action.

Having found compounds 1 and 2 to be of interest, we designed, synthesized, and tested a series of derivatives with the aim of optimizing activity. Furthermore, since the 9-(phenylhydrazono) compounds II of type 1 may exist in different tautomeric forms,[2] we synthesized and investigated some analogues with "fixed" tautomeric structures.

Pharmacological investigation of all these new derivatives was carried out on the racemic compounds.

Chemistry. The 9-(arylhydrazono)tetrahydropyridopyrimidines **11–33** and **35–40** were prepared from the tetrahydropyridopyrimidines **3–6** by diazonium coupling, under conditions (method A) reported earlier[2] (Scheme I). With 5-aminotetrazole, the diazonium chloride was formed in situ[4] (method A-2).

The carboxylic acids **41** and **42** were obtained from the carboxamides **39** and **40** by hydrolysis in hot concentrated hydrochloric acid (method B).

The 9-hydrazonotetrahydropyridopyrimidines **34** and **43–45** were synthesized by reacting the appropriate hydrazines with either the 9-bromotetrahydropyridopyrimidine (**7**) (method C) or with the 9-hydroxydihydropyridopyrimidine (**8**) (method D) (Scheme II). Reaction of the 9-bromo derivative was accompanied by oxidation.[5]

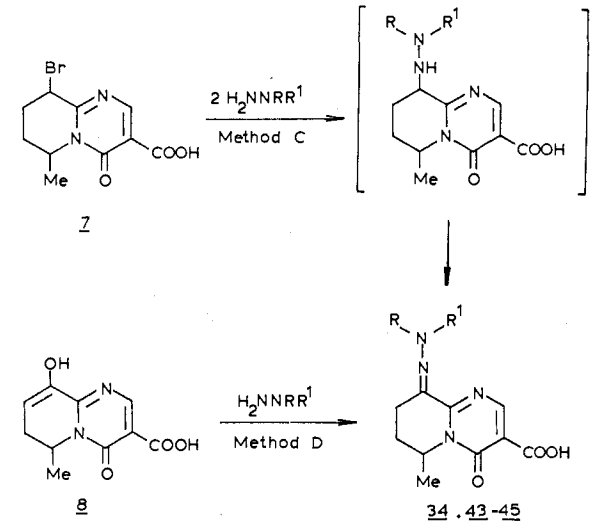
The analogues with "fixed" tautomeric structures, **46–49**, were prepared from the tetrahydropyridopyrimidines (**9** or **10**) by reaction with aryldiazonium chlorides (methods E and F) (Scheme III).

Biological Results and Structure–Activity Relationships

The pharmacological data obtained on the new derivatives in the rat PCA test[6] are presented in Table I.

Since the antiallergic activity of some types of compounds showed a negative π dependence,[7] i.e., the activity

Scheme II

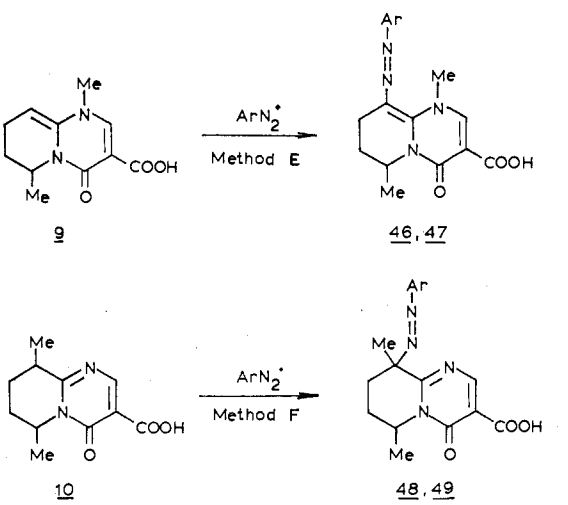


7

8

34 . 43-45

Scheme III



9

46, 47

10

48, 49

increased with decreasing π values, we synthesized and tested derivatives **11** and **12** where the carboxy group (π = −0.32)[8] of **1** and **2** was replaced by a hydroxamic acid group (π = −1.87).[8] The hydroxamic acids, however, did not have any antiallergic activity.

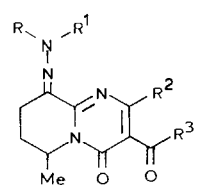
Of the di- or trisubstituted phenyl compounds made in this study, only the 9-[(3,5-dimethoxyphenyl)hydrazono] derivative (**27**) retained some of the oral activity of **1**. Di- and trisubstitution on the phenyl group lowered the solubility of these compounds considerably. Consequently, of the 19 various derivatives (**13–31**), only 6 could be investigated intravenously. Two of these compounds **27** and **29**, displayed higher activities than those of **1** or **2**.

Replacement of the *N*-phenyl group of **1** by a 2-naphthyl or 3-pyridyl group (in compounds **33** and **35**, respectively) did not affect the intravenous potency, whereas replacement by a tetrazolyl group led to an inactive compound, **36**. Neither of these compounds, however, had the potency of **1** when administered orally.

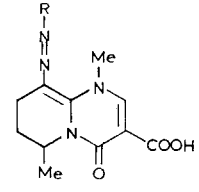
The slight activity observed for the ester **37** may be a consequence of partial enzymatic hydrolysis and the formation of the carboxylic acid **38**.

(3) DeVos, C.; Dessy, F.; Hermecz, I.; Mészáros, Z.; Breining, T. *Int. Arch. Allergy Appl. Immunol.* **1982**, *67*, 352.
(4) Caution: We have had a detonation when trying to prepare compound **36** by method A-1 on a 1-mmol scale!
(5) Breining, T.; Hermecz, I., unpublished results.
(6) The biological methods used are identical with that of ref 2.
(7) Cramer III, R. D.; Snader, K. M.; Willis, C. R.; Charkin, L. W.; Thomas, J.; Sutton, B. M. *J. Med. Chem.* **1979**, *22*, 714.
(8) Hansch, C.; Leo, A. J. "Substituent Constants for Correlation Analysis in Chemistry and Biology"; Willey: New York, 1979; pp 82 and 84.

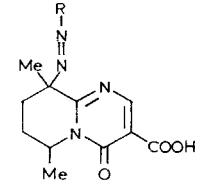
Table I. 9-Hydrazonotetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones



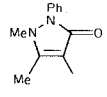
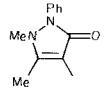
11–45



46, 47



48, 49

compd	R	R^1	R^2	R^3	method	yield, %	recrystn solvent	mp, °C	formula	anal.	rat PCA ID_{50},[a] μmol/kg iv	rat PCA ID_{50},[a] μmol/kg po
1											0.6	1.2
2											0.48	>100
11	Ph	H	H	NHOH	A-1	48	EtOH	230	$C_{16}H_{17}N_5O_3$	C, H, N	>100	>100
12	2-COOH-Ph	H	H	NHOH	A-1	67	*b*	>240	$C_{17}H_{17}N_5O_5$	C, H, N	>100	>100
13	2,3-Me_2-Ph	H	H	OH	A-1	79	$MeNO_2$	232–234	$C_{18}H_{20}N_4O_3$	C, H, N	ins	>100
14	3,4-Me_2-Ph	H	H	OH	A-1	97	EtOH[c]	252–253	$C_{18}H_{20}N_4O_3$	C, H, N	6.5	>100
15	3,5-Me_2-Ph	H	H	OH	A-1	88	*b*	248–250	$C_{18}H_{20}N_4O_3$	C, H, N	ins	>320
16	2,6-Me_2-Ph	H	H	OH	A-1	79	MeOH[c]	192–193	$C_{18}H_{20}N_4O_3$	C, H, N	ins	>320
17	2,4,6-Me_3-Ph	H	H	OH	A-1	40	benzene	195–197	$C_{19}H_{22}N_4O_3$	C, H, N	ins	>320
18	2,4,5-Me_3-Ph	H	H	OH	A-1	75	DMF	224–226	$C_{19}H_{22}N_4O_3$	C, H, N	ins	>320
19	2,4-Cl_2-Ph	H	H	OH	A-1	84	DMF	242–244	$C_{16}H_{14}N_4O_3Cl_2$	C, H, Cl, N	ins	>100
20	3,4-Cl_2-Ph	H	H	OH	A-1	90.5	AcOH	248–250	$C_{16}H_{14}N_4O_3Cl_2$	C, H, Cl, N	0.89	>100
21	3,5-Cl_2-Ph	H	H	OH	A-1	86	EtOH[c]	260	$C_{16}H_{14}N_4O_3Cl_2$	C, H, Cl, N	13.3	>100
22	2,6-Cl_2-Ph	H	H	OH	A-1	56	AcOH	230–232	$C_{16}H_{14}N_4O_3Cl_2$	C, H, Cl, N	ins	>100
23	2-Cl-4-Br-Ph	H	H	OH	A-1	80	AcOH	245–247	$C_{16}H_{14}N_4O_3BrCl$	C, H, N	ins	>100
24	2-Cl-6-Me-Ph	H	H	OH	A-1	94	AcOH	205–207	$C_{17}H_{17}N_4O_3Cl$	C, H, N	ins	>100
25	4-Br-3-Me-Ph	H	H	OH	A-1	91	$MeNO_2$	250–252	$C_{17}H_{17}N_4O_3Br$	C, H, N	ins	>100
26	5-Cl-2-OH-Ph	H	H	OH	A-1	70	DMF–MeOH	245–246	$C_{16}H_{15}N_4O_4Cl$	C, H, N	ins	>100
27	3,5-$(MeO)_2$-Ph	H	H	OH	A-1	62	AcOH	252–254	$C_{18}H_{20}N_4O_5 \cdot H_2O$	C, H, N	0.42	100
28	2,4-$(MeO)_2$-5-Cl-Ph	H	H	OH	A-1	54	DMF–MeOH	240	$C_{18}H_{19}N_4O_5Cl$	C, H, N	ins	>100
29	3,4-(OCH_2O)-Ph	H	H	OH	A-1	81	AcOH	226–227	$C_{17}H_{16}N_4O_5 \cdot H_2O$	C, H, N	0.33	>100
30	3,5-$(NO_2)_2$-Ph	H	H	OH	A-1	77	EtOH[c]	260	$C_{16}H_{14}N_6O_7$	C, H, N	3.4	>100
31	3,5-$(CF_3)_2$-Ph	H	H	OH	A-1	62	EtOH[c]	252–254	$C_{18}H_{14}N_4O_3F_6$	C, H, N	ins	>100
32	1-naphthyl	H	H	OH	A-1	64	AcOH	240–242	$C_{20}H_{18}N_4O_3$	C, H, N	ins	>320
33	2-naphthyl	H	H	OH	A-1	48	$MeNO_2$	211–212	$C_{20}H_{18}N_4O_3$	C, H, N	0.77	>100
34	2-pyridyl	H	H	OH	D	66	MeCN	233–234	$C_{15}H_{15}N_5O_3$	C, H, N	3.2	>100
35	3-pyridyl	H	H	OH	A-1	41	DMF	220–221	$C_{15}H_{15}N_5O_3 \cdot HCl$	C, H, N	0.54	>320
36	5-tetrazolyl	H	H	OH	A-2	75	*b*	213–215	$C_{11}H_{12}N_8O_2 \cdot H_2O$	C, H, N	>100	>100
37		H	H	OEt	A-1	55	EtOAc	163–165	$C_{23}H_{16}N_6O_4$	C, H, N	95	>100
38		H	H	OH	A-1	79	EtOH[c]	225 dec	$C_{21}H_{22}N_6O_4$	C, H, N	31	>100
39	Ph	H	Me	NH_2	A-1	80	$MeNO_2$[c]	235–237	$C_{17}H_{19}N_5O_2$	C, H, N	ins	>100

40	Ph	H	Et	NH_2	A-1	56	MeOH[c]	225–227	$C_{18}H_{21}N_5O_2$	C, H, N	>100
41	Ph	H	Me	OH	B	61	MeOH[c]	242–244 dec	$C_{17}H_{18}N_4O_3$	C, H, N	>320
42	Ph	H	Et	OH	B	35	MeOH[c]	206–207 dec	$C_{18}H_{20}N_4O_3$	C, H, N	>320
43	H	H	H	OH	C	61	50% EtOH	227	$C_{10}H_{12}N_4O_3$	C, H, N	>100
44	Me	H	H	OH	C	45	MeOH	218–220	$C_{11}H_{14}N_4O_3$	C, H, N	>100
45	Ph	Me	H	OH	D	73	MeCN	189–190	$C_{17}H_{18}N_4O_3$	C, H, N	>100
46	Ph				E	21	DMF	228–230 dec	$C_{17}H_{18}N_4O_3$	C, H, N	>320
47	2-COOH-Ph				E	50	b	205–206	$C_{18}H_{18}N_4O_5 \cdot H_2O$	C, H, N	>100
48	Ph				F	46	50% EtOH	136–138	$C_{17}H_{18}N_4O_3$	C, H, N	>100
49	2-COOH-Ph				F	54	50% EtOH	128–130	$C_{18}H_{18}N_4O_5 \cdot H_2O$	C, H, N	>100
DSCG											

40	>100	
41	>100	>320
42	>100	>320
43	42	>100
44	17.5	>100
45	52.4	>100
46	ins	>320
47	>100	>100
48	35.0	>100
49	>100	>100
DSCG	1.0	inactive

[a] All data are considered significant at $p \leq 0.05$ as determined by Student's t test. [b] Dissolved in 5% NaOH and precipitated with acetic acid. [c] Refluxed in the solvent given, ins = insoluble.

When the phenyl group of the 9-(phenylhydrazono) moiety of **1** was replaced by a hydrogen atom or a methyl group, the resulting compounds (**43** and **44**, respectively) exhibited only $^1/_{70}$th and $^1/_{30}$th of the intravenous activity of **1**.

Introduction of an alkyl group into the 2-position of the pyridopyrimidine ring resulted in completely inactive compounds **41** and **42**. We have already concluded[2] that the 3-carboxy group is essential for the activity. The substituent at the 2-position presumably sterically prevents the biofunctional 3-carboxylic acid moiety from interacting with the active site of the receptor.

The decreased potencies of the "fixed" structure models **45–49** indicate that the NH group of the 9-hydrazono moiety plays an important role in the biological activity. It may either take part directly in the binding to the receptor, or, by forming an intramolecular hydrogen bond to the N1 atom, it may stabilize the aryl group and the pyridopyrimidine ring in an arrangement that is optimum for the biological activity. Hydrogen bonding has similarly been described as an essential structural factor in antiallergic compounds by other authors.[7,9–12]

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–F, may be considered as general methods. Yields were not maximized.

2-Alkyl-6-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamides (5 and 6). 2-Alkyl-6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide[13] (20 mmol) in acetic acid (120 mL) was hydrogenated over 10% Pd/C (1 g) at ambient temperature under atmospheric pressure. After absorption of the theoretical amount of hydrogen (2 mol equiv), the catalyst was filtered off, and the filtrate was evaporated in vacuo to give the crude product. Compound **5** (2.9 g, 66%) was recrystallized from EtOH, mp 191–192 °C. Anal. ($C_{11}H_{15}N_3O_2$) C, H, N. Compund **6** (4.0 g, 85%) was recrystallized from H_2O, mp 147–148 °C. Anal. ($C_{12}H_{17}N_3O_2$) C, H, N.

6,9-Dimethyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylic Acid (10). Ethyl 9-formyl-6-methyl-4-oxo-1,6,7,8-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate[14] (15.8 g, 60 mmol) was hydrogenated in a mixture of ethanol (150 mL) and concentrated hydrochloric acid (6 mL) over 10% Pd/C (1 g) at ambient temperature under atmospheric pressure. After the absorption of the theoretical amount of hydrogen (2 mol equiv), the catalyst was filtered off. The filtrate was diluted with water (150 mL), and the pH was adjusted to 7 with 10% Na_2CO_3 solution. The aqueous layer was extracted with chloroform. The organic phase was dried (Na_2SO_4) and evaporated. To the crude ethyl 6,9-dimethyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (14.8 g), water (50 mL) and sodium hydroxide (7.0 g) were added, and the reaction mixture was stirred for 1 h. The pH was adjusted to 3 with 10% hydrochloric acid. The precipitated acid **10** (10.6 g) was

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filtered off and recrystallized from ethanol, mp 126–127 °C. Anal. ($C_{11}H_{14}N_2O_3$) C, H, N.

Method A-1. Diazonium coupling was carried out as described earlier.[2] Compounds **5** and **6** were dissolved in dimethyl sulfoxide. The tendency of the 9-hydrazonopyridopyrimidines to form stable hydrates is reflected in some of the elemental analyses.

Method A-2. A solution of sodium 6,7,8,9-tetrahydropyridopyrimidinecarboxylate[15] (4; 2.3 g, 10 mmol) and sodium nitrite (0.69 g, 10 mmol) in water (10 mL) was added dropwise in a period of 1.5 h to a stirred, chilled (−5 °C) solution of 5-aminotetrazole hydrate (1.03 g, 10 mmol) in 1:1 diluted hydrochloric acid (5 mL). The reaction mixture was stirred at 0 °C for 4 h and allowed to stand overnight in a refrigerator.

The precipitated crystals were filtered and washed with water. The crude product was dissolved in 5% NaOH solution, the solution was decolorized with active charcoal and filtered, and the filtrate was acidified with acetic acid. The precipitated product **36** was collected by filtration.

Method B. A solution of 2-alkyl-6-methyl-9-(phenylhydrazino)-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxamide (**39** or **40**) (20 mmol) in concentrated hydrochloric acid (10 mL) was gently refluxed for 5 h. After cooling to room temperature, the mixture was diluted with water (10 mL). For dissolution, 10% NaOH solution was added to the reaction mixture. The aqueous solution was decolorized with active charcoal and filtered, and the filtrate was acidified with acetic acid. The precipitated product (**41** or **42**) was collected by filtration.

Method C. To a suspension of 9-bromotetrahydropyridopyrimidinecarboxylic acid[16] (**7**; 2.87 g, 10 mmol) in methanol (30 mL) was added hydrazinehydrate or methylhydrazine (22 mmol). The reaction mixture was gently warmed up and stirred at ambient temperature for 24 h. The precipitated crystalline substance (**43**) was filtered off and dissolved in water (15 mL). The pH of the solution was adjusted to 6–6.5 with acetic acid. The precipitated product was filtered off, washed with water, dried, and recrystallized.

When preparing **44**, the reaction mixture was evaporated to dryness. The residue was dissolved in water (10 mL), and the pH was adjusted to 3.5 with 10% hydrochloric acid. The precipitated product was filtered off, washed with water, dried, and recrystallized.

Method D. A mixture of 9-hydroxy-6,7-dihydropyridopyrimidinecarboxylic acid[17] (**8**; 4.44 g, 20 mmol) and naphthyl- or phenylhydrazine (22 mmol) in ethanol (50 mL) was refluxed for 2 h. After the mixture was cooled to 0 °C, the precipitated product **34** or **45** was filtered off and recrystallized.

Method E. Sodium acetate (6 g) was added to a chilled (-5 °C) solution of phenyldiazonium chloride, prepared[18] from 10 mmol of aniline, in 1:1 diluted hydrochloric (5 mL), and a solution of sodium 1,6-dimethyl-1,6,7,8-tetrahydropyridopyrimidinecarboxylate[19] (**9**; 2.11 g, 10 mmol) in water (5 mL) was added dropwise over 1 h. The reaction mixture was allowed to stand overnight in a refrigerator. The precipitated product was filtered off, washed with boiling water and then with boiling ethanol, and recrystallized.

Method F. The procedure is similar to method E, but sodium 6,9-dimethyl-6,7,8,9-tetrahydropyridopyrimidinecarboxylate (**10**) was applied instead of 1,6-dimethy-1,6,7,8-tetrahydropyridopyrimidinecarboxylic acid (**9**). The reaction mixture was stirred at −5 °C for 3 h and allowed to stand overnight in a refrigerator. The crystalline product was filtered off, washed with water, and recrystallized.

Registry No. (±)-1, 77713-55-4; (±)-**2**, 77713-79-2; (±)-**3**, 85762-24-9; (±)-4·Na, 85762-25-0; (±)-**5**, 85762-26-1; (±)-**6**, 85762-27-2; **7**, 70943-70-3; (±)-**8**, 85762-28-3; (±)-**9**·Na, 85762-29-4; (±)-**10**·Na, 85762-30-7; (±)-11, 85762-31-8; (±)-**12**, 85762-32-9; (±)-**13**, 85762-33-0; (±)-**14**, 85762-34-1; (±)-**15**, 85762-35-2; (±)-**16**, 85762-36-3; (±)-**17**, 85762-37-4; (±)-**18**, 85762-38-5; (±)-**19**, 77713-67-8; (±)-**20**, 77713-69-0; (±)-**21**, 85762-39-6; (±)-**22**, 77713-68-9; (±)-**23**, 85762-40-9; (±)-**24**, 85762-41-0; (±)-**25**, 85762-42-1; (±)-**26**, 85762-43-2; (±)-**27**, 85762-44-3; (±-**28**, 85762-45-4; (±)-**29**, 85762-46-5; (±)-**30**, 85762-47-6; (±)-**31**, 85762-48-7; (±)-**32**, 77713-85-0; (±)-**33**, 77713-86-1; (±)-**34**, 85762-49-8; (±)-**35**·HCl, 85762-50-1; (±)-**36**, 85762-51-2; (±)-**37**, 85762-52-3; (±)-**38**, 85762-53-4; (±)-**39**, 85762-54-5; (±)-**40**, 85762-55-6; (±)-**41**, 85762-56-7; (±)-**42**, 85762-57-8; (±)-**43**, 77713-59-8; (±)-**44**, 77713-60-1; (±)-**45**, 85762-58-9; (±)-**46**, 85762-59-0; (±)-**47**, 85762-60-3; **48**, 85762-61-4; **49**, 85762-62-5; 2,6-dimethyl-4-oxo-4*H*-pyrido[1,2-*a*]pyridine-3-carboxamide, 85762-63-6; 2-ethyl-6-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyridine-3-carboxamide, 85762-64-7; ethyl (±)-9-formyl-6-methyl-4-oxo-1,6,7,8-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate, 85762-65-8; ethyl 6,9-dimethyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate, 85762-66-9; hydrazine, 302-01-2; methylhydrazide, 60-34-4; 2-pyridylhydrazine, 4930-98-7; phenylhydrazine, 100-63-0; 1-naphthyldiazonium, 15511-25-8; 2-naphthyldiazonium, 36097-38-8; 3-pyridyldiazonium, 35332-74-2; 1,5-dimethyl-2-phenyl-4-diazonio-1*H*-pyrazol-3-one, 14051-47-9; 5-aminotetrazole, 4418-61-5; PhN_2^+, 2684-02-8; $2\text{-}HO_2CC_6H_4N_2^+$, 17333-86-7; $2,3\text{-}Me_2C_6H_3N_2^+$, 45751-65-3; $3,4\text{-}Me_2C_6H_3N_2^+$, 45804-40-8; $3,5\text{-}Me_2C_6H_3N_2^+$, 45798-36-5; $2,6\text{-}Me_2C_6H_3N^{2+}$, 45739-17-1; $2,4,6\text{-}Me_3C_6H_2N_2^+$, 45860-24-0; $2,4,5\text{-}Me_3C_6H_2N_2^+$, 85762-67-0; $2,4\text{-}Cl_2C_6H_3N_2^+$, 27165-13-5; $3,4\text{-}Cl_2C_6H_3N_2^+$, 30930-66-6; $3,5\text{-}Cl_2C_6H_3N_2^+$, 40529-17-7; $2,6\text{-}Cl_2C_6H_3N_2^+$, 45739-20-6; $2\text{-Cl-}4\text{-}BrC_6H_3N_2^+$, 60811-26-9; $2\text{-Cl-}6\text{-}MeC_6H_3N_2^+$, 85070-45-7; $4\text{-Br-}3\text{-}MeC_6H_3N_2^+$, 85762-68-1; $5\text{-Cl-}2\text{-}HOC_6H_3N_2^+$, 45762-72-9; $3,5\text{-}(MeO)_2C_6H_3N_2^+$, 72470-94-1; $2,4\text{-}(MeO)_2\text{-}5\text{-}ClC_6H_2N^{2+}$, 57432-47-0; $3,4\text{-}(OCH_2O)C_6H_3N_2^+$, 45891-56-3; $3,5\text{-}(NO_2)_2C_6H_3N_2^+$, 46331-60-6; $3,5\text{-}(CF_3)_2C_6H_3N_2^+$, 29684-26-2.

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