13.25 (broad, 1 H, OH); ^{13}C NMR (Me_2SO-d_6) δ 16.9 (q, 6-Me), 19.8 (t, C-8), 23.6 (t, C-7), 46.6 (d, C-6), 109.8 (s, C-3), 131.5 (s, C-9), 156.9 (s, C-9a), 158.4 (d, C-2), 162.3 (s, C-4) and 144.1 (s, C-1′), 114.2 (d, C-2′), 129.3 (d, C-3′), 122.3 (d, C-4′) of Ph: UV (Me_2SO) λ_{max} 416 nm (ε 30650), 294 (5150).

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

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

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

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

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

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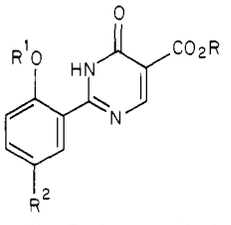
Some 2-(2-alkoxyphenyl)- and 2-[2-(alkenyloxy)phenyl]-5-(1*H*-tetrazol-5-yl)pyrimidin-4(3*H*)-ones were prepared and found to be about 5–10 times more potent than the corresponding pyrimidine-5-carboxylic acids when tested orally against passive cutaneous anaphylaxis in the rat. Structure–activity relationships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

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

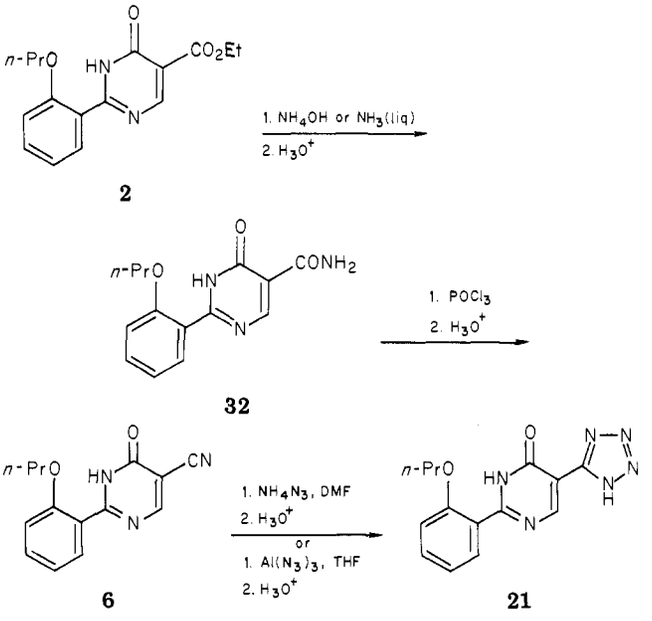


1, R = H, Et; R^1 = C_1–C_5 lower alkyl, allyl; R^2 = MeO, Cl, NH_2, NMe_2

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

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

Scheme I



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

(1) P. F. Juby, T. W. Hudyma, M. Brown, J. M. Essery, and R. A. Partyka, *J. Med Chem.*, **22**, 263 (1979).
(2) P. F. Juby and R. A. Partyka, U.S. Patent 4082751 (1978).

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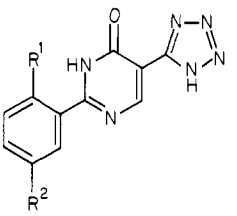
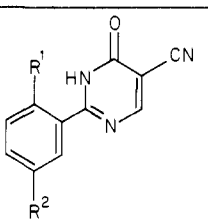
Table I. 2-Phenyl-5-(1*H*-tetrazol-5-yl)pyrimidin-4(3*H*)-ones



no.	R^1	R^2	formula[a]	mp,[b] °C	crystn solvent[c]	method[d]	yield, %	PCA ID_{50},[e] mg/kg iv	PCA ID_{50},[e] mg/kg po
3	H	H	$C_{11}H_8N_6O$	297–299	A	A	67		100
4	MeO	H	$C_{12}H_{10}N_6O_2$	282–283	A	B	36		0.1
5	EtO	H	$C_{13}H_{12}N_6O_2$	289–290	A	A	50	0.02	0.09
6	*n*-PrO	H	$C_{14}H_{14}N_6O_2$	247–248	A or B	A, D	60, 41	0.004	0.04
7	*i*-PrO	H	$C_{14}H_{14}N_6O_2$	275–276	A or B	A, C, D	34, 10, 38	0.02	0.04
8	*n*-BuO	H	$C_{15}H_{16}N_6O_2$	244–247	B	A	46		0.07
9	*i*-BuO	H	$C_{15}H_{16}N_6O_2$	230–231	A	A	55		0.1
10	*s*-BuO	H	$C_{15}H_{16}N_6O_2$	240–242	C	A	49		0.05
11	*n*-$C_5H_{11}O$	H	$C_{16}H_{18}N_6O_2$	236–238	D	D	38		0.4
12	CH_2=$CHCH_2O$	H	$C_{14}H_{12}N_6O_2$	230.5–232	A	B	30		0.24
13	c-$PrCH_2O$	H	$C_{15}H_{14}N_6O_2$	252–254	B	A	63		0.07
14	*n*-PrO	MeO	$C_{15}H_{16}N_6O_3$	257–260	B	A	80		0.03
15	*n*-PrO	NO_2	$C_{14}H_{13}N_7O_4$	251–252	B		61		5
16	*n*-PrO	NH_2	$C_{14}H_{15}N_7O_2$[f]	261–262	B		79		0.1
17	*n*-PrO	NMe_2	$C_{16}H_{19}N_7O_2$	258–259	E		35		0.4
DSCG								0.3	>30

[a] All compounds were analyzed for C, H, and N. All results are within ±0.4% of the theoretical values except where noted. [b] All compounds melted with decomposition. [c] A = AcOH; B = $MeOCH_2CH_2OH$; C = EtOH; D = *i*-PrOH; E = MeCN; F = H_2O; G = MeOH; H = benzene; I = *n*-hexane; J = AcOEt; K = $HCONMe_2$; L = toluene; M = 95% EtOH. [d] See Experimental Section. [e] All data are considered significant at $p \leq 0.05$ as determined by Student's *t* test. [f] N: calcd, 31.30; found, 30.58.

Table II. 1,6-Dihydro-6-oxo-2-phenylpyrimidine-5-carbonitriles



no.	R^1	R^2	formula[a]	mp, °C	crystn solvent[c]	method[d]	yield, %
18	H	H	$C_{11}H_7N_3O$	301–303	A	A	77
19	MeO	H	$C_{12}H_9N_3O_2$	245–246	A	A	54
20	EtO	H	$C_{13}H_{11}N_3O_2$	186–187	A	A	68
21	*n*-PrO	H	$C_{14}H_{13}N_3O_2$	171–172	A	A	61
22	*i*-PrO	H	$C_{14}H_{13}N_3O_2$[g]	174–175	A–F	A, D	35, 79
23	*n*-BuO	H	$C_{15}H_{15}N_3O_2$	171.5–173.5	D	A	28
24	*i*-BuO	H	$C_{15}H_{15}N_3O_2$[h]	186–187	A–F	A	58
25	*s*-BuO	H	$C_{15}H_{15}N_3O_2$	152–158	G	A	19
26	CH_2=$CHCH_2O$	H	$C_{14}H_{11}N_3O_2$	162–164	H–I	B	69
27	c-$PrCH_2O$	H	$C_{15}H_{13}N_3O_2$	187–189	J	C	60
28	*n*-PrO	MeO	$C_{15}H_{15}N_3O_3$	192–194	D	A	83

[a,c,d] See corresponding footnotes to Table I. [g] C: calcd, 65.87; found, 64.83. [h] C: calcd, 66.90; found, 66.23. N: calcd, 15.61; found, 14.49.

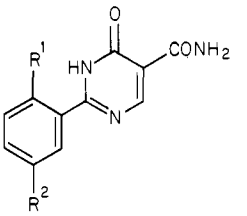
NH_4N_3/DMF or $Al(N_3)_3$/THF for the conversion of the nitriles (Table II) to the tetrazoles was arbitrary in most cases. The less nucleophilic $Al(N_3)_3$/THF complex was used, however, in the preparation of the 2-methoxyphenyl and 2-(allyloxy)phenyl analogues **4** and **12**, respectively, when in both cases it was discovered that the use of NH_4N_3/DMF resulted in extensive dealkylation of the ethers.

Extensive acid-catalyzed dealkylation, as well as dehydration, also occurred in the attempted conversion of the 2-(cyclopropylmethoxy)phenyl amide **38** to the corresponding nitrile **27** when $POCl_3$ was used, followed by the usual aqueous acid workup. This problem was overcome by isolating the intermediate chloropyrimidine **40** and subjecting this to base-catalyzed hydrolysis as outlined in Scheme II.

The nitriles may also be prepared by condensation of ethyl ethoxymethylenecyanoacetate (**42**) with 1 equiv of the appropriate benzamidine in ethanol or DMF, followed by cyclization of the intermediate cyanoacrylate. This route is illustrated with the 2-isopropoxyphenyl compound **22** in Scheme III and is analogous to an earlier synthesis of the unsubstituted phenyl analogue by Nishigaki et al.[3]

(3) S. Nishigaki, K. Senga, K. Aida, T. Takabatake, and F. Yoneda, *Chem. Pharm. Bull.*, 18, 1003 (1970).

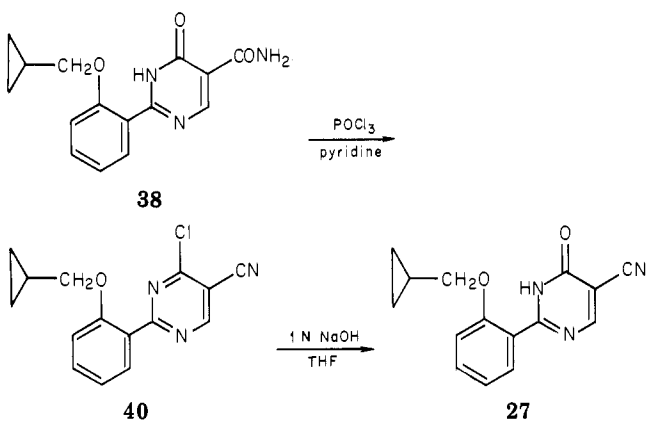
Table III. 1,6-Dihydro-6-oxo-2-phenylpyrimidine-5-carboxamides



no.	R^1	R^2	formula[a]	mp, °C	crystn solvent[c]	method[d]	yield, %
29	H	H	$C_{11}H_9N_3O_2$	297–298[i]	K	A	47
30	MeO	H	$C_{12}H_{11}N_3O_3$	218–219	K	A	72
31	EtO	H	$C_{13}H_{13}N_3O_3$[j]	236–238	K	A	77
32	*n*-PrO	H	$C_{14}H_{15}N_3O_3$	225–226	K	A	75
33	*i*-PrO	H	$C_{14}H_{15}N_3O_3$	200–201	K	A	62
34	*n*-BuO	H	$C_{15}H_{17}N_3O_3$	181–183	E	A	70
35	*i*-BuO	H	$C_{15}H_{17}N_3O_3$	230–231	K	A	83
36	*s*-BuO	H	$C_{15}H_{17}N_3O_3$	183–184.5	L	B	88
37	CH_2=$CHCH_2O$	H	$C_{14}H_{13}N_3O_3$	205–207	C	B	97
38	c-$PrCH_2O$	H	$C_{15}H_{15}N_3O_3$	215–217	M	B	100
39	*n*-PrO	MeO	$C_{15}H_{17}N_3O_4$	206–207	E	A	42

[a,c,d] See corresponding footnotes to Table I. [i] D. H. Kim and A. Santilli, *J. Heterocycl. Chem.*, 8, 715 (1971), mp 292–295 °C dec. [j] N: calcd, 16.21; found, 15.77.

Scheme II

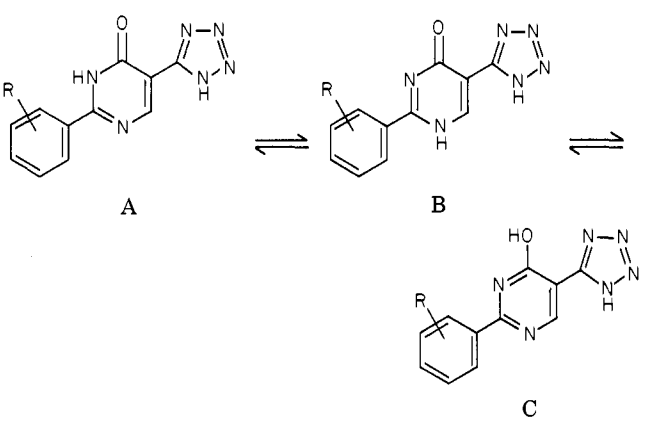


These workers reported that optimum yields of the intermediate cyanoacrylate were obtained by using molar ratios of benzamidine to ethyl ethoxymethylenecyanoacetate of 2 or 3:1. We were unable to isolate any cyanoacrylate **43** from treatment of ethyl ethoxymethylenecyanoacetate (**42**) with 2 equiv of 2-isopropoxybenzamidine **41**, obtaining instead a fair yield of the unwanted amino ester **44**. This undesired pathway may be the result of base catalysis by the excess 2-isopropoxybenzamidine, since Shen et al.[4] and Mitter and Palit[5] have previously reported the formation of a mixture of both cyclized nitrile(s) and amino ester from a base-catalyzed condensation of benzamidines with ethyl ethoxymethylenecyanoacetate. Benzamidine itself, when used in excess with ethyl ethoxymethylenecyanoacetate, may not have been a strong enough base for Nishigaki et al. to have obtained more than trace amounts of amino ester.[3]

Two alternative syntheses of the 2-phenyl-5-(tetrazol-5-yl)pyrimidinones are also illustrated in Scheme III. The cyanoacrylate **43** was converted directly to the 2-isopropoxyphenyl compound **7** with NH_4N_3/DMF but not with $Al(N_3)_3$/THF, the latter complex giving additional unwanted amino ester **44**. More efficiently, the 2-(2-*n*-propoxyphenyl)-, 2-(2-isopropoxyphenyl)-, and 2-[2-(*n*-pentyloxy)phenyl]-5-(tetrazol-5-yl)pyrimidinones **6**, **7**, and **11**, respectively, were all isolated in about 40% yields from treatment of the appropriate benzamidine with ethyl ethoxymethylenecyanoacetate and NH_4N_3 in DMF in one-pot reactions.

Finally, the disubstituted 2-phenyl-5-(tetrazol-5-yl)pyrimidinones **15–17** were obtained directly from 2-(2-*n*-propoxyphenyl)-5-(1*H*-tetrazol-5-yl)pyrimidin-4(3*H*)-one (**6**), as outlined in Scheme IV.

Analogous to the 1,6-dihydro-6-oxo-2-phenylpyrimidine-5-carboxylic acids and esters,[1] we have shown the final products as pyrimidin-4(3*H*)-ones A rather than



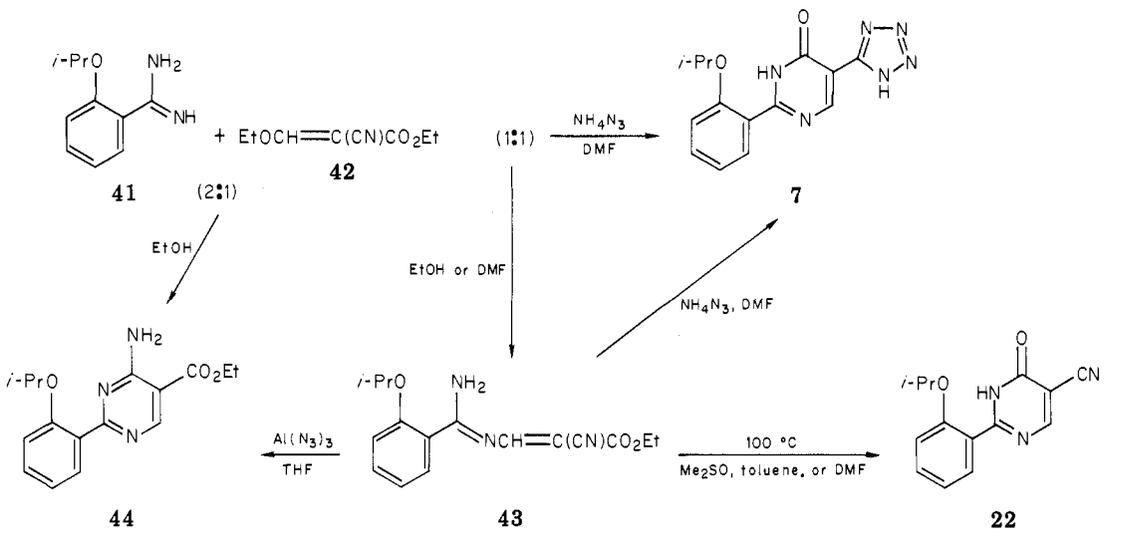
pyrimidin-4(1*H*)-ones B or 4-hydroxypyrimidines C. Support for A comes from the strong IR absorption bands that are observed for each compound in the region of 1640–1665 cm^{-1} (amide C=O) and the similarities between the UV spectra of **6** and 1,6-dihydro-6-oxo-2-(2-ethoxyphenyl)pyrimidine-5-carboxylic acid.[1] The designation of the 1*H* form for the tetrazole ring is arbitrary.

Structure–Activity Relationships and Discussion

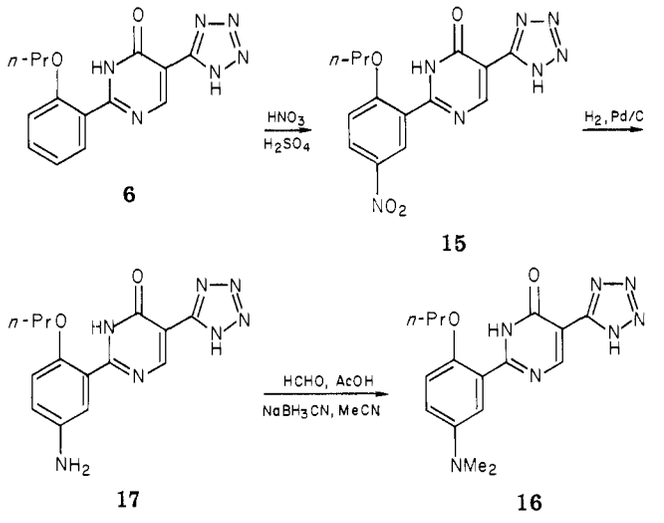
With the present series of compounds we have replaced the carboxy group of some of the 1,6-dihydro-6-oxo-2-phenylprimidine-5-carboxylic acid antiallergy agents[1] with the tetrazol-5-yl group. Like the acids, the tetrazoles were tested for antiallergy activity in the passive cutaneous anaphylaxis (PCA) model[6] in the rat by oral and, in some

(4) T. Y. Shen, G. L. Walford, and B. E. Witzel, U.S. Patent 3 660 403 (1972).
(5) P. C. Mitter and N. Palit, *Q. J. Indian Chem. Soc.*, **2**, 61 (1925).

Scheme III



Scheme IV



cases, intravenous routes of administration. In each case, the dose of compound required to inhibit the response by 50% (ID_{50}) was determined. The results, together with comparative data for DSCG, are shown in Table I.

Herbst's concept[7] of replacing the carboxy group in biologically active molecules with the comparably acidic tetrazol-5-yl group with retention of activity has now been tested for compounds over a broad range of therapeutic categories. The results have been so variable that it is impossible to predict the outcome of a new substitution. There are cases, for example, where the tetrazole analogues are (a) significantly more potent than the corresponding acids,[8,9] (b) comparable in activity to the acids,[10,11] (c) less active than the acids,[12,13] or (d) have no significant activity.[14,15] In the present case, tetrazole antiallergy compounds have resulted that are orally in the range of 5–10 times more potent than the corresponding carboxylic acids. In addition, the 2-*n*-propoxyphenyl compound **6** was found to be approximately 75 times more potent than DSCG when both were administered intravenously. The nonacidic intermediate amides and nitriles had insignificant activity.

In our preceding paper[1] we showed that optimal antiallergy activity in the carboxylic acid series depended on the presence of both an unsubstituted NH group on the pyrimidine nucleus and a small to medium size *o*-alkoxy or *o*-alkenyloxy group on the benzene ring. We postulated that these arrangements allowed the operation of intramolecular hydrogen bonding and, hence, a preferred coplanarity of the benzene and pyrimidine rings. The SAR among the compounds of this limited series of tetrazoles are quite similar to those of the carboxylic acids. Peak activity is observed with ortho ether substituents having three to four carbon atoms.

Compound **6** (BL-5255[16]) is now in clinical trial for the prophylactic treatment of asthma.

Experimental Section

Biological Methods. Male Sprague-Dawley rats were used in a modified version of the rat PCA screen as described by Ovary.[6] The interval between sensitization and challenge was 24 h. Where possible, test compounds (including all tetrazoles) were solubilized with aqueous $NaHCO_3$; remaining compounds were suspended in an aqueous sodium citrate solution containing Tween 40/sodium carboxymethylcellulose. Test compounds were administered iv or po 1 min or 10 min (optimum times), respectively, prior to antigen challenge. DSCG, solubilized in saline, was administered iv at the time of challenge and po arbitrarily 30 min prior to challenge.

Chemical Methods. IR and NMR spectra were obtained for all compounds and were consistent with assigned structures. IR spectra were recorded on either a Beckman IR 9 or IR 4240 spectrophotometer. ^1H NMR spectra were obtained using a Perkin-Elmer R12B 60-MHz spectrometer. Chemical shifts (δ) were measured downfield from Me_4Si. UV spectra were recorded

(6) Z. Ovary, in "Immunological Methods", J. F. Ackroyd, Ed., F. A. Davis, Philadelphia, 1964, pp 259–283.
(7) R. M. Herbst, in "Essays in Biochemistry", S. Graff, Ed., Wiley, New York, 1956, p 141.
(8) A. Nohara, H. Kuriki, T. Saijo, H. Sugihara, M. Kanno, and Y. Sanno, *J. Med. Chem.*, **20**, 141 (1977).
(9) D. J. Drain, B. Davy, M. Horlington, J. G. B. Howes, J. M. Scruton, and R. A. Selway, *J. Pharm. Pharmacol.*, **23**, 857 (1971).
(10) P. F. Juby, T. W. Hudyma, and M. Brown, *J. Med. Chem.*, 11, 111 (1968).
(11) T. K. Schaaf and H.-J. Hess, *J. Med. Chem.*, **22**, 1340 (1979).
(12) P. F. Juby and T. W. Hudyma, *J. Med. Chem.*, **12**, 396 (1969).
(13) J. K. Elwood, R. M. Herbst, and G. L. Kilgour, *J. Biol. Chem.*, **240**, 2073 (1965).
(14) P. M. Gilis, A. Haemers, and W. Bollaert, *Eur. J. Med. Chem.*, **15**, 499 (1980).
(15) B. Brouwer-van Straaten, D. Solinger, C. van de Westeringh, and H. Veldstra, *Recl. Trav. Chim. Pays-Bas*, **77**, 1129 (1958).
(16) P. Siminoff, F. C. Reed III, J. E. Schurig, and P. F. Juby, *Monogr. Allergy*, **14**, 318 (1979).

on a Beckman Model Acta III spectrophotometer. Where analyses are indicated only by symbols of the elements, results obtained are within ±0.4% of the theoretical values. Melting points are uncorrected.

1,6-Dihydro-6-oxo-2-phenylpyrimidine-5-carboxamides (Table III). Method A. We prepared amides **29–35** and **39** by heating the appropriate ethyl 1,6-dihydro-6-oxo-2-phenylpyrimidine-5-carboxylate[1] with excess concentrated NH_4OH in a bomb on a steam bath for 2.5–4 h. The products were isolated after removal of the excess NH_4OH and acidification of the residues with aqueous HCl.

Method B. We prepared amides **36–38** by heating the appropriate ethyl 1,6-dihydro-6-oxo-2-phenylpyrimidine-5-carboxylate[1] with excess NH_3 (liq) in a bomb on a steam bath for 4.5 h. The excess NH_3 was removed, and the residues were treated with aqueous acid (HCl or AcOH) to yield the products.

Ethyl 2-Cyano-3-(2-isopropoxybenzamidino)acrylate (43). Ethyl ethoxymethylenecyanoacetate (2.85 g, 16.8 mmol) was added to an ice-cold solution of 2-isopropoxybenzamidine[1] (3.0 g, 16.8 mmol) in ethanol (21 mL). The mixture was stirred at 5 °C for 1.5 h. The cyanoacrylate **43** (3.9 g, 77%) was collected by filtration and had mp 117–119 °C. Recrystallization from MeCN gave a bright yellow solid, mp 123–124 °C. Anal. ($C_{16}H_{19}N_3O_3$) C, H, N.

1,6-Dihydro-6-oxo-2-phenylpyrimidine-5-carbonitriles (Table II). Method A. Nitriles **18–25** and **28** were prepared from the corresponding amides in a manner similar to that described for the preparation of 1,6-dihydro-6-oxo-2-(2-ethoxyphenyl)pyrimidine-5-carbonitrile (**20**) as follows. A solution of 1,6-dihydro-6-oxo-2-(2-ethoxyphenyl)pyrimidine-5-carboxamide (**31**; 5.5 g, 21 mmol) in $POCl_3$ (160 mL) was heated under reflux for 3.5 h. The solution was evaporated under reduced pressure to a thick oil, which was treated with cold water with vigorous stirring. The mixture was filtered. The collected solid was washed with water, dried, and recrystallized from glacial AcOH to give **20** (3.48 g).

Caution. Care should be taken to remove as much residual $POCl_3$ as possible prior to the treatment of the concentrated reaction mixture with water. In one large-scale experiment, entrained $POCl_3$ decomposed with explosive violence. A preferred procedure is to concentrate the reaction mixture, remove additional $POCl_3$ by azeotroping with toluene, and then carefully add a solution of the residue in CH_2Cl_2 to water with good stirring.

Method B. In the preparation of 1,6-dihydro-6-oxo-2-[2-(allyloxy)phenyl]pyrimidine-5-carbonitrile (**26**) it was necessary to modify method A slightly in order to ensure complete hydrolysis of the intermediate 2-[2-(allyloxy)phenyl]-4-chloropyrimidine-5-carbonitrile. After removal of the $POCl_3$ under reduced pressure, the residual gum was treated with ice–water. The mixture was warmed to 25 °C and then heated on a steam bath for 15 min. The workup was then completed as in method A.

Method C. 1,6-Dihydro-6-oxo-2-[2-(cyclopropylmethoxy)phenyl]pyrimidine-5-carbonitrile (27). 1,6-Dihydro-6-oxo-2-[2-(cyclopropylmethoxy)phenyl]pyrimidine-5-carboxamide (13.6 g, 47.7 mmol) was added to a cold, stirred solution of pyridine (19.2 mL, 18.85 g, 0.238 mol) in $POCl_3$ (136 mL), and the mixture was then heated under reflux for 15 min. The excess $POCl_3$ was removed under reduced pressure, and the residue poured onto ice/CH_2Cl_2. The mixture was neutralized with $NaHCO_3$. The CH_2Cl_2 layer was separated, dried (Na_2SO_4), and concentrated to give crude 2-[2-(cyclopropylmethoxy)phenyl]-4-chloropyrimidine-5-carbonitrile (**40**) as a viscous oil. The oil was treated with 1 N NaOH (200 mL) and tetrahydrofuran (136 mL). The mixture was allowed to stand at 25 °C for 18 h. The mixture was washed with diethyl ether and filtered, and the filtrate was acidified with AcOH. The precipitate was recrystallized from toluene to give **27** (7.6 g), mp 188–190 °C. Two recrystallizations from AcOEt gave the analytical sample.

Method D. 1,6-Dihydro-6-oxo-2-(2-isopropoxyphenyl)pyrimidine-5-carbonitrile (22). A solution of the cyanoacrylate **43** (0.60 g, 1.99 mmol) in Me_2SO (15 mL) was heated by means of an oil bath maintained at 100 °C for 18 h. The cooled mixture was poured into ice–water (400 mL). The mixture was filtered to give **22** (0.4 g, 79%), mp 182–184 °C.

2-Phenyl-5-(1H-tetrazol-5-yl)pyrimidin-4(3H)-ones (Table I). Method A. Using the general conditions of Finnegan et al.,[17] we prepared tetrazolylprimidinones **3**, **5–10**, **13**, and **14**, from the corresponding nitriles in a manner similar to that described for the preparation of 2-(2-*n*-propoxyphenyl)-5-(1*H*-tetrazol-5-yl)-pyrimidin-4(3*H*)-one (**6**) below.

A mixture of 1,6-dihydro-6-oxo-2-(2-*n*-propoxyphenyl)pyrimidine-5-carbonitrile (**21**; 2.81 g, 0.011 mol), NaN_3 (0.788 g, 0.0121 mol), and NH_4Cl (0.647 g, 0.0121 mol) in DMF (22 mL) was heated at 125 °C for 16 h. The solvent was removed under reduced pressure, and the residue was treated with water (40 mL) and acidified with 6 N HCl. The solid was collected by filtration, washed with water followed by acetone, and recrystallized from glacial AcOH to give **6** as pale yellow needles (1.97 g): mp 247–248 °C; IR (KBr) 1657 (amide C=O) cm^{-1}; UV λ_{max} (95% EtOH) 253 nm (ϵ 8729), 338 (16114).

Method B. Tetrazolylpyrimidinones **4** and **12** were prepared from the corresponding nitriles by the method described for 2-(2-methoxyphenyl)-5-(1*H*-tetrazol-5-yl)pyrimidin-4(3*H*)-one (**4**) as follows. Sodium azide (283 mg, 4.35 mmol) was added to a solution of $AlCl_3$ (193 mg, 1.45 mmol) in THF (8 mL).[18] The mixture was stirred under reflux for 0.5 h. 1,6-Dihydro-6-oxo-2-(2-methoxyphenyl)pyrimidine-5-carbonitrile (**19**; 300 mg, 1.32 mmol) was then added, and the mixture was stirred under reflux for 24 h. The cooled mixture was diluted with water (15 mL) and acidified with 6 N HCl. The mixture was filtered, and the collected solid was recrystallized from glacial AcOH to give **4** (130 mg), mp 282–283 °C with decomposition.

Method C. 2-(2-Isopropoxyphenyl)-5-(1*H*-tetrazol-5-yl)pyrimidin-4(3*H*)-one (**7**) was also prepared as follows. A mixture of cyanoacrylate **41** (600 mg, 1.99 mmol), NaN_3 (159 mg, 2.44 mmol), and NH_4Cl (131 mg, 2.44 mmol) in DMF (15 mL) was heated at 127 °C for 21 h. The cooled mixture was poured into ice–water (400 mL) and acidified to pH 2 with 6 N HCl. The mixture was filtered, and the collected solid was recrystallized from 2-methoxyethanol to give **7** (60 mg), mp 274–277 °C.

Method D. Tetrazolylpyrimidinones **6** and **7** were also prepared directly from the corresponding benzamidines by the method described for **11** below.

Ethyl ethoxymethylenecyanoacetate (24.6 g, 0.145 mol) was added to a cooled (ice bath) solution of 2-(*n*-pentyloxy)benzamidine (30 g, 0.145 mol) in dry DMF (120 mL). Twenty minutes later, NaN_3 (11.5 g, 0.178 mol) and NH_4Cl (9.5 g, 0.178 mol) were added, the ice bath was removed, and the mixture was heated by means of an oil bath maintained at 123–127 °C for 24 h. The cooled mixture was poured into ice–water, acidified with concentrated HCl, and filtered. The collected solid was recrystallized from 2-methoxyethanol to give **11** (18.1 g), mp 236–238 °C with decomposition. Recrystallization from 2-methoxyethanol, followed by 2-propanol, gave the analytical sample, mp 236–238 °C with decomposition.

2-(5-Nitro-2-*n*-propoxyphenyl)-5-(1*H*-tetrazol-5-yl)pyrimidin-4(3*H*)-one (Table I, 15). Tetrazolylpyrimidinone **6** (1.03 g, 3.46 mmol) was added over a period of 20 min to a cooled (5 °C) mixture of 70% HNO_3 (1.7 mL, 26.9 mmol) and 96% H_2SO_4 (2 mL). The mixture was allowed to stand at room temperature for 2 h and then poured into ice–water (200 mL). The precipitate was recrystallized from 2-methoxyethanol to give **15** (0.73 g).

2-(5-Amino-2-*n*-propoxyphenyl)-5-(1*H*-tetrazol-5-yl)pyrimidin-4(3*H*)-one (Table I, 16). A mixture of **15** (5.0 g) and 10% Pd/C (4.0 g) in 2-methoxyethanol (900 mL) was shaken with H_2 at an initial pressure of 50 psi for 19 h. The mixture was filtered, and the filtrate was evaporated to dryness to yield **16** (3.6 g), mp 250–253 °C with decomposition. Recrystallization from 2-methoxyethanol gave the analytical sample.

2-[5-(Dimethylamino)-2-*n*-propoxyphenyl]-5-(1*H*-tetrazol-5-yl)pyrimidin-4(3*H*)-one (Table I, 17). To a suspension of **16** (0.50 g, 1.6 mmol) in MeCN (40 mL) was added 37% HCHO in water (1.32 mL, 16.0 mmol). $NaBH_3CN$ (0.302 g, 4.8 mmol) was then added, followed by glacial AcOH (1.67 mL). The suspension was stirred at room temperature for 15 min and then heated under reflux for 3 h. The mixture was cooled in an ice

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bath. The precipitate was recrystallized from MeCN to give 17 (0.19 g).

Ethyl 4-Amino-2-(2-isopropoxyphenyl)pyrimidine-5-carboxylate (44). Method A. Ethyl ethoxymethylenecyanoacetate (0.855 g, 5.05 mmol) was added with stirring to an ice-cold solution of 2-isopropoxybenzamidine[1] (1.66 g, 9.3 mmol) in ethanol (10 mL). The solution was allowed to stand at 0–5 °C for 17 h. The solution was cooled (dry ice/2-propanol), and 44 (0.6 g, 39.5%), mp 132–134 °C, was collected by filtration. Recrystallization from MeCN gave an analytical sample, mp 133–135 °C. Anal. ($C_{16}H_{19}N_3O_3$) C, H, N.

Method B. Sodium azide (0.54 g, 8.3 mmol) was added to a solution of $AlCl_3$ (0.37 g, 2.78 mmol) in THF (16.5 mL).[18] The mixture was stirred under reflux for 0.5 h. The mixture was cooled to −45 °C, and the cyanoacrylate 43 (0.69 g, 2.3 mmol) was added in small portions. After 1 h at −45 °C, followed successively by 1 h at 5 °C, 1 h at 25 °C, and 18 h at reflux, the mixture was cooled and poured onto ice-water (400 mL). The mixture was acidified to pH 3 with 6 N HCl and then filtered. The pH of the filtrate was adjusted to 6 with saturated $NaHCO_3$ solution. After the solution was cooled, stirred, and triturated for 2 h, the resultant solid (0.355 g, 51%) was collected by filtration and recrystallized from toluene–Skellysolve B to give 44, mp 129–134 °C.

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Tricyclics with Analgesic and Antidepressant Activity. 2. [[(Alkylamino)ethyl]thio]dibenzo[*b,f*]thiepins and 10,11-Dihydro Derivatives[1]

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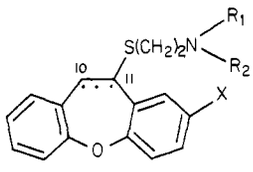
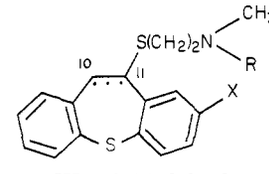
A series of [[(alkylamino)ethyl]thio]dibenz[*b,f*]thiepins (III) and their 10,11-dihydro derivatives (IV) was synthesized and subjected to broad analgesic/CNS screening. Preliminary results indicated a combination of analgesic/antidepressant profiles, similar to that observed for the [[(alkylamino)ethyl]thio]dibenz[*b,f*]oxepins (I) and their corresponding dihydro derivatives (II). The most active congener from the present series, **10b**, shows an antinociceptive potency in the pentazocine range as assessed by phenyl-*p*-quinone-induced writhing (PQW) and tail flick in mice. It is also more than twice as active as imipramine in preventing tetrabenazine-induced ptosis (TBZ), a test widely recognized to be of predictive value for clinically efficacious antidepressants.

A previous publication[1] from these laboratories has described a series of [[(alkylamino)ethyl]thio]dibenz[*b,f*]oxepins (I) and their 10,11-dihydro derivatives (II) as



I, 10,11-dehydro
II, 10,11-dihydro

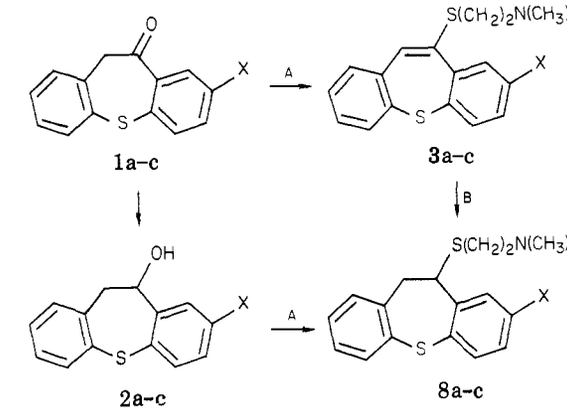


III, 10,11-dehydro
IV, 10,11-dihydro

potential analgesic agents. Results from animal studies indicated that these compounds, in general, showed a low propensity for addiction and tolerance, and many congeners, especially those bearing a fluorine substituent at the C-2 position, further displayed a unique pharmacological profile that combines the desired analgesic activity with an added component of antidepressant-like properties. The latter feature would seem particularly attractive in view of the growing body of clinical evidence[3-5] that implicates the close relationship between chronic pain and depression and the demonstrated effectiveness of many tricyclic antidepressants in alleviating pain associated with a variety of conditions. In this paper we report the synthesis and preliminary pharmacology of a related series of [[(alkylamino)ethyl]thio]dibenzo[*b,f*]thiepins (III) and the corresponding 10,11-dihydro derivatives (IV).[6]

Chemistry. The initial target compounds, i.e., **3a–c** and **8a–c**, were synthesized according to the procedures outlined in Scheme I. Dehydrative coupling of ketones

Scheme I[a]



[a] a, X = H; b, X = F; c, X = Cl.

1a–c[7] with β-(dimethylamino)ethanethiol in the presence of boron trifluoride etherate and glacial acetic acid (method A) afforded vinyl sulfides **3a–c** (type III) in good yields.

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