Notes

Synthesis and Antiallergy Activity of 10-Oxo-10*H*-pyrido[1,2-*a*]thieno[3,2-*d*]pyrimidines and 10-Oxo-10*H*-pyrido[1,2-*a*]thieno[3,4-*d*]pyrimidines

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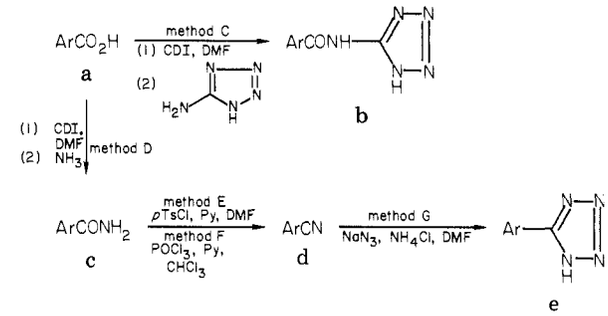
Synthesis and antiallergy activity of 10-oxo-10*H*-pyrido[1,2-*a*]thieno[3,2-*d*]pyrimidines (**2** and **3**) and 10-oxo-10*H*-pyrido[1,2-*a*]thieno[3,4-*d*]pyrimidines (**4** and **5**) are described. The activity, shown by these compounds in the rat passive cutaneous anaphylaxis (PCA) test, is compared to the PCA data previously reported for a series of 4-oxo-4*H*-pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidines. 10-Oxo-*N*-1*H*-tetrazol-5-yl-10*H*-pyrido[1,2-*a*]thieno[3,4-*d*]pyrimidine (**2b**), 10-oxo-7-(1*H*-tetrazol-5-yl)-10*H*-pyrido[1,2-*a*]thieno[3,4-*d*]pyrimidine (**4e**), and 3,10-dihydro-10-oxo-7-(1*H*-tetrazol-5-yl)-1*H*-pyrido[1,2-*a*]thieno[3,4-*d*]pyrimidine (**7e**) gave a 100% inhibition in the rat PCA test at a dose of 5 mg/kg. The activity displayed by these compounds is comparable to that of the most active compounds in the 4-oxo-4*H*-pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidine series.

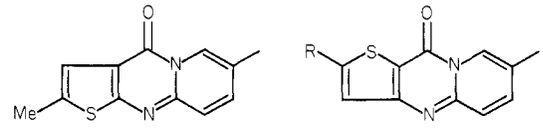
Since the introduction of disodium cromoglycate[1,2] into clinical practice there has been a continuing search for antiallergy drugs, which inhibit the antigen-induced release of the mediators of allergic reactions. A wide variety of compounds[3-6] have been tested and have shown activity in the rat passive cutaneous anaphylaxis (PCA) model. Recent additions to the growing list of PCA active compounds include a series of substituted pyrido[2,1-*b*]-quinazolinecarboxylic acids.[7,8] We previously described[9] the synthesis and antiallergic activity of a series of 4-oxo-4*H*-pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidines (**1**), which may be regarded as sulfur isosteres of the pyrido-quinazoline series. Due to the potent antiallergic activity displayed by these compounds, it was of interest to synthesize and test the isomeric 10-oxo-10*H*-pyrido[1,2-*a*]-thieno[3,2-*d*]pyrimidines (**2** and **3**) and 10-oxo-10*H*-pyrido[1,2-*a*]thieno[3,4-*d*]pyrimidines (**4** and **5**). The corresponding dihydro derivatives, 3,10-dihydro-10-oxo-1*H*-pyrido[1,2-*a*]thieno[3,2-*d*]pyrimidines (**6**) and 3,10-dihydro-10-oxo-1*H*-pyrido[1,2-*a*]thieno[3,4-*d*]pyrimidines (**7**), were also prepared. In this paper we compare the antiallergic activity of the 3 isomeric series of pyrido-thienopyrimidines.

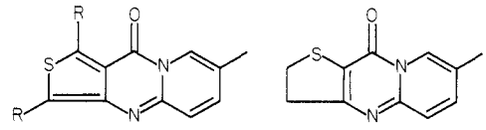
The compounds were synthesized by the routes shown in Scheme I from acids **2a–7a**. The synthesis of acids **2a**, **4a**, **6a**, and **7a** has been described.[10] The synthesis of acids **3a** and **5a** and carboxamides **3c** and **5c** is shown in Scheme

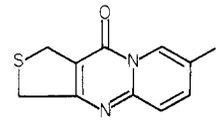
Scheme I[a]



[a]Ar is:







II. Fusion of 8[11] with either 6-chloro-3-pyridinecarboxylic acid or 6-chloro-3-pyridinecarboxamide gave **3a** and **3c**, respectively. In a similar fashion, fusion of 9[12] with either

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Table I. Inhibition of Rat PCA by Pyrido[1,2-*a*]thieno[3,2-*d*]pyrimidines and Pyrido[1,2-*a*]thieno[3,4-*d*]pyrimidines

compd	formula	anal.[a]	method	yield, %	mp, °C	recrystn solvent	rat PCA test: % inhibn at 5 mg/kg, ip, dose
1a							100[b]
1b							25[b]
1e							100[b]
2a[c]	$C_{11}H_6N_2O_3S$				335 dec		28
2b	$C_{12}H_7N_7O_2S \cdot {}^1/_5DMF$	C, H, N	C	47	295-296	DMF	100
2c	$C_{11}H_7N_3O_2S$	C, H, N	D	48	319-320	DMF	NT[d]
2d	$C_{11}H_5N_3OS$	C, H, N	E	62	263-264	DMF	NT
2e	$C_{11}H_6N_6OS$	C, H, N	G	55	300 dec	DMF	70
3a	$C_{12}H_8N_2O_3S$	C, H, N	A	33	338-340	MeOH[e]	61
3b	$C_{13}H_9N_7O_2S$	C, H, N	C	36	342-344	pyridine	21
3c	$C_{12}H_9N_3O_2S$	C, H, N	B	15	375-377	pyridine	NT
3d	$C_{12}H_7N_3OS$	C, H, N	F	89	258-259	MeOH	NT
3e	$C_{12}H_8N_6OS$	C, H, N	G	80	321-325	pyridine	51
4a[c]	$C_{11}H_6N_2O_3S$				320 dec		41
4b	$C_{12}H_7N_7O_2S \cdot {}^1/_5DMF$	C, H; N[f]	C	52	280 dec	DMF	49
4c	$C_{11}H_7N_3O_2S$	C, H, N	D	88	340 dec	TMF	NT
4d	$C_{11}H_5N_3OS$	C, H, N	E	71	233-234	2-PrOH	NT
4e	$C_{11}H_6N_6OS$	C, N; H[g]	G	24	300 dec		100
5a	$C_{13}H_{10}N_2O_3S$	C, H, N	A	7	336 dec	MeOH[e]	70
5b	$C_{14}H_{11}N_7O_2S$	C, H; N[h]	C	63	300 dec	pyridine	50
5c	$C_{13}H_{11}N_3O_2S$	C, H, N	B	3	272-275	MeOH	NT
5d	$C_{13}H_9N_3OS$	C, H, N	F	54	242-244	MeOH	NT
5e	$C_{13}H_{10}N_6OS$	C, H, N	G	60	292 dec	pyridine	47
6a[c]	$C_{11}H_8N_2O_3S$				325 dec		46
6c	$C_{11}H_9N_3O_2S$	C, H, N	D	67	334 dec		NT
6d	$C_{11}H_7N_3OS$	C, H, N	E	70	261-263	MeOH	NT
6e	$C_{11}H_8N_6OS$	C, H, N	G	66	297 dec	DMF	N[i]
7a[c]	$C_{11}H_8N_2O_3S$				311-312	DMF	N[i]
7b	$C_{12}H_9N_7O_2S$	C, H, N	C	74	290	DMF	33
7c	$C_{11}H_9N_3OS$	C, H, N	D	66	285	DMF	NT
7d	$C_{11}H_7N_3OS$	H, N; C[j]	E	59	256-257	MeOH	NT
7e	$C_{11}H_8N_6OS \cdot {}^1/_6DMF$	C, H, N	G	80	285	MeOH/DMF	100
SC[k]							89[l]

[a] Analyses shown are correct to ±0.4% unless otherwise noted. [b] See ref 9. [c] See ref 10. [d] NT signifies an intermediate not tested in the PCA test. [e] Insoluble compounds were washed with methanol to obtain an analytical sample. [f] N: calcd, 30.75; found, 30.28. [g] H: calcd, 2.24; found, 2.78. [h] N: calcd, 28.23; found, 27.80. [i] N signifies compounds were inactive at test dose. [j] C: calcd, 57.63; found, 57.09. [k] SC = sodium cromoglycate. [l] Tested at 10 mg/kg, ip; see ref 13.

6-chloro-3-pyridinecarboxylic acid or 6-chloro-3-pyridinecarboxamide gave **5a** and **5c**, respectively. Table I lists the compounds prepared by these methods and their activity in the rat PCA model.

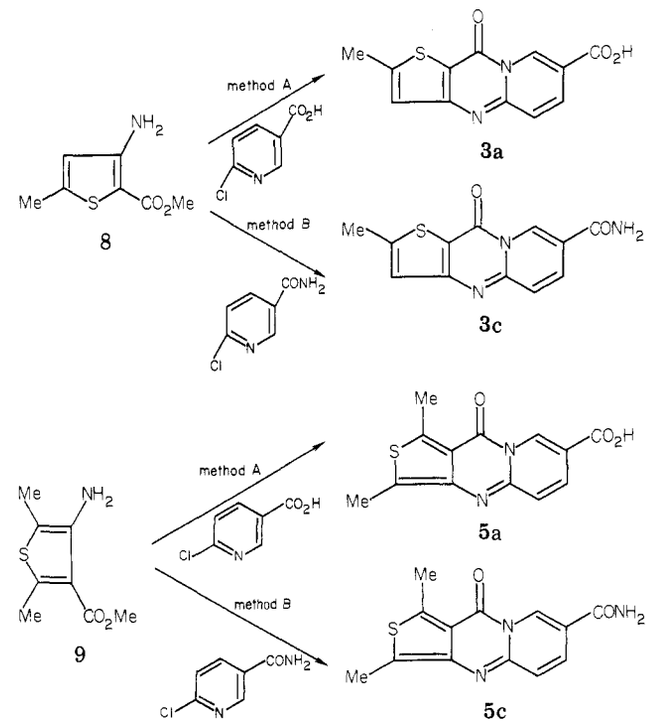
The acids **2a–7a** were all less active than acid **1a**. Methyl-substituted acid **3a** showed a 61% inhibition at a dose of 5 mg/kg compared to a 100% inhibition for **1a** at the same dose. The tetrazoles **2e**, **4e**, and **7e** were substantially more active than the corresponding carboxylic acids **2a**, **4a**, and **7a**, and, in particular, tetrazoles **4e** and **7e** showed good activity. The acids **3a**, **5a**, and **6a** were more active than the corresponding tetrazoles **3e**, **5e**, and **6e**. Thus, in these series, whether the carboxylic acid or tetrazole is the preferred compound depends on that particular isomer. Amidotetrazole **2b** was more active than **1b**, whereas methyl-substituted amidotetrazole **3b** showed weak activity similar to that of **1b**.

Thus, compounds **2b**, **4e**, and **7e** show activity similar to that of the most active compounds in the 4-oxo-4*H*-pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidine series.

Experimental Section

Melting points were measured with a Thomas-Hoover capillary melting point apparatus without correction. NMR spectra were recorded on a Varian EM 390 instrument at 90 MHz with Me_4Si as internal standard. Infrared spectra were recorded on a Beckman IR-9 or IR-7 prism grating instrument with a Digital FTS-14 interferometer. Ultraviolet spectra were recorded on a Cary Model 118 spectrophotometer.

Scheme II



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Rat Reaginic Passive Cutaneous Anaphylaxis (PCA). The PCA test[14] involved immunization of rats with 1 mg of ovalbumin intramuscularly and approximately 10^{10} *Bordetella pertussis* organisms, as pertussis vaccine (Parke, Davis & Co.), intraperitoneally. Fourteen days later, the rats were bled, and the serum was prepared. Suitable dilutions of antiserum were injected intradermally at various sites on the back of rats 48 h before an intravenous injection of 1 mg of ovalbumin in 1 mL of physiological saline and 0.25% Evans blue. Thirty minutes later, the animals were killed in ether, the dorsal skin was reflected, and the mean orthogonal diameter of the anaphylactic wheal was measured. For intraperitoneal dosing, the drugs were suspended in 1% gum tragacanth in physiological saline and given 10–15 min before intravenous antigen challenge. Groups of five animals were used for all dose levels and control groups.

To quantitate the PCA test, we graphed the mean diameter of the wheal at each dilution of antiserum in the control group as a function of the relative antiserum concentration. The line, fitted by the least-squares equation, was extrapolated to the value at "zero" antiserum concentration (base value). The following equation was then used to calculate the percent inhibition:

$$\% \text{ inhibn} = 1 - \left(\frac{\text{diameter of drug} - \text{base value}}{\text{diameter of control} - \text{base value}} \right) \times 100$$

at the highest concentration of antiserum used.

The statistical significance of the results was determined by Student's t test ($p \leq 0.05$). Usually an inhibition of 12 to 15% was found to be significant.

Method A. 2-Methyl-10-oxo-10*H*-pyrido[1,2-*a*]thieno-[3,2-*d*]pyrimidine-7-carboxylic Acid (3a). A mixture of methyl 3-amino-5-methyl-2-thiophenecarboxylate (8;[11] 1 g, 0.0058 mol) and 6-chloro-3-pyridinecarboxylic acid (0.914 g, 0.0058 mol) was heated in an oil bath at 180 °C for 2 h. The mixture was cooled, dissolved in hot methanol, and cooled to give **3a** (0.5 g).

Method B. 2-Methyl-10-oxo-10*H*-pyrido[1,2-*a*]thieno-[3,2-*d*]pyrimidine-7-carboxamide (3c). A mixture of 8 (2.7 g, 0.0158 mol) and 6-chloro-3-pyridinecarboxamide (2.5 g, 0.0158 mol) was heated at 180–190 °C for 1 h. The mixture was cooled, suspended in hot $CHCl_3$, and filtered to give **3c** (0.6 g).

Method C. 10-Oxo-*N*-1*H*-tetrazol-5-yl-10*H*-pyrido[1,2-*a*]thieno[3,2-*d*]pyrimidine-7-carboxamide (2b). A mixture of 10-oxo-10*H*-pyrido[1,2-*a*]thieno[3,2-*d*]pyrimidine-7-carboxylic acid (1.0 g, 0.0041 mol) and 1,1′-carbonyldiimidazole (1.35 g, 0.0082 mol) in dimethylformamide (10 mL) was heated at 90–100 °C with stirring under nitrogen for 1.5 h. 5-Aminotetrazole hydrate (0.42 g, 0.0041 mol) was added, and the resulting mixture was heated at 100 °C for 1–5 h. The precipitate was filtered off, washed with tetrahydrofuran, and recrystallized from dimethylformamide to give **2b** (0.6 g): ^{1}H NMR (trifluoroacetic acid) δ 10.21 (d, 1, Ar H), 9.03 (dd, 1, Ar H), 8.50 (d, 1, Ar H), 8.27 (d, 1, Ar H), 7.60 (d, 1, Ar H); UV (MeOH) λ_{max} 350 nm (ϵ 12 400), 261 (30 500); IR (KBr) ν_{max} 1695, 1595 cm^{-1}.

Method D. 10-Oxo-10*H*-pyrido[1,2-*a*]thieno[3,2-*d*]pyrimidine-7-carboxamide (2c). A mixture of 10-oxo-10*H*-pyrido-[1,2-*a*]thieno[3,2-*d*]pyrimidine-7-carboxylic acid (2.5 g, 0.01 mol) and 1,1′-carbonyldiimidazole (1.7 g, 0.01 mol) in dimethylformamide (25 mL) was heated at 90–95 °C for 1 h under nitrogen. The solution was cooled in an ice bath, and anhydrous ammonia was bubbled through for 15 min. The resulting mixture was stirred at ice-bath temperature for 2 h and at room temperature for 1 h. The reaction mixture was cooled, and the precipitate was filtered off. The precipitate was washed with tetrahydrofuran and recrystallized from dimethylformamide to give **2c** (1.2 g).

Method E. 10-Oxo-10*H*-pyrido[1,2-*a*]thieno[3,2-*d*]pyrimidine-7-carbonitrile (2d). A mixture of 10-oxo-10*H*-pyrido-[1,2-*a*]thieno[3,2-*d*]pyrimidine-7-carboxamide (1.4 g, 0.006 mol), *p*-toluenesulfonyl chloride (1.6 g, 0.008 mol), and pyridine (1.4 mL, 0.017 mol) in dimethylformamide (10 mL) was heated at 95 °C for 75 min. The mixture was cooled, diluted with water (5 mL), and stirred. The precipitate was filtered, washed with water and then with ethanol, and dried. Recrystallization from dimethylformamide gave **2d** (0.8 g).

Method F. 2-Methyl-10-oxo-10*H*-pyrido[1,2-*a*]thieno-[3,2-*d*]pyrimidine-7-carbonitrile (3d). A mixture of 2-methyl-10-oxo-10*H*-pyrido[1,2-*a*]thieno[3,2-*d*]pyrimidine-7-carboxamide (0.6 g, 0.0023 mol), pyridine (10 mL), phosphorus oxychloride (25 mL), and chloroform (25 mL) was refluxed for 3 h. The solvents were removed under reduced pressure, and the residue was treated with ice–water (100 mL). The precipitate was filtered and recrystallized from methanol to give **3d** (0.5 g).

Method G. 10-Oxo-7-(1*H*-tetrazol-5-yl)-10*H*-pyrido[1,2-*a*]thieno[3,2-*d*]pyrimidine (2e). A mixture of 10-oxo-10*H*-pyrido[1,2-*a*]thieno[3,2-*d*]pyrimidine-7-carbonitrile (0.6 g, 0.0026 mol), sodium azide (0.56 g, 0.0086 mol), and ammonium chloride (0.46 g, 0.0036 mol) in dimethylformamide (75 mL) was heated at 100–105 °C for 18 h under nitrogen. The reaction mixture was cooled, poured into ice–water (700 mL), and acidified with concentrated hydrochloric acid (1 mL). The precipitate was filtered, washed with water and then with acetone, and dried. Recrystallization from dimethylformamide gave **2e** (0.39 g): ^{1}H NMR (trifluoroacetic acid) δ 10.18 (dd, 1, Ar H), 9.13 (dd, 1, Ar H), 8.48 (d, 1, Ar H), 8.28 (d, 1, Ar H), 7.56 (d, 1, Ar H); UV (MeOH) λ_{max} 373 nm (ϵ 13 800), 355 (8400), 257 (37 000); IR (KBr) ν_{max} 1695, 1645 cm^{-1}.

10-Oxo-7-(1*H*-tetrazol-5-yl)-10*H*-pyrido[1,2-*a*]thieno[3,4-*d*]pyrimidine (4e): ^{1}H NMR (trifluoroacetic acid) δ 9.14 (d, 1, Ar H), 8.73 (d, 1, Ar H), 7.9–7.7 (m, 2, Ar H), 7.25 (d, 1 Ar H); UV (MeOH) λ_{max} 400 nm (ϵ 3140), 349 (6480), 333 9550), 317 (9700), 268 (36 000), 226 (17 900); IR (KBr) ν_{max} 1715, 1660 cm^{-1}.

3,10-Dihydro-10-oxo-7-(1*H*-tetrazol-5-yl)-1*H*-pyrido[1,2-*a*]thieno[3,4-*d*]pyrimidine (7e): ^{1}H NMR (trifluoroacetic acid) δ 10.20 (d, 1, Ar H), 9.29 (dd, 1, Ar H), 8.40 (d, 1, Ar H), 4.8–4.3 (m, 4, CH_2CH_2); UV (MeOH) ν_{max} 346 nm (ϵ 12 100), 239 (23 600); IR (KBr) ν_{max} 1640 cm^{-1}.

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Registry No. **2a**, 76575-93-4; **2b**, 76575-95-6; **2c**, 76575-96-7; **2d**, 76575-97-8; **2e**, 76575-98-9; **3a**, 76575-70-7; **3b**, 76575-75-2; **3c**, 76575-72-9; **3d**, 76575-73-0; **3e**, 76575-74-1; **4a**, 76575-87-6; **4b**, 76575-88-7; **4c**, 76575-89-8; **4d**, 76575-90-1; **4e**, 76602-34-1; **5a**, 76575-76-3; **5b**, 76575-82-1; **5c**, 76575-79-6; **5d**, 76575-80-9; **5e**, 76575-81-0; **6a**, 76575-94-5; **6c**, 76576-08-4; **6d**, 76576-09-5; **6e**, 76576-10-8; **7a**, 76575-86-5; **7b**, 76576-04-0; **7c**, 76576-05-1; **7d**, 76576-06-2; **7e**, 76576-07-3; **8**, 76575-71-8; **9**, 76575-77-4; 6-chloronicotinic acid, 5326-23-8; 6-chloronicotinamide, 6271-78-9; 5-aminotetrazole, 4418-61-5; sodium azide, 26628-22-8.