mol) in THF. Addition of H_2O (500 mL) to the reaction gave **15a**, mp 233 °C (toluene). Anal. ($C_{17}H_{17}BrO_4$) H; C: calcd, 55.90; found, 56.75.

4,5-Dimethyl-6-oxo-7-propyl-6*H*-indeno[5,4-*b*]furan-2-carboxylic Acid (16a). A solution of **15a** (1.2 g, 0.0033 mol) and DBN (0.8 mL) in Me_2SO (8 mL) was stirred at 25 °C for 1 h and then treated with H_2O (30 mL), HCl (5 mL), and EtOH (20 mL) to give **16a** as a red solid: mp 242 °C (CH_3NO_2); ^1H NMR (Me_2SO) δ 0.90 (t, 3, propyl C_3 H), 1.30–1.70 (m, 2, propyl C_2 H), 2.20 (s, 3, C_4 CH_3), 2.30 (s, 3, C_5 CH_3), 2.0–2.7 (m, 2, propyl C_1 H), 7.30 (s, 1, C_8 H), 7.68 (s, 1, C_1 H). Anal. ($C_{17}H_{16}O_4$) C, H.

4,5-Dimethyl-6-oxo-7-propylidene-7,8-dihydro-6*H*-indeno[5,4-*b*]furan-2-carboxylic Acid (17a). A stirred solution of **15a** (0.8 g, 0.0022 mol) and anhydrous LiBr (0.49 g, 0.0056 mol) in DMF (10 mL) was heated at 95 °C under N_2 for 1 h and then poured into H_2O (100 mL) to give **17a**: mp 301 °C (EtOH); ^1H NMR (Me_2SO) δ 1.12 (t, 3, propylidene C_3 H), 2.35 (s, 3, C_4 CH_3), 2.50 (s, 3, C_5 CH_3), 2.70–3.40 (m, 2, propylidene C_2 H), 3.65 (s, 2, C_8 H), 6.70 (t, 1, propylidene C_1 H), 7.75 (s, 1, C_1 H).

4,5-Dimethyl-6-oxo-7-bromo-7-propyl-1,2,7,8-tetrahydro-6*H*-indeno[5,4-*b*]furan-2-carboxylic Acid (15b). A stirred suspension of **14** (1.4 g, 0.005 mol) in AcOH (15 mL) was treated with Br_2 (0.8 g, 0.005 mol) in AcOH (5 mL) over a 3-min period, poured into H_2O (100 mL) containing $NaHSO_3$ (1 g), extracted with Et_2O, washed with H_2O, and dried ($MgSO_4$), and the Et_2O was evaporated to give **15b** as a white solid, mp 78 °C.

4,5-Dimethyl-6-oxo-7-propyl-1,2-dihydro-6*H*-indeno[5,4-*b*]furan-2-carboxylic Acid (16b). A solution of **15b** (0.7 g, 0.0019 mol) and DBN (0.5 mL) in Me_2SO (5 mL) was stirred at 25 °C for 1.5 h, poured into H_2O, acidified with HCl, extracted into Et_2O, washed with H_2O, and dried ($MgSO_4$), and the Et_2O was evaporated to give **16b**: mp 212 °C (CH_3NO_2); ^1H NMR (Me_2SO-d_6) δ 0.85 (t, 3, propyl C_3 H), 1.20–1.80 (m, 2, propyl C_2 H), 2.00 (s, 3, C_4 CH_3), 2.06 (s, 3, C_5 CH_3), 3.20–3.60 (m, 4, C_1 H and propyl C_1 H), 5.25 (m, 1, C_2 H), 7.48 (s, 1, C_8 H). Anal. ($C_{17}H_{18}O_4$) C, H.

4,5-Dimethyl-6-oxo-7-propylidene-1,2,7,8-tetrahydro-6*H*-indeno[5,4-*b*]furan-2-carboxylic Acid (17b). A stirred solution of **15b** (0.7 g, 0.0019 mol) and LiBr (0.5 g, 0.0057 mol) in DMF (10 mL) was heated at 95 °C under N_2 for 1 h and then poured into H_2O (50 mL) to give **17b**: mp 229 °C (EtOH); ^1H NMR (Me_2SO-d_6) δ 1.02 (t, 3, propylidene C_3 H), 2.00–2.60 (m, 2, propylidene C_2 H), 2.20 (s, 6, $ArCH_3$), 3.40 (s, 2, C_8 H), 3.25–3.80 (m, 2, C_1 H), 5.25 (m, 1, C_2 H), 6.55 (t, 1, propylidene C_1H). Anal. ($C_{17}H_{18}O_4$) C, H.

Acknowledgment. The authors are indebted to Dr. G. M. Fanelli, Jr., and the late Dr. L. S. Watson and their staffs for the biological data, to Dr. W. C. Randall and staff for the elemental analyses, to A. Augenblick for the glass capillary GC studies, and to Dr. R. F. Hirschmann for encouragement during the course of this investigation.

Notes

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

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A series of 4-oxo-4*H*-pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidines with substitutions in the 2, 3, and 7 positions was prepared. The compounds were evaluated in the rat passive cutaneous anaphylaxis test for antiallergy activity. Several compounds had potent oral activity and were found to be superior to disodium cromoglycate and doxantrazole. Structure–activity relationships are discussed.

Allergic reactions and bronchial asthma in particular are thought to be the result of an antigen–antibody combination on the mast cell with subsequent release of the mediators of immediate hypersensitivity which include histamine, leukotrienes, and various kinins.[2] The clinical manifestations of the allergic reaction are elicited by the subsequent interaction of the mediators with the end organ smooth muscle or mucous membranes. Traditionally, symptomatic treatment of allergies and bronchial asthma has been provided by β-sympathomimetic agents, methylxanthines, corticosteroids, and anticholinergics. The introduction of disodium cromoglycate (DSCG) in 1967 provided an agent which inhibited the release of mediators of anaphylaxis from sensitized mast cells and thus provided a prophylactic treatment for allergies and bronchial asthma.[3] The major disadvantages of DSCG are that it is not orally effective and that it must be used as an insufflated powder.

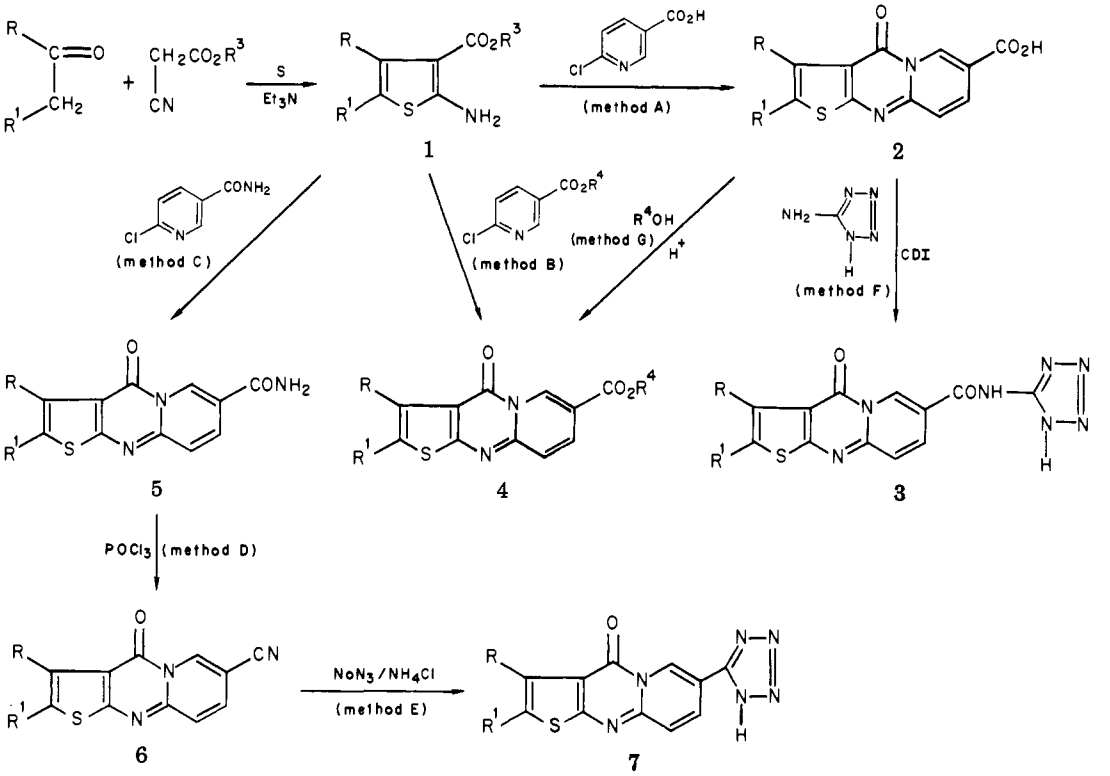
A great deal of research has gone into developing orally active antiallergy agents.[4] Recent papers have described the antiallergy activity of the 3,4-dihydro-4-oxothieno[2,3-*d*]pyrimidine-2-carboxylates[5] and the pyrido[2,1-*b*]quinazolinecarboxylic acids.[6]

In this paper, we describe the synthesis of some novel 4-oxo-4*H*-pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidines which exhibit oral antiallergy activity.

(1) F. J. Tinney, W. A. Cetenko, J. J. Kerbleski, D. T. Connor, R. J. Sorenson, and D. J. Herzig, "Abstracts of Papers", 180th National Meeting of the American Chemical Society, Las Vegas, NV, Aug 24–29, 1980, American Chemical Society, Washington, DC, 1980, Abstr MEDI 60.
(2) A. S. Rebuck, *Drugs*, 7, 344 (1974).
(3) J. S. G. Cox, *Nature (London)*, 216, 1328 (1967).
(4) S. C. Bell and R. J. Capetola, *Annu. Rep. Med. Chem.*, 14, 51 (1979).
(5) D. L. Temple, J. P. Yevich, R. R. Covington, C. A. Hanning, R. J. Seidehamel, H. K. Mackey, and M. J. Bartek, *J. Med. Chem.*, 22, 505 (1979).
(6) J. W. Tilley, R. A. Le Mahieu, M. Carson, R. W. Kierstead, H. W. Baruth, and B. Yaremko, *J. Med. Chem.*, 23, 92 (1980).

0022-2623/81/1824-0878$01.25/0

Scheme I



Chemistry. The 4-oxo-4*H*-pyrido[1,2-*a*]thieno[2,3-*d*]-pyrimidines were prepared according to the routes shown in Schemes I and II.

The starting 2-amino-3-thiophenecarboxylic esters (**1**) were readily obtained by previously described methods.[7,8]

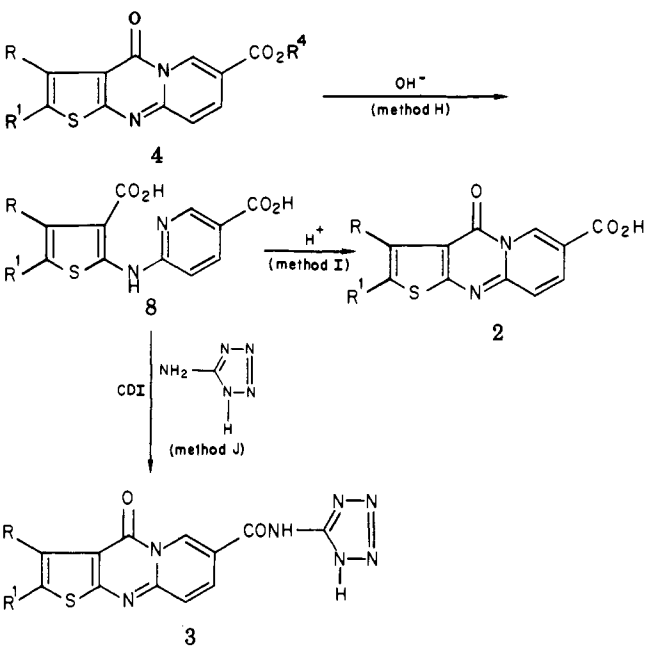
Fusion of **1** with either 6-chloro-3-pyridinecarboxylic acid, methyl 6-chloro-3-pyridinecarboxylate, or 6-chloro-3-pyridinecarboxamide provided the 7-substituted 4-oxo-4*H*-pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidines (**2**, **4**, and **5**; Scheme I).

The 7-(*N*-1*H*-tetrazol-5-ylcarboxamido) compounds (**3**) were obtained by coupling the 7-carboxy derivatives (**2**) with 5-aminotetrazole in the presence of *N*,*N*′-carbonyldiimidazole (CDI).

The 7-(1*H*-tetrazol-5-yl) derivatives (**7**) were obtained by dehydration of **5** to **6** with $POCl_3$ and subsequent conversion of the carbonitrile derivatives (**6**) with NaN_3 and NH_4Cl in DMF to **7**.

An alternate route for preparing **2** and **3** is shown in Scheme II. Treatment of **4** with NaOH in EtOH affords the ring-opened derivative **8**, which can be isolated and subsequently converted to **2** by refluxing in aqueous HCl or converted to **3** by coupling with 5-aminotetrazole in the presence of CDI.

Scheme II



Results and Discussion

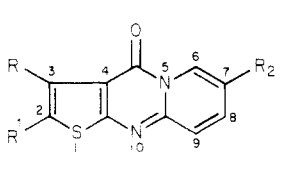
Compounds **2a–g**, **3a–f**, **4a,b,d,e**, **5a,b,d,e**, **6a,b,g**, and **7a–g** were evaluated for antiallergy activity in the rat passive cutaneous anaphylaxis (PCA) test as described under Experimental Section. The results, including those for DSCG and doxantrazole, an orally effective antiallergy agent,[9] are summarized in Table I. The 2, 3, and 7 positions in the pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidines were varied. Generally, incorporation of an acidic functional group (carboxyl or tetrazole) in the 7 position gave compounds with potent activity (**2a–e**, **7a–c**, and **7f**). With the exception of compounds **3b** and **3f**, substitution of the acidic carboxamidotetrazole functionality in the 7 position gave weakly active compounds.

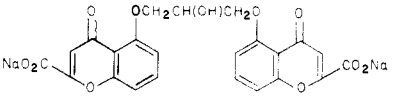
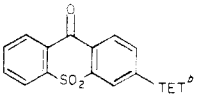
Substitution of lower alkyl groups in the 2 position generally gave optimum activity. Compounds having higher alkyl or aromatic groups in the 2 position or 2,3-disubstituted alkyl derivatives had reduced activity.

Seven compounds, **2a–c**, **4a**, **6a**, **7b**, and **7c**, showed significant oral activity in the PCA test. Compounds **2b** and **7b** are two of the most potent orally active compounds

(7) K. Gewald, *Chem. Ber.*, **98**, 3571 (1965).
(8) K. Gewald, E. Schinke, and H. Bottcher, *Chem. Ber.*, **99**, 94 (1966).
(9) J. F. Batchelor, L. G. Garland, A. F. Green, D. T. D. Hughes, M. J. Follenfant, J. H. Gorvin, H. F. Hodson, and J. E. Tateson, *Lancet*, 1169 (1975).

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



no.	R	R^1	R^2	formula	anal.	method	mp, °C	recrystn solv[a]	rat PCA test: % inhibn 5 mg/kg, ip	rat PCA test: % inhibn 5 mg/kg, po
2a	H	CH_3	CO_2H	$C_{12}H_8N_2O_3S$	C, H, N	A	312–315	M	100	62
7a	H	CH_3	TET[b]	$C_{12}H_8N_6OS$	C, H, N	E	330–340 dec	P	100	N[c]
3a	H	CH_3	CONH-TET[d]	$C_{13}H_9N_7O_2S$	C, H, N	F	306–310 dec		25	N[c]
5a	H	CH_3	$CONH_2$	$C_{12}H_9N_3O_2S$	C, H, N	C	350–354	P	100	38
6a	H	CH_3	CN	$C_{12}H_7N_3OS$	C, H, N	D	256–258	A	88	100
2b	H	C_2H_5	CO_2H	$C_{13}H_{10}N_2O_3S$	C, H, N	A	258–260	A	100[e]	69[f]
4a	H	C_2H_5	CO_2CH_3	$C_{14}H_{12}N_2O_3S$	C, H, N	B	151–152	M	100	75
7b	H	C_2H_5	TET[b]	$C_{13}H_{10}N_6OS$	C, H, N	E	293–295 dec	P	97[g]	38[f]
3b	H	C_2H_5	CONH-TET[d]	$C_{14}H_{11}N_7O_2S$	C, H, N	F	310–312 dec		62	N[c]
5b	H	C_2H_5	$CONH_2$	$C_{13}H_{11}N_3O_2S$	C, H, N	C	278–280	P	46	N[c]
6b	H	C_2H_5	CN	$C_{13}H_9N_3OS$	C, H, N	D	223–224	A	13	N[c]
2c	H	C_3H_7	CO_2H	$C_{14}H_{12}N_2O_3S$	C, H, N	A	250–254	P	68	18[h]
7c	H	C_3H_7	TET[b]	$C_{14}H_{12}N_6OS$	C, H, N	E	288–292 dec	P	100	67
5c	H	C_3H_7	$CONH_2$	$C_{14}H_{13}N_3O_2S$	C, H, N	C	260–264	P		
6c	H	C_3H_7	CN	$C_{14}H_{11}N_3OS$	C, H, N	D	217–218	A		
2d	H	i-C_3H_7	CO_2H	$C_{14}H_{12}N_2O_3S$	C, H, N	A	264–266	E	100	
4b	H	i-C_3H_7	$CO_2C_2H_5$	$C_{16}H_{16}N_2O_3S$	C, H, N	G	122–123	E	63	
7d	H	i-C_3H_7	TET[b]	$C_{14}H_{12}N_6OS$	C, H, N	E	288 dec	P-E	28	
3c	H	i-C_3H_7	CONH-TET[d]	$C_{15}H_{13}N_7O_2S$	C, H; N[i]	F	307 dec	P	30	
5d	H	i-C_3H_7	$CONH_2$	$C_{14}H_{13}N_3O_2S$	H, N; C[j]	C	280–282	D	100	
6d	H	i-C_3H_7	CN	$C_{14}H_{11}N_3OS$	C, H, N	D	225–226	P		
2e	H	C_4H_9	CO_2H	$C_{15}H_{14}N_2O_3S$	C, H, N	A; I	252–254	E	52	
4c	H	C_4H_9	CO_2CH_3	$C_{16}H_{16}N_2O_3S$	H, N; C[k]	B	137–138	M		
7e	H	C_4H_9	TET[b]	$C_{15}H_{14}N_6OS$	C, H, N	E	281 dec	D-M	26	
3d	H	C_4H_9	CONH-TET[d]	$C_{16}H_{15}N_7O_2S$	C, H, N	F; J	293 dec	P	18	
5e	H	C_4H_9	$CONH_2$	$C_{15}H_{15}N_3O_2S$	C, H, N	C	266–267	A	25	N[c]
6e	H	C_4H_9	CN	$C_{15}H_{13}N_3OS$	C, H, N	D	216–217	P		
2f	H	C_6H_5	CO_2H	$C_{17}H_{10}N_2O_3S$	C, H, N	A	387–392	P	17	17
7f	H	C_6H_5	TET[b]	$C_{17}H_{10}N_6OS$	C, H, N	E	310–312 dec	P	84	N[c]
3e	H	C_6H_5	CONH-TET[d]	$C_{18}H_{11}N_7O_2S$	C, H, N	F	324–328 dec		17	N[c]
5f	H	C_6H_5	$CONH_2$	$C_{17}H_{11}N_3O_2S \cdot C_2H_4O_2$	C, H, N	C	348–352	A		
6f	H	C_6H_5	CN	$C_{17}H_9N_3OS$	C, H, N	D	349–351	P		
2g	CH_3	CH_3	CO_2H	$C_{13}H_{10}N_2O_3S$	C, H, N	A	364–368	P	28	N[c]
7g	CH_3	CH_3	TET[b]	$C_{13}H_{10}N_6OS \cdot 0.6C_5H_5N$	C, H, N	E	292–294 dec	P	30	21
3f	CH_3	CH_3	CONH-TET[d]	$C_{14}H_{11}N_7O_2S$	C, H, N	F	297–300 dec		94[l]	N[c]
5g	CH_3	CH_3	$CONH_2$	$C_{13}H_{11}N_3O_2S$	C, H, N	C	361–363	P		
6g	CH_3	CH_3	CN	$C_{13}H_9N_3OS$	C, H, N	D	306–307	A	14	
4d	CH_3	H	CO_2CH_3	$C_{13}H_{10}N_2O_3S$	C, H, N	B	208–209	C-M	23	
4e	CH_3	$CO_2C_2H_5$	CO_2CH_3	$C_{16}H_{14}N_2O_5S$	C, H, N	B	210–212	C-M	N[c]	
disodium cromoglycate										*m*
doxantrazole										*n*

[a] M, MeOH; P, pyridine; A, HOAc; E, EtOH; D, DMF; C, CH_2Cl_2. If no solvent is indicated, compound was obtained analytical from reaction. [b] For TET, see structure above col heads. [c] N, no significant activity at this dose level. [d] For CONH-TET, see structure above column heads. [e] When tested iv, 33% inhibition, 0.1 mg/kg. [f] Tested at 0.5 mg/kg. [g] When tested iv, 56% inhibition, 0.1 mg/kg. [h] Tested at 1.0 mg/kg. [i] N: calcd, 27.59; found, 27.01. [j] C: calcd, 58.52; found, 58.05. [k] C: calcd, 60.74; found, 60.24. [l] When tested iv, 18% inhibition, 0.01 mg/kg. [m] Inactive; ID_{50} (dose required to achieve 50% inhibition in PCA test) 1-2 mg/kg, iv. [n] ID_{50}, 5 mg/kg; ID_{50}, 1.5 mg/kg, iv.

reported in this series. They are approximately 10 times more active than doxantrazole. Collectively, the 4-oxo-4*H*-pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidines with substitutions in the 2, 3, and 7 positions present a novel class of potent, orally active antiallergy agents.

Experimental Section

Rat Reaginic Passive Cutaneous Anaphylaxis (PCA). The PCA test[10] 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

(10) D. J. Herzig, P. R. Schumann, E. J. Kusner, L. Robichaud, R. E. Giles, B. Dubnick, M. von Strandtmann, S. Klutchko, M. Cohen, and J. Shavel, Jr., "Immunopharmacology", M. E. Rosenthale and H. C. Mansmann, Eds., Spectrum Publications, New York, 1975, pp 103–124.

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 oral or intraperitoneal dosing, the drugs were suspended in 1% gum tragacanth in physiological saline and given 10–15 min before intravenous antigen challenge. For intravenous dosing, the compounds were dissolved in the saline/ovalbumin/Evans blue solution and given with the antigen. If necessary, the compounds were first dissolved in a slight molar excess of sodium bicarbonate and then diluted into the antigen solution. Groups of five animals were used for all dose levels and control groups.

To quantitate the PCA test, the mean diameter of the wheal at each dilution of antiserum in the control group was graphed 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

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

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.

Chemistry. Melting points were determined in a Thomas-Hoover capillary melting point apparatus or a Mel-Temp apparatus. Infrared (IR) data were recorded on a Beckman IR-9 or IR-7 prism grating instrument on a Digilab FTS-14 interferometer. Nuclear magnetic resonance measurements (NMR) were made on a Bruker WH-90 pulsed Fourier transform instrument. Homogeneity of the products was determined by ascending thin-layer chromatography (TLC) on silica gel coated glass plates using principally the following solvent systems: (1) HOAc–MeCN–toluene, 1:9:10; (2) HOAc–MeOH–$CHCl_3$, 1:2:14; and (3) MeOH–$CHCl_3$, 1:3. The TLC of the compounds described in Table I were homogeneous single spots when visualized with UV and/or I_2 vapors. The IR and NMR spectra of the compounds were compatible with the structures. Microanalysis for C, H, and N gave results within 0.4% of theory unless otherwise indicated.

The starting 2-amino-3-thiophenecarboxylic esters (1) were obtained by the following general method described for the 5-butyl derivative or are reported in the literature.[7,8,11,12]

Methyl 2-Amino-5-butyl-3-thiophenecarboxylate (1a). Et_3N (150 mL, 1.08 mol) was added to a stirred suspension of methyl cyanoacetate (198.18 g, 2 mol) and S (64.12 g, 2 mol) in 250 mL of DMF under a N_2 atmosphere. Hexanal (200.3 g, 2 mol) was added dropwise with stirring to this mixture over 50 min while the temperature was maintained at 50 °C. The solution was allowed to reach room temperature, then stirred for 21 h, and poured into 3 L of H_2O, and the aqueous layer was extracted with 2 L of Et_2O (2×). The Et_2O layer was separated and washed successively with 2 L of H_2O (2×) and 2 L of saturated NaCl solution (2×), dried over anhydrous Na_2SO_4 and evaporated: yield 187 g (44%) of **1a**, mp 62–63 °C, after recrystallization from hexane. Anal. ($C_{10}H_{15}NO_2S$) C, H, N.

Following the previous procedure, **2-ethyl 4-methyl 5-amino-3-methyl-2,4-thiophenedicarboxylate (1b)** was obtained, mp 110–111 °C. Anal. ($C_{10}H_{13}NO_4S$) C, H, N. **Ethyl 2-amino-5-propyl-3-thiophenecarboxylate** was obtained in a similar manner but was not purified.

Representative general procedures for preparation of the compounds in Table I are listed as methods A to J. The reported yields for the products obtained were not maximized.

Method A. 2-Ethyl-4-oxo-4*H*-pyrido[1,2-*a*]thieno[2,3-*d*]-pyrimidine-7-carboxylic Acid (2b). A mixture of methyl 2-amino-5-ethyl-3-thiophenecarboxylate[12] (55.5 g, 0.3 mol) and 6-chloro-3-pyridinecarboxylic acid (47.1 g, 0.3 mol) was heated in an oil bath at 165 °C for 4.5 h under N_2. The mixture was cooled and extracted with hot $CHCl_3$, the residue was dissolved in hot pyridine and cooled, and the precipitate was recrystallized from HOAc to give 12 g (15%) of **2b**: mp 258–260 °C. Anal. ($C_{13}H_{10}N_2O_3S$) C, H, N.

Method B. Methyl 2-Ethyl-4-oxo-4*H*-pyrido[1,2-*a*]-thieno[2,3-*d*]pyrimidine-7-carboxylate (4a). A mixture of ethyl 2-amino-5-ethyl-3-thiophenecarboxylate[8] (10 g, 0.05 mol) and methyl 6-chloro-3-pyridinecarboxylate (8.61 g, 0.05 mol) was heated in a wax bath at 178–188 °C for 3 h under N_2. The distillate was collected in a Dean–Stark trap attached to the reaction flask. The mixture was cooled, dissolved in hot MeOH, cooled, and 5.5 g (38%) of **4a** was obtained after recrystallization from MeOH, mp 151–152 °C. Anal. ($C_{14}H_{12}N_2O_3S$) C, H, N.

Method C. 2-(1-Methylethyl)-4-oxo-4*H*-pyrido[1,2-*a*]-thieno[2,3-*d*]pyrimidine-7-carboxamide (5d). A mixture of 6-chloro-3-pyridinecarboxamide (24.0 g, 0.154 mol) and ethyl 2-amino-5-(1-methylethyl)-3-thiophenecarboxylate[11] (32.8 g, 0.154 mol) was heated in a wax bath at 178–182 °C for 3 h and 25 min and then at 180–196 °C for 65 min under N_2. The mixture was cooled, suspended in hot MeOH, and filtered to yield 8.9 g (20%) of **5d** after recrystallization from DMF: mp 280–282 °C; IR (KBr) 3390, 3190, 1685 cm^{-1}; NMR (Me_2SO-d_6) δ 1.35 (d, 6 H), 3.25 (m, 1 H), 7.25 (s, 1 H), 7.60 (d, 1 H), 8.20 (dd, 1 H), 9.45 (d, 1 H), 7.70, 8.40 (amide, 2 H). Anal. ($C_{14}H_{13}N_3O_2S$) C, H, N.

Method D. 2-(1-Methylethyl)-4-oxo-4*H*-pyrido[1,2-*a*]-thieno[2,3-*d*]pyrimidine-7-carbonitrile (6d). Compound **5d** (8.7 g, 0.03 mol) in 250 mL of $POCl_3$ and 250 mL of $CHCl_3$ was refluxed on a steam bath for 4 h under N_2. The $CHCl_3$ and excess $POCl_3$ were evaporated in vacuo, and the residue was treated with 2 L of ice–H_2O. The resulting precipitate was filtered to yield 5.3 g (65%) of **6d** after recrystallization from pyridine: mp 225–226 °C; IR (KBr) 2240, 1700, 1635, 1550, 1520 cm^{-1}; NMR (Me_2SO-d_6) δ 1.35 (d, 6 H), 3.30 (m, 1 H), 7.30 (s, 1 H), 7.65 (d, 1 H), 7.95 (dd, 1 H), 9.45 (d, 1 H). Anal. ($C_{14}H_{11}N_3OS$) C, H, N.

Method E. 2-(1-Methylethyl)-7-(1*H*-tetrazol-5-yl)-4*H*-pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidin-4-one (7d). A mixture of **6d** (5.1 g, 0.019 mol), NaN_3 (6.5 g, 0.1 mol), and NH_4Cl (5.35 g, 0.1 mol) in 150 mL of DMF was stirred and heated at 124 °C for 22 h under N_2. The reaction mixture was cooled and filtered, and the filtrate was evaporated. The residue was treated with 1 L of H_2O and acidified with concentrated HCl. The resulting precipitate was collected and suspended in hot H_2O, and the suspension was cooled and filtered to yield 3.3 g (56%) of **7d** after recrystallization from pyridine–EtOH, mp 288 °C dec. Anal. ($C_{14}H_{12}N_6OS$) C, H, N.

Method F. 2-(1-Methylethyl)-4-oxo-*N*-1*H*-tetrazol-5-yl-4*H*-pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidine-7-carboxamide (3c). A mixture of **2d** (2.88 g, 0.01 mol) and CDI (3.31 g, 0.02 mol) in 100 mL of DMF was stirred and heated in a wax bath at 105 °C for 90 min under N_2. The mixture was cooled and stirred at room temperature for 30 min, 5-aminotetrazole monohydrate (1.03 g, 0.01 mol) was added, and the resulting mixture was stirred and heated at 105 °C for 2 h and 15 min under N_2. The mixture was allowed to stand overnight at room temperature, the precipitate was filtered, and the filtrate was evaporated in vacuo. The residue was stirred in boiling MeOH, and the mixture was cooled and filtered. The precipitate was combined with the previous precipitate to yield 1.8 g (51%) of **3c** after recrystallization from pyridine: mp 307 °C dec; IR (KBr) 3070, 3195 (3000–3500), 1695, 1543 cm^{-1}; NMR (Me_2SO-d_6) δ 1.35 (d, 6 H), 3.20 (m, 1 H), 7.25 (s, 1 H), 7.60 (d, 1 H), 8.25 (dd, 1 H), 9.75 (d, 1 H), 15.0 (br, 2 H). Anal. ($C_{15}H_{13}N_7O_2S$) C, H, N.

Method G. Ethyl 2-(1-Methylethyl)-4-oxo-4*H*-pyrido-[1,2-*a*]thieno[2,3-*d*]pyrimidine-7-carboxylate (4b). A cooled suspension of **2d** (1.4 g, 0.0049 mol) in 150 mL of EtOH was saturated with HCl. The mixture was stirred and refluxed in a wax bath at 128 °C for 18 h under N_2. The EtOH was evaporated in vacuo to yield 0.43 g (28%) of **4b** after recrystallization from EtOH, mp 122–123 °C. Anal. ($C_{16}H_{16}N_2O_3S$) C, H, N.

Method H. 6-[(5-Butyl-3-carboxy-2-thienyl)amino]-3-pyridinecarboxylic Acid (8). A mixture of **4c** (0.94 g, 0.003 mol), 35 mL of 1 N NaOH, and 25 mL of EtOH was refluxed for 55 min. The resulting solution was evaporated to dryness, and the residue was dissolved in hot H_2O, filtered, cooled, and acidified

(11) E. B. Pedersen and D. Carlsen, *Tetrahedron*, **33**, 2089 (1977).
(12) K. E. Nielsen and E. B. Pedersen, *Acta Chem. Scand., Ser. B*, **32**, 303 (1978).

with HOAc. The precipitate was separated, washed with H_2O, and dried to yield 0.7 g (73%) of 8 after recrystallization from HOAc, mp 217 °C dec. Anal. ($C_{15}H_{16}N_2O_4S$) C, H, N.

Method I. 2-Butyl-4-oxo-4*H*-pyrido[1,2-*a*]thieno[2,3-*d*]-pyrimidine-7-carboxylic Acid (2e). A mixture of 8 (1.0 g, 0.0031 mol), 25 mL of concentrated HCl, and 25 mL of H_2O was refluxed in a wax bath under a N_2 atmosphere at a bath temperature of 142 °C for 17 h and 45 min. The suspension was cooled to room temperature, and the precipitate was separated, washed with H_2O, and then washed with Et_2O and dried to yield 0.6 g (64%) of 2e after recrystallization from EtOH, mp 252–254 °C. Anal. ($C_{15}H_{14}N_2O_3S$) C, H, N.

Method J. 2-Butyl-4-oxo-*N*-1*H*-tetrazol-5-yl-4*H*-pyrido-[1,2-*a*]thieno[2,3-*d*]pyrimidine-7-carboxamide (3d). A mixture of 8 (3.2 g, 0.01 mol) and CDI (9.93 g, 0.06 mol) in 100 mL of DMF was heated in a wax bath under a N_2 atmosphere with stirring at 100 to 108 °C for 70 min, cooled, and stirred at room temperature for 1 h. To the previous mixture was added 5-aminotetrazole monohydrate (2.06 g, 0.02 mol), and the mixture was heated at 100–108 °C for 90 min. The solvent was evaporated, the residue dissolved in DMF, filtered, and cooled, and the precipitate was collected and washed with MeOH to yield 1.2 g (34%) of **3d** after recrystallization from pyridine, mp 293 °C dec. Anal. ($C_{16}H_{15}N_7O_2S$) C, H, N.

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Synthesis and Serotonin-like Activity of 2-Amino-5,8-dimethoxy-6-methyl-1,2-dihydronaphthalene

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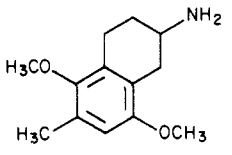
As a new type of rigid analogue for hallucinogenic phenethylamines, 2-amino-5,8-dimethoxy-6-methyl-1,2-dihydronaphthalene was synthesized. Evaluation in the rat fundus preparation showed it to be a much weaker serotonin agonist than its 1,2,3,4-tetrahydro homologue. Both the dihydro and tetrahydro compounds were able to elicit the serotonin syndrome in rats, but with the dihydro compound also appearing weaker in this assay. Both rigid analogues were less potent than the known hallucinogen 1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM).

Our continuing interest in structure-activity relationships of centrally active phenethylamines has led us to examine several rigid congeners of hallucinogenic 1-phenyl-2-aminopropanes ("amphetamines").

In particular, several years ago the synthesis and pharmacology were reported for the tetrahydronaphthalene congener 1 of the known hallucinogenic agent



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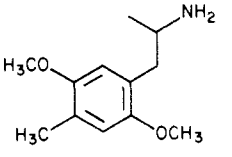

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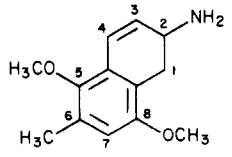

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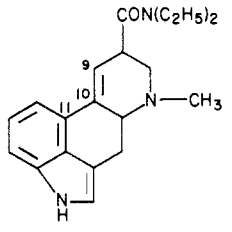

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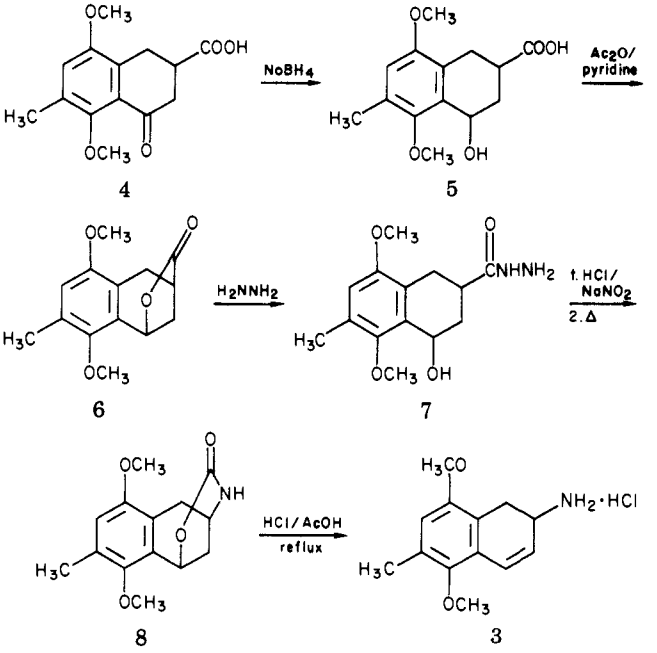
1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM, STP, **2**).[1] Compound 1 was found to be nondisruptive in the conditioned avoidance response in rats and to possess pharmacological effects quite different from hallucinogens such as DOM (**2**). The tetrahydronaphthalene congener 1 also proved to be a weak serotonin agonist in the rat fundus preparation.[1]

Scheme I



Recently, we reported that 2-amino-1,2-dihydronaphthalene possessed amphetamine-like action in mice and rats.[2] This is to be contrasted with the sedative activity of 2-amino-1,2,3,4-tetrahydronaphthalene.[3] This

(1) D. E. Nichols, C. F. Barfknecht, J. P. Long, R. T. Standridge, H. G. Howell, R. A. Partyka, and D. C. Dyer, *J. Med. Chem.*, 17, 161 (1974).

(2) M. B. Nichols, G. K. W. Yim, B. A. Hathaway, and D. E. Nichols, 10th Annual Meeting of the Society for Neuroscience, Cincinnati, OH, Nov 1980, Society for Neuroscience, Bethesda, MD, 1980, Abstr 245.15.

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