mixture was cooled and diluted with $H_2O$, and the phases were separated. The aqueous phase was extracted once with $Et_2O$, and the $Et_2O$ phase was added to the toluene phase. The combined toluene-$Et_2O$ phases were washed once with 2 N HCl, and the aqueous phases were combined. The aqueous solution was decolorized with charcoal, filtered, and evaporated to dryness. The residue was recrystallized from MeOH-$Et_2O$: yield 1.40 g (56%); mp 244-245 °C.

# Antiallergics: 3-(1*H*-Tetrazol-5-yl)-4*H*-pyrimido[2,1-*b*]benzothiazol-4-ones

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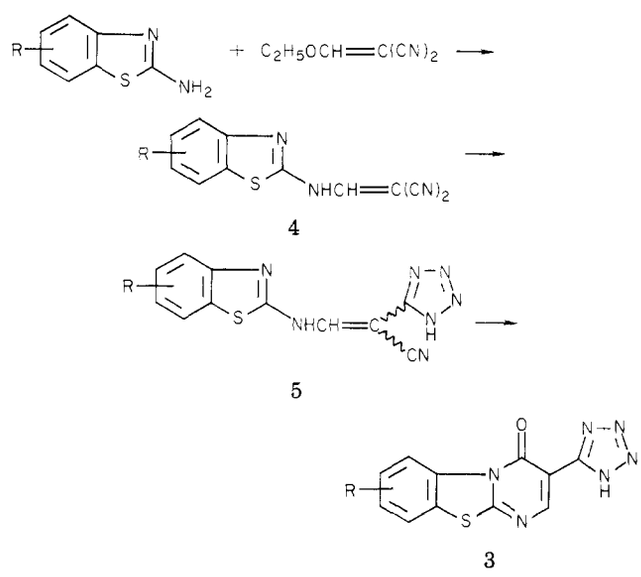
A short series of the title compounds was prepared and evaluated for both antiallergic and bronchodilator activity. Members of the series exhibit good oral activity in the rat PCA test, the most potent being the parent compound, 3-(1*H*-tetrazol-5-yl)-4*H*-pyrimido[2,1-*b*]benzothiazol-4-one, and its 8-chloro derivative. The latter two compounds are considerably more potent than either disodium chromoglycate or theophylline as antiallergic agents and also show significant bronchodilator activity.

The various types of drug therapy available for bronchial asthma include bronchodilators, antiallergy agents, anticholinergics, steroids, and prostaglandins.[1] Of these agents, bronchodilators, including both β-agonists and nonadrenergics such as theophylline, have long been the primary drugs of choice. Although they are quite efficacious, the use of these agents is often limited by the patient's intolerance of their potentially severe side effects.

While the advent of disodium chromoglycate (DSCG) has afforded an alternative to bronchodilator therapy, this drug has not fulfilled initial expectations. As an antiallergic agent, DSCG appears to act mainly by inhibiting the release of various chemical mediators of anaphylaxis from mast cells. Recently, however, at least some of its effects have been attributed to inhibition of reflex mechanisms, reduction of bronchial hyperactivity, and other nonimmunologic modes of action.[2-5] In addition to its lack of oral absorption, which necessitates topical administration, DSCG lacks the broad efficacy of bronchodilators and as a prophylactic drug can prevent, but not alleviate, an asthmatic attack.

Recent work in our laboratories has focused on the development of superior agents acting as either bronchodilators, as mediator release inhibitors, or by a combination of these mechanisms. We have previously reported a series of thieno[2,3-*d*]pyrimidine-5-carboxylic acid derivatives as orally active mediator release inhibitors having no bronchodilator component.[6] Subsequently, we have described 4-substituted imidazo[1,2-*a*]purin-9-ones as bronchodilators having greater potency and fewer side-effect liabilities than theophylline in animal models.[7] Members of this series also show significant antiallergic activity.

Scheme I




Oral antiallergic activity has been reported for various other molecules containing a pyrimidine ring, including the 2-aryl-8-azapurinones **1**[8-10] and the 6-oxo-2-phenylpyrimidine-5-carboxylic acids **2**.[11] The activity of such compounds is greatly enhanced by the introduction of *o*-alkoxy groups on the aryl ring, an observation which has been further corroborated by unpublished studies of several structurally analogous series of fused pyrimidines in our laboratories. It has been suggested that the substituent effect may be attributable to intramolecular hydrogen bonding between the alkoxy oxygen and the proton of the pyrimidinone ring NH moiety.[9] Such bonding should stabilize a conformation of these molecules in which the aryl and heterocyclic rings are coplanar and which may be

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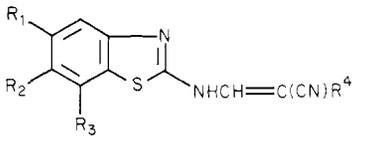
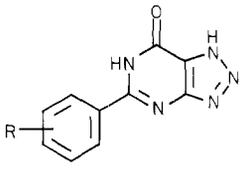
Table I. Intermediate [(Benzothiazolylamino)methylene]propanedinitriles (4) and Cyanotetrazolethenylbenzothiazolamines (5)



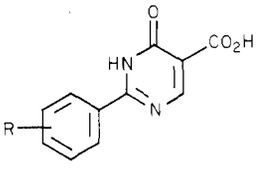
| no. | $R_1$ | $R_2$ | $R_3$ | $R_4$ | % yield | mp, °C | formula[a] | recrystn solvent | method |
|---|---|---|---|---|---|---|---|---|---|
| **6** | H | H | H | CN | 67 | 186-187 | $C_{11}H_6N_4S$ | EtOH | A |
| **7** | Cl | H | H | CN | 64 | 238-240 | $C_{11}H_5ClN_4S$[b] | EtOH | A |
| **8** | H | Cl | H | CN | 60 | 219-224 | $C_{11}N_5ClN_4S$[b] | EtOH | A |
| **9** | $CH_3$ | $CH_3$ | H | CN | 91 | 225 | $C_{13}H_{10}N_4S$[b] | EtOH | A |
| **10** | $CH_3$ | H | $CH_3$ | CN | 73 | 239-241 | $C_{13}H_{10}N_4S$ | EtOH | A |
| **11** | H | $CH_3O$ | H | CH | 87 | 198-200 | $C_{12}H_8N_4OS$ | EtOH | A |
| **12** | H | H | H | 5-$CHN_4$[c] | 88 | 263-265 | $C_{11}H_7N_7S\cdot 0.25H_2O$ | *i*-PrOH | B |
| **13** | Cl | H | H | 5-$CHN_4$ | 41 | 173-178 | $C_{11}H_6ClN_7S$[b] | DMF/MeCN | B |
| **14** | H | Cl | H | 5-$CHN_4$ | 35 | 205-206 | $C_{11}H_6ClN_7S$[b] | DMF/MeCN | B |
| **15** | $CH_3$ | $CH_3$ | H | 5-$CHN_4$ | 94 | 224-228 | $C_{13}H_{11}N_7S$[b] | *d* | B |
| **16** | $CH_3$ | H | $CH_3$ | 5-$CHN_4$ | 98 | 250-253 | $C_{13}H_{11}N_7S\cdot H_2O$ | DMF/MeCN | B |
| **17** | H | $CH_3O$ | H | 5-$CHN_4$ | 98 | 231-235 | $C_{12}H_9N_7OS$[b] | DMF/$H_2O$ | B |

[a] Analyzed compounds had C, H, and N analyses within ±0.40% of theoretical values, unless otherwise indicated. [b] Analytically pure material not obtained. Impure materials reacted in the subsequent step. [c] 5-$CHN_4$ = 5-1*H*-tetrazolyl. [d] Purified by dissolving in 1 N NaOH and reprecipitating with 1 N HCl.

optimal for biological activity. The coplanarity of the azapurine and phenyl rings of an *o*-alkoxy substituted compound of type **1** has been established by X-ray analysis.[12]

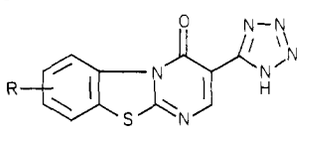


**1**



**2**

We were thus motivated to investigate compounds in which the aryl and pyrimidine rings are locked into a mutually coplanar conformation by an atomic bridge. This paper describes the synthesis and biological activity of a brief series of such compounds, 3-(1*H*-tetrazol-5-yl)-4*H*-pyrimido[2,1-*b*]benzothiazol-4-ones (**3**).



**3**

**Chemistry.** Compounds of type **3** were synthesized via the reaction sequence shown in Scheme I. The 2-aminobenzothiazoles utilized as starting materials were either commercially available or were prepared from the appropriately substituted anilines via literature methods.[13,14]

Base-catalyzed reaction of the 2-aminobenzothiazoles with ethoxymethylenemalononitrile in ethanol (method A) afforded the dinitriles **4**. Treatment of **4** with sodium azide and ammonium chloride in DMF at 80 °C (method B) gave the cyanotetrazoles **5**. While most of the intermediates of types **4** and **5** listed in Table I were not obtained in analytical purity, even after recrystallization, their NMR and IR spectra were consistent with the assigned structures. In all cases, the impure materials were successfully employed in subsequent reactions.

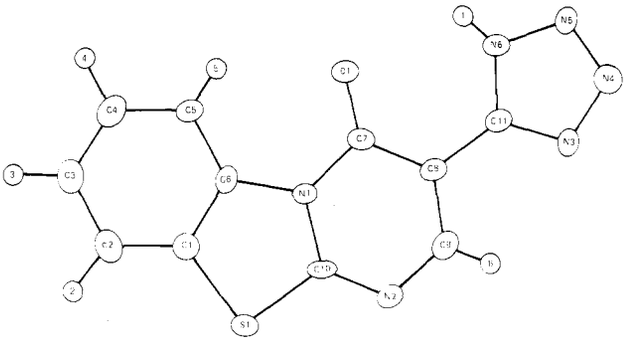


**Figure 1.** Drawing of single molecule of 3-(1*H*-tetrazol-5-yl)-4*H*-pyrimido[2,1-*b*]benzothiazol-4-one(**19**) showing 50% probability ellipsoids.

Conversion of the cyanotetrazoles to the title compounds **3** listed in Table II was, in general, achieved by heating at 95 °C in concentrated sulfuric acid (method C). Compound **18** was prepared by this method and also by cyclization of **12** in trifluoracetic acid and 48% HBr (method D). Treatment of **12** in refluxing ethanolic HCl gave the imine **20** (method E). Compound **18** was converted to its potassium salt **19** with methanolic KOH (method F).

While the $^1H$ and $^{13}C$ NMR spectra of the title compounds of type **3** and their synthetic precursors **4** and **5** are consistent with the assigned structures, unequivocal structural verification cannot be made on the basis of these spectral data. There is literature precedent for the behavior of 2-aminobenzothiazoles and related compounds as ambident nucleophiles; for example, the reaction of 2-aminobenzothiazole with dimethyl acetylenedicarboxylate affords a mixture of isomeric oxopyrimido[2,1-*b*]benzothiazoles.[15] Thus, it is possible that the endocyclic nitrogen of the 2-aminobenzothiazoles which we utilized could undergo reaction with ethoxymethylenemalononitrile to give compounds of type **26**, which are isomeric with **4**. Since there was no evidence of mixture formation in the initial condensation step, either the exo- or endocyclic nitrogen must participate exclusively in this reaction. The structures of the ensuing products of the

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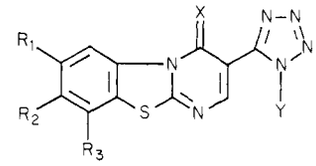
Table II. 3-(1*H*-Tetrazol-5-yl)-4*H*-pyrimido[2,1-*b*]benzothiazol-4-ones



| no. | $R_1$ | $R_2$ | $R_3$ | X | Y | % yield | mp, °C | formula[a] | recrystn solvent | method |
|---|---|---|---|---|---|---|---|---|---|---|
| **18** | H | H | H | O | H | 63 | 329-330 | $C_{11}H_6N_6OS$ | DMF | C |
| | | | | | | 77 | | | | D |
| **19** | H | H | H | O | K | 71 | 336-339 | $C_{11}H_5N_6OS\cdot K\cdot 1.5H_2O$ | MeOH | F |
| **20** | H | H | H | NH | H | 15 | 274-275 | $C_{11}H_7N_7S\cdot HCl$ | DMF | E |
| **21** | Cl | H | H | O | H | 32 | 318-319 | $C_{11}H_5ClN_6OS$ | DMF | C |
| **22** | H | Cl | H | O | H | 38 | 300-301 | $C_{11}H_5N_6ClOS\cdot 0.5H_2O$ | DMF | C |
| **23** | $CH_3$ | $CH_3$ | H | O | H | 12 | 328-346 | $C_{13}H_{10}N_6OS$ | DMF | C |
| **24** | $CH_3$ | H | $CH_3$ | O | H | 34 | 293-295 | $C_{13}H_{10}N_6OS$ | DMF/MeCN | C |
| **25** | H | $CH_3O$ | H | O | H | 48 | 304 | $C_{12}H_8N_6O_2S$ | DMF | C |

[a] All compounds had C, H, and N analyses within ±0.40% of theoretical values.

Table III. X-Ray Data for Compound **19**[a]

Bond Distances

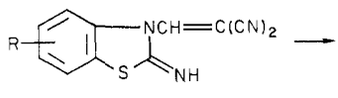
| atom 1 | atom 2 | distance, Å | atom 1 | atom 2 | distance, Å | atom 1 | atom 2 | distance, Å |
|---|---|---|---|---|---|---|---|---|
| S1 | C1 | 1.749 (5) | N4 | N5 | 1.302 (5) | C4 | C5 | 1.388 (6) |
| S1 | C10 | 1.732 (4) | N5 | N6 | 1.352 (4) | C4 | H4 | 1.04 (5) |
| O1 | C7 | 1.229 (4) | N6 | C11 | 1.349 (5) | C5 | C6 | 1.400 (5) |
| N1 | C6 | 1.422 (5) | N6 | H1 | 0.79 (5) | C5 | H5 | 0.90 (4) |
| N1 | C7 | 1.410 (5) | C1 | C2 | 1.384 (6) | C7 | C8 | 1.432 (5) |
| N1 | C10 | 1.386 (5) | C1 | C6 | 1.395 (5) | C8 | C9 | 1.376 (5) |
| N2 | C9 | 1.352 (5) | C2 | C3 | 1.396 (6) | C8 | C11 | 1.455 (5) |
| N2 | C10 | 1.300 (5) | C2 | H2 | 1.02 (4) | C9 | H6 | 0.88 (4) |
| N3 | N4 | 1.358 (5) | C3 | C4 | 1.394 (6) | | | |
| N3 | C11 | 1.322 (5) | C3 | H3 | 1.01 (4) | | | |

Bond Angles

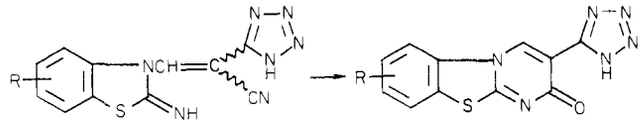
| atom 1 | atom 2 | atom 3 | angle, deg | atom 1 | atom 2 | atom 3 | angle, deg | atom 1 | atom 2 | atom 3 | angle, deg |
|---|---|---|---|---|---|---|---|---|---|---|---|
| C1 | S1 | C10 | 91.0 (2) | C1 | C2 | H2 | 128.0 (2) | O1 | C7 | C8 | 125.5 (4) |
| C6 | N1 | C7 | 126.1 (3) | C3 | C2 | H2 | 114.0 (2) | N1 | C7 | C8 | 113.4 (4) |
| C6 | N1 | C10 | 113.0 (3) | C2 | C3 | C4 | 120.2 (4) | C7 | C8 | C9 | 120.4 (4) |
| C7 | N1 | C10 | 120.8 (4) | C2 | C3 | H3 | 119.0 (3) | C7 | C8 | C11 | 120.0 (4) |
| C9 | N2 | C10 | 115.9 (4) | C4 | C3 | H3 | 120.0 (3) | C9 | C8 | C11 | 119.6 (4) |
| N4 | N3 | C11 | 106.3 (3) | C3 | C4 | C5 | 121.9 (4) | N2 | C9 | C8 | 124.1 (4) |
| N3 | N4 | N5 | 110.9 (3) | C3 | C4 | H4 | 122.0 (2) | N2 | C9 | H6 | 117.0 (3) |
| N4 | N5 | N6 | 106.2 (3) | C5 | C4 | H4 | 116.0 (2) | C8 | C9 | H6 | 119.0 (3) |
| N5 | N6 | C11 | 108.5 (3) | C4 | C5 | C6 | 117.8 (4) | S1 | C10 | N1 | 112.2 (3) |
| N5 | N6 | H1 | 118.0 (4) | C4 | C5 | H5 | 123.0 (2) | S1 | C10 | N2 | 122.5 (3) |
| C11 | N6 | H1 | 134.0 (4) | C6 | C5 | H5 | 119.0 (2)Z | N1 | C10 | N2 | 125.3 (4) |
| S1 | C1 | C2 | 126.4 (4) | N1 | C6 | C1 | 111.9 (4) | N3 | C11 | N6 | 108.1 (4) |
| S1 | C1 | C6 | 111.9 (3) | N1 | C6 | C5 | 127.8 (4) | N3 | C11 | C8 | 125.2 (4) |
| C2 | C1 | C6 | 121.7 (4) | C1 | C6 | C5 | 120.3 (4) | N6 | C11 | C8 | 126.6 (4) |
| C1 | C2 | C3 | 118.2 (4) | O1 | C7 | N1 | 121.1 (4) | | | | |

[a] Crystal data: Single-crystal diffractometry, graphite monochromatized Cu K$\alpha$, $\lambda$ = 1.54184 Å. Monoclinic cell parameters and calculated volume: $a$ = 9.903 (5), $b$ = 12.697 (4), $c$ = 8.369 (4) Å, $\beta$ = 91.58 (3)°, $v$ = 1051.9 Å$^3$. For $z$ = 4 and $M_r$ = 270.27, the calculated density is 1.71 g/cm$^3$. Space group $P2_1/c$.

reaction sequence are determined by the nature of the initial adducts, and if **26** was indeed the correct adduct



**26**



**27** **28**

structure, then subsequent tetrazole formation and cyclization would lead to **27** and **28**, respectively. In order to resolve this ambiguity, we obtained a single-crystal X-ray analysis of the parent member of the series, **19**. As shown in Figure 1, the X-ray study established the structure of **19** to be 3-(1*H*-tetrazol-5-yl)-4*H*-pyrimido-[2,1-*b*]benzothiazol-4-one and not the isomeric benzothiazol-2-one of type **28**. Pertinent X-ray data are listed in Table III.

## Biological Results

Compounds of type **1** were tested for antiallergic activity by oral administration in the rat passive cutaneous anaphylaxis (PCA) test, and the results are presented in Table IV. The parent member of the series, **18**, was biologically evaluated as its water-soluble potassium salt **19**, whereas the other compounds were solubilized in dilute aqueous sodium hydroxide solution for testing.

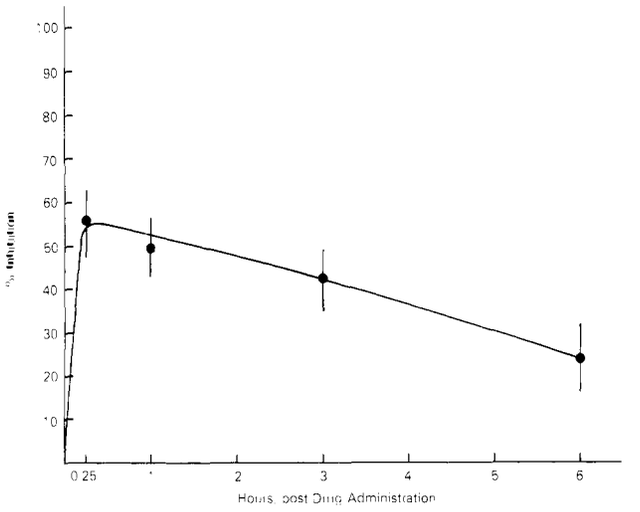



**Figure 2.** Time–response curve in the rat PCA test for compound **19** administered orally at 0.15 mg/kg. Vertical bars represent standard errors of the means.

Compound **19** and the 8-chloro derivative **21** were both quite potent in the PCA test, having $ED_{50}$ values of 0.08 and 0.07 mg/kg, respectively. However, the other aromatic substitutents evaluated resulted in a five- to several-hundred-fold decrease in potency. A dramatic 400-fold difference in potency was observed between the 8-chloro (**21**) and 7-chloro (**22**) isomers. The imine **20**, which may be converted in vivo to **18** (or an ionized species, such as **19**), retains a good, though diminished, level of activity.

As anticipated, compound **19** was even more effective in the PCA test when administered intravenously ($ED_{50}$ = 0.0049 mg/kg) and, thus, has ~60 times the intrinsic potency of DSCG. As illustrated in Figure 2, **19** exhibits good duration of action, showing statistically significant inhibition of the PCA response for up to 6 h.

Compounds **19** and **21** were evaluated for bronchodilator activity by measuring their inhibition of methacholine-induced bronchospasm in rats following intraduodenal (i. duo.) dosing. As shown in Figure 3, both compounds have significant activity at lower dose levels than does theophylline; however, they exhibit flat dose–response curves and barely achieve 50% inhibition of bronchospasm at doses up to 30 mg/kg. Thus, both **19** and **21** appear to be potent bronchodilators of limited capacity.

Table IV. Antiallergic Activity of 3-(1*H*-Tetrazol-5-yl)-4*H*-pyrimido[2,1-*b*]benzothiazol-4-ones

| compd | PCA[a] (rat) $ED_{50}$ (mean ± SE), mg/kg po | allergic bronchospasm[a] (rat) $ED_{50}$ (mean ± SE), mg/kg i. duo. |
|---|---|---|
| **19** | 0.08 ± 0.13 | 0.38 ± 0.27<br>13.2 (0.02),[b] 37.4 (0.1)<br>59.3 (1.0), 61.0 (10.0) |
| **20** | 8.1 ± 1.9 | |
| **21** | 0.07 ± 0.01 | 0.11 ± 0.04<br>21 (0.01),[b] 51.5 (0.1)<br>63.2 (0.3), 73.5 (1.0)<br>79.0 (3.0) |
| **22** | 29.7 ± 11.1 | |
| **23** | 35 (25)[b] | |
| **24** | 1.96 ± 0.64 | |
| **25** | 1.9 ± 0.62 | |
| theophylline | 41.5 ± 11.5 | 22.4 ± 5.9 |
| DSCG | 0.3 ± 0.1[c] | 61.6 (2)[b,c] |

[a] Drug administered 15 min prior to antigen challenge. [b] Percent inhibition at indicated dose. [c] Administered intravenously.

In the inhibition of allergen-induced bronchospasm in rats, a test which responds to the effects of both antiallergic agents and bronchodilators, compounds **19** and **21** have $ED_{50}$ values of 0.38 and 0.11 mg/kg, respectively. Theophylline was approximately two orders of magnitude less potent in this test ($ED_{50}$ = 22.4 mg/kg), while a single 2 mg/kg iv dose of DSCG produced a 61.6% inhibition of bronchospasm.

In conclusion, 3-(1*H*-tetrazol-5-yl)-4*H*-pyrimido[2,1-*b*]-benzothiazol-4-ones, such as compounds **19** and **21**, have been found to exhibit a profile of activity in animal models which suggests their potential use as orally active agents for the treatment of respiratory disease.

## Experimental Section

**Method A. 1-[(Benzothiazol-2-ylamino)methylene]-propanedinitrile (6).** To a solution of Na (0.4 g) in 150 mL of absolute EtOH was added 2-aminobenzothiazole (12.0 g, 0.08 mol) and ethoxymethylenemalononitrile (9.76 g, 0.08 mol), and the mixture was refluxed for 1 h. After the mixture cooled, a yellow crystalline precipitate was collected to give 13.2 g (67%)

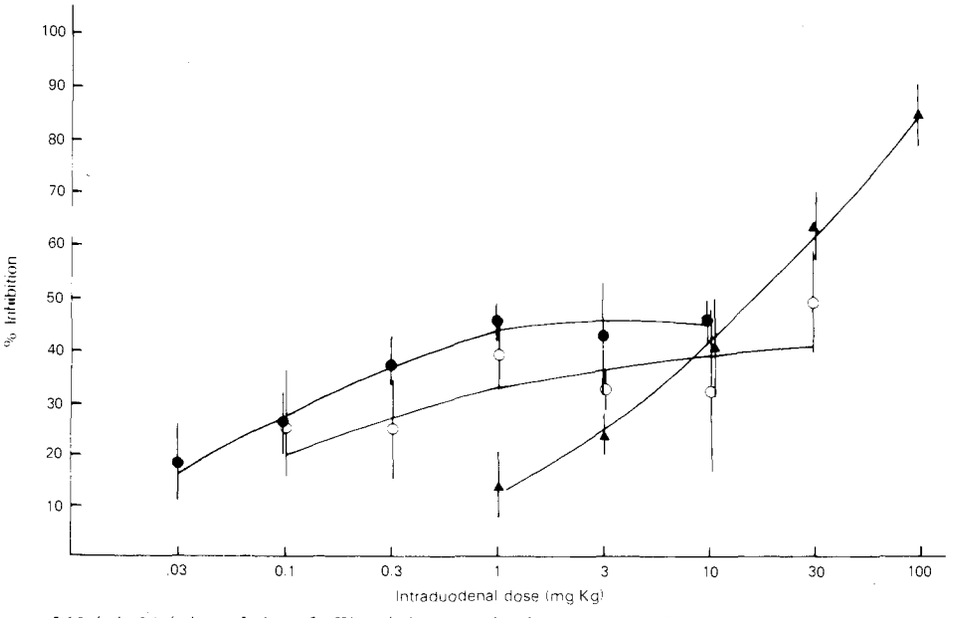



**Figure 3.** The effects of **19** (●), **21** (○), and theophylline (▲) on methacholine-induced bronchospasm in anesthesized rats. Test drugs were administered 15 min prior to intravenous methacholine. Vertical bars represent standard errors of the means.

of 6. Recrystallization from EtOH afforded an analytical sample, mp 186–187 °C.

**Method B. *N*-[2-Cyano-2-(1*H*-tetrazol-5-yl)ethenyl]-benzothiazol-2-amine Hydrate (12).** 2-[(Benzothiazol-2-ylamino)methylene]propanedinitrile (6; 7.5 g, 0.033 mol), $NaN_3$ (2.3 g, 0.033 mol), and $NH_4Cl$ (1.8 g, 0.033 mol) were stirred at 80 °C in 40 mL of DMF for 16 h. The reaction mixture was poured into 150 mL of $H_2O$ and acidified with 10 mL of HOAc to produce a yellow precipitate, which was collected and afforded 8.0 g of 12. Recrystallization from *i*-PrOH gave pure 12, mp 263–265 °C.

**Method C. 3-(1*H*-Tetrazol-5-yl)-4*H*-pyrimido[2,1-*b*]-benzothiazol-4-one (18).** A solution of *N*-[2-cyano-2-(1*H*-tetrazol-5-yl)ethenyl]benzothiazol-2-amine (12; 7.29 g, 0.027 mol) in 18 mL of $H_2SO_4$ was heated with stirring at 95 °C for 1 h. It was cooled and then carefully diluted with 7 mL of $H_2O$, followed by heating again at 95 °C for 2 h. This solution was cooled and diluted with 18 mL of $H_2O$, precipitating the crude product. This solid was dissolved in 7.5 mL of 40% NaOH and then acidified to precipitate 4.59 g (63%) of 18, mp 320 °C. Recrystallization from DMF gave analytically pure material, mp 329–330 °C.

**Method D.** *N*-[2-Cyano-2-(1*H*-tetrazol-5-yl)ethenyl]benzothiazol-2-amine (0.35 g, 0.0013 mol) was heated on a steam bath with 5 mL of $CF_3CO_2H$ and 10 mL of 48% HBr for 1 h. $CF_3CO_2H$ was removed under reduced pressure to afford 0.27 g (77%) of 18.

**Method E. 3-(1*H*-Tetrazol-5-yl)-4*H*-pyrimido[2,1-*b*]-benzothiazol-4-imine Hydrochloride (20).** *N*-[2-Cyano-2-(1*H*-tetrazol-5-yl)ethenyl]benzothiazol-2-amine (12; 3.0 g, 0.011 mol) was refluxed in 50 mL of 2 *N* ethanolic HCl for 4 h. The resulting yellow precipitate was collected. Crystallization from DMF afforded 0.5 g of 20, mp 274–275 °C.

**Method F. 3-(1*H*-Tetrazol-5-yl)-4*H*-pyrimido[2,1-*b*]-benzothiazol-4-one Potassium Salt (19).** 3-(1*H*-Tetrazol-5-yl)-4*H*-pyrimido[2,1-*b*]benzothiazol-4-one (3.5 g, 0.013 mol) was treated with 85% KOH (0.83 g, 0.013 mol) in 5 mL of water with stirring. The solution was stirred with Darco at 80–90 °C for 0.5 h and filtered through Celite, and the filtrate was diluted with 35 mL of EtOH. After the solution was left standing for 16 h, the solid was collected by filtration and air-dried to provide 3.08 g (71%) of 19, mp 326–328 °C. Recrystallization from MeOH raised the melting point to 336–339 °C.

**Biological Test Methods.** The tests employing rat passive cutaneous anaphylaxis, inhibition of methacholine bronchospasm in rats, and inhibition of allergic bronchospasm in sensitized rats were performed as previously described.[7]

**Acknowledgment.** The X-ray analyses of compound 29 were performed by the Molecular Structure Corp., College Station, TX. Other spectral and analytical data were obtained under the supervision of Charles M. Combs.

# *Notes*

## Pyridoquinoxaline *N*-Oxides. 2. Synthesis and Antibacterial Activity of Tricyclic Lactams[1]

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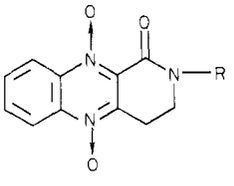
A series of novel 3,4-dihydropyrido[3,4-*b*]quinoxalin-1(2*H*)-one 5,10-dioxides was synthesized using an intramolecular amidation reaction. The lactams were screened in vitro and in vivo against *Salmonella choleraesuis*, *Pasteurella multocida*, and *Escherichia coli*. An *N*-methyl analogue was the most potent member of this series, with antibacterial activity comparable to that of the commercially important quinoxaline 1,4-dioxide carbadox.

Quinoxaline 1,4-dioxides (QNO's) featuring carboxamide side chains,[2a] including fused five-ring lactams,[2b] are known to have good antibacterial activity. Based on our interest in the pyridoquinoxalines,[1] we chose to investigate the synthesis and antibacterial activity of the tricyclic 3,4-dihydropyrido[3,4-*b*]quinoxalin-1(2*H*)-one 5,10-dioxides 1.



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**Synthesis.** We envisioned the desired lactams 1 as arising from the corresponding aminoethyl esters 2 by intramolecular amidation (Scheme I). A likely starting material for the synthesis of 2 was methyl 3-[2-(phenylsulfonyl)ethyl]quinoxaline-2-carboxylate (3). The phenylsulfonylethyl side chain in 3 was viewed as a latent vinyl group which could be unmasked by elimination of benzenesulfinic acid under basic conditions. The resulting unsaturated QNO 4 could then undergo Michael addition with amines to give the intermediate amino esters 2.

Preparation of precursor 3 involved condensation[3] of benzofurazan 1-oxide (BFO) with methyl 3-oxo-5-(phenylthio)pentanoate in the presence of catalytic amounts of calcium hydroxide to give the sulfide 5. The crude sulfide was treated with *m*-chloroperbenzoic acid to afford sulfone 3 in 40% overall yield. Reaction of 3 with primary amines in acetonitrile gave the targeted lactams **1a–h** in good yield (Table I). None of the proposed aminoethyl ester intermediates 2 could be detected under the reaction conditions. However, evidence for the intermediacy of 2 was obtained by treatment of sulfone 3 with diethylamine in acetonitrile to give the open-chained amino ester 6.

**Biology.** The 3,4-dihydropyrido[3,4-*b*]quinoxalin-1-ones (**1a–h**) were screened in vitro and in vivo against Gram-

(1) For paper 1 in this series, see E. A. Glazer and L. R. Chappel *J. Med. Chem.*, under Articles in this issue.

(2) (a) F. Seng, C. Buchheim, K. Ley, O. Gloebusch, K. G. Metzer, and W. Elberfeld, U.S. Patent 3682906 (1972); K. Ley, O. Globusch, U. Eholzer, C. Stammheim, K. Nast, C. Buchheim, and K. G. Metzer, U.S. Patent 3600391 (1972). (b) T. H. Cronin and P. D. Hammen, U.S. Patent 3753387 (1973).

(3) (a) M. J. Haddadin and C. H. Issidorides, *Tetrahedron Lett.*, 3253 (1965). (b) *Heterocycles*, 4, 767 (1976).

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